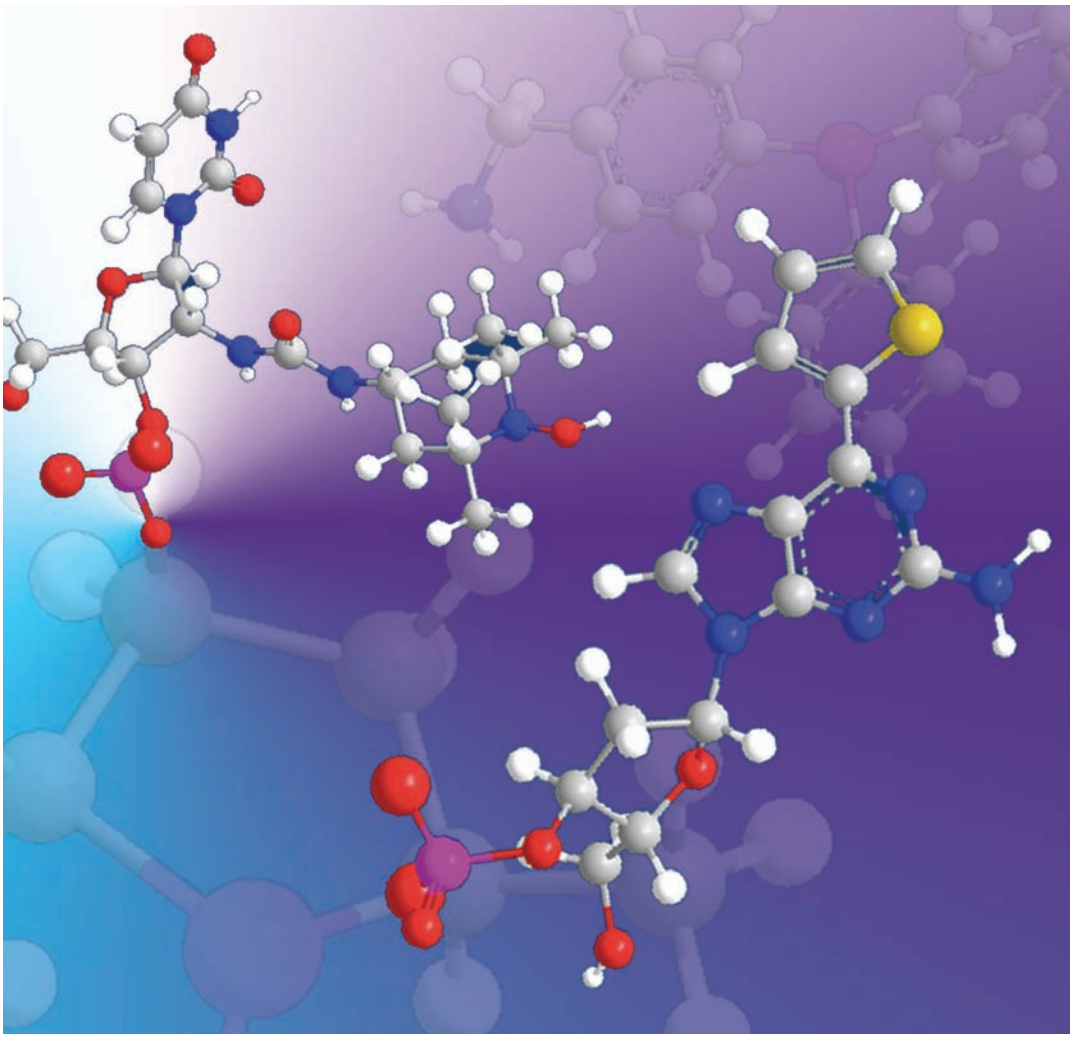
Specialist Periodical Reports

Editors D W Allen and J C Tebby

Organophosphorus Chemistry

Volume 35



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Organophosphorus Chemistry

Volume 35

A Specialist Periodical Report

Organophosphorus Chemistry

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A Review of the Literature Published between July 2002 and June 2004

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Preface

Organophosphorus chemistry continues to generate a very large volume of literature, with no sign of any decline in activity. In this volume, we have increased our period of coverage of the literature, bringing it up to June 2004, in order to try to remedy the increasingly evident problem that our team of writers has in putting together these volumes in a timely manner. Our coverage of the above period is complete apart from the absence of the usual chapter on ylide chemistry. This deficiency, and the fact that this volume will not appear until early 2006, reflect the conflicting pressures which our authors are facing in collecting the information and in finding the substantial time needed to write these usually comprehensive reports. In consequence, it is probable that this volume will be last in the current style. Future volumes are likely to offer a more selective and critical coverage of the area, since the increasing availability of computer-aided literature search facilities makes attempts to provide comprehensive coverage unnecessary.

The period under review has seen the publication of several important books and general reviews. François Mathey has contributed a new book on heterocyclic organophosphorus compounds (*Phosphorus-Carbon Heterocyclic Chemistry: The Rise of a New Domain; Elsevier, 2001*) and Louis Quin and Anthony Williams have compiled a valuable new data resource on ^{31}P NMR spectroscopy (*Practical Interpretation of P-31 NMR Spectra and Computer-Assisted Structure Verification; Advanced Chemistry Development, Toronto, 2004*). A review of odd-electron bonds and biradicals in main group element chemistry (H. Grutzmacher and F. Breher, *Angew Chem. Int. Ed.*, 2002, **41**, 4006) contains much that is relevant to organophosphorus chemistry. A special edition of the journal *Phosphorus, Sulfur, Silicon and the Related Elements* (2004, **179**, issue 4–5, 649) was devoted to the proceedings of the Tenth International Symposium on Inorganic Ring Systems held in August 2003 in Vermont, USA and this again contains much relevant material.

Once again, the drive for improved performance in transition metal ion-catalysed processes has continued to stimulate the synthesis of new types of organophosphine and tervalent phosphorus-ester and -amide ligands. Activity in the chemistry of heteroaromatic phosphorus ring systems and low-coordination number p_π-bonded systems has also remained at a high level. New mechanistic insights into the Mitsunobu reaction have been reported, and interest in synthetic applications of Staudinger/Mitsunobu procedures has continued to develop.

The chemistry of phosphonium salts and phosphine chalcogenides has also continued to develop, although no major advances have appeared, doubtless reflecting the maturity of the area.

In the area of mononucleotide chemistry, extensive work has been reported on the chemistry of polyphosphates, in particular that of dinucleoside and

sugar nucleoside pyrophosphates. This reflects the reliability and flexibility of phosphoramidate methods which have been developed over the past few years. Similarly, a wide range of oligonucleotide building blocks, incorporating extensive structural modifications when compared to the natural nucleoside structures, have been described.

The review of polynucleotide chemistry focuses on oligonucleotide modifications, the largest group of which involves novel nucleobases that are used not only for duplex stabilisation and tertiary structures, but find application in understanding the mode of action of other biological molecules, conjugation with small molecules as well as macromolecules, and in nanotechnology devices. Advances also relate to sugar and backbone modifications. Noteworthy emerging areas include templated organic synthesis, and single molecule detection.

The three years since SPR 33 have seen considerable activity in the field of hypervalent phosphorus chemistry especially in the area of hexacoordinate and pseudo-hexacoordinate phosphorus compounds. In this respect, the Holmes' group has made further, substantial contributions to the subject of N, O and S donor interactions at hypervalent phosphorus and the relevance of such interactions to the mechanism of phosphoryl transfer enzymes. The utility of proazaphosphatranes as catalysts (or co-catalysts) has been established by Verkade *et al.* in an impressive range of synthetic procedures and both Kawashima and Akiba have reported outstanding work on bicyclic phosphorane systems, carbaphosphatranes and the relevance of anti-apicophilic phosphorane systems to the mechanism of the Wittig reaction. The Lacour group has detailed the use of C_2-symmetric hexacoordinated phosphate anions for enantiodifferentiation of organic and organometallic cations and last, but not least, Gillespie *et al.* have produced a thought-provoking review on bonding in penta- and hexacoordinated molecules. After 25 years Dennis Hall is retiring as an author to this publication. We thank him for his invaluable contributions.

Over the two year period covered, there have been impressive advances in several areas of P(V) chemistry. For example, biological aspects of quinquevalent phosphorus acids chemistry continue to increase in importance. A wide variety of natural and unnatural phosphates including inositols, lipids, some carbohydrates and their phosphonates, phosphinates and fluorinated analogues have been synthesized. Highlights include the asymmetric synthesis of phosphates, access to enantiomerically pure α-fluorinated phosphonate mimetics and a fluorescent porphyrin conjugate. Special attention has been paid to the synthesis of phosphorus analogues of all types of amino acids and some peptides. Numerous investigations of phosphate ester hydrolysis and related reactions continue to be reported. They include fluorescent monitoring probes and control of stereoselectivity of enzymatic hydrolysis of phosphonates. There have been interesting studies of phosphate complexation with lanthanide, zinc and copper complexes, the latter involving host-guest concepts. Interest in approaches to easier detoxification of insecticides continues. A number of new and improved stereoselective synthetic procedures have been elaborated.

Notable were highly enantioselective additions of N-phosphonyl imines with dialkyl zinc or hydroxyketones and a one-pot reaction of alkynylzirconocenes with alkynyl phosphazenes and zinc carbenoids to give single isomer cyclopropylphosphonamides. The importance of enantioselective and dynamic kinetic asymmetric transformations is illustrated in many publications. Other interesting reports cover the use of phosphoramidates for the synthesis of allylic amines as well as the first example of C–P cleavage of α-aminophosphono acids using periodate.

Two books have appeared on phosphazene chemistry reflecting its continuing wide development. There has been keen interest in acyclic phosphazenes and the ever-useful Staudinger reaction has been employed to produce novel tricyclic oxazoles, linear oligophosphazenes, as well as a series of aryloxypolyphosphazenes with potential for producing dendrimeric structures. Phosphoranimines have been prepared in high yields and their use in aza-Wittig reactions has paved the way for the preparation of a wide variety of natural products. A novel *N*-trimethylsilylphosphoranimine cationic salt has been prepared in which the NP bond approaches that of a triple bond. The basicity of a number of phosphazene bases (P1-P4) in the gas phase has been calculated and it was found that Bu^t-P4 was by far the strongest phosphazene base (even stronger than Verkade's superbase). It was used in UV-vis spectrophotometric titrations of acids and in various synthetic procedures. Thus Et-P2 was utilised in the asymmetric synthesis of disubstituted *N*-tosyl aziridines whereas Bu^t-P2 reacted with *O*-acyl hydroxamic acid derivatives to yield 2,3-dihydro-4-isoxazole carboxylic esters. Bu^t-P1, Et-P2 or BEMP has been used to solubilise α- amino acids to facilitate the synthesis of peptides. Other applications include dehydrochlorination, polymer modifiers, host-guest reactions and the tribology of phosphorylated carbon-coated surfaces, enhanced conductivity and fuel cell membranes. Various networks have been prepared by radical polymerization using phosphazenes as crosslinking reagents and a polyphosphazene has been utilised in bucky ball chemistry. Biomedical applications include membrane separations, biodegradable polymers and controlled drug release experiments.

In conclusion, we would thank our team of contributors for their efforts in writing for these volumes in recent years. As noted above, this volume may represent the end of an era which has extended over more than 35 years, the first volume having appeared in 1970 under the editorship of Professor Stuart Trippett. It would be a serious omission in writing this preface if we failed to note the passing of Professor Leopold Horner (1911–2005) who contributed so much to the development of organophosphorus chemistry, particularly to the development of routes to chiral phosphines and, of course, to the Horner modification of the Wittig reaction.

D.W. Allen and J.C. Tebby

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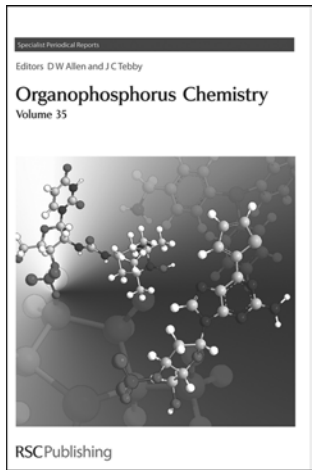

Cover
A selection of organophosphorus molecules, image reproduced by permission of Dr David Loakes

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Abbreviations

BAD	Benzamide adenine dinucleotide
cDPG	Cyclodiphospho D-glycerate
CE	Capillary electrophoresis
CK	Creatine kinase
CPE	Controlled potential electrolysis
Cpmp	1-(2-chlorophenyl)-4-methoxylpiperidin-2-yl
CV	Cyclic voltammetry
DETPA	Di(2-ethylhexyl)thiophosphoric acid
DMAD	Dimethylacetylene dicarboxylate
DMF	Dimethylformamide
DMPC	Dimyristoylphosphatidylcholine
DRAMA	Dipolar restoration at the magic angle
DSC	Differential scanning calorimetry
DTA	Differential thermal analysis
ERMS	Energy resolved mass spectrometry
ESI-MS	Electrospray ionization mass spectrometry
EXAFS	Extended X-ray absorption fine structure
FAB	Fast atom bombardment
Fpmp	1-(2-fluorophenyl)-4-methoxylpiperidin-2-yl
HPLC	High-performance liquid chromatography
LA-FTICR	Laser ablation Fourier Transform ion cyclotron resonance
MALDI	Matrix assisted laser desorption ionization
MCE	Micellar electrokinetic chromatography
MIKE	Mass-analysed ion kinetic energy
PAH	Polycyclic aromatic hydrocarbons
QDA	Hydroquinone-*O*,*O*′-diacetic acid
PMEA	9-[2-(phosphonomethoxy)ethyl] adenine
SATE	*S*-acyl-2-thioethyl
SIMS	Secondary ion mass spectrometry
SSAT	Spermidine/spermine-N1-acetyltransferase
SSIMS	Static secondary ion mass spectrometry
TAD	Thiazole-4-carboxamide adenine dinucleotide
tBDMS	tert-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TGA	Thermogravimetric analysis
TLC	Thin-layer chromatography
TOF	Time of flight
XANES	X-Ray absorption near edge spectroscopy

Organophosphorus Chemistry, Volume 35

Phosphines and Related Tervalent Phosphorus Systems

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1 Introduction

As this chapter covers two years of the literature relating to the above area, it has been necessary to be somewhat selective in the choice of publications cited. Nevertheless, it is hoped that most significant developments have been noted. The period under review has seen the publication of a considerable number of review articles, and most of these are cited in the relevant sections. In addition, several reviews having a broad relevance to the chemistry of phosphines have appeared, relating to the chemistry of silicon-based phosphines,[1] and the specific contribution of phosphorus in dendrimer chemistry[2] and that of related nanomaterials.[3]

2 Phosphines

2.1 Preparation. – *2.1.1 From Halogenophosphines and Organometallic Reagents*. This approach has been applied widely in the synthesis of a range of sterically-crowded monophosphines, some of which have attracted considerable interest in the development of new homogeneous transition metal catalyst systems, the bulky phosphine facilitating the formation of catalytically-active low-coordinate species. Typical of these are tris(2,4,6-triisopropylphenyl)phosphine (prepared by a modified Grignard procedure, together with the corresponding arsine, stibine and bismuthine),[4] tris(α-methylbenzyl)phosphine, also obtained by a Grignard procedure and isolated in both racemic and enantiomerically pure forms,[5] and an extensive range of *o*-alkyl-substituted arylphosphines.[6,7] Two groups have reported the synthesis of the bowl-shaped tris(alkyl-substituted terphenyl)phosphines (1) using organolithium reagents.[8,9] Organolithium routes have also been used to prepare phosphines bearing fluorenyl[10] and indenyl[11,12] substituents. The bulky, aryl-functionalised trialkylphosphine (2) has been prepared in a stepwise manner

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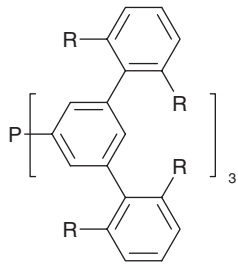
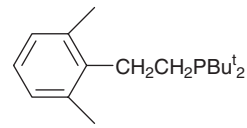
from the Grignard reagent 2,6-$Me_2C_6H_3CH_2CH_2MgCl$, *t*-butylphosphonous dichloride, and *t*-butyllithium.[13] Bulky *ortho*-methyl-substituted arylphosphines bearing additional alkyl or alkoxy groups in the *para*-position have been obtained by Grignard routes and subsequently made water-soluble by sulfonation.[14]

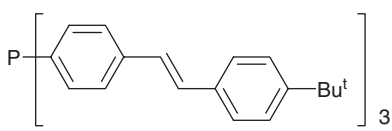


(1) R = H, Me or Pr^i



(2)

A wide range of phosphines bearing other functional groups has been prepared *via* the reactions of organometallic reagents with halogenophosphines. Phosphines bearing perfluoroalkyl-[15] and perfluoroalkylsilylaryl-[16] substituents have been prepared, the latter by a combinatorial approach which resulted in 108 different molecules. The tris(4-styrylphenyl)phosphine (3) has been prepared and converted into a range of simple derivatives, the luminescence properties of which have been of interest.[17] A convenient route to the styrylphosphine (4) is afforded by the simple Grignard reaction of 4-bromostyrene with magnesium, followed by addition of chlorodiphenylphosphine, giving the phosphine in 52% yield on a 30g scale. Direct radical polymerisation of the latter has given a range of phosphinated polystyrenes.[18]



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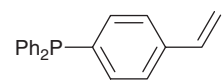
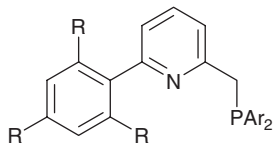


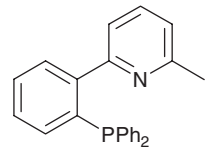
(4)

Selective lithiation of alkyl- or aryl-pyridines is the key to the synthesis of a range of new phosphinopyridine ligands, e.g., (5),[19,20] (6),[21] and a fused phosphinomethylpyridinoferrocene.[22] A similar approach has been used in the synthesis of chelating phosphino-oxazoline ligands, e.g., (7),[23,24] (8),[25] (9),[26] and (10),[27] and also of related phosphino-imidazolines,[28] phosphinoalkylimines, e.g., (11),[29–31] and a phosphinodiimine system.[32] Among a range of P,O-donor ligands prepared *via* organolithium reagents

are the phenacyldiarylphosphines (12),[33] further 2-phosphinophenols,[34,35] and a bulky *ortho*-amidoarylphosphine.[36] Metallation of diethyl benzylphosphonate, followed by treatment with chlorodiphenylphosphine, has given the β-phosphonato-phosphine (13).[37] Three distinct groups of functionalised phosphines, (14), (15), and the heteroarylphosphine (16), have been developed as ligands for palladium-catalysed aryl aminations, each system having been obtained by the reaction of aryllithium reagents with halogenophosphines.[38] Among other heteroarylphosphines prepared in this way are a series of 2-phosphino-N-aryl-pyrroles[39] and -indoles,[40] the diphosphinopyrazole (17),[41] and further examples of bis(phosphino)oligothiophenes.[42] A new approach to the 1-phosphabicyclo[3,3,0]octane system (18) starts from the Grignard reaction of 4-chloro-hepta-1,6-diene with magnesium in THF, which proceeds without rearrangement. Conversion to 1-allyl-3-butenylphosphonous dichloride, followed by reduction with lithium aluminium hydride affords 1-allyl-3-butenylphosphine which undergoes radical-promoted cyclisation to form the bicyclic system.[43] Several reports of the synthesis of alkynylphosphines have appeared. Metallation at the terminal alkyne carbon of an imine derived from 4-ethynylbenzaldehyde, using lithium diisopropylamide, followed by treatment with chlorodimethylphosphine, affords the long chain phosphine (19), of interest as a source of metallomesogens.[44] The reaction of a diethynylsilane with ethylmagnesium bromide, followed by an organodichlorophosphine has given the cyclic ethynylphosphine system (20).[45] A 1, 4-dilithiobutadiyne reagent has been used in the synthesis of 1,4-bis(diphenylphosphino)butadiyne.[46] Sequential treatment of *o*-dibromobenzene with butyllithium and chlorodiphenylphosphine, followed by a second lithiation step and addition of dichloro(bis-isopropyl)silane, provides a practical route to the *o*-chlorosilyl-functionalised phosphine (21).[47] Lithiation of 4bromobenzonitrile, addition of chlorodiphenylphosphine, and subsequent reduction of the nitrile group with lithium aluminium hydride, yields the phosphinobenzylamine (22). A related procedure from 2-bromo-4′-cyanobiphenyl gives (23). The reactivity of the aminobenzylic groups of (22) and (23) was subsequently utilised to give a range of hydrophilic phosphines bearing carbohydrate side chains.[48] A triarylphosphine having dimethylaminomethyl groups in every available *meta*-position has also been reported.[49] Interest in the chemistry of phosphines bearing 1,2-dicarboranyl substituents has continued. A Grignard procedure has been used to prepare the tris(dicarboranylmethyl) analogue (24) of tribenzylphosphine from 1-bromomethyl-*o*-dicarba-*closo*-dodecaborane in 82% yield. The phosphine has a ^{31}P n.m.r. chemical shift of −13.6 ppm, and forms the related phosphine oxide on prolongued treatment with hydrogen peroxide. Although it forms a complex with gold(I), the bulkiness of the molecule prevents alkylation at phosphorus, even with methyl triflate.[50] Further studies of the chemistry of 1,2-bis(phosphino)-1,2-dicarba-*closo*-carboranes have been reported,[51] as have full details of the synthesis of (phosphino-*o*-carboranyl)silanes.[52]



(5) R = H, Me or Pr^i
Ar = Ph, *o*-tol or Mes



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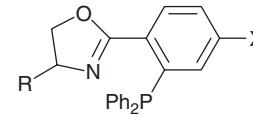
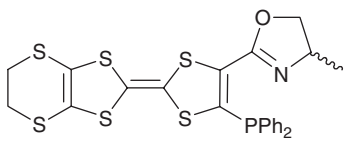


(7) R = Me, Pr^i or Bu^t;
X = H, F, Cl, NMe_2 or OMe



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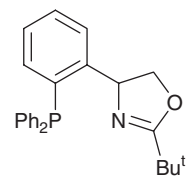

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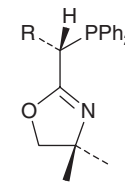
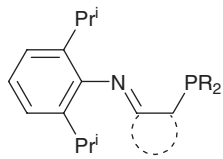


(10) R = H or Me



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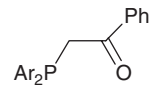
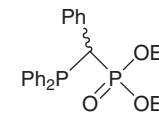


(12) Ar = Ph or bulky aryl



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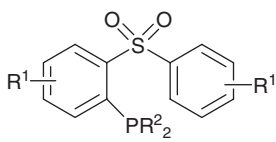
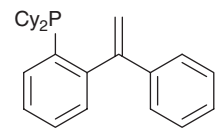


(14) R^1 = H or Me
R^2 = Cy, Pr^i or Bu^t



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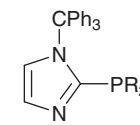
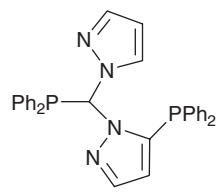


(16) R = Cy or Pr^i



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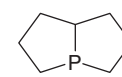

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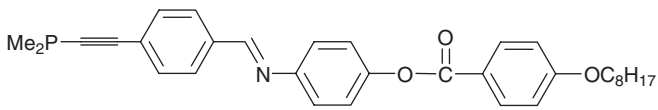

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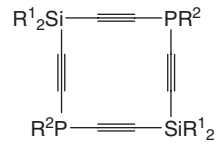
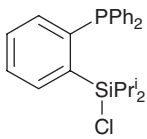


(20) $R^1 = R^2 = Ph$; $R^1 = Ph$, $R^2 = Bu^t$; $R^1 = Pr^i$, $R^2 = Ph$



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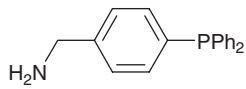

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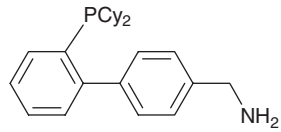
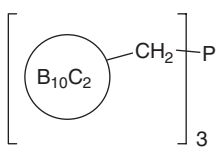


(23)

The ferrocene system remains a favourite building block for the synthesis of new phosphines. Among new ferrocenylmonophosphines prepared *via* reactions of lithioferrocenes with halogenophosphines are the chiral systems (25) and (26),[53] a series of chiral aryl(phosphino)ferrocenes (27),[54,55] the chiral bis(ferrocenyl)monophosphines (28),[56] and the bulky phosphines (29)[57] and (30).[58] Also reported is a wide range of monophosphinoferrocenes bearing a donor group either *ortho* to phosphorus (31)[59,60] or in the remote ring (32), involving alkoxy,[61] thioether,[62,63] or sulfinyl[64] groups. Progress has also been made on the synthesis of ferrocenylphosphines bearing two or more phosphine groups. Among new systems reported are the diphosphinoferrocenophane (33),[65] the diphosphines (34)[66] and (35),[67] and the tetraphosphine '*manphos*' (36).[68] New ferrocenyldiphosphines incorporating additional donor groups have been described, including the chiral C_2-symmetrical system (37)[69] and a ferrocenyldiphosphine involving a chiral oxazoline group.[70] New phosphines based on other metallocene scaffolds have also been reported, including osmocene,[71] benzenechromium tricarbonyl,[72,73] and the related cyclopentadienylrhenium(I) tricarbonyl system.[74,75]



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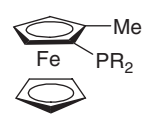
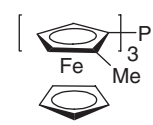


(25) R = Ph, Cy or Bu^t



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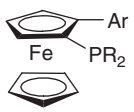
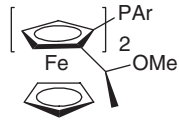
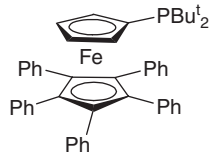


(27) R = Ph or Cy
Ar = *o*-$MeOC_6H_4$,
p-$MeOC_6H_4$,
3,5-$(CF_3)_2$ C_6H_3 or Ph



(28) Ar = *p*-$CF_3C_6H_4$,
p-$MeOC_6H_4$,
3,5- $(CF_3)_2C_6H_3$ or Ph



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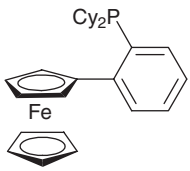

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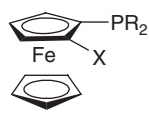
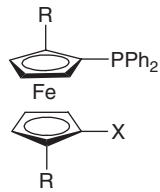
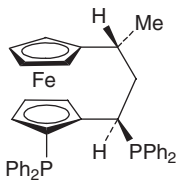


(31) X = SR, SAr, S(O)Bu^t,
or $CONR_2$



(32) R = H or alkyl;
X = OMe, SMe or S(O)Ar



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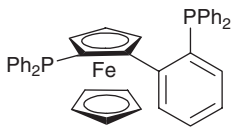

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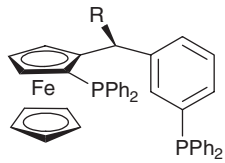
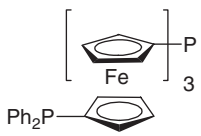
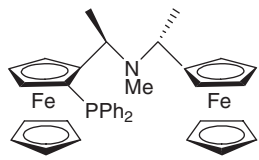


(35) R = Me or Et



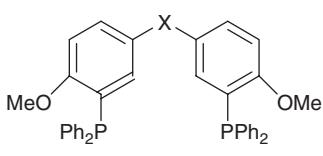
(36)



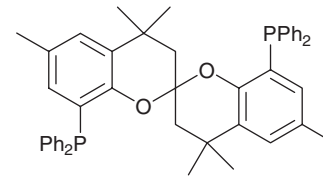
(37)

Organolithium reagents have been widely employed in the synthesis of new diphosphines, including chiral 2,2′-bis(phosphino)biphenyls,[76,77] a series of new diphosphine ligands based on bisphenol A backbones, e.g., (38),[78,79] various 2,2′-bis(phosphino)diphenylamines,[80,81] and the C_2-symmetric *trans*-coordinating ligand 'SPANphos' (39).[82] The norbornene-based diphosphine (40) has been obtained and shown to undergo a ruthenium-catalysed metathesis polymerisation of the norbornene moiety to give the polymeric diphosphine (41).[83] Dendrimer systems incorporating diphosphinoethane moieties have also been prepared.[84] The synthesis of phosphines based on the [2,2]paracyclophane skeleton has continued to develop and several new systems have been described. Studies of the electrophilic substitution of 4,12-dibromo[2,2]paracyclophane have enabled the introduction of a range of functional groups into the basic

structure, these intermediates being easily converted into the desired functionalised phosphines (42) by lithiation and treatment with a halogenophosphine.[85] Phosphinoparacyclophanes involving oxazoline[86] and imidazolium moieties[87] have also been described. Further development of the '*xantphos*' system (43) has been reported, new diphosphines including those in which perfluoroalkyl- or perfluoroalkylaryl- substituents are present at phosphorus,[88,89] and a range of related molecules in which the diarylphosphino unit is the heterocyclic phenoxaphosphine system, e.g., (44).[90,91] A related dicationic phenoxaphosphine-based diphosphine ligand has also been prepared *via* the introduction of imidazolium units into the xanthene skeleton.[92] Among other heterocyclic phosphines prepared *via* the reactions of organometallic reagents with halogenophosphines are the chiral pentacyclic dodecahydrophenoxaphosphine (45),[93,94] the 1,2-diphosphaacenaphthene (46), the naphtho[1,8-b,c]phosphete (47),[95] and the benzophosphepine (48).[96] Routes to halogenophosphines of type (49) have been developed, these being key intermediates for the synthesis of a range of monodentate and bidentate ligands involving the binaphthylphosphepin system.[97,98] A simple route to the phospholanes (50) is afforded by the reactions of dihalophosphines with an aluminacyclopentane intermediate derived from an alkene and a simple organoaluminium reagent in the presence of a zirconium catalyst.[99]



(38) X = CMe_2, 1,2-C_6H_{10}, o-C_6H_4, C(Me)Ph or $SiMe_2$



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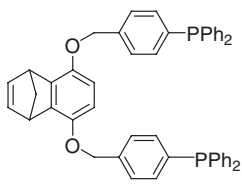

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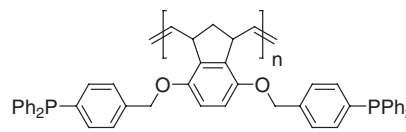

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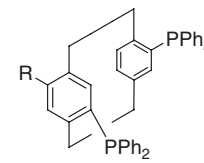
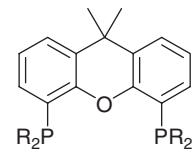
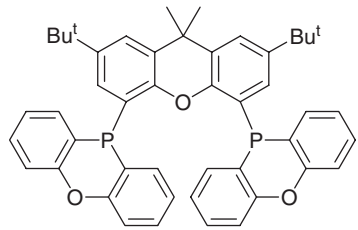


(42) R = OMe, CH_2OH, CH_2OTIPS or CH_2OCPh_3



(43)

R = CF_3 or *p*-$C_6H_4C_6F_{13}$



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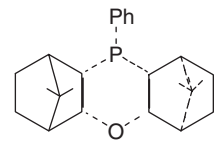

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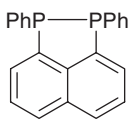
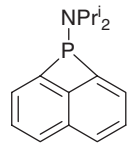


(46)



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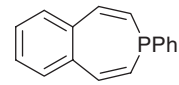

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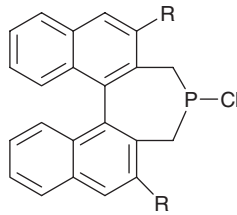
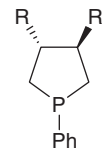


(49) R = H or Ph



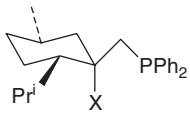
(50) R = Bu or hexyl

2.1.2 Preparation of Phosphines from Metallated Phosphines. Lithio-organophosphide reagents continue to dominate this approach to phosphine synthesis, although related sodium-, potassium-, and even caesium- organophosphide reagents also find use. Further work has been reported on the stabilisation of the $(CF_3)_2P^-$ anion with weak Lewis acids, enabling the structural characterisation of a salt with the (18-crown-6)potassium complex cation. The X-ray study reveals almost discrete phosphide anions, with an unusually short P–C distance of 184 pm, indicating a negative hyperconjugation effect. The $(CF_3)_2P^-$ anion, and also the related $(C_6F_5)_2P^-$ anion, have also been stabilised by coordination to pentacarbonyltungsten, which has little effect on the electronic and geometric properties of the organophosphide ions.[100] The proton affinities of the anions $PhPH^-$ and 2,6-$(CF_3)_2C_6H_3PH^-$ have been compared by a theoretical treatment, shedding light on the substituent effect of the 2, 6-bis(trifluoromethyl)phenyl group.[101] The reactions of secondary phosphines with alkyl halides in DMF in the presence of caesium hydroxide and molecular sieves afford a convenient and highly efficient general synthesis of tertiary

phosphines and diphosphines.[102,103] These conditions have also been shown to promote ring-opening of epoxides in the presence of primary- or secondary-phosphines, with the formation of 2-hydroxyalkylphosphines.[104] Epoxide ring-opening has also been achieved using potassium diphenylphosphide, providing a route to the enantiopure phosphine (51, X=OH).[105] Related reactions of thiiranes with lithium-and potassium-diphenylphosphides have given chiral 2-mercaptoalkylphosphines, e.g., (51, X=SH)[106] and 1-(diphenylphosphino) butane-2-thiol.[107] The reactions of lithiophosphide reagents with alkyl-halides or -tosylates have been used to prepare chelating ligand systems, e.g., the phosphinoalkylpyrazole (52)[108] and the rigid phosphino-amide donor (53).[109] Related reactions of sodio-organophosphide reagents have also given phosphino-amides, e.g., (54),[110] heteroalkynes, e.g., (55),[111] the chiral naphthyl-(ethyl)phosphine (56),[112] and (3-dimethylphosphino)propanethiol.[113] The secondary phosphine (57), obtained by treatment of a carbonyl-protected bromoalkyl derivative of camphor with lithium phenylphosphide, undergoes a proton-catalysed hydrolysis, followed by a stereoselective, base-catalysed addition of P–H to the carbonyl group to give the phospholane (58). This is stable under polar protic conditions, but reverts to the phosphinoketone (59) in a non-polar solvent.[114] Direct displacement of halogen from aromatic systems by organophosphide reagents has also continued to find use in phosphine synthesis. Displacement of fluorine by potassium diarylphosphide reagents is the key step in the synthesis of N-aryl substituted *ortho*-diphenylphosphinoanilines, of interest for the formation of anionic phosphino-amido metal complexes,[115] and the *ortho*-diphenylphosphinohydrazones (60).[116] A range of metallophosphide reagents and *ortho*-haloaryl imidazolines has been utilised in the synthesis of the phosphinoarylimidazolines (61), capable of being electronically tuned in three different regions of the molecule.[117] Displacement of chlorine from an 8-chloroquinoline by lithium diphenylphosphide has enabled the preparation of the related 8-(diphenylphosphino)quinoline.[118] Other routes to phosphines involving attack of metallophosphide reagents at carbon have also been reported. Treatment of spiro[2,4]hepta-4,6-dienes with either lithium- or potassium-diorganophosphide reagents proceeds with opening of the spiro-cyclopropane ring to give phosphinoalkylcyclopentadienyl ligands, e.g., (62), from which a range of ruthenium[119,120] and rhodium[121] metallocene complexes has been prepared. Metallophosphides have also been shown to displace a variety of groups bound to the arene rings of arene-chromium and -manganese complexes to form the related phosphinoarene systems.[122] Acylphosphines are among the products of the reactions of lithium dialkylphosphides with benzocyclobutenone chromium complexes.[123] Lithium mono(organo)phosphide reagents have been shown to add to fulvenes to give the phosphinoalkyl-substituted cyclopentadienides (63), subsequently used in the synthesis of catalytically-active constrained geometry titanium-and zirconium- metallocene complexes.[124] Treatment of dialkylcarbodiimides with lithium diphenylphosphide, followed by protonation of the intermediate anion, yields the phosphinoguanidines (64).[125] Phosphino[2,2]paracyclophanes (65) have been obtained by treatment of cyclopalladated oxazolinyl[2,2]paracyclophanes with

potassium diphenylphosphide.[126] An efficient strategy for the synthesis of diphenylphosphino(trialkyl)stannanes in almost quantitative yield is afforded by the reaction of sodium diphenylphosphide (from the cleavage of triphenylphosphine in liquid ammonia) with chlorotrialkylstannanes.[127] Whereas displacement of chlorine from chlorosilanes by lithium mono(organo)phosphide reagents proceeds normally to give a series of silyl-substituted secondary phosphines,[128,129] the reaction of lithium bis(trimethylsilyl)phosphide with sterically crowded aryltrifluorosilanes results in the elimination of fluorotrimethylsilane and formation of the lithiophosphides (66).[130] The cyclic phosphine (67) has been obtained by treatment of a tris(2-iodoethyl)silane with dilithium phenylphosphide, and subsequently transformed in a series of steps to give the bicyclic system (68), having Me_3P-like steric and electronic properties.[131] Good yields of perfluoroalkyldiphenylphosphines have been obtained *via* an $S_{RN}1$ mechanism in the reactions of sodium diphenylphosphide with iodoperfluoroalkanes under irradiation in HMPA and DMPU as solvents. Related reactions in liquid ammonia or tetraglyme are dominated by halogen-metal exchange, and only poor yields of phosphines are achieved.[132] Applications of borane-protected metallophosphide reagents continue to appear. The alkylation of secondary phosphine-borane adducts with a variety of electrophiles has been achieved with good to excellent yields in a two-phase system, using aqueous potassium hydroxide as the base, and tetrabutylammonium bromide as a phase-transfer catalyst.[133] Alkylation of the P-lithiated borane adduct of diphenylphosphine with ethyl chloroacetate affords an easy route to the related borane-protected phosphinoacetate ester, which is easily transformed into a series of chiral amides, subsequently involved in a study of diastereoselective alkylation at the carbon adjacent to phosphorus.[134] In related work, diastereoselective Michael-addition of borane-protected lithium diphenylphosphide to chiral amides derived from crotonic acid has also been studied, enabling a synthesis of the chiral phosphinocarboxylic acids (69), useful synthetic intermediates.[135] Borane-protected lithium diphenylphosphide has also found application in the synthesis of phosphino derivatives of C_{60}.[136] Linear hybrid aminoborane/phosphinoborane chains have been prepared from the reactions of P- or C-lithiated phosphinoborane adducts with dimethylamine-chloroborane.[137] The reaction of a borane-protected P-lithiated phospholane reagent with 1,2-ethylene ditosylate is the key to a simple route to the new bis(phospholanyl)ethane ligand (70).[138] Phosphido-borane reagents have also been used in the synthesis of a wide range of chiral P,N-chelating ligands with pseudo-C_2 and pseudo-C_s symmetry based on chiral pyrrolidine and phospholane rings, or on dinaphthodihydroazepine and dinaphthodihydrophosphepine moieties.[139] The reactions of chiral cyclic sulfate esters with dilithio(organo)phosphide reagents continue to be widely exploited for the synthesis of new phospholanes. An improved route to the simple secondary phospholane (71) has been developed, enabling the introduction of the chiral phospholane ring as a substituent in ferrocene and arenechromium complexes, e.g., (72).[140] The cyclic sulfate route has been applied in the synthesis of other ferrocenylphospholanes, e.g., (73)[141] and (74),[142] an

ortho-phenylenebis(phospholane),[143] the bis(phospholanyl)maleic anhydride (75),[144] and a series of P-arylphospholanes bearing either chiral amine[145] or chiral dioxolanyl substituents in the *ortho*-position to phosphorus.[146] This route has also been used in the synthesis of sterically crowded phospholanes, e.g., (76).[147,148]



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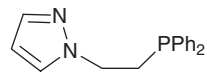

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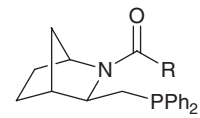
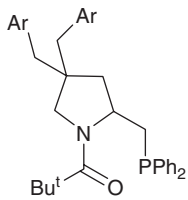
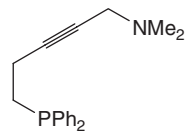


(53) R = Me or Bu^t



(54) Ar = 2,4,6-$Me_3C_6H_2$ or 2,4,6-$Pr^i_3C_6H_2$



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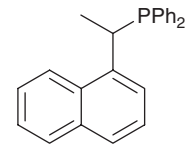

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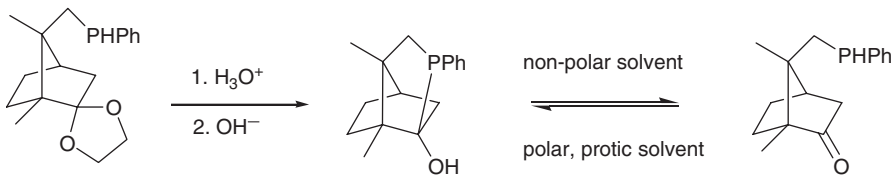
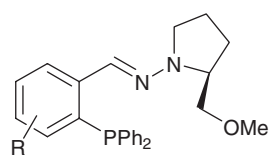


(57) (58) (59)



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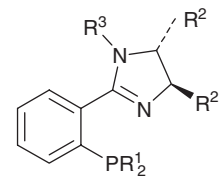

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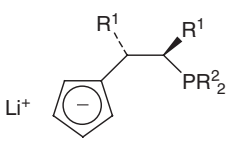
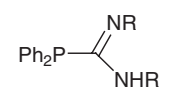
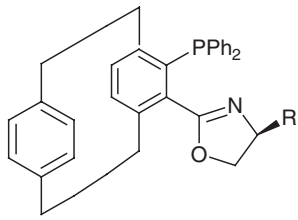


(62) R^1 = H, Me, Ph, Cy, CH_2OTBS; R^2 = Ph or Mes

(63)



(64) R = Cy or Pr^i



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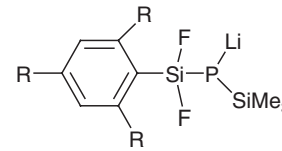
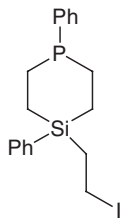


(66) R = aryl or Bu^t



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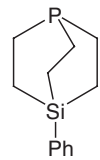

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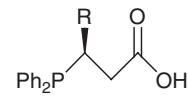
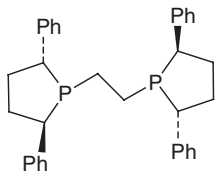


(69) R = Et, Pr^i or Ph



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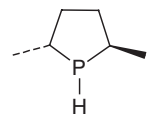

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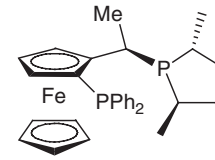

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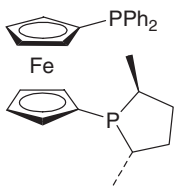

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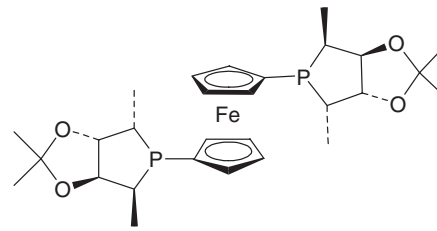

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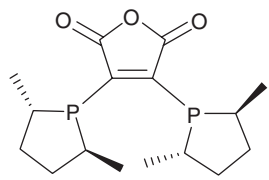

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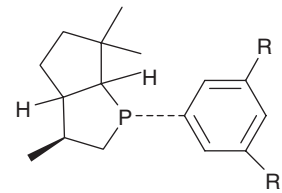
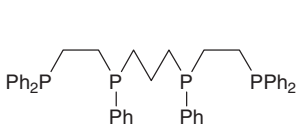


(76) R = H, Me or Bu^t

Metallophosphide reagents have been applied widely in the synthesis of new chelating ligands involving two or more phosphorus atoms, and sometimes other additional donor centres. A convenient general procedure has been developed for the synthesis of a range of long chain α,ω-bis(diphenylphosphino)alkanes involving 18-32 methylene bridges.[149] Also reported are the linear tetraphosphine (77),[150] a series of new linear arene-bridged bis(1,4-diphenylphosphinoethoxy) systems, e.g., (78),[151] unsymmetrical bis (diarylphosphino)propanes having partly fluorinated aryl substituents,[152] and various unsymmetrical arsino(phosphino)ethanes having bulky groups at phosphorus and arsenic, together with new chiral diphosphino-ethane[153] and –propane[154,155] systems, e.g., (79). Further reports have appeared of the synthesis of carbohydrate-based diphosphines, e.g., the rigid isomannide-based system (80),[156] the water-soluble α,α-trehalose-based phosphinophosphinite (81)[157] and both a diphosphino- and a tetraphosphino-α-cyclodextrin system.[158,159] A new 1,3-alternate- bis(diphosphinoethyl)calix[4]arene system has also been prepared.[160] A new water-soluble arene-sulfonated 2,2′-bis (diphenylphosphino)biphenyl and other diphosphines involving a sulfonated dibenzophosphole system have also been described.[161] Metallophosphide routes have been applied to the preparation of a wide range of di-, tri- and tetra-phosphines bearing additional donor or other reactive functional groups. Findeis and Gade have described the synthesis of a series of di-and triphosphines bearing alkenyl, alkynyl[162,163] and hydroxyalkyl groups,[164] e.g., (82), these acting as linkers for the synthesis of phosphino-functional dendrimers and related catalyst systems. Various chiral oxo- and oxy-functional diphosphines, e.g., (83), have been prepared from the camphor system.[165,166] Chiral C_2-symmetric 1,4-dioxanyldiphosphines, e.g., (84), have been prepared from tartrate esters.[167] Routes to a number of P,P,N-donor systems have been developed, including a *trans*-chelating 1,5-bis(di-*t*-butylphosphino)-2-(*S*)-dimethylaminopentane,[168] 2,2′-bis(diphenylphosphino)diphenylamine,[169] and a series of tripod ligands (85) involving phosphine and dialkylamine or N-pyrazolyl donors.[170,171] A phosphide route has also been used to prepare 2-(diphenylphosphinoethyl)-3,5-dimethylpyrazole.[172] The diphosphinodiazadienes (86) have been prepared by treatment of a bis(imidoyl chloride) with sodium diphenylphosphide.[173,174] Diphosphines,[175,176] e.g., (87) and a tetraphosphine,[177] which also incorporate pyridine moieties, have been described. New ferrocenylphosphines involving Si–P linkages (88) have been prepared from the reactions of a bis(chlorosilyl)ferrocene with lithium diorganophosphide reagents.[178]



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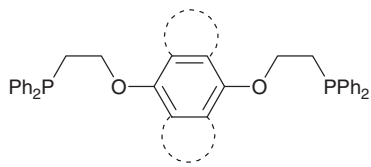

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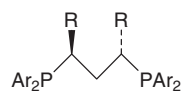

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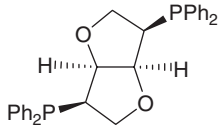

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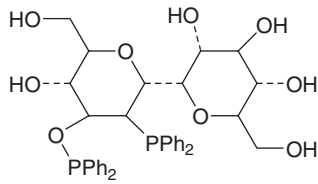

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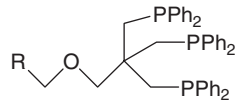
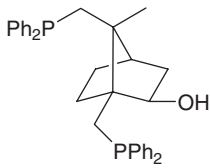


(82) R = HC≡C, H_2C=CH or CH_2OMe



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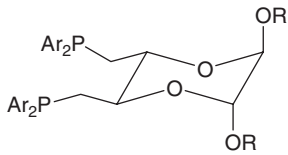

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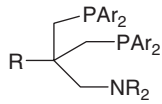
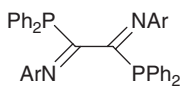


(85) R = Me, Ph or CH_2OMe
Ar = Mes or Ph

R_2N = Et_2N or



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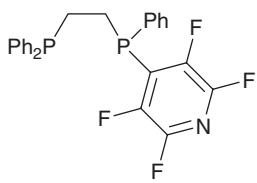

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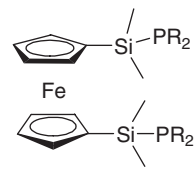
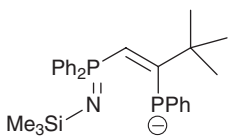


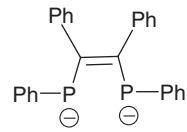
(88) R = Me or Ph

The structural characterisation of metallophosphide species (and their complexes with other ligands) continues to attract interest. New polyphosphide anions, (together with a variety of other products, including halogenophosphines, diphosphenes and diphosphines), are formed in the reactions of phosphorus trichloride with alkyl-sodium,-potassium and -zinc reagents.[179] A range of sodium oligophosphane-α,ω-diide systems has been characterised from the reactions of phenyldichlorophosphine with sodium.[180] The reaction of lithium phenylphosphide with $MeAlCl_2$ results in the selective formation of the anion $[PhP(H)–PPh]^-$, isolated as a tetrameric lithium salt.[181] The reactions of lithium- or sodium-cyclohexylphosphide with tris(dimethylamino)arsine in the presence of various ligands lead to the formation of the five-membered, heterocyclic phosphinoarsenide $[(CyP)_4AsLi]$, isolated as a series of complexes.[182] The ability of mono(borane-protected)diorganophosphide ions to form complexes with lithium and aluminium acceptors has been investigated and a range of complexes structurally characterised.[183] Various alkali metal silylphosphides have also been prepared and characterised.[184,185] Lithium-, potassium- and tin-salts of monoanionic P,N-centred (iminophosphorano)

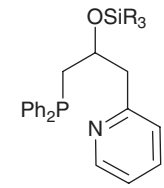
1-phosphaallyl ligands, e.g., (89), have been obtained from the initial reaction of an N-(trimethylsilyl)phosphoranimine of an alkynyldiphenylphosphine with potassium phenylphosphide.[186] Magnesium organophosphides have been obtained from the reactions of dibutylmagnesium with primary or secondary phosphines, and structurally characterised. Related calcium, strontium and barium organophosphides have also been prepared.[187,188] A zinc organophosphide has been obtained and structurally characterised.[189] Phosphido derivatives of the main group 13 elements continue to generate much interest. New systems include a tetraanionic alumino(mesityl)phosphide cage complex,[190] and new gallium[191,192] and indium[193] organophosphides. The reactivity of aluminophosphides towards group 13 trialkyls has also been investigated.[194,195] Novel routes to quantum dots of InP and GaP have been developed *via* the thermolysis of the corresponding metal diorganophosphides in 4-ethylpyridine.[196] New main group element organophosphide cluster species involving tin and germanium have also been prepared and structurally characterised.[197,198] A range of cyclic, oligomeric gold organophosphides has been prepared by treatment of gold(I) complexes of secondary phosphines with aqueous ammonia.[199,200] The previously established alkali metal cleavage of the P–P bond of tetraphenyl-1,2-dihydrodiphosphetenes to give the diphosphide anion (90) has been used to prepare anionic cyclic organophosphidoplatinum complexes.[201]



(89)



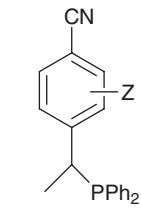
(90)



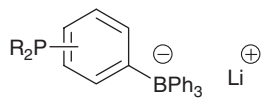
(91)

Interest has also continued in the use of phosphines metallated at atoms other than phosphorus as reagents in synthesis. Reagents of the type R_2PCH_2 Li, easily accessible by metallation of methylphosphines with alkyllithium reagents, have found use in the synthesis of a range of sterically crowded diphosphinomethane ligands,[202,203] the unsymmetrical di(N-pyrrolyl)phosphino-functionalised diphosphinomethane $Ph_2PCH_2P(NC_4H_4)_2$,[204] and various chiral β-aminoethyldiphenylphosphines.[205,206] Related lithiomethylphosphines, protected at phosphorus with borane, have also found wide application in the synthesis of new diphosphines, e.g., a series of P-chirogenic bis(phosphino)ethanes,[207,208] a P-chirogenic 1,2-bis(phospholanyl)ethane,[209] and a P-chirogenic 1,2-bis(ferrocenyl)diphosphinoethane.[210] Derivatives of the alkaloid (-)-cytisine have advantages over the commonly used (-)-sparteine when used in combination with *sec*-butyllithium to desymmetrise prochiral organodimethylphosphine-borane complexes, giving access to the less accessible enantiomer of the chiral lithiomethylphosphine-borane reagent, and hence to a wide range of new chiral systems.[211] Among other applications of C-lithiated alkylphosphine reagents are routes to a series of C-functionalised

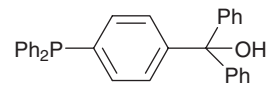
ω-diphenylphosphinoalkylpyridines, e.g., (91),[212] various anionic phosphinoborate ligands, e.g., $[PhB(CH_2P^iPr_2)_3]^-$,[213,214] and the neutral diphosphine $Ph_2Si(CH_2PPh_2)_2$.[215] Borane-protected $Ph_2PCH(Li)CH_3$ has been shown to react with electron-withdrawing aromatic systems *via* an S_NAr mechanism to give functionalised aralkylphosphines, e.g., (92).[216,217] Lithiation of bromoarylphosphines, followed by reactions with conventional electrophilic reagents, provides a route to functionalised arylphosphines, e.g., the phosphinotetraarylborates (93),[218] the phosphinobenzhydrol (94), (an intermediate for the synthesis of helically chiral polymers),[219] a series of *ortho*-silylated benzylphosphines,[220] and the phosphinoarylcycloheptatriene (95).[221] Phenacylphosphines of type (12) have been shown to undergo metallation with potassium hydride to form the related enolate ions, which have been trapped to give the phosphino-phosphates (96).[222] The diphosphinocyclopentadienide reagent (97) has been used to prepare a tetraphosphinoferrocene.[223] Phosphinoferrocenes have also been prepared from the phosphinoindenyl reagent (98).[224] Metallation of diphosphinomethanes at the bridging carbon is a key step in a new route to vinylidene phosphines, e.g., (99).[225] Compounds of this type undergo a Schlenk dimerisation on treatment with either lithium or sodium in THF to give the diphosphinomethanide complexes (100).[226] Similar behaviour occurs with borane-protected 1-phosphino(1-silyl)-alkenes.[227]



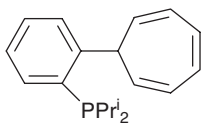
(92) Z = H or electron-withdrawing group



(93)



(94)



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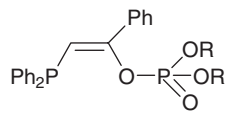

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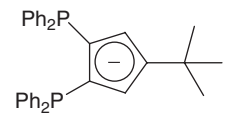

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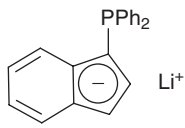
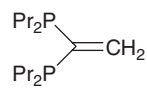
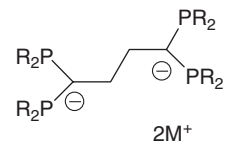


(98)

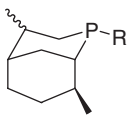


(99)



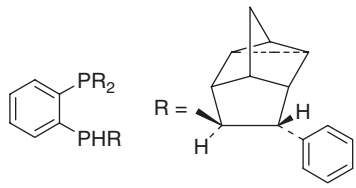
(100)

2.1.3 Preparation of Phosphines by Addition of P–H to Unsaturated Compounds. This method continues to find use in phosphine synthesis, although the number of applications noted in the period under review is relatively small. Conventional thermal- or free radical-initiated conditions have been used for the addition reactions of the (*R*)-(+)-limonene-based secondary phosphine (101, R=H) to alkenes to give a series of new bicyclic tertiary phosphines (101, R=alkyl),[228] the addition of (+)-8-phenyldeltacyclene to 1,2-bis(phosphino)benzene to give the crowded chiral diphosphine (102) as a mixture of two diastereoisomers,[229] addition of secondary phosphines to *N*-vinylpyrroles to give a series of 2-(1-pyrrolyl)ethylphosphines,[230] addition of phenylphosphine to iminium salts to give the linear NPN-ligands (103),[231] and for the addition of diphenylphosphine (in excess) with vinyl-functionalised polyhedral oligomeric silsesquioxane dendrimers.[232] Base-catalysed conditions have been employed in the addition of secondary phosphines to functionalised alkenes, leading to polyfunctional tertiary phosphines in high yield,[233] and also for the regio-and stereo-specific addition of primary and secondary phosphines to aryl(cyano)alkynes, giving functionalised secondary and tertiary phosphines of Z-configuration.[234] Borane complexes of secondary phosphines also undergo addition reactions with alkenes and alkynes. A simple route to alkylarylphosphines on a gram scale is offered by the addition of secondary phosphine-boranes to unactivated alkenes under mild thermal activation, the reaction proceeding in an anti-Markownikov mode. The new chiral phosphines (104) have been obtained by such additions to (−)-β-pinene.[235] Related additions to alkynes have been achieved under thermal and metal-catalysed conditions. Under thermal conditions, additions to terminal alkynes proceed in an anti-Markownikov mode to form largely Z-alkenylphosphine-boranes, whereas reactions promoted by a palladium(0) catalyst give the Markownikov products.[236] Markownikov products have also been isolated from the addition of diphenylphosphine to alkenylalkyl ethers, catalysed by palladium or nickel complexes.[237] Organoytterbium complexes have also been shown to catalyse the addition of secondary phosphines to alkynes, and other carbon-carbon multiple bonds. The regio-and stereo-selectivity of these reactions clearly differ from those of the corresponding radical-promoted additions, the reactions proceeding *via* insertion of alkynes into a Yb-PPh_2 species, followed by protonation.[238] Further studies have been reported of the intramolecular hydrophosphination/cyclisation of primary phosphino-alkynes and -alkenes to form cyclic phosphines in the presence of organolanthanide complexes.[239] Diphenylphosphine has been shown to add diastereoselectively to benzaldimines coordinated to a chromium tricarbonyl acceptor, to form complexed chiral aminoalkylphosphines.[240] The synthesis of P-chiral functionalised secondary phosphines by addition of iron-complexed primary phosphines to alkenes and alkynes has been reviewed.[241] The tricyclic trislactonephosphine (105) has been obtained from the reaction of PH_3 with pyruvic acid.[242] Addition of diphenylphosphine to the isocyanate group of dimethylthiocarbamoyl isothiocyanate leads to the new ambidentate ligand (106).[243]

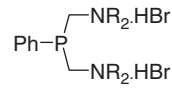


(101)

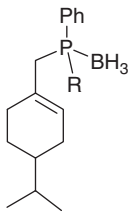
R = e.g., $(CH_2)_nCH_3$, (n = 3-17),$(CH_2)_3CN$ or $(CH_2)_3OCH_2Ph$



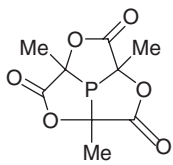
(102)



(103) R = Me or Et



(104) R = Ph or Bu^t



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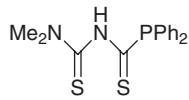
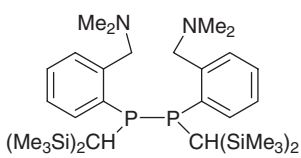


(106)

2.1.4 Preparation of Phosphines by Reduction. Although trichlorosilane remains the reagent of choice for many reduction procedures in phosphorus chemistry, other reagents also continue to find use. Trimethyltin hydride and tributyltin hydride, respectively, have been used to reduce diorganophosphinous chlorides in a large scale, high yield route to the secondary phosphines $(CF_3)_2PH$ and $(C_6H_5)_2PH$.[244] Lithium aluminium hydride has also been used for the reduction of halogenophosphines, in the synthesis of crowded diphosphines, e.g., (107),[245] and (108).[246] Various reducing agents have been compared for their effectiveness in the reduction of chlorophosphine-boranes to the related secondary phosphine-boranes, the main point to emerge being that there needs to be a judicious match between the steric and electronic requirements of both reagent and substrate.[247] The desulfurisation of arylphosphine sulfides with tributylphosphine has been applied in a new route to a series of C-substituted phosphatriptycenes (109), (and, in turn, the related P=Se derivatives).[248] Raney nickel has also been used for the desulfurisation of phosphine sulfides in the synthesis of the phospholane-oxazoline ligands (110).[249] However, a very common strategy in phosphine synthesis continues to be a final stage reduction of phosphine oxides with silane reagents, of which trichlorosilane is the most popular. Among a considerable range of new monophosphines obtained by trichlorosilane reduction, usually in the final step of the synthesis, are the phosphorus core conjugated triaryl-dendrimer unit (111),[250] a range of triarylphosphines bearing branched fluoroalkyl moieties ('split pony tails'), e.g., (112),[251] and a variety of chiral monophosphines,

including the phosphinocarboxylic acid (113),[252] phosphinoaryloxathianes, e.g., (114),[253] a series of axially chiral *ortho*-aminoarylphosphines, e.g., (115)[254,255] and (116),[256] the axially chiral binaphthylphosphine (117),[257] and the chiral arylferrocenylphosphines (118).[258] Trichlorosilane reduction has also been used in the synthesis of phosphino-[6]- and -[7]-helicenes, e.g., (119), which are also chiral systems,[259,260] and a variety of other chiral diphosphines, including the spiro system (120),[261] the C_2-symmetric cyclobutane system (121),[262] and the tetraphenylene (122).[263] In addition, many new chiral 2,2′-diphosphinobiphenyls have been described, including 'SYNPHOS' (123, X=CH_2CH_2)[264,265] and 'DIFLUORPHOS' (123, X=CF_2),[266,267] the related system (124),[268] and others involving simple alkoxy substituents in the biphenyl system[269] and bulky aryl groups at phosphorus.[270] Interest has also continued in the synthesis of 'BINAP' systems (125), with particular reference to the introduction of substituents in the naphthalene system which modify the effectiveness of the molecule as a ligand in catalyst systems[271] or render it water soluble[272] or soluble in supercritical carbon dioxide.[273] BINAP-based phosphines and diphosphines bearing fluorous substituents in the diarylphosphino groups have also been isolated following trichlorosilane reduction.[274] Trichlorosilane reduction is a key step in a route to the new atropisomeric diphosphine ligand 'BINAPFu' (126), resolved into its enantiomeric forms, and shown to be more effective than BINAP in one Heck arylation system.[275] Trichlorosilane has also been employed in the synthesis of fluorous-tagged bis(diarylphosphino)propanes,[276] a range of new bis(diarylphosphinoethyl)amines,[277] and a series of 1,1′-bis(diphenylphosphinoaryl)ferrocenes.[278] Several other reagent systems have been used for the reduction of phosphine oxides, including polymethylhydrosilane/titanium isopropoxide (for the new diphosphinoferrocenes (127)),[279] $LiAlH_4$ (for reduction of chiral 2,5-diphenylphospholane oxides *via* the related triflate salts),[280] and various transition metal tri(t-butyl)siloxides.[281] Hexachlorodisilane has been used for the reduction of phosphine sulfides in the synthesis of the chiral bis(phosphepine) (128).[282] The combination Me_3SiCl–$LiAlH_4$ has been used for the reduction of 2-(ferrocenyl)alkylphosphonic acid derivatives to give the related primary phosphines, surprisingly air-stable compounds.[283] Reduction of alkylphosphonates has also been achieved with $LiAlH_4$ in the synthesis of the primary phosphine $PhSeCH_2CH_2PH_2$.[284]



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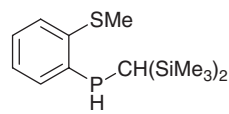

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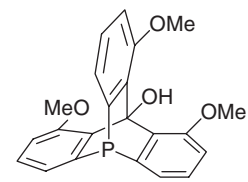

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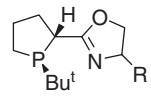
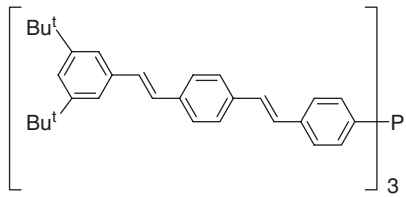


(110) R = Pr^i, Bu^t, Ph or PhCH$_2$



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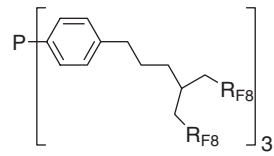
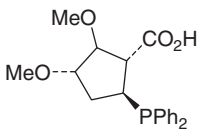


(112)



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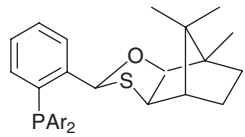
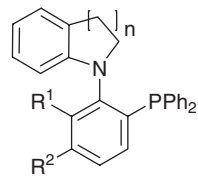
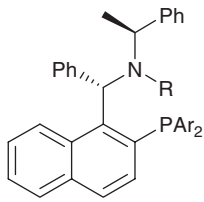


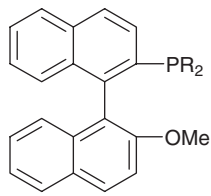
(114) Ar = Ph or 3,5-xylyl



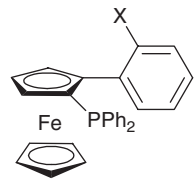
(115) R^1,R^2 = (CH)$_4$; n = 1; R^1,R^2 = H or MeO, n = 1 or 2



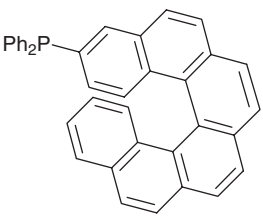
(116) Ar = Ph or p-tol; R = Me or Et



(117) R = cyclopentyl



(118) R = OH, NH$_2$, NHCOR



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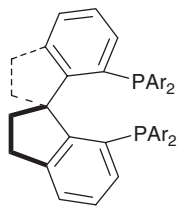

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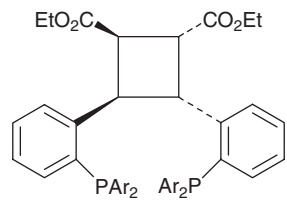

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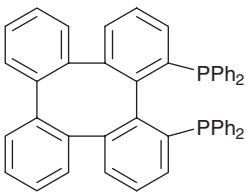

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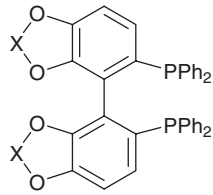

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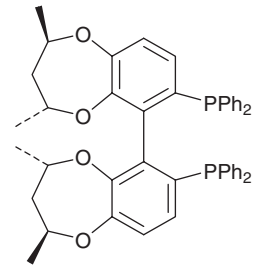

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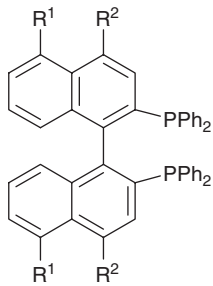
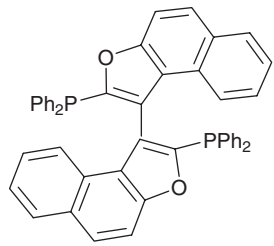


(125) R^1 = H; R^2 = e.g., Me_3Si, CPh_2OH or CH_2NH_2; R^1 = CH_2NH_2 or R_F; R^2 = H



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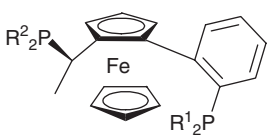
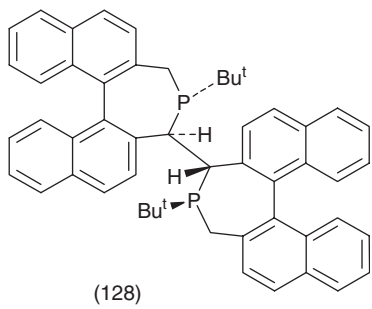


(127) R^1 = Ar; R^2 = Cy, Bu^t or Ar



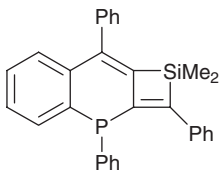
(128)

2.1.5 Miscellaneous Methods of Preparing Phosphines. Useful general reviews of phosphine chemistry which have appeared in the past two years include coverage of the synthesis and applications of primary phosphines,[285] recent developments in the synthesis of chiral phosphetanes,[286] the synthesis of P-modular homochiral bis(phosphines) having a 1,2-disubstituted cyclopentane backbone[287] and new chiral phosphorus ligands for enantioselective hydrogenation.[288] Reviews of the design of chiral ligands for asymmetric catalysis, covering C_2-symmetric P,P-ligands to sterically and electronically non-symmetrical P,N-ligands,[289] chiral P,N-ligands involving pyridine and phosphorus

donor centres,[290] mixed donor phosphine-phosphine oxide ligands,[291] and combinatorial libraries of chiral ligands[292] have also appeared.

The reaction of vinylmagnesium bromide with triphenylphosphite provides an improved route to trivinylphosphine, which can be stored for several months at −32°C without polymerisation. Its reactivity towards a range of reagents, e.g., alkyl halides, chalcogens, borane and boron trihalides, has also been explored.[293] Copper-catalysed cross-coupling of terminal alkynes with chlorophosphines provides a convenient route to phosphinoalkynes.[294] Related nickel- and palladium-catalysed procedures have also been described.[295] Benzynezirconocene has been shown to promote the intramolecular coupling of bis(alkynyl)phosphines with silanes, providing a route to new mono- and tri-cyclic heterocyclic systems, e.g., (129),[296] and a zirconocene-mediated cross-coupling of alkynylphosphines provides a route to 1,3-butadienylphosphines.[297] Olefin metathesis catalysts have been used to achieve the cyclisation of diallyl(phenyl)phosphines to 1-phenyl-3-phospholenes[298] and further studies have been reported on the macrocyclisation of phosphines bearing ω-alkenyl(polymethylene) substituents, coordinated to platinum.[299,300] The synthesis of phosphorus (and sulfur) heterocycles *via* ring-closing olefin metathesis has also been reviewed.[301] An improved synthesis of di(1-adamantyl)alkylphosphines by alkylation of di(1-adamantyl)phosphine, followed by deprotonation of the intermediate phosphonium salt with triethylamine, has been described.[302] This approach has also been used independently in related reactions of di(1-adamantyl)phosphine with *para*-di(bromomethyl)benzene, to yield the cationic, phase-tagged phosphine (130), and related compounds derived from the intermediate salt by treatment with triphenylphosphine.[303] A simple route to the fused phosphirane, dibenzophosphasemibullvalene, (131), has been developed.[304] Further work has been reported on the reactions of the bicyclic system (132) with diGrignard reagents derived from α,ω-dibromoalkanes. It has now been shown that treatment of the initial Grignard reagent adduct of (132) with water yields the secondary cyclic phosphines (133) in 70-80% yield. The biproduct (134) can also be isolated cleanly from the aqueous phase in 90% yield, and recycled back to (132) by treatment with phosphorus trichloride.[305] The established ring-opening of aziridines on treatment with diphenylphosphine has been used to prepare further examples of chiral β-aminophosphines.[306] The regiospecificity of the reaction of diphenylchlorophosphine with enamines derived from β-aminocrotonic acid has been studied, providing routes to enamino-vinyl- and -allyl-phosphines.[307] A similar study of the reactions of propyneiminium salts with diorgano(trimethylsilyl)phosphines has provided access to enamino-allenyl-, -alkynyl- and -butadienyl-phosphines.[308] A convenient route to acylphosphines ('phosphomides') is afforded by the reaction of secondary phosphines with acyl- and aroylchlorides, in the presence of a base.[309] The *o*-phosphinoaryl-ylide (135), bearing a chiral sulfinyl moiety, has been prepared by the reaction of the related phosphinoaryl-methylide with (*S*)-menthyl *p*-tolylsulfinate.[310] Further

examples have been reported of the synthesis of chiral C-functionalised phosphanorbornenes by the cycloaddition of functionalised alkenes to 1-phenyl-3,4- dimethylphosphole, coordinated to a chiral palladium complex as the chiral auxilliary.[311,312] A related achiral cycloaddition of phenylethynyltriethoxysilane has given the triethoxysilyl-functionalised phosphanorbornadiene (136), capable of being anchored, as a rhodium complex, to mesoporous silica.[313] New thiophene-, benzothiophene- and benzofuranoxazoline ligands, e.g., (137), bearing a diphenylphosphino group at different positions of the heterocyclic skeleton, have been prepared and studied as ligands in homogeneous metal-catalysed processes.[314,315] Applications in homogeneous catalysis have also driven the synthesis of a series of N-(*ortho*-diphenylphosphinoaryl)-pyrroles and -pyrazoles.[316] Various established protocols have been explored for the synthesis of diphosphine ligands bearing highly symmetric, bulky substituents at a stereogenic phosphorus atom[317] Full details of routes to the di- and tri-(phosphinomethyl)methanols (138) have been disclosed, these compounds giving rise to multidentate phosphinoalkoxides, of interest as ligands to main group as well as transition metals.[318] Cycloaddition of the azide ion to the bis(phosphino)alkynyl diselenide, $Ph_2P(Se)C{\equiv}CP(Se)Ph_2$, followed by removal of selenium with triethylphosphite, results in the bis(phosphino)-1,2,3 triazole (139), capable of deprotonation at nitrogen to give an anionic diphosphine ligand.[319] Alternative approaches to biaryldiphosphines of type (123, X=CF_2) have also been described.[320] The synthesis of resorcinarene derivatives having four or eight alkynyldiphenylphosphino (or diphenylphosphinito) functional groups has been reported.[321] Routes to fluoro(phosphino)- and diphosphino-stannanes, $R_2Sn(X)PH_2$ (X=F or PH_2),[322] and triphosphinofluorosilanes, $RSi(PH_2)_3$,[323] of interest as reagents for PH_2 transfer under mild conditions, have been developed.



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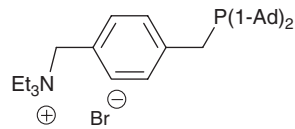

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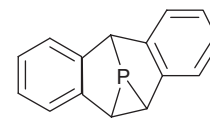

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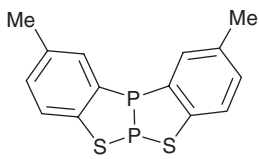
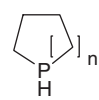
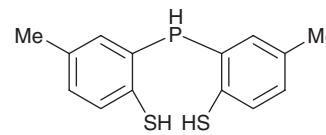


(132)



(133) n = 1 or 2



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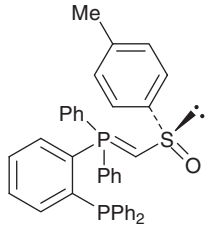

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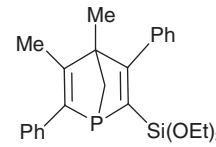

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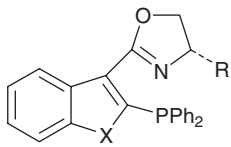
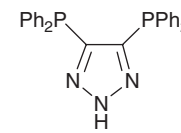


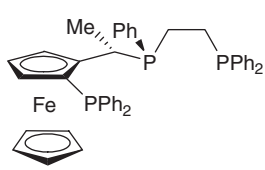
(137) X = O or S;
R = Pr^i, Bu^s or Ph

(138) (n = 2 or 3)



(139)

A wide range of new phosphines based on the ferrocene system has been prepared, using a variety of synthetic methods. Their use in homogeneous catalyst systems has also been reviewed.[324,325] The ephedrine-based oxazaphospholidine-borane route has been applied to the synthesis of eight P-chiral monodentate ferrocenylphosphines of the general structure FcP(Ph)R, (R=aryl or alkyl).[326] The reactivity of ferrocenylmethyl alcohols, esters, ethers and amines towards nucleophiles (often secondary phosphines) has been utilised in the synthesis of new phosphines, including a tridentate system, (140), combining planar-, P- and C-chirality,[327,328] bulky phosphines, e.g., (141) and (142),[329] a ferrocenylmethylphosphine-containing polymer,[330] *rac*-[2-(diphenylphosphino) ferrocenyl]acetic acid and related compounds,[331] and ferrocenylphosphines bearing imidazolium groups, precursors of phosphino-carbene ligands.[332,333] The same approach has been used in the synthesis of new P,N-ferrocenyl ligands, e.g., (143)[334] and (144).[335] The established ring-opening of 1-phenyl-1-phospha[1]-ferrocenophane with phenyllithium has been applied in the synthesis of the new enantiopure phosphino-phosphinito ligand (145).[336]



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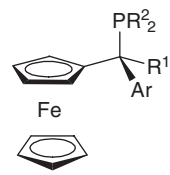
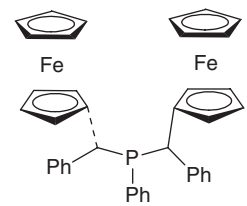


(141) R^1 = H or Ar;
R^2 = Ph or Bu^t;
Ar = Ph, o-anisyl or 1-naphthyl



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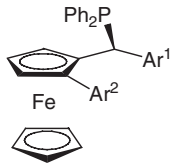
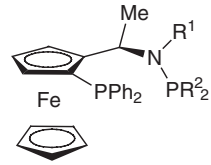
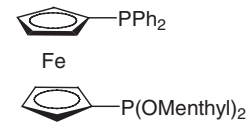


(143) Ar^1 = o-tolyl or 3,5-xylyl; Ar^2 = 2-pyrimidyl, 2-pyridyl or 2-quinolyl

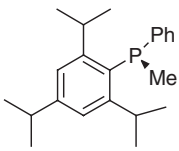


(144) R^1 = H or alkyl; R^2 = Ph or Cy



(145)

Methods for the synthesis of C-functionalised arylphosphines based on the direct introduction of phosphino groups into aryl halides or tosylates, catalysed by a variety of metals, have continued to develop. The reactions of secondary phosphines (and secondary phosphine oxides) with bromo- or iodo-arenes, catalysed by palladium acetate or other palladium complexes, have been used to prepare a range of *ortho*-substituted arylphosphines,[337,338] including enantioselective syntheses of chiral systems, e.g., (146),[339,340] and a series of diphosphine ligands having a barbiturate-binding receptor, e.g., (147).[341] Related palladium- and nickel-catalysed reactions of primary phosphines with *para*-dihalobenzenes have given a series of poly(arylene)phosphines.[342] A palladium[0]-catalyst was used in the synthesis of *para*-diphenylphosphinophenol, subsequently attached to a polyethylene glycol ether support.[343] Related palladium-catalysed reactions of aryl triflates with secondary arylphosphine oxides yield the corresponding tertiary phosphine oxides, subsequently reduced to the phosphines. This approach has been applied in the synthesis of new chirogenic binaphthylmonophosphines,[344] the monoxide of 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene[345] and the chiral P,N-system (148).[346] Palladium-catalysed phosphination of bromoarenes and aryl triflates bearing a wide variety of functional groups has also been achieved by the use of triarylphosphines as the phosphinating reagent.[347,348] A microwave-assisted procedure for the palladium-or nickel-catalysed phosphination of aryl halides and triflates by diphenylphosphine has also been reported.[349] Nickel-catalysed direct phosphination reactions of aryl triflates with secondary phosphines have also been achieved in the synthesis of hexamethyl-2,2′-bis (diarylphosphino)biphenyls,[350] 1-(2-diphenylphosphino-1′-naphthyl)isoquinoline,[351]and the new atropisomeric system (149).[352] Functionalised triarylphosphines have also been prepared by a nickel-catalysed reaction of aryl bromides with chlorodiphenylphosphine, in the presence of zinc dust.[353] This approach has also been used to prepare the unusual 2,8′-disubstituted-1,1′- binaphthyl (150).[354] Copper(I) iodide, in the presence of a base, is an effective and inexpensive reagent for the phosphination of aryl- and vinyl-halides by secondary phosphines, the conditions tolerating the presence of a wide variety of functional groups.[355,356]



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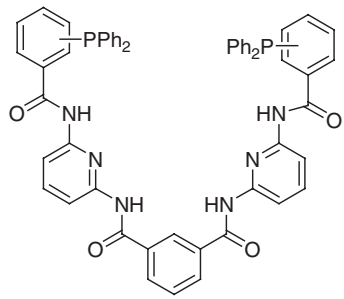

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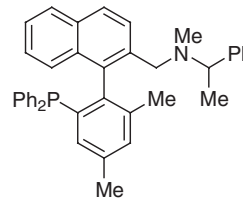

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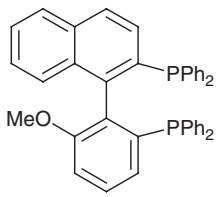

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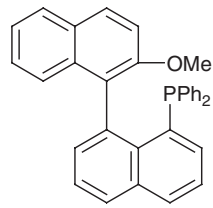

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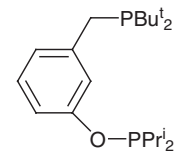
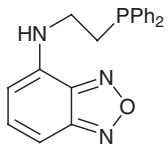


(151)

The reactions of other functional groups present in organophosphines have been widely applied in the synthesis of new phosphines, usually of interest as ligands for use in homogeneous catalyst systems. A series of unsymmetrical PCP′ pincer ligands, e.g., (151), has been obtained *via* reactions of *meta*-phosphinomethyl-phenols and -benzyl alcohols with di(*iso*propyl)chlorophosphine in the presence of base.[357] Unsymmetrical diphosphines of the type $Ph_2P(CH_2)_nNHPPr^i_2$ (n=2 or 3) have been obtained by related reactions of ω-aminoalkylphosphines.[358] The reaction of 2-aminoethyldiphenylphosphine with a fluoronitrobenzoxadiazole yields phosphine (152), of interest as a new reagent for the detection of hydroperoxides, the resulting phosphine oxide fluorescing strongly.[359] N-acylation of phosphinoalkylamines, derived from valinol and proline, with picolinic and quinaldic acids has given a new series of N,P-ligands.[360] N-acylation and -alkylation of 2-(diphenylphosphino)methylpyrroline has been used to provide a series of unsymmetrical terdentate PNN ligands, e.g., (153).[361] Twenty new chiral aminoalkylphosphines of type (154) have been prepared by transformations of related chiral phosphinoalkanoic acids.[362] An eight stage route to the diphosphine (155) has been developed, starting from 5-amino-*iso*phthalic acid dimethyl ester, involving Arbuzov and trichlorosilane reduction stages, and subsequent elaboration of the arylamino group. Covalent binding to silica is then possible *via* the succinimide ester group.[363] The succinimidyl ester of diphenylphosphinopropionic acid has been used as an intermediate in the synthesis of the phosphino-amino acid system (156).[364]



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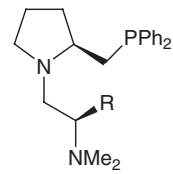

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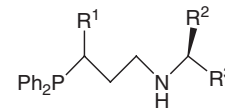

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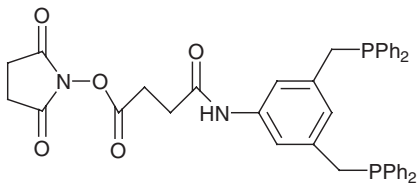

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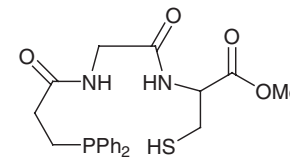
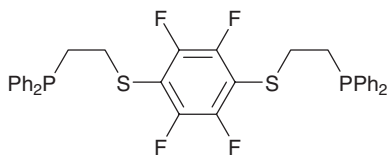


(156)

Phosphino-amino acid components have also been used in a parallel approach in conjunction with natural amino acids to develop β-turn phosphinopeptide ligands.[365] A series of polyphosphorus ligands, of interest for the construction of metallodendrimer systems, has been prepared from the reactions of 3-hydroxypropyldiphenylphosphine with $P(O)Cl_3$ and phenyldichlorophosphine.[366] Dendritic phosphines have also been obtained by N-acylation reactions of 3,4-bis(diphenylphosphino)pyrroline[367,368] and 5,5′-diamino-BINAP,[369] and the synthesis of phosphorus-containing dendrimers has been reviewed.[370] The reactions of thiolate anions with ω-chloroalkylphosphines have given a range of new P,S-donor ligands, including the bis(phosphinoalkyl-thioether)arene (157),[371] the aminoarylthioalkylphosphine $4\text{-}H_2NC_6H_4SCH_2CH_2PPh_2$, from which the phenolic imine (158) was subsequently obtained,[372] and a 3-(diphenylphosphino)propylthio-substituted tetrathiafulvalene.[373] Addition of a trifunctional arenethiol to diphenylvinylphosphine has given the threefold symmetric phosphino-alkylthioether ligand (159), capable of forming macrocyclic metallo complexes.[374] Phosphadithiamacrocycles have also been assembled by the reactions of the isomeric bis(chloromethyl)benzenes with the thiolate anions derived from bis(2-mercaptoethyl)phenylphosphine.[375] Very many new phosphines have been prepared utilising the reactivity of functional groups in the *ortho*- or *para*-positions to phosphorus in an arylphosphine. Thus, e.g., the *spiro*-phosphino-oxazine (160) has been obtained by the reaction of *ortho*-diphenylphosphinobenzonitrile with a *spiro*-aminoalcohol,[376] new chiral arylphosphino-phosphito ligands have been prepared from the reactions of chiral *ortho*-phosphinophenols with chlorophosphites,[377] and treatment of *o*-(diphenylphosphino)benzyl chloride with various 1-substituted imidazoles has given a series of phosphino-imidazolium salts (161), potential precursors of nucleophilic carbene ligands.[378] However, most reports of this nature centre on the reactions of phosphinoarylaldehydes, -carboxylic acids, and -amines. Imine formation from

the commercially available *o*-(diphenylphosphino)benzaldehyde continues to be exploited. Among new phosphinoarylimines reported are those from 2-aminomethylpyridine,[379] 1-phenylazo-2-naphthylamine,[380] chiral sulfinamides,[381,382] chiral monosulfonamido derivatives of *trans*-1,2-diaminocyclohexane,[383] and the primary amines $H_2N(CH_2)_nSePh$ (n=3,4).[384] Imine formation with *o*-diphenylphosphinobenzaldehyde has also been used for the surface functionalisation of dendritic primary alkylamines, giving dendrimeric P,N ligands.[385] Aminal- and thioacetal-like cyclocondensations of *o*-diphenylphosphinobenzaldehyde with chiral amino-amides, disecondary amines, and 3-hydroxypropanethiols has afforded new chiral phosphines, e.g., (162),[386,387] and (163).[388,389] Imine formation from enantiopure 2-formyl-1-phosphanorbornadiene has been utilised to give the new chiral phosphinoimines (164).[390] Phosphino-aldehydes based on ferrocene and cymantrene have also been used in imine formation for the design of new planar chiral ligands.[391] New ferrocenyl phosphino-imine ligands have also been prepared *via* the condensation reactions of primary aminoalkylferrocenylphosphines with aldehydes.[392,393] Related condensation reactions of aminoalkylferrocenes with N,N-dimethylformamide dimethylacetal have given phosphinoferrocenyl-amidine ligands.[394] New phosphino-imines have also been obtained from *o*-aminophenyldiphenylphosphine[395,396] and also from *o*-aminomethylphenyldiphenylphosphine.[397] New water-soluble phosphine systems have been obtained from the N-*poly*-ethoxylation of *o*-aminophenyldiphenylphosphine.[398] New chiral 2,2′-biphenylyl-P,N-ligands have been prepared by N-acylation of 2-amino-2′-diphenylphosphino-biphenyls.[399] Amide and ester formation from *o*- and *p*-diphenylphosphinobenzoic acids has also been exploited in synthesis. Among new phosphines prepared in this way are a series of simple amido derivatives of non-chiral[400] and chiral[401] primary amines, a series of glucosamine-based monophosphines,[402,403] various tripeptide-linked phosphines,[404] and various polystyrene-linked phosphines.[405] Further examples of diphosphines linked *via* amide formation to *vicinal*-diamines have appeared,[406,407] including a polymer-bound system.[408] A diamidodiphosphine has also been prepared from 1,8-diaminonaphthalene, and the same report describes the synthesis of the thiol-ester linked system (165).[409] Crown ether-tagged phosphines have been prepared by amide formation with 2-aminomethyl-18-crown-6, and also by ether-formation involving *para*-diphenylphosphinophenol and mesylated hydroxymethyl-15-crown-5.[410]



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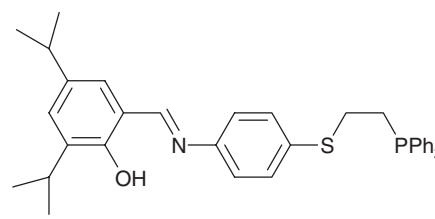

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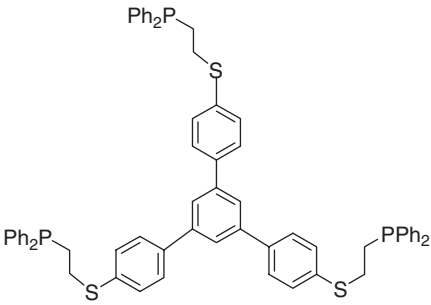

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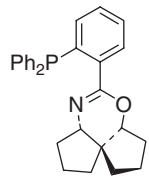

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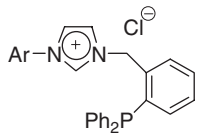

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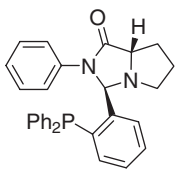
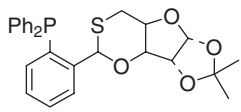
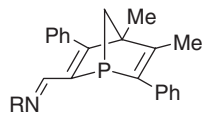


(162)

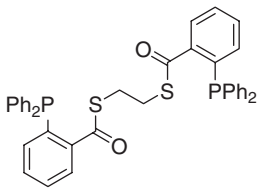


(163)



(164)R = CH_2Ph, CH(Me) Ph(*R* & *S*), Ph or Bu^t

The chemistry of hydroxymethylphosphines continues to develop and this has also led to the synthesis of new phosphines. Full details of the synthesis of ferrocenylhydroxymethylphosphines from the reactions of ferrocenyl primary phosphines with aqueous formaldehyde have appeared.[411] Mannich reactions between hydroxymethylphosphines and amines have been applied in the synthesis of a variety of new aminomethylphosphines. Included among these are aminomethylphosphine derivatives of adenine,[412] the new unsymmetrical phosphine $Ph_2PCH_2NHC_6H_4PPh_2$,[413] a polymer-bound (N-phosphinoethyl)-aminomethylphosphine,[414] and water-soluble aminomethyl(ferrocenylmethyl)-phosphines.[415] Bis(phosphinomethyl)amino systems have also been described, e.g., (166),[416] the amphiphilic and water-soluble systems (167),[417] and a bis(aminomethylphosphine) derived from 3,4-diaminotoluene.[418] The related reactions of bis(hydroxymethyl)organophosphines with primary amines have led to the isolation of new cyclic- and macrocyclic-aminomethylphosphines, e.g., (168).[419,420] A new macrocyclic tetraphosphine has also been isolated from the reaction of a disecondary bis(phosphino)propane with formaldehyde and benzylamine.[421] The new cage-molecule (169) has been obtained from the reaction of tris(hydroxymethyl)phosphine with hexamethylenetetraamine in the presence of sulfamide and formaldehyde.[422] The established reaction of PH_3 with pentane-2,4-dione, giving the phospha-adamantane (170), has been re-examined, and procedures developed for alkylation and arylation at phosphorus.[423] The one-pot reaction of the azine of 2-carboxybenzaldehyde, phenylphosphine and phthaloyl chloride provides a large-scale route to the chiral diazaphospholane system (171), capable of further elaboration *via* the carboxylic acid group to give a series of amidophenyldiazaphospholanes.[424]



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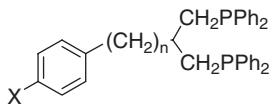
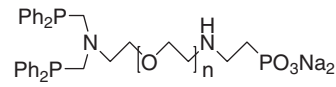
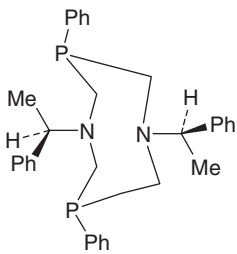


(166) X = e.g., H, CO_2H, COMe or hal n = 0 or 1



(167) n = 1-3



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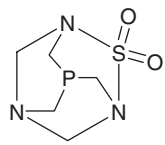

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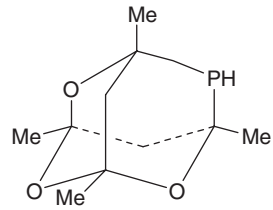

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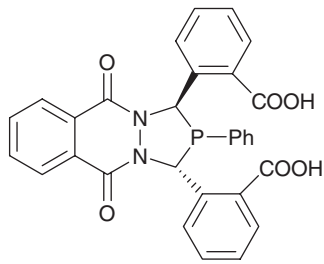
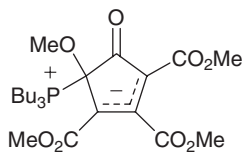


(171)

2.2 Reactions of Phosphines. – *2.2.1 Nucleophilic Attack at Carbon*. The formation of dipolar adducts from the reactions of tertiary phosphines with alkenes and alkynes bearing electron-withdrawing groups attached to the multiple bond, and their subsequent use in synthesis and catalysis, has again proved to be a very active area. A new crystalline adduct, (172), has been isolated from the reaction of tributylphosphine and dimethyl acetylenedicarboxylate, the mechanism involving an unusual rearrangement.[425] A common theme in many of the subsequent reactions of the dipolar adducts is protonation by a third reagent, typically an amine or phenol, to generate a vinylphosphonium salt, which then suffers nucleophilic addition to generate a new ylide (173). In some cases, subsequent intramolecular Wittig reactions then ensue, or an elimination reaction occurs in which the original phosphine is regenerated, to give the final products. Thus, e.g., new phosphorus ylides have been obtained in excellent yield from the reactions of triphenylphosphine, dimethyl acetylenedicarboxylate and strong NH acids, including pyrroles and

indoles,[426] hydantoins,[427] benzimidazoles,[428] saccharin,[429] trifluoroacetamide,[430] phthalimide and succinimide.[431,432] New ylides have also been isolated from the related reactions of triphenylphosphine, dimethyl acetylenedicarboxylate and primary aromatic amines,[433] including various aminophenols,[434] 2-aminothiophenol,[435] and *o*-phenylenediamine.[436] Other NH compounds used to trap the initial dipolar adduct in the triphenylphosphine-dimethyl acetylenedicarboxylate system include perimidines,[437] and various amides derived from aromatic amines, the latter reactions providing routes to 5-oxo-4,5-dihydro-1H-pyrroles.[438,439] Further examples of the trapping of the initial adduct with phenols have also been reported,[440] together with the use of this approach for the synthesis of coumarins,[441,442] including examples of procedures involving catalysis by silica gel,[443] and the use of microwave heating.[444] Vinylphosphonium salts have been obtained from the reactions of the initial adducts of tertiary phosphines and acetylene dicarboxylate esters with hydroxycyclopentenones[445] and hydroxy-4H-pyranones.[446] Related work with β-diketones has given a range of new ylides,[447,448] and provided a route to highly functionalised trifluoromethylated cyclobutenes.[449] Reactions with other carbonyl compounds have also been reported, including those with arylaldehydes,[450] and isatin derivatives, which lead to new γ-spirolactones.[451] In addition to the reactions of tertiary phosphines with acetylene dicarboxylate esters, the related reactions of a variety of other alkynes have also continued to attract attention. These include the reactions of terminal alkynes, usually alkyl propiolates[452,453] and ethynyl ketones,[454,455] dibenzoylacetylene[456,457] (which, in the presence of arylisocyanates yield β-lactam derivatives),[458] and a miscellany of other disubstituted alkynes, in which the tertiary phosphine catalyses reactions of the alkyne with other substrates. Thus, e.g., tertiary phosphines catalyse the zipper cyclisation of aliphatic diyne-dione and yne-dione systems,[459] the formation of furans from γ-acyloxy butynoates,[460] [3+2]-cycloadditions of alkynes with 5-methylenehydantoins[461] and methylenecyclohexanones,[462] the formation of α-vinylfurans from enynes and aldehydes,[463] and the conjugate addition of alcohols to methyl propiolate.[464] Metal-promoted reactions of tertiary phosphine-alkyne systems include a highly selective cross [2+2+2] cycloaddition of two different monoynes.[465] Two consecutive [3+2]-cycloadditions of the diphosphinoketenimine (174) with acetylenic esters give rise to the bicyclic $1\lambda^5,3\lambda^5$-diphospholes (175).[466] The reactivity of tertiary phosphines towards alkenes bearing electron-withdrawing groups has also continued to attract attention. Triphenylphosphine in refluxing methanol reduces maleimides to succinimides in good yield.[467] Further studies have been made of charge-transfer complexes between tervalent phosphorus donors and tetracyanoethylene,[468] and of the reactions with aryl isocyanates of the 1,3-zwitterion derived from triisopropylphosphine and ethyl 2-cyanoacrylate.[469] However, most new work relates to systems in which initial nucleophilic attack by phosphorus at electron-deficient carbon is involved in the catalysis by tertiary phosphines of new bond-forming processes. Included among these are the cyclisation of enones to cyclopentenes and cyclohexenes by tributylphosphine,[470] and a related procedure involving co-catalysis by a palladium

complex,[471] a phosphine-catalysed α-arylation of enones and enals using hypervalent bismuth reagents,[472] a phosphine-mediated [4+2]-annulation of bis(enones) to form decalins,[473] the formation of tetrahydropyridines from a phosphine-catalysed [4+2]-annulation of ethyl 2-methyl-2,3-butadienoate and N-tosylaldimines,[474] the phosphine-catalysed hydration and hydroalkoxylation of activated alkenes,[475] and a phosphine-catalysed Knoevenagel condensation of aldehydes with active methylene compounds to form α-cyanoacrylates and α-cyanoacrylonitriles.[476] Phosphine-catalysed procedures have also been described for the regiospecific allylic amination and dynamic kinetic resolution of Morita-Baylis-Hillman acetates,[477] the conversion of maleic anhydride into acrylate esters,[478] the Michael addition of oximes to activated alkenes,[479] and aza-Michael reactions of αβ-unsaturated compounds with carbamates in the presence of trimethylsilyl chloride.[480] Tributylphosphine has been shown to be an effective catalyst for the ring-opening of aziridines and epoxides,[481,482] (even under aqueous conditions),[483] enabling the development of procedures for the conversion of these substrates to conjugated dienes.[484] Further synthetic applications of the tributylphosphine-carbon disulfide adduct have appeared, providing routes to 4-phosphonyl-1,3-dithioles, 1,3-dithiolanes,[485] and 1,3,4-thiazolidine-2-thiones.[486] The reactions of tributylphosphine with trifluorovinyl(perfluoroalkyl) ethers lead to displacement of fluorine from the trifluorovinyl group with the formation of phosphonium salts, the subsequent reactions of which were studied.[487] A detailed study of the quaternisation of phosphines and amines with iodoethane in aliphatic alcohols has also been described.[488]



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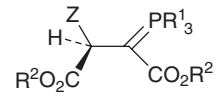
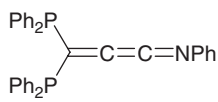


(173) R^1 = alkyl or aryl;
R^2 = alkyl; Z = e.g., OAr or NR_2



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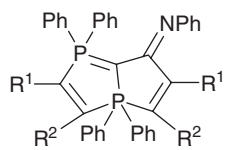


(175) R^1 = H, R^2 = CO_2Me;
R^1 = CO_2Me, R^2 = H;
R^1, R^2 = CO_2Me

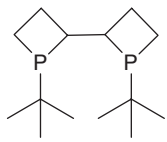
2.2.2 Nucleophilic Attack at Halogen. This field of activity continues to be dominated by applications of well-known phosphine-positive halogen combinations. Alcohols can be oxidised to the related aldehydes and ketones under mild conditions by the DMSO-Ph_3PX_2 system, which provides an alternative to the Swern oxidation.[489] The triphenylphosphine-iodine system has been

shown to be an efficient reagent for the regioselective dehydration of tertiary alcohols.[490] The Ph_3P-CCl_4-Et_3N system has been used for the S_N2-cyclisation of *N*-Boc-β-aminoalcohols to *anti*-2-oxazolidinones[491] and in a new approach for the synthesis of ureas from primary amines.[492] Triphenylphosphine-CX_4 reagents, (X=Cl or Br), have been shown to promote the cyclisation of *N*-acylated α-aminonitriles to 2,4-disubstituted 5-halo-1*H*-imidazoles in good yield.[493] Combination of a perfluoroalkoxy-substituted triarylphosphine with CBr_4 provides a reagent system which converts alcohols to the related bromoalkanes in good yield, the fluorous phosphine oxide being readily separated by liquid-liquid extraction, and subsequently reduced and recycled.[494] The reaction of the Ph_3P-CBr_4 system with 2-*O*-benzyl-1-hydroxy sugars generates a glycosyl bromide *in situ*, which couples with an acceptor alcohol in the presence of *N*,*N*-tetramethylurea or DMF to give an α-glycosyl product in excellent yield. It is suggested that the reagent system plays a multiple role in the reaction sequence, facilitating generation of the glycosyl donor, activation of glycosylation and removal of water.[495,496] Addition of diethylzinc to the triphenylphosphine-tribromofluoromethane system leads to improvements in the generation of the ylide $Ph_3P{=}CBrF$, and its subsequent Wittig reactions with carbonyl compounds in the synthesis of bromofluoroalkenes.[497] The triphenylphosphine-trichloroacetonitrile system has been used as a reagent for the N-acylation of polymer-supported benzylamines[498] and in a general procedure for the preparation of esters from carboxylic acids.[499] The reaction of triphenylphosphine with bis(trichloromethyl) carbonate provides a reagent system that converts thiols into the related disulfides.[500] Triphenylphosphine-*N*-halosuccinimide systems have found use in the synthesis of α-diazoketones from acyloxyphosphonium salts and diazomethane[501] and for highly regioselective deoxyhalogenations at the C-6 positions of *N*-phthaloylchitosan.[502] Tertiary phosphine-DDQ systems, (DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone), have also generated some interest. A series of ferrocenylphosphines has been shown to form 1:1 adducts with DDQ which appear to be radical cation-radical anion salts in which oxidation has occurred at phosphorus, the electron being transferred to DDQ to form the radical anion $DDQ^{\bullet -}$.[503] The triphenylphosphine-DDQ combination, in the presence of halide, cyanide or azide ions, has been shown to be a new, selective and neutral system for the facile conversion of alcohols, thiols, selenols and trimethylsilyl ethers to alkyl-halides, -cyanides,[504,505] and -azides.[506] This system, in the presence of appropriate tetraalkylammonium salts, has also been used for the conversion of diethyl α-hydroxyphosphonates to the related α-halo-, α-azido- and α-thiocyanatophosphonates.[507,508]

2.2.3 Nucleophilic Attack at Other Atoms. A highly efficient general synthesis of secondary- and tertiary- phosphine-borane adducts is afforded by treatment of the phosphine with sodium borohydride in the presence of acetic acid in THF. Any carbonyl groups present in the phosphine undergo concomitant

reduction.[509] Treatment of the trimethylamine-carbomethoxyborane adduct with triphenylphosphine in monoglyme gave the corresponding phosphine-carbomethoxyborane adduct in good yield, a structural study showing unambiguously that the phosphorus atom coordinates to boron, the ester group being unaffected.[510] Various tertiary phosphine-cyanoborane adducts have been prepared by ligand exchange from trimethylamine-cyanoborane, and also by treatment of the phosphine hydrochloride with sodium cyanoborohydride.[511] A trimethylphosphine adduct of a fluorous organoborane has been characterised, and shown to suffer displacement of the phosphine on treatment with dimethylaminopyridine or piperidine at room temperature. The adduct is stable to trimethylamine.[512] Trimethylphosphine has also been shown to form P–B adducts with methyl(methylidene)boranes, $MeB{=}CR_2$.[513] Phosphine-borane adducts have been used as P-protecting systems in the synthesis of the chiral diphosphetanyl (176).[514] The use of borane-protection in the synthesis of P-chiral phosphines has been reviewed,[515] and two groups have reported the enzymatic resolution of hydroxyalkylphosphine-borane adducts.[516,517] The efficiency of a range of amines, and other reagents, for the deprotection of phosphine-borane adducts has been compared, with specific reference to the use of monoethanolamine, diethanolamine and tetrabutylammonium cyanide.[518] The intramolecular hydroboration of borane adducts of unsaturated phosphines has been studied.[519] Heterodehydrocoupling of borane adducts of primary and secondary phosphines leads to the formation of new P–B bonds and offers a route to phosphinoborane rings, chains, and high molecular weight polymers. Further studies of the catalysis of these reactions by rhodium complexes have now been reported[520] and tris(pentafluorophenyl)borane has been shown to catalyse the dehydrocoupling of the $PhPH_2$-BH_3 adduct to form a P–B polymeric system.[521] The reactivity of *closo*- and *nido*-carboranylmonophosphines towards $BH_3 \cdot THF$ (and also to oxygen and sulfur) has been compared, the *nido*-carboranyl substituent conferring a greater electron donor character on the phosphino group.[522] The chemistry of the phosphacarboranes, in which one (or more) phosphorus atoms are members of the cage structure, together with boron and carbon, has also continued to attract attention. Further studies of the reactivity of the cage-phosphorus atoms in such systems have been reported, including reactions with $BH_3 \cdot THF$, O_2, and S_8, and also with transition metal acceptors.[523,524] The crystal structure of the low temperature polymorph of the tetramethyldiphosphine-bis(monoborane) adduct has been determined, providing an insight into the stabilisation of different rotational isomers in the solid state.[525] The structure of the trimethylphosphine-gallane adduct has been determined by a gas-phase electron-diffraction study[526] and the structures of a series of tertiary -phosphine, -arsine and -stibine adducts of trialkylgallium acceptors have been compared.[527] The reactivity of secondary phosphines towards gallium(I) iodide has also been studied.[528]

A relatively stable phosphadioxirane (177), having $\delta^{31}P=-48.3$ ppm, has been obtained from the reaction of the sterically hindered tris (o-methoxyphenyl)phosphine with singlet oxygen at $-80^{\circ}C$. Olefin-trapping experiments show that the phosphadioxirane can undergo non-radical oxygen atom-transfer reactions to form epoxides and the phosphine oxide. With protic solvents, the phosphine oxide is again formed, *via* a hydroxyphosphorane intermediate. At room temperature, the phosphadioxirane rearranges to form the phosphinate ester (178).[529] Triphenylphosphine inserts into the peroxide bond of 1,2-dioxines, leading to ring-contraction products, with loss of triphenylphosphine oxide.[530] Hydroperoxysultams have been shown to act as chemoselective electrophilic oxidants for phosphines and other oxidisable heteroatom compounds.[531] In contrast to the reduction of hydroperoxides by a phosphine, in which initial nucleophilic attack occurs at the hydroxylic oxygen, the related reactions of sterically hindered arene-sulfenic and -selenic acids, ArSOH and ArSeOH, respectively, involve initial attack at sulfur or selenium to give an organothio- or organoseleno-phosphonium hydroxide, which subsequently decomposes to form the phosphine oxide, together with the thiol or selenol.[532] Cyclic selenoxides having an optically active binaphthyl skeleton act as reagents for the enantioselective oxidation of phosphines to the corresponding phosphine oxides.[533] The kinetics and mechanism of oxygen transfer from methylphenylsulfoxide to triarylphosphines in the presence of an oxorhenium(V) complex have been studied.[534] Tertiary phosphines are cleanly and quantitatively converted into the corresponding phosphine oxides on exposure to dry air or dioxygen in dichloromethane solution in the presence of catalytic amounts of tin(IV) iodide.[535] Further examples of transition metal-promoted oxidation of arylphosphines have also been reported.[536] Treatment of the iminodiphosphine $(o\text{-}CN)C_6H_4N{=}P(Ph_2){-}PPh_2$ with dioxygen, hydrogen peroxide or sulfur, results in cleavage of the P–P bond.[537] The dithianylphosphines (179), in which the diphenylphosphino group is equatorial, undergo air oxidation with cleavage of the dithiane ring to form the open chain thioesters (180). The related axial phosphino systems do not behave in this way, possibly due to steric hindrance of axial attack by molecular oxygen.[538] Tris(2-carboxyethyl)phosphine has been used to cleave disulfide bridges in spider venom proteins, prior to protein sequencing by mass spectrometry.[539] The tributylphosphine-diphenyldisulfide combination has been found to promote a one-step, enantiospecific transformation of cyclic five-membered 1,2-diols into their respective 1,2-bis(phenylsulfanyl) derivatives.[540] A tributylphosphine-2-pyridylthioester combination has found use for acylative end-capping of pseudorotaxane systems.[541] Treatment of 4, 5-dihydroxy-1,2-dithianes with tertiary phosphines results in a stereospecific rearrangement to form 4-hydroxy-3-mercaptotetrahydrothiophenes, *via* an initial disulfide-cleavage reaction.[542] A tributylphosphine-promoted selenium-selenium cleavage step is involved in the rearrangement of the heterocyclic P,Se system (181) to give (182).[543]



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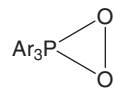
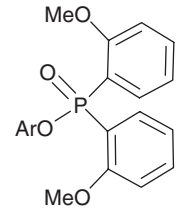
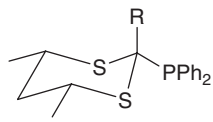


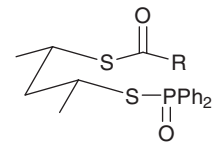
(177) Ar = o-$MeOC_6H_4$



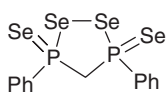
(178) Ar = o-$MeOC_6H_4$



(179) R = Me or Ph



(180) R = Me or Ph



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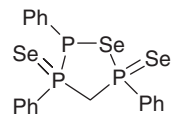

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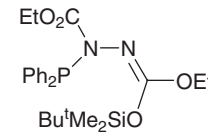
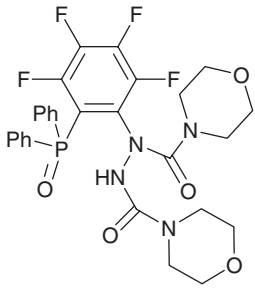


(183)

Reactions involving nucleophilic attack at nitrogen have also continued to attract attention, particularly so in the case of the Mitsunobu and Staudinger procedures. For both of these reactions, many routine synthetic applications have appeared over the past two years which are not noted here unless some novel aspect of the system is also apparent. In conventional Mitsunobu procedures involving the reaction of an alcohol with a carboxylic acid in the presence of the triphenylphosphine-diethyl azodicarboxylate combination, it has been assumed for a long time that the reaction proceeds directly to an alkoxyphosphonium salt which then reacts with the carboxylate anion to form triphenylphosphine oxide and the ester, with inversion of configuration in the original alcohol. However, various experimental observations in recent years have indicated that *acyl*phosphonium intermediates may also be involved under some conditions and lead to products in which the configuration of the original alcohol is retained, *via* direct nucleophilic attack of the alcohol at the carbonyl carbon of the acyloxyphosphonium salt. It has now been shown that when benzoyloxyphosphonium cations are generated directly from the reaction of a tertiary phosphine with benzoyl peroxide (from which an alkoxyphosphonium cation cannot arise directly), subsequent reactions with an alcohol in the absence of a basic species result in formation

of the ester with retention of configuration. In the presence of a base, e.g., the hydrazide anion in a conventional Mitsunobu reaction, the inverted configuration product is formed predominantly *via* an alkoxyphosphonium cation. The latter route arises as a result of a base-induced cross-over in which the acyloxy salt is converted into the alkoxy salt. These results show that the nature of any basic species present or generated in the reaction can have a profound effect on the stereochemistry of esterification using Mitsunobu or related procedures.[544] In N-alkylation reactions promoted by tertiary phosphine-azoester reagents, it has been shown that use of a phosphine more bulky than trimethylphosphine gives a high intramolecular selectivity between primary and secondary alcohol groups. Thus, trimethylphosphine is the only phosphine that enables alkylation of 2-nitrobenzenesulfonamides with a wide range of secondary alcohols, whereas tributylphosphine is selective for primary alcohol groups.[545] Selective monoalkylation of dihydroxycoumarins *via* Mitsunobu dehydroalkylation has been achieved under high intensity ultrasound conditions.[546] In the absence of a proton source, silylphosphines react with diethyl azodicarboxylate to form the adduct (183). However, when the above reagents are combined in the presence of an alcohol and a proton source such as pyridinium *p*-toluenesulfonate, the above adduct is not formed, the reagent system providing a source of a silyl cation which readily converts the alcohol into a silyl ether in good yield.[547] Treatment of pentafluorophenyldiphenylphosphine with azodicarboxylic acid dimorpholide results in the formation of the phosphine oxide (184), *via* initial nucleophilic attack at azo nitrogen, followed by intramolecular displacement of fluorine by the hydrazide anion and hydrolysis of an intermediate fluorophosphorane.[548] Practical improvents to Mitsunobu procedures continue to appear. A chromatography-free procedure is afforded by the use of a combination of an anthracenetagged phosphine (185) and a polymer-supported azodicarboxylate. The anthracene-tagged phosphine allows for removal of the phosphine-phosphine oxide by sequestration through a chemoselective Diels–Alder reaction with a maleimide resin. The polymer-bound azoester facilitates the removal of excess alcohol, reagent, and byproducts by filtration. The pure products are obtained after the filtration by a concentration step.[549] A stereoselective carbon-carbon bond-forming procedure is afforded by Mitsunobu-promoted displacement of chiral secondary benzylic alcohols with triethyl methanetricarboxylate, the reactions proceeding in good yield and with a high degree of inversion. Subsequent saponification and decarboxylation of the products provides chiral 3-aryl-3-substituted propanoic acids without racemisation.[550] The betaine (186) has been used in a modified Mitsunobu procedure with 1,2,4-dithiazolidine-3,5dione as the source of the nucleophile in reactions with alcohols to give the related N-alkyldithiazolidinones, which are easily transformed into amine derivatives under very mild conditions.[551] N-protected amines have also been obtained *via* conventional Mitsunobu routes involving bis(βtrimethylsilylethanesulfonyl)imide as the nucleophile source.[552]



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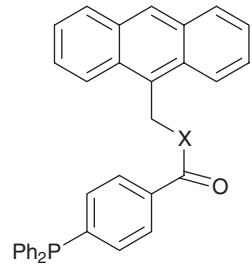
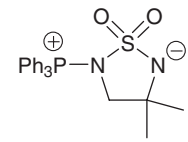


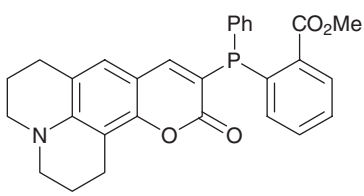
(185) X = O or NH



(186)

The Staudinger reaction of phosphines with azides to form aza-ylides, $R_3P{=}NR$, has found widespread use in synthetic organic chemistry. However, in recent years, the potential of the reaction as a highly chemoselective ligation method in chemical biology for the synthesis of bioconjugates has started to be recognised, the reaction being applicable even in living cells. Developments in this area have now been reviewed.[553] The coumarinylphosphine (187) has been developed as a detectable marker system for use in Staudinger ligation reactions. When treated with an azide-functionalised biomolecule, it is converted to the amidoarylphosphine oxide (188), which, unlike the starting phosphine, is intensely fluorescent, enabling the ligation product (188) to be readily distinguished from excess primary detection reagent.[554] Among other C-functionalised arylphosphines used in Staudinger ligation chemistry are (189, X=CONHR) (which, on treatment with *aryl*azides form phosphine oxides bearing an *ortho*-O-alkyl imidate group rather than the anticipated *ortho*-amido group),[555,556] and (189, X=COOH). The latter can be bound to an amino-functional sensor chip surface *via* the carboxylic acid group, and then used in a Staudinger procedure to immobilize an azidoglycoside on the chip.[557] Various O-acyl derivatives of *ortho*-diphenylphosphinophenol,[558,559] and mercaptomethyldiphenylphosphine[560] have also been used in Staudinger ligation reactions, the latter reagent also being applied in a new synthesis of medium-sized lactams.[561] These have also been prepared *via* a similar approach involving the reaction of tributylphosphine with pentafluorophenyl esters of ω-azidoalkanoic acids.[562] The reaction of trimethylphosphine with azidopeptides is the basis of an alternative strategy for the synthesis of peptide nucleic acids.[563] Staudinger ligation chemistry has also been used for probing glycosyltransferase activities.[564] The mechanism of the Staudinger reaction continues to attract attention. Details of the initial approach of the phosphine to the azido group have been probed using density functional theory.[565] Isocyanates and thiocyanates have been shown to trap *E*-phosphazide intermediates (190) in the Staudinger reaction of triphenylphosphine with azides, to form hydantoins and thiohydantoins, respectively, and this approach has found use in the synthesis of analogues of a pyrrole-imidazole marine alkaloid.[566] In addition to the chemical biology applications noted above, the Staudinger reaction continues to be applied widely in general synthetic chemistry.

Tris(2-carboxyethyl)phosphine has found use for the reduction of azides to amines (and also for deoxygenation of sulfoxides, sulfones, and sulfonyl chlorides).[567] Azides can also be reduced to amines with good regioselectivity by a modification of the Staudinger reaction using trimethylphosphine at low temperatures.[568] The reaction of triarylphosphines with alkylazides and thiocarboxylic acids provides a new approach to the synthesis of amides.[569] Polymer-bound triarylphosphines have been used in Staudinger-based routes to aziridines[570,571] and in reactions with azidocyclodextrins.[572] The Staudinger reaction has found further application in the synthesis of phosphorus-functional dendrimers[573,574] and work in this area has also been reviewed.[575] An interesting new approach to unsymmetrical binol-derived bidentate P,N-ligands is afforded by the reaction of the phosphino-nonaflate (191) with an azide, which proceeds with intramolecular nucleophilic displacement of the nonaflate group by the nitrogen of the intermediate aza-ylide to give, after hydrolysis, the aminoarylphosphine oxide (192), subsequently reduced to the related phosphine with phenylsilane.[576] Further examples of linked Staudinger-aza-Wittig synthetic schemes have also appeared,[577,578] including the first example of such reactions involving a non-cumulated sulfoxy group.[579] The Staudinger reaction has also been used in the synthesis of new mixed donor ligands for use in catalysis, including (193),[580] a series of pyridine- and imidazole-phospha-aza-ylides, e.g., (194)[581] and the crowded system (195).[582] The reaction of metal-coordinated 2-(azidomethyl)phenyl isocyanide with triphenylphosphine has given cationic carbene complexes, *via* intramolecular attack of the intermediate aza-ylide nitrogen at the carbon of the isocyanide group.[583] Nucleophilic attack of phosphorus at nitrogen is also involved in the reactions of α-phosphino-zirconocene complexes with diazoalkenes, giving dipolar adducts, e.g., (196).[584]



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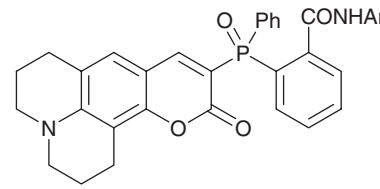

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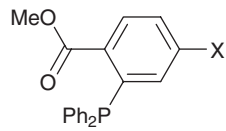

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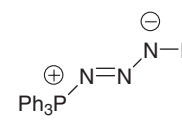

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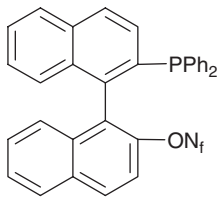

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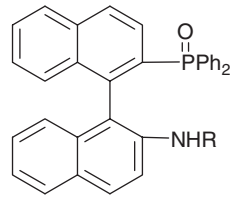
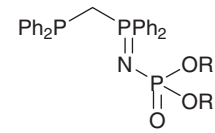
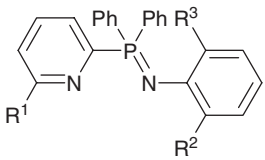


(192)



(193) R = Et or Ph



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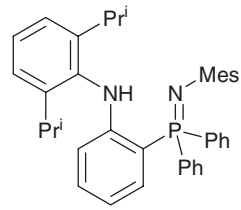

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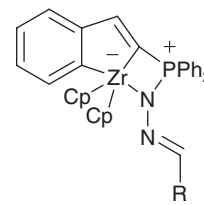
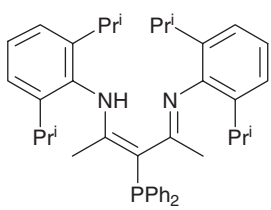


(196)

Reports of nucleophilic attack at atoms other than those above have also appeared. A kinetic study has compared the effectiveness of tertiary phosphines and phosphite esters in the catalysis of the cleavage of the silicon-silicon bond of methylchlorodisilanes, providing evidence for the involvement of a stabilised silylene intermediate.[585] The anion of the γ-phosphino-β-diketimine (197) has been shown to react with arsenic trichloride to give the phosphino-arsino-β-diketimine (198), in which there is a coordinative link from phosphorus to arsenic.[586]



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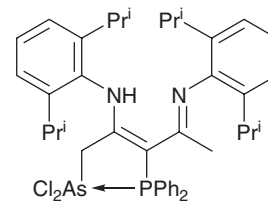
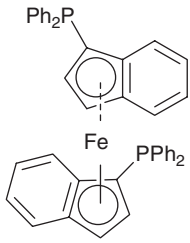


(198)

2.2.4 Miscellaneous Reactions of Phosphines. The effects of substituents at phosphorus on the basicity and donor properties of phosphines have continued to attract the attention of the theoretical chemists. Among recent papers are a quantum chemical study of the protonation of phenylphosphine and its

halogenated derivatives,[587] a discussion as to whether allylphosphine is a carbon or a phosphorus base in the gas phase,[588] the relative merits of QSAR and QALE correlations in assessing donor properties of tervalent P systems[589] and a new assessment of the stereoelectronic profile of phosphine and phosphite ligands.[590] Trimethylphosphine has been used to probe the acid sites in a dealuminated nanosized zeolite using ^{31}P CP/MAS NMR and other NMR techniques.[591] Gas-phase electron diffraction and quantum chemical calculations have been used to probe the molecular structure of phenylphosphine and its analogues,[592] and also that of bis(trichlorosilyl) *t*-butylphosphine[593] A review has appeared of the experimental and theoretical thermochemistry of primary and secondary phosphines, and other P–H compounds[594] and the limitations of theoretical methods for estimating enthalpies of vaporisation of tervalent phosphorus compounds have been considered.[595] Theoretical methods have also been used to probe P–P bond energies and homolytic dissociation enthalpies of tetraalkyldiphosphines.[596] Magnetic field effects on the photodissociation reactions of triarylphosphines in solution, giving diarylphosphanyl radicals, have been studied.[597] The reactivity of radical cations derived from the anodic oxidation of trimesitylphosphine has also been investigated.[598]

The reactivity of phosphinometallocene systems has continued to attract interest. Heats of protonation of 1,1′-bis(diphenylphosphino)-ferrocene and -ruthenocene have been determined by titration calorimetry using triflic acid in 1,2-dichloroethane. The basicity of these phosphines is lower than that of other bidentate phosphines as a result of the π-acceptor character of the metallocene cyclopentadienyl rings.[599] The electrochemistry of a series of ferrocenylmethylphosphines, $FcCH_2PR_2$ (R=Ph, CH_2OH and CH_2CH_2CN), (and their simple oxidised derivatives), has been investigated.[600] The mechanism of the facile *meso* to *rac* isomerization of the bis-planar chiral bis(phosphinoindenyl)iron (199) has been shown to proceed *via* a ring-flipping process.[601] Lithiation of 1-bromo-1′-diphenylphosphinoferrocene, followed by addition of bis(trimethylsilyl) peroxide and subsequent *in situ* hydrolysis of the silylether, has given the first structurally characterised hydroxyferrocenylphosphine (200).[602] The reactions of the phosphinomethylferrocenyl aldehydes (201, X=O) with primary amines have given a series of new chiral iminoferrocenylmethylphosphines (201, X=NR).[603] Ultraviolet photolysis of the metallosilylphosphines (202) results in the formation of the phosphasilaferracyclopropanes (203) that undergo a variety of reactions, including the insertion of small molecules into the three-membered ring to give new heterocyclic systems.[604] Treatment of the phospholanozirconaindane (204) with the aza-ylide $Cl_3P{=}NBu^t$ results in the formation of the heterocyclic system (205), the reactivity of which has been explored.[605] The reactivity of the phosphinoazazirconaindenes (206) towards heterocumulenes, involving additions to the zirconium-nitrogen bond, has also been studied.[606]



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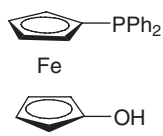

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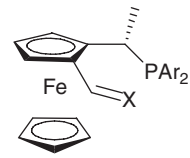
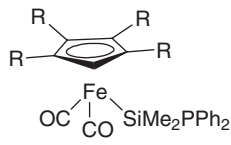
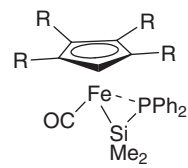


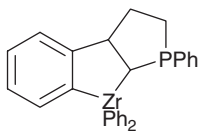
(201) Ar = Ph or 3,5-$(CF_3)_2C_6H_3$



(202) R = H or Me



(203) R= H or Me



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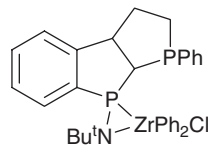

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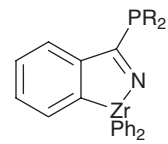
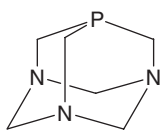


(206)

The use of tertiary phosphines as ligands in a variety of metal ion-catalysed organic reactions has been reviewed.[607] A review of the ligand properties of 2-pyridylphosphines has also appeared.[608] Combinations of triphenylphosphine with aluminium tribromide[609] and titanium tetrachloride[610] have found use as reagents for the reduction of 1,2-dicarbonyl compounds and reductive Claisen-type condensations, respectively. The application of phosphine ligands in homogeneous and related supported catalyst systems continues to generate much interest. Homogeneous catalyst systems based on water-soluble phosphines have been reviewed.[611] A procedure for the selective preparation of tri-, di-, and mono-sulfonated triarylphosphines has been developed, based on a low temperature sulfonation of arylphosphines bearing a range of simple electron-donating substituents, e.g., Me or OMe.[612] Salts of phosphinoarylsulfonates with guanidinium[613] and chiral quaternary ammonium cations have been characterised.[614] The cage-opening reaction of the triazaphosphaadamantane (207) with acetic anhydride to give the water-soluble phosphine (208) has been revisited, the latter (and its oxide) having now been fully characterised both in

solution and in the solid state. The phosphine has a molar solubility in water of 7.4 M, some four times the solubility of the triply sulfonated triphenylphosphine.[615] A series of ω-phosphinoalkylsulphonic acid salts, e.g., $Ph_2P(CH_2)_2S(CH_2)_nSO_3Na$ (n=2 or 3) also have high aqueous solubilities and are effective ligands in rhodium-catalysed hydroformylation reactions.[616] The drive for improved phosphine ligand-based catalyst systems has prompted work on the development of dendrimeric phosphines,[617,618] ionic liquid-soluble chiral diphosphines bearing imidazolium groups,[619] and BINAP-based chiral porous solids.[620] The reactions of tris(3-hydroxypropyl)phosphine with diisocyanatohexane have given a series of oligomeric phosphines for luminescent and stable nanocrystal quantum dots.[621] The reactions of *p*-hydroxyphenylphosphine and various substituted arylbis(hydroxymethyl)phosphines with heterocumulenes have also been explored.[622] Borane reduction of the carbonyl group of *o*-diphenylphosphino(N-2-hydroxyethyl)benzamide has given the related N-functionalised *o*-diphenylphosphinobenzylamine, from which new rhenium complexes have been prepared.[623] A new route to optically active phosphapalladocycles is afforded by the asymmetric exchange of enantiopure cyclopalladated chiral amines with prochiral phosphines.[624]

The *in-out* isomerism of phosphorus bridgehead cage compounds has been reviewed.[625] New phosphorus cage compounds have been isolated from the reactions of tetra-*t*-butyltetraphosphacubane with water in the presence of gallium(I) iodide.[626] The transformation of the stannylphosphine $P(SnMe_3)_3$ into the P-Sn cage system $P_4(SnMe_2)_6$ has also been studied.[627] The reactions of the phosphines Me_3MPMe_2 (M=Si or Sn) with fluoroarenes, which proceed with displacement of fluorine and introduction of the Me_2P moiety, have now been applied to π-complexed fluoroarenes[628] and various fluoroquinolines.[629] A new nickel-catalysed coupling reaction between phosphines of the type Ph_2PCF_2Br with the silylphosphines R_2PSiMe_3 provides a route to the unsymmetrical difluoromethylene-bridged diphosphines $Ph_2PCF_2PR_2$.[630]



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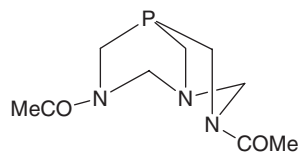

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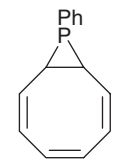
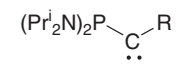


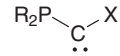
(209)

The conversion of free and $Cr(CO)_5$-complexed 2-vinylphosphiranes into 3-phospholenes has now been studied using density functional theory. It is concluded that this rearrangement has much in common with the vinylcyclopropane-cyclopentene rearrangement, a pericyclic [1,3]-sigmatropic shift

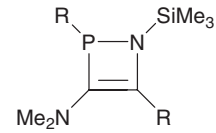
mechanism being implicated.[631] Theoretical and spectroscopic techniques have also been applied to the ability of the phosphirane ring in the fused system (209) to 'walk' around the cyclooctatrienyl ring system.[632] The nucleophilicity of tertiary phosphines has been compared to that of diaminocarbenes and related compounds in a series of $Cr(CO)_5$ complexes, using theoretical methods.[633] The reactivity of phosphinocarbenes has continued to attract attention. Bertrand's group has explored the effects of alkyl and aryl substituents at the carbene carbon on the stability of the (phosphino)(aryl)carbenes (210),[634,635] including studies of ground and excited state reactions.[636] Reactions of (phosphino)(amino)carbenes (211, X=NPr^i_2),[637] and (phosphino)(silyl)carbenes (211, X=Me_3Si) have also been studied by this group. The work on (phosphino)(silyl)carbenes includes a comparison of their reactions with aliphatic and aromatic aldehydes, giving phosphanyloxiranes and other products,[638,639] and a reaction with dimethyl cyanamide to give the azaphosphete (212), *via* the transient formation of nitrile, keteneimine and 1-aza-4λ^3-phosphabutadiene intermediates.[640] Further work has also appeared on the reactions of diphosphanylcarbenes (211, X=R_2P).[641,642] New supramolecular strategies have appeared for the assembly of bidentate phosphine ligands. Thus, 6-phosphino-substituted 2-pyridones self-assemble in the presence of a metal ion to give the hydrogen-bonded diphosphine (213),[643] and zinc-complexed tetraarylporphyrins bearing a single diorganophosphito substituent in one of the aryl groups assemble with a series of pyridylphosphines *via* coordination of the pyridine nitrogen to the zinc atom, giving new, unsymmetrical bidentate P-P′ ligand systems.[644] The tetraphosphine ligand (214) has been separated into its meso and racemic forms, each of which has been converted into the related tetrasulfide.[645] Reviews have appeared of the use of achiral and meso ligands to convey asymmetry in enantioselective catalysis[646] and of the asymmetric synthesis of functionalised phosphines containing stereogenic phosphorus centres, largely *via* cycloaddition reactions of functionalised vinyl compounds with simple phospholes coordinated to chiral palladium complexes.[647] Further evidence as to the non-existence of N→P donor-acceptor interactions in *peri*-(8-dialkylamino)-(1-diphenylphosphino)naphthalenes has been presented.[648,649] Tetraphenyldiphosphine is formed in the reaction of diphenylphosphine with indium(III) tris(cyclopentadienide).[650] The reactions of tri(2-thienyl)phosphine with hexachloroethane, 2-bromothiophene (in the presence of nickel(II) bromide), and 'chloramine T' have given, respectively, chlorotri(2-thienyl)phosphonium chloride, tetra(2-thienyl)phosphonium bromide, and the tosyliminophosphorane (215, X=S). Attempts to generate the homoleptic penta(2-thienyl)phosphorane by the reactions of these intermediates with 2-thienyllithium were unsuccessful. A similar lack of success attended the reaction of the related 2-furyl system (215, X=O) with 2-furyllithium. The corresponding penta(2-furyl- and 2-thienyl)-arsoranes were, however, obtained from the related tosyliminoarsoranes.[651]



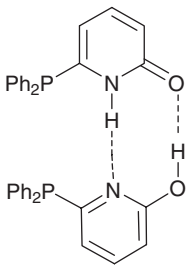
(210) R = Me, Bu^t, Mes or 2,6-$(CF_3)_2C_6H_3$



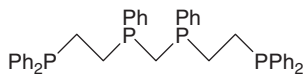
(211) R = Bu^t or R_2N



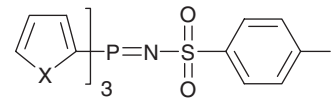
(212) R = Cy_2N



(213)



(214)

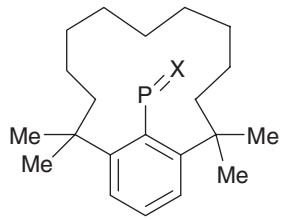


(215)

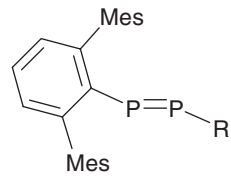
3 p_π-Bonded Phosphorus Compounds

Two major reviews of this area have appeared, one covering the chemistry of stable radicals derived from p_π-bonded phosphorus compounds[652] and a more general overview of the area and its possible future direction.[653] The chemistry of fluorine-containg phospha- and arsa-alkenes has also been reviewed.[654] Among new contributions from the theoretical chemistry community are a quantum chemical study and vibrational analysis of compounds containing carbon-phosphorus multiple bonds,[655] an investigation of one-bond phosphorus-phosphorus indirect nuclear spin–spin coupling tensors using density functional theory,[656] and estimates of the E=C σ- and π- bond energies for E=C, Si, Ge and P.[657] Density functional theory has been applied to gain an understanding of the gas-phase formation of the p_π-bonded, neutral hexaphosphorus species P_6, from $Cp^*_2P_6$.[658] The use of bulky groups for the kinetic stabilisation of diphosphenes and phosphaalkenes has seen further development, examples of new stable systems including the metacyclophanes (216),[659] the diphosphenes (217),[660] (218),[661] (219),[662](220)[663] and (221), together with related phosphaalkenes.[664,665] A diphosphene having two silyl substituents has been isolated from the reaction of a silyldichlorophosphine with sodium.[666] Studies of the reactivity of diphosphenes towards transition metal ions have continued. The reactions of bis(supermesityl)diphosphene and the bis(perfluoroalkylaryl)diphosphene (222) with a ruthenium carbonyl complex have been studied.[667,668] Diphenyldiphosphene, coordinated to a tungsten carbonyl acceptor, has been shown to undergo addition of N,N-dimethylcyanamide to the P=P bond.[669]

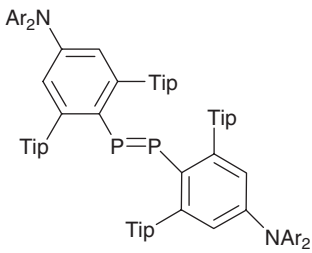
Treatment of the diphosphenium salt (223) with lithium diisopropylamide results in a high yield conversion into the diphosphirane (224), alkylation of which gives a diphosphiranium salt.[670] EPR techniques have been used to study the products of sodium reduction of the bis(diphosphene) (225) and related phosphaalkenes.[671]

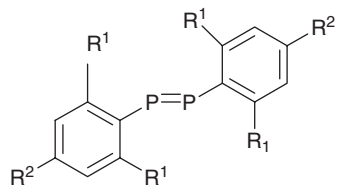


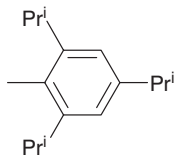
(216) X = PMes* or C═PMes*



(217) R = Mes* or Ph

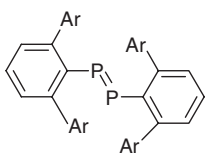




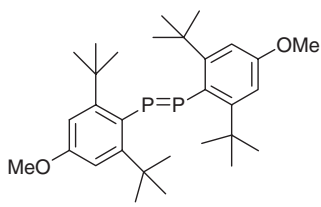
(218) Tip = 

Ar = *p*-$Me_2NC_6H_4$

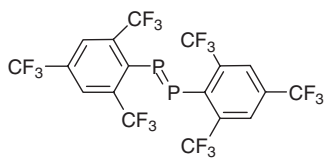
(219) R^1 = $CH(SiMe_3)_2$; R^2 = $CH(SiMe_3)_2$ or $C(SiMe_3)_3$



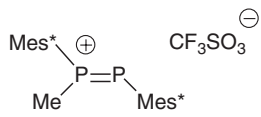
(220) Ar = o-$MeOC_6H_4$



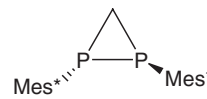
(221)



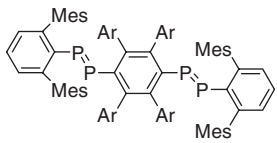
(222)



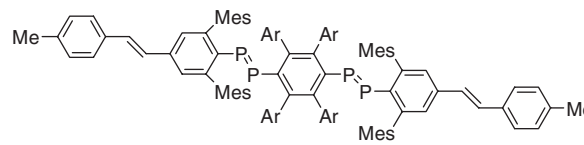
(223)



(224)



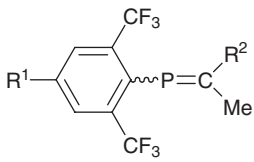
(225) Ar = *p*-Bu^{t}C$_6$H$_4$



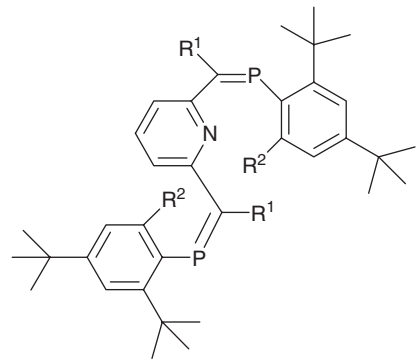
(226)

The synthesis of conjugated polymers of the poly(*p*-phenylenevinylene) type involving diphosphene and phosphaalkene units in the polymer backbone has started to attract interest. Routes to oligomeric systems, e.g., (226),[672] and related polymeric systems,[673,674] including a fluorescent poly(*p*-phenylenephosphaalkene) system[675] have been developed. A convenient route to the new isolable phosphaalkenes (227) is afforded by the base-induced rearrangement of secondary vinylphosphines.[676] Subtle differences have been noted in the ability of the 2,4,6-tri-*t*-butylphenyl and 2,4-di-*t*-butyl-6-methylphenyl groups to stabilise the P=C bond of various diphosphaalkenes of the type (228).[677] Routes to a series of diphosphathienoquinones (229)[678] and the P-metallophosphaalkene (230) (together with the corresponding arsa-and stibaalkenes)[679] have also been developed. New P=C bonded cage isomers derived from hexaphospha-pentaprismane, $P_6C_4{}^tBu_4$ have been obtained by *uv*-irradiation or protonation of the parent system[680] and the stability of a C_{2v}-symmetric P=C bonded tetraphosphabarbaralane system has been assessed by theoretical methods.[681] Studies of the reactivity of phosphaalkene systems have also continued to attract attention. An *ab-initio* study of the Diels-Alder addition of phosphaethene with 1,3-dienes reveals asynchronous transition structures, with activation energies that are lower than that of the parent ethene-butadiene reaction, even though these reactions have similar exothermicities.[682] The substituent effect of the phosphaalkenyl group has been assessed in the series (231) by analysis of linear free energy relationships which indicate that the (*E*)-Mes*P=CH group is a weak electron donor with a predominantly inductive effect on the linked benzene ring. In this respect, the P=C bond is remarkably similar to the C=C bond.[683] Experimental and theoretical studies on the conjugation of the P=C bond with a cyclopropyl group also indicate great similarity between P=C and C=C bonds.[684] Further studies of

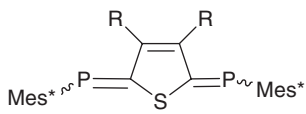
the reactivity of the phosphaalkenes $RP{=}C(NMe_2)_2$, having inverted polarisation of the P=C bond, have also appeared.[685,686] The first polymerisation of a phosphaalkene under either free radical or anionic initiation to give a poly(methylenephosphine) has been reported.[687] Phosphaalkenes have been shown to trap dichlorosilylene (liberated from trichlorosilyltrimethylgermane) by double addition to the P=C bond to form 2-phospha-1,3-diseletanes (232),[688] and reactions of this type have also been reviewed.[689] Considerable interest has been shown in the chemistry of 2-phosphaalkenyllithium and -Grignard reagents. A theoretical study of these compounds has addressed factors affecting their E-Z ratio.[690] Phosphaalkenyllithium reagents have been used in the synthesis of the 1,4-diphosphafulvene (233) *via* the dimerisation of an intermediate 1-phosphaallene[691] The methanesulfanyl-functionalised reagent (234) undergoes oxidative coupling with copper(II) chloride and oxygen to form the 1,4-diphosphabutadiene (235).[692] Lithiation of the 2-bromo-1-phosphaalkene (236) results in an isomerisation to give the phospha-2-propenyllithium reagent (237), subsequently transformed into the bis(phosphaalkene) (238) by copper(II)-mediated coupling.[693] A similar pattern of reactivity is shown by the corresponding phosphaalkenyl Grignard reagents. With aldehydes, β-phosphaallylic alcohols, e.g., (239), are formed, and their reactivity has also been explored.[694] New phosphaalkenes and new heterocyclic and cage compounds have been isolated from the reactions of phosphaalkenyl Grignard reagents with halides of main groups 13,14 and 15[695,696] and also with an iridium(I) halide.[697] Phosphaalkenyllithium and -Grignard reagents have also found use in the synthesis of new 1,3-diphosphapropenes, e.g., (240),[698,699] and the 1,3-diphosphaallyllithium complex (241) in which the lithium ion is located asymmetrically.[700] Further work on related 1-aza-3-phosphaallyllithium complexes has also been reported.[701] Treatment of the phosphaalkene (242) with potassium *t*-butoxide has given the cyclopropylidenephosphaallene (243).[702] Kinetically stabilised 1-phosphaalkenes have been shown to undergo a topochemical [2+2] dimerisation on heating in the solid state to form either diphosphanylidenecyclobutanes or 2,4-dimethylene-1,3-diphosphacyclobutanes.[703] The electronic properties of the phosphaarsaallene Mes*P=C=AsMes* (and the related diarsaallene) have been studied using UV photoelectron spectroscopy and theoretical methods.[704] Theoretical studies have also been reported for the 1,4-diphosphabuta-1,3-diene[705] and 2,3-diphosphabuta-1,3-diene[706,707] systems. The diphosphabutadiene (244) has been shown to undergo an unusual [2+4] cyclodimerisation to form (245).[708] The diphosphinidenecyclobutenes (246) continue to attract interest as diphosphabutadiene ligands for transition metal ions and related catalyst systems.[709,710] Metal complexes of 1,4-diphosphabutadienes,[711] 2,3-diphosphabutadienes,[712] and 1-phospha-buta-1,3-dienes[713] have also been investigated.



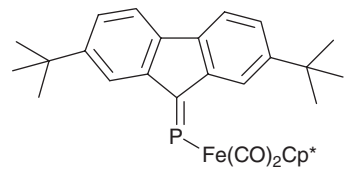
(227) R^1 = H or CF_3; R^2 = Me or Ph



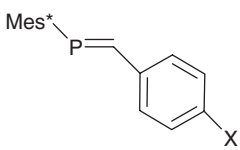
(228) R^1 = H or Bu^t; R^2 = Me or Bu^t



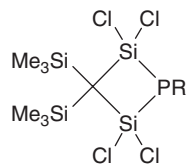
(229) R = H or Br



(230)



(231) X = Br, CHO, COOH, CN, $SiMe_3$ or $SnMe_3$



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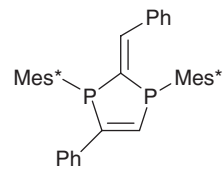

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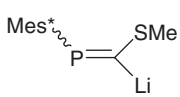

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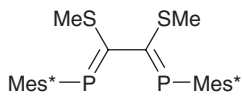

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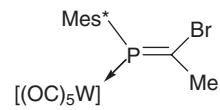

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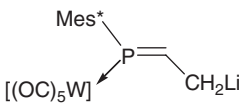

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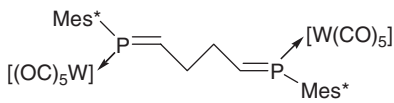

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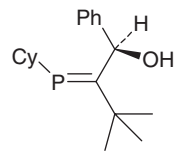

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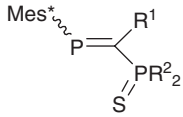
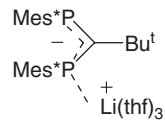


(240) R^1 = Cl or Me; R^2 = Ph or NPr^i_2



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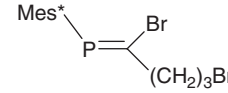

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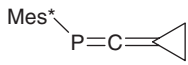

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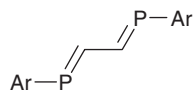

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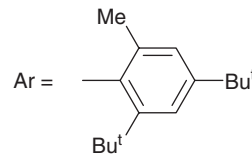
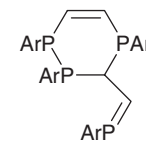
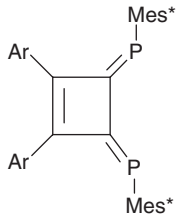




(245)

Interest in the chemistry of phosphaalkynes has continued, although perhaps at a slightly lower level than in recent years. Theoretical studies include consideration of the gas-phase acidities of HC≡P, $CH_3C{\equiv}P$ (and the related arsaalkynes),[714] isomerism in the $FCH_2C{\equiv}P$ system,[715] and calculation of the indirect nuclear spin–spin coupling constants $^1J(^{31}P,^{13}C)$.[716] A review has appeared of efforts to prepare isophosphaalkynes, R–P≡C, still an elusive class of compounds.[717] The first diphosphaalkyne (247) has been prepared and structurally characterised, together with studies of its interactions with transition metals.[718] Diphosphacyclobutenes (248) have been obtained by treatment of the phosphaalkyne Mes*C≡P with a 0.5 mol equivalent of an alkyllithium reagent.[719] The 2*H*-phosphasilirene (249) has been obtained from the reaction of the phosphaalkyne $Bu^tC{\equiv}P$ with a sterically crowded silylene,[720] and the cyclic zircona-thia-phosphacyclobutene (250) is formed from the reaction of a phosphaalkyne-zirconocene complex with triphenylphosphine sulfide.[721] Radical additions to the triple bond of the phosphaalkyne Mes*C≡P have been studied by ESR techniques.[722] The gas-phase reaction of $Bu^tC{\equiv}P$ with B_4H_{10} has given a new *nido*- five vertex phosphacarborane cluster compound having an unusual ^{31}P NMR chemical shift of -500.5 ppm.[723] Interest has also continued in the cyclooligomerisation of phosphaalkynes in the presence of transition metals, with particular reference to the formation and reactions of coordinated diphosphacyclobutadienyl systems. Such ligands display electrophilic character in addition to their usual nucleophilicity.[724] New complexes of this type, (251), involving germanium(II), tin(II) and lead(II),[725,726] have been described, and other novel modes of coordination of phosphaalkynes have been reported.[727,728] The reactions of the phosphaalkyne Mes*C≡P with organolithium reagents, followed by alkylation with iodomethane, have given a series of stable 1,3-diphosphacyclobutane-2,4-diyl systems, e.g., (252),[729,730] and the reactivity of such diradicaloid rings towards the addition of electrons has also been investigated.[731]



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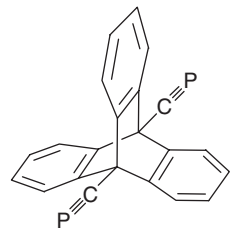
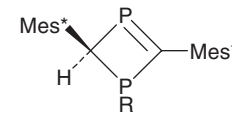
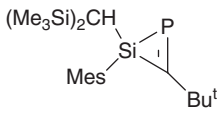


(247)



(248) R = Bu^n, Bu^s, Bu^t or Me



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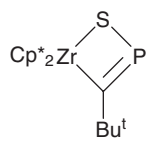

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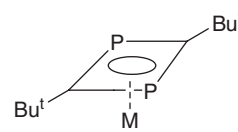

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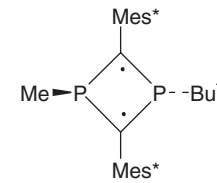
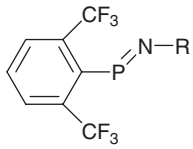


(252)

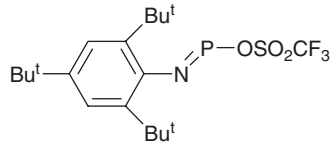
The chemistry of compounds involving p_π-bonds between phosphorus and elements other than carbon has also undergone further development, although only a small number of papers have appeared. New examples of iminophosphenes, RN=PAr, have been prepared (253), involving an electron-acceptor substituent at phosphorus and a donor group at nitrogen, and fully characterised by structural and photoelectron spectroscopic studies, the latter complementing the results of density functional calculations. The data suggest that in these molecules, the aryl group at phosphorus is almost orthogonal to the π(P=N) system, and hence its substituent effect is mainly steric.[732] Conjugation effects in less sterically crowded systems have also been considered by theoretical methods.[733] Evidence has been provided of a reversible iminophosphene-diazadiphosphetidine, monomer-dimer equilibrium involving the iminophosphene (254).[734] Treatment of (254) with chalcogenoimidazolines or 1,3-dimethyldiphenylurea gives Lewis acid-base complexes. Structural studies show that the chalcogen donor atom is associated with the phosphorus atom and also that coordination causes a significant displacement of the OTf anion, the resulting cations being best described as neutral ligand complexes of the phosphadiazonium cation (255).[735] The p_π-bonded species $CH_3OP{=}O\cdot^+$ has been studied in the gas phase by mass spectrometry.[736] Further work has also been reported on the chemistry of the 'phospha-Wittig' reagents, $ArP{=}PMe_3$. On treatment with *ortho*-quinones, the arylphosphinidene unit is converted into a 1,3,2-dioxaphospholane.[737] The arylphosphinidene unit also exchanges reversibly with an aryldichlorophosphine to form a new phospha-Wittig system, the position of equilibrium enabling an assessment of the steric pressures of bulky aryl substituents on the stability of such p_π-bonded molecules.[738] The nature and reactivity of 'free'phosphinidenes, RP**:**, and their more commonly encountered metal complexes, RP=[M], has continued to attract interest. An overview of phosphinidene chemistry has appeared.[739] Differences between singlet phenylphosphinidene and phenylnitrene in terms of

their reactivity towards ring expansion have been the subject of theoretical treatment.[740] The nature of the multiple bond between phosphorus and the metal in phosphinidene-titanium complexes has also received theoretical consideration.[741] The most common way of generating phosphinidene complexes continues to be the thermal decomposition of 7-phosphanorbornadiene tungsten carbonyl adducts, obtained from a Diels-Alder addition of an alkyne to a complexed phosphole. The ability of copper(I) chloride to initiate elimination of the phosphinidene complex has been investigated by theoretical methods, which indicate the involvement of a solvent-assisted mechanism.[742] The thermal elimination route has been used to generate the complexed bis(phosphinidene) (256), subsequently trapped with diphenylacetylene to form the bis(phosphirene) (257). The electronic structure of (256) has been investigated by *ab initio* methods.[743] Phosphinidene-nickel[744] and –cobalt[745] complexes have also been trapped with alkynes to form phosphirenes. Other examples of trapping reactions of phosphinidene-metal complexes reported include reactions with alkenes to form phosphiranes,[746] including 1,4-diphosphaspiropentanes[747] and the phospha[7]triangulanes (258),[748] and also with the malonate ion[749] and azulenes.[750] Weak Lewis base adducts of alkyl- and aryl-halides with terminal phosphinidene complexes (formed by thermolysis of azaphosphirene complexes) are involved as intermediates in reactions with benzyl bromide, 2-bromopyridine and bromobenzene, the overall course of the reaction depending on the nature of the organic halide. With benzyl bromide, insertion of phosphorus into the carbon-bromine bond occurs to give a metal-complexed phosphinous bromide whereas with 2bromopyridine, a halophosphine complex arising from insertion into HBr was isolated. With bromobenzene, the 2,3-dihydro-1,2,3-azadiphosphete complex (259) is formed.[751] Among new terminal phosphinidene metal complexes described are those involving titanium,[752] vanadium,[753] chromium,[754] cobalt, rhodium and iridium,[755,756] and iron, ruthenium and osmium.[757,758] Also reported are niobium complexes of diorganophosphinophosphinidenes, $R_2P–P:$,[759] and a molybdenum complex in which an arylphosphinidene acts as a ten-electron donor.[760] The stabilisation of phosphenium cations, $R_2P:^+$, and other low coordination number phosphorus(III) species, by coordination to phosphorus has continued to be an active topic. Two reviews have been published[761,762] and new complexes involving nitrogen-[763] and phosphorus-[764,765] donor ligands have been prepared and characterised. A simple route to stable complexes (260) of the simple cations P^+ (and As^+) with the chelating diphosphine *diphos* has been described[766] and a series of air-and water-stable tertiary phosphine complexes of arsenium cations, $R_2As:^+$, has been prepared.[767] The reactivity of coordination-stabilised cyclic triphosphenium cations similar to (260), involving five-, six- and seven-membered rings, towards methylation at the cationic phosphorus has been investigated.[768] Gas-phase reactions of phosphenium ions with *cis*- and *trans*-1,2-diaminocyclohexanes have been studied using mass spectrometric techniques[769] and the reactions of the diphenylphosphenium cation with glycals have given a series of phosphonylated sugars.[770] Previously unknown silylene-phosphenium cations, e.g., (261), are likely intermediates in the reactions of

diaminophosphenium ions with singlet silylenes, which result in the formation of chlorosilyldiaminophosphines.[771] Transition metal complexes of phosphenium ligands have been the subject of a review.[772]



(253) R = Bu^t or NMe_2



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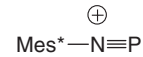

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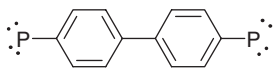

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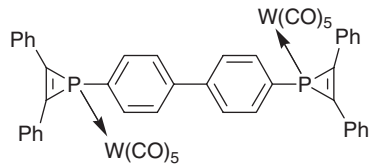

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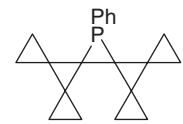

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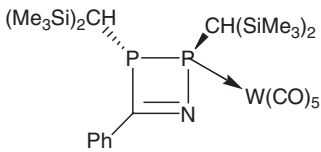

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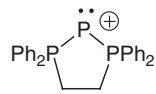

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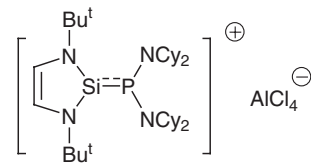
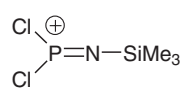


(261)

Although strictly outside the remit of this chapter, it is appropriate to note continued activity in the chemistry of $\sigma^3\lambda^5$-p_π -bonded phosphorus compounds that do not possess a lone pair of electrons at phosphorus. A monomeric metaphosphonate species (262, X=O) has been stabilised by coordination (*via* the P=O bond),[773] and Harger's group has provided evidence of the intermediacy of metathiophosphonates (262, X=S) in the reactions of phosphonamidothioic acids with alcohols.[774] The cation (263) has been stabilised by coordination at phosphorus with 4-dimethylaminopyridine[775] and the reactivity of bis(methylene)phosphoranes (264) and related phosphoranylidene carbenoids has been investigated.[776]

(262) R = alkyl or aryl



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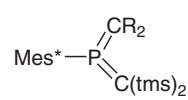


(264)

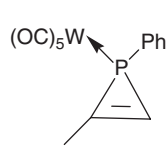
4 Phosphirenes, Phospholes and Phosphinines

Phosphirene chemistry has continued to generate interest over the past two years. The *exo-endo* preferences of double bonds in the tautomeric three-membered ring systems (265), (266) and (267) have received theoretical consideration, and a comparison with related carbon and nitrogen ring systems has been made. The preference may be viewed as a composite of substituent and ring strain effects. The low strain 2*H*-phosphirenes (267) favour endocyclic unsaturation.[777] Treatment of the 1*H*-phosphirene complex (268) with a stable silylene results in the initial formation of the 2-phospha-4-silabicyclo[1,1,0]butane (269) as a reactive intermediate, which subsequently rearranges in the presence of further silylene to give the first isolable 2,3-dihydro-1,3-phosphasilete system (270), and other phosphasiletes.[778] Gas-phase electron ionisation of the chloro-1*H*-phosphirene (271) yields the phosphirenylium cation (272). Mass spectrometric techniques have been used to probe the reactions of (272) with nucleophiles and dienes.[779] Phosphenium cations, $R_2P{:}^+$, are believed to be formed as intermediates in the exchange reactions of the phosphirenium salt (273) with alkynes, to give new phosphirenium salts, e.g., (274).[780] The 2-(phosphirenyl)ethylphosphinidene (275) (generated by thermolysis of a related 2-(phosphirenyl)ethylphosphole in the presence of dimethyl acetylenedicarboxylate) undergoes a self-condensation to give the 2,4-diphosphabicyclobutane (276).[781] The reactivity of the iridaphosphirene system (277) towards electrophiles has been studied, resulting in quaternization at phosphorus to give related iridaphosphirenium salts.[782] The reactions of the 2*H*-azaphosphirene complexes (278) have also attracted further attention. When the complex (278, $R{=}CH(SiMe_3)_2$) is heated in carbon tetrachloride, the chlorophosphine complex (279) is formed.[783] Thermolysis of (278, $R{=}CH(SiMe_3)_2$) in *o*-xylene results in the formation of the 2,3-dihydro-1,2,3-azadiphosphete complex (259) and other products, *via* the intermediate formation of a phosphinidene.[784] The generation of phosphinidene intermediates by thermolysis of 2*H*-azaphosphirene complexes (or 7-phosphanorbornadiene complexes) and subsequent reactions with alkynes and other reagents has provided routes to a variety of heterocyclic compounds, including 2*H*-1,2-azaphospholes,[785,786] 2*H*-1,3,2-diazaphospholes,[787] Δ^3-1,3,5-oxazaphospholenes and 2*H*-1,4,2-diazaphospholes.[788]

(265)

(266)

(267)



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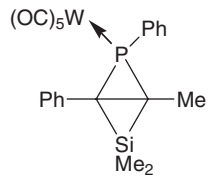

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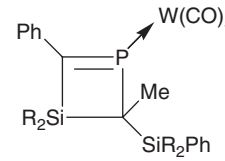

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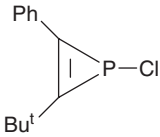

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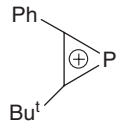

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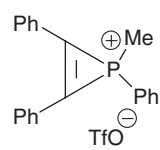

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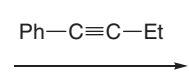

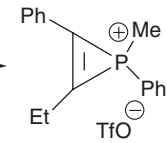

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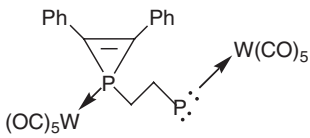

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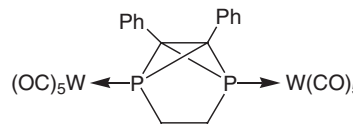

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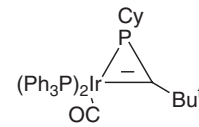

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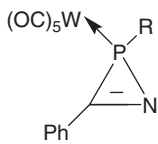

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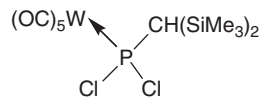
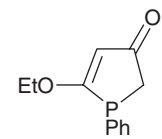


(279)

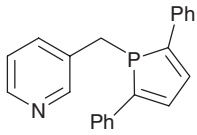


(280)

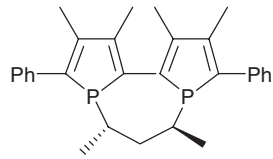
The chemistry of phospholes and related phospholide anion complexes remains a very active area, which also continues to attract the attentions of the theoretical community. Among recent theoretical contributions are a consideration of the stability, structure and bonding in lithium- and beryllium-pentaphospholide systems,[789] the aromaticity of the pentaphospholide anion (and its arsenic analogue) as probed by ring currents,[790] the remarkable influence of fluorine-substitution (either at phosphorus or at a ring carbon) on the electronic and thermochemical properties of phospholes,[791] and the effects of methyl and vinyl substitution at various positions on the geometries, relative stabilities and Diels-Alder reactivities of phospholes.[792] An *ab initio* approach has been used to reinterprete some spectral and thermochemical properties of 1H-phospholes.[793] The synthesis and reactivity of phospholes of reduced

pyramidality as a result of bulky trialkylphenyl substitution at phosphorus has been reviewed.[794] Mathey's group has shown that the electrochemical reduction of phosphole-pentacarbonyltungsten complexes affords the free phospholes in good yield, and this approach has been used in the synthesis of the 4,5-dihydrophosphole (280).[795] The P-pyridinomethylphosphole (281) has been obtained from the reaction of the 2,5-diphenylphospholide anion with 2-chloromethylpyridine.[796] This approach has also been used to prepare a range of phospholes bearing chiral substituents at phosphorus, subsequently used to generate chiral phosphinidine- and phosphaferrocene-complexes by established general procedures.[797] Asymmetric alkylation of the 3,4-dimethyl-5-phenyl-2,2′-biphospholyl dianion with a chiral pentane ditosylate has given the chirally flexible 2,2′-biphosphole (282) as a mixture of three diastereoisomers. By complexation with Pd(II), a chirality control occurs to give an enantiopure complex.[798] The electronic properties of homo- and hetero-oligomers and -polymers involving phosphole rings has continued to attract interest, and a review of their chemistry has appeared.[799] New alternating α,α-thiophene-phosphole oligomers up to seven rings in length have been prepared, the HOMO-LUMO gap decreasing as the length of the conjugated system increases. Conversion of the phosphole unit into the related phosphole sulfide has a major effect on the electronic properties of the system,[800] and this work has led to the first example of the use of organophosphorus-based materials in light-emitting diodes.[801] A route to the dibenzophosphole oxide-arylene polymer system (283) has been developed, these materials behaving as extended π-conjugated polymers in UV-visible absorption spectroscopy, and exhibiting green-blue fluorescence with high quantum yields.[802] A one-pot route to 1,1′-biphospholes bearing phenyl or thienyl substituents at the 2,2′ and 5,5′ positions, e.g., (284), has been described, enabling a study of the ability of the σ-P–P skeleton to connect the π-chromophores. It was established that such through-bond interactions result in a lowering of the optical HOMO-LUMO gap of the molecule, and that oxidation at phosphorus leads to low optical band gap electroactive materials.[803] The reactions of pentafluorophenylphosphonite and -phosphinite esters with activated alkynes, followed by hydrolysis, yield benzophosphole oxides, e.g., (285).[804] Interest has continued in studies of the thermal isomerisation of 1*H*-phospholes to the 2*H*-isomers, and the Diels-Alder and related cycloaddition reactions of the latter. Keglevich's group has studied the rearrangement of slightly aromatic 1*H*-phospholes bearing a 2,4,6-trialkylphenyl substituent at phosphorus and subsequent [4+2]-cycloaddition reactions with alkynes and maleic anhydride, giving new 1-phosphanorbornadienes, e.g., (286), and other products.[805,806] Related reactions of a 1,1′-bis(phospholyl)ferrocene have given the chiral chelating diphosphine (287) as a mixture of diastereoisomers, subsequently separated and resolved.[807] Mathey's group has described hetero-Diels-Alder reactions of transient 2*H*-phospholes with aldehydes, which lead to the adducts (288) as a mixture of isomers.[808] Dimerisation of 1*H*-, 2*H*- and 3*H*-phospholes through [4+2] cycloaddition reactions have been studied by density functional theory, and compared to the related dimerisation of cyclopentadiene.[809] Treatment of

the [4+2]-dimer (289) of 2,5-diphenyl-5*H*-phosphole with iodomethane gives a monophosphonium salt, which, with thallous ethoxide, is converted into the new chelating bis(phospholene), (290) *via* cleavage of the P–P bond.[810] New tricyclic phosphines, e.g., (291), have been obtained *via* intramolecular Diels-Alder reactions of phospholes bearing an allyloxy, allylamino or 3-buten-1-yl substituent at phosphorus.[811] The coordination chemistry of phospholes bearing 2-pyridyl groups in positions 2 and 5 of the phosphole ring has attracted some attention, the formation and reactivity of various palladium[812,813] and ruthenium[814] complexes having been studied. The dialkylaminomethyl(phospholyl)ferrocene (292) has been prepared, this representing a new class of chelating 1,2-disubstituted ferrocene ligand.[815] Metal complexes of phospholide anions have continued to attract interest. Among new chiral phosphaferrocenes described are the phosphaferrocene-oxazoline (293),[816] a phosphaferrocenyl analogue of tamoxifen,[817] and the 1,1′-diphospha[4]ferrocenophane (294).[818] Stereochemical aspects of phosphaferrocenes have seen further study, a 1,1′-diphosphaferrocene-2-carboxaldehyde having been resolved and its absolute configuration determined.[819] The atropisomeric chirality of phosphametallocenes bearing two menthyl substituents in each ring has been investigated by variable temperature NMR techniques.[820] Among investigations of the general reactivity of phosphametallocenes are studies of the titanium-mediated reductive coupling of chiral formylphosphaferrocenes to give bis(phosphaferrocenyl)-substituted ethenes and pinacols,[821] the acylation of 1,1′-diphosphaferrocene with acyl trifluoroacetates,[822]and the oxidation of phosphaferrocenes to form the related phosphaferricinium cations.[823,824] Palladium[825] and gallium[826] complexes of diphosphaferrocenes, involving σ-donation from phosphorus, have also been prepared. Phosphametallocenes in which the phospholide anion is π-bonded to a transition metal other than iron have also generated much interest, reports having appeared concerning the chemistry of phosphatitanocenes,[827,828] phosphazirconocenes,[829] phospharuthenocenes,[830,831] and a phosphacymantrene.[832] Main group phospholide systems have also been reported, involving sodium, potassium, rubidium and caesium,[833] and also phospholides involving the f-block elements samarium and thulium.[834,835] Various σ-bonded bromoborane complexes of a phosphaferrocene have been characterised.[836] The coordination chemistry of the phosphoniobenzophospholides (295) has received further study, the benzophospholide phosphorus being able to form both σ- and π-coordinate links to transition metal ions such as copper,[837] manganese and rhenium,[838] and chromium.[839] Further work on the chemistry of the 3,5-di-*t*-butyl-1,2,4-triphospholide anion (296) has been reported. Scandium salts of this phospholide have been characterised,[840] and various transition metal complexes have been described.[841,842] An improved route to (296) has also led to the isolation of the cationic species *nido*-[3,5-Bu^t_2-1,2,4-C_2P_3]$^+$, isoelectronic with $[C_5R_5]^+$, but having a non-planar, square-based pyramidal structure.[843] Complexes of the pentaphospholide anion have received further study[844] and comment.[845]



(281)



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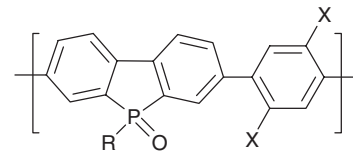
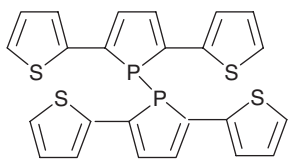


(283) R = Pr^n, $C_6H_{13}{}^n$ or $C_9H_{19}{}^n$
X = $OC_6H_{13}{}^n$ or H



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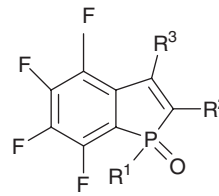
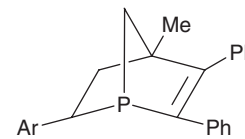
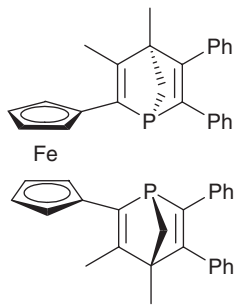


(285) R^1 = EtO or C_6F_5;
R^2 = MeO_2C or Ph;
R^3 = MeO_2C or CN



(286) Ar = 2,4,6-$Pr^i{}_3C_6H_2$
or 2-Me-4, 6-$Pr^i{}_2C_6H_2$



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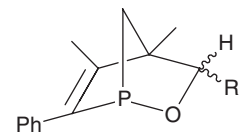

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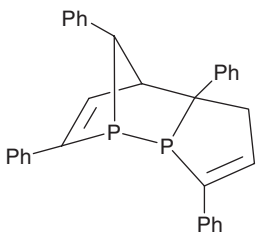

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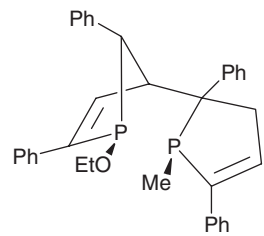

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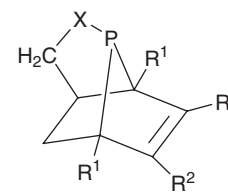
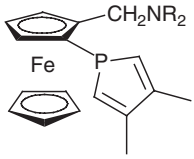
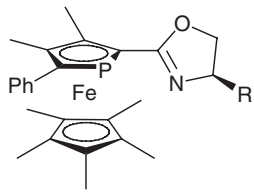


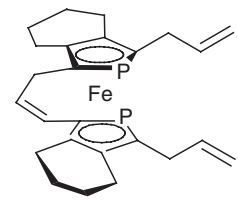
(291) R^1 = H or Ph;
R^2 = H or Me;
X = O. NR or CH_2



(292)



(293) R = Ph or Pr^{i}



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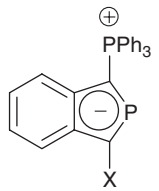
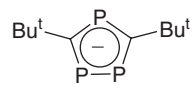
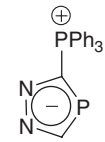


(295) X = H or PPh_2

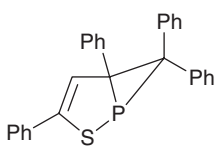


(296)



(297)

Phospholes bearing additional heteroatoms other than phosphorus have also been the subject of further study. Cycloaddition reactions of heterophospholes have received a theoretical treatment[846] and these reactions have also been reviewed.[847] Improvements in the synthesis of fused 1,3-azaphospholes *via* the reactions of N-alkyl-isoquinolinium salts with phosphorus trichloride have been described and their reactivity towards cycloaddition studied.[848] New fused 1,3-azaphospholes derived from N-alkylquinolinium salts,[849] and new 2*H*-1,2,3-diazaphospholes,[850] have also been reported. The phosphonio-1,2,4-diazaphospholide (297) has been characterised[851] and further studies of the coordination chemistry of 1*H*-1,3-benzazaphospholes, leading to complexes of the related benzazaphospholide anion, have been described.[852] Routes to 1,3,4-thia- and -selena-diphospholes[853] and 1,3,4-thiazaphospholes[854] have been developed. Two groups have reported studies of cycloaddition reactions of 1,2-thiaphospholes.[855,856] In the free state, the 1,2-thiaphospholo[a]phosphirane (298) undergoes a cycloreversion reaction and a fragmentation to form a butadienyl hydrosulfide on heating to 120°C. However, thermolysis of metal complexes of (298) results in a ring-expansion reaction to form the dihydrophosphaisoindole (299).[857] The chemistry and complexing ability of 1,2,4-thiadiphospholes and their selenium and tellurium analogues (300) have received further study.[858,859]



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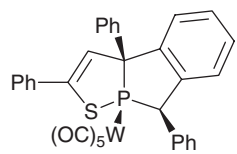

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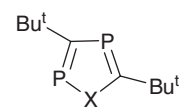
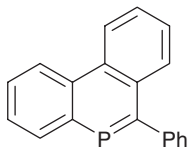


(300) X = S, Se or Te

The chemistry of the potentially aromatic λ^3-phosphinine system (also known as phosphabenzene) has continued to be a very active area. Not surprisingly, several theoretical contributions have appeared, relating to the extent of aromaticity,[860] the relative stabilities of various valence bond isomers,[861,862] the possible existence of Möbius phosphabenzene,[863] and a study of the Diels-Alder reactions of azaphosphabenzenes.[864] Theoretical and experimental techniques have also been applied to a consideration of the electronic properties of a 2,2′-biphosphinine ligand,[865] and the σ-donating and π-accepting properties of phosphinines bearing *ortho*-trimethylsilyl substituents.[866] Reactions involving phosphabenzyne-zirconocene complexes have been the subject of a review.[867] A seven step route has been developed to the fused phosphinine (301),[868] and the 1,4-phosphaboratabenzene system (302) has been characterised as a π-bonded ruthenium complex.[869] 2,4,6-Triphenylphosphinine has been shown to undergo a cofacial oxidative coupling in the presence of a copper(I) perchlorate complex to form a new C_2-symmetric cage compound.[870] Cycloaddition of benzyne to various 2,4,6-trisubstituted phosphinines has given a series of phosphabarrelenes (303), the rhodium complexes of which are highly active catalysts for the isomerisation-free hydroformylation of internal alkenes.[871] Further work has been reported on the reactions of phosphinines with nucleophiles, e.g., alkyllithium reagents, which lead initially to 1-R phosphahexadienyl anions, e.g., (304). The crystal structure of a lithium salt of (304, R=Me) has been determined, and theoretical studies suggest that the negative charge is largely localised on the α-carbons.[872] Treatment of related anions with hexachloroethane, followed by gallium trichloride, has given the 1-methylphosphinium salts (305), which readily add nucleophiles to form λ^5-phosphinines.[873] The coordination chemistry of phosphahexadienyl anions has also attracted interest.[874,875] The reactions of 1,3,5-triphosphabenzenes have also attracted further study. Reduction of 1,3,5-tris-(*t*-butyl)-phosphabenzene with $LiMH_4$ (M=Al or Ga) results in the formation of the triphosphabicyclo[3,1,0]hexane (306). Other bicyclic systems have been isolated from reactions of related complex hydrides.[876] Grignard[877] and organolithium reagents[878,879] undergo 1,4-additions to 1,3,5-tris-(*t*-butyl)-phosphabenzene, giving the anions (307). These give rise to 1,3-diphospholide anions on thermolysis, and can also be alkylated to give $1\lambda^5$,3,5-triphosphabenzenes. 1,3,5-Triphosphabenzenes undergo 1,3-dipolar cycloaddition reactions with nitrile oxides to form new condensed heterocyclic systems[880] and also add to terminal alkynes, giving phosphorus-carbon cage compounds.[881] Cycloaddition reactions of alkynes to 1,3,2-diazaphosphinines, followed by elimination of a nitrile, have been used in the synthesis of new ring-substituted phosphinines, including an extended silacalix-[3]-phosphinine macrocycle.[882,883] Related reactions with propargylphosphines have given new 1,2-azaphosphinines, e.g., (308).[884]



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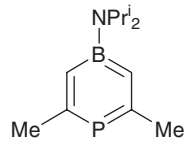

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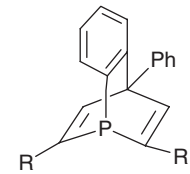
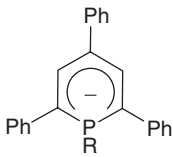


(303) R = Ph, Pr^i or 2,4-xylyl



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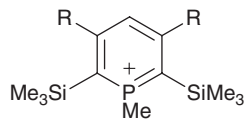
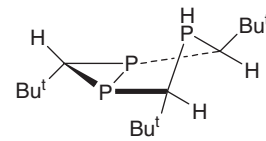


GaCl$_4^-$

(305) R = Ph or Me



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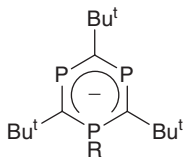
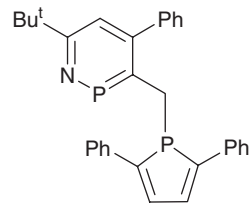
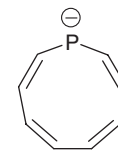


(307)



(308)



(309)

Finally, it is of considerable interest to note the results of a theoretical treatment of the extent to which nine-membered monocycles can be aromatic, and which concludes that the phosphonide anion (309), as yet unknown, favours planar C_{2v} symmetry.[885]

References

1. M.S. Balakrishna, P. Chandrasekaran and P.P. George, *Coord. Chem. Rev.*, 2003, **241**, 87.
2. J.-P. Majoral, A.-M. Caminade and V. Maraval, *Chem. Commun.*, 2002, 2929.
3. A.-M. Caminade and J.-P. Majoral, *Acc. Chem. Res.*, 2004, **37**, 341.
4. S. Sasaki, K. Sutoh, F. Murakami and M. Yoshifuji, *J. Am. Chem. Soc.*, 2002, **124**, 14830.
5. P. Wyatt, H. Ely, J. Charmant, B.J. Daniel and A. Kantacha, *Eur. J. Org. Chem.*, 2003, 4216.
6. H. Riihimäki, P. Suomalainen, H.K. Reinius, J. Suutari, S. Jääskeläinen, A.O.I. Krause, T.A. Pakkanen and J.T. Pursiainen, *J. Mol. Catal. A: Chem.*, 2003, **200**, 69.

7. H. Riihimäki, T. Kangas, P. Suomalainen, H.K. Reinius, S. Jääskeläinen, M. Haukka, A.O.I. Krause, T. A. Pakkanen and J.T. Pursiainen, *J. Mol. Catal. A: Chem*., 2003, **200**, 81.
8. O. Niyomura, M. Tokunaga, Y. Obora, T. Iwasawa and Y. Tsuji, *Angew. Chem. Int. Ed*., 2003, **42**, 1287.
9. Y. Ohzu, K. Goto and T. Kawashima, *Angew. Chem. Int. Ed*., 2003, **42**, 5714.
10. L. Baiget, M. Bouslikhane, J. Escudie, G.C. Nemes, I. Silaghi-Dumitrescu and L. Silaghi-Dumitrescu, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1949.
11. T.J. Malefetse, G.F. Swiegers, N.J. Coville and M.A. Fernandes, *Organometallics*, 2002, **21**, 2898.
12. M. Stradiotto, J. Cipot and R. McDonald, *J. Am. Chem. Soc*., 2003, **125**, 5618.
13. G. Canepa, C.D. Brandt and H. Werner, *Organometallics*, 2004, **23**, 1140.
14. L.R. Moore and K.H. Shaughnessy, *Org. Lett*., 2004, **6**, 225.
15. J.D. Palcic, P.N. Kapoor, D.M. Roddick and R.G. Peters, *Dalton Trans*., 2004, 1644.
16. E. de Wolf, E. Riccomagno, J.J.M. de Pater, B.-J. Deelman and G. van Koten, *J. Comb. Chem*., 2004, **6**, 363.
17. R.C. Smith and J.D. Protasiewicz, *Dalton Trans*., 2003, 4738.
18. M.K.W. Choi, H.S. He and P.H. Toy, *J. Org. Chem*., 2003, **68**, 9831.
19. (*a*) F. Speiser, P. Braunstein and L. Saussine, *Organometallics*, 2004, **23**, 2625; (*b*) F. Speiser, P. Braunstein and L. Saussine, *Organometallics*, 2004, **23**, 2633.
20. (*a*) H.-P. Chen, Y.-H. Liu, S.-M. Peng and S.-T. Liu, *Dalton Trans*., 2003, 1419; (*b*) H.-P. Chen, Y.-H. Liu, S.-M. Peng and S.-T. Liu, *Organometallics*, 2003, **22**, 4893.
21. Y. Fort and A.L. Rodriguez, *J. Org. Chem*., 2003, **68**, 4918.
22. B. Tao and G.C. Fu, *Angew. Chem. Int. Ed*., 2002, **41**, 3892.
23. R.N. Constantine, N. Kim and R.C. Bunt, *Org. Lett*., 2003, **5**, 2279.
24. T. Yamagishi, M. Ohnuki, T. Kiyooka, D. Masui, K. Sato and M. Yamaguchi, *Tetrahedron: Asymmetry*, 2003, **14**, 3275.
25. C. Réthoré, M. Fourmigué and N. Avarvari, *Chem. Commun*., 2004, 1384.
26. D. Liu, W. Tang and X. Zhang, *Org. Lett*., 2004, **6**, 513.
27. F. Speiser, P. Braunstein, L. Saussine and R. Welter, *Organometallics*, 2004, **23**, 2613.
28. F. Menges, M. Neuberger and A. Pfaltz, *Org. Lett*., 2002, **4**, 4713.
29. Z. Guan and W.J. Marshall, *Organometallics*, 2002, **21**, 3580.
30. W. Keim, S. Killat, C.F. Nobile, G.P. Suranna, U. Englert, R. Wang, S. Mecking and D.L. Schröder, *J. Organomet. Chem*., 2002, **662**, 150.
31. J.D. Masuda, P. Wei and D.W. Stephan, *Dalton Trans*., 2003, 3500.
32. N. Burford, M. D'eon, P.J. Ragogna, R. McDonald and M.J. Ferguson, *Inorg. Chem*., 2004, **43**, 734.
33. J.M. Malinoski and M. Brookhart, *Organometallics*, 2003, **22**, 5324.
34. J.S. Kim, A. Sen, I.A. Guzei, L.M. Liable-Sands and A.L. Rheingold, *J. Chem. Soc., Dalton Trans*., 2002, 4726.
35. J. Heinicke, M. Köhler, N. Peulecke, M. He, M.K. Kindermann, W. Keim and G. Fink, *Chem. Eur. J*., 2003, **9**, 6093.
36. W.-M. Dai, Y. Li, Y. Zhang, K.W. Lai and J. Wu, *Tetrahedron Lett*., 2004, **45**, 1999.
37. X. Morise, P. Braunstein and R. Welter, *C. R. Chimie*, 2003, **6**, 91.
38. R.A. Singer, N.J. Tom, H.N. Frost and W.M. Simon, *Tetrahedron Lett*., 2004 **45**, 4715.

39. A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen and M. Beller, *Chem. Commun.*, 2004, 38.
40. F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen and M. Beller, *Chem Eur. J.*, 2004, **10**, 2983.
41. A. Otero, F. Carrillo-Hermosilla, P. Terreros, T. Expósito, S. Rojas, J. Fernández-Baeza, A. Antiñolo and I. López-Solera, *Eur. J. Inorg. Chem.*, 2003, 3233.
42. O. Clot, Y. Akahori, C. Moorlag, D.B. Leznoff, M.O. Wolf, R.J. Batchelor, B.O. Patrick and M. Ishii, *Inorg. Chem.*, 2003, **42**, 2704.
43. F. Krech, B. Krauss, A. Zschunke and C. Mügge, *Z. Anorg. Allg. Chem.*, 2003, **629**, 1475.
44. D. Soulivong, D. Matt, J. Harrowfield and L. Toupet, *Aust. J. Chem.*, 2004 **57**, 157.
45. R. Shiozawa and K. Sakamoto, *Chem. Lett.*, 2003, **32**, 1024.
46. F. Carré, N. Devylder, S.G. Dutremez, C. Guérin, B.J.L. Henner, A. Jolivet and V. Tomberli, *Organometallics*, 2003, **22**, 2014.
47. D. Quintard, M. Keller and B. Breit, *Synthesis*, 2004, **905**.
48. M. Nishimura, M. Ueda and N. Miyaura, *Tetrahedron*, 2002, **58**, 5779.
49. R. Kreiter, R.J.M.K. Gebbink and G. van Koten, *Tetrahedron*, 2003**59**, 3989.
50. A.S. King, G. Ferguson, J.F. Britten and J.F. Valliant, *Inorg. Chem.*, 2004, **43**, 3507.
51. O. Crespo, M.C. Gimeno, P.G. Jones, A. Laguna, J.M. López-de-Luzuriaga, M. Monge, J.L. Pérez and M. Ramón, *Inorg. Chem.*, 2003, **42**, 2061.
52. Y.-J. Lee, J.-D. Lee, S.-J. Kim, S. Keum, J. Ko, I.-H. Suh, M. Cheong and S.O. Kang, *Organometallics*, 2004, **23**, 203.
53. T.E. Pickett, F.X. Roca and C.J. Richards, *J. Org. Chem.*, 2003, **68**, 2592.
54. H.L. Pederson and M. Johannsen, *J. Org. Chem.*, 2002, **67**, 7982.
55. J.F. Jensen and M. Johannsen, *Org. Lett.*, 2003, **5**, 3025.
56. J.W. Han, N. Tokunaga and T. Hayashi, *Helv. Chim. Acta*, 2002, **85**, 3848.
57. N. Kataoka, Q. Shelby, J.P. Stambuli and J.F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553.
58. F.X. Roca and C.J. Richards, *Chem. Commun.*, 2003, 3002.
59. O.G. Mancheño, J. Priego, S. Cabrera, R.G. Arrayás, T. Llamas and J.C. Carretero, *J. Org. Chem.*, 2003, **68**, 3679.
60. C. Metallinos, H. Szillat, N.J. Taylor and V. Snieckus, *Adv. Synth. Catal.*, 2003, **345**, 370.
61. R.C.J. Atkinson, V.C. Gibson, N.J. Long, A.J.P. White and D.J. Williams, *Organometallics*, 2004, **23**, 2744.
62. V.C. Gibson, N.J. Long, A.J.P. White, C.K. Williams, D.J. Williams, M. Fontani and P. Zanello, *J. C. S. Dalton Trans.*, 2002, 3280.
63. J. Kang, J.H. Lee and K.S. Im, *J. Mol. Catal.A: Chem.*, 2003, **196**, 55.
64. S. Nakamura, T. Fukuzumi and T. Toru, *Chirality*, 2004, **16**, 10.
65. P. Liptau, T. Seki, G. Kehr, A. Abele, R. Fröhlich, G. Erker and S. Grimme, *Organometallics*, 2003, **22**, 2226.
66. M. Lotz, G. Kramer and P. Knochel, *Chem. Commun.*, 2002, **9**, 2546.
67. (*a*) K. Tappe and P. Knochel, *Tetrahedron: Asymmetry*, 2004, **15**, 91; (*b*) M. Lotz, K. Polborn and P. Knochel, *Angew. Chem. Int. Ed.*, 2002, **41**, 4708.
68. I.R. Butler, M.G.B. Drew, A.G. Caballero, P. Gerner and C.H. Greenwell, *J. Organomet. Chem.*, 2003, **679**, 59.

69. X.P. Hu, H.L. Chen, H.C. Dai, X.Q. Hu and Z. Zheng, *Chin. Chem. Lett*., 2003, **14**, 1113.
70. L. Wang, W.H. Kwok, A.S.C. Chan, T. Tu, X. Hou and L. Dai, *Tetrahedron: Asymmetry*, 2003, **14**, 2291.
71. O.V. Gusev, A.M. Kalsin, P.V. Petrovskii, K.N. Lyssenko, Y.F. Oprunenko, C. Bianchini, A. Meli and W. Oberhauser, *Organometallics*, 2003, **22**, 913.
72. S.E. Gibson, H. Ibrahim, C. Pasquier and V.M. Swamy, *Tetrahedron: Asymmetry*, 2003, **14**, 1455.
73. S.E. Gibson, H. Ibrahim, C. Pasquier and V.M. Swamy, *Tetrahedron: Asymmetry*, 2004, **15**, 465.
74. C. Bolm, L. Xiao and M. Kesselgruber, *Org. Biomol. Chem*., 2003, **1**, 145.
75. C. Bolm, L. Xiao, L. Hintermann, T. Focken and G. Raabe, *Organometallics*, 2004, **23**, 2362.
76. T. Shibata, H. Tsuruta, H. Danjo and T. Imamoto, *J. Mol. Catal. A: Chem*., 2003, **196**, 117.
77. L. Qiu, J. Wu, S. Chan, T.T.-L. Au-Yeung, J.-X. Ji, R. Guo, C.-C. Pai, Z. Zhou, X. Li, Q.-H. Fan and A.S.C. Chan, *Proc. Nat. Acad. Sci. USA*, 2004, **101**, 5815.
78. J.I. van der Vlugt, J.M. Bonet, A.M. Mills, A.L. Spek and D. Vogt, *Tetrahedron Lett*., 2003, **44**, 4389.
79. J.I. van der Vlugt, M.M.P. Grutters, A.M. Mills, H. Kooijman, A.L. Spek and D. Vogt, *Eur. J. Inorg. Chem*., 2003, 4361.
80. A.M. Winter, K. Eichle, H.-G. Mack, S. Potuznik, H.A. Mayer and W.C. Kaska, *J. Organomet. Chem*., 2003, **682**, 149.
81. L. Fan, B.M. Foxman and O.V. Ozerov, *Organometallics*, 2004, **23**, 326.
82. Z. Freixa, M.S. Beentjes, G.D. Batema, C.B. Dieleman, G.P.F. van Strijdonk, J.N.H. Reek, P.C.J. Kamer, J. Fraanje, K. Goubitz and P.W.N.M. van Leeuwen, *Angew. Chem. Int. Ed*., 2003, **42**, 1284.
83. Y.-C. Yang and T.-Y. Luh, *J. Org. Chem*., 2003, **68**, 9870.
84. J.J. Becker and M.R. Gagné, *Organometallics*, 2003, **22**, 4984.
85. B. Dominguez, A. Zanotti-Gerosa and W. Hems, *Org. Lett*., 2004, **6**, 1927.
86. X.-W. Wu, K. Yuan, W. Sun, M.-J. Zhang and X.-L. Hou, *Tetrahedron: Asymmetry*, 2003, **14**, 107.
87. T. Focken, G. Raabe and C. Bolm, *Tetrahedron: Asymmetry*, 2004, **15**, 1693.
88. A.G. Sergeev, G.A. Artamkina and I.P. Beletskaya, *Tetrahedron Lett*., 2003, **44**, 4719.
89. D.J. Adams, D.J. Cole-Hamilton, D.A.J. Harding, E.G. Hope, P. Pogorzelec and A.M. Stuart, *Tetrahedron*, 2004, **60**, 4079.
90. R.P.J. Bronger, S.M. Silva, P.C.J. Kamer and P.W.N.M. van Leeuwen, *Chem. Commun*., 2002, 3044.
91. R.P.J. Bronger, J.P. Bermon, J. Herwig, P.C.J. Kamer and P.W.N.M. van Leeuwen, *Adv. Synth. Catal*., 2004, **346**, 789.
92. R.P.J. Bronger, S.M. Silva, P.C.J. Kamer and P.W.N.M. van Leeuwen, *Dalton Trans*., 2004, 1590.
93. R. Haigh, K.M.A. Malik and P.D. Newman, *Chem. Commun*., 2002, 2558.
94. K.M.A. Malik and P.D. Newman, *Dalton Trans*., 2003, 3516.
95. T. Misuta, T. Nakazono and K. Miyoshi, *Angew. Chem. Int. Ed*., 2002, **41**, 3897.
96. S. Yasuike, T. Kiharada, T. Tsuchiya and J. Kurita, *Chem. Pharm. Bull*., 2003, **51**, 1283.

97. K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen and M. Beller, *Tetrahedron Lett*., 2002, **43**, 4977.
98. Y. Chi and X. Zhang, *Tetrahedron Lett*., 2002, **43**, 4849.
99. U.M. Dzhemilev, A.G. Ibragimov, R.R. Gilyazev and L.O. Khafizova, *Tetrahedron*, 2004, **60**, 1281.
100. B. Hoge, C. Thösen, T. Herrmann and I. Pantenburg, *Inorg. Chem*., 2003, **42**, 3633.
101. K. Miqueu, J.-M. Sotiropoulos, G. Pfister-Guillouzo, V. Rudzevich, V. Romanenko and G. Bertrand, *Eur. J. Inorg. Chem*., 2004, 381.
102. M.T. Honaker, B.J. Sandefur, J.L. Hargett, A.L. McDaniel and R.N. Salvatore, *Tetrahedron Lett*., 2003, **44**, 8373.
103. M.T. Honaker and R.N. Salvatore, *Phosphorus, Sulfur, Silicon, Relat. Elem*., 2004, **179**, 277.
104. D.L. Fox, A.A. Robinson, J.B. Frank and R.N. Salvatore, *Tetrahedron Lett*., 2003, **44**, 7579.
105. J. Duran, D. Oliver, A. Polo, J. Real, J. Benet-Buchholz and X. Fontrodona, *Tetrahedron: Asymmetry*, 2003, **14**, 2529.
106. J. Duran, N. Brugat, A. Polo, C. Segura, J. Real, X. Fontrodona and J. Benet-Buchholz, *Organometallics*, 2003, **22**, 3432.
107. A. Dervisi, R.L. Jenkins, K.M.A. Malik, M.B. Hursthouse and S. Coles, *Dalton Trans*., 2003, 1133.
108. S. Burling, L.D. Field, B.A. Messerle, K.Q. Vuong and P. Turner, *Dalton Trans*., 2003, 4181.
109. S.A. Modin, P. Pinho and P.G. Andersson, *Adv. Synth. Catal*., 2004, **346**, 549.
110. T. Soeta, K. Nagai, H. Fujihara, M. Kuriyama and K. Tomioka, *J. Org. Chem*., 2003, **68**, 9723.
111. G. Ebeling, M.R. Meneghetti, F. Rominger and J. Dupont, *Organometallics*, 2002, **21**, 3221.
112. J.K.-P. Ng, G.-K. Tan, J.J. Vittal and P.-H. Leung, *Inorg. Chem*., 2003, **42**, 7674.
113. K. Matsuzaki, H. Kawaguchi, P. Voth, K. Noda, S. Itoh, H.D. Takagi, K. Kashiwabara and K. Tatsumi, *Inorg. Chem*., 2003, **42**, 5320.
114. I.V. Komarov, A. Spannenberg, J. Holz and A. Börner, *Chem. Commun*., 2003, 2240.
115. (*a*) L.-C. Liang, W.-Y. Lee and C.-H. Hung, *Inorg. Chem*., 2003, **42**, 5471; (*b*) L.-C. Liang, M.-H. Huang and C.-H. Hung, *Inorg. Chem*., 2004, **43**, 2166.
116. T. Mino, E. Komatsumoto, S. Nakadai, H. Toyoda, M. Sakamoto and T. Fujita, *J. Mol. Catal. A: Chem*., 2003, **196**, 13.
117. C.A. Busacca, D. Grossbach, R.C. So, E.M. O'Brien and E.M. Spinelli, *Org. Lett*., 2003, **5**, 595.
118. W.-H. Sun, Z. Li, H. Hu, B. Wu, H. Yang, N. Zhu, X. Leng and H. Wang, *New J. Chem*., 2002, **26**, 1474.
119. J.S.T. Gorman, V. Lynch, B.L. Pagenkopf and B. Young, *Tetrahedron Lett*., 2003, **44**, 5435.
120. A. Doppiu and A. Salzer, *Eur. J. Inorg. Chem*., 2004, 2244.
121. S. Ciruelos, A. Doppiu, U. Englert and A. Salzer, *J. Organomet. Chem*., 2002, **663**, 183.
122. V. Comte, J.P. Tranchier, F. Rose-Munch, E. Rose, D. Perrey, P. Richard and C. Moïse, *Eur. J. Inorg. Chem*., 2003, 1893.
123. M. Schnebel, I. Weidner, R. Wartchow and H. Butenschön, *Eur. J. Org. Chem*., 2003, 4363.

124. S. Bredeau, G. Altenhof, K. Kunz, S. Döring, S. Grimme, G. Kehr and G. Erker, *Organometallics*, 2004, **23**, 1836.
125. (*a*) M.P. Coles and P.B. Hitchcock, *Chem. Commun*., 2002, 2794; (*b*) J. Grundy, M.P. Coles and P.B. Hitchcock, *Dalton Trans*., 2003, 2573.
126. C. Bolm, K. Wenz and G. Raabe, *J. Organomet. Chem*., 2002, **662**, 23.
127. S.E. Martin, M. Bonaterra and R.A. Rossi, *J. Organomet. Chem*., 2002 **664**, 223.
128. T. Koch, E. Hey-Hawkins, M. Galan-Fereres and M.S. Eisen, *Polyhedron*, 2002, **21**, 2445.
129. G. Altenhoff, S. Bredeau, G. Erker, G. Kehr, O. Kataeva and R. Fröhlich, *Organometallics*, 2002, **21**, 4084.
130. A.S. Ionkin and W.J. Marshall, *Organometallics*, 2003, **22**, 4136.
131. A. Ochida, K. Hara, H. Ito and M. Sawamura, *Org. Lett*., 2003, **5**, 2671.
132. S.E. Vaillard, A. Postigo and R.A. Rossi, *Organometallics*, 2004, **23**, 3003.
133. H. Lebel, S. Morin and V. Paquet, *Org. Lett*., 2003, **5**, 2347.
134. J.-P. Ebran, P. Jubault, X. Pannecoucke and J.-C. Quirion, *Tetrahedron: Asymmetry*, 2003, **14**, 1637.
135. M. Léautey, G. Castelot-Deliencourt, X. Pannecoucke and J.-C. Quirion, *Tetrahedron Lett*., 2002, **43**, 9237.
136. S. Ballot and N. Noiret, *Tetrahedron Lett*., 2003, **44**, 8811.
137. C.A. Jaska, A.J. Lough and I. Manners, *Inorg. Chem*., 2004, **43**, 1090.
138. C.J. Pilkington and A. Zanotti-Gerosa, *Org. Lett*., 2003, **5**, 1273.
139. J.-L. Vasse, R. Stranne, R. Zalubovskis, C. Gayet and C. Moberg, *J. Org. Chem*., 2003, **68**, 3258.
140. W. Braun, B. Calmuschi, J. Haberland, W. Hummel, A. Liese, T. Nickel, O. Stelzer and A. Salzer, *Eur. J. Inorg. Chem*., 2004, 2235.
141. S. Basra, J.G. de Vries, D.J. Hyett, G. Harrison, K.M. Heslop, A.G. Orpen, P.G. Pringle and K. von der Luehe, *Dalton Trans*., 2004, 1901.
142. D. Liu, W. Li and X. Zhang, *Org. Lett*., 2002, **4**, 4471.
143. A. Bayer, P. Murszat, U. Thewalt and B. Rieger, *Eur. J. Inorg. Chem*., 2002, 2614.
144. J. Holz, A. Monsees, H. Jiao, J. You, I.V. Komarov, C. Fischer, K. Drauz and A. Börner, *J. Org. Chem*., 2003, **68**, 1701.
145. D.J. Brauer, K.W. Kottsieper, S. Rossenbach and O. Stelzer, *Eur. J. Inorg. Chem*., 2003, **9**, 1748.
146. A. Zhang and T.V. RajanBabu, *Org. Lett*., 2004, **6**, 1515.
147. (*a*) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc*., 2003, **125**, 4166; (*b*) E. Vedejs, O. Daugulis, L.A. Harper, J.A. MacKay and D.R. Powell, *J. Org. Chem*., 2003, **68**, 5020.
148. E. Vedejs, O. Daugulis and N. Tuttle, *J. Org. Chem*., 2004, **69**, 1389.
149. W. Mohr, C.R. Horn, J. Stahl and J.A. Gladysz, *Synthesis*, 2003, 1279.
150. C.M. Habeck, C. Hoberg, G. Peters, C. Näther and F. Tuczek, *Organometallics*, 2004, **23**, 3252.
151. B.J. Holliday, P.A. Ulmann, C.A. Mirkin, C.L. Stern, L.N. Zakharov and A.L. Rheingold, *Organometallics*, 2004, **23**, 1671.
152. U.W. Meier, F. Hollmann, U. Thewalt, M. Klinga, M. Leskelä and B. Rieger, *Organometallics*, 2003, **22**, 3905.
153. G. Fries, J. Wolf, K. Ilg, B. Walfort, D. Stalke and H. Werner, *Dalton Trans*., 2004, 1873.

154. N.V. Dubrovina, V.I. Tararov, A. Monsees, R. Kadyrov, C. Fischer and A. Börner, *Tetrahedron: Asymmetry*, 2003, **14**, 2739.
155. Z. Herseczki, I. Gergely, C. Hegedüs, A. Szöllösy and J. Bakos, *Tetrahedron: Asymmetry*, 2004, **15**, 1673.
156. C. Carcedo, A. Dervisi, I.A. Fallis, L. Ooi and K.M.A. Malik, *Chem. Commun.*, 2004, 1236.
157. K. Ohe, K. Morioka, K. Yonehara and S. Uemura, *Tetrahedron: Asymmetry*, 2002, **13**, 2155.
158. E. Engeldinger, D. Armspach, D. Matt and P.G. Jones, *Chem. Eur. J.*, 2003, **9**, 3091.
159. L. Poorters, D. Armspach and D. Matt, *Eur. J. Org. Chem.*, 2003, 1377.
160. S. Kim, J.S. Kim, O.J. Shon, S.S. Lee, K.-M. Park, S.O. Kang and J. Ko, *Inorg. Chem.*, 2004, **43**, 2906.
161. O. Herd, D. Hoff, K.W. Kottsieper, C. Liek, K. Wenz, O. Stelzer and W.S. Sheldrick, *Inorg. Chem.*, 2002, **41**, 5034.
162. R.A. Findeis and L.H. Gade, *J. Chem. Soc., Dalton Trans.*, 2002, 3952.
163. R.A. Findeis and L.H. Gade, *Dalton Trans.*, 2003, 249.
164. R.A. Findeis and L.H. Gade, *Eur. J. Inorg. Chem.*, 2003, 99.
165. I.V. Komarov, A. Monsees, R. Kadyrov, C. Fischer, U. Schmidt and A. Börner, *Tetrahedron: Asymmetry*, 2002, **13**, 1615.
166. I.V. Komarov, A. Monsees, A. Spannenberg, W. Baumann, U. Schmidt, C. Fischer and A. Börner, *Eur. J. Org. Chem.*, 2003, 138.
167. W. Li, J.P. Waldkirch and X. Zhang, *J. Org. Chem.*, 2002, **67**, 7618.
168. V.F. Kuznetsov, A.J. Lough and D.G. Gusev, *Chem. Commun.*, 2002, 2432.
169. L.-C. Liang, J.-M. Lin and C.-H. Hung, *Organometallics*, 2003, **22**, 3007.
170. R. Faissner, G. Huttner, E. Kaifer and P. Rutsch, *Eur. J. Inorg. Chem.*, 2003, 1681.
171. R. Faissner, G. Huttner, E. Kaifer, P. Kircher, P. Rutsch and L. Zsolnai, *Eur. J. Inorg. Chem.*, 2003, 2219.
172. G. Esquius, J. Pons, R. Yáñez, J. Ros, R. Mathieu, B. Donnadieu and N. Lugan, *Eur. J. Inorg. Chem.*, 2002, 2999.
173. D. Walther, S. Liesicke, L. Böttcher, R. Fischer, H. Görls and G. Vaughan, *Inorg. Chem.*, 2003, **42**, 625.
174. D. Walther, S. Liesicke, R. Fischer, H. Görls, J. Weston and A. Batista, *Eur. J. Inorg. Chem.*, 2003, 4321.
175. R.M. Bellabarba, M. Nieuwenhuyzen and G.C. Saunders, *Organometallics*, 2003, **22**, 1802.
176. S. Doherty, E.G. Robins, M. Nieuwenhuyzen, P.A. Champkin and W. Clegg, *Organometallics*, 2002, **21**, 4147.
177. C. Zimmermann, W. Bauer, F.W. Heinemann and A. Grohmann, *Z. Naturforsch., B: Chem. Sci.*, 2002, **57**, 1256.
178. K.S. Coleman, S. Turberville, S.I. Pascu and M.L.H. Green, *J. Organomet. Chem.*, 2004, **689**, 770.
179. N. Wiberg, A. Worner, H.W. Lerner and K. Karaghiosoff, *Z. Naturforsch., B: Chem. Sci.*, 2002, **57**, 1027.
180. J. Geier, H. Rüegger, M. Wörle and H. Grützmacher, *Angew. Chem. Int. Ed.*, 2003, **42**, 3951.
181. F. García, S.M. Humphrey, R.A. Kowenicki, M. McPartlin and D.S. Wright, *Dalton Trans.*, 2004, 977.

182. A. Bashall, F. García, A.A. Hopkins, J.A. Wood, M. McPartlin, A.D. Woods and D.S. Wright, *Dalton Trans*., 2003, 1143.
183. G. Müller and J. Brand, *Organometallics*, 2003, **22**, 1463.
184. M. Westerhausen, S. Weinrich, B. Schmid, S. Schneiderbauer, M. Suter, H. Nöth and H. Piotrowski, *Z. Anorg. Allg. Chem*., 2003, **629**, 625.
185. H.-W. Lerner, M. Wagner and M. Bolte, *Chem. Commun*., 2003, 990.
186. Z.-X. Wang and Y.-X. Li, *Organometallics*, 2002, **21**, 4641.
187. S. Blair, K. Izod, W. Clegg and R.W. Harrington, *Eur. J. Inorg. Chem*., 2003, 3319.
188. S. Blair, K. Izod and W. Clegg, *Inorg. Chem*., 2002, **41**, 3886.
189. A. Bashall, J.M. Cole, F. García, A. Primo, A. Rothenberger, M. McPartlin and D.S. Wright, *Inorg. Chim. Acta*, 2003, **354**, 41.
190. F. García, R. Haigh, M. McPartlin and D.S. Wright, *Chem. Commun*., 2003, 2052.
191. C. von Hänisch and B. Rolli, *Phosphorus, Sulfur, Silicon, Relat. Elem*., 2004, **179**, 749.
192. S. Weinrich, H. Piotrowski, M. Vogt, A. Schulz and M. Westerhausen, *Inorg. Chem*., 2004, **43**, 3756.
193. O.T. Beachley Jr., D.J. MacRae, M.R. Churchill, A.Y. Kovalevsky and E.S. Robirds, *Organometallics*, 2003, **22**, 3991.
194. F. Thomas, S. Schulz, H. Mansikkamäki and M. Nieger, *Angew. Chem. Int. Ed*., 2003, **42**, 5641.
195. F. Thomas, S. Schulz, H. Mansikkamäki and M. Nieger, *Organometallics*., 2003, **22**, 3471.
196. M. Green and P. O'Brien, *J. Mat. Chem*., 2004, **14**, 629.
197. M. McPartlin, A.D. Woods, C.M. Pask, T. Vogler and D.S. Wright, *Chem. Commun*., 2003, 1524.
198. D. Nikolova, C. von Hänisch and A. Adolf, *Eur. J. Inorg. Chem*., 2004, 2321.
199. D.M. Stefanescu, H.F. Yuen, D.S. Glueck, J.A. Golen and A.L. Rheingold, *Angew. Chem. Int. Ed*., 2003, **42**, 1046.
200. D.M. Stefanescu, H.F. Yuen, D.S. Glueck, J.A. Golen, L.N. Zakharov, C.D. Incarvito and A.L. Rheingold, *Inorg. Chem*., 2003, **42**, 8891.
201. C. Tirla, N. Mézailles, L. Ricard, F. Mathey and P. Le Floch, *Inorg. Chem*., 2002, **41**, 6032.
202. F. Eisenträger, A. Göthlich, I. Gruber, H. Heiss, C.A. Kiener, C. Krüger, J.U. Notheis, F. Rominger, G. Scherhag, M. Schultz, B.F. Straub, M.A.O. Volland and P. Hofmann, *New J. Chem*., 2003, **27**, 540.
203. G. Hoge, H.-P. Wu, W.S. Kissel, D.A. Pflum, D.J. Greene and J. Bao, *J. Am. Chem. Soc*., 2004, **126**, 5966.
204. A.D. Burrows, M.F. Mahon, S.P. Nolan and M. Varrone, *Inorg. Chem*., 2003, **42**, 7227.
205. J. Andrieu, P. Richard, J.-M. Camus and R. Poli, *Inorg. Chem*., 2002, **41**, 3876.
206. J.-M. Camus, J. Andrieu, P. Richard and R. Poli, *Eur. J. Inorg. Chem*., 2004, 1081.
207. A. Ohashi, S. Kikuchi, M. Yasutake and T. Imamoto, *Eur. J. Org. Chem*., 2002, 2535.
208. K.V.L. Crépy and T. Imamoto, *Tetrahedron Lett*., 2002, **43**, 7735.
209. G. Hoge, *J. Am. Chem. Soc*., 2003, **125**, 10219.
210. N. Oohara, K. Katagiri and T. Imamoto, *Tetrahedron: Asymmetry*, 2003, **14**, 2171.
211. M.J. Johansson, L.O. Schwartz, M. Amedjkouh and N.C. Kann, *Eur. J. Org. Chem*., 2004, 1894.

212. W.J. Drury III, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard and A. Pfaltz, *Angew. Chem. Int. Ed.*, 2004, **43**, 70.
213. (*a*) T.A. Betley and J.C. Peters, *Inorg. Chem.*, 2003, **42**, 5074; (*b*) L. Turculet, J.D. Feldman and T.D. Tilley, *Organometallics*, 2003, **22**, 4627.
214. J.C. Thomas and J.C. Peters, *Inorg. Chem.*, 2003, **42**, 5055.
215. J.C. Thomas and J.C. Peters, *J. Am. Chem. Soc.*, 2003, **125**, 8870.
216. C.M.A. Sánchez, M.J. Iglesias and F.L. Ortiz, *Tetrahedron Lett.*, 2002, **43**, 9611.
217. C.M.A. Sánchez, M.J. Iglesias, I.J.P. Álvarez and F.L. Ortiz, *Tetrahedron Lett.*, 2003, **44**, 8441.
218. C.M. Thomas and J.C. Peters, *Inorg. Chem.*, 2004, **43**, 8.
219. M. Reggelin, S. Doerr, M. Klussmann, M. Schultz and M. Holbach, *Proc. Nat. Acad. Sci. USA*, 2004, **101**, 5461.
220. U.H. Berlekamp, A. Mix, B. Neumann, H.-G. Stammler and P. Jutzi, *J. Organomet. Chem.*, 2003, **667**, 167.
221. M. Tamm, B. Dressel, K. Baum, T. Lügger and T. Pape, *J. Organomet. Chem.*, 2003, **677**, 1.
222. X. Morise, P. Braunstein and R. Welter, *Inorg. Chem.*, 2003, **42**, 7752.
223. J.-C. Hierso, A. Fihri, R. Amardeil, P. Meunier, H. Doucet, M. Santelli and B. Donnadieu, *Organometallics*, 2003, **22**, 4490.
224. O.J. Curnow and G.M. Fern, *Organometallics*, 2002, **21**, 2827.
225. K. Izod, W. McFarlane and B.V. Tyson, *Eur. J. Org. Chem.*, 2004, 1043.
226. K. Izod, W. McFarlane, B.V. Tyson, W. Clegg, R.W. Harrington and S.T. Liddle, *Organometallics*, 2003, **22**, 3684.
227. K. Izod, W. McFarlane, B.V. Tyson, W. Clegg and R.W. Harrington, *Chem. Commun.*, 2004, 570.
228. C. Crause, L. Bennie, L. Damoense, C.L. Dwyer, C. Grove, N. Grimmer, W.J. van Rensburg, M.M. Kirk, K.M. Mokheseng, S. Otto and P.J. Steynberg, *Dalton Trans.*, 2003, 2036.
229. H. Brunner, S. Dormeier and M. Zabel, *Eur. J. Inorg. Chem.*, 2002, 2594.
230. B.A. Trofimov, S.F. Malysheva, B.G. Sukhov, N.A. Belogorlova, E.Y. Schmidt, L.N. Sobenina, V.A. Kuimov and N.K. Gusarova, *Tetrahedron Lett.*, 2003, **44**, 2629.
231. P.B. Hitchcock, T.H. Lee and G.J. Leigh, *Dalton Trans.*, 2003, 2276.
232. (*a*) L. Ropartz, K.J. Haxton, D.F. Foster, R.E. Morris, A.M.Z. Slawin and D.J. Cole-Hamilton, *Dalton Trans.*, 2002, 4323; (*b*) K.J. Haxton, D.J. Cole-Hamilton and R.E. Morris, *Dalton Trans.*, 2004, 1665.
233. T. Bunlaksananusorn and P. Knochel, *Tetrahedron Lett.*, 2002, **43**, 5817.
234. N.K. Gusarova, S.I. Shaikhudinova, S.N. Arbuzova, T.I. Vakul'skaya, B.G. Sukhov, L.M. Sinegovskaya, M.V. Nikitin, A.G. Mal'kina, N.A. Chernysheva and B.A. Trofimov, *Tetrahedron*, 2003, **59**, 4789.
235. D. Mimeau, O. Delacroix and A.-C. Gaumont, *Chem. Commun.*, 2003, 2928.
236. D. Mimeau and A.-C. Gaumont, *J. Org. Chem.*, 2003, **68**, 7016.
237. M.A. Kazankova, M.S. Shulyupin and I.P. Beletskya, *Synlett.*, 2003, 2155.
238. K. Takaki, G. Koshoji, K. Komeyama, M. Takeda, T. Shishido, A. Kitani and K. Takehira, *J. Org. Chem.*, 2003, **68**, 6554.
239. A.M. Kawaoka, M.R. Douglass and T.J. Marks, *Organometallics*, 2003, **22**, 4630.
240. J.-M. Camus, J. Andrieu, R. Poli, P. Richard, C. Baldoli and S. Maiorana, *Inorg. Chem.*, 2003, **42**, 2384.

241. W. Malisch, B. Klüpfel, D. Schumacher and M. Nieger, *J. Organomet. Chem.*, 2002, **661**, 95.
242. R.G. Kostyanovsky, O.N. Krutius, A.A. Stankevich, L.V. Vilkov, E.G. Atavin, Y.V. Vishnevsky and A.A. Ivanov, *Mendeleev Commun.*, 2004, **14**, 89.
243. J.D. Crane and A. Herod, *Inorg. Chem. Commun.*, 2004, **7**, 38.
244. B. Hoge, T. Herrmann, C. Thösen and I. Pantenburg, *Inorg. Chem.*, 2003, **42**, 3623.
245. S. Blair, K. Izod, R. Taylor and W. Clegg, *J. Organomet. Chem.*, 2002, **656**, 43.
246. S. Blair, K. Izod, R.W. Harrington and W. Clegg, *Organometallics*, 2003, **22**, 302.
247. H. Lam, D.J. Aldous and K. K.(M.) Hii, *Tetrahedron Lett.*, 2003, **44**, 5213.
248. J. Kobayashi, T. Agou and T. Kawashima, *Chem. Lett.*, 2003, **32**, 1144.
249. W. Tang, W. Wang and X. Zhang, *Angew. Chem. Int. Ed.*, 2003, **42**, 943.
250. Y. Wang, M.I. Ranasinghe and T. Goodson III, *J. Am. Chem. Soc.*, 2003, **125**, 9562.
251. M. Wende, F. Seidel and J.A. Gladysz, *J. Fluorine Chem.*, 2003, **124**, 45.
252. H. Inoue, Y. Nagaoka and K. Tomioka, *J. Org. Chem.*, 2002, **67**, 5864.
253. (*a*) H. Nakano, Y. Okuyama, R. Takahashi and R. Fujita, *Heterocycles*, 2003, **61**, 471; (*b*) H. Nakano, Y. Suzuki, C. Kabuto, R. Fujita and H. Hongo, *J. Org. Chem.*, 2002, **67**, 5011.
254. T. Mino, Y. Tanaka, T. Yabusaki, D. Okumura, M. Sakamoto and T. Fujita, *Tetrahedron: Asymmetry*, 2003, **14**, 2503.
255. T. Mino, Y. Tanaka, Y. Sato, A. Saito, M. Sakamoto and T. Fujita, *Tetrahedron Lett.,* 2003, 44, 4677; see related corrigendum: T. Mino, Y. Tanaka, Y. Sato, A. Saito, M. Sakamoto and T. Fujita, *Tetrahedron Lett.*, 2003, 44, 5759.
256. Y. Wang, X. Li and K. Ding, *Tetrahedron: Asymmetry*, 2002, **13**, 1291.
257. Y. Kawashima, K. Okano, K. Nozaki and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 347.
258. J.F. Jensen, I. Søtofte, H.O. Sørensen and M. Johannsen, *J. Org. Chem.*, 2003, **68**, 1258.
259. F. Teplý, I.G. Stará, I. Starý, A. Kollárovič, D. Šaman, Š. Vyskočil and P. Fiedler, *J. Org. Chem.*, 2003, **68**, 5193.
260. K. Paruch, L. Vyklický, D.Z. Wang, T.J. Katz, C. Incarvito, L. Zhakharov and A.L. Rheingold, *J. Org. Chem.*, 2003, **68**, 8539.
261. J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 4404.
262. D. Zhao and K. Ding, *Org. Lett.*, 2003, **5**, 1349.
263. J.-F. Wen, W. Hong, K. Yuan, T.C.W. Mak and H.N.C. Wong, *J. Org. Chem.*, 2003, **68**, 8918.
264. S.D. de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Tetrahedron Lett.*, 2003, **44**, 823.
265. S.D. de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Eur. J. Org. Chem.*, 2003, 1931.
266. S. Jeulin, S.D. de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Angew. Chem. Int. Ed.*, 2004, **43**, 320.
267. S. Jeulin, S.D. de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Proc. Nat. Acad. Sci. USA*, 2004, **101**, 5799.
268. L. Qiu, J. Qi, C.-C. Pai, S. Chan, Z. Zhou, M.C.K. Choi and A.S.C. Chan, *Org. Lett.*, 2002, **4**, 4599.
269. E. Gorobets, G.-R. Sun, B.M.M. Wheatley, M. Parvez and B.A. Keay, *Tetrahedron Lett.*, 2004, **45**, 3597.

270. J.-P. Henschke, A. Zanotti-Gerosa, P. Moran, P. Harrison, B. Mullen, G. Casy and I.C. Lennon, *Tetrahedron Lett*., 2003, **44**, 4379.
271. A. Hu, H.L. Ngo and W. Lin, *Angew. Chem. Int. Ed*., 2004, **43**, 2501.
272. M. Berthod, C. Saluzzo, C. Mignani and M. Lemaire, *Tetrahedron: Asymmetry*, 2004, **15**, 639.
273. M. Berthod, C. Mignani and M. Lemaire, *Tetrahedron: Asymmetry*, 2004, **15**, 1121.
274. J. Bayardon, M. Cavazzini, D. Maillard, G. Pozzi, S. Quici and D. Sinou, *Tetrahedron: Asymmetry*, 2003, **14**, 2215.
275. N.G. Andersen, M. Parvez, R. McDonald and B.A. Keay, *Can. J. Chem*., 2004, **82**, 145.
276. K.S.A. Vallin, Q. Zhang, M. Larhed, D.P. Curran and A. Hallberg, *J. Org. Chem*., 2003, **68**, 6639.
277. S.L. Parisel, N.D. Moorcroft, A. Jutand, D.J. Aldous and K.K.(M). Hii, *Org. Biomol. Chem*., 2004, **2**, 301.
278. R. Stead and J. Xiao, *Lett. in Org. Chem*., 2004, **1**, 148.
279. T. Sturm, W. Weissensteiner and F. Spindler, *Adv. Synth. Catal*., 2003, **345**, 160.
280. F. Guillen, M. Rivard, M. Toffano, J.-Y. Legros, J.-C. Daran and J.-C. Fiaud, *Tetrahedron*, 2002, **58**, 5895.
281. A.S. Veige, LeG.M. Slaughter, E.M. Lobkovsky, P.T. Wolczanski, N. Matsunaga, S.A. Decker and T.R. Cundari, *Inorg. Chem*., 2003, **42**, 6204.
282. W. Tang, W. Wang, Y. Chi and X. Zhang, *Angew. Chem. Int. Ed*., 2003, **42**, 3509.
283. W. Henderson and S.R. Alley, *J. Organomet. Chem*., 2002, **656**, 120.
284. A.V. Martynov, N.A. Makhaeva, V.A. Potapov and S.V. Amosova, *Russ. J. Gen. Chem*., 2003, **73**, 1151.
285. K.V. Katti, N. Pillarsetty and K. Raghuraman, *Topics in Current Chem*., 2003, **229**, 121.
286. A. Marinetti and J.-P. Genêt, *C. R. Chimie*, 2003, **6**, 507.
287. L. Dahlenburg, *Eur. J. Inorg. Chem*., 2003, 2733.
288. W. Tang and X. Zhang, *Chem. Rev*., 2003, **103**, 3029.
289. A. Pfaltz and W.J. DruryIII, *Proc. Nat. Acad. Sci. USA*, 2004, **101**, 5723.
290. G. Chelucci, G. Orrù and G.A. Pinna, *Tetrahedron*, 2003, **59**, 9471.
291. V.V. Grushin, *Chem. Rev*., 2004, **104**, 1629.
292. C. Gennari and U. Piarulli, *Chem. Rev*., 2003, **103**, 3071.
293. (*a*) U. Monkowius, S. Nogai and H. Schmidbaur, *Organometallics*, 2003, **22**, 145; (*b*) U. Monkowius, S. Nogai and H. Schmidbaur, *Dalton Trans*., 2003, 987.
294. V.V. Afanasiev, I.P. Beletskaya, M.A. Kazankova, I.V. Efimova and M.U. Antipin, *Synthesis*, 2003, 2835.
295. I.P. Beletskaya, V.V. Afanasiev, M.A. Kazankova and I.V. Efimova, *Org. Lett*., 2003, **5**, 4309.
296. (*a*) N. Pirio, S. Bredeau, L. Dupuis, P. Schütz, B. Donnadieu, A. Igau, J.-P. Majoral, J.-C. Guillemin and P. Meunier, *Tetrahedron*, 2004, **60**, 1317; (*b*) Y. El Harouch, V. Cadierno, A. Igau, B. Donnadieu and J.P. Majoral, *J. Organomet. Chem*., 2004, **689**, 953.
297. Z. Xi, W. Zhang and T. Takahashi, *Tetrahedron Lett*., 2004, **45**, 2427.
298. C.A. Slinn, A.J. Redgrave, S.L. Hind, C. Edlin, S.P. Nolan and V. Gouverneur, *Org. Biomol. Chem*., 2003, **1**, 3820.
299. E.K. Bauer, F. Hampel and J.A. Gladysz, *Organometallics*., 2003, **22**, 5567.
300. T. Shima, E.K. Bauer, F. Hampel and J.A. Gladysz, *Dalton Trans*., 2004 **9**, 1012.

301. M.D. McReynolds, J.M. Dougherty and P.R. Hanson, *Chem. Rev*., 2004, **104**, 2239.
302. A. Tewari, M. Hein, A. Zapf and M. Beller, *Synthesis*, 2004, 935.
303. H. Remmele, A. Köllhofer and H. Plenio, *Organometallics*, 2003, **22**, 4098.
304. J. Geier, G. Frison and H. Grützmacher, *Angew. Chem. Int. Ed*., 2003, **42**, 3955.
305. G. Baccolini, C. Boga and M. Galeotti, *Angew. Chem. Int. Ed*., 2004, **43**, 3058.
306. L. Dahlenburg and R. Götz, *Eur. J. Inorg. Chem*., 2004, 888.
307. A.N. Kostyuk, Y.V. Syvaschenko, D.M. Volochnyuk, N.V. Lysenko, A.A. Tolmachev and A.M. Pinchuk, *Tetrahedron Lett*., 2003, **44**, 6487.
308. M. Reisser, A. Maier and G. Maas, *Eur. J. Org. Chem*., 2003, 2071.
309. R.A. Baber, M.L. Clarke, A.G. Orpen and D.A. Ratcliffe, *J. Organomet. Chem*., 2003, **667**, 112.
310. R. Zurawinski, B. Donnadieu, M. Mikolajczyk and R. Chauvin, *Organometallics*, 2003, **22**, 4810.
311. T.-W. Teo, S. Selvaratnam, J.J. Vittal and P.-H. Leung, *Inorg. Chim. Acta*, 2003, **352**, 213.
312. Y. Qin, H. Lang, J.J. Vittal, G.-K. Tan, S. Selvaratnam, A.J.P. White, D.J. Williams and P.-H. Leung, *Organometallics*, 2003, **22**, 3944.
313. F. Goettmann, D. Grosso, F. Mercier, F. Mathey and C. Sanchez, *Chem. Commun*., 2004, 1240.
314. L.F. Tietze and J.K. Lohmann, *Synlett*, 2002, 2083.
315. T.G. Kilroy, P.G. Cozzi, N. End and P.J. Guiry, *Synlett*, 2004, 106.
316. R.A. Singer, S. Caron, R.E. McDermott, P. Arpin and N.M. Do, *Synthesis*, 2003, 1727.
317. F. Maienza, F. Spindler, M. Thommen, B. Pugin, C. Malan and A. Mezzetti, *J. Org. Chem*., 2002, **67**, 5239.
318. G. Müller and A. Feustel, *Organometallics*, 2003, **22**, 3049.
319. S. Trofimenko, A.L. Rheingold and C.D. Incarvito, *Angew. Chem. Int. Ed*., 2003, **42**, 3506.
320. F. Leroux, J. Gorecka and M. Schlosser, *Synthesis*, 2004, **9**, 326.
321. D.J. Eisler and R.J. Puddephatt, *Can. J. Chem*., 2004, **82**, 185.
322. M. Driess, K. Merz and C. Monsé, *Chem. Commun*., 2003, 2608.
323. M. Driess, C. Monsé, D. Bläser, R. Boese, H. Bornemann, A. Kuhn and W. Sander, *J. Organomet. Chem*., 2003, **686**, 294.
324. T.J. Colacot, *Chem. Rev*., 2003, **103**, 3101.
325. L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng and X.-L. Hou, *Acc. Chem. Res*., 2003, **36**, 659.
326. E.A. Colby and T.F. Jamison, *J. Org. Chem*., 2003, **68**, 156.
327. P. Barbaro, C. Bianchini, G. Giambastiani and A. Togni, *Chem. Commun*., 2002, 2672.
328. P. Barbaro, C. Bianchini, G. Giambastiani, D. Masi, S.L. Parisel and A. Togni, *Synthesis*, 2004, 345.
329. (*a*) Z.-Y. Tang, Y. Lu and Q.-S. Hu, *Org. Lett*., 2003, **5**, 297; (*b*) R. Dorta, D. Broggini, R. Stoop, H. Rüegger, F. Spindler and A. Togni, *Chem. Eur. J*., 2004, **10**, 267.
330. Q.-S. Hu, Y. Lu, Z.-Y. Tang and H.-B. Yu, *J. Am. Chem. Soc*., 2003, **125**, 2856.
331. P. Štěpnička and I. Císařová, *Organometallics*, 2003, **22**, 1728.
332. H. Seo, H. Park, B.Y. Kim, J.H. Lee, S.U. Son and Y.K. Chung, *Organometallics*, 2003, **22**, 618.
333. S. Gischig and A. Togni, *Organometallics*, 2004, **23**, 2479.
334. R.J. Kloetzing, M. Lotz and P. Knochel, *Tetrahedron: Asymmetry*, 2003, **14**, 255.

335. N.W. Boaz, S.D. Debenham, E.B. Mackenzie and S.E. Large, *Org. Lett*., 2002, **4**, 2421.
336. J.-C. Hierso, F. Lacassin, R. Broussier, R. Amardeil and P. Meunier, *J. Organomet. Chem*., 2004, **689**, 766.
337. C. Korff and G. Helmchen, *Chem. Commun*., 2004, 530.
338. C. Baillie and J. Xiao, *Tetrahedron*, 2004, **60**, 4159.
339. J.R. Moncarz, N.F. Laritcheva and D.S. Glueck, *J. Am. Chem. Soc*., 2002, **124**, 13356.
340. J.R. Moncarz, T.J. Brunker, J.C. Jewett, M. Orchowski, D.S. Glueck, R.D. Sommer, K.-C. Lam, C.D. Incarvito, T.E. Concolino, C. Ceccarelli, L.N. Zakharov and A.L. Rheingold, *Organometallics*, 2003, **22**, 3205.
341. (*a*) H.S. Sørensen, J. Larsen, B.S. Rasmussen, B. Laursen, S.G. Hansen, T. Skrydstrup, C. Amatore and A. Jutand, *Organometallics*, 2002, **21**, 5243; (*b*) J. Larsen, B.S. Rasmussen, R.G. Hazell and T. Skrydstrup, *Chem. Commun*., 2004, 202.
342. Z. Jin and B.L. Lucht, *J. Organomet. Chem*., 2002, **653**, 167.
343. A. Köllhofer and H. Plenio, *Chem. Eur. J*., 2003, **9**, 1416.
344. N.J. Kerrigan, E.C. Dunne, D. Cunningham, P. McArdle, K. Gilligan and D.J. Gilheany, *Tetrahedron Lett*., 2003, **44**, 8461.
345. S. Gladiali, R. Taras, R.M. Ceder, M. Rocamora, G. Muller, X. Solans and M. Font-Bardia, *Tetrahedron Asymmetry*, 2004, **15**, 1477.
346. G. Bringmann, R.-M. Pfeifer, P. Schreiber, K. Hartner, M. Schraut and M. Breuning, *Tetrahedron*, 2004, **60**, 4349.
347. F.Y. Kwong, C.W. Lai, M. Yu, Y. Tian and K.S. Chan, *Tetrahedron*, 2003, **59**, 10295.
348. F.Y. Kwong, C.W. Lai, M. Yu and K.S. Chan, *Tetrahedron*, 2004, **60**, 5635.
349. A. Stadler and C.O. Kappe, *Org. Lett*., 2002, **4**, 3541.
350. J.P. Henschke, M.J. Burk, C.G. Malan, D. Herzberg, J.A. Peterson, A.J. Wildsmith, C.J. Cobley and G. Casy, *Adv. Synth. Catal*., 2003, **345**, 300.
351. C.W. Lim, O. Tissot, A. Mattison, M.W. Hooper, J.M. Brown, A.R. Cowley, D.I. Hulmes and A.J. Blacker, *Org. Proc. Res. Dev*., 2003, **7**, 379.
352. G. Michaud, M. Bulliard, L. Ricard, J.-P. Genêt and A. Marinetti, *Chem. Eur. J*., 2002, **8**, 3327.
353. E. Le Gall, M. Troupel and J.-Y. Nédélec, *Tetrahedron*, 2003, **59**, 7497.
354. S. Vyskočil, L. Meca, I. Tišlerová, I. Císařová, M. Polášek, S.R. Harutyunyan, Y.N. Belokon, R.M.J. Stead, L. Farrugia, S.C. Lockhart, W.L. Mitchell and P. Kočovský, *Chem. Eur. J*., 2002, **8**, 4633.
355. D. Van Allen and D. Venkataraman, *J. Org. Chem*., 2003, **68**, 4590.
356. D. Gelman, L. Jiang and S.L. Buchwald, *Org. Lett*., 2003, **5**, 2315.
357. M.R. Eberhard, S. Matsukawa, Y. Yamamoto and C.M. Jensen, *J. Organomet. Chem*., 2003, **687**, 185.
358. T. Appleby, S.M. Aucott, M.L. Clarke, A.M.Z. Slawin and J.D. Woollins, *Polyhedron*, 2002, **21**, 2639.
359. M. Onoda, S. Uchiyama, A. Endo, H. Tokuyama, T. Santa and K. Imai, *Org. Lett*., 2003, **5**, 1459.
360. A.V. Malkov, J.B. Hand and P. Kočovský, *Chem. Commun*., 2003, 1948.
361. X. Cheng and K.K.(M). Hii, *Tetrahedron: Asymmetry*, 2003, **14**, 2045.
362. M. Léautey, P. Jubault, X. Pannecoucke and J.-C. Quirion, *Eur. J. Org. Chem*., 2003, 3761.
363. R. Chanthateyanonth and H. Alper, *J. Mol. Catal. A: Chem*., 2003, **201**, 23.

364. R. Visentin, R. Rossin, M.C. Giron, A. Dolmella, G. Bandoli and U. Mazzi, *Inorg. Chem.*, 2003, **42**, 950.
365. S.J. Greenfield, A. Agarkov and S.R. Gilbertson, *Org. Lett.*, 2003, **5**, 3069.
366. M.B. Peori and A.K. Kakkar, *Organometallics*, 2002, **21**, 3860.
367. G.D. Engel and L.H. Gade, *Chem. Eur. J.*, 2002, **8**, 4319.
368. B. Yi, Q.-H. Fan, G.-J. Deng, Y.-M. Li, L.-Q. Qiu and A.S.C. Chan, *Org. Lett.*, 2004, **6**, 1361.
369. G.-J. Deng, Q.-H. Fan, X.-M. Chen and G.-H. Liu, *J. Mol. Catal. A: Chem.*, 2003, **193**, 21.
370. A.-M. Caminade, V. Maraval, R. Laurent, C.-O. Turrin, P. Sutra, J. Leclaire, L. Griffe, P. Marchand, C. Baudoin-Dehoux, C. Rebout and J.-P. Majoral, *C. R. Chimie*, 2003, **6**, 791.
371. M.S. Masar III, M.V. Ovchinnikov, C.A. Mirkin, L.N. Zakharov and A.L. Rheingold, *Inorg. Chem.*, 2003, **42**, 6851.
372. N.C. Gianneschi, C.A. Mirkin, L.N. Zakharov and A.L. Rheingold, *Inorg. Chem.*, 2002, **41**, 5326.
373. P. Pellon, G. Gachot, J. Le Bris, S. Marchin, R. Carlier and D. Lorcy, *Inorg. Chem.*, 2003, **42**, 2056.
374. M.V. Ovchinnikov, B.J. Holliday, C.A. Mirkin, L.N. Zakharov and A.L. Rheingold, *Proc. Nat. Acad. Sci. USA*, 2002, **99**, 4927.
375. L. Esriche, J.A. Muñoz, R. Kivekäs, R. Sillampää and J. Casabó, *Eur. J. Inorg. Chem.*, 2002, 3258.
376. S.M. Lait, M. Parvez and B.A. Keay, *Tetrahedron: Asymmetry*, 2004, **15**, 155.
377. A. Suárez, M.A. Méndez-Rojas and A. Pizzano, *Organometallics*, 2002, **21**, 4611.
378. A.-E. Wang, J. Zhong, J.-H. Xie, K. Li and Q.-L. Zhou, *Adv. Synth. Catal.*, 2004, **346**, 595.
379. J.-P. Masson, A.A. Bahsoun, M.-T. Youinou and J.A. Osborn, *C R Chimie*, 2002, **5**, 303.
380. Z. Zhu, T. Kajino, M. Kojima and K. Nakajima, *Inorg. Chim. Acta*, 2003, **355**, 197.
381. L.B. Schenkel and J.A. Ellman, *Org. Lett.*, 2003, **5**, 545.
382. L.B. Schenkel and J.A. Ellman, *J. Org. Chem.*, 2004, **69**, 1800.
383. C.Z. Flores-López, L.Z. Flores-López, G. Aguirre, L.H. Hellberg, M. Parra-Hake and R. Somanathan, *J. Mol. Catal. A: Chem.*, 2004, **215**, 73.
384. S.E. Durran, M.R.J. Elsegood and M.B. Smith, *New J. Chem.*, 2002 **26**, 1402.
385. D.P. Catsoulacos, B.R. Steele, G.A. Heropoulos, M. Micha-Scretas and C.G. Screttas, *Tetrahedron Lett.*, 2003, **44**, 4575.
386. K. Shibatomi and Y. Uozumi, *Tetrahedron: Asymmetry*, 2002, **13**, 1769.
387. M.-J. Jin, S.-H. Kim, S.-J. Lee and Y.-M. Kim, *Tetrahedron Lett.*, 2002, **43**, 7409.
388. H. Nakano, J. Yokoyama, R. Fujita and H. Hongo, *Tetrahedron Lett.*, 2002, **43**, 7761.
389. H. Nakano, J. Yokoyama, Y. Okuyama, R. Fujita and H. Hongo, *Tetrahedron: Asymmetry*, 2003, **14**, 2361.
390. F. Mercier, F. Brebion, R. Dupont and F. Mathey, *Tetrahedron: Asymmetry*, 2003, **14**, 3137.
391. J.H. Lee, S.U. Son and Y.K. Chung, *Tetrahedron: Asymmetry*, 2003, **14**, 2109.
392. (*a*) Xian. Hu, H. Dai, Xin. Hu, H. Chen, J. Wang, C. Bai and Z. Zheng, *Tetrahedron: Asymmetry*, 2002, **13**, 1687; (*b*) Xian. Hu, H. Dai, C. Bai, H. Chen

and Z. Zheng, *Tetrahedron: Asymmetry*, 2004, **15**, 1065; (*c*) H. Dai, X. Hu, H. Chen, C. Bai and Z. Zheng, *J. Mol. Catal. A: Chem.*, 2004, **211**, 17.
393. (*a*) H. Dai, X. Hu, H. Chen, C. Bai and Z. Zheng, *Tetrahedron: Asymmetry*, 2003, **14**, 1467; (*b*) X. Hu, H. Chen, H. Dai and Z. Zheng, *Tetrahedron: Asymmetry*, 2003, **14**, 3415; (*c*) H. Dai, X. Hu, H. Chen, C. Bai and Z. Zheng, *J. Mol. Catal. A: Chem.*, 2004, **209**, 19.
394. (*a*) Xian. Hu, H. Chen, Xin. Hu, H. Dai, C. Bai, J. Wang and Z. Zheng, *Tetrahedron Lett.*, 2002, **43**, 9179; (*b*) Xian. Hu, H. Chen, H. Dai, Xin. Hu and Z. Zheng, *Tetrahedron: Asymmetry*, 2003, **14**, 2073.
395. W.-Q. Hu, X.-L. Sun, C. Wang, Y. Gao, Y. Tang, L.-P. Shi, W. Xia, J. Sun, H.-L. Dai, X.-Q. Li, X.-L. Yao and X.-R. Wang, *Organometallics*, 2004, **23**, 1684.
396. P.-Y. Shi, Y.-H. Liu, S.-M. Peng and S.-T. Liu, *Organometallics*, 2002, **21**, 3203.
397. I. Fernández, M.J. Mancheño, M. Gómez-Gallego, M.A. Sierra, T. Lejon and L.K. Hansen, *Organometallics*, 2004, **23**, 1851.
398. C. Liu, J. Jiang, Y. Wang, F. Cheng and Z. Jin, *J. Mol. Catal. A: Chem.*, 2003, **198**, 23.
399. Y. Liang, S. Gao, H. Wan, Y. Hu, H. Chen, Z. Zheng and X. Hu, *Tetrahedron: Asymmetry*, 2003, **14**, 3211.
400. H.Y. Kwon, S.Y. Lee, B.Y. Lee, D.M. Shin and Y.K. Chung, *Dalton Trans.*, 2004, 921.
401. Y.-H. Lee, Y.K. Kim, J.-H. Son and K.H. Ahn, *Bull. Korean Chem. Soc.*, 2003, **24**, 225.
402. (*a*) S. Parisot, R. Kolodziuk, C. Goux-Henry, A. Iourtchenko and D. Sinou, *Tetrahedron Lett.*, 2002, **43**, 7397; (*b*) R. Kolodziuk, A. Penciu, M. Tollabi, E. Framery, C. Goux-Henry, A. Iourtchenko and D. Sinou, *J. Organomet. Chem.*, 2003, **687**, 384.
403. M. Tollabi, E. Framery, C. Goux-Henry and D. Sinou, *Tetrahedron: Asymmetry*, 2003, **14**, 3329.
404. B. Breit and A. Ch. Laungani, *Tetrahedron: Asymmetry*, 2003, **14**, 3823.
405. (*a*) D. Rentsch, R. Hany, S. Barthélémy and R. Steinauer, *Tetrahedron Lett.*, 2003, **44**, 6987; (*b*) A. Dahan and M. Portnoy, *Org. Lett.*, 2003, **5**, 1197.
406. S. Burger, B. Therrien and G. Süss-Fink, *Eur. J. Inorg. Chem.*, 2003, 3099.
407. L.F. Tietze, J.K. Lohmann and C. Stadler, *Synlett*, 2004, 1113.
408. C.E. Song, J.W. Yang, E.J. Roh, S. Lee, J.H. Ahn and H. Han, *Angew. Chem. Int. Ed.*, 2002, **41**, 3852.
409. S. Burger, B. Therrien and G. Süss-Fink, *Inorg. Chim Acta.*, 2004, **357**, 1213.
410. T. Jackson and A. Routledge, *Tetrahedron Lett.*, 2003, **44**, 1305.
411. W. Henderson and S.R. Alley, *J. Organomet. Chem.*, 2002, **658**, 181.
412. Q. Zhang, G. Hua, P. Bhattacharyya, A.M.Z. Slawin and J.D. Woollins, *Eur. J. Inorg. Chem.*, 2003, 2426.
413. Q. Zhang, S.M. Aucott, A.M.Z. Slawin and J.D. Woollins, *Eur. J. Inorg. Chem.*, 2003, 1635.
414. A. Mansour and M. Portnoy, *Tetrahedron Lett.*, 2003, **44**, 2195.
415. A.A. Karasik, R.N. Naumov, R. Sommer, O.G. Sinyashin and E. Hey-Hawkins, *Polyhedron*, 2002, **21**, 2251.
416. S.E. Durran, M.R.J. Elsegood, N. Hawkins, M.B. Smith and S. Talib, *Tetrahedron Lett.*, 2003, **44**, 5255.
417. XB. Ma and XK. Fu, *J. Mol. Catal. A: Chem.*, 2003, **195**, 47.
418. Q. Zhang, T. Ly, A.M.Z. Slawin and J.D. Woollins, *Rev. Roum. Chim.*, 2002, **47**, 1015.

419. A.A. Karasik, R.N. Naumov, O.G. Sinyashin, G.P. Belov, H.V. Novikova, P. Lönnecke and E. Hey-Hawkins, *Dalton Trans.*, 2003, 2209.
420. A.S. Balueva, R.M. Kuznetsov, S.N. Ignat'eva, A.A. Karasik, A.T. Gubaidullin, I.A. Litvinov, O.G. Sinyashin, P. Lönnecke and E. Hey-Hawkins, *Dalton Trans.*, 2004, 442.
421. R.N. Naumov, A.A. Karasik, O.G. Sinyashin, P. Lönnecke and E. Hey-Hawkins, *Dalton Trans.*, 2004, 357.
422. D.J. Darensbourg, J.C. Yarbrough and S.J. Lewis, *Organometallics*, 2003, **22**, 2050.
423. G. Adjabeng, T. Brenstrum, J. Wilson, C. Frampton, A. Robertson, J. Hillhouse, J. McNulty and A. Capretta, *Org. Lett.*, 2003, **5**, 953.
424. T.P. Clark and C.R. Landis, *J. Am. Chem. Soc.*, 2003, **125**, 11792.
425. R.A. Aitken, S.J. Costello, A.M.Z. Slawin and N.J. Wilson, *Eur. J. Org. Chem.*, 2003, 623.
426. I. Yavari, M. Adib, F. Jahani-Mogaddam and M.H. Sayahi, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 545.
427. I. Yavari, N. Zabarjad-Shiraz, M.T. Maghsoodlou and N. Hazeri, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 759.
428. I. Yavari and V. Hadigheh-Rezvan, *Phosphorus, Sulfur, Silicon*, 2002 **177**, 1127.
429. I. Yavari and M. Bayat, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2537.
430. S. Asghari and M. Zaty, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2183.
431. M.R. Islami, Z. Hassani and H. Sheibani, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2547.
432. A. Ramazani, N. Noshiranzadeh and B. Mohammadi, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 539.
433. I. Yavari, M. Adib and L. Hojabri, *Tetrahedron*, 2002, **58**, 7213.
434. I. Yavari, M. Adib and L. Hojabri, *Tetrahedron*, 2002, **58**, 6895.
435. A.A. Esmaili, M. Ghereghloo, M.R. Islami and H.R. Bijanzadeh, *Tetrahedron*, 2003, **59**, 4785.
436. M.R. Islami, Z. Hassani, H. Sheibani, B. Abdolahzadeh and N. Etminan, *Tetrahedron*, 2003, **59**, 4993.
437. I. Yavari, M. Adib, F. Jahani-Moghaddam and H.R. Bijanzadeh, *Tetrahedron*, 2002, **58**, 6901.
438. I. Yavari, M. Aghazadeh and M. Tafazzoli, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 1101.
439. I. Yavari, M. Adib, S. Abdolmohammadi and M. Aghazadeh, *Monatshefte für Chemie*, 2003, **134**, 1093.
440. I. Yavari, F. Nourmohammadian and H.R. Bijanzadeh, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 1147.
441. R. Hekmatshoar, Y. Sh. Beheshtiha, M.M. Heravi and K. Asadollah, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 703.
442. K. Rad-Moghadam and M. Mohseni, *Monatshefte für Chemie*, 2004, **135**, 817.
443. A. Ramazani and A. Souldozi, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2663.
444. A. Ramazani and A. Souldozi, *Phosphorus, Sulfur, Silicon*, 2004, **179**, 529.
445. (*a*) A. Ramazani, B. Mohammadi and N. Noshiranzadeh, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 545; (*b*) A. Ramazani, B. Mohammadi and N. Noshiranzadeh, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 767.
446. A. Ramazani, B. Mohammadi, N. Noshiranzadeh and A. Azizian, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1717.

447. A. Ramazani, N. Noshiranzadeh and B. Mohammadi, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 761.
448. I. Yavari, F. Nasiri and H. Djahaniani, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2627.
449. M.H. Mosslemin, I. Yavari, M. Anary-Abbasinejad and M.R. Nateghi, *Synthesis*, 2004, 1029.
450. C.-Q. Li and M. Shi, *Org. Lett*., 2003, **5**, 4273.
451. A.A. Esmaili and A. Bodaghi, *Tetrahedron*, 2003, **59**, 1169.
452. I. Yavari and H. Norouzi-Arasi, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 87.
453. R. Baharfar, A. Ostadzadeh and A. Abbasi, *J. Chem. Res*., 2004, 37.
454. (*a*) I. Yavari, A. Alizadeh and M. Anary-Abbasinejad, *Phosphorus Sulfur Silicon*, 2002, **177**, 81; (*b*) I. Yavari, A. Alizadeh and M. Anary-Abbasinejad, *Phosphorus Sulfur Silicon*, 2002, **177**, 2379.
455. I. Yavari, M. Anary-Abbasinejad, A. Alizadeh and A. Habibi, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2523.
456. I. Yavari, A. Alizadeh and M. Anary-Abbasinejad, *Tetrahedron Lett*., 2002, **43**, 9449.
457. I. Yavari and A. Alizadeh, *Phosphorus, Sulfur, Silicon*, 2004, **179**, 1003.
458. I. Yavari and A. Alizadeh, *Synthesis*, 2004, 237.
459. H. Kuroda, I. Tomita and T. Endo, *Org. Lett*., 2003, **5**, 129.
460. C.-K. Jung, J.-C. Wang and M.J. Krische, *J. Am. Chem. Soc*., 2004, **126**, 4118.
461. T.Q. Pham, S.G. Pyne, B.W. Skelton and A.H. White, *Tetrahedron Lett*., 2002, **43**, 5953.
462. Y. Du and X. Lu, *J. Org. Chem*., 2003, **68**, 6463.
463. H. Kuroda, E. Hanaki, H. Izawa, M. Kano and H. Itahashi, *Tetrahedron*, 2004, **60**, 1913.
464. M. Wende and J.A. Gladysz, *J. Am. Chem. Soc*., 2003, **125**, 5861.
465. R. Takeuchi and Y. Nakaya, *Org. Lett*., 2003, **5**, 3659.
466. J. Ruiz, F. Marquínez, V. Riera, M. Vivanco, S. García-Granda and M.R. Díaz, *Chem. Eur. J*., 2002, **8**, 3872.
467. B. Pal, P.K. Pradhan, P. Jaisankar and V.S. Giri, *Synthesis*, 2003, 1549.
468. M.I. Mohamed, *Bulgarian Chem. Commun*., 2003, **35**, 183.
469. Yu. G. Gololobov, P.V. Petrovskii, E.M. Ivanova, O.A. Linchenko, R. Schmutzler, L. Ernst, P.G. Jones, A. Karaçar, M. Freytag and S. Okucu, *Russ. Chem. Bull., Int. Ed*., 2003, **52**, 427.
470. P.M. Brown, N. Käppel and P.J. Murphy, *Tetrahedron Lett*., 2002, **43**, 8707.
471. B.J. Jellerichs, J.-R. Kong and M.J. Krische, *J. Am. Chem. Soc*., 2003, **125**, 7758.
472. P.K. Koech and M.J. Krische, *J. Am. Chem. Soc*., 2004, **126**, 5350.
473. M. Couturier, F. Ménard, J.A. Ragan, M. Riou, E. Dauphin, B.M. Andresen, A. Ghosh, K. Dupont-Gaudet and M. Girardin, *Org. Lett*., 2004, **6**, 1857.
474. X.-F. Zhu, J. Lan and O. Kwon, *J. Am. Chem.Soc*., 2003, **125**, 4716.
475. I.C. Stewart, R.G. Bergman and F.D. Toste, *J. Am. Chem. Soc*., 2003, **125**, 8696.
476. J.S. Yadav, B.V.S. Reddy, A.K. Basak, B. Visali, A.V. Narsaiah and K. Nagaiah, *Eur. J. Org. Chem*., 2004, 546.
477. C.-W. Cho, J.-R. Kong and M.J. Krische, *Org. Lett*., 2004, **6**, 1337.
478. G.R.A. Adair, M.G. Edwards and J.M.J. Williams, *Tetrahedron Lett*., 2003, **44**, 5523.
479. D. Bhuniya, S. Mohan and S. Narayanan, *Synthesis*, 2003, 1018.
480. L.-W. Xu and C.-G. Xia, *Tetrahedron Lett*., 2004, **45**, 4507.
481. X.-L. Hou, R.-H. Fan and L.-X. Dai, *J. Org. Chem*., 2002, **67**, 5295.
482. R.-H. Fan and X.-L. Hou, *Tetrahedron Lett*., 2003, **44**, 4411.
483. R.-H. Fan and X.-L. Hou, *J. Org. Chem*., 2003, **68**, 726.

484. R.-H. Fan, X.-L. Hou and L.-X. Dai, *J. Org. Chem.*, 2004, **69**, 689.
485. C.-F. Xu, Y.-X. Liu, W.-H. Wang, R.-Z. Cao and L.-Z. Liu, *Heteroatom Chem.*, 2002, **13**, 633.
486. Y. Liu, X. Chen, M. Xue, R. Cao and L. Liu, *Synthesis*, 2003, 195.
487. H.-J. Frohn and V.V. Bardin, *J. Fluorine Chem.*, 2003, **123**, 43.
488. L.M.V. Pinheiro, A.R.T. Calado and J.C.R. Reis, *Org. Biomol. Chem.*, 2004, **2**, 1330.
489. A. Bisai, M. Chandrasekhar and V.K. Singh, *Tetrahedron Lett.*, 2002, **43**, 8355.
490. E.J. Alvarez-Manzaneda, R. Chahboun, E.C. Torres, E. Alvarez, R. Alvarez-Manzaneda, A. Haidour and J. Ramos, *Tetrahedron Lett.*, 2004, **45**, 4453.
491. G. Madhusudhan, G.O. Reddy, J. Ramanatham and P.K. Dubey, *Tetrahedron Lett.*, 2003, **44**, 6323.
492. S. Porwanski, S. Menuel, X. Marsura and A. Marsura, *Tetrahedron Lett.*, 2004, **45**, 5027.
493. Y.-L. Zhong, J. Lee, R.A. Reamer and D. Askin, *Org. Lett.*, 2004, **6**, 929.
494. L. Desmaris, N. Percina, L. Cottier and D. Sinou, *Tetrahedron Lett.*, 2003, **44**, 7589.
495. Y. Shingu, Y. Nishida, H. Dohi and K. Kobayashi, *Org. Biomol. Chem.*, 2003, **1**, 2518.
496. Y. Nishida, Y. Shingu, H. Dohi and K. Kobayashi, *Org. Lett.*, 2003, **5**, 2377.
497. X. Lei, G. Dotheuil, X. Pannecoucke and J.-C. Quirion, *Org. Lett.*, 2004, **6**, 2101.
498. I. Vágó and I. Greiner, *Tetrahedron Lett.*, 2002, **43**, 6039.
499. D.O. Jang, D.H. Cho and J.-G. Kim, *Synth. Commun.*, 2003, **33**, 2885.
500. (*a*) W.-K. Su, X.-R. Liang, Y.-S. Li and Y.-M. Zhang, *Youji Huaxue*, 2003, **23**, 1019; (*b*) W.-K. Su, X.-R. Liang, Y.-S. Li and Y.-M. Zhang, *Chem. Abstr.*, **140**, 110822.
501. E. Cuevas-Yañez, M.A. García, M.A. de la Mora, J.M. Muchowski and R. Cruz-Almanza, *Tetrahedron Lett.*, 2003, **44**, 4815.
502. T. Satoh and N. Sakairi, *Chem. Lett.*, 2003, **32**, 1162.
503. D.A. Durfey, R.U. Kirss, C. Frommen and W.M. Reiff, *Inorg. Chim. Acta*, 2004, **357**, 311.
504. N. Iranpoor, H. Firouzabadi, G. Aghapour and A.R. Vaezzada, *Tetrahedron*, 2002, **58**, 8689.
505. N. Iranpoor, H. Firouzabadi, B. Akhlaghinia and N. Nowrouzi, *J. Org. Chem.*, 2004, **69**, 2562.
506. N. Iranpoor, H. Firouzabadi, B. Akhlaghinia and N. Nowrouzi, *Tetrahedron Lett.*, 2004, **45**, 3291.
507. H. Firouzabadi, N. Iranpoor and S. Sobhani, *Tetrahedron*, 2004, **60**, 203.
508. H. Firouzabadi, N. Iranpoor and S. Sobhani, *Synthesis*, 2004, 290.
509. J. McNulty and Y. Zhou, *Tetrahedron Lett.*, 2004, **45**, 407.
510. K. Vyakaranam, G. Rana, S. Li, C. Zheng, B.F. Spielvogel, J.A. Maguire and N.S. Hosmane, *Inorg. Chem. Commun.*, 2002, **5**, 458.
511. K. Vyakaranam, G. Rana, K. Grelck, B.F. Spielvogel, J.A. Maguire and N.S. Hosmane, *Inorg. Chim. Acta*, 2003, **343**, 383.
512. H. Luong, M.D. Eelman and M. Stradiotto, *Can. J. Chem.*, 2004, **82**, 533.
513. P. Paetzold, U. Englert, R. Finger, T. Schmitz, A. Tapper and R. Ziembinski, *Z. Anorg. Allg. Chem.*, 2004, **630**, 508.
514. T. Imamoto, N. Oohara and H. Takahashi, *Synthesis*, 2004, 1353.
515. M.J. Johansson and N.C. Kann, *Mini-Reviews in Org. Chem.*, 2004, **1**, 233.
516. B. Faure, G. Iacazio and M. Maffei, *J. Mol. Catal. B: Enzymatic*, 2003, **26**, 29.

517. K. Shioji, Y. Kurauchi and K. Okuma, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 833.
518. D.B.G. Williams, H. Lombard, M. van Niekerk, P.P. Coetzee and C.W. Holzapfel, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2799.
519. (*a*) M. Scheideman, P. Shapland and E. Vedejs, *J. Am. Chem. Soc.*, 2003, **125**, 10502; (*b*) P. Shapland and E. Vedejs, *J. Org. Chem.*, 2004, **69**, 4094.
520. C.A. Jaska and I. Manners, *J. Am. Chem. Soc.*, 2004, **126**, 1334.
521. J.-M. Denis, H. Forintos, H. Szelke, L. Toupet, T.-N. Pham, P.-J. Madec and A.-C. Gaumont, *Chem. Commun.*, 2003, 54.
522. R. Núñez, C. Viñas, F. Teixidor, R. Sillanpää and R. Kivekäs, *J. Organomet. Chem.*, 2002, **657**, 224.
523. (*a*) A.M. Shedlow, D.E. Kadlecek, J.C. Clapper, S.E. Rathmill, P.J. Carroll and L.G. Sneddon, *J. Am. Chem. Soc.*, 2003, **125**, 200; (*b*) D.E. Kadlecek, A.M. Shedlow, S.O. Kang, P.J. Carroll and L.G. Sneddon, *J. Am. Chem. Soc.*, 2003, **125**, 212; (*c*) D. Hong, S.E. Rathmill, P.J. Carroll and L.G. Sneddon, *J. Am. Chem. Soc.*, 2003, **125**, 16058.
524. (*a*) B. Štíbr, J. Holub, M. Bakardjiev, I. Pavlík, O.L. Tok and B. Wrackmeyer, *Eur. J. Inorg. Chem.*, 2003, 2524; (*b*) B. Štíbr, J. Holub, M. Bakardjiev, I. Pavlík, O.L. Tok, I. Císařoví, B. Wrackmeyer and M. Herberhold, *Chem. Eur. J.*, 2003, **9**, 2239.
525. G. Müller and J. Brand, *Z. Naturforsch. B: Chem. Sci.*, 2004, **59**, 1.
526. C.Y. Tang, R.A. Coxall, A.J. Downs, T.M. Greene, L. Kettle, S. Parsons, D.W.H. Rankin, H.E. Robertson and A.R. Turner, *Dalton Trans.*, 2003, 3526.
527. A. Kuczkowski, S. Schulz and M. Nieger, *Appl. Organometal. Chem.*, 2004, **18**, 244.
528. R.J. Baker, H. Bettentrup and C. Jones, *Eur. J. Inorg. Chem.*, 2003, 2446.
529. D.G. Ho, R. Gao, J. Celaje, H.-Y. Chung and M. Selke, *Science (Washington DC)*, 2003, **302**, 259.
530. B.W. Greatrex and D.K. Taylor, *J. Org. Chem.*, 2004, **69**, 2577.
531. F.G. Gelalcha and B. Schulze, *J. Org. Chem.*, 2002, **67**, 8400.
532. K. Goto, K. Shimada, M. Nagahama, R. Okazaki and T. Kawashima, *Chem. Lett.*, 2003, **32**, 1080.
533. Y. Miyake, A. Yamauchi, Y. Nishibayashi and S. Uemura, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 381.
534. N. Koshino and J.H. Espenson, *Inorg. Chem.*, 2003, **42**, 5735.
535. W. Levason, R. Patel and G. Reid, *J. Organomet. Chem.*, 2003, **688**, 280.
536. E.C. Carson and S.J. Lippard, *J. Am. Chem. Soc.*, 2004, **126**, 3412.
537. Z. Fei, R. Scopelliti and P.J. Dyson, *Eur. J. Inorg. Chem.*, 2004, 530.
538. B. Gordillo, Z.J. Domínguez, N. Sánchez, R. González, M. Salas and E. Barragán, *Tetrahedron Lett.*, 2003, **44**, 5293.
539. C. Legros, M.-L. Célérier and C. Guette, *Rapid Commun. Mass Spectrom.*, 2004, **18**, 1317.
540. J. Skarżewski, A. Gupta, E. Wojaczyńska and R. Siedlecka, *Synlett*, 2003, 1615.
541. N. Kihara, N. Nakakoji and T. Takata, *Chem. Lett.*, 2002, **31**, 924.
542. S.H. Lee and H. Kohn, *Heterocycles*, 2003, **60**, 47.
543. P. Kilian, P. Bhattacharyya, A.M.Z. Slawin and J.D. Woollins, *Eur. J. Inorg. Chem.*, 2003, 1461.
544. J. McNulty, A. Capretta, V. Laritchev, J. Dyck and A.J. Robertson, *Angew. Chem. Int. Ed.*, 2003, **42**, 4051.
545. C.A. Olsen, M.R. Jørgensen, M. Witt, I.R. Mellor, P.N.R. Usherwood, J.W. Jaroszewski and H. Franzyk, *Eur. J. Org. Chem.*, 2003, 3288.

546. G. Cravotto, S. Chimichi, B. Robaldo and M. Boccalini, *Tetrahedron Lett*., 2003, **44**, 8383.
547. M. Hayashi, Y. Matsuura and Y. Watanabe, *Tetrahedron Lett*., 2004, **45**, 1409.
548. Yu.G. Trishin and V.I. Namestnikov, *Russ. J. Gen. Chem*., 2003, **73**, 1491.
549. P. Lan, J.A. Porco Jr., M.S. South and J.J. Parlow, *J. Comb. Chem*., 2003, **5**, 660.
550. M.C. Hillier, J.-N. Desrosiers, J.-F. Marcoux and E.J.J. Grabowski, *Org. Lett*., 2004, **6**, 573.
551. M.E. Wood, D.J. Cane-Honeysett and M.D. Dowle, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2046.
552. D.M. Dastrup, M.P. VanBrunt and S.M. Weinreb, *J. Org. Chem*., 2003, **68**, 4112.
553. M. Köhn and R. Breinbauer, *Angew. Chem. Int. Ed*., 2004, **43**, 3106.
554. G.A. Lemieux, C.L. de Graffenried and C.R. Bertozzi, *J. Am. Chem. Soc*., 2003, **125**, 4708.
555. J.A. Restituyo, L.R. Comstock, S.G. Petersen, T. Stringfellow and S.R. Rajski, *Org. Lett*., 2003, **5**, 4357.
556. E. Saxon, S.J. Luchansky, H.C. Hang, C. Yu, S.C. Lee and C.R. Bertozzi, *J. Am. Chem. Soc*., 2002, **124**, 14893.
557. T. Sato, S. Fujita, M.C.Z. Kasuya, K. Hatanaka and T. Yamagata, *Chem. Lett*., 2004, **33**, 580.
558. R. Merkx, D.T.S. Rijkers, J. Kemmink and R.M.J. Liskamp, *Tetrahedron Lett*., 2003, **44**, 4515.
559. A. Bianchi and A. Bernardi, *Tetrahedron Lett*., 2004, **45**, 2231.
560. (*a*) M.B. Soellner, B.L. Nilsson and R.T. Raines, *J. Org. Chem*., 2002, **67**, 4993; (*b*) B.L. Nilsson, R.J. Hondal, M.B. Soellner and R.T. Raines, *J. Am. Chem. Soc*., 2003, **125**, 5268; (*c*) M.B. Soellner, K.A. Dickson, B.L. Nilsson and R.T. Raines, *J. Am. Chem. Soc*., 2003, **125**, 11790.
561. O. David, W.J.N. Meester, H. Bieräugel, H.E. Schoemaker, H. Hiemstra and J.H. van Maarseveen, *Angew. Chem. Int. Ed*., 2003, **42**, 4373.
562. H. Fuwa, Y. Okamura, Y. Morohashi, T. Tomita, T. Iwatsubo, T. Kan, T. Fukuyama and H. Natsugari, *Tetrahedron Lett*., 2004, **45**, 2323.
563. F. Debaene and N. Winssinger, *Org. Lett*., 2003, **5**, 4445.
564. H.C. Hang, C. Yu, M.R. Pratt and C.R. Bertozzi, *J. Am. Chem. Soc*., 2004, **126**, 6.
565. W.Q. Tian and Y.A. Wang, *J. Org. Chem*., 2004, **69**, 4299.
566. P.M. Fresneda, M. Castañeda, M.A. Sanz and P. Molina, *Tetrahedron Lett*., 2004, **45**, 1655.
567. A.-M. Faucher and C. Grand-Maitre, *Synth. Commun*., 2003, **33**, 3503.
568. P.T. Nyffeler, C.-H. Liang, K.M. Koeller and C.-H. Wong, *J. Am. Chem.Soc*., 2002, **124**, 10773.
569. S.-D. Park, J.-H. Oh and D. Lim, *Tetrahedron Lett*., 2002, **43**, 6309.
570. I. McCort, S. Ballereau, A. Duréault and J.C. Depezay, *Tetrahedron*, 2002, **58**, 8947.
571. S. Fürmeier and J.O. Metzger, *Eur. J. Org. Chem*., 2003, 649.
572. S. Porwanski, B. Kryczka and A. Marsura, *Tetrahedron Lett*., 2002, **43**, 8441.
573. V. Maraval, J. Pyzowski, A.-M. Caminade and J.-P. Majoral, *J. Org. Chem*., 2003, **68**, 6043.
574. R.-M. Sebastián, L. Griffe, C.-O. Turrin, B. Donnadieu, A.-M. Caminade and J.-P. Majoral, *Eur. J. Inorg. Chem*., 2004, 2459.
575. J.-P. Majoral, A.-M. Caminade, R. Laurent and P. Sutra, *Heteroatom Chem*., 2002, **13**, 474.

576. P.N.M. Botman, O. David, A. Amore, J. Dinkelaar, M.T. Vlaar, K. Goubitz, J. Fraanje, H. Schenk, H. Hiemstra and J.H. van Maarseveen, *Angew. Chem. Int. Ed.*, 2004, **43**, 3471.
577. M.I. García-Moreno, P. Díaz-Pérez, C.O. Mellet and J.M.G. Fernández, *J. Org. Chem.*, 2003, **68**, 8890.
578. P. Langer, I. Freifeld and H. Shojaei, *Chem. Commun.*, 2003, 3044.
579. K. Hemming, C. Loukou, S. Elkatip and R.K. Smalley, *Synlett*, 2004, 101.
580. V. Cadierno, P. Crochet, J. Díez, J. García-Álvarez, S.E. García-Garrido, S. García-Granda, J. Gimeno and M.A. Rodriguez, *Dalton Trans.*, 2003, 3240.
581. L.P. Spencer, R. Altwer, P. Wei, L. Gelmini, J. Gauld and D. W. Stephan, *Organometallics*, 2003, **22**, 3841.
582. G.C. Welch, W.E. Piers, M. Parvez and R. McDonald, *Organometallics*, 2004, **23**, 1811.
583. M. Basato, F. Benetollo, G. Facchin, R.A. Michelin, M. Mozzon, S. Pugliese, P. Sgarbossa, S.M. Sbovata and A. Tassan, *J. Organomet. Chem.*, 2004 **689**, 454.
584. V. Cadierno, M. Zablocka, B. Donnadieu, A. Igau and J.-P. Majoral, *New J. Chem.*, 2003, **27**, 675.
585. C. Garcia-Escomel, P. Mekarbane, C. Martin, P. Grenouillet and C. de Bellefon, *Inorg. Chim. Acta*, 2003, **350**, 407.
586. P.J. Ragogna, N. Burford, M. D'eon and R. McDonald, *Chem. Commun.*, 2003, 1052.
587. P.-C. Nam, P. Gerbaux and M.T. Nguyen, *Eur. J. Mass Spectrom.*, 2003, **9**, 257.
588. M. del Carmen Sicilia, O. Mó, M. Yáñez, J.-C. Guillemin, J.-F. Gal and P.-C. Maria, *Eur. J. Mass Spectrom.*, 2003, **9**, 245.
589. C. Babij and A.J. Poë, *J. Phys. Org. Chem.*, 2004, **17**, 162.
590. K.D. Cooney, T.R. Cundari, N.W. Hoffman, K.A. Pittard, M.D. Temple and Y. Zhao, *J. Am. Chem. Soc.*, 2003, **125**, 4318.
591. W. Zhang, X. Han, X. Liu and X. Bao, *J. Mol. Catal. A: Chem.*, 2003, **194**, 107.
592. V.A. Naumov, M.A. Tafipol'ski and S. Samdal, *Russ. J. Gen. Chem.*, 2003, **73**, 896.
593. S.L. Hinchley, H.E. Robertson, D.W.H. Rankin and W.W. du Mont, *J. Chem. Soc., Dalton Trans.*, 2002, 3787.
594. V.V. Ovchinnikov, *Phosphorus, Sulfur, Silicon*, 2004, **179**, 115.
595. E.V. Sagadeev, Yu.G. Safina, V.F. Sopin and R.A. Cherkasov, *Russ. J. Gen. Chem.*, 2003, **73**, 1702.
596. (*a*) K.B. Borisenko and D.W.H. Rankin, *J. Chem. Soc., Dalton Trans.*, 2002, 3135; (*b*) B. Borisenko and D.W.H. Rankin, *Inorg. Chem.*, 2003, **42**, 7129.
597. Y. Sakaguchi and H. Hayashi, *J. Phys. Chem. A*, 2004, **108**, 3421.
598. V.A. Zagumennov and E.V. Nikitin, *Russ. J. Electrochem.*, 2003, **39**, 1236.
599. A.R. O'Connor and C. Nataro, *Organometallics*, 2004, **23**, 615.
600. A.J. Downard, N.J. Goodwin and W. Henderson, *J. Organomet. Chem.*, 2003, **676**, 62.
601. O.J. Curnow, G.M. Fern, M.L. Hamilton, A. Zahl and R. van Eldik, *Organometallics*, 2004, **23**, 906.
602. R.C.J. Atkinson, V.C. Gibson, N.J. Long, A.J.P. White and D.J. Williams, *Dalton Trans.*, 2004, 1823.
603. P. Barbaro, C. Bianchini, G. Giambastiani and A. Togni, *Tetrahedron Lett.*, 2003, **44**, 8279.

604. (*a*) M. Okazaki, K. Satoh, K.A. Jung, H. Tobita and H. Ogino, *Organometallics*, 2004, **23**, 1971; (*b*) M. Okazaki, K.A. Jung, K. Satoh, H. Okada, J. Naito, T. Akagi, H. Tobita and H. Ogino, *J. Am. Chem. Soc*., 2004, **126**, 5060.
605. K. Owsianik, M. Zablocka, B. Donnadieu and J.-P. Majoral, *Angew. Chem. Int.Ed*., 2003, **42**, 2176.
606. V. Cadierno, M. Zablocka, B. Donnadieu, A. Igau and J.-P. Majoral, *Organometallics*, 2002, **21**, 3215.
607. D.H. Valentine Jr. and J.H. Hillhouse, *Synthesis*, 2003, 2437.
608. F. Baier, Z. Fei, H. Gornitzka, A. Murso, S. Neufeld, M. Pfeiffer, I. Rüdenauer, A. Steiner, T. Stey and D. Stalke, *J. Organomet. Chem*., 2002, **661**, 111.
609. S. Kikuchi and Y. Hashimoto, *Synlett*, 2004, 1267.
610. Y. Hashimoto, H. Konishi and S. Kikuchi, *Synlett*, 2004, 1264.
611. N. Pinault and D.W. Bruce, *Coord. Chem. Rev*., 2003, **241**, 1.
612. H. Gulyás, A. Szöllõsy, P. Szabó, P. Halmos and J. Bakos, *Eur. J. Org. Chem*., 2003, 2775.
613. A.D. Burrows, R.W. Harrington, M.F. Mahon and S.J. Teat, *Eur. J. Inorg. Chem*., 2003, 1433.
614. R. Dorta, L. Shimon and D. Milstein, *J. Organomet. Chem*., 2004, **689**, 751.
615. D.J. Darensbourg, C.G. Ortiz and J.W. Kamplain, *Organometallics*, 2004, **23**, 1747.
616. E. Paetzold, G. Oehme, C. Fischer and M. Frank, *J. Mol. Catal. A: Chem*., 2003, **200**, 95.
617. M. Koprowski, R.-M. Sebastián, V. Maraval, M. Zablocka, V. Cadierno, B. Donnadieu, A. Igau, A.-M. Caminade and J.-P. Majoral, *Organometallics*, 2002, **21**, 4680.
618. P. Wu, G. Deng, Q. Fan, Q. Zeng, C. Wang, L. Wan and C. Bai, *Chem. Lett*., 2002, **31**, 706.
619. S. Lee, Y.J. Zhang, J.Y. Piao, H. Yoon, C.E. Song, J.H. Choi and J. Hong, *Chem. Commun*., 2003, 2624.
620. A. Hu, H.L. Ngo and W. Lin, *J. Am. Chem. Soc*., 2003, **125**, 11490.
621. S. Kim and M.G. Bawendi, *J. Am. Chem. Soc*., 2003, **125**, 14652.
622. F.Z. Baimukhametov, V.F. Zheltukhin, S.N. Ignat'eva, A.S. Balueva, G.N. Nikonov and O.G. Sinyashin, *Russ. J. Gen. Chem*., 2003, **73**, 1691.
623. T. Kniess, J.D.G. Correia, A. Domingos, E. Palma and I. Santos, *Inorg. Chem*., 2003, **42**, 6130.
624. V.V. Dunina, E.D. Razmyslova, O.N. Gorunova, M.V. Livantsov and Y.K. Grishin, *Tetrahedron: Asymmetry*, 2003, **14**, 2331.
625. I. Bauer and W.D. Habicher, *Coll. Czech. Chem. Commun*., 2004, **69**, 1195.
626. R.J. Baker, H. Bettentrup and C. Jones, *Acta Crystallogr. Section C: Cryst. Struct. Commun*., 2003, **59**, 339.
627. O. Fuhr and D. Fenske, *Z. Anorg. Allg. Chem*., 2004, **630**, 244.
628. L.I. Guryunov, J. Grobe and V.D. Shteingarts, *Russ. J. Org. Chem*., 2004, **40**, 583.
629. E.V. Panteleeva, V.D. Shteingarts, J. Grobe, B. Krebs, M.U. Triller and H. Rabeneck, *Z. Anorg. Allg. Chem*., 2003, **629**, 71.
630. M.L. Clarke, A.G. Orpen, P.G. Pringle and E. Turley, *Dalton Trans*., 2003, 4393.
631. R.E. Bulo, A.W. Ehlers, S. Grimme and K. Lammertsma, *J. Am. Chem. Soc*., 2002, **124**, 13903.
632. (*a*) R.E. Bulo, H. Jansen, A.W. Ehlers, F.J.J. de Kanter, M. Schakel, M. Lutz, A.L. Spek and K. Lammertsma, *Angew. Chem. Int. Ed*., 2004, **43**, 714; (*b*) R.E. Bulo, H.

Jansen, A.W. Ehlers, F.J.J. de Kanter, M. Schakel, M. Lutz, A.L. Spek and K. Lammertsma, *ibid.* **43**, 3748.
633. M.-T. Lee and C.-H. Hu, *Organometallics*, 2004, **23**, 976.
634. E. Despagnet, H. Gornitzka, A.B. Rozhenko, W.W. Schoeller, D. Bourissou and G. Bertrand, *Angew. Chem. Int. Ed.*, 2002, **41**, 2835.
635. E. Despagnet-Ayoub, S. Solé, H. Gornitzka, A.B. Rozhenko, W.W. Schoeller, D. Bourissou and G. Bertrand, *J. Am. Chem. Soc.*, 2003, **125**, 124.
636. E. Despagnet-Ayoub, H. Gornitzka, D. Bourissou and G. Bertrand, *Eur. J. Org. Chem.*, 2003, 2039.
637. N. Merceron-Saffon, H. Gornitzka, A. Baceiredo and G. Bertrand, *J. Organomet. Chem.*, 2004, **689**, 1431.
638. O. Illa, H. Gornitzka, V. Branchadell, A. Baceiredo, G. Bertrand and R.M. Ortuño, *Eur. J. Org. Chem.*, 2003, 3147.
639. O. Illa, H. Gornitzka, A. Baceiredo, G. Bertrand, V. Branchadell and R.M. Ortuño, *J. Org. Chem.*, 2003, **68**, 7707.
640. D. Amsallem, S. Mazières, V. Piquet-Fauré, H. Gornitzka, A. Baceiredo and G. Bertrand, *Chem. Eur. J.*, 2002, **8**, 5306.
641. T. Cantat, N. Mézailles, N. Maigrot, L. Ricard and P. Le Floch, *Chem. Commun.*, 2004, 1274.
642. J. Ruiz, M.E.G. Mosquera, G. García, E. Patrón, V. Riera, S. García-Granda and F. Van der Maelen, *Angew. Chem. Int. Ed.*, 2003, **42**, 4767.
643. B. Breit and W. Seiche, *J. Am. Chem. Soc.*, 2003, **125**, 6608.
644. V.F. Slagt, M. Röder, P.C.J. Kamer, P.W.N.M. van Leeuwen and J.N.H. Reek, *J. Am. Chem. Soc.*, 2004, **126**, 4056.
645. P. Nair, G.K. Anderson and N.P. Rath, *Organometallics*, 2003, **22**, 1494.
646. P.J. Walsh, A.E. Lurain and J. Balsells, *Chem. Rev.*, 2003, **103**, 3297.
647. P.-H. Leung, *Acc. Chem. Res.*, 2004, **37**, 169.
648. G.P. Schiemenz, *Z. Anorg. Allg. Chem.*, 2002, **628**, 2597.
649. (*a*) G.P. Schiemenz, C. Näther and S. Pörksen, *Z. Naturforsch., B: Chem. Sci.*, 2003, **58**, 663; (*b*) G.P. Schiemenz, S. Petersen and S. Pörksen, *Z. Naturforsch., B: Chem. Sci.*, 2003, **58**, 715.
650. O.T. Beachley Jr., D.J. MacRae and A.Yu. Kovalevsky, *Organometallics*, 2003, **22**, 1690.
651. U.V. Monkowius, S. Nogai and H. Schmidbaur, *Dalton Trans.*, 2004, 1610.
652. P.P. Power, *Chem. Rev.*, 2003, **103**, 789.
653. F. Mathey, *Angew. Chem. Int. Ed.*, 2003, **42**, 1578.
654. J. Grobe and D. Le Van, *J. Fluorine Chem.*, 2004, **125**, 801.
655. E. Kurita, Y. Tomonaga, S. Matsumoto, K. Ohno and H. Matsuura, *J. Mol. Struct. (THEOCHEM)*, 2003, **639**, 53.
656. M.A. Forgeron, M. Gee and R.E. Wasylishen, *J. Phys. Chem. A*, 2004, **108**, 4895.
657. V.G. Avakyan, S.L. Guselnikov and L.E. Gusel'nikov, *J. Organomet. Chem.*, 2003, **686**, 257.
658. M. Reiher and D. Schröder, *Chem. Eur. J.*, 2002, **8**, 5501.
659. K. Toyota, A. Nakamura and M. Yoshifuji, *Chem. Commun.*, 2002, 3012.
660. R.C. Smith, E. Urnezius, K.-C. Lam, A.L. Rheingold and J.D. Protasiewicz, *Inorg. Chem.*, 2002, **41**, 5296.
661. S. Sasaki, H. Aoki, K. Sutoh, S. Hakiri, K. Tsuji and M. Yoshifuji, *Helv. Chim. Acta*, 2002, **85**, 3842.
662. T. Sasamori, N. Takeda and N. Tokitoh, *J. Phys. Org. Chem.*, 2003, **16**, 450.
663. A.S. Ionkin and W.J. Marshall, *Heteroatom Chem.*, 2003, **14**, 360.

664. K. Toyota, S. Kawasaki, A. Nakamura and M. Yoshifuji, *Chem. Lett*., 2003, **32**, 430.
665. K. Toyota, S. Kawasaki and M. Yoshifuji, *Tetrahedron. Lett*., 2002, **43**, 7953.
666. N. Wiberg, A. Worner, H.-W. Lerner and K. Karaghiosoff, *Z. Naturforsch., B: Chem. Sci*., 2002, **57**, 1027.
667. M. Freytag, P.J. Dyson, L. Ernst, P.G. Jones and R. Schmutzler, *Inorg. Chem. Commun*., 2002, **5**, 808.
668. M. Freytag, F.T. Edelmann, L. Ernst, P.G. Jones and R. Schmutzler, *Z. Anorg. Allg. Chem*., 2004, **630**, 377.
669. N.H.T. Huy, L. Ricard and F. Mathey, *Organometallics*, 2003, **22**, 1346.
670. S. Loss, C. Widauer, H. Rüegger, U. Fleischer, C.M. Marchand, H. Grützmacher and G. Frenking, *Dalton Trans*., 2003, 85.
671. C. Dutan, S. Shah, R.C. Smith, S. Choua, T. Berclaz, M. Geoffroy and J.D. Protasiewicz, *Inorg. Chem*., 2003, **42**, 6241.
672. R.C. Smith and J.D. Protasiewicz, *Eur. J. Inorg. Chem*., 2004, **1**, 998.
673. R.C. Smith and J.D. Protasiewicz, *J. Am. Chem. Soc*., 2004, **126**, 2268.
674. V.A. Wright and D.P. Gates, *Angew. Chem. Int. Ed*., 2002, **41**, 2389.
675. R.C. Smith, X. Chen and J.D. Protasiewicz, *Inorg. Chem*., 2003, **42**, 5468.
676. M. Yam, C.-W. Tsang and D.P. Gates, *Inorg. Chem*., 2004, **43**, 3719.
677. A.S. Ionkin and W.J. Marshall, *Heteroatom Chem*., 2002, **13**, 662.
678. F. Murakami, S. Sasaki and M. Yoshifuji, *Angew. Chem. Int. Ed*., 2002, **41**, 2574.
679. L. Weber, L. Pumpenmeier, H.-G. Stammler and B. Neumann, *Dalton Trans*., 2004, 659.
680. M.M. Al-Ktaifani, P.B. Hitchcock and J.F. Nixon, *Inorg. Chim. Acta*., 2003, **356**, 103.
681. M. Reiher and B. Kirchner, *Angew. Chem. Int. Ed*., 2002, **41**, 3429.
682. C.S. Wannere, R.K. Bansal and P. von R. Schleyer, *J. Org. Chem*., 2002, **67**, 9162.
683. A. Termaten, M. van der Sluis and F. Bickelhaupt, *Eur. J. Org. Chem*., 2003, 2049.
684. S. Kimura, S. Ito, M. Yoshifuji and T. Veszprémi, *J. Org. Chem*., 2003, **68**, 6820.
685. P. Rosa, C. Gouverd, G. Bernardinelli, T. Berclaz and M. Geoffroy, *J. Phys. Chem. A*, 2003, **107**, 4883.
686. L. Weber, M. Meyer, H.-G. Stammler and B. Neumann, *Organometallics*, 2003, **22**, 5063.
687. C.-W. Tsang, M. Yam and D.P. Gates, *J. Am. Chem. Soc*., 2003, **125**, 1480.
688. W.-W. du Mont, T. Gust, E. Seppälä, C. Wismach, P.G. Jones, L. Ernst, J. Grunenberg and H.C. Marsmann, *Angew. Chem. Int. Ed*., 2002, **41**, 3829.
689. W.-W. du Mont, T. Gust, E. Seppälä and C. Wismach, *J. Organomet. Chem*., 2004, **689**, 1331.
690. Y. Naruse, M. Sugiura and S. Inagaki, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2447.
691. S. Ito, S. Sekiguchi and M. Yoshifuji, *J. Org. Chem*., 2004, **69**, 4181.
692. S. Ito, S. Kimura and M. Yoshifuji, *Bull. Chem. Soc. Jpn*., 2003, **76**, 405.
693. S. Ito, S. Kimura and M. Yoshifuji, *Chem. Lett*., 2002, **31**, 708.
694. M. Brym, C. Jones, M. Waugh, E.M. Hey-Hawkins and F. Majoumo, *New J. Chem*., 2003, **27**, 1614.
695. C. Jones, P.C. Junk, A.F. Richards and M. Waugh, *New J. Chem*., 2002, **26**, 1209.
696. S. Aldridge, C. Jones, P.C. Junk, A.F. Richards and M. Waugh, *J. Organomet. Chem*., 2003, **665**, 127.
697. M. Brym, C. Jones and A.F. Richards, *J. Chem. Soc. Dalton Trans*., 2002, 2800.
698. H. Liang, S. Ito and M. Yoshifuji, *Org. Biomol. Chem*., 2003, **1**, 3054.

699. (*a*) S. Ito, H. Liang and M. Yoshifuji, *Chem. Commun*., 2003, 398; (*b*) H. Liang, S. Ito and M. Yoshifuji, *Org. Lett*., 2004, **6**, 425.
700. S.T. Liddle and K. Izod, *Chem. Commun*., 2003, **1**, 772.
701. Z.-X. Wang, D.-Q. Wang and J.-M. Dou, *J. Organomet. Chem*., 2003, **665**, 205.
702. S. Ito, S. Kimura and M. Yoshifuji, *Org. Lett*., 2003, **5**, 1111.
703. S. Ito, S. Sekiguchi and M. Yoshifuji, *Eur. J. Org. Chem*., 2003, 4838.
704. K. Miqueu, J.-M. Sotiropoulos, P. Baylère, S. Joantéguy, G. Pfister-Guillouzo, H. Ranaivonjatovo, J. Escudié and M. Bouslikhane, *J. Mol. Struct*., 2004, **690**, 53.
705. W.W. Schoeller and D. Eisner, *Inorg. Chem*., 2004, **43**, 2585.
706. E.A. Ishmaeva, D.V. Chachkov and Ya. A. Vereshchagin, *Russ. J. Org. Chem*., 2003, **39**, 1553.
707. O. Kwon, J. Choo, S. Kim and Y. Kwon, *J. Mol. Struct. (THEOCHEM)*, 2004, **685**, 185.
708. A.S. Ionkin and W.J. Marshall, *Heteroatom Chem*., 2003, **14**, 231.
709. F. Ozawa, S. Kawagishi, T. Ishiyama and M. Yoshifuji, *Organometallics*, 2004, **23**, 1325.
710. F. Ozawa, T. Ishiyama, S. Yamamoto, S. Kawagishi, H. Murakami and M. Yoshifuji, *Organometallics*, 2004, **23**, 1698.
711. A. Moores, N. Mézailles, L. Ricard, F. Mathey and P. Le Floch, *Chem. Commun*., 2003, 1914.
712. M.H. Araujo, P.B. Hitchcock, J.F. Nixon, U. Kuehner and O. Stelzer, *Chem. Commun*., 2003, 1092.
713. M. Perruzini, P. Barbaro, V. Bertolasi, C. Bianchini, I. de los Rios, N. Mantovani, L. Marvelli and R. Rossi, *Dalton Trans*., 2003, 4121.
714. O. Mó, M. Yáñez, J.-C. Guillemin, El. H. Riague, J.-F. Gal, P.-C. Maria and C.D. Poliart, *Chem. Eur. J*., 2002, **8**, 4919.
715. X.M. Li, H.T. Yu, H.G. Fu, Z.S. Li and J.Z. Sun, *Chin. Chem. Lett*., 2004, **15**, 250.
716. B. Wrackmeyer, *Z. Naturforsch., B: Chem. Sci*., 2003, **58**, 1041.
717. L. Weber, *Eur. J. Inorg. Chem*., 2003, 1843.
718. M. Brym and C. Jones, *Dalton Trans*., 2003, 3665.
719. S. Ito, H. Sugiyama and M. Yoshifuji, *Chem. Commun*., 2002, 1744.
720. N. Tokitoh, H. Suzuki, N. Takeda, T. Kajiwara, T. Sasamori and R. Okazaki, *Silicon Chem*., 2002, (pub. 2004), **1**, 313.
721. S.E. d'Arbeloff-Wilson, P.B. Hitchcock, J.F. Nixon, H. Kawaguchi and K. Tatsumi, *J. Organomet. Chem*., 2003, **672**, 1.
722. D. Gigmes, Y. Berchadsky, J.-P. Finet, D. Siri and P. Tordo, *J. Phys. Chem. A*, 2003, **107**, 9652.
723. P.N. Condick, M.A. Fox, R. Greatrex, C. Jones and D.L. Ormsby, *Chem. Commun*., 2002, 1448.
724. C. Topf, T. Clark, F.W. Heinemann, M. Hennemann, S. Kummer, H. Pritzkow and U. Zenneck, *Angew. Chem. Int. Ed*., 2002, **41**, 4047.
725. M.D. Francis and P.B. Hitchcock, *Organometallics*, 2003, **22**, 2891.
726. G. Anderson, J.C. Green and M.D. Francis, *Organometallics*, 2003, **22**, 2897.
727. A.D. Burrows, N. Carr, M. Green, J.M. Lynam, M.F. Mahon, M. Murray, B. Kiran, M.T. Nguyen and C. Jones, *Organometallics*, 2002, **21**, 3076.
728. D. Lentz, H. Michael-Schulz and M. Reuter, *Z. Anorg. Allg. Chem*., 2004, **630**, 563.
729. H. Sugiyama, S. Ito and M. Yoshifuji, *Angew. Chem. Int. Ed*., 2003, **42**, 3802.
730. H. Sugiyama, S. Ito and M. Yoshifuji, *Chem. Eur. J*., 2004, **10**, 2700.

731. M. Sebastian, M. Nieger, D. Szieberth, L. Nyulászi and E. Niecke, *Angew. Chem. Int. Ed.*, 2004, **43**, 637.
732. K. Miqueu, J.-M. Sotiropoulos, G. Pfister-Guillouzo, V.L. Rudzevich, H. Gornitzka, V. Lavallo and V.D. Romanenko, *Eur. J. Inorg. Chem.*, 2004, 2289.
733. A.B. Rozhenko, M.I. Povolotskii and W.W. Schoeller, *Russ. J. Gen. Chem.*, 2004, **74**, 500.
734. N. Burford, T.S. Cameron, K.D. Conroy, B. Ellis, M. Lumsden, C.L.B. Macdonald, R. McDonald, A.D. Phillips, P.J. Ragogna, R.W. Schurko, D. Walsh and R.E. Wasylishen, *J. Am. Chem. Soc.*, 2002, **124**, 14012.
735. N. Burford, A.D. Phillips, H.A. Spinney, K.N. Robertson and T.S. Cameron, *Inorg. Chem.*, 2003, **42**, 4949.
736. L.N. Heydorn, P.C. Burgers, P.J.A. Ruttink and J.K. Terlouw, *Int. J. Mass Spectrom.*, 2003, **228**, 759.
737. X. Chen, R.C. Smith and J.D. Protasiewicz, *Chem. Commun.*, 2004, 146.
738. R.C. Smith, S. Shah, E. Urnezius and J.D. Protasiewicz, *J. Am. Chem. Soc.*, 2003, **125**, 40.
739. K. Lammertsma, *Topics in Current Chem.*, 2003, **229**, 95.
740. J.M. Galbraith, P.P. Gaspar and W.T. Borden, *J. Am. Chem. Soc.*, 2002, **124**, 11669.
741. G. Chung and M.S. Gordon, *Organometallics*, 2003, **22**, 42.
742. K. Lammertsma, A.W. Ehlers and M.L. McKee, *J. Am. Chem. Soc.*, 2003, **125**, 14750.
743. N.H. Tran-Huy, H.T. Le, F. Mathey and M.T. Nguyen, *J. Chem. Soc. Perkin Trans.*, 2002, **9**, 2140.
744. R. Waterman and G.L. Hillhouse, *Organometallics*, 2003, **22**, 5182.
745. J. Sánchez-Nieves, B.T. Sterenberg, K.A. Udachin and A.J. Carty, *J. Am. Chem. Soc.*, 2003, **125**, 2404.
746. R. Waterman and G.L. Hillhouse, *J. Am. Chem. Soc.*, 2003, **125**, 13350.
747. N.H.T. Huy, R. Salemkour, N. Bartes, L. Ricard and F. Mathey, *Tetrahedron*, 2002, **58**, 7191.
748. J.C. Slootweg, M. Schakel, F.J.J. de Kanter, A.W. Ehlers, S.I. Kozhushkov, A. de Meijere, M. Lutz, A.L. Spek and K. Lammertsma, *J. Am. Chem. Soc.*, 2004, **126**, 3050.
749. C. Compain, N.H.T. Huy and F. Mathey, *Heteroatom Chem.*, 2004, **15**, 258.
750. R.E. Bulo, A.W. Ehlers, F.J.J. de Kanter, M. Schakel, M. Lutz, A.L. Spek, K. Lammertsma and B. Wang, *Chem. Eur. J.*, 2004, **10**, 2732.
751. A.A. Khan, C. Wismach, P.G. Jones and R. Streubel, *Chem. Commun.*, 2003, 2892.
752. F. Basuli, L.A. Watson, J.C. Huffman and D.J. Mindiola, *Dalton Trans.*, 2003, 4228.
753. F. Basuli, B.C. Bailey, J.C. Huffman, M.-H. Baik and D.J. Mindiola, *J. Am. Chem. Soc.*, 2004, **126**, 1924.
754. Z. Weng, W.K. Leong, J.J. Vital and L.Y. Goh, *Organometallics*, 2003, **22**, 1657.
755. (*a*) A.J. Termaten, T. Nijbacker, M. Schakel, M. Lutz, A.L. Spek and K. Lammertsma, *Organometallics*, 2002, **21**, 3196; (*b*) A.J. Termaten, H. Aktas, M. Schakel, A.W. Ehlers, M. Lutz, A.L. Spek and K. Lammertsma, *Organometallics*, 2003, **22**, 1827.
756. A.J. Termaten, M. Schakel, A.W. Ehlers, M. Lutz, A.L. Spek and K. Lammertsma, *Chem. Eur. J.*, 2003, **9**, 3577.

757. A.J. Termaten, T. Nijbacker, M. Schakel, M. Lutz, A.L. Spek and K. Lammertsma, *Chem. Eur. J.*, 2003, **9**, 2200.
758. B.T. Sterenberg, K.A. Udachin and A.J. Carty, *Organometallics*, 2003, **22**, 3927.
759. J.S. Figueroa and C.C. Cummins, *Angew. Chem. Int. Ed.*, 2004, **43**, 984.
760. M.E. García, V. Riera, M.A. Ruiz, D. Sáez, H. Hamidov, J.C. Jeffery and T. Riis-Johannessen, *J. Am. Chem. Soc.*, 2003, **125**, 13044.
761. W.W. Schoeller, *Topics in Current Chem.*, 2003, **229**, 75.
762. N. Burford and P.J. Ragogna, *J. Chem. Soc., Dalton Trans.*, 2002, 4307.
763. N. Burford, P. Losier, A.D. Phillips, P.J. Ragogna and T.S. Cameron, *Inorg. Chem.*, 2003, **42**, 1087.
764. N. Burford, P.J. Ragogna, R. McDonald and M.J. Ferguson, *Chem. Commun.*, 2003, 2066.
765. N. Burford, P.J. Ragogna, R. McDonald and M.J. Ferguson, *J. Am. Chem. Soc.*, 2003, **125**, 14404.
766. B.D. Ellis, M. Carlesimo and C.L.B. MacDonald, *Chem. Commun.*, 2003, 1946.
767. K.A. Porter, A.C. Willis, J. Zank and S.B. Wild, *Inorg. Chem.*, 2002, **41**, 6380.
768. K.B. Dillon and R.J. Olivey, *Heteroatom Chem.*, 2004, **15**, 150.
769. R.S. Thompson, L.P. Guler, E.D. Nelson, Y.-Q. Yu and H.I. Kenttämaa, *J. Org. Chem.*, 2002, **67**, 5076.
770. A. Takano, H. Fukuhara, T. Ohno, M. Kutsuma, T. Fujimoto, H. Shirai, R. Iriye, A. Kakehi and I. Yamamoto, *J. Carbohydrate Chem.*, 2003, **22**, 443.
771. R. Pietschnig, *Chem. Commun*, 2004, 546.
772. H. Nakazawa, *Adv. in Organomet. Chem.*, 2004, **50**, 108.
773. R. Menye-Biyogo, F. Delpech, A. Castel, H. Gornitzka and P. Rivière, *Angew. Chem. Int. Ed.*, 2003, **42**, 5610.
774. M.J.P. Harger and C. Preston, *Chem. Commun.*, 2003, 2200.
775. E. Rivard, K. Huynh, A.J. Lough and I. Manners, *J. Am. Chem. Soc.*, 2004, **126**, 2286.
776. T. Baumgartner, P. Moors, M. Nieger, H. Hupfer and E. Niecke, *Organometallics*, 2002, **21**, 4919.
777. T.P.M. Goumans, A.W. Ehlers, K. Lammertsma and E.-U. Würthwein, *Eur. J. Org. Chem.*, 2003, 2941.
778. J.C. Slootweg, F.J.J. de Kanter, M. Schakel, A.W. Ehlers, B. Gehrhus, M. Lutz, A.M. Mills, A.L. Spek and K. Lammertsma, *Angew. Chem. Int. Ed.*, 2004, **43**, 3474.
779. A.A. Sabino, M.N. Eberlin, L.A.B. Moraes and K.K. Laali, *Org. Biomol. Chem.*, 2003, **1**, 395.
780. N.E. Brasch, I.G. Hamilton, E.H. Krenske and S.B. Wild, *Organometallics*, 2004, **23**, 299.
781. M. White, L. Ricard and F. Mathey, *Organometallics*, 2003, **22**, 4825.
782. M. Brym, C. Jones and M. Waugh, *Dalton Trans.*, 2003, 2889.
783. A.A. Khan, C. Wismach, P.G. Jones and R. Streubel, *Dalton Trans.*, 2003, 2483.
784. E. Ionescu, P.G. Jones and R. Streubel, *Chem. Commun.*, 2002, 2204.
785. R. Streubel, N. Hoffmann, G. von Frantzius, C. Wismach, P.G. Jones, H.-M. Schiebel, J. Grunenberg, H. Vong, P. Chaigne, C. Compain, N.H.T. Huy and F. Mathey, *Organometallics*, 2003, **22**, 5427.
786. N. Hoffmann, C. Wismach, L. Ernst, H.-M. Schiebel, P.G. Jones and R. Streubel, *Eur. J. Inorg. Chem.*, 2003, 1815.
787. A.A. Khan, C. Neumann, C. Wismach, P.G. Jones and R. Streubel, *J. Organomet. Chem.*, 2003, **682**, 212.

788. C. Neumann, A.P. Junquera, C. Wismach, P.G. Jones and R. Streubel, *Tetrahedron*, 2003, **59**, 6213.
789. E.J.P. Malar, *Inorg. Chem.*, 2003, **42**, 3873.
790. F. De Proft, P.W. Fowler, R.W.A. Havenith, P. von R. Schleyer, G. Van Lier and P. Geerlings, *Chem. Eur. J.*, 2004, **10**, 940.
791. D. Delaere, N.-N. Pham-Tran and M.T. Nguyen, *Chem. Phys. Lett.*, 2004, **383**, 138.
792. K. Geetha, T.C. Dinadayalane and G.N. Sastry, *J. Phys. Org. Chem.*, 2003, **16**, 298.
793. D. Delaere, N.-N. Pham-Tran and M.T. Nguyen, *J. Phys. Chem. A.*, 2003, **107**, 7514.
794. G. Keglevich, *Targets in Heterocyclic Systems*, 2002, **6**, 245.
795. D.G. Yakhvarov, Y.H. Budnikova, N.H.T. Huy, L. Ricard and F. Mathey, *Organometallics*, 2004, **23**, 1961.
796. C. Thoumazet, M. Melaimi, L. Ricard, F. Mathey and P. Le Floch, *Organometallics*, 2003, **22**, 1580.
797. X. Sava, A. Marinetti, L. Ricard and F. Mathey, *Eur. J. Inorg. Chem.*, 2002, 1657.
798. C. Ortega, M. Gouygou and J.-C. Daran, *Chem. Commun.*, 2003, 1154.
799. M. Hissler, P.W. Dyer and R. Réau, *Coord. Chem. Revs.*, 2003, **244**, 1.
800. C. Hay, C. Fave, M. Hissler, J. Rault-Berthelot and R. Réau, *Org. Lett.*, 2003, **5**, 3467.
801. C. Fave, T.-Y. Cho, M. Hissler, C.-W. Chen, T.-Y. Luh, C.-C. Wu and R. Réau, *J. Am. Chem. Soc.*, 2003, **125**, 9254.
802. Y. Makioka, T. Hayashi and M. Tanaka, *Chem. Lett.*, 2004, **33**, 44.
803. C. Fave, M. Hissler, T. Kárpáti, J. Rault-Berthelot, V. Deborde, L. Toupet, L. Nyulászi and R. Réau, *J. Am. Chem. Soc.*, 2004, **126**, 6058.
804. Yu.G. Trishin, V.I. Namestnikov and V.K. Bel'skii, *Russ. J. Gen. Chem.*, 2004, **74**, 189.
805. G. Keglevich, R. Farkas, T. Imre, K. Ludányi, A. Szöllösy and L. Töke, *Heteroatom Chem.*, 2003, **14**, 316.
806. G. Keglevich, L. Nyulászi, T. Chuluunbaatar, B.-A. Namkhainyambuu, K. Ludányi, T. Imre and L. Töke, *Tetrahedron*, 2002, **58**, 9801.
807. G. Frison, F. Brebion, R. Dupont, F. Mercier, L. Ricard and F. Mathey, *C. R. Chimie*, 2002, **5**, 245.
808. P. Toullec, L. Ricard and F. Mathey, *J. Org. Chem.*, 2003, **68**, 2803.
809. T. Dinadayalane and G.N. Sastry, *Organometallics*, 2003, **22**, 5526.
810. B. Deschamps, L. Ricard and F. Mathey, *Organometallics*, 2003, **22**, 1356.
811. E. Mattman, F. Mercier, L. Ricard and F. Mathey, *J. Org. Chem.*, 2002 **67**, 5422.
812. F. Leca, M. Sauthier, B. le Guennic, C. Lescop, L. Toupet, J.-F. Halet and R. Réau, *Chem. Commun.*, 2003, 1774.
813. F. Leca, M. Sauthier, V. Deborde and L. Toupet, and R. Réau, *Chem. Eur. J.*, 2003, **9**, 3785.
814. A. Caballero, F.A. Jalón, B.R. Manzano, M. Sauthier, L. Toupet and R. Réau, *J. Organomet. Chem.*, 2002, **663**, 118.
815. S. Mourgues, D. Serra, F. Lamy, S. Vincendeau, J.-C. Daran, E. Manoury and M. Gouygou, *Eur. J. Inorg. Chem.*, 2003, 2820.
816. R. Shintani and G.C. Fu, *Org. Lett.*, 2002, **4**, 3699.
817. K. Kowalski, A. Vessières, S. Top, G. Jaouen and J. Zakrzewski, *Tetrahedron Lett.*, 2003, **44**, 2749.

818. M. Ogasawara, T. Nagano and T. Hayashi, *Organometallics*, 2003, **22**, 1174.
819. A. Kłys, J. Zakrzewski and L. Jerzykiewicz, *Tetrahedron Asymmetry*, 2003, **14**, 3343.
820. M. Ogasawara, K. Yoshida and T. Hayashi, *Organometallics*, 2003, **22**, 1783.
821. S.O. Agustsson, C. Hu, U. Englert, T. Marx, L. Wesemann and C. Ganter, *Organometallics*, 2002, **21**, 2993.
822. D. Plażuk and J. Zakrzewski, *Synth. Commun.*, 2004, **34**, 99.
823. X. Sava, L. Ricard, F. Mathey and P. Le Floch, *J. Organomet. Chem.*, 2003, **671**, 120.
824. X. Sava, L. Ricard, F. Mathey and P. Le Floch, *Inorg. Chim. Acta*, 2003, **350**, 182.
825. M. Melaimi, L. Ricard, F. Mathey and P. Le Floch, *J. Organomet. Chem.*, 2003, **684**, 189.
826. X. Sava, M. Melaimi, N. Mézailles, L. Ricard, F. Mathey and P. Le Floch, *New J. Chem.*, 2002, **26**, 1378.
827. T.K. Hollis, Y.J. Ahn and F.S. Tham, *Chem. Commun.*, 2002, 2996.
828. T.K. Hollis, Y.J. Ahn and F.S. Tham, *Organometallics*, 2003, **22**, 1432.
829. L.-S. Wang and T.K. Hollis, *Org. Lett.*, 2003, **5**, 2543.
830. M. Ogasawara, T. Nagano, K. Yoshida and T. Hayashi, *Organometallics*, 2002, **21**, 3062.
831. (*a*) D. Carmichael, F. Mathey, L. Ricard and N. Seeboth, *Chem. Commun.*, 2002, 2976; (*b*) D. Carmichael, J. Klankermayer, L. Ricard and N. Seeboth, *Chem. Commun.*, 2004, 1144.
832. P. Toullec, L. Ricard and F. Mathey, *Organometallics*, 2003, **22**, 1340.
833. M. Westerhausen, M.W. Ossberger, A. Keilbach, C. Gückel, H. Piotrowski, M. Suter and H. Nöth, *Z. Anorg. Allg. Chem.*, 2003, **629**, 2398.
834. F. Nief, D. Turcitu and L. Ricard, *Chem. Commun.*, 2002, 1646.
835. D. Turcitu, F. Nief and L. Ricard, *Chem. Eur. J.*, 2003, **9**, 4916.
836. M. Scheibitz, J.W. Bats, M. Bolte and M. Wagner, *Eur. J. Inorg. Chem.*, 2003, 2049.
837. D. Gudat, M. Nieger, K. Schmitz and L. Szarvas, *Chem. Commun.*, 2002, 1820.
838. D. Gudat, B. Lewall, M. Nieger, I. Detmer, L. Szarvas, P. Saarenketo and G. Marconi, *Chem. Eur. J.*, 2003, **9**, 661.
839. Z. Bajko, J. Daniels, D. Gudat, S. Häp and M. Nieger, *Organometallics*, 2002, **21**, 5182.
840. G.K.B. Clentsmith, F.G.N. Cloke, J.C. Green, J. Hanks, P.B. Hitchcock and J.F. Nixon, *Angew. Chem. Int. Ed.*, 2003, **42**, 1038.
841. M.M. Al-Ktaifani, P.B. Hitchcock and J.F. Nixon, *J. Organomet. Chem.*, 2003, **665**, 101.
842. F.W. Heinemann, M. Zeller and U. Zenneck, *Organometallics*, 2004, **23**, 1689.
843. J.M. Lynam, M.C. Copsey, M. Green, J.C. Jeffrey, J.E. McGrady, C.A. Russell, J.M. Slattery and A.C. Swain, *Angew. Chem. Int. Ed.*, 2003, **42**, 2778.
844. V.A. Miluykov, O.G. Sinyashin, P. Loennecke and E. Hey-Hawkins, *Mendeleev Commun.*, 2003, **13**, 212.
845. H. Sitzmann, *Angew. Chem. Int. Ed.*, 2002, **41**, 2723.
846. T. Jikyo, J. Schatz and G. Maas, *J. Phys. Org. Chem.*, 2003, **16**, 504.
847. R.K. Bansal, Ne. Gupta and Ni. Gupta, *Heteroatom Chem.*, 2004, **15**, 271.
848. R.K. Bansal, A. Dandia, N. Gupta and D. Jain, *Heteroatom Chem.*, 2003, **14**, 560.
849. P. Sharma, A. Kumar and P. Pandey, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 583.
850. V. Padmavathi, T.V.R. Reddy, K.A. Reddy and D.B. Reddy, *J. Heterocyclic Chem.*, 2003, **40**, 149.

851. L. Szarvas, Z. Bajko, S. Fusz, S. Burck, J. Daniels, M. Nieger and D. Gudat, *Z. Anorg. Allg. Chem.*, 2002, **628**, 2303.
852. J. Heinicke, N. Gupta, S. Singh, A. Surana, O. Kühl, R.K. Bansal, K. Karaghiosoff and M. Voight, *Z. Anorg. Allg. Chem.*, 2002, **628**, 2869.
853. C. Peters, U. Fischbeck, F. Tabellion and M. Regitz, and F. Preuss, *Z. Naturforsch., B: Chem. Sci.*, 2003, **58**, 44.
854. (*a*) S. Sharma, *Int. J. Chem. Sci.*, 2003, **1**, 245; (*b*) S. Sharma, *Chem. Abstr.*, **141**, 38670.
855. J. Dietz, J. Renner, U. Bergsträsser, P. Binger and M. Regitz, *Eur. J. Org. Chem.*, 2003, 512.
856. J. Kerth, T. Jikyo and G. Maas, *Eur. J. Org. Chem.*, 2003, 1894.
857. T. Jikyo and G. Maas, *Chem. Commun.*, 2003, 2794.
858. S.E. d'Arbeloff-Wilson, P.B. Hitchcock, J.F. Nixon and L. Nyulászi, *J. Organomet. Chem.*, 2002, **655**, 7.
859. M.L. Helm, P.B. Hitchcock, J.F. Nixon, L. Nyulászi and D. Szieberth, *J. Organomet. Chem.*, 2002, **659**, 84.
860. C. Lepetit, V. Peyrou and R. Chauvin, *Phys. Chem. Chem. Phys.*, 2004, **6**, 303.
861. I. Yavari, M. Nikpoor-Nezhati and S. Dehghan, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 485.
862. I. Yavari, S. Dehghan and M. Nikpoor-Nezhati, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 869.
863. J. Jeevanandam, E.J.P. Malar and R. Gopalan, *Organometallics*, 2003, **22**, 5454.
864. (*a*) L. Pacureanu and M. Mracec, *Revista de Chimie*, 2003, **54**, 399; (*b*) L. Pacureanu and M. Mracec, *Chem. Abstr.*, **140**, 253634.
865. F. Hartl, T. Mahabiersing, P. Le Floch, F. Mathey, L. Ricard and P. Rosa, *Inorg. Chem.*, 2003, **42**, 4442.
866. V.R. Ferro, S. Omar, R.H. González-Jonte and J.M. García de la Vega, *Heteroatom Chem.*, 2003, **14**, 160.
867. J.-P. Majoral, A. Igau, V. Cadierno and M. Zablocka, *Topics in Current Chem.*, 2002, **220**, 53.
868. P. de Koe and F. Bickelhaupt, *Z. Naturforsch., B: Chem. Sci.*, 2003, **58**, 782.
869. A.J. Ashe III, Z. Bajko, M.D. Carr and J.W. Kampf, *Organometallics*, 2003, **22**, 910.
870. T. Kojima, Y. Ishioka and Y. Matsuda, *Chem. Commun.*, 2004, 366.
871. B. Breit and E. Fuchs, *Chem. Commun.*, 2004, 694.
872. A. Moores, L. Ricard, P. Le Floch and N. Mézailles, *Organometallics*, 2003, **22**, 1960.
873. A. Moores, L. Ricard and P. Le Floch, *Angew. Chem. Int. Ed.*, 2003, **42**, 4940.
874. A. Moores, N. Mézailles, L. Ricard, Y. Jean and P. Le Floch, *Organometallics*, 2004, **23**, 2870.
875. (*a*) M. Doux, N. Mézailles, M. Melaimi, L. Ricard and P. Le Floch, *Chem. Commun.*, 2002, 1566; (*b*) M. Doux, N. Mézailles, L. Ricard and P. Le Floch, *Eur. J. Inorg. Chem.*, 2003, 3878.
876. C. Jones and M. Waugh, *Dalton Trans.*, 2004, 1971.
877. J. Renner, U. Bergsträsser, P. Binger and M. Regitz, *Angew. Chem. Int. Ed.*, 2003, **42**, 1863.
878. J. Steinbach, J. Renner, P. Binger and M. Regitz, *Synthesis*, 2003, 1526; (see also Erratum, *Synthesis*, 2003, 2274).
879. J. Steinbach, P. Binger and M. Regitz, *Synthesis*, 2003, 2720.

880. S. Weidner, J. Renner, U. Bergsträsser, M. Regitz and H. Heydt, *Synthesis*, 2004, 241.
881. H. Disteldorf, J. Renner, H. Heydt, P. Binger and M. Regitz, *Eur. J. Org. Chem.*, 2003, 4292.
882. A. Moores, N. Mézailles, N. Maigrot, L. Ricard, F. Mathey and P. Le Floch, *Eur. J. Inorg. Chem.*, 2002, 2034.
883. M. Doux, L. Ricard, F. Mathey, P. Le Floch and N. Mézailles, *Eur. J. Inorg. Chem.*, 2003, 687.
884. N. Maigrot, M. Melaimi, L. Ricard and P. Le Floch, *Heteroatom Chem.*, 2003, **14**, 326.
885. P. von R. Schleyer, L. Nyulászi and T. Kárpáti, *Eur. J. Org. Chem.*, 2003, 1923.

Phosphonium Salts and Phosphine Chalcogenides

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1 Phosphonium Salts

1.1 Preparation. – Not surprisingly, conventional quaternization reactions of tertiary phosphines have continued to be widely used in the synthesis of phosphonium salts, usually required as intermediates for Wittig procedures. Among new salts prepared in this way are the diphosphonium salt (1),[1] various *p*-dialkylaminobenzylphosphonium (2)[2] and 4-imidazolylmethylphosphonium (3)[3] salts, the 2,2,2-trifluoroethylphosphonium triflate (4)[4] and (5), the latter being obtained in high yield from an iodoalkyl precursor using an ultra high pressure quaternization procedure. Quaternization under conventional conditions is compromised by undesired intramolecular cyclisation reactions.[5] The reaction of triphenylphosphine with β-haloaminoesters derived from the ring-opening of oxazolines has given the β-phosphonio-L-alanine salts (6).[6] Whereas the reaction of $H_2C{=}(CH_2Cl)_2$ with dimethylphenylphosphine in refluxing N,N-dimethylacetamide gives the expected allylic diphosphonium salt (7), related reactions with triarylphosphines result in the formation of the allyl-vinyl diphosphonium salts (8). Allyl-vinyl diphosphonium salts (9) and (10) have also been obtained from the reactions of 2,3-dibromopropene and 1,3-dibromopropene, respectively, with triphenylphosphine under the same conditions, no catalyst being needed for the displacement of the vinylic bromine. These salts have been shown to undergo *ortho*-metallation reactions on treatment with a platinum(II) complex in refluxing 2-methoxyethanol.[7] Two routes to the bis(phosphonioalkyl)calix[4]arene (11) have been developed, this system having been shown to have anion-receptor properties.[8] Treatment of 2-hydroxymethylporphyrins with thionyl chloride in dry pyridine yields the corresponding 2-chloromethylporphyrins, which undergo quaternization in boiling chloroform to give the related triphenyl[(porphyrin-2-yl)methyl]phosphonium salts. These have been used for the synthesis of porphyrin dimers and higher oligomers.[9] The tetraphosphonioarylporphyrin system (12) has been obtained by treatment of the corresponding tetrakis(pentafluorophenyl)porphyrin with triethylphosphine in the presence of trimethylsilyl triflate in an application of the SASAPOS method (self-activated silyl-assisted polyonio substitution).[10] This approach was initially developed by Weiss and Pühlhofer in the

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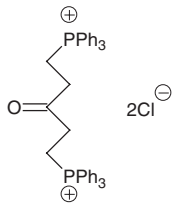
synthesis of the salt (13) from the reaction of pentafluorobenzoyl chloride with triphenylphosphine, trimethylsilyl triflate and aqueous triflic acid.[11] P-chirogenic trialkylphosphonium salts, e.g., (14) and (15), have been prepared by treatment of the related chiral tertiary phosphine-borane adducts with either HBF_4 or triflic acid. The salts are resistant to racemisation in methanol or water, even at elevated temperatures, and may be used instead of the free phosphines in the rhodium-catalysed asymmetric hydrogenation of enamides.[12] A series of 2-ureidocytosines bearing a phosphonioalkyl functionality, e.g., (16), has been prepared by a simple quaternization approach. In solution, these self-assemble in an anti-parallel manner to form a hydrogen-bonded dimer which is found to catalyse the ring-opening of epoxides in the presence of thiols.[13]



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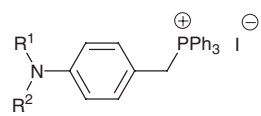

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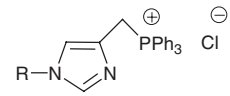

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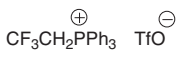

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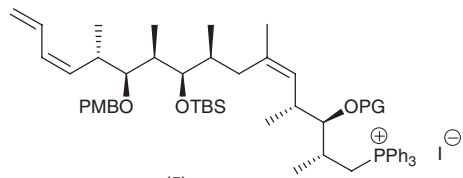

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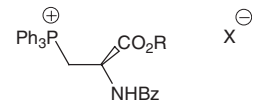
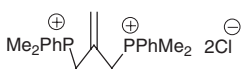
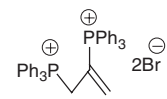


(6)



(7)

(8) Ar = Ph or *p*-C_6H_4



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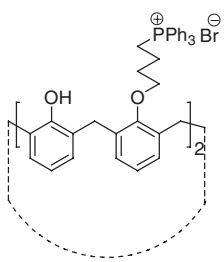

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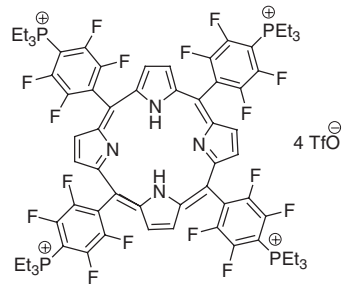

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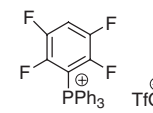

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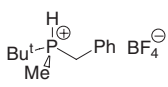

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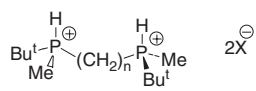
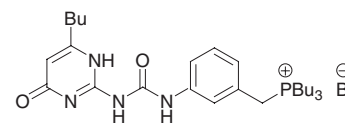
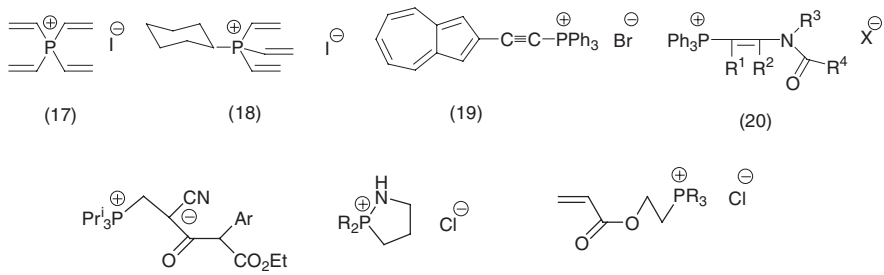


(15) X = BF_4 or TfO
n = 1 or 2



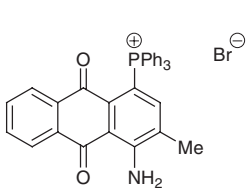
(16)

A high yield route to the tetravinylphosphonium salt (17) has been developed, starting from PH_3. Radical-promoted addition to vinyl acetate yields tris(2-acetoxyethyl)phosphine. Quaternization with 2-iodoethanol, followed by acetylation of the hydroxyalkylphosphonium salt gives tetrakis(2-acetoxyethyl)phosphonium iodide, which undergoes a base-promoted elimination to form (17). A similar approach has given the cyclohexyltrivinylphosphonium salt (18).[14] The 2-(2-azulenyl)ethynylphosphonium salt (19) has been obtained from the reaction of 2-bromoethynylazulene with triphenylphosphine. Subsequent treatment of this salt with *o*-substituted anilines provides a route to 2-(2-azulenyl)benzoazoles.[15] Full details have now appeared of the synthesis of β-(N-acylamino)vinylphosphonium salts (20) from the reactions of carbonyl-stabilised ylides with imidoyl chlorides.[16] Further work has also been reported on the properties of the zwitterions (21) obtained from the reactions of the tris(isopropyl)phosphine-ethyl 2-cyanoacrylate adduct with arylisocyanates.[17] Zwitterionic phosphonio-carborane systems have also been prepared and structurally characterised.[18] A convenient one-pot synthesis of 1,2-azaphospholanium salts (22) is provided by the intramolecular alkylation of 3-halopropylaminophosphines.[19] A series of water-soluble and thermosensitive copolymers bearing phosphonium groups has been prepared by the copolymerisation of acryloyloxyethyltrialkylphosphonium salts (23) with n-butyl methacrylate and N-isopropylacrylamide.[20]



Interest has continued in the synthesis of arylphosphonium salts by metal ion-catalysed routes from aryl halides. Nickel(II)-catalysed replacement of bromine in 1-amino-2-methyl-4-bromoanthraquinone by triphenylphosphine occurs readily under mild conditions (boiling ethanol) to give the phosphonioanthraquinone salt (24), the carbonyl group acting as a coordination template for the metal ion, facilitating replacement of the halogen. The extent to which the phosphonium group may be involved in hypercoordination from the adjacent carbonyl oxygen atom has been investigated by X-ray crystallography which shows considerable distortion of bond angles about phosphorus in the direction of trigonal bipyramidal geometry, the phosphorus-oxygen distance (2.661Å) being well within the sum of the van der Waals radii. The related stibonium salt has also been prepared, this showing a stronger interaction between the Group 15 atom and the carbonyl oxygen, the antimony-oxygen distance being 2.497Å. In both structures, the Group 15 element and the adjacent carbonyl oxygen atom are bent out of the plane of the anthraquinone system. However, the extent of out of plane deformation is smaller in the case

of the larger antimony atom, suggesting that there is a genuine hypercoordinative interaction which increases as the Group is descended.[21] In related work, the salt (25) has been obtained from the nickel(II)-catalysed displacement of bromine from 2-(2-bromophenyl)benzimidazole by tri(2-furyl)phosphine. X-Ray structural studies of the phosphoniobenzimidazole salt reveal the existence of a significant hypervalent coordinative interaction between heterocyclic nitrogen and the phosphonium centre, which also appears to be retained in solution, the ^{31}P nmr spectrum showing a highly shielded phosphorus atom, $\delta^{31}P = ca - 40$ ppm in $CDCl_3$. The nitrogen-phosphorus distance is 2.67Å, this being the shortest observed in structures of this type, a consequence of the electron-withdrawing properties of the 2-furyl substituents at phosphorus. In contrast, the N-P interaction in the quinolylmethylphosphonium salt (26) is much less developed, with an N-P distance of 3.511Å.[22] A hypervalent intramolecular coordinative interaction between nitrogen and the phosphonium centre also appears to be present in the *ortho*-oximinoarylphosphonium salt (27), obtained from the nickel(II)-catalysed reaction of triphenylphosphine with the oxime of *ortho*-bromoacetophenone, the nitrogen-phosphorus distance being 2.78Å.[23] However, on the basis of NMR coupling constant data, Schiemenz *et al*. have continued to argue that, in spite of the short nitrogen-phosphorus distances observed in the *peri*-naphthalene system (28), there is no evidence of such dative coordinative interactions, the short N-P distances being an artefact of the *peri*-substitution pattern in the naphthalene system.[24] A crystallographic study of the BOC-salt (29) reveals no unusual features, confirming the expected structure.[25]



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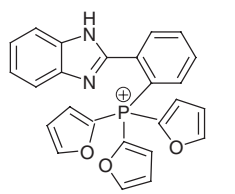

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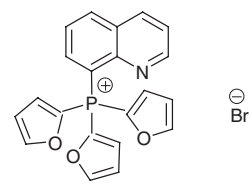

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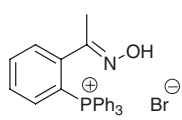

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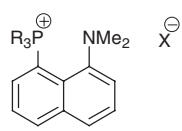

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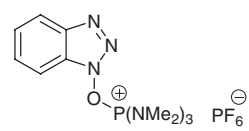


(29)

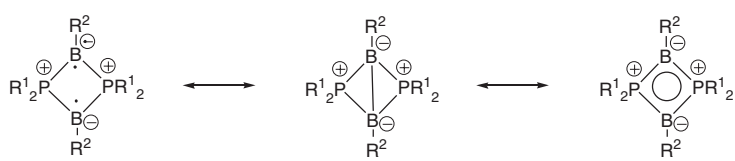
As is usual, phosphonium cations have been used to stabilise unusual anions. The salt $(Ph_4P)_2HP_7$, involving the hydrogenheptaphosphide anion, has been prepared as an ammonia solvate from the reaction of K_3P_7 with tetraphenylphosphonium bromide in liquid ammonia, and characterised by low-temperature X-ray structural analysis.[26] The reaction between the cyclic

diiodoorganotellurane, $C_4H_8TeI_2$, and triphenylphosphine has given, serendipitously, the first triphenylmethylphosphonium salts containing the $[C_4H_8TeI_4]^{2-}$ and $[TeI_6]^{2-}$ anions.[27] Phosphonium salts involving a mixed valence bromotellurate(IV)-selenate(II) anion[28] and the hexaazidotellurate(IV) anion[29] have also been prepared and characterised. A study of the reactions of germanium tetrachloride with primary and secondary phosphines has led to the isolation of the salts $[CyPH_3]^+[GeCl_3]^-$ and $[Ph_2PH_2]^+[GeCl_3]^-$.[30] Electrospray Fourier transform mass spectrometry of combinations of the cations $MePh_3P^+$ or Ph_4P^+ with cyanoferrate anions in the gas phase has identified the existence of nanocluster cation-anion aggregates, the study leading to a consideration of the principles of association of such ions in crystals. Multiple phenyl embraces, often observed in crystals involving such cations, are not influential in these systems.[31] However, phenyl embraces and π-stacking are influential in controlling the supramolecular structure of tetraphenylphosphonium *p*-sulfonatocalix[4]arene.[32] Among a wide range of other unusual anions stabilised by phosphonium cations reported in the period under review are diiodobromide,[33] 4-azidobenzenesulfonate,[34] $[Mg(BH_4)_2]^{2-}$,[35] various complex haloberyllates[36] and other halometallates,[37] haloorgano-stannates[38] and -plumbates,[39] $[NiPS_4]^-$ chains,[40] a series of polyazidotitanates[41] and a one-dimensional cyclic tetrameric metavanadate, $[V_4O_{11}]^{2-}$.[42] Treatment of diphenyltrichlorophosphorane with chlorine has led to the isolation of the salt $[Ph_2PCl_2]^+Cl_3^-$ as a chlorine solvate. A related reaction with indium trichloride gave the salt $[Ph_2PCl_2^+]_2\,[InCl_5]^{2-}$.[43] A reinvestigation of tetramethylfluorophosphorane, originally prepared by Schmidbaur's group in 1972, has revealed that it has an ionic structure, $Me_4P^+F^-$, in the solid state, which is stable below 120°C. Above this temperature, it sublimes, having a phosphorane structure in the gas phase.[44] The crystallisation and crystal structures of three new crystalline forms of the salt $MePh_3P^+I_3^-$ have been described, this compound now having been shown to exist in four polymorphic forms.[45]

1.2 Reactions of Phosphonium Salts. – The thermal stability of alkyl- and arylphosphonium salts incorporated into montmorillonite layered silicates as components of nanocomposite systems has been studied using thermogravimetry and pyrolysis GC-MS techniques. The alkylphosphonium silicates undergo initial degradation *via* two pathways, β-elimination and a nucleophilic displacement at phosphorus, reflecting the varying environments in the silicate. On the other hand, arylphosphonium silicates decompose *via* either a reductive elimination involving a five coordinate intermediate or radical generation through cleavage of a P-phenyl bond.[46] A theoretical study has shown that whereas α-phosphonium groups destabilise a methyl radical, the effect on an adjacent benzyl radical depends on the extent of alkylation at phosphorus.[47] Structure, bonding and reactivity in the 1,3-diphospha-2,4-diboretane system (30–32) has received considerable attention, with particular reference to the extent of their diradicaloid character. Substituent effects on electronic structures have received both theoretical consideration[48,49] and solid state structural investigations.[50] The radical-type reactivity of these systems has also been the subject of an experimental study.[51] NMR enantiodifferentiation of alkyltriphenylphosphonium salts

bearing a stereogenic centre on the alkyl group has been shown to be facilitated by the chiral shift reagent BINPHAT (33).[52]

Relatively few new aspects of the reactivity of phosphonium salts have been reported in the period under review. Treatment of aminophenylpropenyltriphenylphosphonium salts (34) with an acid anhydride in the presence of a tertiary amine results in the formation of 1,3-diacylindoles.[53] Amino(phosphonio)carbenes, e.g., (35), have been shown to undergo nucleophilic intermolecular as well as intramolecular substitution reactions at the carbene centre, enabling the synthesis of a variety of carbenes from a single carbene precursor. Thus, e.g., treatment of (35) with 2,6-$Me_2C_6H_3SLi$ results in displacement of di-*t*-butyl(methyl)phosphine to form the carbene 2,6-$Me_2C_6H_3SC(:)NPr^i_2$ in quantitative yield.[54] Phosphonium salt intermediates are involved in the reaction of Bayliss-Hillman acetates with phosphonium ylides, which provide a one-pot route to 5-arylpent-4-enoate derivatives.[55] A study of the reactivity of electrophilic species also containing a phosphonium group has shown that the latter may dramatically enhance the reactivity of the electrophilic centre. Thus, e.g., treatment of the phosphonioaldehyde (36) with benzene and triflic acid results in quantitative formation of the salt (37). Allyl- and propargyl-phosphonium salts also undergo similar C-arylation reactions *via* dicationic electrophilic phosphonium intermediates.[56] Phosphonium salt intermediates are also involved in the reactions of epoxides with carbon dioxide, which, in the presence of catalytic amounts of phenol, sodium iodide and a tertiary phosphine, result in the formation of five-membered cyclic carbonates.[57] The reactivity of oxo- and amino-phosphonium salts has also received some attention.The glycosyl-methyldiphenylphosphonium iodide (38) has been shown to act as an efficient glycosyl donor, enabling the synthesis of α-disaccharides in high yields at room temperature without the assistance of acid-promoters.[58] A quantum chemical approach has been applied to an assessment of the stability of the diphosphonium salts (39), with particular reference to the P–P bond energy.[59] A study of the sequential deprotonation of the tetraanilinophosphonium cation (40) has been reported, various intermediate species leading to the final trianion (41) having been characterised.[60] New routes to azides and diazonium compounds are afforded by the reactions of lithio-amides and -hydrazonides, respectively, with azidotris(diethylamino)phosphonium bromide (42), *via* initial nucleophilic attack of the anion on the azide group.[61,62] A range of new tris(dialkylamino)oxophosphonium salts similar to BOP has been prepared and shown to have useful properties as peptide coupling reagents.[63]



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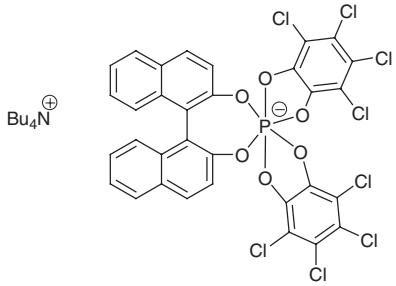

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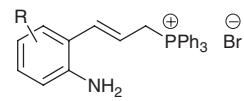

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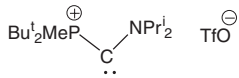

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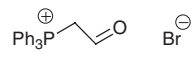

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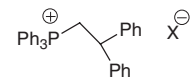

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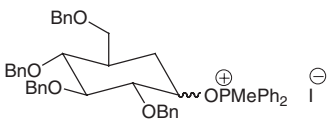

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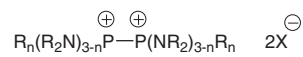

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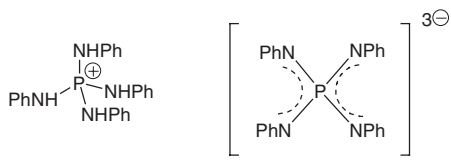
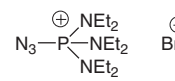


(40) (41)



(42)

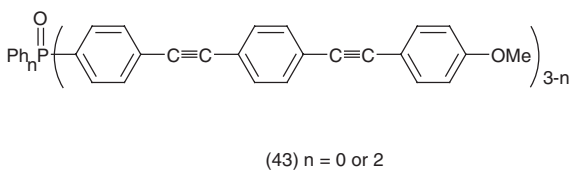
Considerable interest also attaches to the use of phosphonium salts as reagents and ionic liquid solvents in synthetic work in areas other than the Wittig reaction. A study of the phase properties of a series of methyltri(*n*-decyl)phosphonium salts has shown that they act as ordered, room-temperature ionic liquids.[64] The ability of a series of ionic liquid trihexyl(tetradecyl)phosphonium salts to solvate a coumarin dye has been investigated.[65] Ionic liquid phosphonium salts have found use as solvents in the Suzuki coupling of aryl halides[66] and in the electrodeposition of very electropositive metals.[67] Trihexyl(tetradecyl)phosphonium decanoate is an effective promoter of the Henry nitroaldol reaction of nitromethane and aromatic aldehydes.[68]Acetonyltriphenylphosphonium bromide and its polymer-supported analogues act as catalysts for the protection of carbonyl compounds as acetals or thioacetals.[69] Tetrabutylphosphonium chloride acts as a catalyst for the dehydrochlorination of hydrochlorosilanes in their coupling reactions with alkyl halides[70] and conjugated dienes or alkynes.[71] Methyltriphenylphosphonium iodide catalyses the addition of trimethylsilyl cyanide to aldehydes to give cyanohydrin trimethylsilyl ethers.[72] The reaction of alcohols with an excess of (cyanomethyl)trimethylphosphonium iodide in the presence of a base, followed

by aqueous hydrolysis, results in the clean formation of nitriles having two more carbon atoms than were present in the original alcohol. The reaction is applicable to benzylic, allylic and aliphatic alcohols without β-branching.[73] Triphenylphosphonium perchlorate has been found to catalyse the diastereoselective synthesis of *cis*-fused pyrano- and furano-benzopyrans,[74] mono- and bis-intramolecular imino Diels-Alder reactions in the synthesis of tetrahydrochromanoquinolines[75] and indolylquinolines,[76] and also the synthesis of a variety of 3,4-dihydropyrimidin-2(1H)-ones.[77] Tetraalkylphosphonium salts catalyse a selective, solvent-free N,N-dibenzylation of primary aliphatic amines with dibenzyl carbonate.[78] A fast and mild method for the nitration of activated aromatic rings is provided by the use of benzyltriphenylphosphonium nitrate in the presence of methanesulfonic anhydride, under solvent-free conditions.[79] A considerable number of reports of the application of phosphonium salts bearing oxidising anions have appeared, these compounds having the advantage of being soluble in non-aqueous aprotic solvents such as acetonitrile, which facilitates product isolation. Butyltriphenylphosphonium dichromate has found use for the conversion of thiocarbonyls to the corresponding carbonyl compounds.[80] A kinetic study has shown that the oxidation of benzylic alcohols by butyltriphenylphosphonium dichromate involves hydride transfer *via* a dichromate ester intermediate.[81] Butyltriphenylphosphonium periodate has been used for the conversion of α-sulfinyl oximes and α-sulfinyl hydrazones to the corresponding β-ketosulfoxides in high yields and high enantiomeric purity.[82] Tetraphenylphosphonium monoperoxosulfate is the reagent of choice for asymmetric epoxidation reactions mediated by iminium salts under non-aqueous conditions.[83] Benzyltriphenylphosphonium monoperoxosulfate has been used in a highly selective iodination of phenols using potassium iodide,[84] for the dethioacetalisation of 1,3-dithiolanes,[85] and for the selective oxidation of sulfides and thiols in both solution and solid-state conditions.[86,87] Both benzyl- and butyl-triphenylphosphonium peroxodisulfate salts have found use for the transformation of thiocarbonyls to the related carbonyl compounds.[88] Benzyltriphenylphosphonium peroxodisulfate is a useful reagent for the oxidation of thiols to the corresponding symmetric disulfides[89] and for the oxidative cleavage of phenylhydrazones and semicarbazones to their parent carbonyl compounds.[90] Allyltriphenylphosphonium peroxodisulfate has been shown to be an efficient reagent for the oxidation of primary and secondary alcohols and silyl- and THP-ethers under non-aqueous conditions.[91]

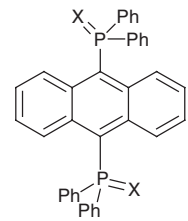
2 Phosphine Chalcogenides

2.1 Preparation. – The direct oxidation of tertiary phosphines with oxygen, hydrogen peroxide, sulfur, selenium or tellurium has continued to be widely applied in the synthesis of new phosphine chalcogenides. Included among these are the fluorescent systems (43)[92] and (44),[93] the chelating pincer-ligand disulfide (45),[94] the ferrocenyl systems (46)[95] and (47),[96] and a series of indenylphosphine chalcogenides (48).[97] Direct oxidation reactions (and other

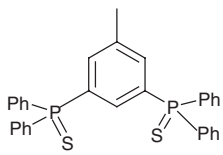
routes) have been used in the synthesis of a series of chalcogenides, e.g., (49), derived from 2,6-bis(diphenylphosphinomethyl)pyridine.[98,99] The diselenide (50) has been prepared by direct reaction of the parent diphosphine with selenium. A comparison of the $^{1}J(^{31}P\text{-}^{77}Se)$ coupling constant of (50) with those of a range of other phosphine selenides indicates that the parent diphosphine is a poorer σ-donor than BINAP as a result of the electron-withdrawing properties of the furan ring.[100] Direct oxidation with elemental tellurium of N-metallated aminodiphosphines has afforded new anionic phosphine telluride ligands, e.g., (51).[101] The synthesis of monochalcogenide derivatives of diphosphines has also proved to be of interest. Hydrogen peroxide oxidation of a mono(borane-protected)-bis(phospholane), followed by deprotection with DABCO, has given the chiral bis(phosphine) monoxide (52, X = O), used as a chiral ligand in an asymmetric catalytic synthesis of α-chiral amines.[102] The direct oxidation of BINAP and other chiral diphosphines with one equivalent of sulfur in benzene or THF has enabled the isolation (after chromatography) of a series of chiral monosulfides, e.g., (52, X = S), (53), and (54).[103,104] Treatment of the tetraphosphine (55) with an excess of hydrogen peroxide, sulfur or selenium gave the expected tetraphosphine tetra-oxide, -sulfide or -selenide (56, X = O, S, or Se), respectively. However, treatment of the tetraphosphine (55) with two equivalents of selenium, initially in hexane, followed by dichloromethane and finally toluene, enabled the isolation of the diselenide (57) in 44% yield.[105,106]



(43) n = 0 or 2



(44) X = O, S or Se



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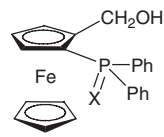
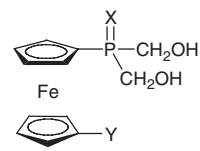
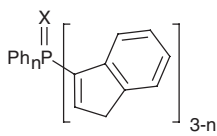


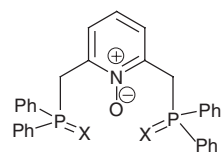
(46) X = O or S



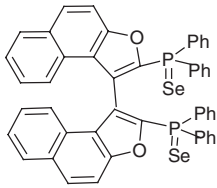
(47) X = O, S or Se;
Y = P(X)(CH$_2$OH)$_2$ or H



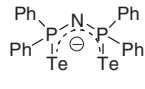
(48) n = 0,1 or 2;
X = O, S or Se



(49) X = O or S



(50)



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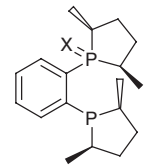
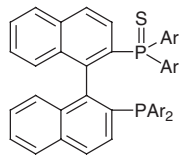
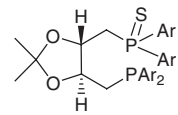


(52)



(53) Ar = Ph or *p*-tol



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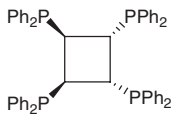

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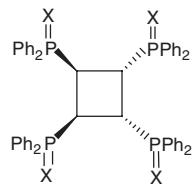
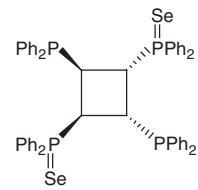


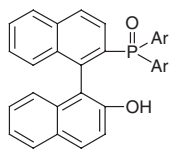
(56) X = O, S or Se



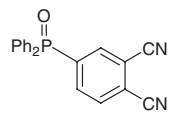
(57)

Apart from direct oxidation, other methods for the introduction of the phosphine oxide group have also been used. The reaction of diarylphosphinyl chlorides with an organolithium reagent has given the chiral hydroxyarylphosphine oxide (58), subsequently resolved *via* a camphorsulfonyl derivative.[107] The nickel-catalysed Tavs reaction of 4-bromophthalonitrile with ethyl diphenylphosphinite has given the phosphine oxide (59), subsequently converted to the phthalocyanine tetra(phosphine oxide) (60) and related metal complexes.[108] The reactions of ethyl bis(pentafluorophenyl)phosphonite with activated alkynes proceed *via* two-stage cycloaddition processes, leading, after hydrolysis of intermediate fluorophosphoranes, to the benzophosphole oxides (61).[109] Russian workers have continued to explore the synthesis of phosphine oxides from the reactions of alkyl halides and elemental phosphorus in the presence of a superbase, e.g., KOH-dioxan. The main product of the reaction of allyl bromide with white phosphorus is the triallylphosphine oxide (62), together with smaller amounts of its prototropic isomers bearing prop-1-enyl substituents.[110] A related reaction of red phosphorus with 1-chloromethylnaphthalene gave the tris(1-naphthylmethyl)phosphine oxide (63) in 70% yield, of interest as a complexing luminophore.[111] Improved yields of phosphine oxides from the superbase-promoted reactions of red phosphorus with arylalkenes have been obtained by the use of red phosphorus formed by radiation-induced polymerisation of white phosphorus, rather than by the use of the usual thermally transformed allotrope, attributable to defect structures in the irradiated material.[112] A combinatorial library of fluorescent polymer-bound phosphine sulfides

(64) has been prepared by introduction of a dialkylphosphoryl group into various polymer-bound chloromethylanthracene units using a reagent generated *in situ* from diethyl phosphonate and an alkylmagnesium halide, followed by conversion of the resulting anthracylmethylphosphine oxides to the related sulfides by treatment with P_4S_{10}. These have been shown to act as sensor materials for the detection of metal ions.[113]



(58)



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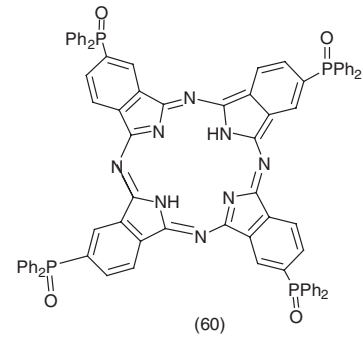

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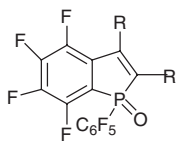

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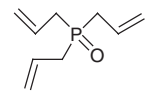

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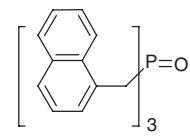

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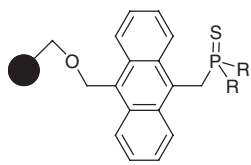
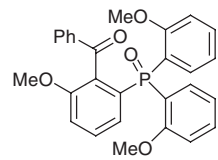


(64) R = Bu^n, Bu^i or 1,1-dimethylpropyl



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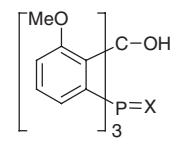


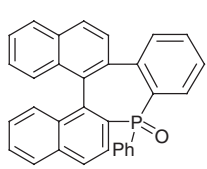
(66)

Most newly-reported phosphine oxides, however, have been prepared by transformation of the carbon skeletons of other phosphine oxides. A novel route to the 9-phosphatriptycene system involves *ortho*-metallation of tris(*o*-anisyl)phosphine oxide and treatment with phenyl chloroformate to generate (65), which, with LDA (2-equivalents), is converted into the 9-phosphatriptycene oxide (66, X = O). Treatment of the latter with P_4S_{10} provides the related sulfide (66, X = S). The phosphatriptycene selenide (66, X = Se) has also been obtained (by direct reaction of the parent phosphatriptycene with selenium), the $^1J(^{31}P\text{-}^{77}Se)$ coupling constant (827 Hz), indicating that the phosphorus orbital bonded to selenium has a significantly greater degree of *s*-character than that in, e.g., tris(*o*-anisyl)phosphine selenide (732 Hz).[114] The behaviour of 2,2′-bis(diphenylphosphinoyl)-1,1′-binaphthyl (BINAP(O)$_2$) towards various lithium and magnesium amides has been studied, leading to the isolation of new phosphine oxides, e.g., (67) and (68).[115] Various regioisomeric pairs of

carboxylate-functionalised triarylphosphine oxides bearing the 9,10-dihydro-9, 10-ethanoanthracene moiety, e.g., (69), have been obtained by the cycloaddition of unsaturated esters to 2-anthryldiphenylphosphine oxide.[116] A route to the phenyltelluroalkylphosphine oxide (70), is afforded by the metallation of diphenyl(methyl)phosphine oxide, followed by treatment with phenyltellurium bromide. This compound is a useful reagent for the synthesis of vinylic tellurides *via* Horner-Wittig procedures.[117] β-Phenyltellurovinylphosphine oxides (71), (accessible from the hydrotelluration of alkynylphosphine oxides), have been shown to undergo a palladium-catalysed cross-coupling reaction with alkenes to form the 1,3-dienylphosphine oxides (72).[118] Two groups have reported the application of ruthenium-catalysed olefin cross-metathesis reactions for the synthesis of vinyl- and allyl-phosphine oxides, and related diphosphine oxides.[119,120] Highly regio-controlled palladium-catalysed cross-coupling reactions of terminal alkynes with allenylphosphine oxides provide routes to the isomeric enynylphosphine oxides (73) and (74).[121] Palladium-catalysed Suzuki coupling reactions of triarylphosphine oxides having a reactive substituent at the 4-position (usually bromo or triflate) with a series of arylboronic acids have given a range of phosphine oxides bearing a biaryl group, e.g., (75), this being a precursor for the synthesis of poly(arylene) ether phosphine oxide polymers arising from nucleophilic displacement reactions of the fluoroaryl groups.[122] In related work, palladium-catalysed Heck coupling reactions of bromoarylphosphine oxides with alkenes have given linear alkenyl-substituted arylphosphine oxides. Amination and methoxycarbonylation reactions have also been shown to be feasible.[123] Triarylphosphine oxides of type (76) undergo polymerisation to form (polyarylene)phosphine oxides (77), the basis of some new high-performance materials.[124] The reactions of 1-thioxophosphorinanones with terminal alkynes in the presence of base have given a series of aryloxypropynyl alcohol derivatives, e.g., (78).[125,126] UV-irradiation of the phosphaferrocenophane (79) in the presence of trimethylphosphite results in a ring-opening rearrangement to form the new phosphine sulfide (80). In the presence of trimethylphosphine, the rearrangement follows a different course, resulting in the zwitterion (81).[127] Ethoxylation of tris (*p*-hydroxyphenyl)phosphine oxide has given a range of polyethoxylated derivatives (82), which have found use as a phase-separable homogeneous catalyst component in a rhodium-catalysed hydroformylation of higher alkenes.[128] The reactions of the chlorosulfonylarylphosphine oxide (83) with an aminoalkyl-β-cyclodextrin have given various phosphoryl tethered β-cyclodextrins, e.g., (84), which act as chiral molecular recognition systems for alicyclic alcohols and acids, and alanine derivatives.[129] In a similar approach, treatment of the functionalised phosphine oxide (85), (obtained from the reaction of tris(chloromethyl)phosphine oxide with dimethyl 5-mercaptoisophthalate), with (1*R*,2*R*)-diaminocyclohexane has given the phosphine oxide (86), isolated as two conformational isomers. The major isomer (10:1) has a bowl-shaped C_3-symmetric structure, with the phosphoryl group directed to the interior of the bowl, and shows a remarkable selectivity for binding asparagine derivatives. In the minor isomer, the phosphoryl group is directed to the outside of the bowl.[130] The anion of (chloromethyl)diphenylphosphinoyl chloride has been shown to

react with various 4-substituted nitrobenzenes in the *ortho* position to the nitro group, with displacement of a proton to give the benzylphosphine oxides (87) by a vicarious nucleophilic substitution mechanism.[131] A series of new chiral aminoalkylphosphine oxides, e.g., (88) and (89), has been prepared by the addition of chiral primary amines to vinyldiphenylphosphine oxide in methanol.[132] Carbamoyl- and thiocarbamoyl-derivatives (90) of 3-aminopropyldimethylphosphine oxide have been prepared by the reaction of the aminopropylphosphine oxide with isocyanates and isothiocyanates.[133] A similar addition of fluorinated hydrazines to the allenylphosphine oxides (91) has afforded the hydrazone derivatives (92). Related compounds have also been prepared by the reactions of phenacylphosphine oxides with the hydrazines.[134] Routes to various linear enediyne phosphine oxides and sulfides, e.g., (93), have been developed. Their cobalt(I)-mediated cyclisations, giving complexed tricyclic compounds bearing phosphine oxide substituents, e.g., (94) have also been explored.[135] The cleavage of phosphine sulfide-functionalised peptides bound to the Kaiser oxime resin by aminooxazoline reagents has given a series of oxazolinyl-peptide phosphine sulfides (95).[136] Palacios' group has described routes to a series of heteroarylphosphine oxides. The aryliminophosphine oxides (96), easily accessible from the reactions of aromatic amines with phenacylphosphine oxides, have been shown to react with DMF-dimethylacetal to form the quinolylphosphine oxides (97).[137] The phosphazenylalkyldiphenylphosphine oxide (98), obtained from the reaction of triphenylphosphine with azidomethyldiphenylphosphine oxide, has been converted *via* the amidine (99) into the oxazinylphosphine oxide (100).[138] Routes to 2*H*-aziridinylphosphine oxides (101) have undergone further development, and these compounds have been shown to react with carboxylic acids to form the ketamidophosphine oxides (102), which cyclise to the oxazolylphosphine oxides (103) in the presence of the triphenylphosphine-hexachloroethane reagent.[139,140] Conversion of 2*H*-aziridinylphosphine oxides to pyrazinylphosphine oxides (104) has also been described.[141] A multistep route from D-glucose (as a chiral template) to the 19-norvitamin D A-ring phosphine oxide (105) has been developed.[142] A regioselective synthesis of phosphonylated sugars, e.g., (106), is afforded by the reactions of glycals with the diphenylphosphenium cation.[143] The synthesis of sugar analogues based on phospholene- and phospholane-oxide systems has also attracted much interest. Chromium trioxide oxidation of 2-phospholene oxide sugar analogues provides a convenient chemo- and regio-selective route to the 4-oxo-2-phospholene-1-oxides (107).[144] Sodium peroxide has been used as a reagent for the stereospecific synthesis of the 2,3-epoxides (108) from 2-phospholene-1-oxides.[145] Oxidation of 3-phospholene oxides using *m*-chloroperbenzoic acid has given a series of 3,4-epoxyphospholane oxides (109), which have been shown to rearrange in the presence of a chiral base to form P,C-chirogenic 4-hydroxy-2-phospholene derivatives, e.g., (110), with up to 52% ee.[146] In related work, it has also been shown that the 3,4-epoxides are converted into the enantioenriched, P-stereogenic *trans*-3-hydroxy-4-azido- and *trans*-3-hydroxy-4-cyano-functionalised phospholane oxides (111) on treatment with trimethylsilyl-azide and -cyanide, respectively, in the presence of the

salen-Al complex.[147] Bromohydrin derivatives of 2-phospholene oxides, e.g., (112), have found further use in synthesis. Treatment with potassium carbonate in methanol provides a route to the *erythro*-2,3-epoxides, which, with dimethylsulfonium methylide, are converted into the allylic alcohols (113).[148] Routes from (112, R = Ph) (and related O-methyl ethers) to new deoxyphosphasugar-pyrimidine nucleosides, e.g., (114),[149] and deoxyphosphasugar-sugar disaccharides[150] have been developed. An expedient cyclopentannulation route to the 2-phosphabicyclo[3,3,0]octene system (115) is provided by the treatment of 1-phenyl-3-phospholene-oxides and -sulfides with two equivalents of LDA, followed by quenching the metallated intermediates with 1,3-dihaloalkanes.[151] Keglevich's group has continued to develop its study of cycloaddition reactions of unsaturated cyclic phosphine chalcogenides, e.g., phospholene-, phosphole- and 1,2-dihydrophosphinine-oxides, and the ability of such adducts to undergo thermally-induced elimination to form low-coordinate $\sigma^3\lambda^5$-species, mainly methylenephosphine oxides and sulfides, capable of acting as phosphorylating agents. Much of their earlier work on reactions of 1,2-dihydrophosphinine oxides has now been reviewed.[152] Among new work in this area is a study of the formation and subsequent fragmentation of 2-phosphabicyclo[2,2,2]oct-5-ene-2-oxides (116), and related bicyclo[2,2,2]octa-5,7-diene-2-oxides (117), obtained *via* Diels-Alder additions of 1,2-dihydrophosphinine-oxides with maleimides and related compounds[153] and acetylenic esters,[154] respectively. With tetracyanoethylene, 1,2-dihydrophosphinine oxides undergo a complex mode of cycloaddition to form the 2,8-diphosphatricyclododeca-3,5,9-triene 2,8-dioxides (118).[155,156] Diels-Alder dimerisation of 1,2-dihydrophosphinine oxides has also been reported, giving new 2-phosphabicyclo[2,2,2]oct-5-ene-2-oxides, e.g., (119).[157,158] The Baeyer-Villeger oxidation of the 7-phosphanorbornene 7-oxides (120) using *m*-chloroperbenzoic acid results in the formation of the P-aryl-2,3-oxaphosphabicyclo[2,2,2]octene oxides (121) as a mixture of isomers.[159] Anions derived from dialkyl phosphites or diphenylphosphine oxide have been shown to undergo Michael-type additions to 1,2-dihydrophosphinine oxides to form the 1,2,3,6-tetrahydrophosphinine-1-oxides (122) as a single diastereoisomer.[160] The bicyclic phosphino-phosphine sulfide (123) has been obtained from a chiral palladium complex-promoted Diels-Alder addition between 3,4-dimethyl-1-phenylphosphole 1-sulfide and diphenylvinylphosphine, the (R_P)-*exo* adduct being obtained with high stereoselectivity in the initial complex.[161]



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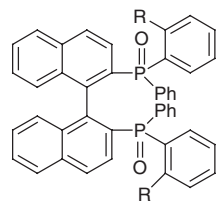
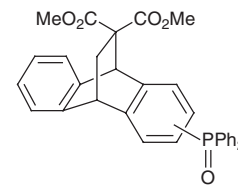
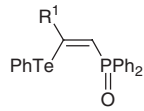


(68) R = Li, MgBr or TMS



(69)

(70)



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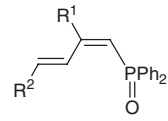
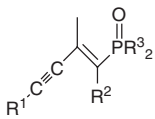
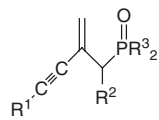


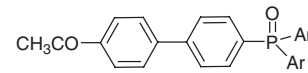
(72) R^1 = Ph or Bu;
R^2 = Ph or $COCH_3$



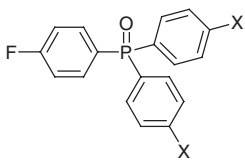
(73) R^1 = e.g., Bu or Ph;
R^2 = H or Me;
R^3 = Ph or NPr^i_2



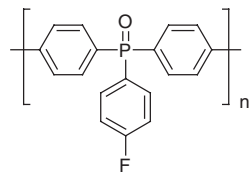
(74) R^1 = *e.g.*, Bu or Ph;
R^2 = H or Me;
R^3 = Ph or NPr^i_2



(75) Ar = *p*-FC_6H_4



(76) X = Cl or mes



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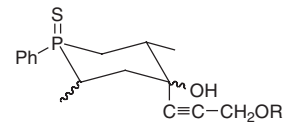
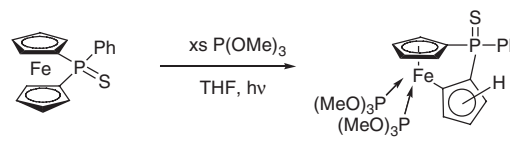


(78) R = Ph or $PhCH_2$



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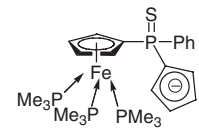

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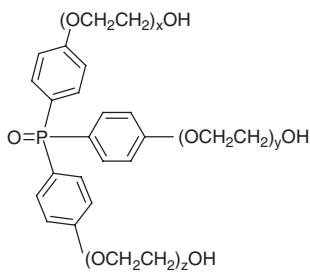

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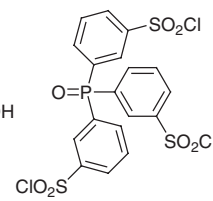

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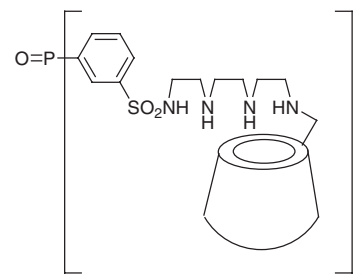

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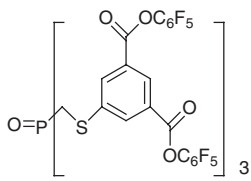

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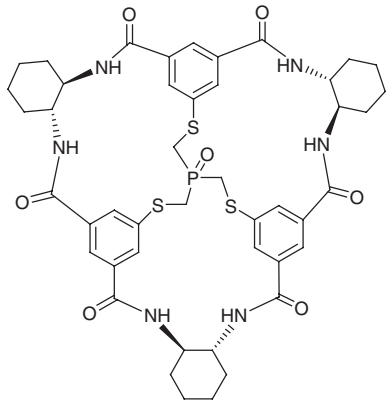

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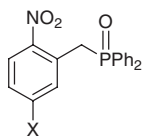
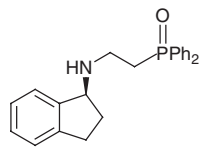


(87) X = Cl or Br



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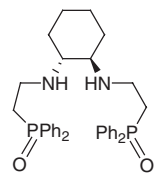

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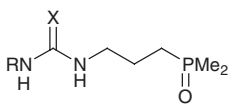
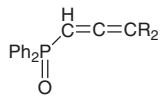
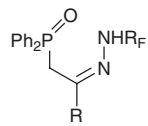


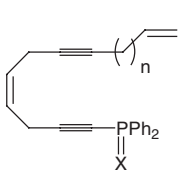
(90) X = O or S



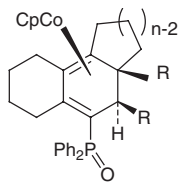
(91) R = H or Me



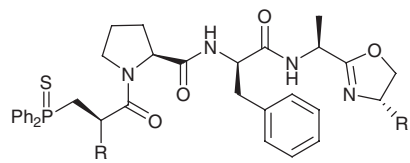
(92) R = Me or Pr^{i};
R_F = CH_2CF_3 or C_6F_5



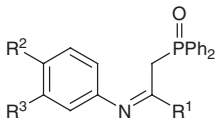
(93) n = 3 or 4;
X = O or S



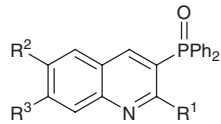
(94)



(95) R = CO_2Me, Pr^{i} or Bu^{t}



(96) R^1 = H, Me or Et;
R^2 = H, Me, Cl or OMe;
R^3 = H, Me, CF_3 or OMe



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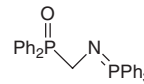

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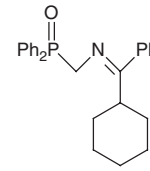

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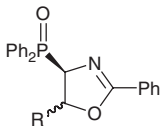

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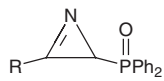
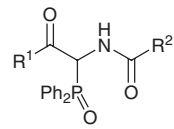
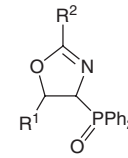


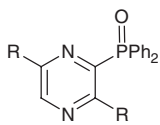
(101) R = Me or Et



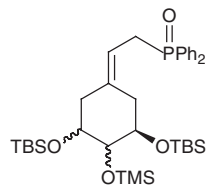
(102) R^1 = Me or Et;
R^2 = *e.g.*, Me, Ph or vinyl



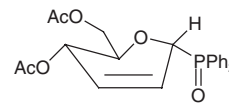
(103)



(104) R = Me, Et or Ph



(105)



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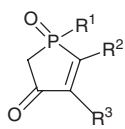
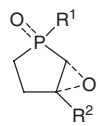


(107)



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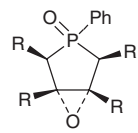
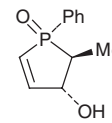
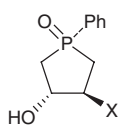


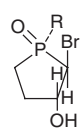
(109) R = H or Me



(110)



(111) X = N_3 or CN



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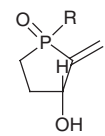

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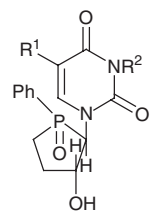

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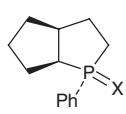
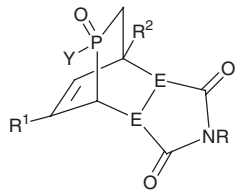
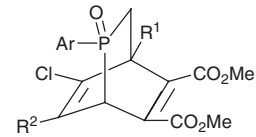


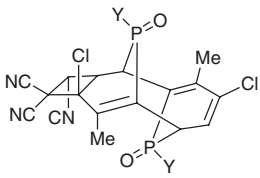
(115) X = O or S



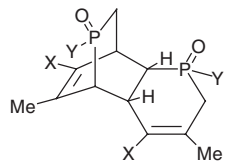
(116) Y = Me, Ph, or 2,4,6-$Pr^i_3C_6H_2$; R^1, R^2 = H or Me; E = CH or N



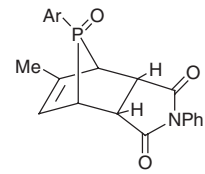
(117) Ar = *o*-tol or *p*-tol; R^1,R^2 = H or Me



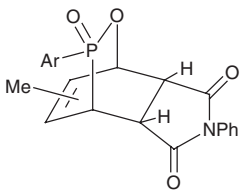
(118) Y = Ph, *o*-tol, *p*-tol or Et



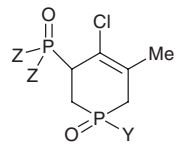
(119) Y = Me or Ph; X = H or Cl



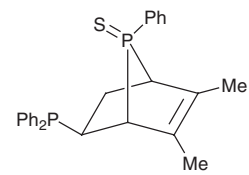
(120) Ar = *p*-tol, Mes, 2,4,6-$Pr^i_3C_6H_2$ or Ph



(121)

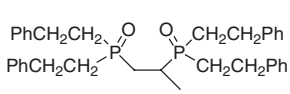


(122) Y = Ph or EtO; Z = Ph or RO

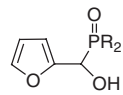


(123)

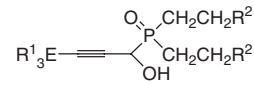
Phosphine oxides have also been prepared using secondary phosphine oxides as building blocks. These compounds have been shown to undergo double base-promoted P-H additions to methylacetylene to form ditertiary phosphine oxides having a chiral carbon atom, e.g., (124).[162] Triethylboron-catalysed anti-Markownikov radical addition of diphenylphosphine oxide to alkenes, unsaturated acids, allylic alcohols and other unsaturated species has given a wide range of new functionalised phosphine oxides under mild conditions.[163] Further examples of additions to carbonyl groups have also appeared, providing routes to the furan derivatives (125),[164] the trialkylsilyl- and trialkylgermyl-alkynyl hydroxyalkylphosphine oxides (126),[165] the hydroxyethenylphosphine oxides (127),[166] and the arylhydroxymethylphosphine oxides (128).[167] The reaction of an αω-disecondary amine with formaldehyde and di(*p*-tolyl)phosphine oxide has given the bis(aminomethylphosphine oxide) (129).[168] The 3,4-dihydro-2H-pyrroline N-oxide derivative (130) has been prepared *via* the alkylation of a secondary phosphine oxide using 5-chloropentan-2-one, followed by cyclisation with ammonia. This compound, and a related molecule derived from ethyl phenylphosphinate, act as spin trapping agents for oxygen-centred radicals.[169]



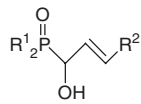
(124)

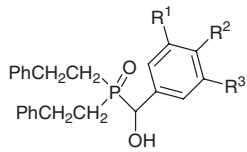


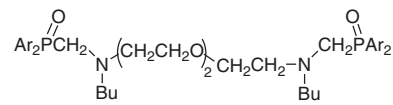
(125) R = Bu^n, $C_6H_{13}{}^n$, $PhCH_2CH_2$ or 4-$PyCH_2CH_2$



(126) R^1 = Me or Et;
R^2 = Ph or 2-Py;
E = Si or Ge







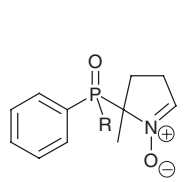
(127) R^1 = Bu^n, $C_6H_{13}{}^n$, or $PhCH_2CH_2$;
R^2 = H, Me or OPh

(128) R^1 = H or OMe;
R^2,R^3 = H, OH or OMe;

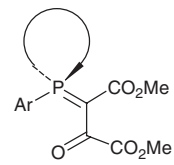
(129) Ar = *p*-Tolyl

2.2 Reactions. – Keglevich's group has continued to study the reactions of sterically-bulky cyclic tertiary phosphine oxides with electron-withdrawing alkynes, which lead to stabilised ylides (131) in an inverse Wittig protocol. Further examples of this have now been described[170] and a theoretical study has shown that pentacovalent spiro-oxaphosphoranes involving a four membered oxaphosphete ring system (132), in which the oxygen atom is equatorial, are likely intermediates in these reactions.[171] Treatment of the tris(phosphine oxide) (133) with butyllithium results in a double-deprotonation to give what may be the first formal phosphorus-stabilised 1,2-dianion (134), isolated as a THF-solvated lithium cluster complex.[172] Tertiary phosphine selenides have been shown to react with chlorine at −90°C to give the phosphonium salts $[R_3PSeCl]^+Cl^-$ which then undergo deselenisation to form the chlorophosphonium salts $[R_3PCl]^+Cl^-$.[173] Secondary phosphine oxides react with diacetoxyiodobenzene in the presence of sodium alkoxides to yield alkyl diorganophosphinate esters, involvement of the intermediates (135) being suggested on the basis of ^{31}P NMR studies.[174] The reactions of tris(2-pyridyl)phosphine oxides with arenesulfenyl- and -selenyl chlorides proceed with P-C cleavage, resulting in the formation of areneseleno- and arenethio-bipyridyls. Similar reactions occur with arenesulfinyl chlorides to give arenesulfonylbipyridyls.[175] Thiols have been shown to undergo oxidation to disulfides on treatment with triphenylphosphine oxide and bis(trichloromethyl) carbonate, the phosphine oxide being reduced to triphenylphosphine. This may therefore provide a convenient new general method for reducing triarylphosphine oxides to the related phosphines.[176] Further applications of the Hendrickson reagent, $[Ph_3POPPh_3]^+$ OTf^-, arising from the dissolution of triphenylphosphine oxide in triflic anhydride, have appeared. It has been applied in the synthesis of thiazolines,[177] oxazole- and thiazole- units in a macrocyclic antibiotic,[178] and in a direct synthesis of sulfonamides and activated sulfonate esters from sulfonic acids.[179] A polymer-supported version of the Hendrickson reagent has also been developed and found to have

advantages in product isolation over the non-supported system for a range of dehydration reactions leading to ester and amide formation.[180] The Hendrickson reagent can be used in place of Mitsunobu reagents (triphenylphosphine and a dialkyl azodicarboxylate ester) for the esterification of primary alcohols. However, secondary alcohols such as menthol undergo elimination of water, attributed to the presence in the reaction mixture of trialkylammonium triflate salts. In the presence of azide ion, the Hendrickson reagent can also be used to convert a primary alcohol into an alkyl azide in high yield.[181] Secondary phosphine oxides have continued to find applications as reagents in synthesis, diethylphosphine oxide promoting a radical-cyclisation reaction in the synthesis of indolones from an acyclic amide precursor, in water.[182] The reactions of dibenzylphosphine oxide with α,β-unsaturated *O*-methyloximes have been investigated, leading to the isolation of a wide range of tertiary phosphine oxide products. Thus, e.g., with the *O*-methyl ether of benzylideneacetone oxime, the methoxyiminophosphine oxide (136) is formed by attack at the β-carbon. Aldoxime-*O*-methyl ethers, on the other hand, can give rise to phospholene oxides, e.g., (137), obtained from 2-methylpent-2-enal *O*-methyloxime.[183] The photolysis of acylphosphine oxides, generating both acyl- and diorganophosphinoyl-radicals, has continued to attract attention for the initiation of polymerization reactions of alkenes.[184,185] Various tertiary phosphine oxides have been shown to act as catalysts in the stereoselective allylation of *N*-acylhydrazones.[186]



(130) R = Me or OEt



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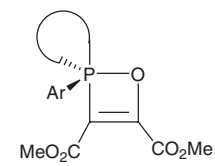
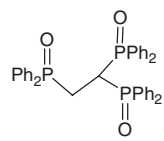
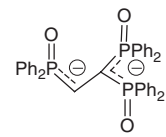


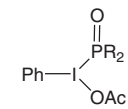
(132)



(133)



(134)



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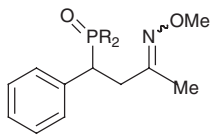
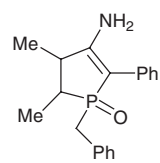
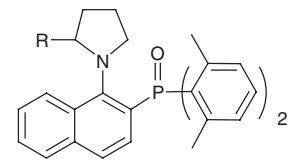


(136) R = $PhCH_2$



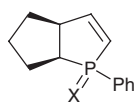
(137)



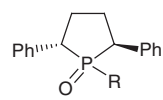
(138) R = H, CH_2OH, CH_2OMe, CH_2OBn or $CH_2N(C_4H_4)$

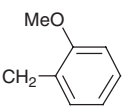
2.3 Structural and Physical Aspects. – Tertiary phosphine oxides have been shown to form 1:1 molecular donor-acceptor complexes with [60]- and [70]-fullerenes, formation constants for complex formation having been determined by an NMR spectroscopic method from the systematic variation of chemical shifts of specific protons of the donor phosphine oxide in the presence of the fullerene.[187] Detailed NMR studies have also been reported of the conformations in solution of the phosphine oxides (138)[188] and a series of chiral phospholene- and phospholane-chalcogenides, e.g., (139).[189] The enantiomeric purity of P-chirogenic phospholene oxides has been determined by ^{1}H- and ^{31}P-NMR techniques using the classical Kagan chiral amides as NMR chiral shift reagents.[190] The efficient enantiodiscrimination of the chiral phospholane oxides (140) has been shown to be possible by the use of phosphorus-coupled ^{13}C-NMR spectroscopy in the presence of a chiral weakly-ordering polypeptide liquid crystalline phase. This approach allows determination of the enantiomeric composition and is a new efficient alternative to classical methods of chiral analysis.[191] The chiral racemic diphosphine dioxide (141, X = O) has been resolved into its enantiomers by a classical approach involving fractional crystallisation of its diastereoisomeric adducts with (+)-(2*S*,3*S*)-di-O-benzoyltartaric acid, followed by neutralisation. One racemic form of the disulfide (141, X = S) and two racemic forms of the monosulfide (142), have been obtained by reactions of the parent diphosphine with sulfur, and subsequently characterised by NMR spectroscopy and X-ray crystallography.[192] The enantiomers of *t*-butyl-1-(2-methylnaphthyl)phosphine oxide (143) have been separated using a chiral HPLC column. Vibrational absorption and circular dichroism spectra have been measured for both enantiomers, enabling a determination of their absolute configurations.[193] The first enzymatic desymmetrizations of prochiral phosphine oxides have been reported. Bis(methoxycarbonylmethyl)phenylphosphine oxide was subjected to hydrolysis in the presence of a pig liver-esterase to give the chiral monoacetate (144) in 92% yield and 72% ee. Similarly, prochiral bis(hydroxymethyl)phenylphosphine oxide was desymmetrized using either a lipase-catalysed acetylation or hydrolysis of the corresponding diacetyl derivative to give the chiral monoacetate (145) in 76% yield and with e.e's up to 79%. The absolute configurations of these monoesters were determined by means of chemical correlation.[194] Interest in the structural characterisation of hydrogen-bonded adducts of phosphine-oxides and -sulfides has continued. Infrared spectroscopy and theoretical techniques have been used to study the energetics of intramolecular hydrogen bonds and conformations of the ω-diphenylphosphoryl- and ω-diphenylthiophosphoryl-substituted aliphatic alcohols (146)[195] and also molecular interactions in the carboxy(diphenylphosphinoyl)cyclopentanone (147).[196] Intramolecular hydrogen bonding in the salts (148) has been studied in the solid state by X-ray structural work and in solution by multinuclear NMR techniques.[197] The first complex of triphenylphosphine oxide with a chiral substrate has been obtained by crystallising the phosphine oxide in the presence of *S*-(−)-1,1′-bi-2,2′-naphthol (BINOL), resulting in the formation of a 1:2 (BINOL): (Ph_3PO) complex, the structure of which has been determined by X-ray crystallography. A complex of the same

stoichiometry has also been isolated by the use of racemic BINOL. In the homochiral complex, the phosphine oxide molecules appear to exist in only one enantiomeric form.[198] Interactions between β-cyclodextrin and a monosulfonated triphenylphosphine oxide have been investigated in aqueous solution by NMR, UV-visible absorption and ESMS techniques. Titration and continuous variation plots point to the formation of 1:1 inclusion complexes.[199] Solid state X-ray structural studies have been reported of the adduct of cyclohexylamine hydrochloride and the tris(phosphine oxide) (149), and also of the di(phosphine oxide) (150), in which weak $C_{(phenyl)}$–H ⋯ $O_{(oxide)}$ hydrogen bonds are identified.[200] Phosphorus-oxygen coordination leading to pseudotrigonal bipyramidal geometries in the anionic phosphine oxide (151) and hydrogen bonding interactions with tris(2-hydroxy-3,5-dimethylbenzyl)amine have also been the subject of a structural study.[201] A structural study of the phosphine oxide (152), obtained by hydrogen peroxide oxidation of tris(*o*-dimethylaminomethylphenyl)phosphine, has shown that the geometry about phosphorus is tetrahedral, no intramolecular coordination to phosphorus from the N-oxide units being apparent.[202] Among other phosphine chalcogenides which have been the subject of X-ray crystallographic studies are the thioxo-phosphorinane (153),[203] tris(2-pyridyl)phosphine oxide,[204] and the ionic system (154) which involves an unusual anion.[205] The gas phase structure of tris(*t*-butyl)phosphine oxide has been determined by a new method which links the gas-phase electron diffraction refinement process with computational methods in a dynamic interaction of theory and experiment. This approach has revealed a shorter phosphorus-oxygen distance than was found by a less sophisticated analysis, and is consistent with the molecule being regarded as $Bu^t_3P{=}O$ rather than $Bu^t_3P^+{-}O^-$.[206]

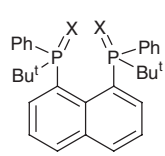


(139) X = O, S or Se

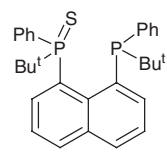




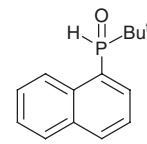
(140) R = Ph, $PhCH_2$, or Me



(141)



(142)



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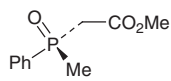
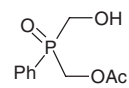
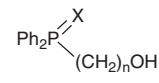


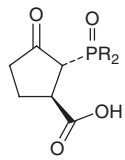
(144)



(145)



(146) X = O or S; n = 1-3



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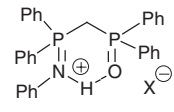
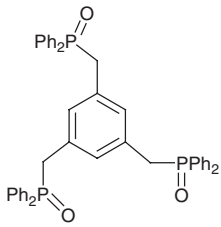


(148) X = Br or BF_4



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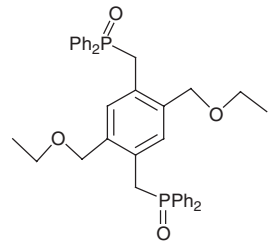

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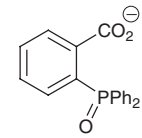

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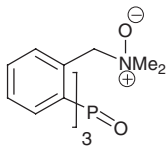

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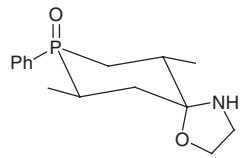

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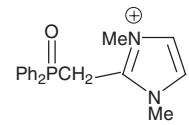
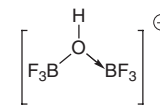
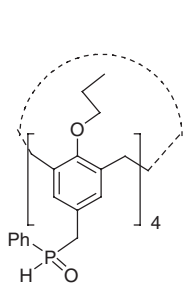




(154)

2.4 Phosphine Chalcogenides as Ligands. – This continues to be an active area, although few applications of these ligands in catalysis have been noted. Significant interest, however, continues to be shown in the use of phosphine oxides as selective extraction agents for various metal ions. This is particularly evident in the design and complexing abilities of calixarene systems bearing several phosphine oxide groups. The secondary phosphine oxide-functionalised calix[4]arene (155) is an easily accessible key intermediate for the synthesis of the upper rim carbamoylmethylphosphine oxide (156) and diphosphine dioxide (157) systems, both of which have useful binding properties for lanthanide and actinide ions.[207] Related calix[4]arenes bearing diphenylphosphine oxide substituents at the upper rim demonstrated high selectivity for iron (III).[208] Lower rim poly(phosphine oxide)-functionalised calix[4]arenes (158, n = 4, R = Ph or Me) have also been prepared, and shown to have uses as extraction agents for thorium(IV) and europium(III) ions[209] and also for complex formation with cobalt(II), nickel(II), copper(II) and zinc(II).[210] A related *p-t*-butylcalix[6]arene bearing dimethylphosphinylmethyloxy-substituents (158, n = 6, R = Me) has also been prepared and shown to complex strongly to lanthanide ions.[211] The donor properties of bis(diphenylphosphinoyl)alkanes have continued to attract

attention. Complexes of bis(diphenylphosphinoyl)methane with the uranyl ion[212] and also scandium and various lanthanide ions[213,214] have been characterised in the solid state and in solution. The donor properties of 1,2-bis(diphenylphosphinoyl)ethane and the chiral dioxides (159) and (160) towards a di(rhodium) carboxylate have been compared using low-temperature ^{1}H and ^{31}P NMR spectroscopy. The dioxide (160) shows a distinct preference for binding through $Ph_2P(O)$ rather than $Ph(Bu^t)P(O)$, presumably due to the bulky *t*-butyl group.[215] Two-dimensional coordination polymers of praseodymium(III) with 1,2-bis(diphenylphosphinoyl)ethane and the pyridine-based dioxide (161) have also been characterised.[216] Considerable interest has been shown in the ligand properties of the anionic bidentate sulfur and selenium donors (162), complexes of indium(III),[217] arsenic(III), antimony(III), bismuth(III),[218] mercury,[219] and gold(III) and silver(I)[220] having been investigated. Palladium(II) complexes of the neutral mono- and di-disulfides (163, E = lone pair) and (163, E = S), respectively, have also been studied.[221] Further work has appeared on the properties of rhodium(I) complexes of the anionic disulfide (164) with regard to their ability to carry small molecules such as CO, O_2, CO_2, CS_2 and SO_2.[222] A variety of (phosphine selenide)-carbonyl cluster complexes has been isolated from the reactions of the diselenide (165) with ruthenium- and iron- carbonyl complexes of the type $[M_3(CO)_{12}]$.[223] Unusual polynuclear copper(I) complexes have been obtained from the reactions of a series of bis(diphenylselenophosphinoyl)alkanes (166) with copper(I) halides in acetonitrile, the length of the alkane spacer and the nature of the halide ion influencing the structure of the resulting complexes.[224] Tetraalkyldiphosphine disulfides (167) have continued to attract interest as ligands, complexes with silver(I) and copper(I),[225] and a rhenium bromocarbonyl acceptor,[226] having been characterised. Sulfido(carbonyl)rhenium clusters have been obtained from the ditertiary diphosphine disulfide (168) and the crowded but electron rich monosulfide (169).[227]



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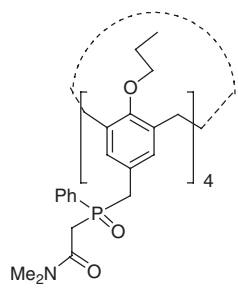

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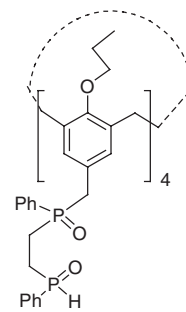
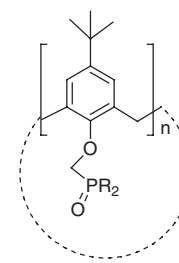
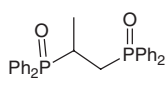


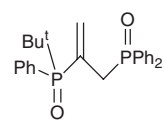
(157)



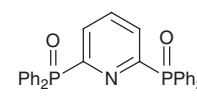
(158)



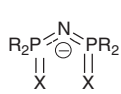
(159)



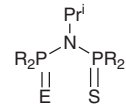
(160)



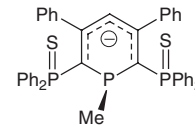
(161)



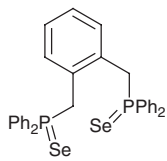
(162) X = S or Se; R = Ph or Pr^i



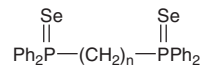
(163)



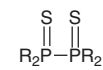
(164)



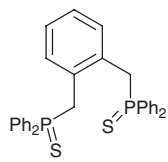
(165)



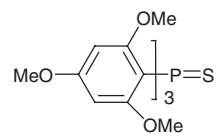
(166) n = 1-4



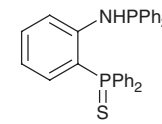
(167) R = Me, Et, Pr^n, Bu^n or Ph



(168)



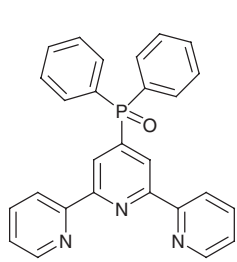
(169)



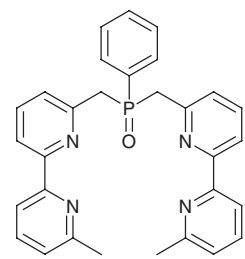
(170)

Among other monotertiary triarylphosphine chalcogenide ligands studied are triphenylphosphine oxide, triphenylphosphine sulfide and triphenylphosphine selenide, from which a series of tungsten carbonyl complexes has been prepared.[228] This family of ligands has also found application in the formation of complexes with rhodium (I) cyclooctadiene, which catalyse the efficient carbonylation of methanol.[229] The reactions of a series of monodentate tertiary phosphine selenides with $[Ru_3(CO)_{12}]$ have been shown to involve cleavage of the phosphorus-selenium bond, the selenium being transferred to the metal. In contrast, normal mononuclear phosphine selenide complexes have been obtained from the reactions of diphenyl(2-pyridyl)phosphine selenide with palladium(II) and platinum(II) acceptors.[230,231] Complexes of the phosphinoaminoarylphosphine sulfide (170) with ruthenium, rhodium and iridium acceptors have been characterised. Not surprisingly, the aminophosphine moiety coordinates preferentially to these metals, but complexes involving additional coordination from the phosphine sulfide group were also prepared.[232] Monotertiary phosphine oxides bearing other donor groups have also been prepared and their coordination chemistry studied. The first bis(phosphine) monoxide complexes of copper(I) have been prepared from bis(diphenylphosphino)methane monoxide and bis(diphenylphosphino)ethane monoxide. Coordination from both phosphorus and phosphine oxide oxygen was observed in one case, the expected preferential coordination of the softer phosphorus donor to copper(I) dominating behaviour in solution.[233] Cobalt(II) and cobalt(III) complexes of the terpyridylphosphine oxide (171) have been characterised.[234] The bis(bipyridyl)phosphine oxide (172) forms luminescent complexes with

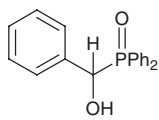
lanthanide ions, which can be used for the detection of anions.[235] A new triphenylphosphine oxide complex of terbium(III) has been shown to exhibit strong electroluminescence properties.[236] Other reports of lanthanide (and actinide) complexes involving triphenylphosphine oxide as a ligand have also appeared.[237,238] Among other complexes of triphenylphosphine oxide recently described are molybdenum complexes involving dithiophosphates as co-ligands,[239] stable complexes of diorganotin cations,[240] and salts of polyhalotellurate anions involving protonated phosphine oxide units, formed from the reactions of triphenylphosphine with tellurium tetrahalides under ambient conditions in THF.[241] Tris(4-fluorophenyl)phosphine oxide has been shown to have a remarkable co-ligand effect for the stabilisation of chiral lanthanum complex catalysts used in a highly selective epoxidation of conjugated enones.[242] A series of complexes of oxodiperoxomolybdenum with trialkylphosphine oxides and triphenylphosphine oxide has been prepared and shown to oxidise indoles to various indolone products.[243] The chiral hydroxymethylphosphine oxide (173) has been prepared in 67% yield by the reaction of diphenylphosphine with benzaldehyde in THF in air at 40°C and used as a ligand in a rhodium(I)-catalysed hydroformylation of alkenes. It has also been partially resolved using an enzyme, and used in an enantioselective hydroformylation.[244] Triethylphosphine oxide and tri(*n*-propyl)phosphine oxide have been used as ligands in the synthesis of various hexanuclear halomolybdenum cluster complexes.[245] Trialkylphosphine oxides have also been used as co-ligands for the stabilisation of silver nanaocrystals.[246] Tris(*t*-butyl)phosphine oxide has found use as a bulky ligand for the stabilisation of a new family of monocyclopentadienylscandium bis-alkyls.[247] Scandium(III) halide complexes of a range of phosphine- and arsine-oxides have been studied in solution and in the solid state.[248] Lanthanide complexes of the fluoroalkylphosphine oxide (174) have been characterised.[249] Various metal complexes of the carboxyalkylphosphine oxide (175) have been characterised in solution, some being accessed by *in-situ* oxidation of the parent trialkylphosphine.[250]



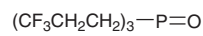
(171)



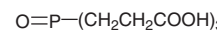
(172)



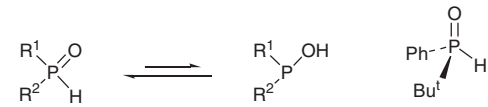
(173)



(174)



(175)



(176) (177) (178)

The properties of secondary phosphine oxides and sulfides as ligands have also been the subject of recent papers. In solution, these compounds exist in equilibrium between the pentavalent phosphine oxide form (176) and the trivalent phosphinite form (177). It is the phosphinite form that coordinates (*via* phosphorus) to a transition metal ion. Air-stable P-stereogenic secondary phosphine oxides and sulfides are configurationally stable in the presence of metal ions both in solution and in the solid state, and have the potential to act as chiral monodentate ligands for asymmetric catalysis. It has now been shown that both chiral forms of the secondary phosphine oxide (178) are useful ligands for asymmetric palladium-catalysed carbon-carbon bond formation.[251] In a similar vein, a series of chiral secondary phosphine oxides of the type (176) has been prepared from the reactions of Grignard reagents with bulky dichlorophosphines and resolved into their enantiomers by preparative chiral HPLC. These ligands have been applied in an iridium(I)-catalysed asymmetric hydrogenation of imines, with good enantioselectivities.[252]

References

1. M. Stivanello, L. Leoni and R. Bortolaso, *Org. Proc. Res. Dev.*, 2002, **6**, 807.
2. L. Porrès, B.K.G. Bhatthula and M. Blanchard-Desce, *Synthesis*, 2003, 1541.
3. S. Harusawa, M. Kawamura, S. Koyabu, T. Hosokawa, L. Araki, Y. Sakamoto, T. Hashimoto, Y. Yamamoto, A. Yamatodani and T. Kurihara, *Synthesis*, 2003, 2844.
4. T. Hanamoto, N. Morita and K. Shindo, *Eur. J. Org. Chem.*, 2003, 4279.
5. A.B. Smith (III), B.S. Freeze, I. Brouard and T. Hirose, *Org. Lett.*, 2003, **5**, 4405.
6. F. Meyer, A. Laaziri, A.M. Papini, J. Uziel and S. Jugé, *Tetrahedron: Asymmetry*, 2003, **14**, 2229.
7. C. Gracia, G. Marco, R. Navarro, P. Romero, T. Soler and E.P. Urriolabeitia, *Organometallics*, 2003, **22**, 4910.
8. A. Hamdi, K.C. Nam, B.J. Ryu, J.S. Kim and J. Vicens, *Tetrahedron Lett.*, 2004, **45**, 4689.
9. E.E. Bonfantini, A.K. Burrell, W.M. Campbell, M.J. Crossley, J.J. Gosper, M.M. Harding, D.L. Officer and D.C.W. Reid, *J. Porphyrins and Phthalocyanines*, 2002, **6**, 708.
10. R. Weiss, F. Pühlhofer, N. Jux and K. Merz, *Angew. Chem. Int. Ed.*, 2002, **41**, 3815.
11. F.G. Pühlhofer and R. Weiss, *Eur. J. Org. Chem.*, 2004, 1002.
12. H. Danjo, W. Sasaki, T. Miyazaki and T. Imamoto, *Tetrahedron Lett.*, 2003, **44**, 3467.
13. K. Ohsaki, K. Konishi and T. Aida, *Chem. Commun.*, 2002, 1690.
14. U.V. Monkowius, S.D. Nogai and H. Schmidbaur, *J. Am. Chem. Soc.*, 2004, **126**, 1632.
15. S. Ito, S. Moriyama, M. Nakashima, M. Watanabe, T. Kubo, M. Yasunami, K. Fujimori and N. Morita, *Heterocycles*, 2003, **61**, 339.
16. R. Mazurkiewicz, B. Fryczkowska, R. Gabański, R. Luboradzki, A. Włochowicz and W. Mól, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2589.

17. Yu.G. Gololobov, V.I. Galkin, P.V. Petrovskii, O.A. Linchenko, E.M. Zueva, L.G. Mubarakova, R.A. Cherkasov, R. Schmutzler, L. Ernst, P.G. Jones and M. Freytag, *Russ. Chem. Bull. Int. Ed.*, 2003, **52**, 1920.
18. J. Bould, A. Laromaine, C. Viñas, F. Teixidor, L. Barton, N.P. Rath, R.E.K. Winter, R. Kivekäs and R. Sillanpää, *Organometallics*, 2004, **23**, 3335.
19. I.M. Aladzheva, D.I. Lobanov, O.V. Bykhovskaya, P.V. Petrovskii, K.A. Lyssenko and T.A. Mastryukova, *Heteroatom Chem.*, 2003, **14**, 596.
20. T. Nonaka, H. Li, K. Makinose, T. Ogata and S. Kurihara, *J. Applied Polymer Sci.*, 2003, **90**, 1139.
21. D.W. Allen, S.J. Coles, M.B. Hursthouse and S.M. Khan, *Inorg. Chim. Acta*, 2004, **357**, 265.
22. D.W. Allen, S.J. Coles, M.E. Light and M.B. Hursthouse, *Inorg. Chim. Acta*, 2004, **357**, 1558.
23. D.W. Allen, M.E. Light and M.B. Hursthouse, *J. Chem. Res. (S)*, 2002, 537.
24. G.P. Schiemenz, C. Nather and S. Porksen, *Z. Naturforschung, B: Chem. Sci.*, 2003, **58**, 59.
25. K. Sierosławski, B. Picur and T. Lis, *J. Mol. Struct.*, 2003, **657**, 93.
26. J.C. Aschenbrenner and N. Korber, *Z. Anorg. Allg. Chem.*, 2004, **630**, 31.
27. P.C. Srivastava, Sangeeta Bajpai, Smriti Bajpai, C. Ram, R. Kumar, J.P. Jasinski and R.J. Butcher, *J. Organomet. Chem.*, 2004, **689**, 194.
28. V. Janickis, M. Heberhold and W. Milius, *Z. Anorg. Allg. Chem.*, 2003, **629**, 29.
29. R. Haiges, J.A. Boatz, A. Vij, M. Gerken, S. Schneider, T. Schroer and K.O. Christe, *Angew. Chem. Int. Ed.*, 2003, **42**, 5847.
30. L. Apostolico, M.F. Mahon, K.C. Molloy, R. Binions, C.S. Blackman, C.J. Carmalt and I.V. Parkin, *Dalton Trans.*, 2004, 470.
31. P.A.W. Dean, K. Fisher, D. Craig, M. Jennings, O. Ohene-Fianko, M. Scudder, G. Willet and I. Dance, *Dalton Trans.*, 2003, 1520.
32. M. Makha, C. L. Raston, A.N. Sobolev and A.H. White, *Chem. Commun.*, 2004, 1066.
33. O.N. Kazheva, G.G. Alexandrov, O.A. D'yachenko, M.S. Chernov'yants, S.S. Simonyan and E.O. Lykova, *Russ. J. Coord. Chem.*, 2003, **29**, 819.
34. F. Biesemeier, K. harms and U. Mueller, *Z. Kristallographie-New Cryst. Struct.*, 2004, **219**, 41.
35. V.D. Makhaev, A.P. Borisov, A.S. Antsyshkina and G.G. Sadikov, *Zh. Neorganicheskoi Khimii*, 2004, **49**, 371.
36. (*a*) B. Neumüller, F. Weller and K. Dehnicke, *Z. Anorg. Allg. Chem.*, 2003, **629**, 2195; (*b*) B. Neumüller and K. Dehnicke, *Z. Anorg. Allg. Chem.*, 2003, **629**, 2529; (*c*) B. Neumüller and K. Dehnicke, *Z. Anorg. Allg. Chem.*, 2004, **630**, 347.
37. (*a*) S. Rabe, W. Bubenheim and U. Mueller, *Z. Kristallographie-New Cryst. Struct.*, 2004, **219**, 101; (*b*) M. Wojtaś, R. Jakubas, Z. Ciunik and W. Medycki, *J. Solid State Chem.*, 2004, **177**, 1575.
38. (*a*) K. Jurkschat and E.R.T. Tiekink, *App. Organomet. Chem.*, 2003, **17**, 819; (*b*) K. Jurkschat, G. Reeske, M. Schürmann and E.R.T. Tiekink, *App. Organomet. Chem.*, 2003, **17**, 885.
39. D. Weber, S H. Hausner, A. Eisengräber-Pabst, S. Yun, J A. Krause-Bauer and H. Zimmer, *Inorg. Chim. Acta*, 2004, **357**, 125.
40. S. Coste, M. Bujoli-Doeuff, G. Loyuarn, D. Massiot, R. Brec and S. Jobic, *New J. Chem.*, 2003, **27**, 1228.
41. R. Haiges, J.A. Boatz, S. Schneider, T. Schroer, M. Yousufuddin and K.A. Christe, *Angew. Chem. Int. Ed.*, 2004, **43**, 3148.

42. S. Sharma, A. Ramanan, P.Y. Zavalij and M.S. Whittingham, *Cryst. Eng. Comm.*, 2002, **4**, 601.
43. J. Taraba and Z. Zak, *Inorg. Chem.*, 2003, **42**, 3591.
44. A. Kornath, F. Neumann and H. Oberhammer, *Inorg. Chem.*, 2003, **42**, 2894.
45. H. Chow, P.A.W. Dean, D.C. Craig, N.T. Lucas, M. Scudder and I.G. Dance, *New J. Chem.*, 2003, **27**, 704.
46. W. Xie, R. Xie, W.-P. Pan, D. Hunter, B. Koene, L.-S. Tan and R. Vaia, *Chem. Mater.*, 2002, **14**, 4837.
47. K.-S. Song, L. Liu and Q.-X. Guo, *J. Org. Chem.*, 2003, **68**, 4604.
48. M. Seierstad, C.R. Kinsinger and C.J. Cramer, *Angew. Chem. Int. Ed.*, 2002, **41**, 3894.
49. W.W. Schoeller, A. Rozhenko, D. Bourissou and G. Bertrand, *Chem. Eur. J.*, 2003, **9**, 3611.
50. D. Scheschkewitz, H. Amii, H. Gornitzka, W.W. Schoeller, D. Bourissou and G. Bertrand, *Angew. Chem. Int. Ed.*, 2004, **43**, 585.
51. H. Amii, L. Vranicar, H. Gornitzka, D. Bourissou and G. Bertrand, *J. Am. Chem. Soc.*, 2004, **126**, 1344.
52. V. Hebbe, A. Londez, C. Goujon-Ginglinger, F. Meyer, J. Uziel, S. Jugé and J. Lacour, *Tetrahedron Lett.*, 2003, **44**, 2467.
53. S. Taira, H. Danjo and T. Imamoto, *Tetrahedron Lett.*, 2002, **43**, 8893.
54. N. Merceron-Saffon, A. Baceiredo, H. Gornitzka and G. Bertrand, *Science (Washington DC, USA)*, 2003, **301**, 1223.
55. Y.J. Im, J.E. Na and J.N. Kim, *Bull. Korean Chem. Soc.*, 2003, **24**, 511.
56. Y. Zhang, S.L. Aguirre and D.A. Klumpp, *Tetrahedron Lett.*, 2002, **43**, 6837.
57. J.-W. Huang and M. Shi, *J. Org. Chem.*, 2003, **68**, 6705.
58. T. Mukaiyama, Y. Kobashi and T. Shintou, *Chem. Lett.*, 2003, **32**, 900.
59. V.A. Zagumennov, A.N. Vedernikov, E.V. Nikitin and B.N. Solomonov, *Russ. J. Gen. Chem.*, 2003, **73**, 921.
60. J.F. Bickley, M.C. Copsey, J.C. Jeffery, A.P. Leedham, C.A. Russell, D. Stalke, A. Steiner, T. Stey and S. Zacchini, *Dalton Trans.*, 2004, 989.
61. S.P. Klump and H. Shechter, *Tetrahedron Lett.*, 2002, **43**, 8421.
62. M. McGuiness and H. Shechter, *Tetrahedron Lett.*, 2002, **43**, 8425.
63. F. Hoffmann, L. Jäger and C. Griehl, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 299.
64. H. Chen, D.C. Kwait, Z.S. Gönen, B.T. Weslowski, D.J. Abdallah and R.G. Weiss, *Chem. Mater.*, 2002, **14**, 4063.
65. N. Ito, S. Arzhantsev, M. Heitz and M. Maroncelli, *J. Phys. Chem. B*, 2004, **108**, 5771.
66. J. McNulty, A. Capretta, J. Wilson, J. Dyck, G. Adjabeng and A. Robertson, *Chem. Commun.*, 2002, 1986.
67. A.I. Bhatt, I. May, V.V. Volkovich, M.E. Hetherington, B. Lewin, R.C. Thied and N. Ertok, *J. Chem. Soc., Dalton Trans.*, 2002, 4532.
68. J. McNulty, J. Dyck, V. Larichev, A. Capretta and A.J. Robertson, *Letters in Org. Chem.*, 2004, **1**, 137.
69. Y.-S. Hon, C.-F. Lee, R.-J. Chen and Y.-F. Huang, *Synth. Commun.*, 2003, **33**, 2829.
70. S.-H. Kang, J.S. Han, B.R. Yoo, M.E. Lee and I.N. Jung, *Organometallics*, 2003, **22**, 529.
71. S.-H. Kang, J.S. Han, M.E. Lee, B.R. Yoo and I.N. Jung, *Organometallics*, 2003, **22**, 2551.
72. R. Córdoba and J. Plumet, *Tetrahedron Lett.*, 2003, **44**, 6157.
73. F. Zaragoza, *J. Org. Chem.*, 2002, **67**, 4963.
74. M. Anniyappan, D. Muralidharan and P.T. Perumal, *Tetrahedron*, 2002, **58**, 10301.

75. M. Anniyappan, D. Muralidharan and P.T. Perumal, *Tetrahedron Lett*., 2003, **44**, 3653.
76. Y. Zyulykama, R. Nagarajan and P.T. Perumal, *Synthetic Commun*., 2004, **34**, 1309.
77. P. Shanmugam and P.T. Perumal, *J. Chem. Res. S*, 2003, 601.
78. A. Loris, A. Perosa, M. Selva and P. Tundo, *J. Org. Chem*., 2004, **69**, 3953.
79. A.R. Hajipour and A.E. Ruoho, *Phosphorus, Sulfur, Silicon*, 2004, **179**, 221.
80. I. Mohammadpoor-Baltork, H.R. Memarian, A.R. Hajipour and K. Bahrami, *Bull. Korean Chem. Soc*., 2003, **24**, 1002.
81. A. Goyal, S. Kothari and K. K. Banerji, *J. Chem. Res. S*, 2002, 363.
82. A.R. Hajipour and A.E. Ruoho, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2653.
83. P.C.B. Page, D. Barros, B.R. Buckley, A. Ardakani and B.A. Marples, *J. Org. Chem*., 2004, **69**, 3595.
84. A.R. Hajipour and H. Adibi, *J. Chem. Res*., 2004, 294.
85. A.R. Hajipour, S.E. Mallakpour, I. Mohammadpoor-Baltork and H. Adibi, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2805.
86. A.R. Hajipour, S.E. Mallakpour and H. Adibi, *J. Org. Chem*., 2002, **67**, 8666.
87. A.R. Hajipour, S.E. Mallakpour and H. Adibi, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2277.
88. I. Mohammadpoor-Baltork, M.M.M. Sadeghi and K. Esmayilpour, *J. Chem. Res. S*, 2003, 348.
89. A.R. Hajipour and A.E. Ruoho, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1277.
90. M. Tajbakhsh, I. Mohammadpoor-Baltork and F. Ramzanian-Lehmali, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2621.
91. M. Tajbakhsh, M.M. Lakouraj and A. Fadavi, *Synthetic Commun*., 2004, **34**, 1173.
92. R. Métivier, R. Amengual, I. Leray, V. Michelet and J.-P. Genêt, *Org. Lett*., 2004, **6**, 739.
93. Z. Fei, N. Kocher, C.J. Mohrschladt, H. Ihmels and D. Stalke, *Angew. Chem. Int. Ed*., 2003, **42**, 783.
94. T. Kanbara and T. Yamamoto, *J. Organomet. Chem*., 2003, **688**, 15.
95. P. Štěpnička and I. Císařová, *New. J. Chem*., 2002, **26**, 1389.
96. W. Henderson and S.R. Alley, *J. Organomet. Chem*., 2002, **658**, 181.
97. J.J. Adams, D.E. Berry, O.J. Curnow, G.M. Fern, M.L. Hamilton, H.J. Kitto and J.R. Pipal, *Aust. J. Chem*., 2003, **56**, 1153.
98. X.-M. Gan, R.T. Paine, E.N. Duesler and H. Nöth, *Dalton Trans*., 2003, 153.
99. X.-M. Gan, E.N. Duesler, S. Parveen and R.T. Paine, *Dalton Trans*., 2003, 4704.
100. N.G. Andersen, M. Parveez, R. McDonald and B.A. Keay, *Can. J. Chem*., 2004, **82**, 145.
101. G.G. Briand, T. Chivers and M. Parvez, *Angew. Chem. Int. Ed*., 2002, **41**, 3468.
102. A.A. Boezio, J. Pytkowicz, A. Côté and A.B. Charette, *J. Am. Chem. Soc*., 2003, **125**, 14260.
103. C.J. Chapman, C.G. Frost, M.P. Gill-Carey, G. Kociok-Köhn, M.F. Mahon, A.S. Weller and M.C. Willis, *Tetrahedron: Asymmetry*, 2003, **14**, 705.
104. J. W. Faller, J.C. Wilt and J. Parr, *Org. Lett*., 2004, **6**, 1301.
105. T. Stampfl, G. Czermak, R. Gutman, C. Langes, H. Kopacka, K.-H. Ongania and P. Brüggeller, *Inorg. Chem. Commun*., 2002, **5**, 490.
106. T. Stampfl, R. Gutman, G. Czermak, C. Langes, A. Dumfort, H. Kopacka, K.-H. Ongania and P. Brüggeller, *Dalton Trans*., 2003, 3425.
107. Y. Luo, F. Wang, G. Zhu and Z. Zhang, *Tetrahedron: Asymmetry*, 2004, **15**, 17.
108. G. Märkl, K. Gschwendner, I. Rötzer and P. Kreitmeier, *Helv. Chim. Acta*, 2004, **87**, 825.

109. Yu. G. Trishin, V.I. Namestnikov and V.K. Bel'skii, *Russ. J. Gen. Chem.*, 2004, **74**, 189.
110. S. Malysheva, B. Sukhov, N. Gusarova, S. Shaikhudinova, T. Kazantseva, N. Belogorlova, V. Kuimov and B. Trofimov, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 425.
111. N.K. Gusarova, B.A. Trofimov, S.F. Malysheva, B.G. Sukhov, V.A. Kuimov, N.A. Belogorlova, V.I. Smirnov and N.B. Kurmankulov, *Russ. J. Gen. Chem.*, 2004, **74**, 635.
112. N.K. Gusarova, S.I. Shaikhudinova, B.G. Sukhov, T.I. Kazantseva, S.F. Malysheva, Yu.V. Smetannikov, N.P. Tarasova, V.A. Kuimov and B.A. Trofimov, *Russ. Chem. Bull. Int. Ed.*, 2003, **52**, 511.
113. M. Castillo and I.A. Rivero, *ARKIVOC*, 2003, 193.
114. J. Kobayashi, T. Agou and T. Kawashima, *Chem. Lett.*, 2003, **32**, 1144.
115. M. Widhalm and K. Mereiter, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 1233.
116. Y. Okada, K. Okeya, Y. Murata, N. Aoki, T. Aoki, M. Sugitani, S. Yasui, Y. Sawada and F. Ogura, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 821.
117. C.C. Silveira, A.L. Braga and R.C. Guadagnin, *Tetrahedron Lett.*, 2003, **44**, 5703.
118. A.L. Braga, C.R.B. Rhoden, G. Zeni, C.C. Silveira and L.H. Andrade, *J. Organomet. Chem.*, 2003, **682**, 35.
119. O.M. Demchuk, K.M. Pietrusiewicz, A. Michrowska and K. Grela, *Org. Lett.*, 2003, **5**, 3217.
120. F. Bisaro and V. Gouverneur, *Tetrahedron Lett.*, 2003, **44**, 7133.
121. M. Rubin, J. Markov, S. Chuprakov, D.J. Wink and V. Gevorgyan, *J. Org. Chem.*, 2003, **68**, 6251.
122. M. Czupik, N. Bankey and E. Fossum, *Synth. Commun.*, 2004, **34**, 705.
123. L. Xu, J. Mo, C. Baillie and J. Xiao, *J. Organomet. Chem.*, 2003, **687**, 301.
124. L.A. Rusch-Salazar and V.V. Sheares, *J. Polymer Sci., A: Polymer Chem.*, 2003, **41**, 2277.
125. (*a*) A.P. Logunov, *Izv. Nat. Akad. Nauk Respub. Kazakhstan, Ser. Khim.*, 2003, (4), 60; (*b*) A.P. Logunov, *Chem. Abstr.*, 2003, **141**, 38672.
126. (*a*) A.P. Logunov, *Izv. Nat. Akad. Nauk Respub. Kazakhstan, Ser. Khim.*, 2003, (5), 60; (*b*) A.P. Logunov, *Chem. Abstr.*, 2003, **141**, 260812.
127. T. Mizuta, Y. Imamura and K. Miyoshi, *J. Am. Chem. Soc.*, 2003, **125**, 2068.
128. L. Xiaozhong, L. Hongmei and K. Fanzhi, *J. Organomet. Chem.*, 2002, **664**, 1.
129. Y. Liu, L. Li, X.-Y. Li, H.-Y. Zhang, T. Wada and Y. Inoue, *J. Org. Chem.*, 2003, **68**, 3646.
130. K.H. Lee, D.H. Lee, S. Hwang, O.S. Lee, D.S. Chung and J.-I. Hong, *Org. Lett.*, 2003, **5**, 1431.
131. N.J. Lawrence, J. Liddle and D. Jackson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2260.
132. M.S. Rahman, M. Oliana and K.K. (M.) Hii, *Tetrahedron: Asymmetry*, 2004, **15**, 1835.
133. V. Lachkova, H. Keck, R. Scopelliti, W. Kläui, S. Varbanov and G. Hägele, *Z. Naturforsch. B: Chem. Sci.*, 2004, **59**, 221.
134. Z. Hassen, A.B. Akacha and B. Hajjem, *J. Fluorine Chem.*, 2003, **121**, 177.
135. F. Slowinski, C. Aubert and M. Malacria, *J. Org. Chem.*, 2003, **68**, 378.
136. S.R. Gilbertson and P. Lan, *Tetrahedron Lett.*, 2002, **43**, 6961.
137. F. Palacios, D. Aparicio and J. Vicario, *Eur. J. Org. Chem.*, 2002, 4131.
138. F. Palacios, A.M.O. de Retana and J. Pagalday, *Eur. J. Org. Chem.*, 2003, 913.
139. F. Palacios, D. Aparicio, A.M.O. de Retana, J.M. de los Santos, J.I. Gil and J.M. Alonso, *J. Org. Chem.*, 2002, **67**, 7283.
140. F. Palacios, A.M.O. de Retana, J.I. Gil and J.M. Alonso, *Tetrahedron: Asymmetry*, 2002, **13**, 2541.

141. F. Palacios, A.M.O. de Retana, J.I. Gil and R.L. de Munain, *Org. Lett*., 2002, **4**, 2405.
142. M. Shimizu, Y. Iwasaki, Y. Shibamoto, M. Sato, H.F. DeLuca and S. Yamada, *Bioorg. Med. Chem. Lett*., 2003, **13**, 809.
143. A. Takano, H. Fukuhara, T. Ohno, M. Kutsuma, T. Fujimoto, H. Shirai, R. Iriye, A. Kakehi and I. Yamamoto, *J. Carbohydrate Chem*., 2003, **22**, 443.
144. V.K. Reddy, L.N. Rao, M. Maeda, B. Haritha and M. Yamashita, *Heteroatom Chem*., 2003, **14**, 320.
145. M. Yamashita, V.K. Reddy, L.N. Rao, B. Haritha, M. Maeda, K. Suzuki, H. Totsuka, M. Takahashi and T. Oshikawa, *Tetrahedron Lett*., 2003, **44**, 2339.
146. Z. Pakulski, M. Koprowski and K.M. Pietrusiewicz, *Tetrahedron*, 2003, **59**, 8219.
147. Z. Pakulski and K.M. Pietrusiewicz, *Tetrahedron: Asymmetry*, 2004, **15**, 41.
148. V.K. Reddy, B. Haritha, T. Oshikawa and M. Yamashita, *Tetrahedron Lett*., 2004, **45**, 2851.
149. M. Yamashita, V.K. Reddy, P.M. Reddy, Y. Kato, B. Haritha, K. Suzuki, M. Takahashi and T. Oshikawa, *Tetrahedron Lett*., 2003, **44**, 3455.
150. B. Haritha, V.K. Reddy, T. Oshikawa and M. Yamashita, *Tetrahedron Lett*., 2004, **45**, 1923.
151. Z. Pakulski, R. Kwiatosz and K.M. Pietrusiewicz, *Tetrahedron Lett*., 2003, **44**, 5469.
152. G. Keglevich, *Current Org. Chem*., 2002, **6**, 891.
153. G. Keglevich, H. Szelke, A. Tamás, V. Harmat, K. Ludányi, A.G. Vaskó and L. Tőke, *Heteroatom Chem*., 2002, **13**, 626.
154. G. Keglevich, H. Szelke, A. Bálint, T. Imre, K. Ludányi, Z. Nagy, M. Hanusz, K. Simon, V. Harmat and L. Tőke, *Heteroatom Chem*., 2003, **14**, 443.
155. G. Keglevich, J. Kovács, A. Szöllősy, A. Kovács, A. Szabó, K. Ludányi, I. Kádas and L. Tőke, *Heteroatom Chem*., 2003, **14**, 29.
156. J. Kovács, T. Imre, K. Ludányi, L. Tőke and G. Keglevich, *Synth. Commun*., 2004, **34**, 1033.
157. G. Keglevich, J. Kovács, K. Ludányi and L. Tőke, *Heterocyclic Commun*., 2002, **8**, 31.
158. G. Keglevich, J. Kovács, T. Körtvélyesi, G. Parlagh, T. Imre, K. Ludányi, L. Hegedűs, M. Hanusz, K. Simon, A. Márton, G. Marosi and L. Tőke, *Heteroatom Chem*., 2004, **15**, 97.
159. S. Jankowski, G. Keglevich, T. Nonas, H. Forintos, M. Główka and J. Rudziński, *Tetrahedron,* 2004, **60**, 2789; (See also corrigendum: *Tetrahedron,* 2004, **60**, 5117.).
160. G. Keglevich, M. Sipos, T. Imre, K. Ludányi, D. Szieberth and L. Tőke, *Tetrahedron Lett*., 2002, **43**, 8515.
161. Y. Qin, S. Selvaratnam, J.J. Vital and P.-H. Leung, *Organometallics*, 2002, **21**, 5301.
162. B.A. Trofimov, B.G. Sukhov, S.F. Malysheva, N.A. Belogorlova, S.N. Arbuzova, S.P. Tunik and N. K. Gusarova, *Russ. J. Org. Chem*., 2004, **40**, 129.
163. P. Rey, J. Taillades, J.C. Rossi and G. Gros, *Tetrahedron Lett*., 2003, **44**, 6169.
164. N.I. Ivanova, N.K. Gusarova, E.A. Nikitina, S.A. Medvedeva, M.L. Al'pert and B.A. Trofimov, *Chem. Heterocyclic Comp*., 2004, **40**, 426.
165. N.K. Gusarova, A.M. Reutskaya, N.I. Ivanova, A.S. Medvedeva, M.M. Demina, P.S. Novopashin, A.V. Afonin, A.I. Albanov and B.A. Trofimov, *J. Organomet. Chem*., 2002, **659**, 172.
166. N.I. Ivanova, N.K. Gusarova, E.A. Nikitina, A.I. Albanov, L.M. Sinegovskaya, M.V. Nikitin, N.A. Konovalova and B.A. Trofimov, *Phosphorus, Sulfur, Silicon*, 2004, **179**, 7.
167. N.I. Ivanova, A.M. Reutskaya, N.K. Gusarova, S.A. Medvedeva, A.V. Afonin, I.A. Ushakov, A.A. Tatarinova and B.A. Trofimov, *Russ. J. Gen. Chem*., 2003, **73**, 1354.

168. R.I. Vasil'ev, N.V. Durmanova, A.R. Garifzyanov and R.A. Cherkasov, *Russ. J. Gen. Chem.*, 2003, **73**, 994.
169. K. Shioji, S. Tsukimoto, H. Tanaka and K. Okuma, *Chem. Lett.*, 2003, **32**, 604.
170. G. Keglevich, H. Forintos, A. Ujvári, T. Imre, K. Ludányi, Z. Nagy and L. Tőke, *J. Chem. Research*, 2004, 432.
171. G. Keglevich, T. Körtvélyesi, H. Forintos and S. Lovas, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1645.
172. K. Izod, W. McFarlane and W. Clegg, *Chem. Commun.*, 2002, 2532.
173. E. Krawczyk, A. Skowrońska and J. Michalski, *J. Chem. Soc.*, 2002, 4471.
174. S. Makowiec and J. Rachon, *Heteroatom Chem.*, 2003, **14**, 352.
175. Y. Uchida, M. Matsumoto and H. Kawamura, *Heteroatom Chem.*, 2003, **14**, 72.
176. Y.S. Li, X.R. Liang and W.K. Su, *Org. Prep. Proc. Int.*, 2003, **35**, 613.
177. S.-L. You, H. Razavi and J.W. Kelly, *Angew. Chem. Int. Ed.*, 2003, **42**, 83.
178. S.-L. You and J.W. Kelly, *J. Org. Chem.*, 2003, **68**, 9506.
179. S. Caddick, J.D. Wilden and D.B. Judd, *J. Am. Chem. Soc.*, 2004, **126**, 1024.
180. K.E. Elson, I.D. Jenkins and W.A. Loughlin, *Tetrahedron Lett.*, 2004, **45**, 2491.
181. K.E. Elson, I.D. Jenkins and W.A. Loughlin, *Org. Biomol. Chem.*, 2003, **1**, 2958.
182. T.A. Khan, R. Tripoli, J.J. Crawford, C.G. Martin and J.A. Murphy, *Org. Lett.*, 2003, **5**, 2971.
183. V.D. Kolesnik and A.V. Tkachev, *Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 624.
184. (*a*) C.S. Colley, D.C. Grills, N.A. Besley, S. Jockusch, P. Matousek, A.W. Parker, M. Towrie, N.J. Turro, P.M.W. Gill and M.W. George, *J. Am. Chem. Soc.*, 2002, **124**, 14952; (*b*) M. Weber and N.J. Turro, *J. Phys. Chem. A*, 2003, **107**, 326.
185. C. Dursun, M. Degirmenci, Y. Yagci, S. Jockusch and N.J. Turro, *Polymer*, 2003, **44**, 7389.
186. C. Ogawa, H. Konishi, M. Sugiura and S. Kobayashi, *Org. Biomol. Chem.*, 2004, **2**, 446.
187. S. Bhattacharya, S. Banerjee, S.K. Nayak, S. Chattopadhyay and A.K. Mukherjee, *Spectrochim. Acta A*, 2004, **60**, 1099.
188. Y. Sakamoto, K. Kondo, M. Tokunaga, K. Kazuta, H. Fujita, Y. Murakami and T. Aoyama, *Heterocycles*, 2004, **63**, 1345.
189. D. Magiera, S. Moeller, Z. Drzazga, Z. Pakulski, K.M. Pietrusiewicz and H. Duddeck, *Chirality*, 2003, **15**, 391.
190. Z. Pakulski, O.M. Demchuk, R. Kwiatosz, P.W. Osiński, W. Świerczyńska and K.M. Pietrusiewicz, *Tetrahedron: Asymmetry*, 2003, **14**, 1459.
191. M. Rivard, F. Guillen, J.-C. Fiaud, C. Aroulanda and P. Lesot, *Tetrahedron: Asymmetry*, 2003, **14**, 1141.
192. J. Omelańczuk, A. Karaçar, M. Freytag, P.G. Jones, R. Bartsch, M. Mikołajczyk and R. Schmutzler, *Inorg. Chim. Acta*, 2003, **350**, 583.
193. F. Wang, Y. Wang, P.L. Polavarapu, T. Li, J. Drabowicz, K.M. Pietrusiewicz and K. Zygo, *J. Org. Chem.*, 2002, **67**, 6539.
194. P. Kiełbasiński, R. Żurawiński, M. Albrycht and M. Mikołajczyk, *Tetrahedron: Asymmetry*, 2003, **14**, 3379.
195. R.R. Shagidullin, A.V. Chernova, S.A. Katsyuba, L.V. Avvakumova and Rif. R. Shagidullin, *Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 55.
196. A. Kolbe, M. Plass, R. Żurawiński, P. Kiełbasiński and M. Mikołajczyk, *Spectrochim. Acta A*, 2003, **59**, 2875.
197. C. López-Leonardo, M. Alajarin, P. Llamas-Lorente, D. Bautista, M.L. Jimeno, I. Alkorta and J. Elguero, *Structural Chem.*, 2003, **14**, 391.

198. S. Chandrasekhar, G. Kulkarni, B. Muktha and T.N.G. Row, *Tetrahedron: Asymmetry*, 2003, **14**, 3769.
199. M. Canipelle, L. Caron, H. Bricout, S. Tilloy and E. Monflier, *New J. Chem.*, 2003, **27**, 1603.
200. R. Kruszynski and W. Wieczorek, *Heteroatom Chem.*, 2004, **15**, 233.
201. A. Chandrasekharan, N.V. Timosheva, R.O. Day and R.R. Holmes, *Inorg. Chem.*, 2003, **42**, 3285.
202. A. Chandrasekharan, N.V. Timosheva, R.O. Day and R.R. Holmes, *Inorg. Chem.*, 2002, **41**, 5235.
203. (*a*) A.A. Espenbetov, A.P. Logunov, G.T. Maishinova and B.M. Butin, *Izvest. Nat. Akad. Nauk Respub. Kazakhstan, Ser. Khim.*, 2003, (5), 17; (*b*) A.A. Espenbetov, A.P. Logunov, G.T. Maishinova and B.M. Butin, *Chem. Abstr.*, 2003, **141**, 260811.
204. R.J. Bowen, M.A. Fernandes, P.W. Gitari and M. Layh, *Acta Cryst.C: Cryst. Struct. Commun.*, 2004, **60**, o–258.
205. N. Kuhn, M. Göhner and M. Steimann, *Z. Anorg. Allg. Chem.*, 2003, **629**, 595.
206. S.L. Hinchley, M.F. Haddow and D.W.H. Rankin, *Dalton Trans.*, 2004, 384.
207. L. Atamas, O. Klimchuk, V. Rudzevich, V. Pirozhenko, V. Kalchenko, I. Smirnov, V. Babain, T. Efremova, A. Varnek, G. Wipff, F. Arnoud-Neu, M. Roch, M. Saadioui and V. Böhmer, *J. Supramol. Chem.*, 2002, **2**, 421.
208. (*a*) M. Kyoda, H. Maekawa, Y. Sadai and I. Nishiguchi, *Advances in Technology of Materials and Materials Processing Journal*, 2004, **6**, 29; (*b*) M. Kyoda, H. Maekawa, Y. Sadai and I. Nishiguchi, *Chem. Abstr.*, 2004, **141**, 332253.
209. M. R. Yaftian, R. Taheri and D. Matt, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1225.
210. V. Videva, A.-S. Chauvin, S. Varbanov, C. Baux, R. Scopelliti, M. Mitewa and J.-C.G. Bünzli, *Eur. J. Inorg. Chem.*, 2004, 2173.
211. F. de M. Ramírez, S. Varbanov, C. Cécile, G. Muller, N. Fatin-Rouge, R. Scopelliti and J.-C.G. Bünzli, *J. Chem. Soc., Dalton Trans.*, 2002, 4505.
212. S. Kannan, N. Rajalakshmi, K.V. Chetty, V. Venugopal and M.G.B. Drew, *Polyhedron*, 2004, **23**, 1527.
213. J. Fawcett and A.W.G. Platt, *Polyhedron*, 2003, **22**, 967.
214. A.M.J. Lees and A.W.G. Platt, *Inorg. Chem.*, 2003, **42**, 4673.
215. T. Gáti, A. Simon, G. Tóth, A. Szmigielska, A.M. Maj, K.M. Pietrusiewicz, S. Moeller, D. Magiera and H. Duddeck, *Eur. J. Inorg. Chem.*, 2004, 2160.
216. Z. Spichal, M. Necas, J. Pinkas and J. Novosad, *Inorg. Chem.*, 2004, **43**, 2776.
217. G.L. Abbati, M.C. Aragoni, M. Arca, F.A. Devillanova, A.C. Fabretti, A. Garau, F. Isaia, V. Lippolis and G. Verani, *Dalton Trans.*, 2003, 1515.
218. D.J. Crouch, M. Helliwell, P. O'Brien, J.-H. Park, J. Waters and D.J. Williams, *Dalton Trans.*, 2003, 1500.
219. D.J. Crouch, P.M. Hatton, M. Helliwell, P. O'Brien and J. Raftery, *Dalton Trans.*, 2003, 2761.
220. S. Canales, O. Crespo, M.C. Gimeno, P.G. Jones, A. Laguna, A. Silvestru and C. Silvestru, *Inorg. Chim. Acta*, 2003, **347**, 16.
221. S.K. Mandal, G.A.N. Gowda, S.S. Krishnamurthy, C. Zheng, S. Li and N.S. Hosmane, *J. Organomet. Chem.*, 2003, **676**, 22.
222. M. Doux, N. Mézailles, L. Ricard and P. Le Floch, *Organometallics*, 2003, **22**, 4624.
223. D. Belletti, C. Graiff, C. Massera, A. Minareelli, G. Predieri, A. Tiripicchio and D. Acquotti, *Inorg. Chem.*, 2003, **42**, 8509.
224. T.S. Lobana, Rimple, A. Castineiras and P. Turner, *Inorg. Chem.*, 2003, **42**, 4731.
225. H. Liu, M.J. Calhorda, M.G.B. Drew and V. Félix, *Inorg. Chim. Acta*, 2003, **347**, 175.

226. O.S. Sentürk, H.A. Shekhel, B.T. Sterenberg, K.A. Udachin, S. Sert, U. Özdemir and F.U. Sarikahya, *Polyhedron*, 2003, **22**, 1659.
227. D. Belletti, C. Graiff, V. Lostao, R. Pattacini, G. Predieri and A. Tiripicchio, *Inorg. Chim. Acta*, 2003, **347**, 137.
228. J.B. Cook, B.K. Nicholson and D.W. Smith, *J. Organomet. Chem.*, 2004, **689**, 860.
229. P. Das, P. Chutia and D.K. Dutta, *Chem. Lett.*, 2002, **31**, 766.
230. D. Belletti, D. Cauzzi, C. Graiff, A. Minarelli, R. Pattacini, G. Predieri and A. Tiripiccio, *J. Chem. Soc., Dalton Trans.*, 2002, 3160.
231. D. Belletti, C. Graiff, C. Massera, G. Predieri and A. Tiripiccio, *Inorg. Chim. Acta*, 2003, **350**, 421.
232. S.M. Aucott, A.M.Z. Slawin and J.D. Woollins, *Polyhedron*, 2003, **22**, 361.
233. D. Saravanabharathi, M. Nethaji and A.G. Samuelson, *Polyhedron*, 2002, **21**, 2793.
234. E.C. Constable, C.E. Housecroft, M. Neuburger and A.G. Schneider, *Inorg. Chem. Commun.*, 2003, **6**, 912.
235. L.J. Charbonnière, R. Ziessel, M. Montalti, L. Prodi, N. Zaccheroni, C. Boehme and G. Wipff, *J. Am. Chem. Soc.*, 2002, **124**, 7779.
236. H. Xin, F. Y. Li, M. Shi, Z.Q. Bian and C.H. Huang, *J. Am. Chem. Soc.*, 2003, **125**, 7166.
237. J.-C. Berthet, M. Nierlich and M. Ephritikhine, *Polyhedron*, 2003, **22**, 3475.
238. M.J. Glazier, W. Levason, M.L. Matthews, P.L. Thornton and M. Webster, *Inorg. Chim. Acta*, 2004, **357**, 1083.
239. N. Manwani, M.C. Gupta, R. Ratnani, J.E. Drake, M.B. Hursthouse and M.E. Light, *Inorg. Chim. Acta*, 2004, **357**, 939.
240. J. Beckmann, D. Dakternieks, A. Duthie and C. Mitchell, *Dalton Trans.*, 2003, 3258.
241. S.M. Närhi, R. Oilunkaniemi, R.S. Latinen and M. Ahlgrén, *Inorg. Chem.*, 2004, **43**, 3742.
242. R. Kino, K. Daikai, T. Kawanami, H. Furuno and J. Inanaga, *Org. Biomol. Chem.*, 2004, **2**, 1822.
243. C.I.A. Kiraz, T.J. Emge and L.S. Jiminez, *J. Org. Chem.*, 2004, **69**, 2200.
244. H.J. Clark, R. Wang and H. Alper, *J. Org. Chem.*, 2002, **67**, 6224.
245. L.F. Szczepura, B.A. Ooro and S.R. Wilson, *J. Chem. Soc. Dalton Trans.*, 2002, 3112.
246. M. Green, N. Allsop, G. Wakefield, P.J. Dobson and J.L. Hutchison, *J. Mater. Chem.*, 2002, **12**, 2671.
247. L.D. Henderson, G.D. MacInnis, W.E. Piers and M. Parvez, *Can. J. Chem.*, 2004, **82**, 162.
248. N.J. Hill, W. Levason, M.C. Popham, G. Reid and M. Webster, *Polyhedron*, 2002, **21**, 1579.
249. V.V. Semenov, N.F. Cherepennikova, L.G. Klapshina, M.A. Lopatin, T.G. Mushtina, N.P. Makarenko, S.Ya. Korshev, G.A. Domrachev, W.E. Douglas and B.A. Bushuk, *Russ. J. Coord. Chem.*, 2004, **30**, 435.
250. A. Krężel, R. Latajka, G.D. Bujacz and W. Bal, *Inorg. Chem.*, 2003, **42**, 1994.
251. W.-M. Dai, K.K.Y. Yeung, W.H. Leung and R.K. Haynes, *Tetrahedron: Asymmetry*, 2003, **14**, 2821.
252. X.-B. Jiang, A.J. Minnaard, B. Hessen, B.L. Feringa, A.L.L. Duchateau, J.G.O. Andrien, J.A.F. Boogers and J.G. de Vries, *Org. Lett.*, 2003, **5**, 1503.

Tervalent Phosphorus Acid Derivatives

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1 Introduction

As this chapter covers two years of the literature relating to the above area, it has been necessary to be somewhat selective in the choice of publications cited. Nevertheless, it is hoped that most significant developments have been noted. As in previous reports, attempts have been made to minimise the extent of overlap with other chapters, in particular those concerned with the synthesis of nucleic acids and nucleotides to which the chemistry of tervalent phosphorus esters and amides contributes significantly, the use of known halogenophosphines as reagents for the synthesis of phosphines (see Chapter 1), and the reactions of dialkyl- and diaryl-phosphite esters in which the contribution of the phosphonate tautomer, $(RO)_2P(O)H$, is the dominant aspect, which are usually covered elsewhere in these volumes.

The period under review has seen the publication of a considerable number of review articles, and most of these are cited in the appropriate sections. Once again, there has been considerable interest in tervalent phosphorus-ester and -amide chemistry that relates to the preparation of new, often chiral, ligand systems for use in metal-catalysed homogeneous catalysis. Several major reviews of this area have appeared, covering recent developments in the area of asymmetric catalysis using organometallic complexes of ligands which contain two or three P–O or P–N bonds,[1] the use of chiral ferrocenylphosphorus(III) ligands involving phosphite, phosphoramidite and aminophosphine donor groups,[2,3] and the use of chiral phosphites and phosphoramidites in a wide range of asymmetric syntheses.[4] A new approach in combinatorial asymmetric transition metal-catalysed synthesis relates to the use of *mixtures* of chiral monodentate phosphites, phosphonites and phosphoramidites derived from BINOL and related systems as ligands and work in this area has also been reviewed.[5,6] Another major review covers the synthesis and reactivity of diphosphines in which the phosphorus atoms are bridged by heteroatoms such as oxygen, nitrogen, sulfur and selenium, compounds which hitherto have received little coverage compared with that of their

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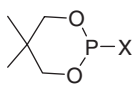
carbon-bridged analogues such as bis(diphenylphosphino)methane.[7] The applicability limits of calculation methods for estimating the enthalpy of vaporisation of organophosphorus compounds, including tervalent phosphorus acid derivatives, have been reviewed.[8] Research into the mechanisms of nucleophilic substitution reactions of tervalent phosphorus acid derivatives has been reviewed with emphasis on the reactions of phosphoramidites.[9]

2 Halogenophosphines

A clean route to dichlorophenylphosphine is provided by carrying out the long-established Friedel-Crafts reaction of benzene and phosphorus trichloride in ionic liquid media derived from butylpyridinium chloride and aluminium trichloride, the system allowing an easy product isolation procedure.[10] New simple high yield procedures for the synthesis of the heterocyclic halophosphites (1, X=Cl or F) have been developed. The chlorophosphite was obtained *via* the reaction of 2,2-dimethyl-1,3-propanediol with phosphorus trichloride at room temperature, in the absence of base or solvent, and was converted into the fluorophosphite by treatment with antimony pentafluoride.[11] Chlorophosphites $(RO)_2PCl$ have also been obtained, in quantitative yield, by treatment of secondary phosphites $(RO)_2P(O)H$ with dichloro(2,4,6-tribromophenoxy)(1,2-diphenoxy)phosphorane.[12] Treatment of the ephedrine-derived aminophosphine-boranes (2) with a solution of hydrogen chloride in toluene provides a route to highly enantiomerically-enriched chlorophosphine-boranes (3), the cleavage of the P–N bond proceeding with inversion of configuration at phosphorus. These compounds are important new electrophilic building blocks for the stereoselective synthesis of chiral phosphorus compounds.[13] They can also be reduced using a variety of complex hydride reagents to the related secondary phosphine-boranes.[14] The heterocyclic bromophosphines (4) and (5) have been obtained *via* the reactions of various indoline derivatives with phosphorus tribromide and used as intermediates for the synthesis of a range of heterocyclic phosphorus compounds.[15] The reactions of bulky organometallic reagents with simple halogenophosphine precursors have been widely employed in the synthesis of new halogenophosphines. Among new arylhalogenophosphines bearing trifluoromethyl substituents in the aryl rings prepared in this way and characterised by X-ray crystallography are the primary dibromophosphine (6) and the secondary halogenophosphines (7) and (8).[16] The 9-triptycenyldichlorophosphine (9) has been obtained from the reactions of 9-triptycenyllithium (one equivalent) with phosphorus trichloride, the related reactions with $AsCl_3$, $SbCl_3$ and $BiCl_3$ yielding the heavier Group 15 congeners.[17] Treatment of indenyllithium with di(isopropyl)aminodichlorophosphine yields the monochloro(amino)phosphine (10), subsequently converted into the chiral dicarboranyl(amino)indenylphosphine (11) from which a series of rare-earth complexes has been prepared.[18] The ketiminylchlorophosphine system (12) has been obtained from the reaction of a lithiated β-diketimine with dichlorophenylphosphine. Reduction of (12) with potassium

naphthalenide provides the heterocyclic dihydroazadiphosphole (13).[19] Treatment of a magnesium salt of the linked silylamido(cyclopentadienyl) ligand $[Me_2Si(C_5Me_4)NBu^t]^{2-}$ with phosphorus trichloride results in the initial formation of the bicyclic chlorophosphine (14) which rearranges to give (15) as the final product. The corresponding reactions with arsenic- and antimony-trichlorides result in the isomeric systems (16). Chloride abstraction from (15) and (16) provides the related phosphenium, arsenium and stibenium cations which again reveal interesting structural differences.[20] Dilithiation of 2,2′-dimethyl-1,1′-binaphthyl, followed by treatment with phosphorus trichloride (or Et_2NPCl_2 followed by hydrogen chloride) yields the chiral phosphinous chloride (17), a key intermediate for the synthesis of a range of chiral tervalent phosphorus acid derivatives, and tertiary phosphines.[21,22] The chiral phosphinous chloride (18, R=Me) has been obtained from the reaction of an *ortho*-lithiated chiral benzylamine with the reagent $(Me_3Si)_2CHPCl_2$, reduction with $LiAlH_4$ giving the related secondary phosphine.[23] In related work, it has been shown that whereas $LiAlH_4$ reduction of (18, R=H) under reflux conditions in ether-THF yields the expected secondary phosphine, when the reduction is carried out at lower temperatures, the P,P-diphosphine (19) is formed as a significant biproduct. The latter may be obtained in much higher yield from the reaction of the lithiated secondary phosphine with lead(II) iodide. This study also reports that $LiAlH_4$ reduction of the crowded phosphonous dichloride $(Me_3Si)_2CHPCl_2$ yields the diphosphine (20).[24] The thioether-functionalised chlorophosphine (21) has been prepared from $(Me_3Si)_2CHPCl_2$ by treatment with *ortho*-lithiated thioanisole, and reduced, *in situ*, to the related secondary phosphine.[25] Treatment of 1,2-bis(dichlorophosphino)ethane with the bulky Grignard reagent $(Me_3Si)_2CHMgCl$ generates the bis(chlorophosphine) (22). This has been shown to react with the base DBN (1,5-diazabicyclo[4,3,0]non-5-ene) to give an adduct which, on deprotonation with *t*-butyllithium, generates the anionic species (23), isolated as a magnesium-DBN complex.[26] The bis(trimethylsilyl)phosphine (24, X=tms) is converted into the chlorophosphine (24, X=Cl) on treatment with hexachloroethane. Controlled thermolysis of the latter at 90°C in toluene results in the clean formation of the dibenzophosphasemibullvalene (25), probably *via* an intermediate phosphinidene.[27] Heating a solution of the 2H-azaphosphirene complex (26) in carbon tetrachloride at 70°C results in the selective formation of the complexed dichlorophosphine (27).[28] Woollins' group has continued to explore the chemistry of the *peri*-bis(dichlorophosphino)naphthalene system (28). A new synthetic pathway to this compound starts with chlorination of the thiophosphonic anhydride (29), which provides the dipolar adduct (30), involving an intramolecular P(III)–P(V) interaction.[29] Treatment of the latter with methyldichlorophosphite provides the bis(dichlorophosphine) (28) in almost quantitative yield. On subsequent treatment with magnesium, the bis(dichlorophosphine) is converted into the polymeric diphosphine (31), insoluble in common organic solvents. Halogenation of (31) with bromine and iodine gave the bis(dibromophosphine) (32) and the diiododiphosphine (33), respectively.[30] Treatment of the bis(dichlorophosphine) (28) with oxygen (in excess, for prolongued

periods) yielded mainly the monoxide (34), with only *ca* 10% of the corresponding dioxide. Also isolated in small amounts was the partial hydrolysis product (35).[31] The outcome of the reaction between 1,8-dilithionaphthalene and dichlorophosphines $RPCl_2$ is dependent on the nature of the R group at phosphorus. Thus, the reaction with phenyldichlorophosphine leads to the diphosphine (36) whereas with $^{i}Pr_2NPCl_2$, the naphtho[1,8-*bc*]phosphete (37) is formed.[32]



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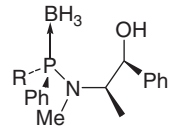
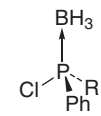


(2) R = e.g., Me, Bu^{t}, Cy, *o*-Tol, *o*-An, 1-Naphthyl, 2-Naphthyl



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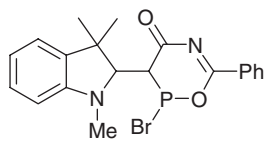

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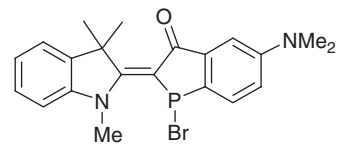

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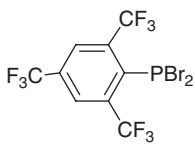

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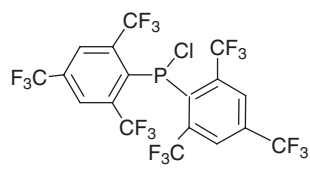

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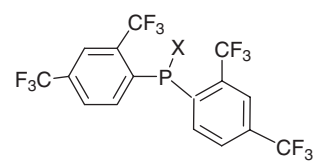
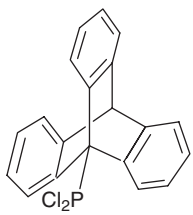


(8) X = Cl or Br



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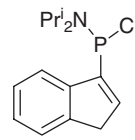

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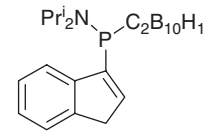

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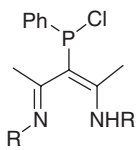

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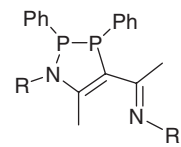

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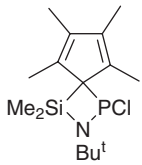

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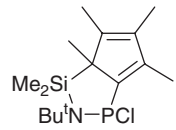

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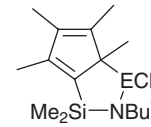
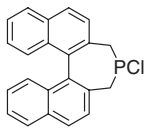


(16) E = As or Sb



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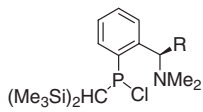

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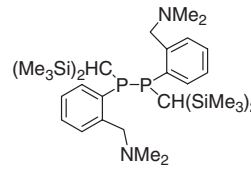

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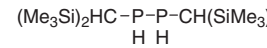

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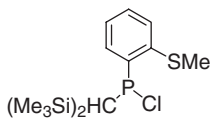

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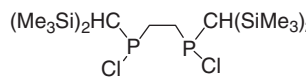

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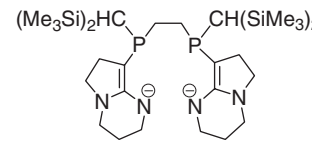

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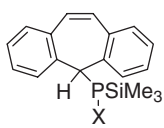

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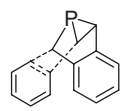

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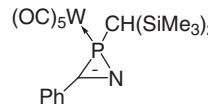

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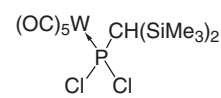

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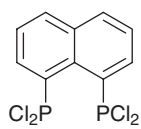

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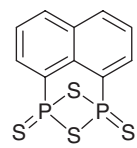

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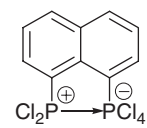

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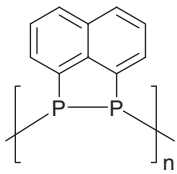

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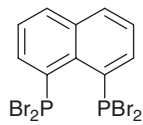

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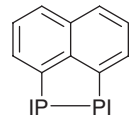

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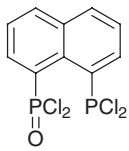

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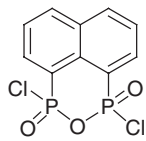

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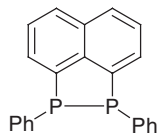

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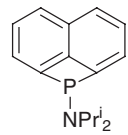
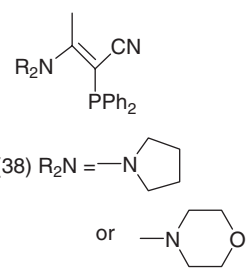
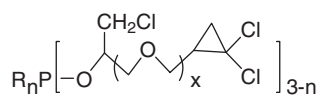


(37)

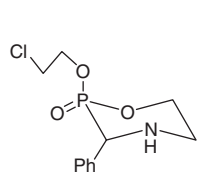
Among a miscellany of other studies of the reactivity of halogenophosphines reported in the period under review are the derivatisation of free OH groups of acylglycerols in vegetable oils using chlorophosphines, followed by detection using ^{31}P NMR,[33] the reactions of chlorodiphenylphosphine with enamine derivatives of β-aminocrotonic acid giving, e.g., the enaminophosphines (38),[34] the opening of the epoxide ring of oxiranes bearing 2,2-dichlorocyclopropyl substituents to give P(III)-esters of type (39),[35] the reactions of chlorophosphites with β-aldiminoalcohols to give heterocyclic phosphonates, e.g., (40),[36] and a Mannich-type reaction involving *p*-tolyldichlorophosphine, methyl ethyl ketone and 1,2-diaminopropane, which results in the formation of a new 1,4,2-diazaphosphorine-2-oxide.[37] The cyclic bis(phosphinous chloride) (41) has been shown to react with N,N′-dimethyl-N,N′-bis(trimethylsilyl)urea to form initially the bicyclic system (42), which gradually rearranges to form the more thermodynamically stable urea-bridged diphosphine (43).[38] Cyclic chlorophosphites and related isothiocyanato-, azido-, and amido-phosphites (44) undergo a cycloaddition reaction with diisopropyl azodicarboxylate to form new stable crystalline pentacoordinate phosphoranes, e.g., (45), in which the nitrogen atom, rather than the oxygen, occupies an apical position of the trigonal bipyramid.[39]



(38) R_2N = —N



(39) R = Ph, *p*-Tol or $ClCH_2CH_2$; n = 1 or 2; x = 0 or 1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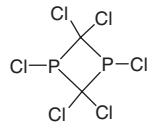
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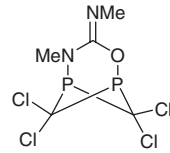
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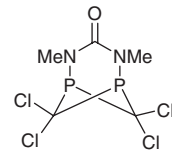
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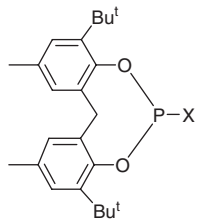
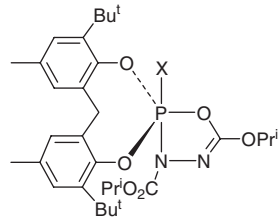

(44) X = Cl, N_3, NCS or NHMe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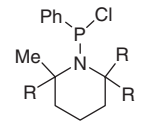
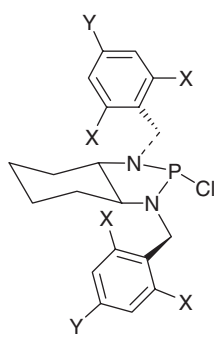
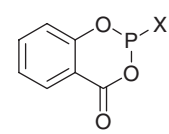

(46) R = H or Me

Halogenophosphines have also attracted a number of structural, physicochemical, and theoretical studies. Rotational barriers in a series of methyl-substituted piperidinochlorophosphines (46) have been measured by variable temperature NMR studies.[40] NMR techniques have also been used to study the mechanism of halogen exchange in the phosphorus(III) halide (47).[41] The configurational stability of chlorophosphines has been investigated by density functional theory studies, together with experimental studies. The presence of HCl in the medium was found to catalyse the P-centre chiral inversion at room temperature, the reaction involving a two-step mechanism. The configurational stability of chirogenic chlorophosphines can be protected using borane adducts.[42] Quantum chemical calculations and ^{35}Cl NQR techniques have been used to probe structural features of alkyldichlorophosphines.[43] Theoretical methods have also been applied to the study of the molecular structure and conformational preferences of a wide range of halogenophosphines, including 1,3,2-diheterophospholenes,[44,45] P-chloro- and -isocyanato-1,3,2-benzodioxaphosphinan-4-ones, (48),[46] the chlorodithiophosphite $ClP(SMe)_2$,[47] and also various cyanophosphines.[48]

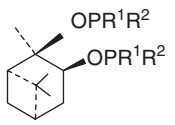

(47) X = H, F, Cl, Y = H, Bu^t or CN


(48) X = Cl or NCO

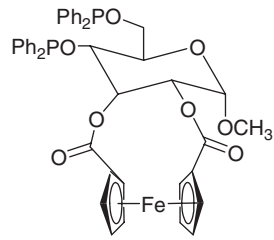
3 Tervalent Phosphorus Esters

3.1 Phosphinites. – As in recent years, most of the interest in this area has centred around the synthesis and evaluation of new ligand systems for use in homogeneous catalysis, in which phosphinite donor centres either replace or complement conventional phosphino or other donor centres in previously designed systems, many of which are chiral. In most cases, the phosphinite centre is introduced *via* the reaction of an alcohol or phenol with a chlorophosphorus(III) precursor, in the presence of a base. However, the synthesis of vicinal bis(diphenylphosphinites) derived from chiral vicinal diols by this classical approach tends to give impure products, probably as a result of traces of water in the diols. These problems have now been overcome using a metal-template procedure in which the diol is added to palladium(II)- or platinum(II)-complexes of diphenylchlorophosphine in anhydrous THF.[49,50] The conventional approach, however, has continued to be widely applied in the synthesis of new phosphinites. Among these are the chiral bis(phosphinites) (49),[51] the ferrocenylglucose bis(phosphinite) (50),[52] the long chain asymmetric bis(phosphinite) (51) (and a related bisphosphite),[53] the 'large bite' bis(phosphinite) (52),[54] the reduced BINAP bis(phosphinite) system (53),[55] and the pincer ligand bis(phosphinites) (54).[56] Conventional phosphinylation methods have also been used to prepare the silica-linked tris(diphenylphosphinite) (55).[57] The reactions of silanols with chlorophosphines in the presence of a base have been used in the synthesis of a bis(diphenylphosphinite)-derivatised silsesquioxide.[58] Puddephatt's group has continued to explore the synthesis[59] and coordination chemistry[60,61] of resorcinarenes bearing four or eight diphenylphosphinito groups, e.g., (56). Among new chiral monophosphinite systems prepared conventionally are a range of aminoacid based diphenylphosphinites, e.g., (57),[62] the cinchonidine- and quinine-based phosphinites (58), subsequently used for the asymmetric desymmetrization of *meso*-1,2-diols,[63] and the complexed cyclopentadienyl phosphinite (59).[64] Mathey's group has described interesting new approaches to the synthesis of chiral phosphinites. Treatment of 1-cyanophospholes with lithium alkoxides of allylic alcohols results in the initial formation of the corresponding 1-allyloxyphospholes, which rearrange at 25°C to form tricyclic phosphinites, e.g., (60).[65] The reaction of 1-cyano-3,4-dimethylphosphole with the dilithium salt of (*R,R*)-1,2-diphenyl-1,2-ethanediol gave the diphosphinite (61), which then underwent a cycloaddition reaction with N-phenylmaleimide to give the chiral system (62).[66] In yet another approach, treatment of the phosphonium salt (63) with thallous ethoxide gave the mixed phosphinite-phosphine (64).[67] Considerable interest has been shown in the synthesis of phosphinites which bear other non-phosphorus donor atoms or groups. Among these are a series of phosphinite-oxazolines, e.g., (65),[68,69] various sulfur-phosphinite donors, e.g., (66),[70,71] aminophosphine-phosphinites, e.g., (67),[72,73] and a variety of phosphine-phosphinites, e.g., the unsymmetrical pincer ligand (68),[74] the camphane system (69),[75] and the αα-trehalose derivative (70).[76] The phosphine-phosphinite (71) also has a nitrogen donor centre.[77] Among other new phosphinites also bearing a nitrogen

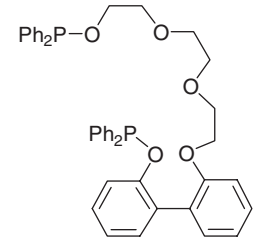
donor atom are the aminoalkynylphosphinite (72),[78] various pyridine-based systems, e.g., (73) (together with related phosphite esters),[79] the bis(phosphinite) (74),[80] and the 3-pyridylmethylphosphinite (75).[81] The synthesis, structure and properties of the cyclic thiaphosphinites (76) have been reviewed.[82]



(49) R^1,R^2 = Ph, Cy or Bu^t



(50)



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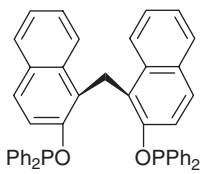

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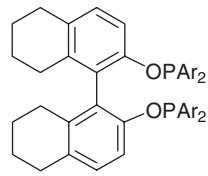
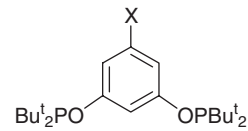
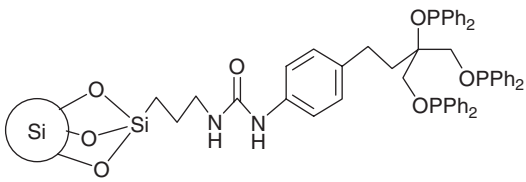


(53) Ar = 3,5-$Me_2C_6H_3$



(54) X = H, MeO, Me, C_6F_5 or 3,5-$(CF_3)_2C_6H_3$



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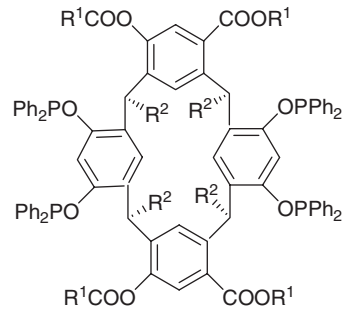
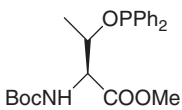


(56) R^1 = e.g., OCH_2Ph, Cy, 2-thienyl; R^2 = CH_2CH_2Ph



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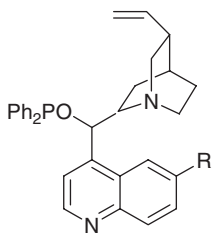
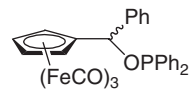


(58) R = H or Me



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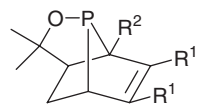
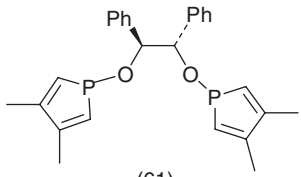


(60) R^1 = H or Me; R^2 = H or Ph



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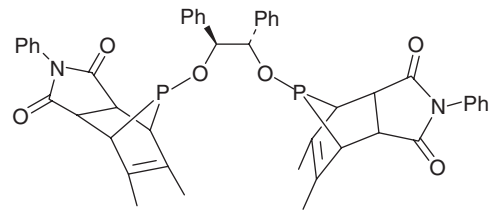

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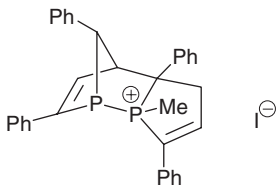

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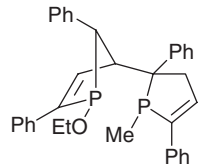

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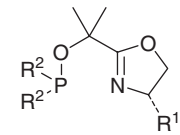
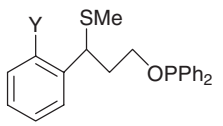
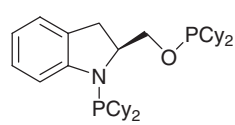


(65) R^1 = Pr^i or Bu^t; R^2 = Ph or *o*-tol



(66) Y = H or NMe_2



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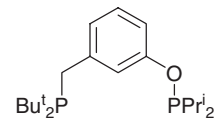

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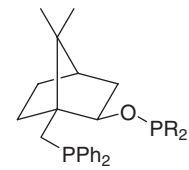
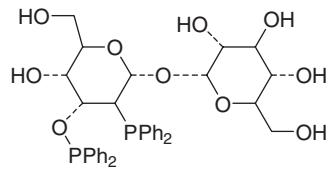
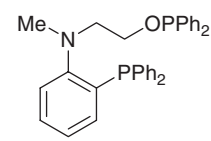


(69) R = Ph, Mes or Cy



(70)



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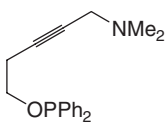

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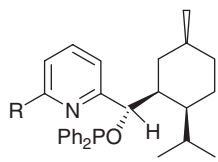

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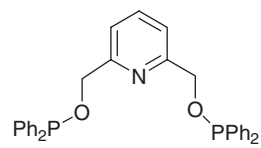

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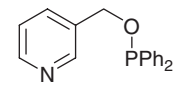
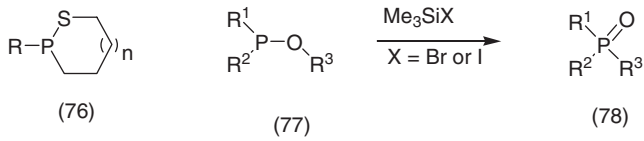
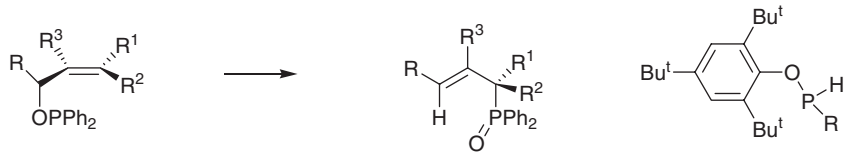


(75)

Apart from their properties as ligands, other aspects of the reactivity of phosphinite esters have been of interest. It has been shown that phosphinite esters (77) undergo the Michaelis-Arbuzov rearrangement to give the phosphine oxides (78) between room temperature and 80°C in the presence of trimethylsilyl halides, the reaction not needing the presence of any alkyl halide.[83] The rearrangement proceeds even more efficiently at room temperature in the

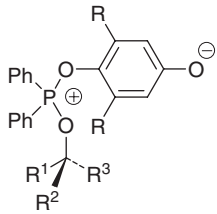
presence of stronger Lewis acids such as trimethylsilyl triflate or boron trifluoride etherate.[84] Allylic phosphinites (79) have been shown to undergo a stereoselective [2,3]-sigmatropic rearrangement on heating to form the (E)-allylic phosphine oxides (80).[85]



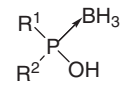


The synthesis, characterisation and thermolysis of a new class of phosphinite-borane adducts derived from the bulky phosphinites (81) has been investigated. The borane adducts undergo an unusual thermally-induced phenol-elimination reaction when heated to between 100 and 140°C to give highly cross-linked phosphorus-boron polymeric materials.[86] Phosphonium salts formed *in situ* from sugar-derived alkyl diphenylphosphinite esters are key intermediates in a new method for the α-selective glycosylation of glycosyl acceptors, forming α-disaccharides in high yield without the assistance of any acid catalysts.[87] Methylphosphonium salts derived from alkyl diphenylphosphinites formed *in situ* from lithium alkoxides ROLi and chlorodiphenylphosphine have been shown to react with Grignard reagents R′MgX to form the cross-coupled products R–R′ in a one-pot procedure.[88] The reaction between alkyl diphenylphosphinite esters and 1,4-quinones leads to the intermediate betaines (82). In the presence of carboxylic acids, alcohols or phenols, these are protonated and are then subject to nucleophilic attack (with inversion of configuration) at the alkoxy group by carboxylate, alkoxide, or phenate anions to form esters or ethers, together with a *p*-hydroxyphenyl diphenylphosphinate, under mild and neutral conditions. This approach has been reported in a series of papers by Mukaiyama *et al.* for the synthesis of esters of primary, inverted secondary- and tertiary-alcohols,[89,90] and benzylic alcohols,[91] and also for the synthesis of alkyl-aryl and diaryl ethers.[92,93] In these reactions, the initial diphenylphosphinite is formed *in situ*, usually from an alcohol and chlorodiphenylphosphine in the presence of a base. An alternative access to the phosphinite esters is provided by the reaction of *N,N*-dimethylaminodiphenylphosphine with the alcohol in dichloromethane at 40°C.[94] Ether formation by this approach has also been described using tetrafluoro-1,4-benzoquinone instead of the more commonly employed 2,6-dimethyl-1,4-benzoquinone.[95] Arising from their involvement as ligands in metal ion-catalysed reactions, studies have been made of *ortho*-metallation reactions

undergone by aryl phosphinite (and phosphite) esters in the presence of palladium complexes.[96,97]



(82) R = H or Me

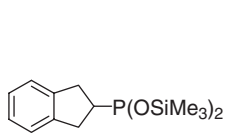


(83)

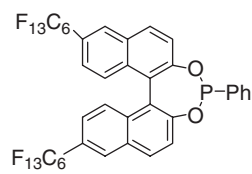
The chemistry of secondary phosphine oxides, $R_2P(H)O$ and their phosphinous acid tautomers, R_2POH, has continued to attract attention. The study of the phosphinous acid tautomers has been aided by the development of stereoselective procedures for direct conversion of secondary phosphine oxides to the phosphinous acid-boranes (83). Treatment of the secondary phosphine oxide with either a base-borane complex or boron trifluoride and sodium borohydride provides the phosphinous acid-borane with predominant inversion of configuration at phosphorus.[98] The phosphinous acid tautomers are usually trapped as ligands in metal complexes and further examples of this behaviour have been noted.[99] Discrimination of enantiomeric forms of chiral phosphinous acids, Ph(R)OH, coordinated to a chiral rhodium complex, has been studied by NMR.[100] Palladium complexes of di(*t*-butyl)phosphinous acid have found application as homogeneous catalysts.[101,102] A lithium salt of the tellurophosphinite Ph_2PTeH has been prepared and structurally characterised.[103]

3.2 Phosphonites. – Compared to other phosphorus(III) acid esters, relatively little well-defined work has appeared on the synthesis and reactions of phosphonites. Routes to these compounds are often described in papers which are mainly concerned with work on related phosphite esters. Radical addition of bis(trimethylsilyloxy)phosphine to indene has given the phosphonite (84).[104] A series of new phosphonites and diphosphonites bearing perfluoroalkyl substituents, e.g., (85) and (86), has been described, together with related phosphites.[105,106] Among a new series of 'short-bite' chiral phosphorus(III) ester ligands prepared is the diphosphonite (87)[107] Selective *ortho*-lithiation of 9,9-dimethylxanthene or 2,7-dimethylphenoxathiin, followed by treatment with $(Et_2N)_2PCl$ gave bis(diethylamino)phosphines, which were then treated with the appropriate bis(phenol) to give new chelating bis(phosphonites), e.g., (88).[108,109] The synthesis of phosphinites bearing other donor centres has also developed. Among new systems of this type described recently are the ferrocenylphosphino-menthylphosphonite (89)[110] and the bis(phosphinoalkyl)phosphonites (90).[111] Also reported are phosphonites containing nitrogen donor centres, including the chiral systems (91),[112] (92),[113] and (93).[114] Studies of the reactivity of phosphonites have also been few and far between. Woollins' group has explored the reactivity of the bis(phosphonite) (94) towards oxygen, sulfur and selenium, a complete series of mono- and di-oxidised

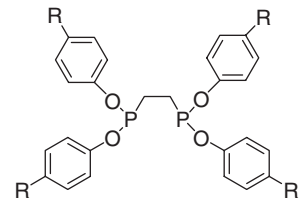
derivatives having been prepared and fully characterised by NMR and X-ray crystallography, providing much new data on structural aspects of *peri*-disubstituted naphthalene diphosphorus compounds.[115] A variety of products has been obtained from the action of hydrogen chloride on the cyclic phosphonite ester (95).[116] The cyclic hydroxyaryl phosphonite (96) has been shown to be transformed into the phosphite (97) and other phosphite transformation products in the presence of rhodium(I) during the course of a rhodium-catalysed hydroformylation reaction.[117] The bis(phosphonite) (98) has also found use as a ligand in rhodium-catalysed hydroformylation reactions.[118] Applications of chiral phosphonites (and related phosphites and phosphoramidites) derived from BINOL as ligands in asymmetric catalysis have been reviewed.[119]



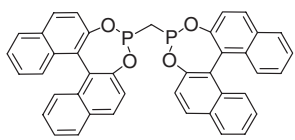
(84)



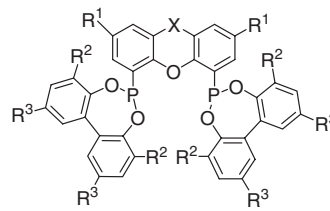
(85)



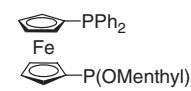
(86) R = C_6F_{13}



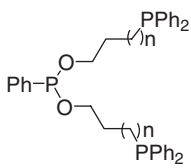
(87)



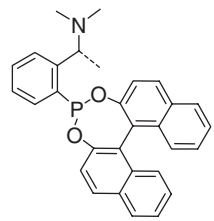
(88) R^1 = H or Me; R^2, R^3 = H, Bu^t or OMe; X = S or CMe_2



(89)



(90) n = 1 or 8



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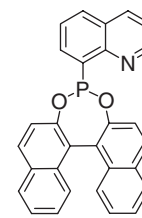

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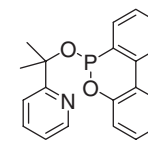

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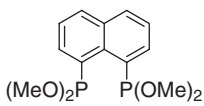

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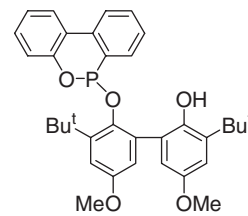

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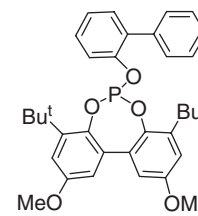

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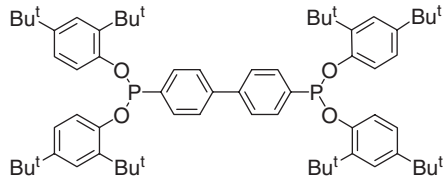
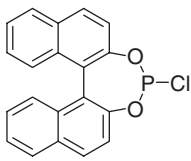


(98)

3.3 Phosphites. – The synthesis of new phosphite esters remains a significant area of activity, much of it directed towards the synthesis of phosphite ligands of interest in metal-catalysed reactions. The chiral BINOL-derived chlorophosphite (99) has again been widely used in the design of new mono-, di- and polyphosphite ligands. Among new monophosphite systems derived from phosphitylation of BINOL are (100),[120] (101),[121] and a series of acylphosphites.[122] BINOL phosphites derived from the steroidal alcohol deoxycholic acid[123] and various carbohydrate alcohols[124,125] have also been prepared. The partially reduced H_8-BINOL monophosphites (102) are also easily accessible and have shown good performance in rhodium-catalysed hydrogenation reactions.[126] Routes to other new axially chiral biphenyls have enabled the synthesis of the atropisomeric phosphites (103)[127] and (104).[128] Among other new cyclic monophosphite esters reported are the chiral ligand (105),[129] the phosphitylated dihydroquercitin (106),[130] and the benzodioxaphosphorin (107).[131] A new route to fluorous phenols has given access to the triarylphosphites (108).[132] Established routes to phosphites have been exploited in the synthesis of a wide range of new cyclic phosphites having two or more phosphite units. The reactions of chlorophosphites with bisphenols have given macrocyclic bis-, tris- and tetrakis-phosphites, e.g., (109),[133] and related macrobicyclic systems.[134] Phosphitylation of 2,2′-dihydroxybiphenyls and related BINOLs is key to the synthesis of a variety of cyclic bis(phosphites), e.g., (110),[135,136] furanoside bis(phosphites), e.g., (111),[137] and chiral pyrophosphites, e.g., (112).[138] Transesterification of triphenylphosphite with pentaerythritol and dipentaerythritol provides a route to a variety of bicyclic phosphites, e.g., the bis(phosphite) (113) and the mixed donor pyridine-functionalised phosphite (114).[139] The synthesis of mixed donor P,N-bidentate ligands by Russian workers has been reviewed.[140] Among new phosphites also bearing nitrogen donor centres are the pyridinoamides (115),[141] the phosphito-isoquinoline (116),[142] various amino-, imino-,[143] and oxazolinophosphites,[144,145] and the tripodal N-centred tris(phosphites) (117).[146] The tris(zinc(II) porphyrinyl)phosphite (118) has been prepared and shown to form supramolecular multicomponent assemblies with quinuclidine and acceptor metal ions.[147] In related work, zinc-complexed tetraarylporphyrins bearing a single diorganophosphito substituent in one of the aryl groups have also been prepared and shown to assemble with a series of pyridylphosphines *via* coordination of the pyridine nitrogen to the zinc atom, giving new, unsymmetrical bidentate P–P′ ligand systems.[148] Other phosphine-phosphite[149,150] and also phosphite-thioether[151] systems have been described. Phosphites derived from

incompletely condensed silsesquioxanes,[152] β-cyclodextrins,[153] calixarenes,[154] and calix[4]resorcinarenes[155] have also been prepared. The synthesis of a series of phosphite dendrimers has also been achieved, these compounds forming metal complexes in which the metals are attached to the branching points within the dendrimer.[156]



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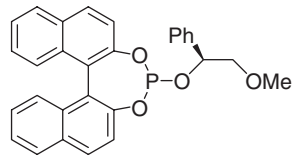

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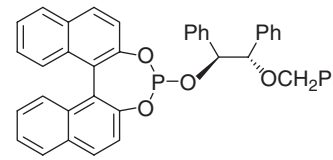

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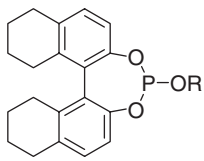
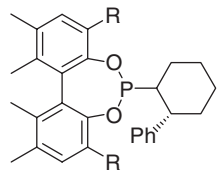
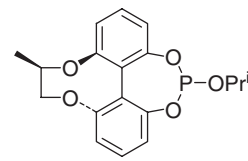


(102) R = Pr^i or CH(Me)Ph



(103) R = H, Me, Br or Bu^t



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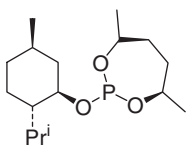

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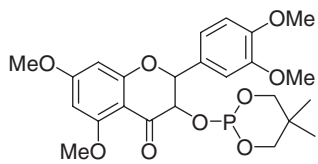

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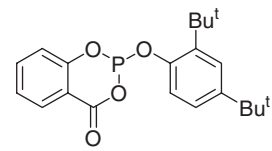

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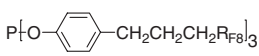
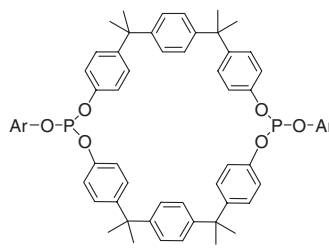
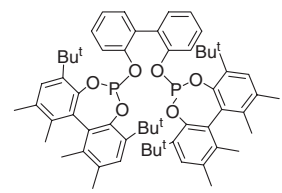


(108) $R_{F8} = (CH_2)_7CF_3$



(109) Ar = 2,6-Bu^t_2-4-MeC_6H_2



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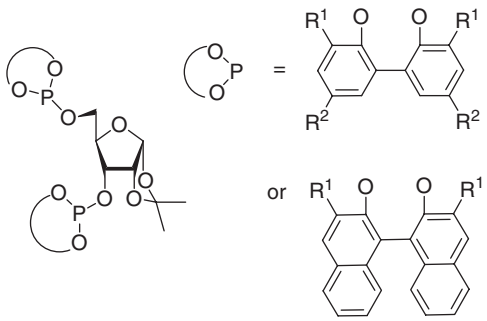
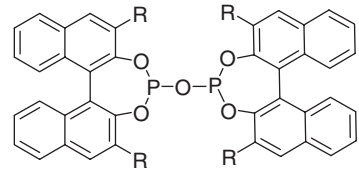
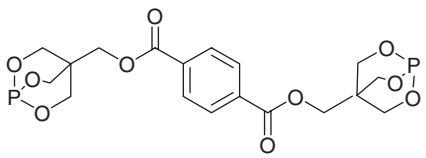


(111) R^1, R^2 = H, $SiMe_3$, or Bu^t



(112) R = H, Me or Br



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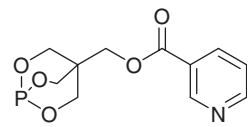

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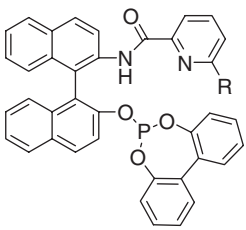
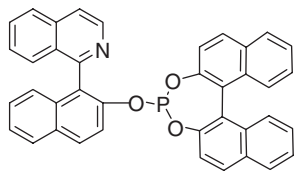


(115) R = H or Me



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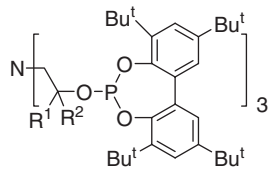


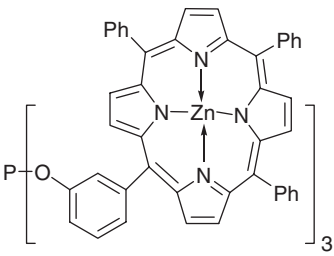
(117) R^1, R^2 = H or Me

Apart from their behaviour as ligands in metal catalyst systems, studies of the reactivity of phosphites towards a wide variety of other substrates have attracted attention. New aspects and applications of the classical Michaelis-Arbuzov reaction and its variants continue to appear. Evidence of the thermal disproportionation of methyltriaryloxyphosphonium halides formed in the reactions of triarylphosphites with alkyl halides, together with the formation of P–O–P intermediates, has been reported.[157] The Michaelis-Arbuzov reaction has been used in the synthesis of phosphonate-based styrene-divinylbenzene resins[158] and polyphosphonated chelation therapy ligands.[159] Treatment of electron-rich benzylic alcohols dissolved in triethylphosphite with one equivalent of iodine affords a low-temperature one-pot route to the related benzylic phosphonates, compounds which are otherwise difficult to prepare.[160] Upper-rim chloromethylated thiacalix[4]arenes have also been shown to undergo phosphonation on treatment with a phosphite ester in chloroform at room temperature.[161] The nickel(II)-catalysed reaction of aryl halides with phosphite esters in high boiling solvents, e.g., diphenyl ether, (the Tavs reaction), has also

found application in the synthesis of upper-rim calix[4]arene phosphonates[162] Diethyl arylphosphonates are rapidly accessible in good yield from nickel(II) and palladium(II)-catalysed reactions of aryl halides with triethylphosphite under microwave radiation.[163] No metal ion catalyst is needed in the reaction of nitro-activated chlorothiophenes with triethylphosphite, which proceed in the absence of a solvent under mild conditions to give the related nitrothienylphosphonates.[164] γ-Azido-α-diazo-β-ketoesters have been shown to react with trimethylphosphite under mild conditions in a tandem Staudinger-Arbuzov rearrangement sequence to form γ-(dimethylphosphorylamino) -α-diazo-β-ketoesters, e.g., (119).[165] Reactions of phosphite esters with α-halocarbonyl and related compounds have also continued to be reported. Both Arbuzov and Perkow pathways have been observed in the reactions of trialkylphosphites with mono-and di-acylals of halo-substituted acetic acids.[166] Aza-Perkow pathways are involved in the reactions of trihaloacetimidoyl chlorides with trialkylphosphites.[167] The reaction between triethylphosphite and 2-bromo-1,3-dicarbonyl compounds has been used to generate enolphosphate intermediates, subsequently alkylated to form β-substituted-αβ-unsaturated carbonyl compounds.[168] Mechanistic and synthetic aspects of the reactions of γ-halogeno-αβ-unsaturated carbonyl compounds with trialkylphosphites, leading to a variety of functionalised phosphate esters, have also been explored.[169] A reductive methylation/phosphorylation pathway is involved in the reaction of trimethylphosphite with 3,4-diazacyclopentadienone *N*-oxides, which results in the phosphate (120).[170] A new protocol has been developed for the O-methylation of phenolic compounds using trimethylphosphite (or trimethylphosphate) under solvent-free and microwave conditions.[171] Conditions have been established for the selective hydrolysis of the bicyclic phosphites (121) to give the related dihydrogen phosphites (122).[172] A study of the hydrolysis of the cyclic phosphites (123, X=OPh) (and the related phosphoramidites, $X=NMe_2$) to the cyclic phosphites (124), in the presence of intentionally added water, has shown that hydrolysis is inhibited by the addition of simple additives such as KF, K_2CO_3, or Et_3N.[173] Further examples of the formation of glycosydic linkages *via* the intermediacy of glycosylphosphites have appeared.[174,175] The reaction of a protected glucopyranoside with triethylphosphite and trimethylsilyl trifluoromethanesulfonate has been shown to lead to the formation of the seven-membered phostone system (125).[176] A new reaction of vicinal sulfonyliminocarboxylates (126) with phosphite esters involves a chelotropic 1,4-cycloaddition of the phosphite to form an intermediate cyclophosphorane, followed by a 1,2-shift of the sulfonyl group, resulting in the iminophosphoranes (127).[177] A new class of semistabilised phosphorus ylides (128) derived from phosphites is accessible *in-situ* from the reaction of trialkylphosphites with a carbene-transfer reagent system, affording high *E*-selectivities in Wittig olefination reactions.[178] A route to stabilised ylides derived from phosphites is afforded by the reactions of phosphite esters with electron-withdrawing acetylenes such as dibenzoylacetylene or dimethyl acetylenedicarboxylate, the resulting 1:1 intermediate ylides then being trapped with a variety

of reagents.[179,180] Nucleophilic attack of phosphite esters at carbon is also the key step in reactions with a benzylidenemalonitrile, giving the phosphonates (129),[181] with α-ketoallenes, initially giving the cyclic phosphoranes (130),[182] and with various benzoxazinones, giving phosphonated isoindolines and indoles.[183] The reactions of trialkylphosphites with the naphtho[2,1-b]furanylium cation[184] and 3-acetylcoumarin[185] have also been explored. Oxidation reactions of phosphites have also attracted attention. Sterospecific oxidation of trialkylphosphites obtained enantioselectively by the condensation of racemic dialkylphosphorochloridites with an alcohol in the presence of a chiral amine has provided the first asymmetric synthesis of trialkylphosphates.[186] Whereas arylphosphites are normally unreactive towards singlet oxygen, indirect oxidation to the phosphates occurs in a dye-sensitized co-photooxidation in the presence of dimethylsulfide.[187] Triarylphosphites are also oxidised by diarylselenoxides by a concerted oxygen-transfer mechanism.[188] Trimethylphosphite has found use as a trap for alkoxy radicals formed from the ring-opening of oxiranylcarbinyl radicals formed from haloepoxides in the presence of free-radical initiators.[189] The reaction of epoxides with trialkylphosphites in the presence of trimethylsilyl chloride and lithium perchlorate in diethylether occurs regioselectively to form the phosphonates (131).[190] Combinations of trimethylphosphite with trimethylsilyl chloride or acetic acid, again in the presence of lithium perchlorate in diethylether, have found use in the synthesis of α-hydrazinophosphonates and N-hydroxy-α-aminophosphonates.[191] α-Aminophosphonates have also been prepared by the reactions of aldehydes, secondary amines and trialkylphosphites in the presence of ethereal lithium perchlorate[192] or aluminium trichloride.[193] Further applications have been described of the use of triethylphosphite as a coupling reagent in the synthesis of new extended analogues of tetrathiafulvalene,[194] and heterohalogenated tetrathiafulvalenes.[195] Anomalous ring cleavage of 1,3-dithiole- and 1,3-diselenole-2-thiones has been observed under cross-coupling conditions using triethylphosphite.[196] Organophosphites continue to be of interest as stabilisers in PVC formulations[197] and as ligands in asymmetric transition metal catalysis, where again the utility of mixtures of different monodentate phosphites (and phosphonite) esters has been noted.[198] Bulky triarylphosphite ligands have been shown to undergo *ortho*-metallation reactions in the presence of platinum and palladium salts, the resulting complexes having significant catalytic activity in Stille and Suzuki coupling reactions.[199] The tricyclic phosphite (132) has also shown superior properties as a ligand in metal-catalysed olefin hydrogenation and hydroformylation reactions.[200] Interest in the chemistry of secondary phosphites has also continued, with particular reference to their tautomerism and the involvement of the P(III) hydroxyphosphite tautomers as intermediates in reactions. A novel double dealkylation of a trialkylphosphite in the presence of acid and a ruthenium salt has enabled the characterisation of the monoester $MeOP(OH)_2$ as a ligand.[201] When dimethylphosphite (normally viewed as dimethyl phosphonate) is used as the phosphorus component of the Mitsunobu reaction, the course of the reaction changes and leads to products arising from free-radical pathways.[202] The reaction of diallylphosphite with bis(trimethylsilyl)acetamide or trimethylsilyl chloride yields

the phosphite (133), which, on exposure to phosgene in toluene, is converted into the bis(phosphonomethyl)phosphoric acid ester (134).[203] Treatment of the bicyclic thiophosphite (135) with di(Grignard) reagents derived from αω-dibromoalkanes, followed by a further Grignard reagent or sodium alkoxide, and final treatment with sulfur and water, provides a simple route to the dithiaphosphepin system (136).[204] Among theoretical treatments of phosphite esters reported are studies of the molecular and conformational preferences of trimethylphosphite, both as a free ligand and also in the metal-coordinated state,[205] the estimation of barriers to atropisomerism of dibenzo[d,f][1,3,2]dioxaphosphepin moieties of bis(phosphite) ligands,[206] and the ring closure of 2-hydroxyethyl ethylene phosphites to form bicyclic spirophosphoranes, a new P(III) insertion reaction.[207] A structural and microstructural description of the glacial state of triphenylphosphite has been achieved from powder synchrotron X-ray diffraction data and Raman scattering studies.[208]



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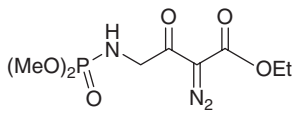

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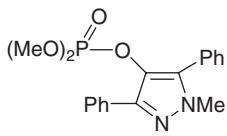

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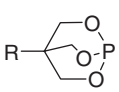
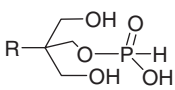


(121) R = Me or Et



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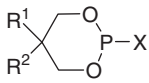
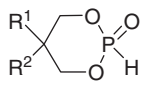


(123) R^1 = Me or Et; R^2 = Me, Et or Pr; X = OPh or NMe_2



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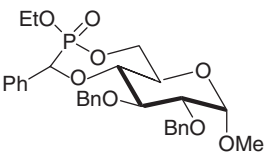

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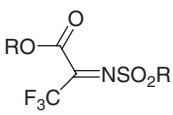

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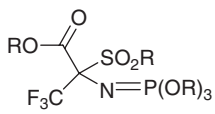

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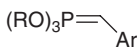

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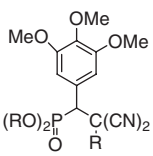

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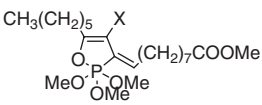
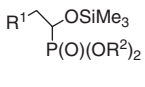
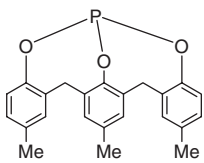


(130) X = H or Cl



(131) R^1 = alkyl or aryl; R^2 = Me or Et



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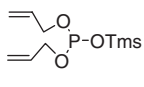

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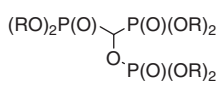
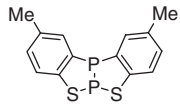


(134) R = alkyl



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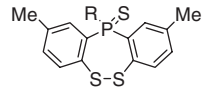
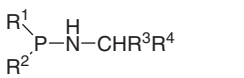


(136) R = alkyl. aryl, alkenyl or alkoxy

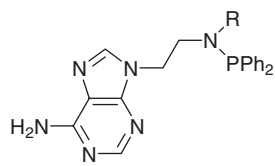
4 Tervalent Phosphorus Amides

4.1 Aminophosphines. – The synthesis and use of aminophosphines as ligands have been reviewed.[209] Racemic chlorophosphines of the type R^1R^2PCl have been shown to react stereoselectively with chiral amines (1-phenylethylamine or aminoacid esters) in the presence of triethylamine to give the diastereomerically enriched aminophosphines (137), which were isolated as diastereomerically pure crystalline borane complexes.[210,211] This approach has also been used in the synthesis of chiral *t*-butylphenylphosphine oxide, *via* the acid hydrolysis of an intermediate chiral aminophosphine.[212] Among other new monoaminophosphines prepared by treatment of primary or secondary amines with chlorophosphines in the presence of a base are the adenine derivatives (138),[213] the phosphinoalkylaminophosphines (139),[214] the aminophosphine-phosphine sulfide (140),[215] and the hydrazinophosphines (141)[216] and (142).[217] New aminophosphines and amino(chloro)phosphines bearing trialkylsilyl and other sterically bulky substituents at nitrogen have been prepared *via* treatment of N-lithiated amines with chlorophosphines and characterised by X-ray crystallography and NMR studies.[218,219] The first fully-characterised NH-functional monophosphinourea derivative (143) has been obtained as a crystalline solid in almost quantitative yield from the reaction of N,N′-dimethylurea with chlorodiphenylphosphine in the presence of triethylamine in THF.[220] A detailed study of the reactions of anilines, bearing electron-withdrawing substituents in the benzene ring, with chlorodiphenylphosphine and inorganic or organic bases in different solvents and in varying stoichiometry has shown that, in addition to the aminophosphines (144), both diphosphinoamines (145) and the phosphinophosphazenes (146) can be isolated in varying amounts. In the case of the reaction of pentafluoroaniline with chlorodiphenylphosphine and butyllithium in equimolar amounts, the phosphazene is the sole product. The latter compounds arise from the intermediacy of a P-lithiophosphazide anion, a tautomer of the N-lithioamide expected to be formed in the reaction mixture.[221,222] The perfluoroalkylaminophosphine (147) has been prepared for ligand applications in fluorous biphasic solvent systems.[223] Polymer-bound aminoalcohols have been transformed by conventional chemistry into a series of polymer-supported aminophosphine-phosphine and -phosphinite ligands, e.g., (148).[224] The anticipated high basicity of the tris(guanidyl)phosphine (149) stimulated several attempts to prepare it. However, these only led to the isolation of the corresponding phosphine oxide.[225] Considerable interest has been shown in the synthesis of bis(aminophosphines) and many new examples have been described. These include the simple benzene- and pyridine-bridged systems

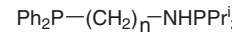
(150)[226,227] and (151),[228] the bis(phosphinoamides) (152),[229] the alkylene-bridged system (153)[230] various phosphinoamines derived from atropisomeric 2,2′-diamino-1,1′-binaphthyl and related partially-reduced systems,[231,232] and the arene sulfonylaminophosphines (154) and (155).[233] Also described are bis(aminophosphines) (and related phosphoramidites) derived from heterocyclic secondary amines such as phenazine, piperazine and homopiperazine, e.g., (156),[234] (157)[235,236] and (158).[237] N-Pyrrolylaminophosphines have also attracted attention. Among new pyrrolyl- (and related indolyl)-phosphines described is the chiral sulfonylated derivative (159),[238] the 7-aza-*N*-indolylphosphines (160),[239] the cyanopyrrolylphosphines (161),[240] the unsymmetrical di(N-pyrrolyl)phosphino-functionalised dppm analogue (162),[241] and the heterocyclic aminophosphine (163).[242] Other heterocyclic aminophosphines prepared include chiral diazaphospholidines, e.g., (164),[243] (165),[244] and (166), the latter resulting from a ring-contraction of the diazadiphosphocine (167) on treatment with phenylmagnesium bromide,[245] and also the atropisomeric system (168).[246] A crowded diazaphospholidine system has also been used for the stabilisation of the optically pure phosphino(silyl)carbene (169).[247] Aminophosphine-stabilised C-phosphanyl-C-chloroiminium salts (170) have been prepared as electrophilic carbene synthetic equivalents.[248] In addition to the ferrocenylbis(diazaphospholidine) (165) noted above, other new ferrocene-based chiral aminophosphines, e.g., (171)[249] and (172),[250] have also been prepared. Chiral aminophosphine-oxazoline hybrid ligands have continued to attract attention, new examples including (173)[251,252] and (174).[253] Routes to four-membered ring aminophosphines (diphosphazanes) have undergone further development, new systems reported including (175),[254] (176),[255] and (177).[256] The pyridyl-functionalised diphosphazane (178) has been prepared as part of a study of the oligomerisation of phospha(III)zanes.[257] Both diphosphazanes and triphosphazanes (179) have been identified as products of oligomerisation of the iminophosphines R–N=P–X.[258] The 1,2-bis(diazasilaphosphetidino)ethane chelating ligand (180) has also been prepared.[259]



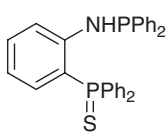
(137) R^1 = Bu^t or Ph;
R^2 = Ph or Mes;
R^3 = Ph, Bu^i or Pr^i;
R^4 = Me or CO_2Me



(138) R = H or Pr^i



(139) n = 2 or 3



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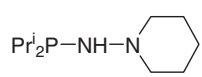
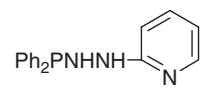
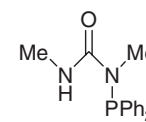


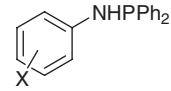
(141)



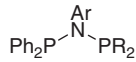
(142)



(143)



(144) X = *o*-, *m*-, *p*-CN, *o*-C_6H_5 or *o*-CF_3



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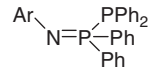

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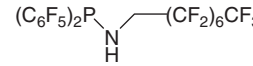

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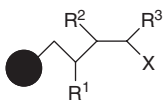
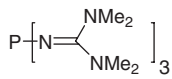


(148) R^1 = H, Me or Ar; R^2 = H, Me or Pr^i; X = PPh_2 or $OPPh_2$



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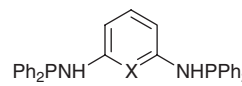
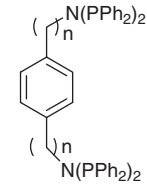
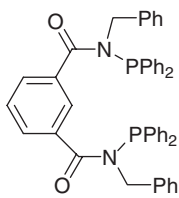


(150) X = CH or N



(151) n = 0 or 1



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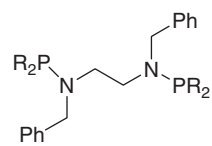
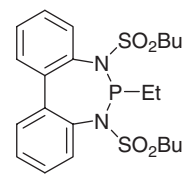


(153) R = Ph or Pr^i



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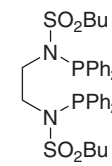

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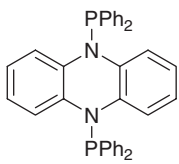

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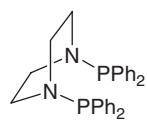

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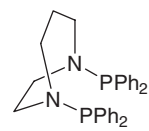

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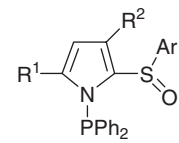
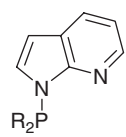
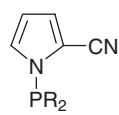


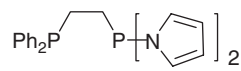
(159) R^1, R^2 = H or Me



(160) R = Ph or N-pyrrolyl



(161) R = Ph or N-pyrrolyl



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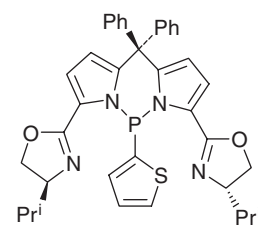

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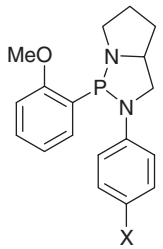
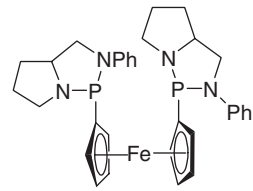


(164) X = Ph, OMe or Br



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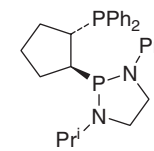

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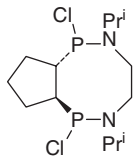

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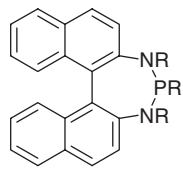

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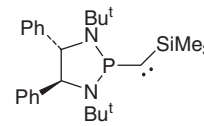

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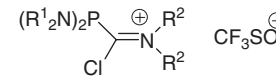
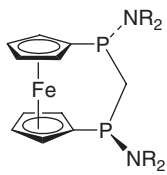


(170) R^1 =Pr^i; R^2 = Me or Pr^i



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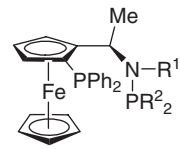
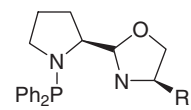
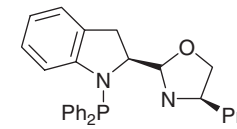


(172) R^1 = H, Me, Et or Pr; R^2 = Ph or Cy



(173) R = Pr^i or Bu^t; Ar = *e.g.*,Ph, *o*-Tol, 2-EtPh



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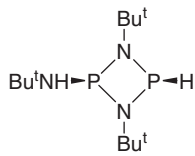

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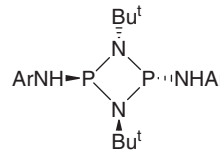
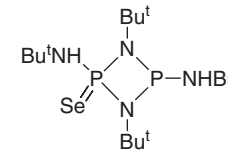


(176)



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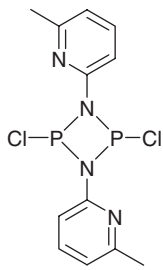
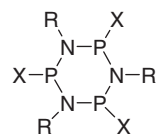
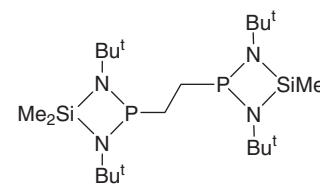


(178)



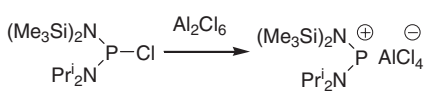
(179) R = Mes* or 2,6-Pr$^i_2$C$_6$H$_3$; X = Cl or OSO$_2$CF$_3$



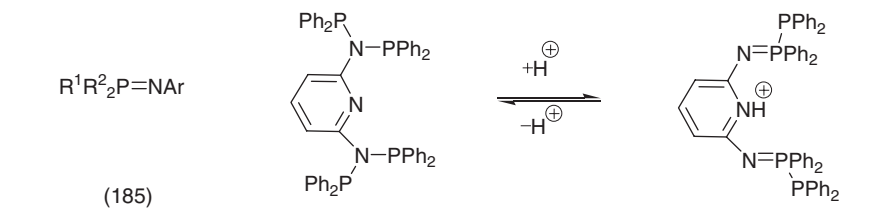
(180)

Treatment of the crowded amino(chloro)phosphine (181) with aluminium chloride results in chloride abstraction to yield the phosphenium salt (182). With potassium-graphite in THF, (181) is converted into the diphosphine (183), which undergoes reversible dissociation on heating *in vacuo* to form the stable radical (184), which reverts to the diphosphine on cooling. The structure of the radical has been determined in the gas phase by electron diffraction.[260,261] In contrast, the reaction of *o*-cyanophenylamino(diphenyl)phosphine with potassium-graphite proceeds with proton-abstraction to give a 'free' phosphinamide anion, isolated as a potassium complex.[262] The ligand donor properties of P–N bonded phosphinoamides have been reviewed.[263] A new route to iminophosphoranes (185) is provided by alkylation of arylaminophosphines, followed by deprotonation with triethylamine.[264] Surprisingly, protonation of diphosphinoamines attached to pyridine at the *ortho*-position, e.g., (186), results in a quantitative transformation to iminophosphoranes, e.g., (187), which is reversed on treatment with base, the system therefore having potential as a new type of molecular switch.[265] Iminophosphorane tautomers have also been recognised as intermediates in the reactions of the aminophosphine $Bu^tP(NH_2)_2$ with Group 13 metal trialkyls, which result in the formation of the eight-membered ring heterocycles (188).[266] In contrast, the reactions of $Bu^tP(NHBu^t)_2$ with base-stabilised aluminium hydrides proceed *via* the aminophosphine form at the 'hard' nitrogen atoms with elimination of dihydrogen to give the H-bridged dimer (189). Related reactions with boranes, gallanes and indanes take place at the softer phosphorus atom to give simple adducts.[267] Aminophosphines of the type Ph_2PNHAr have been shown to act as iminophosphoranyl synthons, undergoing addition of the P–H bond of the iminophosphorane tautomer to the vinyl group of P-vinyliminophosphoranes to give the bis(iminophosphoranes) (190).[268] Treatment of the borane adduct of the diazaphospholidine (164, X=Ph) with phenyllithium results in an unusual addition/nucleophilic aromatic substitution reaction, to give the diazaphosphaazulene (191).[269] Insertion of carbon fragments into the P(III)–N bond of aminophosphines and aminobis(phosphines) occurs on treatment with paraformaldehyde, resulting in the insertion of a methylene group, followed by oxidation at phosphorus to give, e.g., the phosphine oxides (192). Similarly, the reaction of aromatic aldehydes with aminophosphines results in insertion of 'ArCH' into the P–N bond to give the phosphine oxides (193), whereas with aliphatic aldehydes, P–N bond cleavage occurs, giving α-hydroxyalkylphosphine oxides.[270] Treatment of bis[bis(dialkylamino)phosphino]methanes (194) with bis(trifluoromethyl)acrylonitrile results in the formation of the ylides (195), which gradually decompose at room temperature to form the amino(fluoro)phosphinoiminophosphorane (196).[271] A procedure has been developed for the determination of the absolute configurations of chiral phenylcarbinols from the ^{31}P-NMR spectra of the diastereoisomers formed in the reactions of the alcohol with the chiral phospholidine derivatising agents (197), formed *in situ* from chiral diamines of known absolute configuration.[272] The diselenide (198) has been obtained in good yield and on a large scale from the reaction of the

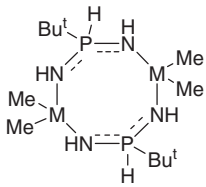
parent bis(phosphino)amine with selenium in concentrated solutions in toluene.[273] The reaction of tris(dimethylamino)phosphine with a rotaxanated disulfide has been shown to lead to cleavage of the S–S bond, resulting in the formation of a stable tris(dialkylamino)thiophosphonium salt in rotaxane form.[274] The synthesis, reactions, and catalytic applications of the bicyclic triaminophosphines (proazaphosphatranes) (199) have continued to attract attention and this area has been reviewed.[275] Among new catalytic applications of these compounds reported by Verkade's group is their use in various palladium-catalysed procedures, including the Stille cross-coupling of aryl chlorides,[276] amination reactions of aryl halides,[277,278] and the direct α-arylation of nitriles with aryl bromides.[279] Proazaphosphatrane ligands have also found use in the Bayliss-Hillman reaction,[280] the dimerisation of allyl phenyl sulfone,[281] the head to tail dimerisation of methyl acrylate,[282] and for the regioselective Michael addition of a βγ-unsaturated ester and a nitrile to a variety of αβ-unsaturated ketones.[283] Verkade has also reported the Staudinger reactions of (199, R=Me or Pr^i) with various arenesulfonylazides, which lead to the ionic phosphazides (200) and (201), together with other products, depending on the initial triaminophosphine structure.[284] Alkyldiaminophosphines, in particular (202), have shown promise as ligands in expanding the scope of the Stille cross-coupling reaction to alkyl halides.[285] Interest in the coordination chemistry of aminophosphines has also continued, recent reports including studies of Group 6 transition metal carbonyl complexes[286] and the reactivity of dialkylamino- and bis(dialkylamino)-phosphines in the coordination sphere of metals.[287]



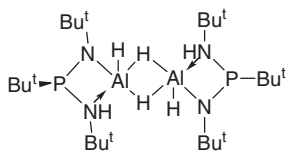
(181) (182) (183) (184)



(185) (186) (187)



(188) M = Al, Ga or In



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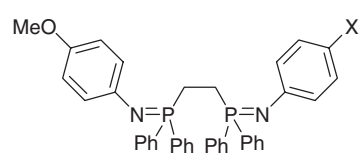

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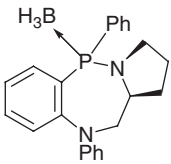

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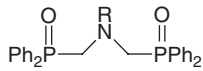
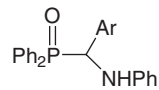


(192) R = Me, Pr or Bu



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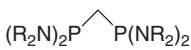

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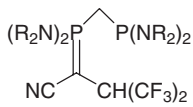

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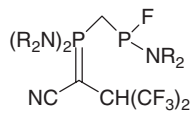
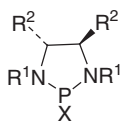
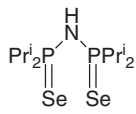


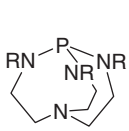
(196)



(197) X = NMe_2 or Cl;
R^1 = Me or CH_2tms;
R^2 = Ph or -$(CH_2)_4$-



(198)



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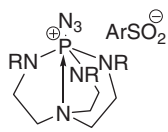

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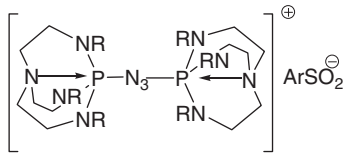

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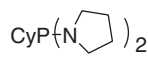
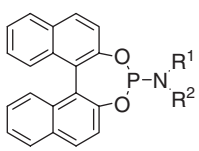


(202)

4.2 Phosphoramidites and Related Compounds. – The synthesis of phosphoramidites has continued to be a very active area, being driven by the need to develop new, more effective, chiral ligands for use in metal-promoted homogeneous catalysis. Phosphoramidites derived from BINOL continue to dominate the field, and although many of the publications noted are now mainly concerned with applications in catalysis, the synthesis of new BINOL-derived compounds has also been reported, including schemes for the parallel synthesis of ligand libraries of monodentate BINOL-phosphoramidites (203), linked to *in situ* screening for catalytic activity.[288,289] New polymer-bound BINOL-phosphoramidites have also been described, including (204)[290] and (205),[291] and compounds derived from the free-radical polymerisation of phosphoramidites bearing a *p*-styrylamino substituent.[292] New monomeric BINOL-phosphoramidites have also been prepared, including (206)[293] and mixed phosphoramidite-phosphite and -phosphinites, e.g., (207).[294] Applications in catalysis of BINOL-phosphoramidites have attracted much interest. Monodentate BINOL-phosphoramidites offer a breakthrough in rhodium-catalysed asymmetric

hydrogenation of alkenes[295] and α- or β- dehydroaminoacid derivatives,[296,297] acting as more accessible, effective replacements for bidentate chiral phosphines, and affording high enantioselectivities. Other applications include their use in promoting highly enantioselective conjugate additions of dialkylzinc reagents to acyclic nitroalkenes,[298] asymmetric allylic-substitution,[299] -amination,[300] and -alkylation,[301] conjugate addition reactions of arylboronic acids[302] and Meldrum's acid,[303] the enantioselective desymmetrization of *meso*-cyclic allylic bisdiethylphosphates,[304] and the asymmetric borane reduction of the N-phenylimine of acetophenone.[305] New phosphoramidites (208) derived from H_8-BINOL have been prepared and applied as ligands for the catalytic hydrogenation of enamides[306] and α-dehydroaminoacids.[307] Also reported is a series of new chiral phosphoramidites based on 2,2′-dihydroxybiphenyls, e.g., (209),[308] and (210).[309] In addition to these atropisomeric systems, the synthesis of a wide variety of new phosphoramidites, many of which are chiral, has been reported. Among new chiral monodentate systems is a range of heterocyclic compounds derived from 2-(2-hydroxyphenyl)-1*H*-benzimidazole, e.g., (211) (from which a series of stable pentacovalent phosphoranes has also been obtained *via* reactions with 3,5-di-t-butylcatechol),[310] the phospholidines (212),[311] a series of spirophosphoramidites (213)[312,313] which also have applications in catalysis,[314,315] the 1,3,2-oxazaphospholidinones (214),[316] the protected pentaerythritol derivatives (215),[317] the D-mannitol derivatives (216),[318] and the P-chirogenic diaminophosphine oxide (217), this representing a new class of chiral phosphorus ligand which displays its activity *via* the P(III) tautomer.[319] The selective phosphitilation of dihydroquercitins has been explored and a number of new phosphoramidites described.[320,321] A silsesquioxanylphosphoramidite has also been prepared.[322] Various monodentate and bidentate phosphoramidites involving the same phosphoramidite unit have been prepared. Included among these are pyrrole-based phosphoramidites, e.g., (218),[323] various catechol-based phosphoramidites, e.g., (219),[324] and the ethylene-bridged oxazaphosphorinanones (220).[325] Among large ring heterocyclic phosphoramidites prepared are ten-membered ring systems, e.g., (221),[326] and the 16-membered macrocycle (222).[327] New phosphoramidite ligands bearing additional donor centres have also attracted interest and among these are the urea derivative (223)[328] and a series of phospholidines of type (212) which bear a chiral aminoalkoxy substituent at phosphorus.[329]



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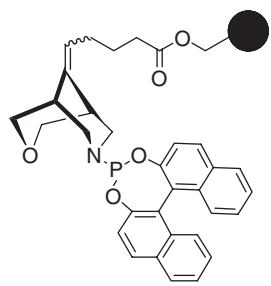

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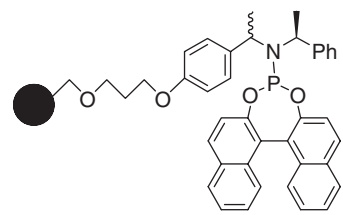

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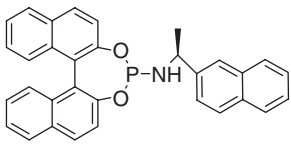

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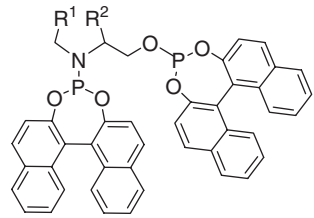
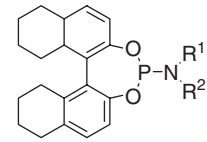
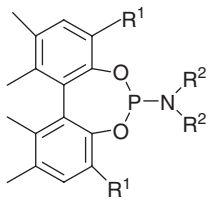


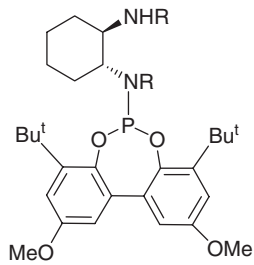
(207) R^1, $R^2 = (CH_2)_2$; $R^1 = H$, $R^2 = Et$



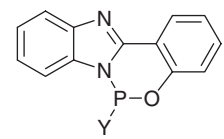
(208) R^1,$R^2 = (CH_2)_4$; R^1,R^2 = Me or Et; R^1 = (*R*)-CH(Me)Ph, R^2 = H or Me



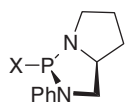
(209) R^1 = H, Me, Bu^t, Ph or Br; R^2 = Me or Pr^i



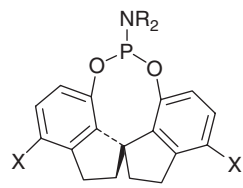
(210) R = Me, Et, Bz or Pr^i



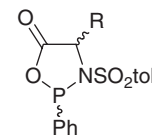
(211) Y = NMe_2,Cl or Ph



(212) X = *e.g.*, OPh, O-Ad, O-Men, OMe



(213) R = Me, Et, Pr^i, Cy or (*R*)-CH(Me)Ph; X = H or OMe



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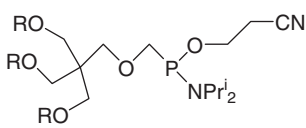
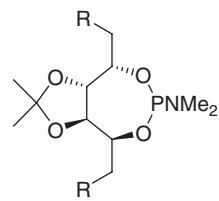
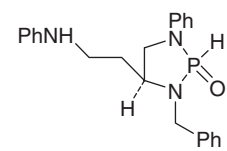


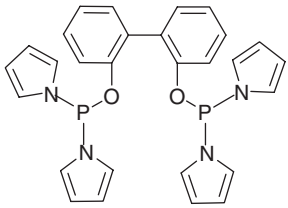
(215) R = DMtr, Lev or TBDMS



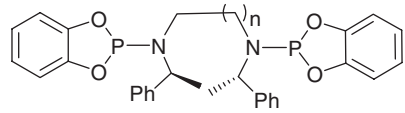
(216) R = Me, Et, Bu^i or Ph



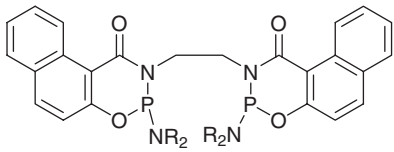
(217)



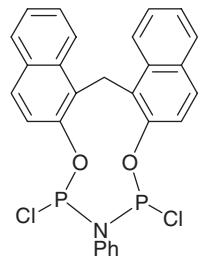
(218)



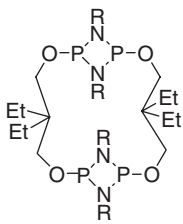
(219) n = 1 or 2



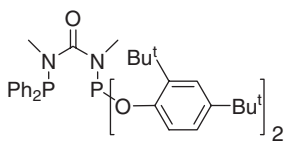
(220) R_2N = NMe_2, NEt_2, N-morpholinyl or NHPh



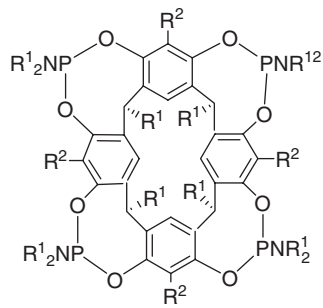
(221)



(222) R = Bu^t



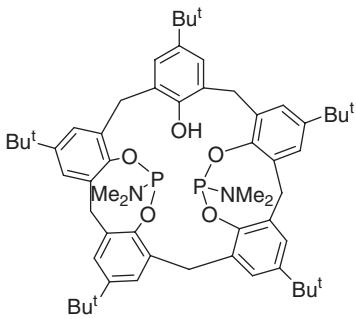
(223)



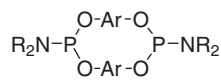
(224) R^1 = alkyl; R^2 = H or CH_2NR_2

The reactions of triaminophosphines and diamidoarylphosphites with macrocyclic phenolic compounds have continued to be applied in the synthesis of cyclic phosphocavitand amidophosphite derivatives (224) of calix[4]resorcinarenes.[330,331] The first heterobimetallic complexes of such ligands have been prepared.[332] Also reported is a study of the selective oxidative imination of these phosphocavitands with phenyl azide, only three of the four phosphorus atoms undergoing the reaction.[333] The amidophosphitylation of phenols has also been used to prepare new phosphoramidite derivatives, e.g., (225), of calix[5]arenes, the larger cavity, compared to calix[4]arenes, providing greater flexibility in interactions with metal ions.[334] Further work has appeared on the spontaneous dismutation of diamidoarylphosphites, to form cyclo(bis-amidoarylphosphites) (226) and phosphorus triamides, that occurs in solution at room temperature. Substituent and solvent effects have now been explored.[335] The naphthylene bis(diamidophosphite) (227) undergoes a similar dismutation to

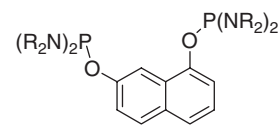
form the unsymmetrical diphosphacyclophane (228).[336] The reactions of cyclic phosphoramidites with dialkyl azodicarboxylates lead to products that are quite different to the familiar phosphoniobetaines involved as the key intermediates in related Mitsunobu reactions of tertiary phosphines. Thus, e.g., treatment of the cyclic phosphoramidites (229) with a dialkyl azodicarboxylate results in the formation of the phosphinimines (230). The mechanism of these reactions has been investigated by solution NMR studies, revealing the involvement of penta- and hexa-coordinate phosphorus intermediates.[337] The chiral oxazaphospholanes (231) have been shown to undergo a stereoselective redox addition reaction with aromatic aldehydes to form the cyclic phosphinimines (232), potential precursors of α-hydroxyphosphonate esters of medicinal interest.[338] The reactions of the oxazaphospholanes (233) with carboxylic acid chlorides also result in oxidation at phosphorus, with the formation of the cyclic phosphonamidates (234).[339] On treatment with azides, the allyloxydiazaphospholidines (235) form the expected phosphinimines (236). These undergo a palladium-catalysed [3,3]-sigmatropic rearrangement to form the phosphoramidates (237), precursors of allylic amines.[340] Phosphoramidites have been shown to be efficient, 'green' organocatalysts for the Michael reaction.[341] They have also found use in the synthesis of phosphito-alkoxytitanium gel materials,[342] and as reagents in a phosphoramidite approach to the phospholipid 'cardiolipin'.[343]



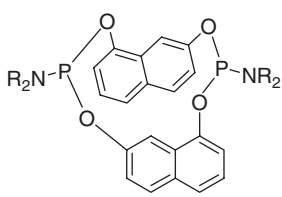
(225)



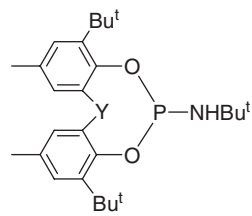
(226)



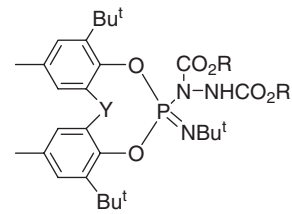
(227) R_2N = NMe_2, NEt_2, $NPri^2$ or N-morpholinyl



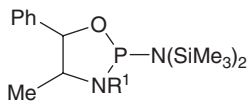
(228)



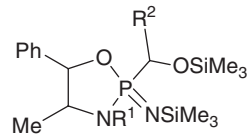
(229) Y = S or CH_2



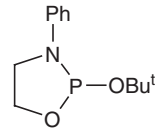
(230)



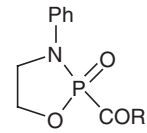
(231) R^1 = Me or Pr^i



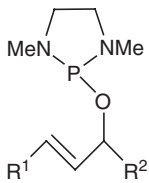
(232) R^2 = -C_6H_4X



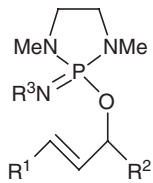
(233)



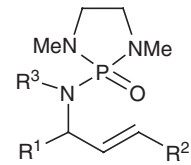
(234)



(235) R^1 = H, Et or Ph; R^2 = H or Me



(236) R^3 = Tos or P(O)$(OPh)_2$



(237)

References

1. J. Ansell and M. Wills, *Chem. Soc. Rev.*, 2002, **31**, 259.
2. T.J. Colacot, *Chem. Rev.*, 2003, **103**, 3101.
3. L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng and X.-L. Hou, *Acc. Chem. Res.*, 2003, **36**, 659.
4. O. Molt and T. Schrader, *Synthesis*, 2002, 2633.
5. D. Peña, A.J. Minnaard, J.A.F. Boogers, A.H.M. de Vries, J.G. de Vries and B.L. Feringa, *Org. Biomol. Chem.*, 2003, **1**, 1087.
6. (*a*) M.T. Reetz, T. Sell, A. Meiswinkel and G. Mehler, *Angew. Chem. Int. Ed.*, 2003, **42**, 790; (*b*) M.T. Reetz, *Chimica Oggi*, 2003, **21**, 5.
7. T. Appleby and J.D. Woollins, *Coord. Chem. Rev.*, 2002, **235**, 121.
8. E.V. Sagadeev, Yu.G. Safina, V.F. Sopin and R.A. Cherkasov, *Russ. J. Gen. Chem.*, 2003, **73**, 1702.
9. E. Nurminen and H. Lönnberg, *J. Phys. Org. Chem.*, 2004, **17**, 1.
10. Z.-W. Wang and L.-S. Wang, *Green Chem.*, 2003, **5**, 737.
11. R.M. Matos, L.C.G. de Lima, E. de Souza, A.L.A.B. de Souza, M.B.G. de Lima and D.S. Raslan, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 2859.
12. H. Byrd, P.C. Bharara, T.A. Sullens, J.D. Harden and G.M. Gray, *Inorg. Chim. Acta*, 2002, **338**, 240.
13. C. Bauduin, D. Moulin, E.B. Kaloun, C. Darcel and S. Jugé, *J. Org. Chem.*, 2003, **68**, 4293.
14. H. Lam, D.J. Aldhous and K.K.(M). Hii, *Tetrahedron Lett.*, 2003, **44**, 5213.
15. A.A. Chekotylo, A.N. Kostyuk, A.M. Pinchuk and A.A. Tolmachev, *Heteroatom Chem.*, 2003, **14**, 23.

16. A.S. Batsanov, S.M. Cornet, K.B. Dillon, A.E. Goeta, P. Hazendonk and A.L. Thompson, *J. Chem. Soc., Dalton Trans.*, 2002, 4622.
17. R.J. Baker, M. Brym, C. Jones and M. Waugh, *J. Organomet. Chem.*, 2004 **689**, 781.
18. Hong Wang, Haiping Wang, H.-W. Li and Z. Xie, *Organometallics*, 2004, **23**, 875.
19. P.B. Hitchcock, M.F. Lappert and J.E. Nycz, *Chem. Commun.*, 2003, 1142.
20. R.J. Wiacek, C.L.B. Macdonald, J.N. Jones, J.M. Pietryga and A.H. Cowley, *Chem. Commun.*, 2003, 430.
21. Y. Chi and X. Zhang, *Tetrahedron Lett.*, 2002, **43**, 4849.
22. K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen and M. Beller, *J. Organomet. Chem.*, 2003, **675**, 91.
23. S. Blair, K. Izod and W. Clegg, *J. Organomet. Chem.*, 2003, **688**, 92.
24. S. Blair, K. Izod, R. Taylor and W. Clegg, *J. Organomet. Chem.*, 2002, **656**, 43.
25. S. Blair, K. Izod, R.W. Harrington and W. Clegg, *Organometallics.*, 2003, **22**, 302.
26. A.S. Ionkin and W.J. Marshall, *Heteroatom Chem.*, 2003, **14**, 197.
27. J. Geier, G. Frison and H. Grützmacher, *Angew. Chem. Int. Ed.*, 2003, **42**, 3955.
28. A.A. Khan, C. Wismach, P.G. Jones and R. Streubel, *Dalton Trans.*, 2003, 2483.
29. P. Kilian, D. Philp, A.M.Z. Slawin and J.D. Woollins, *Eur. J. Inorg. Chem.*, 2003, 249.
30. P. Kilian, A.M.Z. Slawin and J.D. Woollins, *Chem. Eur. J.*, 2003, **9**, 215.
31. P. Kilian, H.L. Milton, A.M.Z. Slawin and J.D. Woollins, *Inorg. Chem.*, 2004 **43**, 2252.
32. T. Mizuta, T. Nakazono and K. Miyoshi, *Angew. Chem. Int. Ed.*, 2002, **41**, 3897.
33. J. Schiller, R. Suss, M. Petkovic and K. Arnold, *J. Food Lipids*, 2002, **9**, 185.
34. A.N. Kostyuk, Y.V. Svyaschenko, D.M. Volochnyuk, N.V. Lysenko, A.A. Tolmachev and A.M. Pinchuk, *Tetrahedron Lett.*, 2003, **44**, 6487.
35. Yu.N. Mitrasov, E.A. Simakova, I.I. Antonova, A.S. Pikalev and V.G. Skvortsov, *Russ. J. Gen. Chem.*, 2004, **74**, 306.
36. M.N. Dimukhametov, E.V. Bajandina, E.Yu. Davydova, I.A. Litvinov, A.T. Gubaidullin, A.B. Dobrynin, T.A. Zyablikova and V.A. Alfonsov, *Heteroatom Chem.*, 2003, **14**, 56.
37. (*a*) E. Fagadar-Cosma and G. Fagadar-Cosma, *Revista de Chimie, (Bucharest, Romania)*, 2004, **55**, 338; (*b*) E. Fagadar-Cosma and G. Fagadar-Cosma, *Chem. Abstr.*, 2004, **141**, 411000.
38. I. Schevchenko, A.K. Fischer, P.G. Jones and R. Schmutzler, *Z. Anorg. Allg. Chem.*, 2002, **628**, 1903.
39. N.S. Kumar, P. Kommana, J.J. Vittal and K.C.K. Swamy, *J. Org. Chem.*, 2002, **67**, 6653.
40. J. Anagnostis and M.M. Turnbull, *Polyhedron*, 2004, **23**, 125.
41. S.L. Renard, J. Fisher, C.A. Kilner, M. Thornton-Pett and T.P. Kee, *J. Chem. Soc., Dalton Trans.*, 2002, 2921.
42. S. Humbel, C. Bertrand, C. Darcel, C. Bauduin and S. Jugé, *Inorg. Chem.*, 2003, **42**, 420.
43. (*a*) A.N. Osipenko, G.B. Soifer and S.N. Shurov, *Z. Neorganicheskoi Khim.*, 2004, **49**, 669; (*b*) A.N. Osipenko, G.B. Soifer and S.N. Shurov, *Chem. Abstr.*, 2004, **141**, 332260.
44. V.A. Naumov, M.A. Tafipol'skii, R.N. Zaitdinova and M. Dokkouri, *Russ. J. Gen. Chem.*, 2003, **73**, 1497.
45. E.G. Nesterova, R.M. Minyaev and V.I. Minkin, *Russ. J. Org. Chem.*, 2003 **39**, 1167.

46. Ya.A. Vereshchagina, D.V. Chachkov and E.A. Ishmaeva, *Russ. J. Org. Chem.*, 2003, **39**, 1367.
47. A.V. Belyakov, A.N. Khramov and V.A. Naumov, *J. Mol. Struct.*, 2004, **698**, 59.
48. E.A. Ishmaeva, V.E. Kataev, Ya.A. Vereshchagina, G.R. Fattakhova, Z.G. Bazhanova and A.V. Kataev, *Russ. J. Gen. Chem.*, 2003, **73**, 888.
49. P. Bergamini, V. Bertolasi, M. Cattabriga, V. Ferretti, U. Loprieno, N. Mantovani and L. Marvelli, *Eur. J. Inorg. Chem.*, 2003, 918.
50. P. Bergamini, V. Bertolasi and F. Milani, *Eur. J. Inorg. Chem.*, 2004, 1277.
51. D. Hobuss, C. Thöne, S. Laschat and A. Baro, *Synthesis*, 2003, 2053.
52. A.A. Nazarov, C.G. Hartinger, V.B. Arion, G. Giester and B.K. Keppler, *Tetrahedron*, 2002, **58**, 8489.
53. J.M. Butler, M.J. Jablonsky and G.M. Gray, *Organometallics*, 2003, **22**, 1081.
54. M.S. Balakrishna, R. Panda and J.T. Mague, *J. Chem. Soc., Dalton Trans.*, 2002, 4617.
55. R. Guo, T.T.-L. Au-Yeung, J. Wu, M.C.K. Choi and A.S.C. Chan, *Tetrahedron: Asymmetry*, 2002, **13**, 2519.
56. I. Göttker-Schnetmann, P. White and M. Brookhart, *J. Am. Chem. Soc.*, 2004, **126**, 1804.
57. E. Dulièr, M. Devillers and J. Marchand-Brynaert, *Organometallics*, 2003 **22**, 804.
58. J.I. van der Vlugt, M. Fioroni, J. Ackerstaff, R.W.J.M. Hanssen, A.M. Mills, A.L. Spek, A. Meetsma, H.C.L. Abbenhuis and D. Vogt, *Organometallics*, 2003, **22**, 5297.
59. D.J. Eisler and R.J. Puddephatt, *Can. J. Chem.*, 2004, **82**, 185.
60. D.J. Eisler and R.J. Puddephatt, *Inorg. Chem.*, 2003, **42**, 6352.
61. D.J. Eisler and R.J. Puddephatt, *Inorg. Chem.*, 2003, **42**, 8192.
62. P.W. Galka and H.-B. Kraatz, *J. Organomet. Chem.*, 2003, **674**, 24.
63. S. Mizuta, M. Sadamori, T. Fujimoto and I. Yamamoto, *Angew. Chem. Int. Ed.*, 2003, **42**, 3383.
64. M.F. Mayer and M.M. Hossain, *J. Organomet. Chem.*, 2002, **654**, 202.
65. E. Mattmann, F. Mercier, L. Ricard and F. Mathey, *J. Org. Chem.*, 2002, **67**, 5422.
66. M. Clochard, E. Mattmann, F. Mercier, L. Ricard and F. Mathey, *Org. Lett.*, 2003, **5**, 3093.
67. B. Deschamps, L. Ricard and F. Mathey, *Organometallics*, 2003, **22**, 1356.
68. (*a*) F. Menges and A. Pfaltz, *Adv. Synth. Catal.*, 2002, **344**, 40; (*b*) S. P. Smidt, F. Menges and A. Pfaltz, *Org. Lett.*, 2004, **6**, 2023.
69. G. Jones and C.J. Richards, *Tetrahedron: Asymmetry*, 2004, **15**, 653.
70. I.D. Kostas, B.R. Steeele, A. Terzis and S.V. Amosova, *Tetrahedron*, 2003 **59**, 3467.
71. D.A. Evans, F.E. Michael, J.S. Tedrow and K.R. Campos, *J. Am. Chem. Soc.*, 2003, **125**, 3534.
72. V. Turcry, C. Pasquier and F. Agbossou-Niedercorn, *C. R. Chimie*, 2003**6**, 179.
73. F. Agbossou-Niedercorn and I. Suisse, *Coord. Chem. Rev.*, 2003, **242**, 145.
74. M.R. Eberhard, S. Matsukawa, Y. Yamamoto and C.M. Jensen, *J. Organomet. Chem.*, 2003, **687**, 185.
75. A. Monsees and S. Laschat, *Synlett*, 2002, 1011.
76. K. Ohe, K. Morioka, K. Yonehara and S. Uemura, *Tetrahedron: Asymmetry*, 2002, **13**, 2155.
77. I.D. Kostas, *Inorg. Chim. Acta*, 2003, **355**, 424.
78. G. Ebeling, M.R. Meneghetti, F. Rominger and J. Dupont, *Organometallics*, 2002, **21**, 3221.

79. F. Rahm, A. Fischer and C. Moberg, *Eur. J. Org. Chem.*, 2003, 4205.
80. L. Barloy, G. Malaisé, S. Ramdeehul, C. Newton, J.A. Osborn and N. Kyritsakas, *Inorg. Chem.*, 2003, **42**, 2902.
81. K.K. Klausmeyer, R.P. Feazell and J.H. Reibenspies, *Inorg. Chem.*, 2004, **43**, 1130.
82. I.L. Odinets, N.M. Vinogradova and T.A. Mastryukova, *Russ. Chem. Rev.*, 2003, **72**, 787.
83. P.-Y. Renard, P. Vayron and C. Mioskowski, *Org. Lett.*, 2003, **5**, 1661.
84. P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix and C. Mioskowski, *Angew. Chem. Int. Ed.*, 2003, **42**, 2389.
85. F. Liron and P. Knochel, *Chem. Commun.*, 2004, 304.
86. E. Rivard, A.J. Lough and I. Manners, *J. Chem. Soc., Dalton Trans.*, 2002, 2966.
87. T. Mukaiyama, Y. Kobashi and T. Shintou, *Chem. Lett.*, 2003, **32**, 900.
88. T. Shintou, W. Kikuchi and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 676.
89. T. Shintou and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 1100.
90. T. Mukaiyama, T. Shintou and K. Fukumoto, *J. Am. Chem. Soc.*, 2003 **125**, 10538.
91. T. Mukaiyama, T. Shintou and W. Kikuchi, *Chem. Lett.*, 2002, 1126.
92. T. Shintou, W. Kikuchi and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 1645.
93. T. Shintou and T. Mukaiyama, *J. Am. Chem. Soc.*, 2004, **126**, 7359.
94. T. Mukaiyama, W. Kikuchi and T. Shintou, *Chem. Lett.*, 2003, **32**, 300.
95. T. Shintou and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 984.
96. R.B. Bedford, M.E. Blake, S.J. Coles, M.B. Hursthouse and P.N. Scully, *Dalton Trans.*, 2003, 2805.
97. R.B. Bedford, S.L. Hazelwood, M.E. Limmert, J.M. Brown, S. Ramdeehul, A.R. Cowley, S.J. Coles and M.B. Hursthouse, *Organometallics*, 2003, **22**, 1364.
98. M. Stankevič, G. Andrijewski and K.M. Pietrusiewicz, *Synlett.*, 2004, 311.
99. P. Mastrorilli, M. Latronico, C.F. Nobile, G.P. Suranna, F.P. Fanizzi, U. Englert and G. Ciccarella, *Dalton Trans.*, 2004, 1117.
100. D. Magiera, A. Szmigielska, K.M. Pietrusiewicz and H. Duddeck, *Chirality*, 2004, **16**, 57.
101. C. Wolf, R. Lerebours and E.H. Tanzini, *Synthesis*, 2003, 2069.
102. S.P. Khanapure and D.S. Garvey, *Tetrahedron Lett.*, 2004, **45**, 5283.
103. R.P. Davies, M.G. Martinelli, A.E.H. Wheatley, A.J.P. White and D.J. Williams, *Eur. J. Inorg. Chem.*, 2003, 3409.
104. A.A. Prischenko, M.V. Livantsov, O.P. Novikova, L.I. Livantsova, Y.N. Koval' and E.V. Grigor'ev, *Russ. J. Gen. Chem.*, 2003, **73**, 1658.
105. D.J. Adams, W. Chen, E.G. Hope, S. Lange, A.M. Stuart, A. West and J. Xiao, *Green Chem.*, 2003, **5**, 118.
106. D.J. Adams, D. Gudmunsen, E.G. Hope, A.M. Stuart and A. West, *J. Fluorine Chem.*, 2003, **121**, 213.
107. G.-P. Calabró, D. Drommi, G. Bruno and F. Faraone, *Dalton Trans.*, 2004, 81.
108. J.I. van der Vlugt, R. Sablong, P.C.M.M. Magusin, A.M. Mills, A.L. Spek and D. Vogt, *Organometallics*, 2004, **23**, 3177.
109. J.I. van der Vlugt, R. Sablong, A.M. Mills, H. Kooijman, A.L. Spek, A. Meetsma and D. Vogt, *Dalton Trans.*, 2003, 4690.
110. J.-C. Hierso, F. Lacassin, R. Broussier, R. Amardeil and P. Meunier, *J. Organomet. Chem.*, 2004, **689**, 766.
111. M.B. Peori and A.K. Kakkar, *Organometallics*, 2002, **21**, 3860.
112. D.J. Brauer, K.W. Kottsieper, S. Rossenbach and O. Stelzer, *Eur. J. Inorg. Chem.*, 2003, 1748.

113. G. Franció, D. Drommi, C. Graiff, F. Faraone and A. Tiripicchio, *Inorg. Chim. Acta*, 2002, **338**, 59.
114. F. Speiser, P. Braunstein and L. Saussine, *Dalton Trans.*, 2004, 1539.
115. P. Kilian, A.M.Z. Slawin and J.D. Woollins, *Dalton Trans.*, 2003, 3876.
116. S.N. Lazarev, Z.A. Bredikhina and A.A. Bredikhin, *Russ. J. Gen. Chem.*, 2003, **76**, 928.
117. D. Selent, W. Baumann, R. Kempe, A. Spannenberg, D. Röttger, K.-D. Wiese and A. Börner, *Organometallics*, 2003, **22**, 4265.
118. J.-K. Jeon, Y.-K. Park and J.M. Kim, *Chem.Lett.*, 2004, **33**, 174.
119. Z.J. Zhang, B.S. Wan and H.L. Chen, *Progress in Chemistry*, 2002, **14**, 446.
120. M. Ostermeier, B. Brunner, C. Korff and G. Helmchen, *Eur. J. Org. Chem.*, 2003, 3453.
121. P. Scafato, S. Labano, G. Cunsolo and C. Rosini, *Tetrahedron: Asymmetry*, 2003, **14**, 3873.
122. A. Korostylev, A. Monsees, C. Fischer and A. Börner, *Tetrahedron: Asymmetry*, 2004, **15**, 1001.
123. A. Iuliano and P. Scafato, *Tetrahedron: Asymmetry*, 2003, **14**, 611.
124. M.T. Reetz, L.J. Goossen, A. Meiswinkel, J. Paetzold and J.F. Jensen, *Org. Lett.*, 2003, **5**, 3099.
125. (*a*) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu and H. Chen, *Org. Lett.*, 2003, **5**, 4137; (*b*) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu and H. Chen, *J. Org. Chem.*, 2004, **69**, 2355.
126. I. Gergely, C. Hegedüs, H. Gulyás, A. Szöllősy, A. Monsees, T. Riermeier and J. Bakos, *Tetrahedron: Asymmetry*, 2003, **14**, 1087.
127. Z. Hua, V.C. Vassar and I. Ojima, *Org. Lett.*, 2003, **5**, 3831.
128. P. Hannen, H.-C. Militzer, E.M. Vogl and F.A. Rampf, *Chem. Commun.*, 2003, 2210.
129. J.M. Brunel and B. Faure, *J. Mol. Catal. A: Chem.*, 2004, **212**, 61.
130. E.E. Nifant'ev, M.P. Koroteev, G.Z. Kaziev, A.M. Koroteev, L.K. Vasyanina and I.S. Zakharova, *Russ. J. Gen. Chem.*, 2003, **73**, 1686.
131. R.B. Bedford, S.L. Hazlewood and M.E. Limmert, *Chem. Commun.*, 2002, 2610.
132. S. Le Stang, R. Meier, C. Rocaboy and J.A. Gladysz, *J. Fluorine Chem.*, 2003, **119**, 141.
133. I. Bauer and W.D. Habicher, *Tetrahedron Lett.*, 2002, **43**, 5245.
134. I. Bauer, R. Frölich, A.Y. Ziganshina, A.V. Prosvirkin, M. Gruner, E.K. Kazakova and W.D. Habicher, *Chem. Eur. J.*, 2002, **8**, 5622.
135. C.J. Cobley, K. Gardner, J. Klosin, C. Praquin, C. Hill, G.T. Whiteker, A. Zanotti-Gerosa, J.L. Petersen and K.A. Abboud, *J. Org. Chem.*, 2004, **69**, 4031.
136. L. Su, X. Li, W.L. Chan, X. Jia and A.S.C. Chan, *Tetrahedron: Asymmetry*, 2003, **14**, 1865.
137. M. Diéguez, A. Ruiz and C. Claver, *Dalton Trans.*, 2003, 2957.
138. A. Korostylev, D. Selent, A. Monsees, C. Borgmann and A. Börner, *Tetrahedron: Asymmetry*, 2003, **14**, 1905.
139. R.D. Pike, B.A. Reinecke, M.E. Dellinger, A.B. Wiles, J.D. Harper, J.R. Cole, K.A. Dendramis, B.D. Borne, J.L. Harris and W.T. Pennington, *Organometallics*, 2004, **23**, 1986.
140. K.N. Gavrilov, O.G. Bondarev, A.V. Korostylev, A.I. Polosukhin, V.N. Tsarev, N.E. Kadilnikov, S.E. Lyubimov, A.A. Shiryaev, S.V. Zheglov, H.-J. Gais and V.A. Davankov, *Chirality*, 2003, **15**, 97.

141. (*a*) Y. Hu, X. Liang, J. Wang, Z. Zheng and X. Hu, *J. Org. Chem*., 2003, **68**, 4542; (*b*) H. Wan, Y. Hu, Y. Liang, S. Gao, J. Wang, Z. Zheng and X. Hu, *J. Org. Chem*., 2003, **68**, 8277; (*c*) Y. Hu, X. Liang, J. Wang, Z. Zheng and X. Hu, *Tetrahedron: Asymmetry*, 2003, **14**, 3907.
142. A. Korostylev, I. Gridnev and J.M. Brown, *J. Organomet. Chem*., 2003, **680**, 329.
143. (*a*) K.N. Gavrilov, O.G. Bondarev, R.V. Lebedev, A.I. Polosukhin, A.A. Shyryaev, S.E. Lyubimov, P.V. Petrovskii, S.K. Moiseev, V.N. Kalinin, N.S. Ikonnikov, V.A. Davankov and A.V. Korostylev, *J. Organomet. Chem*., 2002, **655**, 204; (*b*) V.N. Tsarev, A.A. Kabro, S.K. Moiseev, V.N. Kalinin, O.G. Bondarev, V.A. Davankov and K.N. Gavrilov, *Russ. Chem. Bull., Int. Ed*., 2004, **53**, 814.
144. O.G. Bondarev, S.E. Lyubimov, A.A. Shiryaev, N.E. Kadilnikov, V.A. Davankov and K.N. Gavrilov, *Tetrahedron: Asymmetry*, 2002, **13**, 1587.
145. S. Gladiali, G. Loriga, S. Medici and R. Taras, *J. Mol. Catal. A: Chem*., 2003, **196**, 27.
146. S.P. Shum, S.D. Pastor, A.D. DeBellis, P.A. Odorisio, L. Burke, F.H. Clarke, G. Rihs, B. Piatek and R.K. Rodebaugh, *Inorg. Chem*., 2003, **42**, 5097.
147. V.F. Slagt, P.W.N.M. van Leeuwen and J.N.H. Reek, *Angew. Chem. Int. Ed*., 2003, **42**, 5619.
148. V.F. Slagt, M. Röder, P.C.J. Kamer, P.W.N.M. van Leeuwen and J.N.H. Reek, *J. Am. Chem. Soc*., 2004, **126**, 4056.
149. A. Suárez, M.A. Méndez-Rojas and A. Pizzano, *Organometallics*, 2002, **21**, 4611.
150. M. Diéguez, O. Pàmies, G. Net, A. Ruiz and C. Claver, *J. Mol. Catal. A: Chem*., 2002, **185**, 11.
151. T. Kanayama, K. Yoshida, H. Miyabe, T. Kimachi and Y. Takemoto, *J. Org. Chem*., 2003, **68**, 6197.
152. (*a*) J.I. van der Vlugt, M.M.P. Grutters, J. Ackerstaff, R.W.J.M. Hanssen, H.C.L. Abbenhuis and D. Vogt, *Tetrahedron Lett*., 2003, **44**, 8301; (*b*) J.I. van der Vlugt, J. Ackerstaff, T.W. Dijkstra, A.M. Mills, H. Kooijman, A.L. Spek, A. Meetsma, H.C.L. Abbenhuis and D. Vogt, *Adv. Synth. Catal*., 2004, **346**, 399.
153. G.I. Kurochkina, M.K. Grachev, A.A. Sutyagin and E.E. Nifant'ev, *Russ. J. Gen. Chem*., 2003, **73**, 1945.
154. S. Steyer, C. Jeunesse, D. Matt, R. Welter and M. Wesolek, *J. Chem. Soc., Dalton Trans*., 2002, 4264.
155. V.I. Maslennikova, R.V. Merkulov, L.K. Vasyanina, I. Bauer, D. Weber, G. Theumer, W.D. Habicher and E.E. Nifantyev, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1489.
156. E. Poniatowska and G.M. Salamończyk, *Tetrahedron Lett*., 2003, **44**, 4315.
157. H.R. Hudson and L. Powroznyk, *ARKIVOC*, 2004, 19.
158. (*a*) A. Popa, G. Ilia, S. Iliescu, C.M. Davidescu, A. Pascariu and A. Bora, *Revista de Chimie (Bucharest Romania)*, 2003, **54**, 834; (*b*) A. Popa, G. Ilia, S. Iliescu, C.M. Davidescu, A. Pascariu and A. Bora, *Chem. Abstr*., 2004, **140**, 236380.
159. P. Even, E. Guenin, M. Benramdane, P. Quidu, D. El-Manouni and M. Lecouvey, *Letters in Org. Chem*., 2004, **1**, 75.
160. S. Zheng, S. Barlow, T.C. Parker and S.R. Marder, *Tetrahedron Lett*., 2003 **44**, 7989.
161. O. Kasyan, D. Swierczynski, A. Drapailo, K. Suwinska, J. Lipkowski and V. Kalchenko, *Tetrahedron Lett*., 2003, **44**, 7167.
162. D. Witt, J. Dziemidowicz and J. Rachon, *Heteroatom Chem*., 2004, **15**, 155.
163. D. Villemin, A. Elbilali, F. Siméon, P.-A. Jaffrès, G. Maheut, M. Mosaddak and A. Hakiki, *J. Chem. Res. (S)*, 2003, 436.

164. T. Erker and N. Handler, *Synthesis*, 2004, 668.
165. M.M. Sá, G.P. Silveira, A.J. Bortoluzzi and A. Padwa, *Tetrahedron*, 2003, **59**, 5441.
166. M.B. Gazizov, L.G. Gaisin, R.A. Khairullin, G.G. Safina, R.F. Karimova and M.A. Petrova, *Russ. J. Gen. Chem.*, 2003, **73**, 1738.
167. Y.V. Rassukana, P.P. Onys'ko, A.G. Grechukha and A.D. Sinitsa, *Eur. J. Org. Chem.*, 2003, 4181.
168. J.Y. Onishi, T. Takuwa and T. Mukaiyama, *Chem. Lett.*, 2003, 994.
169. W. Waszkuć and T. Janecki, *Org. Biomol. Chem.*, 2003, **1**, 2966.
170. J.P. Freeman and M.E. Guay, *Heterocycles*, 2004, **62**, 847.
171. M.R. Saidi and F. Rajabi, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2343.
172. A.M. Koroteev, G.B. Krasnov, M.P. Koroteev, E.E. Nifant'ev, L.N. Kulesheva, M.Yu. Antipin and A.A. Korlyukov, *Russ. J. Org. Chem.*, 2004, **40**, 474.
173. N.S. Kumar, S. Kumaraswamy, M.A. Said and K.C.K. Swamy, *Org. Proc. Res. Dev.*, 2003, **7**, 925.
174. H. Nagai, S. Matsumura and K. Toshima, *Chem. Lett.*, 2002, **31**, 1100.
175. H. Nagai, S. Matsumura and K. Toshima, *Carbohydrate Res.*, 2003, **338**, 1531.
176. J. Moravcova, H. Heissigerova, P. Kocalka, A. Imberty, D. Sykora and M. Fris, *Tetrahedron Lett.*, 2003, **44**, 8797.
177. P.P. Onys'ko, O.A. Suvalova, Y.V. Rassukana, T.I. Chudakova and A.D. Sinitsa, *Tetrahedron Lett.*, 2003, **44**, 1855.
178. V.K. Aggarwaal, J.R. Fulton, C.G. Sheldon and J. de Vicente, *J. Am. Chem. Soc.*, 2003, **125**, 6034.
179. I. Yavari, A. Alizadeh and H. Mohebbi, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1741.
180. I. Yavari, M. Anary-Abbasinejad and Z. Hossaini, *Org. Biomol. Chem.*, 2003, **1**, 560.
181. N.M.Abd. El-Rahman and S.T. Rabei, *Phosphorus, Sulfur, Silicon*, 2003 **178**, 1361.
182. S. Fürmeier, M.M.L. Lau, M.S.F. Lie Ken Jie, A. Lützen and J.O. Metzger, *Eur. J. Org. Chem.*, 2003, 4874.
183. W.M. Abdou, A.A. Kamel and M.D. Khidre, *Heteroatom Chem.*, 2004, **15**, 77.
184. I. Yavari, M. Anary-Abbasinejad and Z. Hossaini, *Polish J. Chem.*, 2004, **78**, 361.
185. F.H. Osman, N.M. Abd. El-Rahman, F.A. El-Samahy and I.S.A. Farag, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 531.
186. Y. Hayakawa, M. Hyodo, K. Kimura and M. Kataoka, *Chem. Commun.*, 2003, 1704.
187. N. Sofikiti and M. Stratakis, *ARKIVOC*, 2003, 30.
188. M. Stratakis, C. Rabalakos and N. Sofikiti, *Tetrahedron Lett.*, 2003, **44**, 349.
189. B. Ding and W.G. Bentrude, *J. Am. Chem. Soc.*, 2003, **125**, 3248.
190. N. Azizi and M.R. Saidi, *Tetrahedron Lett.*, 2003, **44**, 7933.
191. A. Heydari, M. Mehrdad, M. Schaffie, M.S. Abdolrezaie and R. Hajinassirei, *Chem. Lett.*, 2002, **31**, 1146.
192. N. Azizi and M.R. Saidi, *Tetrahedron*, 2003, **59**, 5329.
193. A. Manjula, B.V. Rao and P. Neelakantan, *Synthetic Commun.*, 2003, **33**, 2963.
194. P. Leriche, S. Roquet, N. Pillerel, G. Mabon and P. Frère, *Tetrahedron Lett.*, 2003, **44**, 1623.
195. R. Suizu and T. Imakubo, *Org. Biomol. Chem.*, 2003, **1**, 3629.
196. M. Iyoda, R. Watanabe and Y. Miyake, *Chem. Lett.*, 2004, **33**, 570.
197. M.R. Japukca, M.E. Harr and D.R. Stevenson, *J. Vinyl and Additive Tech.*, 2004, **10**, 99.
198. M.T. Reetz, *Russ. J. Org. Chem.*, 2003, **39**, 392.
199. R.B. Bedford, S.L. Hazelwood, M.E. Limmert, D.A. Albisson, S.M. Draper, P.N. Scully, S.J. Coles and M.B. Hursthouse, *Chem. Eur. J.*, 2003, **9**, 3216.

200. A.B. Kudryavtsev, A.T. Teleshev, E.E. Nifant'ev and W. Linert, *Russ. Chem. Bull.*, 2003, **52**, 2740.
201. C.M. Nagaraja, M. Nethaji and B.R. Jagirdar, *Inorg. Chem. Commun.*, 2004, **7**, 654.
202. S. Munavalli, D.K. Rohrbaugh and H.D. Durst, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1871.
203. V. Gagnard, A. Leydet, V. Barragan and J.-L. Montero, *Heteroatom Chem.*, 2003, **14**, 111.
204. G. Baccolini, C. Boga, G. Guizzardi and S. Ponzano, *Tetrahedron Lett.*, 2002, **43**, 9299.
205. A.A. Belyakov, B. Dalhus, A. Haaland, D.J. Shorokhov and H.V. Volden, *J. Chem. Soc., Dalton Trans.*, 2002, 3756.
206. R. Franke, C. Borgmann, D. Hess and K.-D. Wiese, *Z. Anorg. Allg. Chem.*, 2003, **629**, 2535.
207. J. Kaneti, S.M. Bakalova and M.T. Nguyen, *J. Mol. Struct. (Theochem.)*, 2003, **633**, 35.
208. P. Derollez, O. Hernandez, A. Hedoux, Y. Guinet, O. Masson, J. Lefebvre and M. Descamps, *J. Mol. Struct. (Theochem.)*, 2004, **694**, 131.
209. M.R.I. Zubiri and J.D. Woollins, *Comments on Inorg. Chem.*, 2003, **24**, 189.
210. E.V. Gryshkun, N.V. Andrushko and O.I. Kolodiazhnyi, *Phosphorus, Sulfur, Silicon*, 2004, **179**, 1027.
211. O.I. Kolodiazhnyi, E.V. Gryshkun, N.V. Andrushko, M. Freytag, P.G. Jones and R. Schmutzler, *Tetrahedron: Asymmetry*, 2003, **14**, 181.
212. E.V. Gryshkun, O.A. Kolodyazhnaya and O.I. Kolodyazhnyi, *Russ. J. Gen. Chem.*, 2003, **73**, 1823.
213. Q. Zhang, G. Hua, P. Bhattacharyya, A.M.Z. Slawin and J.D. Woollins, *Dalton Trans.*, 2003, 3250.
214. T. Appleby, S.M. Aucott, M.L. Clarke, A.M.Z. Slawin and J.D. Woollins, *Polyhedron*, 2002, **21**, 2639.
215. S.M. Aucott, A.M.Z. Slawin and J.D. Woollins, *Eur. J. Inorg. Chem.*, 2002, 2408.
216. M.L. Clarke, A.M.Z. Slawin and J.D. Woollins, *Polyhedron*, 2003, **22**, 19.
217. A.M.Z. Slawin, J. Wheatley, M.V. Wheatley and J.D. Woollins, *Polyhedron*, 2003, **22**, 1397.
218. R.C. Samuel, R.P. Kashyap, M. Krawiec, W.H. Watson and R.H. Neilson, *Inorg. Chem.*, 2002, **41**, 7113.
219. B. Wrackmeyer, C. Köhler, W. Milius, J.M. Grevy, Z. García-Hernández and R. Contreras, *Heteroatom Chem.*, 2002, **13**, 667.
220. O. Kühl and P. Lönnecke, *Inorg. Chem.*, 2002, **41**, 4315.
221. Z. Fei, R. Scopelliti and P.J. Dyson, *Dalton Trans.*, 2003, 2772.
222. Z. Fei, R. Scopelliti and P.J. Dyson, *Inorg. Chem.*, 2003, **42**, 2125.
223. M.L. Clarke, *J. Organomet. Chem.*, 2003, **665**, 65.
224. A. Mansour and M. Portnoy, *Tetrahedron Lett.*, 2003, **44**, 2195.
225. M. Freytag, V. Plack, P.G. Jones and R. Schmutzler, *Z. Naturforsch., B:*, 2004, **59**, 499.
226. N. Biricik, Z. Fei, R. Scopelliti and P.J. Dyson, *Helv. Chim. Acta*, 2003, **86**, 3281.
227. F. Majoumo, P. Lönnecke, O. Kühl and E. Hey-Hawkins, *Z. Anorg. Allg. Chem.*, 2004, **630**, 305.
228. K.G. Gaw, M.B. Smith and J.W. Steed, *J. Organomet. Chem.*, 2002, **664**, 294.
229. M.R.I. Zubiri, H.L. Milton, A.M.Z. Slawin and J.D. Woollins, *Polyhedron*, 2004, **23**, 865.

230. M.R.I. Zubiri, H.L. Milton, D.J. Cole-Hamilton, A.M.Z. Slawin and J.D. Woollins, *Polyhedron*, 2004, **23**, 693.
231. R.W. Guo, X.S. Li, J. Wu, W.H. Kwok, J. Chen, M.C.K. Choi and A.S.C. Chan, *Tetrahedron Lett*., 2002, **43**, 6803.
232. X. Chen, R. Guo, Y. Li, G. Chen, C.-H. Yeung and A.S.C. Chan, *Tetrahedron Asymmetry*, 2004, **15**, 213.
233. M.P. Magee, H.-Q. Li, O. Morgan and W.H. Hersch, *Dalton Trans*., 2003, 387.
234. M.R.I. Zubiri, H.L. Milton, D.J. Cole-Hamilton, A.M.Z. Slawin and J.D. Woollins, *Inorg. Chem. Commun*., 2004, **7**, 201.
235. M.R.I. Zubiri, A.M.Z. Slawin, M. Wainwright and J.D. Woollins, *Polyhedron*, 2002, **21**, 1729.
236. M.S. Balakrishna, P.P. George and J.T. Mague, *J. Chem. Res. (S)*, 2003, 576.
237. M.R.I. Zubiri, H.L. Milton, A.M.Z. Slawin and J.D. Woollins, *Inorg. Chim. Acta*., 2004, **357**, 1243.
238. K. Hiroi, I. Izawa, T. Takizawa and K. Kawai, *Tetrahedron*, 2004, **60**, 2155.
239. A.D. Burrows, M.F. Mahon and M. Varrone, *Dalton Trans*., 2003, 4718.
240. A.D. Burrows, M.F. Mahon and M. Varrone, *Inorg. Chim. Acta*, 2003, **350**, 152.
241. A.D. Burrows, M.F. Mahon, S.P. Nolan and M. Varrone, *Inorg. Chem*., 2003 **42**, 7227.
242. I.O. Koshevoy, S.P. Tunik, A.J. Poe, A. Lough, J. Pursiainen and P. Pirilä, *Organometallics*, 2004, **23**, 2641.
243. C.W. Edwards, M.R. Shipton, N.W. Alcock, H. Clase and M. Wills, *Tetrahedron*, 2003, **59**, 6473.
244. G.J. Clarkson, J.R. Ansell, D.J. Cole-Hamilton, P.J. Pogorzelec, J. Whittell and M. Wills, *Tetrahedron: Asymmetry*, 2004, **15**, 1787.
245. L. Dahlenburg and A. Wühr, *Tetrahedron Lett*., 2003, **44**, 9279.
246. M.T. Reetz, H. Oka and R. Goddard, *Synthesis*, 2003, 1809.
247. J. Krysiak, C. Lyon, A. Baceiredo, H. Gornitzka, M. Mikolajczyk and G. Bertrand, *Chem. Eur. J*., 2004, **10**, 1982.
248. N. Merceron, A. Baceiredo, H. Gornitzka and G. Bertrand, *Chem. Commun*., 2002, 2250.
249. I. Shevchenko, D. Shakhnin, H. Zhang, M. Lattman and G.V. Röschenthaler, *Eur. J. Inorg. Chem*., 2003, 1169.
250. N.W. Boaz, S.D. Debenham, E.B. Mackenzie and S.E. Large, *Org. Lett*., 2002, **4**, 2421.
251. G. Xu and S.R. Gilbertson, *Tetrahedron Lett*., 2003, **44**, 953.
252. C. Blanc, J. Hannedouche and F. Agbossou-Niedercorn, *Tetrahedron Lett*., 2003, **44**, 6469.
253. C. Blanc and F. Agbossou-Niedercorn, *Tetrahedron: Asymmetry*, 2004, **15**, 757.
254. A.D. Woods and M. McPartlin, *Dalton Trans*., 2004, 90.
255. D.F. Moser, L. Grocholl, L. Stahl and R.J. Staples, *Dalton Trans*., 2003, 1402.
256. T. Chivers, M. Krahn and G. Schatte, *Inorg. Chem*., 2002, **41**, 4348.
257. A. Bashall, E.M. Doyle, F. Garciá, G.T. Lawson, D.J. Linton, D. Moncrieff, M. McPartlin, A.D. Woods and D.S. Wright, *Chem. Eur. J*., 2002, **8**, 5723.
258. N. Burford, T.S. Cameron, K.D. Konroy, B. Ellis, M. Lumsden, C.L.B. Macdonald, R. McDonald, A.D. Phillips, P.J. Ragogna, R.W. Schurko, D. Walsh and R.E. Wasylishen, *J. Am. Chem. Soc*., 2002, **124**, 14012.
259. I. Schranz, G.R. Lief, S.J. Midstokke and L. Stahl, *Inorg. Chem*., 2002, **41**, 6919.
260. J.-P. Bezombes, P.B. Hitchcock, M.F. Lappert and J.E. Nycz, *Dalton Trans*., 2004, 499.

261. J.-P. Bezombes, K.B. Borisenko, P.B. Hitchcock, M.F. Lappert, J.E. Nycz, D.J. Rankin and H.E. Robertson, *Dalton Trans.*, 2004, 1980.
262. Z. Fei, R. Scopelliti and P.J. Dyson, *Eur. J. Inorg. Chem.*, 2003, 3527.
263. P.W. Roesky, *Heteroatom Chem.*, 2002, **13**, 514.
264. M. Alajarín, C. López-Leonardo and P. Llamas-Lorente, *Synlett*, 2003, 801.
265. Z. Fei, N. Biricik, D. Zhao, R. Scopelliti and P.J. Dyson, *Inorg. Chem.*, 2004 **43**, 2228.
266. T. Bauer, S. Schulz, M. Nieger and I. Krossing, *Chem. Eur. J.*, 2004, **10**, 1729.
267. T. Bauer, S. Schulz, M. Nieger and U. Kessler, *Organometallics*, 2003, **22**, 3134.
268. M. Alajarín, C. López-Leonardo and P. Llamas-Lorente, *Letters in Org. Chem.*, 2004, **1**, 145.
269. J.R. Ansell, N.W. Alcock and M. Wills, *J. Chem. Res. (S)*, 2003, 728.
270. S. Priya, M.S. Balakrishna, J.T. Mague and S.M. Mobin, *Inorg. Chem.*, 2003 **42**, 1272.
271. I. Schevchenko, V. Andrushko, E. Lork and G.-V. Röschenthaler, *Eur. J. Inorg. Chem.*, 2002, 2985.
272. A.-S. Chauvin, G. Bernardinelli and A. Alexakis, *Tetrahedron: Asymmetry*, 2004, **15**, 1857.
273. M. Afzaal, D.J. Crouch, P. O'Brien, J. Raftery, P.J. Skabara, A.J.P. White and D.J. Williams, *J. Mater. Chem.*, 2004, **14**, 233.
274. T. Oku, Y. Furusho and T. Takata, *Org. Lett.*, 2003, **5**, 4923.
275. J.G. Verkade and P.B. Kisanga, *Tetrahedron*, 2003, **59**, 7819.
276. W. Su, S. Urgaonkar and J.G. Verkade, *Org. Lett.*, 2004, **6**, 1421.
277. (*a*) S. Urgaonkar, M. Nagarajan and J.G. Verkade, *Org. Lett.*, 2003, **5**, 815; (*b*) S. Urgaonkar, M. Nagarajan and J.G. Verkade, *J. Org. Chem.*, 2003, **68**, 452.
278. S. Urgaonkar, J.-H. Xu and J.G. Verkade, *J. Org. Chem.*, 2003, **68**, 8416.
279. J. You and J.G. Verkade, *J. Org. Chem.*, 2003, **68**, 8003.
280. J. You, J. Xu and J.G. Verkade, *Angew. Chem. Int. Ed.*, 2003, **42**, 5054.
281. Z. Yu and J.G. Verkade, *Adv. Synth. Catal.*, 2004, **346**, 539.
282. W. Su, D. McLeod and J.G. Verkade, *J. Org. Chem.*, 2003, **68**, 9499.
283. A.E. Wroblewski, V. Bansal, P. Kisanga and J.G. Verkade, *Tetrahedron*, 2003, **59**, 561.
284. N. Thirupathi, X. Liu and J.G. Verkade, *Inorg. Chem.*, 2003, **42**, 389.
285. H. Tang, K. Menzel and G.C. Fu, *Angew. Chem. Int. Ed.*, 2003, **42**, 5079.
286. S. Priya, M.S. Balakrishna and J.T. Mague, *J. Organomet. Chem.*, 2003, **679**, 116.
287. P.W. Dyer, J. Fawcett, M.J. Hanton, R.D.W. Kemmitt, R. Padda and N. Singh, *Dalton Trans.*, 2003, 104.
288. L. Lefort, J.A.F. Boogers, A.H.M. de Vries and J.G. de Vries, *Org. Lett.*, 2004 **6**, 1733.
289. A. Duursma, L. Lefort, J.A.F. Boogers, A.H.M. de Vries, J.G. de Vries, A.J. Minnaard and B.L. Feringa, *Org. Biomol. Chem.*, 2004, **2**, 1682.
290. O. Huttenloch, E. Laxman and H. Waldmann, *Chem. Eur. J.*, 2002, **8**, 4767.
291. A. Mandoli, M. Calamante, B.L. Feringa and P. Salvadori, *Tetrahedron: Asymmetry*, 2003, **14**, 3647.
292. S. Doherty, E.G. Robins, I. Pál, C.R. Newman, C. Hardacre, D. Rooney and D.A. Mooney, *Tetrahedron: Asymmetry*, 2003, **14**, 1517.
293. B. Bartels, C. García-Yebra and G. Helmchen, *Eur. J. Org. Chem.*, 2003, 1097.
294. E. Cesarotti, S. Araneo, I. Rimoldi and S. Tassi, *J. Mol. Catal. A: Chem.*, 2003, **204–205**, 211.
295. M.A. van den Berg, A.J. Minnaard, R.M. Haak, M. Leeman, E.P. Schudde, A. Meetsma, B.L. Feringa, A.H.M. de Vries, C.E.P. Maljaars, C.E. Willans, D. Hyett,

J.A.F. Boojers, H.J.W. Henderickx and J.G. de Vries, *Adv. Synth. Catal.*, 2003, **345**, 308.
296. D. Peña, A.J. Minnaard, J.G. de Vries and B.L. Feringa, *J. Am. Chem. Soc.*, 2002, **124**, 14552.
297. D. Peña, A.J. Minnaard, A.H.M. de Vries, J.G. de Vries and B.L. Feringa, *Org. Lett.*, 2003, **5**, 475.
298. A. Duursma, A.J. Minnaard and B.L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 3700.
299. K. Tissot-Croset, D. Polet and A. Alexakis, *Angew. Chem. Int. Ed.*, 2004, **43**, 2426.
300. T. Ohmura and J.F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15164.
301. A.W. van Zijl, L.A. Arnold, A.J. Minnard and B.L. Feringa, *Adv. Synth. Catal.*, 2004, **346**, 413.
302. J.-G. Boiteau, A.J. Minnaard and B.L. Feringa, *J. Org. Chem.*, 2003, **68**, 9481.
303. T. Watanabe, T.F. Knöpfel and E.M. Carreira, *Org. Lett.*, 2003, **5**, 4557.
304. U. Piarulli, C. Claverie, P. Daubos, C. Gennari, A.J. Minnaard and B.L. Feringa, *Org. Lett.*, 2003, **5**, 4493.
305. L. Kangying, Z. Zhenghong, Z. Guofeng and T. Chuchi, *Heteroatom Chem.*, 2003, **14**, 546.
306. X. Li, X. Jia, G. Lu, T.T.-L. Au-Yeung, K.-H. Lam, T.W.H. Lo and A.S.C. Chan, *Tetrahedron: Asymmetry*, 2003, **14**, 2687.
307. Q. Zeng, H. Liu, A. Mi, Y. Jiang, X. Li, M.C.K. Choi and A.S.C. Chan, *Tetrahedron*, 2002, **58**, 8799.
308. Z. Hua, V.C. Vassar, H. Choi and I. Ojima, *Proc. Nat. Acad. Sci. USA*, 2004 **101**, 5411.
309. C.G. Arena, V. Casilli and F. Faraone, *Tetrahedron: Asymmetry*, 2003, **14**, 2127.
310. J. Hernández-Díaz, A. Flores-Parra and R. Contreras, *Heteroatom Chem.*, 2004, **15**, 307.
311. V.N. Tsarev, S.E. Lyubimov, A.A. Shiryaev, S.V. Zheglov, O.G. Bondarev, V.A. Davankov, A.A. Kabro, S.K. Moiseev, V.N. Kalanin and K.N. Gavrilov, *Eur. J. Org. Chem.*, 2004, 2214.
312. H. Zhou, W.-H. Wang, Y. Fu, J.-H. Xie, W.-J. Shi, L.-X. Wang and Q.-L. Zhou, *J. Org. Chem.*, 2003, **68**, 1582.
313. S.-F. Zhou, Y. Fu, J.-H. Xie, B. Liu, L. Xing and Q.-L. Zhou, *Tetrahedron: Asymmetry*, 2003, **14**, 3219.
314. W.-J. Shi, L.-X. Wang, Y. Fu, S.-F. Zhu and Q.-L. Zhou, *Tetrahedron: Asymmetry*, 2003, **14**, 3867.
315. A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang and Q.-L. Zhou, *Angew. Chem. Int. Ed.*, 2002, **41**, 2348.
316. W.H. Hersch, P. Xu, C.K. Simpson, J. Grob, B. Bickford, M.S. Hamdani, T. Wood and A.L. Rheingold, *J. Org. Chem.*, 2004, **69**, 2153.
317. S.J. Kim, E.-K. Bang and B.H. Kim, *Synlett*, 2003, 1838.
318. A. Bayer, P. Murszat, U. Thewalt and B. Rieger, *Eur. J. Inorg. Chem.*, 2002, 2614.
319. T. Nemoto, T. Matsumoto, T. Masuda, T. Hitomi, K. Hatano and Y. Hamada, *J. Am. Chem. Soc.*, 2004, **126**, 3690.
320. E.E. Nifantyev, M.P. Koroteev, G.Z. Kaziev, I.S. Zakharova, K.A. Lyssenko, L.N. Kuleshova and M.Yu. Antipin, *Tetrahedron Lett.*, 2003, **44**, 6327.
321. E.E. Nifant'ev, T.S. Kukhareva, Z.M. Dzgoeva, L.K. Vasyanina, M.P. Koroteev and G.Z. Kaziev, *Heteroatom Chem.*, 2003, **14**, 399.
322. Z. Fei, R. Schmutzler and F.T. Edelmann, *Z. Anorg. Allg. Chem.*, 2003, **629**, 353.

323. S.C. van der Slot, J. Duran, J. Luten, P.C.J. Kamer and P.W.N.M. van Leeuwen, *Organometallics*, 2002, **21**, 3873.
324. R. Hoen, M. van den Berg, H. Bernsmann, A.J. Minnaard, J.G. de Vries and B.L. Feringa, *Org. Lett.*, 2004, **6**, 1433.
325. Y. Lu, M. Freytag, P.G. Jones and R. Schmutzler, *Z. Anorg. Allg. Chem.*, 2003, **629**, 1953.
326. M.S. Balakrishna and R. Panda, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 1391.
327. P. Kommana, K.V.P.P. Kumar and K.C.K. Swamy, *Ind. J. Chem., Section A: Inorg., Bio-Inorg., Physical., Theoretical and Analytical Chem.*, 2003, **42**, 2371.
328. O. Kühl, *Dalton Trans.*, 2003, 949.
329. K.N. Gavrilov, V.N. Tsarev, A.A. Shiryaev, O.G. Bondarev, S.E. Lyubimov, E.B. Benetsky, A.A. Korlyukov, M.Yu. Antipin, V.A. Davankov and H.-J. Gais, *Eur. J. Inorg. Chem.*, 2004, 629.
330. V.I. Maslennikova, R.V. Merkulov, M.V. Dyagileva, L.K. Vasyanina, K.A. Lyssenko, M.Yu. Antipin, D. Weber, I. Bauer, W.D. Habicher and E.E. Nifantyev, *Tetrahedron*, 2003, **59**, 1753.
331. A.R. Burilov, D.I. Kharitonov, N.I. Bashmakova, T.B. Makeeva, I.L. Nikolaeva, M.A. Pudovik and A.I. Konovalov, *Russ. J. Gen. Chem.*, 2003, **73**, 909.
332. V.I. Maslennikova, O.S. Serkova, L.K. Vasyanina, K.A. Lyssenko, M.Yu. Antipin and E.E. Nifantyev, *J. Organomet. Chem.*, 2003, **677**, 21.
333. V.I. Maslennikova, S.E. Goryukhina, L.K. Vasyanina and E.E. Nifantyev, *Phosphorus, Sulfur, Silicon*, 2002, **177**, 211.
334. P. Sood, M. Koutha, M. Fan, Y. Klichko, H. Zhang and M. Lattman, *Inorg. Chem.*, 2004, **43**, 2975.
335. E.E. Nifantyev, E.N. Rasadkina, P.V. Slitikov and L.K. Vasyanina, *Phosphorus, Sulfur, Silicon*, 2003, **178**, 2465.
336. E.E. Nifantyev, E.N. Rasadkina, Y.B. Evdokimova, A.I. Stash, V.K. Belsky and L.K. Vasyanina, *Heteroatom Chem.*, 2003, **14**, 404.
337. N.S. Kumar, J.P. Kumar, K.V.P.P. Kumar, P. Kommana, J.J. Vital and K.C.K. Swamy, *J. Org. Chem.*, 2004, **69**, 1880.
338. M.J. Cain, A. Cawley, V. Sum, D. Brown, M. Thornton-Pett and T.P. Kee, *Inorg. Chim. Acta*, 2003, **345**, 154.
339. L.K. Sal'keeva, M.T. Nurmagambetova and O.Sh. Kurmanaliev, *Russ. J. Gen. Chem.*, 2003, **73**, 1495.
340. E.E. Lee and R.A. Batey, *Angew. Chem. Int. Ed.*, 2004, **43**, 1865.
341. R.B. Grossman, S. Comesse, R.M. Rasne, K. Hattori and M.N. Delong, *J. Org. Chem.*, 2003, **68**, 871.
342. A.T. Teleshev, L.N. Vasil'eva, E.E. Nifant'ev, M.V. Tsodikov, O.V. Bukhtenko and T.N. Zhdanova, *Russ. Chem. Bull. Int. Ed.*, 2003, **52**, 2083.
343. U.M. Krishna, M.U. Ahmad and I. Ahmad, *Tetrahedron Lett.*, 2004, **45**, 2077.

Quinquevalent Phosphorus Acids

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1 Introduction

The current review is of necessity selective. Over the two year period covered, there has been impressive advances in several areas of P(V) chemistry. For example, biological aspects of quinquevalent phosphorus acids chemistry continue to increase in importance. A wide variety of natural and unnatural phosphates including inositols, lipids, some carbohydrates and their phosphonates, phosphinates and fluorinated analogues has been synthesized. Special attention has been paid to the synthesis of phosphorus analogues of all types of amino acids and some peptides. Numerous investigations of phosphate ester hydrolysis and related reactions continue to be reported. Interest in approaches to easier detoxification of insecticides continues. A number of new and improved stereoselective synthetic procedures have been elaborated. The importance of enantioselective and dynamic kinetic asymmetric transformations is illustrated in many publications.

2 Phosphoric Acids and Their Derivatives

Asymmetric synthesis with chiral cyclic phosphorus auxiliaries has been the subject of a review.[1]

2.1 Synthesis of Phosphoric Acids and Their Derivatives. – A selective and mild synthetic route to long or functionalized chained dialkyl phosphates (1)–(5) has been reported (Figure 1).[2]

Trimethylsilyl phosphorohalidates (6) and (7) have been synthesized from phosphoryl dihalogenofluoride (8) and hexamethyldisiloxane (9). An alternative approach to (7) using bis(trimethylsilyl) phosphorofluoridate (10) has been also elaborated (Scheme 1).[3] Compounds (6) and (10) are involved in a new synthesis of bis(trimethylsilyl) diphosphorodifluoridate (11).[3]

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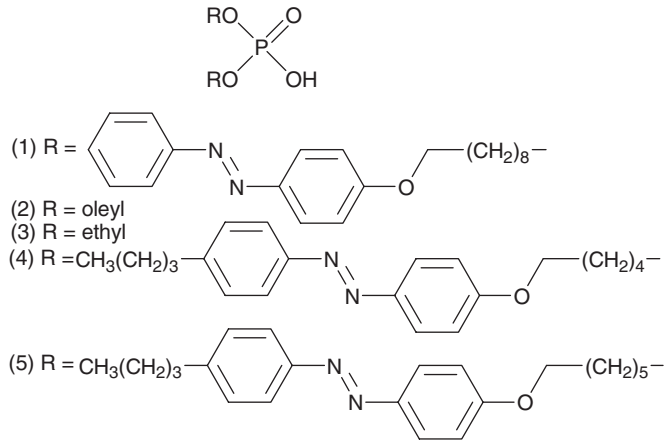
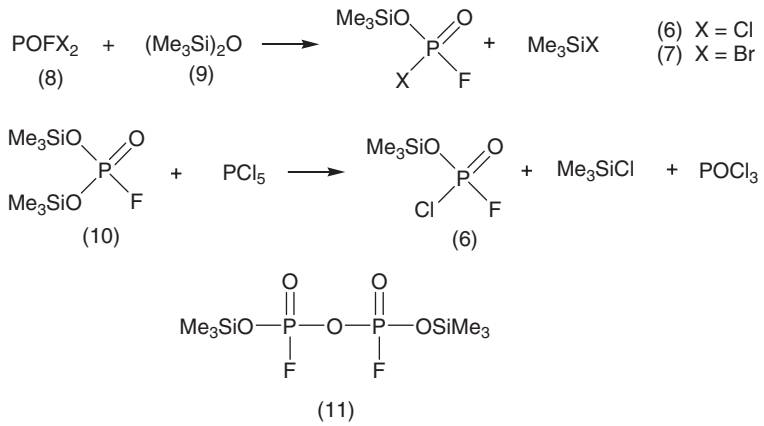


Figure 1



Scheme 1

The first example of the asymmetric synthesis of P-chiral trialkyl phosphates (12) via trialkyl phosphite, in which the keystone is dynamic kinetic resolution in the condensation of a dialkyl phosphorochloridite (13) and an alcohol by the catalytic assistance of a chiral amine has been reported (Figure 2).[4]

2,4-Dinitrophenol (DNP) was employed as an activating reagent with benzyloxy-bis-(diisopropylamino) phosphite to synthesize the cyclic phosphate derivatives (14) from a series of alkane diols HO–$(CH_2)_n$–OH (n=2–6). Included was a cyclic phosphate derivative of carbohydrate (15). The mechanism of activation by 2,4-DNP and cyclization was also described (Figure 3).[5]

A convenient approach to a variety of cyclic enol phosphates (16) and (17) via ring-closing methathesis (RCM) using the second generation Grubbs catalyst (18) has been elaborated (Figure 4).[6]

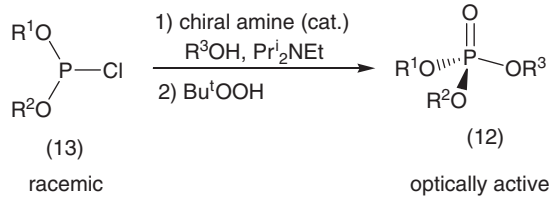


Figure 2

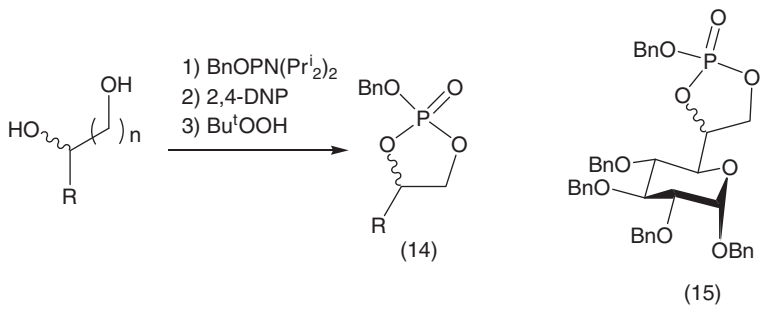


Figure 3

Reactions of alkyl halides with diethyl phosphite in the presence of ammonium acetate/sulfur and acidic aluminia using microwave irradiation provide a simple and general route to thiophosphates.[7] Two diastereoisomers of 1,3,2-dithiadiphosphetane 2-sulfide (19) have been isolated for the first time via the reaction of thioketones (20) with Lawesson's reagent (Figure 5).[8]

The ring-closure reactions of isoquinoline derivatives (21) with phenylphosphonyl chloride afforded a new ring system (see 1,3,2-diazaphosphorinano [6,1-α] isoquinolines (22) and (23) in Scheme 2). Their conformational analysis was performed by ^{1}H, ^{13}C, ^{31}P-NMR.[9]

A simple method for the synthesis of polyfunctional phosphorodithioates (and structural analogues) (24) based on the nucleophilic ring opening reactions of N,N-dialkyl-3-hydroxy(benzyloxy) azetidinium salts (25) and N,N-dibenzyl-2,3-epoxy-propylamine with anions of mono- and dithioacids of phosphorus (26) has been reported (Scheme 3).[10] A new reaction of vicinal sulfonyliminocarboxylates (27) with phosphite occurs with N→C transfer of the RSO_3 group and leads to sulfonyl-substituted trifluorophosphazene derivatives (28) (Scheme 4). The novel rearrangement is interpreted as cheletropic 1,4-cycloaddition and subsequent 1,2-shift of the sulfonyl group in the intermediate phosphorane.[11]

A significant advance in the synthesis of phosphorylated prodrugs has been described. The preparation of various bis-pivaloyloxymethyl (POM) phosphate triesters (29) was accomplished with the use of bis(POM) phosphoryl chloride (30) under mild conditions (Scheme 5).[12]

Phosphorylated 1,6-diphenyl-1,3,5-hexatriene (DPH) (31), a lipophilic dye consisting a fluorophore attached to a phosphate diester was prepared and its

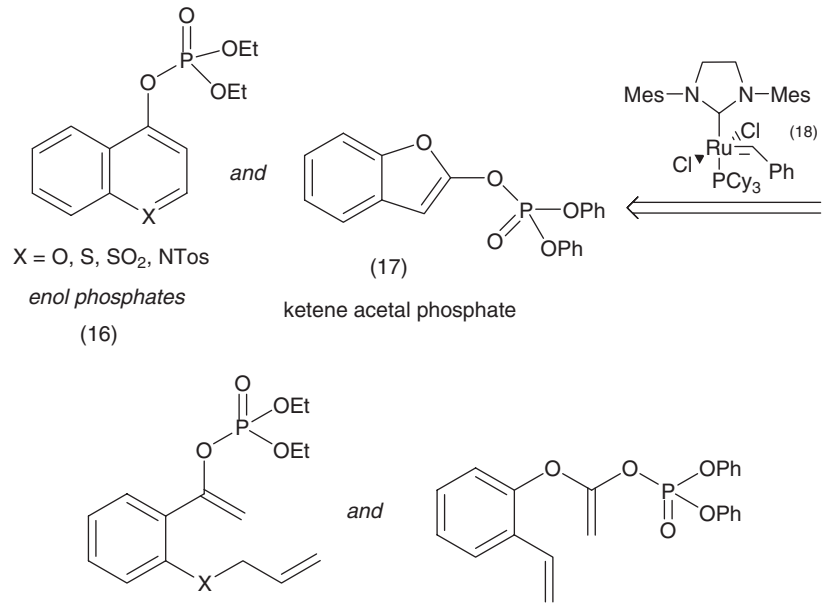


Figure 4

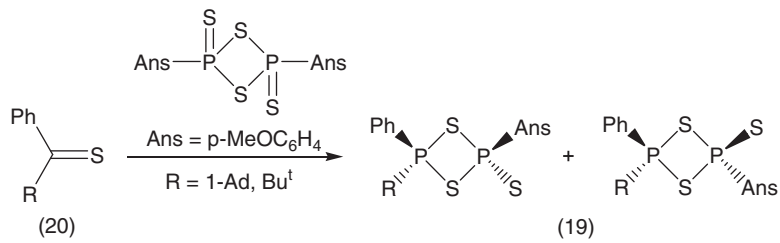
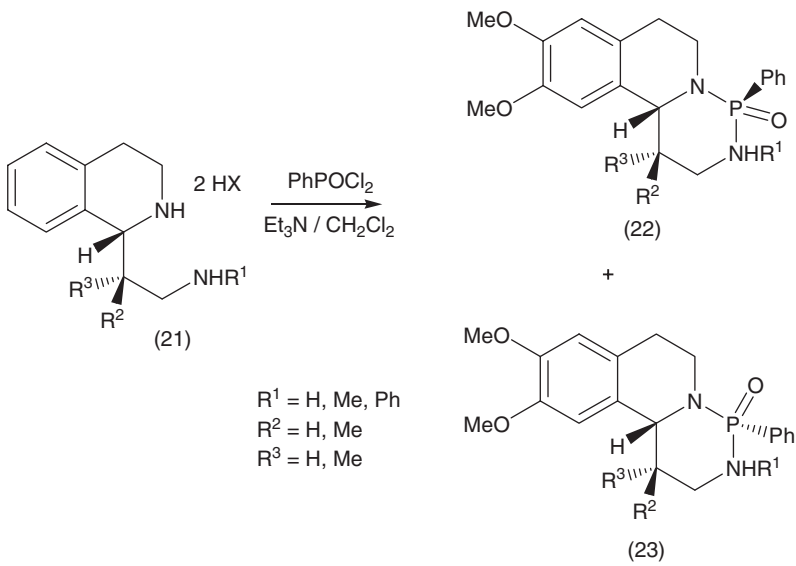


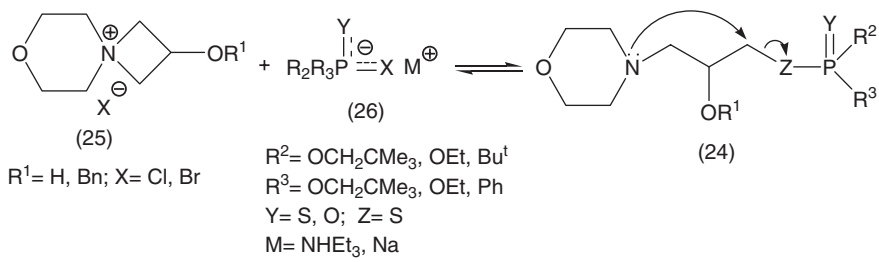
Figure 5

fluorescence behavior in different solvent systems and in a liposomal membrane bilayer was examined (Figure 6a).[13] The eight-step synthesis of the fluorescent porphyrin conjugate (32) featuring a carboranyl phosphate ester attached to the porphyrin via an amide linkage has been disclosed (Figure 6b).[14] Catalytic asymmetric total synthesis of a promising anticancer agent Fostriecin (33) has been performed using method that combined several catalytic asymmetric reactions as shown in Scheme 6.[15]

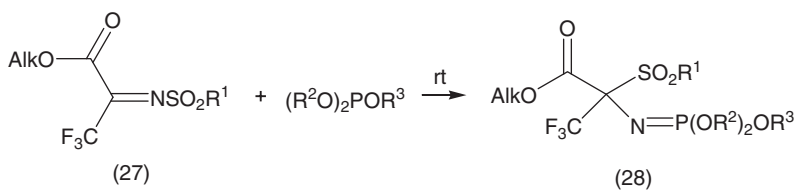
A convenient synthesis of (E)-4-hydroxy-3-methyl-2-butenyl pyrophosphate (34), an intermediate in the deoxyxylulose pathway of isoprenoid biosynthesis, was accomplished by pyrophosphorylation of (E)-4-chloro-2-methyl-2-butene-1-ol (35) (Scheme 7). This route enables convenient access to isotopically



Scheme 2



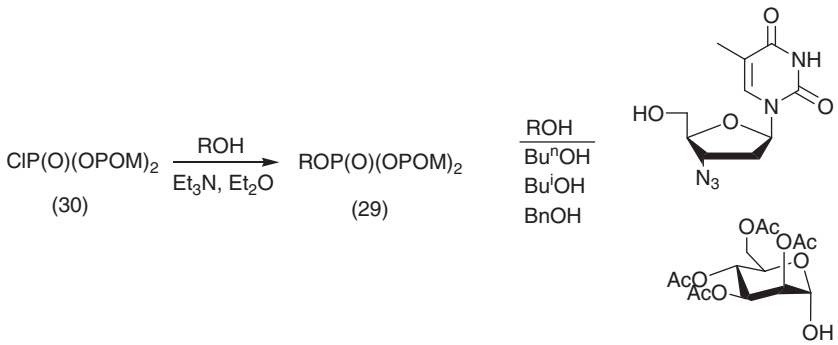
Scheme 3



Scheme 4

labelled product [4-^{13}C] (34) from commercially available [1-^{13}C]-2-propionic acid.[16]

Farnesyl diphosphate analogues (36)–(40) modified in the central isoprene unit have been prepared via the authors stereoselective vinyl triflate-mediated route to isoprenoids. The 7-allyl compound (38) is a modest inhibitor of



Scheme 5

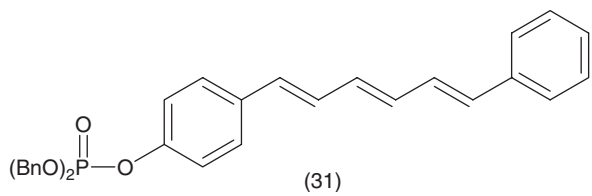


Figure 6a

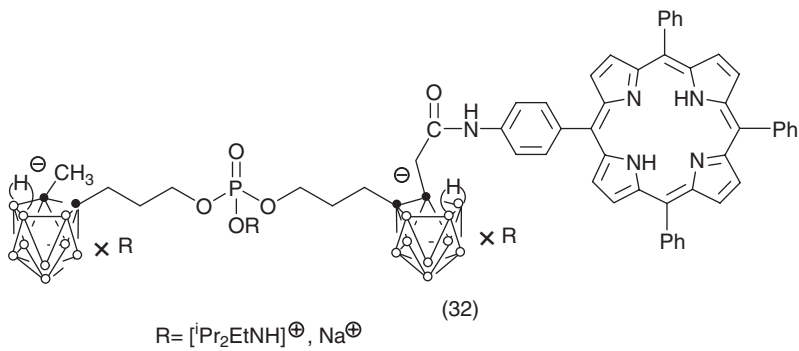
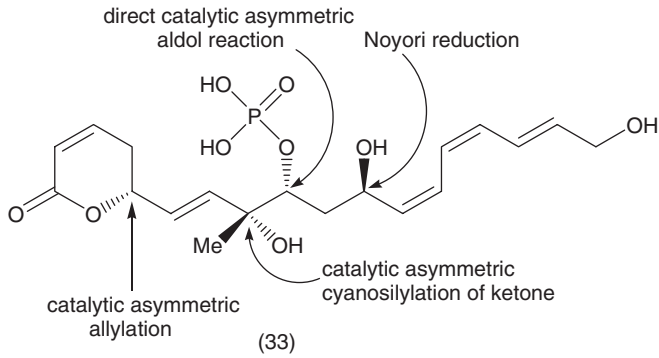


Figure 6b

mammalian protein-farnesyl transferase, but surprisingly the other analogues are effective alternative substrates for this enzyme (Figure 7).[17]

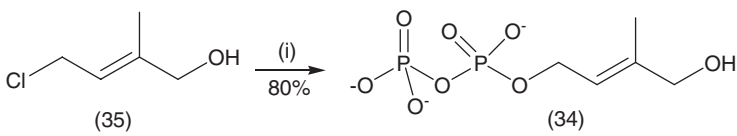
The first catalytic methodology to convert glycals (41) into glycosyl phosphates (42) employing safe, commercially available reagents has been presented (Scheme 8).[18]

A novel and practical synthesis of S-(1- and 2-halogenoalkyl) sugars (43), including some at the anomeric center, has been developed. The synthesis consists of reactions of readily available S-(O,O-dialkyl)phosphorodithioates



(33)

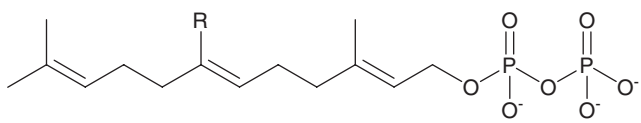
Scheme 6



(35) (34)

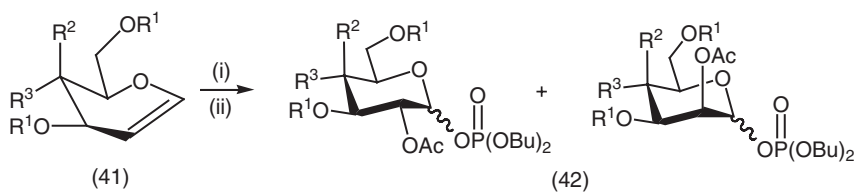
Reagents: (i) $(Bu_4N^+)_3$ pyrophosphate (1.35 equiv.), MeCN

Scheme 7



(36) (R= Et); (37) (R= vinyl); (38) (R= allyl); (39) (R= Pr^i); (40) (R= Bu^i)

Figure 7



(41) (42)

selectivities: from 1.8 : 1 to 50 : 1

Reagents: (i) methylrhenium trioxide (MTO), urea hydrogen peroxide (UHP), $HOP(O)(OBu)_2$, (DBT), $(BMM)BF_4$; (ii) Py, AcO

Scheme 8

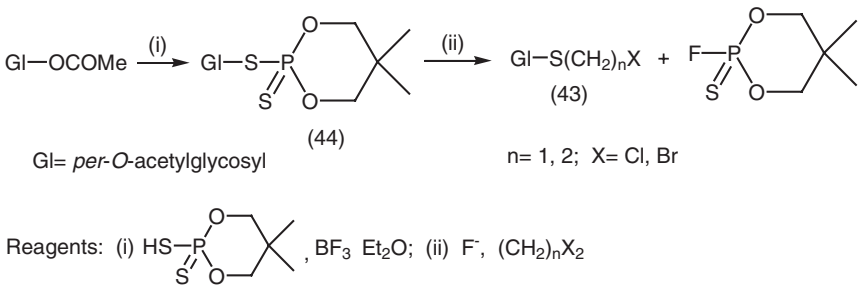
(44) or monothioates at various positions in the carbohydrate ring with fluoride anions. In this reaction the halogenoalkanes play the role of both reactants and solvents. (Scheme 9).[19]

The preparation of inositol and structurally related phosphates continues to be explored. Examples include the synthesis of the enantiomers D- and L-myo-inositol 1,3,4,6-tetrakisphosphate (45) and (46) regioisomers of myo-inositol 1,3,4,5-tetrakisphosphate. Both D- and L-isomers are Ins $(1,4,5)P_3$ 5-phosphatase inhibitors, but not of Ins $(1,4,5)P_3$ 3-kinase (Figure 8).[20]

The synthesis and properties of a malaria candidate glucosyl phosphatidyl inositol (GPI) prototype (47), and one variant, *i.e.*, (48), of the candidate structure has been reported. The approach elaborated addresses the crucially important (vide infra) 0–2 acylation of the inositol moiety, an unusual feature which also occurs in other heavily lipidated GPIs such as CD52 and AchE (Figure 9).[21]

A variable concept for the synthesis of branched glucosyl phosphatidyl inositol (GPI) anchors was established. Its efficiency could be shown by the successful synthesis of the GPI anchor of rat brain Thy-1 (49), and of the scrape prion protein (Figure 10).[22]

A synthetic strategy has been developed that allows reconstruction of the protein – GPI anchor linkage motif (50) (Figure 11).[23]



Scheme 9

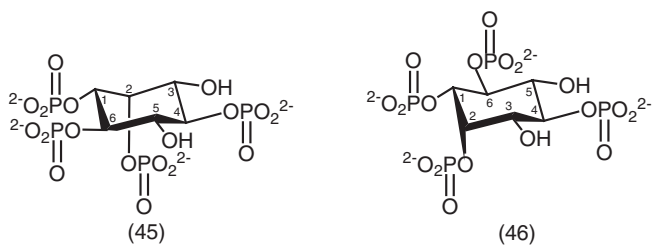


Figure 8

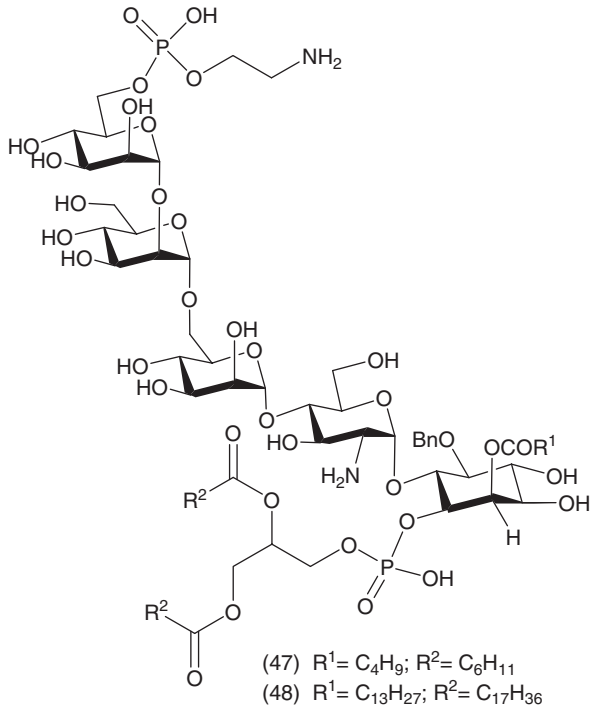


Figure 9

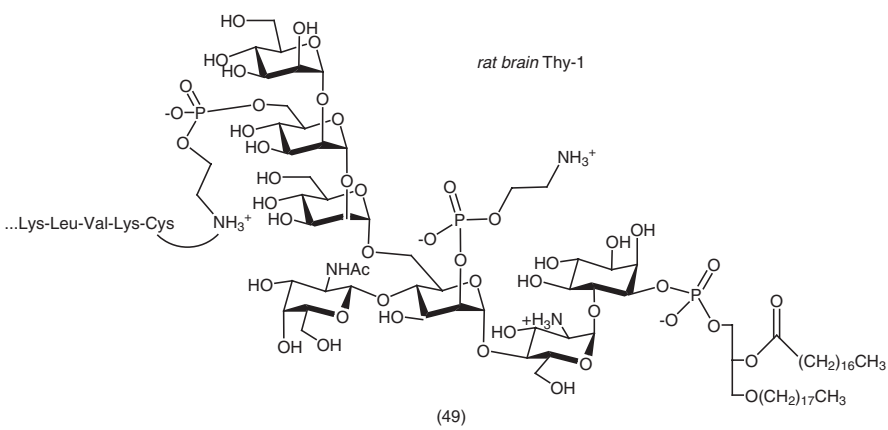


Figure 10

The total synthesis of a novel hybrid lipid Pea-PIP_2 (51), possessing a phosphatidyl ethanolamine (PE) headgroup at the 1-position and a phosphatidyl inositol 4,5-bisphosphate [PtdIns(4,5)P_2] headgroup at the 4-position has been elaborated. Reporter groups (biotin, fluorophores, spin label) were

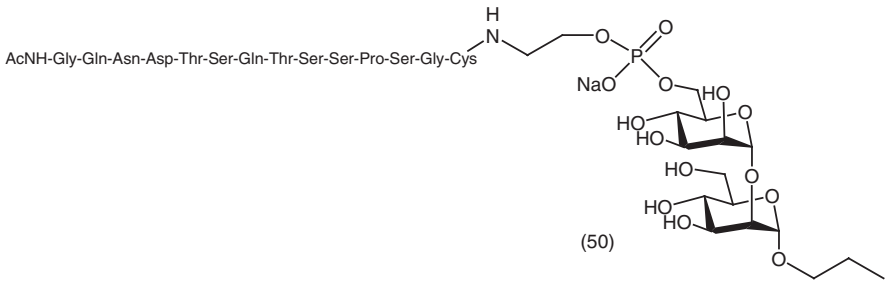


Figure 11

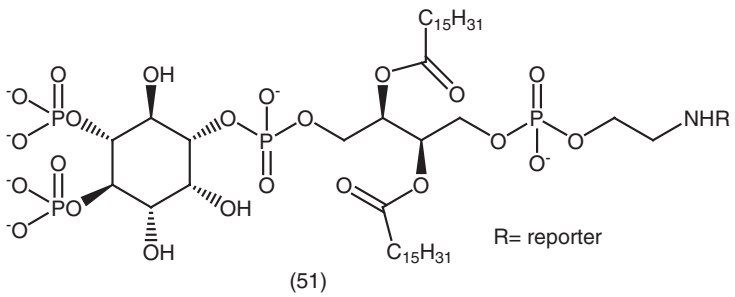


Figure 12

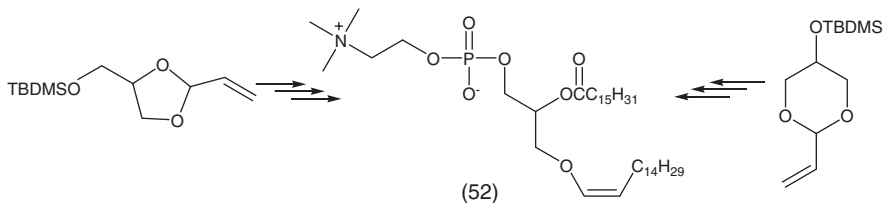


Figure 13

covalently attached to the free amino group of the PE, such that the reporter groups were attracted to the lipid-water interface (Figure 12).[24]

The most efficient method for the synthesis of racemic plasmenylcholines (52), an important class of glycerophospholipids, requires only six steps beginning from the inexpensive starting materials solketal or glycerol and acrolein. This method may also be applicable to the synthesis of chiral plasmenylcholines (Figure 13).[25]

A series of phospholipid analogues (53)–(56) have been prepared and evaluated for their water solubility and inhibition of PLC_{BC}. Their water solubility was enhanced by shortening the acyl side chains, reducing the number of acyl side chains, and by the introduction of a hydroxyl group on the termini of the acyl side chains. The key structural feature that conferred inhibitory activity on

the compounds was the replacement of the two non-bridging oxygen atoms of the phosphodiester group with sulfur atoms (Figure 14).[26]

Practical and versatile routes have been developed to produce structurally related phospholipids that are conformationally restricted or flexible (57) and (58), respectively. The conformationally restricted structures have a cyclopropyl ring in the interfacial region of the phospholipids (Figure 15).[27]

(R)- and (S)-enantiomers of novel lysophosphatidylcholine analogues (59) and (60) have been synthesized from commercially available L- and D-serine as starting materials by a short and efficient method (Scheme 10). These newly designed and prepared lyso PC analogues exhibited much enhanced hyphal transition inhibitory activity against Candida species as compared to the natural lyso PC.[28]

The synthesis and biological activities of sphingosine-1-phosphate stereoisomers and analogues have been reported, e.g. D-erythro-S1P (61) (Figure 16).[29,30]

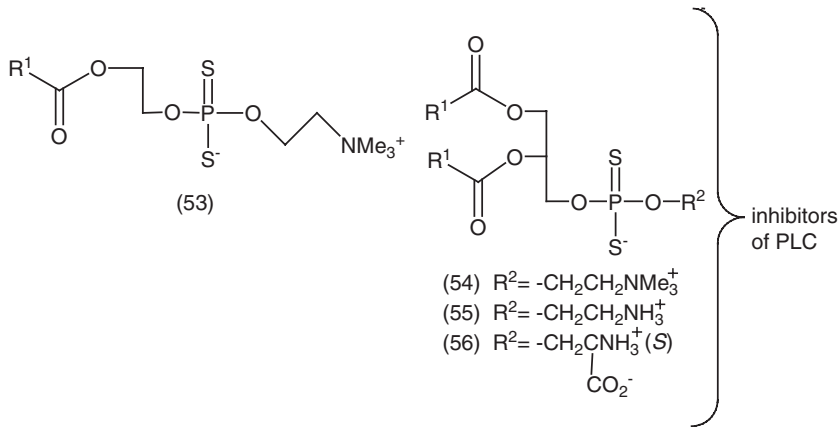


Figure 14

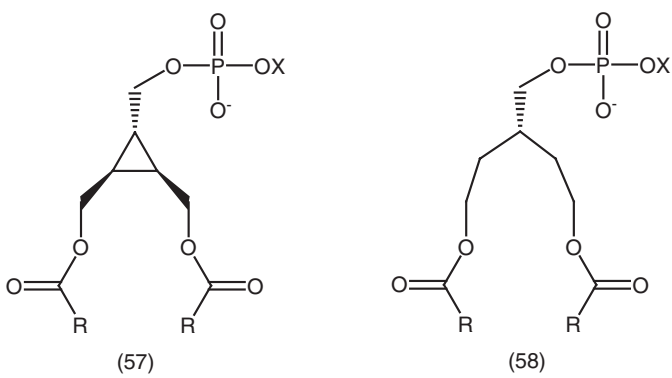


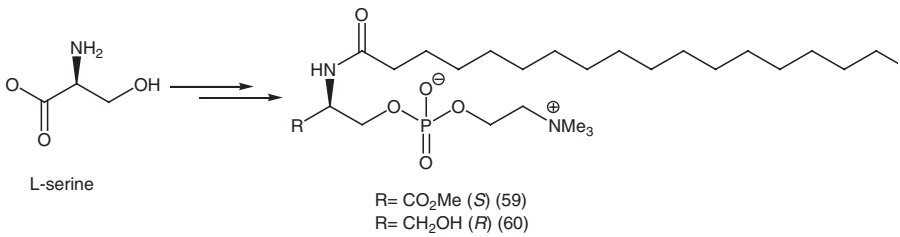
Figure 15

Another report involves the first total synthesis of two photoactivatable analogues of the growth-factor-like mediator sphingosine-1-phosphate (62) and (63) and their differential interaction with protein targets.[31] Benzyl or cyanoethyl phosphochloroamidites (64) and (65) and D-mannose (66) are convenient starting materials for the preparation of a wide range of α-D mannosylphosphate serine derivatives (67) a new class of synthetic glucopeptides (Scheme 11). The best results were obtained with serine derivatives modified by amino protecting or masking groups that provide favorable hydrogen bonding.[32]

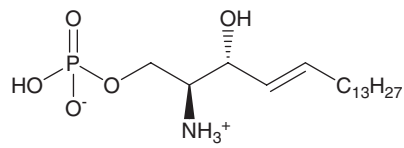
Three 1-(2-nitrophenyl)ethyl phosphoroamino acid building blocks (68), (69) and (70) for solid-phase peptide synthesis have been described (Figure 17).[33]

A new straightforward method of synthesis of dendrimers, using two branched monomers (CA_2 and DB_2) has been desribed (Figure 18).[34]

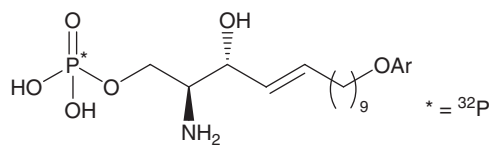
A new illustration of the strong synthetic interest in compounds possessing the P=NP=X (X = O,S) group has been reported. Besides its reactivity with

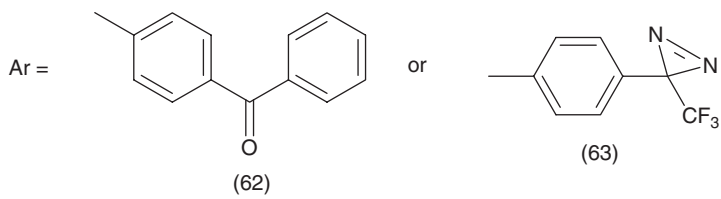


Scheme 10



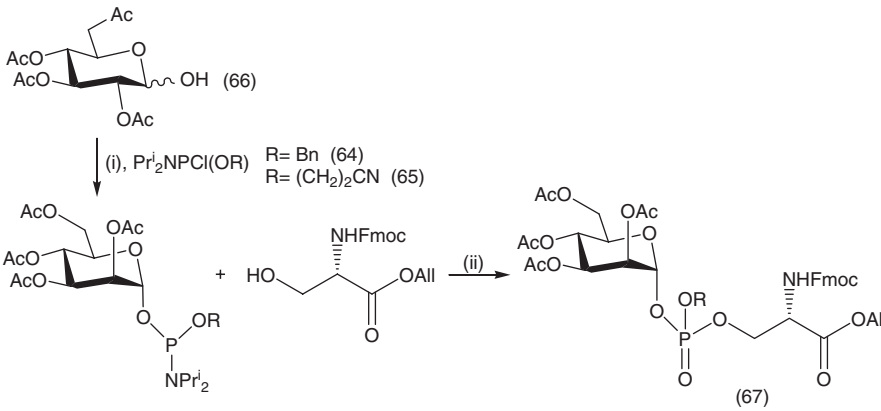
D-*erythro* S1P (61)





(62) (63)

Figure 16



Reagents: (i) DIPEA, CH_2Cl_2; (ii) 1*H*-tetrazole, CH_3CN followed by addition of Bu^tOOH

Scheme 11

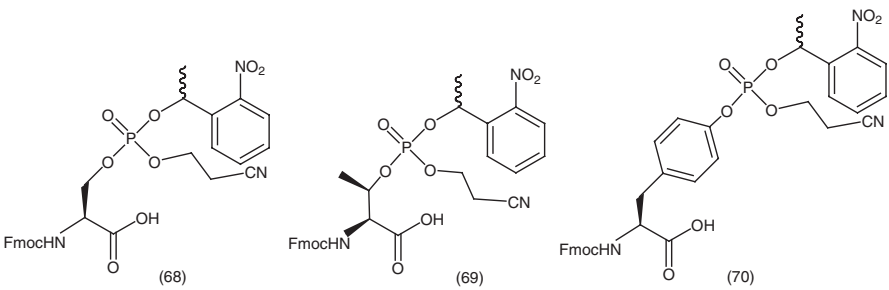


Figure 17

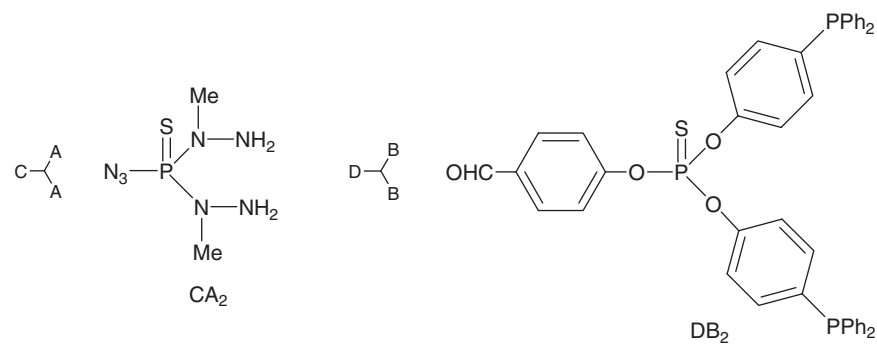


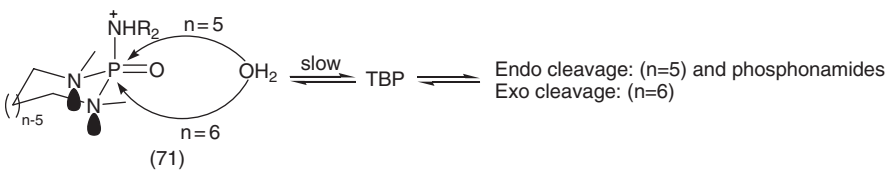
Figure 18

electrophiles, this group is able to activate vinyl groups when included in heterohexatriene $H_2C{=}CHP(R)_2{=}NP(R^1)_2{=}X$ linkage. It has been shown that this linkage reacts readily and cleanly with variously functionalized primary or secondary amines and methylhydrazine.[35]

2.2 Reactions of Phosphoric Acids and Their Derivatives. – Numerous investigations of phosphate ester hydrolysis continue to be reported. The hydrolysis between $1.5 < pH < 4$ of five- and six-membered cyclic phosphoramides (71) has been followed by UV and ^{31}P NMR spectroscopy. Small differences in hydrolysis reactivity for $n = 5$ and $n = 6$ constitutes evidence for syn lone pair catalysis. The product ratios from the hydrolysis shows that in the five-membered rings the main product is the one produced by endocyclic cleavage; meanwhile, in the six- membered cyclic phosphoramide the kinetic product is the one produced by exocyclic cleavage. The syn orientation of two electron pairs on nitrogen stabilizes the transition state of water approach to the phosphoramides by *ca*. 3 kcal/mol^{-1} when compared to the orthogonal attack. (Scheme 12).[36]

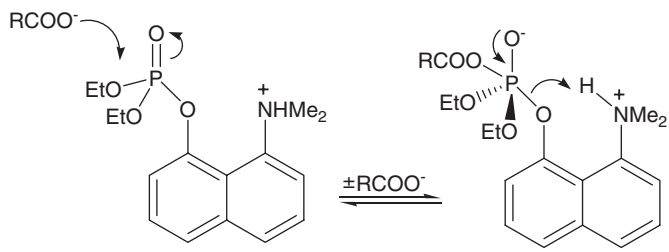
The hydrolysis of diethyl 8-dimethylaminonaphthyl-1-phosphate (72) is catalysed by the neighboring dimethylammonium group, with a rate acceleration, compared with diethyl naphthyl-1-phosphate, of almost 10^6. The reaction is catalysed by oxyanion nucleophiles, and it has been shown that a common nucleophilic mechanism, enhanced by general acid catalysis by the neighbouring dimethylammonium group, accounts for all the observed reactions. The efficiency of general acid catalysis depends on the extent of negative charge development on the leaving group oxygen in the transition state for P–O cleavage, and the strength of the intramolecular hydrogen bond in reactant and transition state. (Scheme 13).[37]

The hydrolysis of the phosphate monoester of 8-(dimethylamino)-1-naphthol (73), involves nucleophilic attack by oxyanions on a phosphate monoester



(71)

Scheme 12

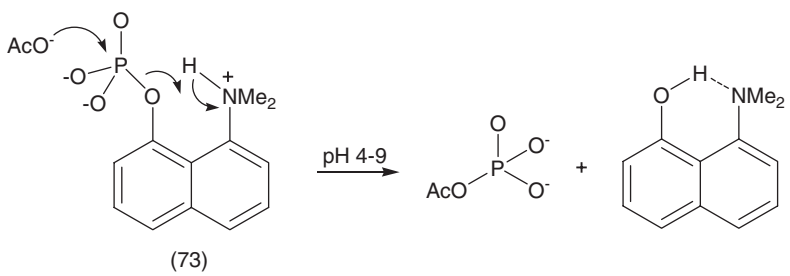


(72)

Scheme 13

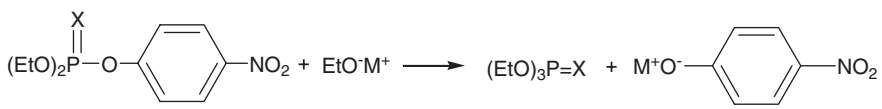
dianion. This is a system known to support efficient intramolecular general acid catalysis (Scheme 14).[38] New fluorescent probes have been synthesized for monitoring the cleavage of phosphodiesters and of carboxylic esters.[39] Significant and differential acceleration of the dephosphorylation of the insecticides, paraoxon (74) and parathion (75), caused by alkali metal ethoxides has been observed. Paraoxon (74) is *ca.* 20–30 times more reactive than parathion (75) toward dissociated EtO^- but *ca.* 2×10^3 times more reactive toward ion-paired EtO^-Li^+ in anhydrous EtOH (Scheme 15).[40]

It was found that La^{3+}-catalysed methanolysis of hydroxy-p-nitrophenyl phosphate (HPNPP) (76) is a model for the RNA transestrification reaction (Scheme 16).[41] The same authors proposed catalytic methanolysis promoted by La^{3+} as a new method for controlled decomposition of paraoxon (74) (Scheme 17). They found that methanolysis of (74) promoted by $La(OTf)_3$ ($Tf{=}OS(O)_2CF_3$) in a methanol medium is billion-fold accelerated.[42] Investigation of the reaction of oximate α-nucleophiles with diisopropylphosphorofluoridate (DFP) (77) and two model phosphonates (78) and (79) has been



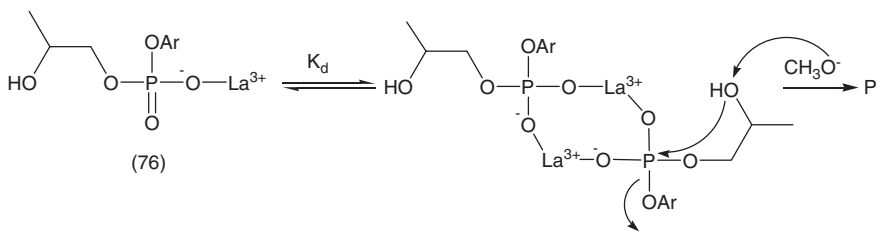
(73)

Scheme 14



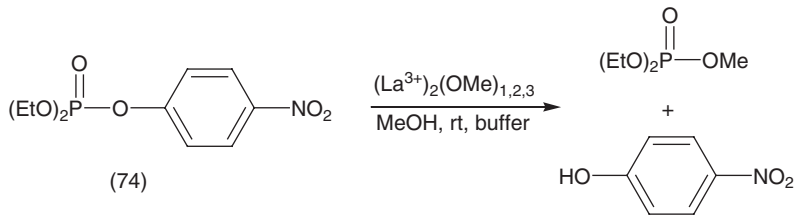
X= O (74), X= S (75), M= Li, Na, K

Scheme 15

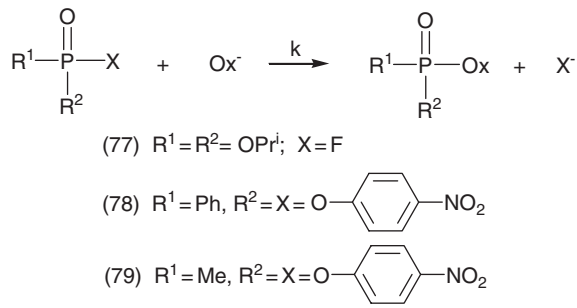


(76)

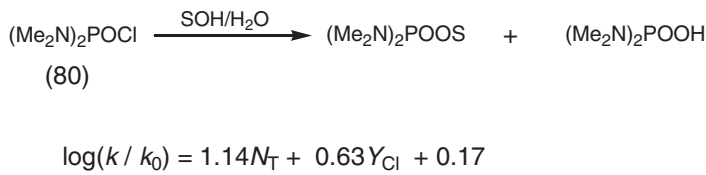
Scheme 16



Scheme 17



Scheme 18



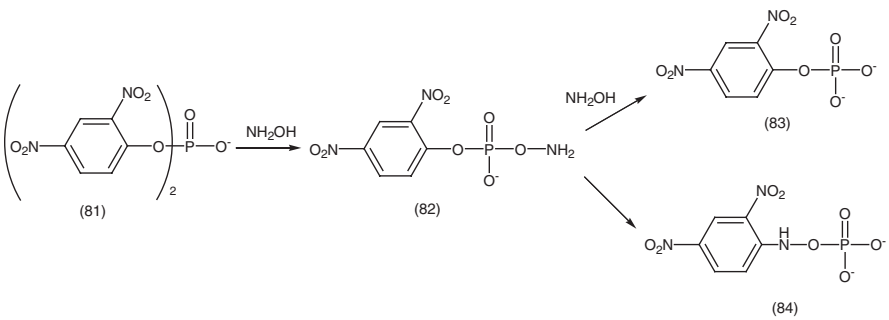
Scheme 19

revealed either a leveling off in reactivity or a bell-shaped behavior in accordance with a critical decoupling of desolvation and bond formation. The relevance of these results to detoxification is also emphasized (Scheme 18).[43]

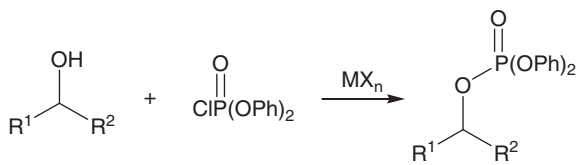
A detailed study of the specific rates of solvolysis of N,N,N′,N′-tetramethyldiamidophosphorochloridate (80) (TMDAPC) with analysis in terms of the extended Grunwald-Winstein equation has been reported (Scheme 19). The stereochemistry of nucleophilic attack at tetracoordinate phosphorus was also discussed.[44] The initial reaction of bis (2,4-dinitrophenyl) phosphate (BDNPP) (81) with hydroxylamine involves release of 1 mol 2,4-dinitrophenoxide ion and formation of a phosphorylated hydroxylamine (82), which reacts readily with further NH_2OH, giving the monoester (83). The intermediate (82) also breaks down by two other independent reactions; one involves intramolecular displacement of aryloxide ion (83) and the other involves migration of the 2,4-dinitrophenyl group from O to N and formation of phosphorylated 2,4-dinitrophenylhydroxylamine (84) (Scheme 20).[45]

Various Lewis acids MX_n have been evaluated as catalysts for the phosphoryl transfer, the most efficient being $TiCl_4$ (Scheme 21). Application of this methodology to the phosphorylation of representative target alcohols is presented.[46]

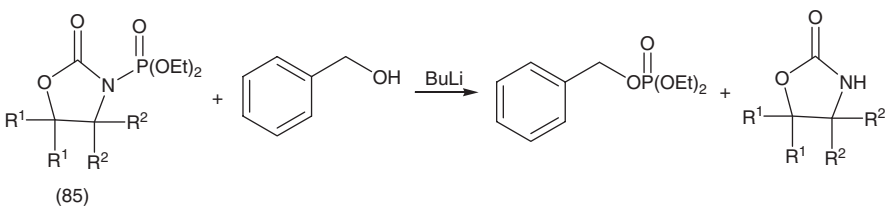
A number of N-phosphoryl oxazolidinones (85) have been prepared and developed as alternative phosphorylating agents suitable for a variety of representative alcohols. (Scheme 22). The 5,5-diphenyl oxazolidinones were determined to be the best framework for such reagents.[47] The oxathiaphospholane methodology has been applied to the synthesis of N-phosphorothioylated amino acids as well as O-phosphorothioylated derivatives of hydroxyamino acids, *i.e.*, serine, threonine and tyrosine. N- and O-(2-thiono-1,3,2,-oxathiaphospholanyl) amino acids methyl esters (86) were prepared in high yield by the reaction of amino acids esters (87) with 2-chloro-1,3,2-oxathiophospholane (88) in pyridine in the presence of elemental sulfur. Compounds (86) were converted into the corresponding methyl or benzyl phosphorothioamides (89) by DBU-assisted treatment with methyl or benzyl alcohol. The DBU-assisted oxathiaphospholane ring opening process did not cause any measurable



Scheme 20



Scheme 21

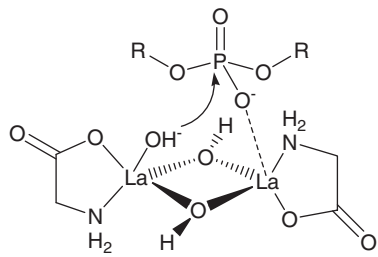


Scheme 22

C-racemization of phosphorothioylated/phosphorylated amino acids (Scheme 23).[48] An oxathiaphospholane approach to one-pot phosphorothioylation of isoprenoid alcohols such as allyl, geranyl, isopentenyl, citronellyl, farnesyl, and phytyl alcohols has also been reported (Scheme 24).[49]

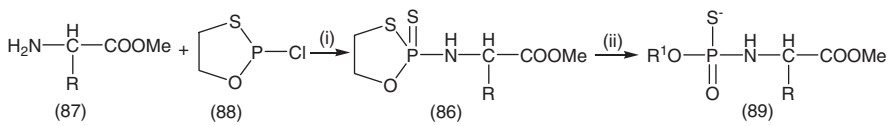
Non-enzymatic systems were used to show that vibrational spectroscopy can provide a sensitive probe of the environment of the phosphoryl group, a group commonly transferred in enzymatic catalysis. The results described provide a foundation for understanding both the bonding behavior of monosubstituted phosphates and the electrostatic environment of the phosphoryl group, including that within enzyme active sites.[50] Physical and kinetic analysis of the cooperative role of metal ions in the catalysis of 2-hydroxypropyl-4-nitrophenyl phosphate (HPNP) cleavage by a dinuclear Zn(II) complex (90) have been reported.[51] Non-coordinating amino H-bond donors adjacent to a zinc (II)-center enhance the affinity of phosphates to the zinc (II) center (Scheme 25).[52]

Unusually high phosphodiesterolytic activity of La(III) hydroxide complexes stabilized by glycine derivatives (91) that surpass all currently known catalytic systems based on trivalent lanthanides was observed (Figure 18a).[53]



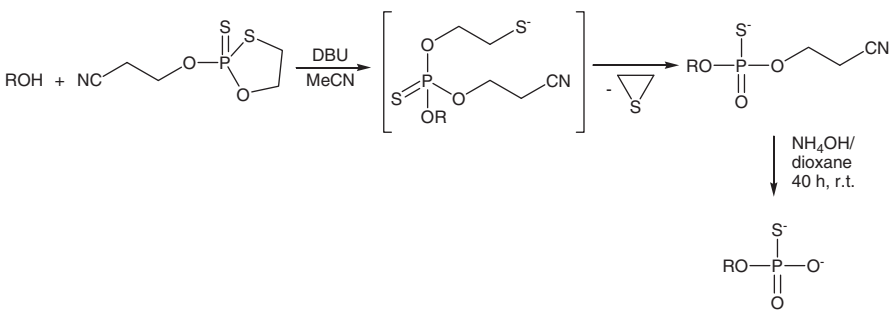
(91)

Figure 18a

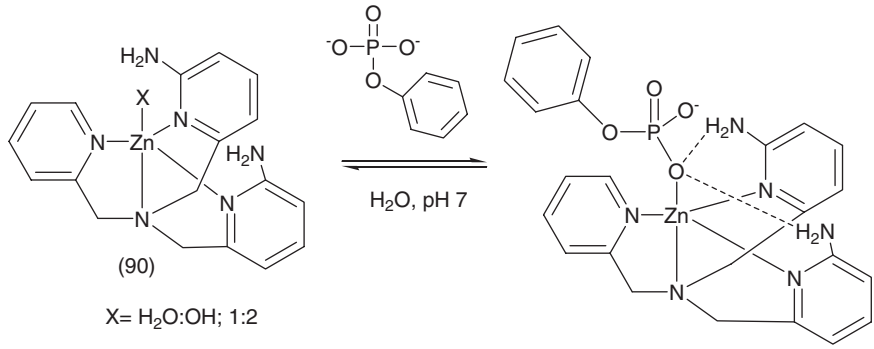


Reagents: (i) S_8, pyridine; (ii) R^1OH, DBU

Scheme 23



Scheme 24



Scheme 25

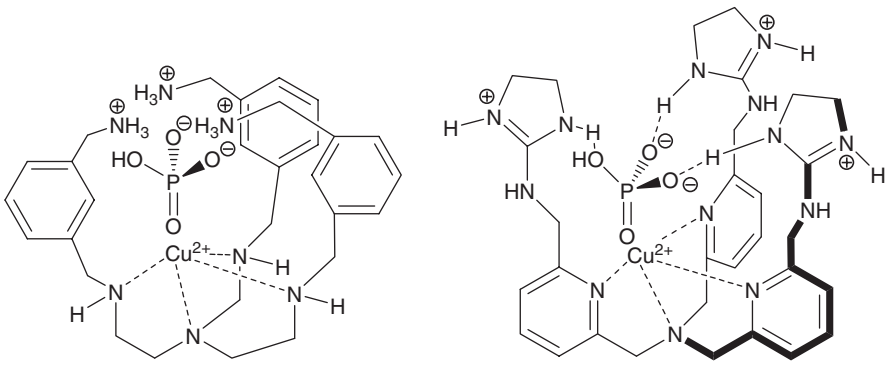
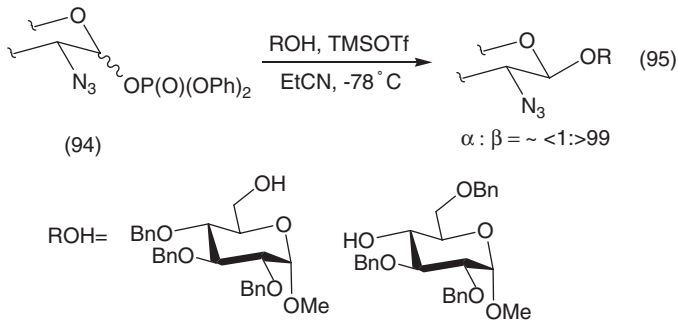


Figure 19

The energetics of phosphate binding to ammonium- and guanidinium-containing metallo-receptors in water has been studied. It was proposed that the binding of the host-guest pairs proceeds through ion-pairing interactions between the charged functional groups on both the host and the guest. The differences in the entropy and enthalpy driving forces for the ammonium (92)- and guanidinium (93)- containing host were postulated to come primarily from differences in the solvation shell of these two groups (Figure 19).[54]

TMSOTf – promoted glycosidations of 2-azido-2-deoxyglycopyranosyl diphenyl phosphates (94) with a variety of glycoside alcohols afforded 1,2-*trans*-β-linked disaccharides (95) in high yield. Furthermore, these reactions proceed with the highest levels of stereoselectivity reported to date for this type of glycosidation (Scheme 26).[55] Organophosphorus and nitro-substituted sulfonate esters of 1-hydroxy-7-azabenzotriazole (96), (97) and (98) are highly efficient fast-acting peptide coupling reagents (Figure 20).[56]



Scheme 26

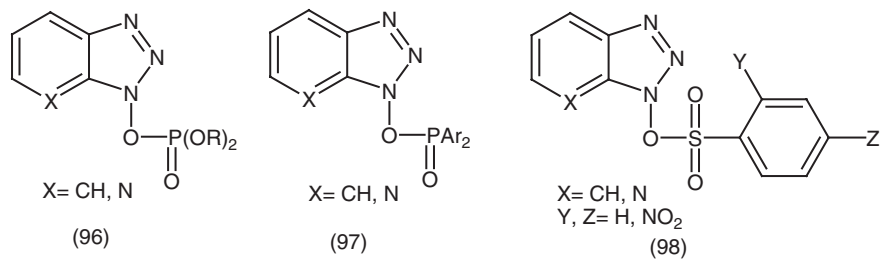


Figure 20

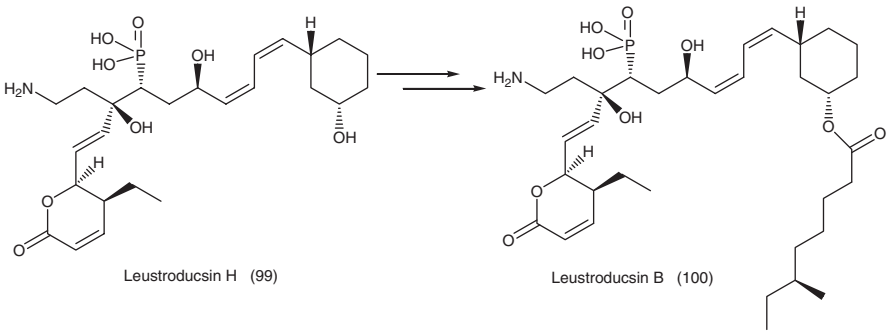


Figure 21

Chemical transformation of Leustroducsin H (99) to Leustroducsin B (100) having various biological activities has been successfully accomplished in 11 steps including enzymatic hydrolysis of phosphate ester (Figure 21).[57]

Zn-chelated glycine ester enolates (101) are highly efficient nucleophiles with respect to Michael acceptor phosphate (102) in the synthesis of trans-methoxycarbonylcyclopropyl- and cycloacetyl-glycines (103) by domino sequences of Michael additions and subsequent ring closures. They react to give the anti

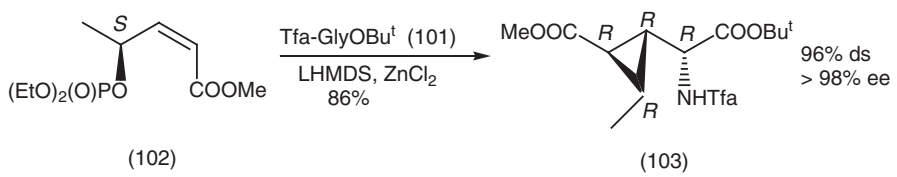
isomers with high yields and excellent diastereo- and enantio-selectivities (e.g. Scheme 27).[58]

A highly regio-, diastereo-, and enantioselective desymmetrisation of five-, six-, and seven-membered meso-cyclic allylic bis-diethyl phosphates (104), (105) and (106), was achieved with diethylzinc using catalytic amounts of $[Cu(OTf)]_2$, C_6H_6 and phosphoramidite ligands (107). The addition of diethylzinc to cyclopentene, cyclohexene, and cycloheptene bis-diethyl phosphates, provided allylic monophosphates (108), (109) and (110) with enantiomeric excess of up to 87, 94 and >98%, respectively (Scheme 28).[59]

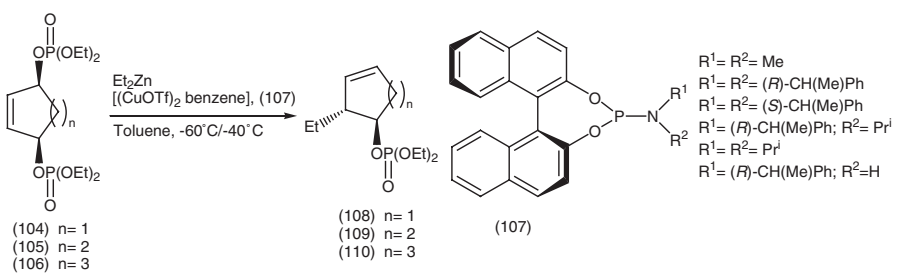
Enantiomerically enriched β-(diphenylphosphatoxy)nitroalkanes (111) undergo radical ionic fragmentation induced by tributyltinhydride and AIBN to give alkene radical cations in contact radical ion pairs. These ion pairs are trapped intramolecularly by the amino groups to give pyrrolidines (112) and piperidines with significant enantioselectivity (~60% ee), indicative of cyclization competing effectively with equilibration within the ion pairs (e.g. Scheme 29).[60] The diastereoselective synthesis of an optically pure spiroketal (113) via an intramolecular tandem hydrogen abstraction reaction, promoted by an alkoxy radical, has been reported (Scheme 30). This methodology can be applied to the generation of radical cations under non-oxidizing conditions.[61]

It was shown that both the nature of the substituent at phosphorus atom and the base used in the deprotonation step have a significant influence on the alkylation of perhydro 1,3,2-benzoxaphosphorinane-2-oxides (114) derived from (−)-S-benzylamino menthol (Scheme 31).[62]

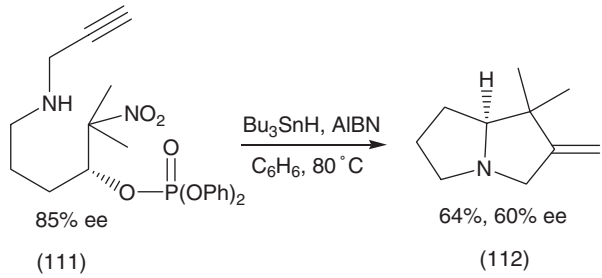
Palladium-catalysed [3,3] sigmatropic rearrangement of (allyloxy)- imino-diazaphospholidines (115) and (116), involving transposition of C–O and C–N



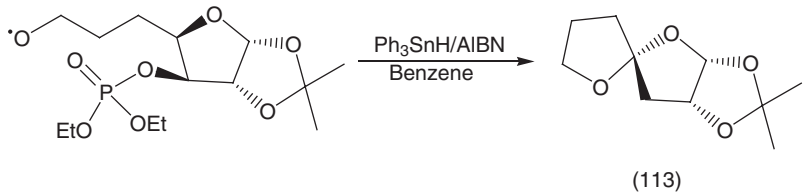
Scheme 27



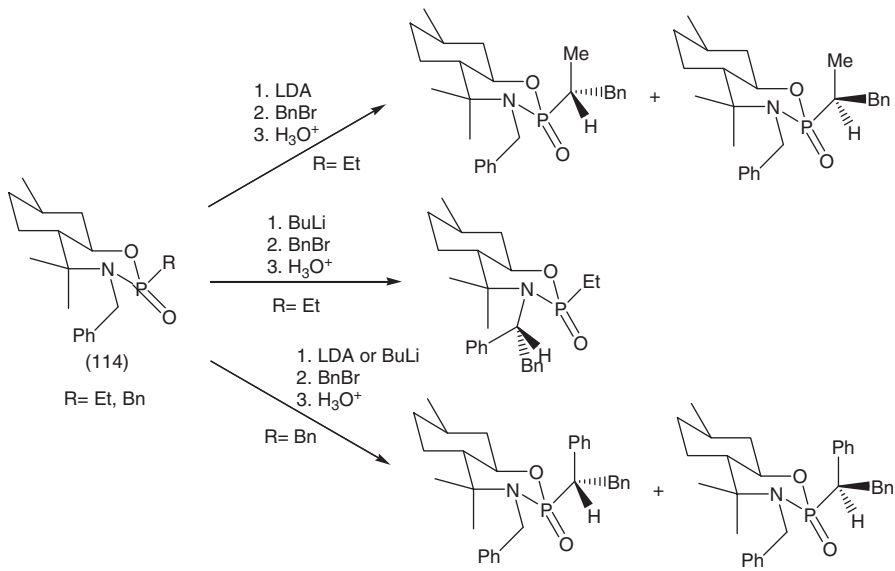
Scheme 28



Scheme 29



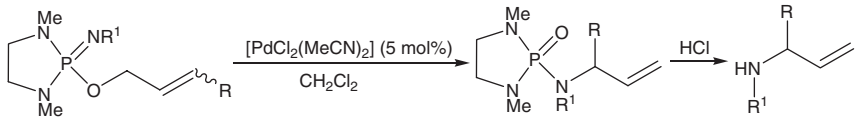
Scheme 30



Scheme 31

functionality, has been developed for the synthesis of allylic amines (117) and tosylamines (118) via phosphoroamides (119) and (120) (Scheme 32).[63]

The same phosphorimidate phosphoramidate rearrangement has been applied to the preparation of allylic amines starting from the phosphoroimidate (121) (e.g. Scheme 33).[64]

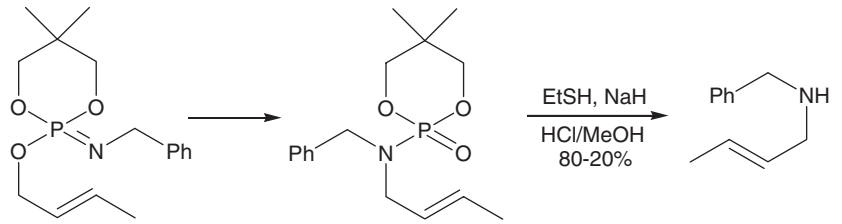


(115) R^1= P(O)(OPh)$_2$
(116) R^1= Ts

(119) R^1= P(O)(OPh)$_2$
(120) R^1= Ts

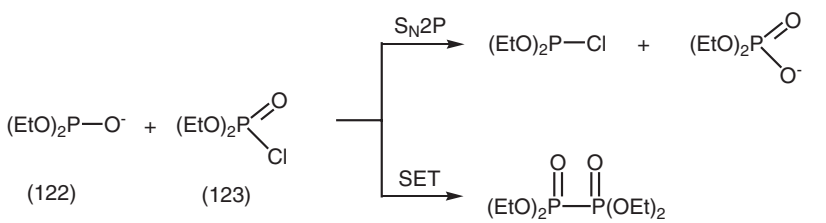
(117) R^1= H$^+$ HCl
(118) R^1= Ts

Scheme 32



(121)

Scheme 33



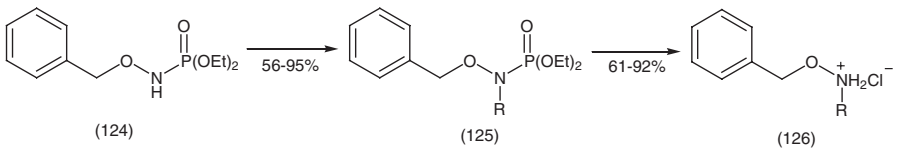
(122) (123)

Scheme 34

Alkali metal salts of diethyl phosphite (122) act as nucleophiles or electron donors in their reaction with diethyl phosphorochloridate (123). Evidence was provided that formation of the direct P(IV)-P(IV) bond proceeds via a single electron transfer process (SET) from phosphite anion to phosphorochloridate (Scheme 34).[65]

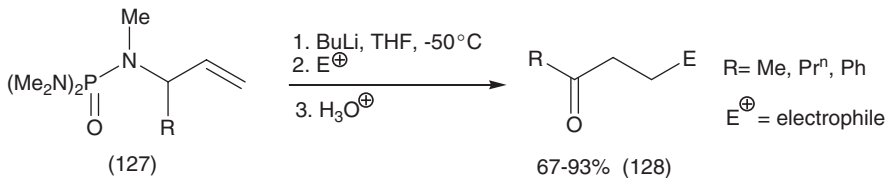
Readily available N-(diethoxyphosphoryl)-benzylhydroxyamine (124) with primary and secondary halides as well as with bis-halides under basic conditions lead to N-alkylated derivatives (125). Facile dephosphorylation afforded appropriate N-substituted O-benzylhydroamines (126) (Scheme 35).[66]

The lithiated anions derived from (1-alkyl-) or (1-phenyl-2-propenyl)- phosphoric triamides (127) can be used as new ketone homoenolate equivalents. The proposed route gives various ketones (128) using an umpolung strategy in contrast to other known routes (Scheme 36).[67] It was shown that isocyanatophosphoryl dichloride (129) is a convenient reagent for the introduction of a carbamoyl group into molecules with π-excessive heterocycles and enamine groups (Scheme 37).[68]

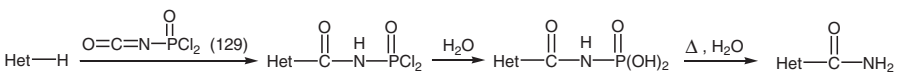


R= Et, Me, Pri, Bu, Allyl, Bn, $(CH_2)_3Br$, $(CH_2)_4Br$, $(CH_2)_3P(O)(OEt)_2$

Scheme 35

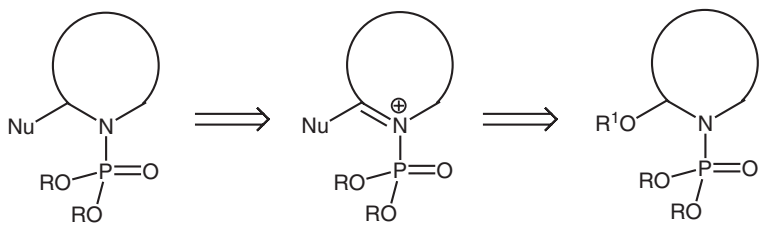


Scheme 36



Het = indoles, pyrroles, indolizines, enamines

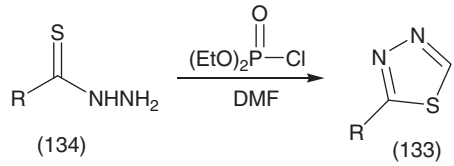
Scheme 37



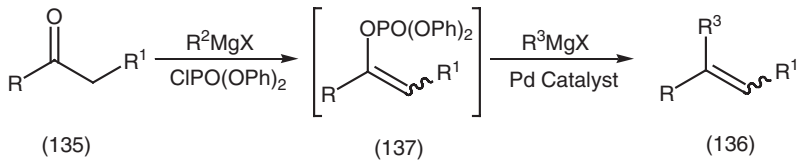
Scheme 38

The synthesis of allylic and non-allylic cyclic N-phosphoryliminium ions (130) based on N,O-acetals (131) and their application in C-C bond formation (132) has been reported. In addition, the influence of a chiral auxiliary on the phosphorus atom has been also investigated (Scheme 38).[69]

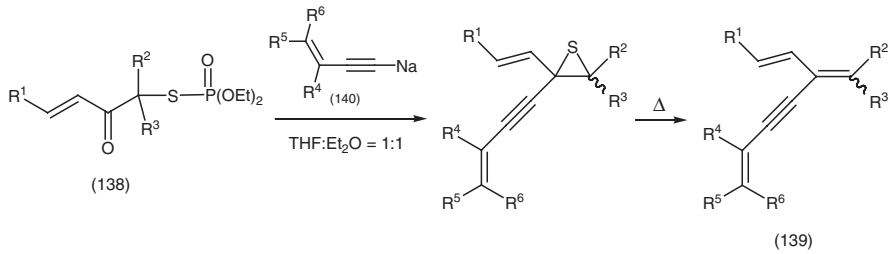
A new cyclising reagent is proposed for the synthesis of 5-unsubstituted 1,3,4-thiadiazoles (133). The latter are formed in good yield by the reaction of thiohydrazides (134) with diethyl chlorophosphate (Scheme 39).[70] A useful, one-pot protocol has been developed for the conversion of enolizable ketones (135) to alkylated or arylated olefins (136) by Pd-catalysed cross coupling of *in-situ* generated enol phosphates (137) with Grignard reagents (Scheme 40).[71]



Scheme 39



Scheme 40

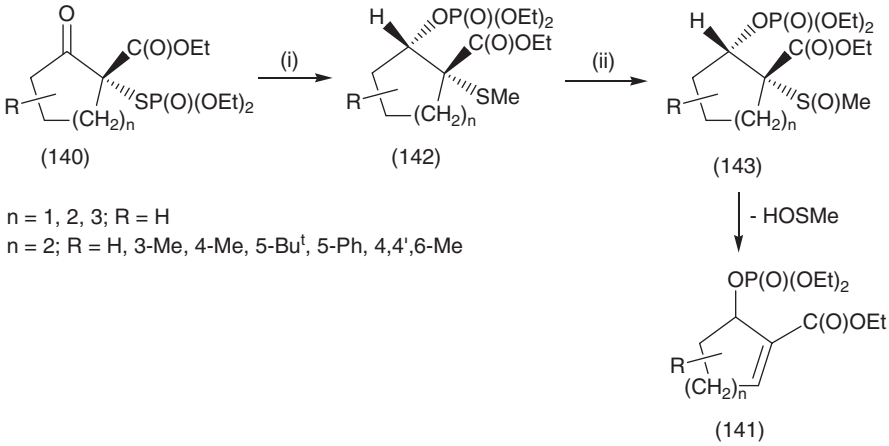


Scheme 41

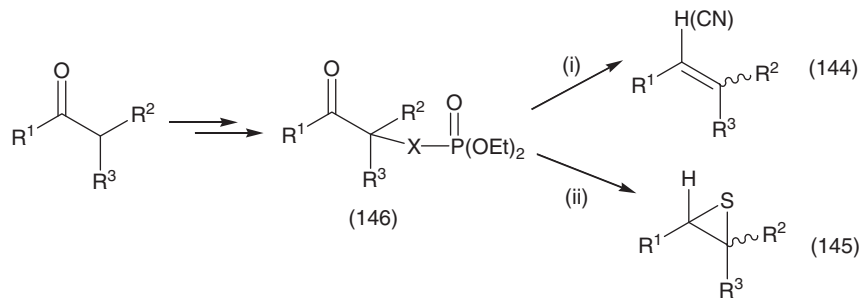
Further examples of the applications of thiophosphates in organic synthesis have been reported. The methodology based on intermediate thiophosphates (138) constitutes a general and convenient route to a wide range of conjugated non-linear trienynes (139). Thiophosphate (138) reacts readily with sodium derivative of dienynes to form (139) in one operation via single and double carbon-carbon bond formation (Scheme 41).[72]

Several new thiophosphates (140) have been prepared. They are useful precursors of novel cyclic compounds (141) which have similar structures to Baylis-Hillman adducts. The synthetic approach to these compounds involves reduction of the carbonyl group by $NaBH_4$ in the presence of methyl iodide which exhibit full axial selectivity. Subsequent oxidation of intermediate sulphides (142) to sulphoxides (143) and cis elimination of the latter affords the desired compounds (141) of defined stereochemistry (Scheme 42). Multifunctionality of the compounds makes them attractive for numerous further important transformations.[73]

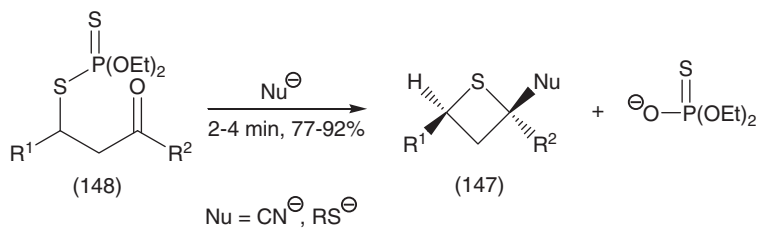
A convenient, general and stereoselective synthesis of trisubstituted and tetrasubstituted alkenes (144), which may contain a cyanide function, as well as trisubstituted episulphides (145) have been elaborated. The method makes use of readily available thiophosphates and selenophosphates (146) (Scheme 43).[74]



Scheme 42



Scheme 43



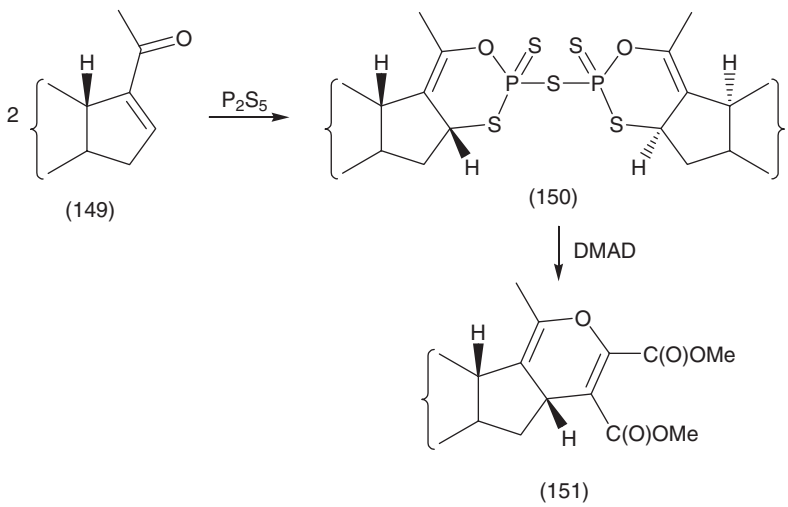
Scheme 44

An expedient solvent-free synthesis of functionalized thietanes (147) by nucleophilic-induced cyclization of phosphorodithioates (148) has been reported (Scheme 44).[75]

The reaction of 16-dehydropregnenolone acetate (16-DPA) (149) with P_4S_{10} afforded a novel adduct 16-DPA-P_2S_5 (150). The adduct undergoes

[4+2]-cycloaddition with alkyne dienophiles to give steroidal (17,16-c) pyrans (151) under thermal conditions (Scheme 45). The reaction provides a new strategy for the activation of conjugated enones towards unreactive dienophiles. [76] Triaryl phosphites selectively reduce aryl selenoxide (152) to selenides (153) via a concerted mechanism for the oxygen transfer from Se to P (Figure 22).[77] Regio- and stereoselective ring-opening reaction of epoxides (154) using organic dithiophosphorus acids (155) as nucleophiles constitutes a practical method for the synthesis of β-hydroxymercaptans (156) (Scheme 46). Furthermore, an enantioselective ring-opening reaction was accomplished with an ee value of 73% in the presence of a chiral (salen)Ti(IV) complex (157).[78]

The functionalization of the periphery of dendrimers continues to attract attention because the properties and applications of these compounds mainly depend on the type of functional end groups they bear. The functionalization of phosphorus-containing dendrimers was easily achieved through thioacylation reactions involving new dendrimers capped with dithioester end groups and various functionalized amines. These reactions were successfully applied to the first generation (12 end groups) (158) and the third generation of the dendrimer (48 end groups) and allowed their functionalization by various amines, alcohols, glycols and azides (e.g. Scheme 47).[79]



Scheme 45

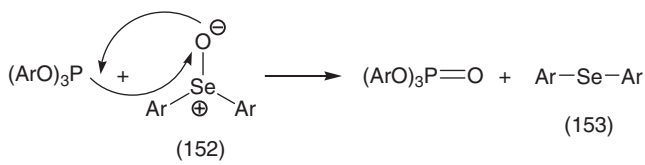
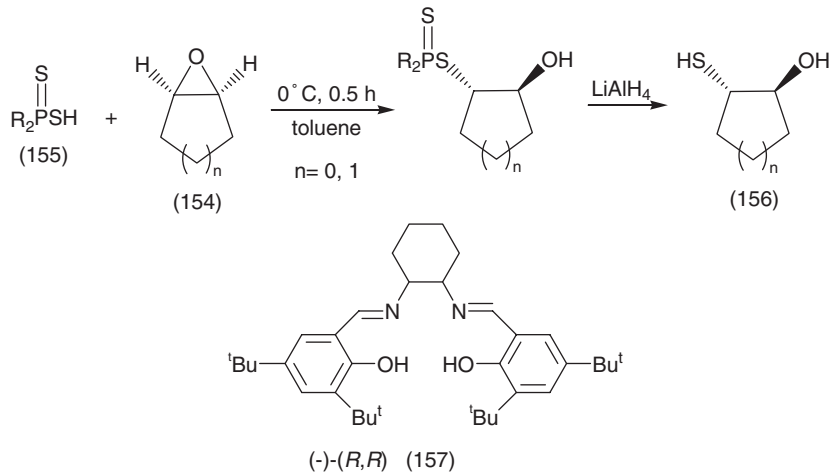
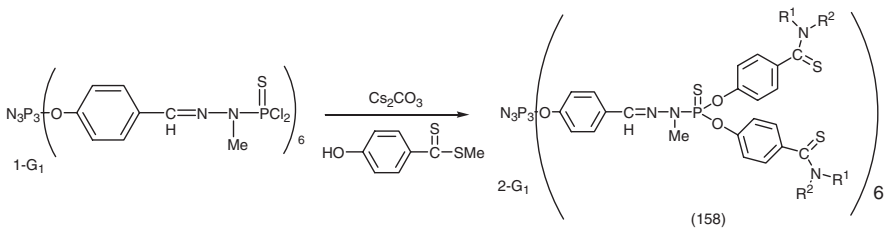


Figure 22



Scheme 46

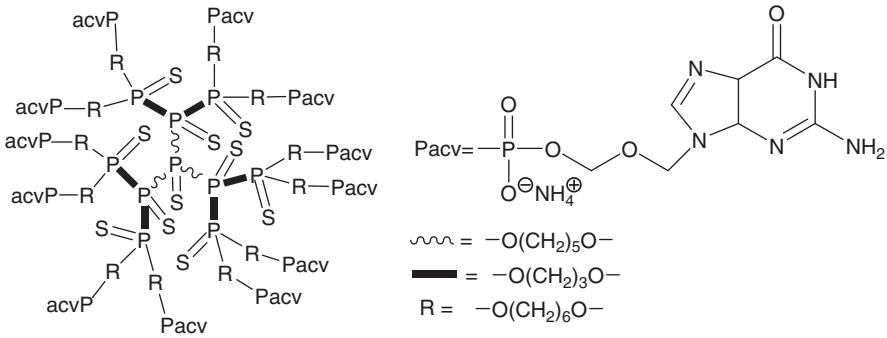


Scheme 47

Analysis of 24 phosphorus-containing dendrimers and dendrons allows conclusions to be drawn about the thermal stability of these compounds. The internal structure of these dendrimers is stable up to very high temperature. The most important factor concerning their stability is the nature of the end groups.[80] Acyclovir was successfully grafted on the surface of thiophosphate dendrimers via thio- and phosphodiester linkages, providing water-soluble prodrug candidates (159) (Figure 23).[81]

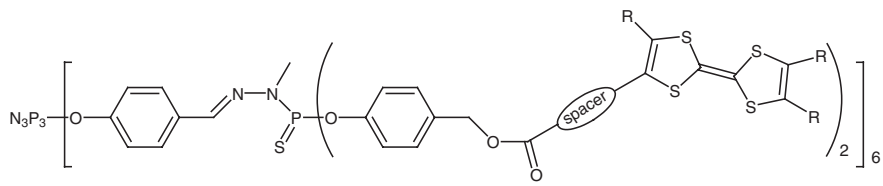
In four dendrimers terminated by 12 electroactive tetrathiafulvalenyl substituents (160), the three dimensional character of the inter- and intra-dendrimeric charge and electron transfer, and hence of the electroconductivity, has been assessed by examination of the electronic spectra of their corresponding neutral state and cation, radical, dication, and mixed-valence salts, including a closed – shell anion (Figure 24).[82]

The N_3 groups linked to thiophosphoryl functions are good leaving groups for regioselective nucleophilic substitutions on macromolecules such as phosphorus macrocycles (161) (e.g. Scheme 48).[83]



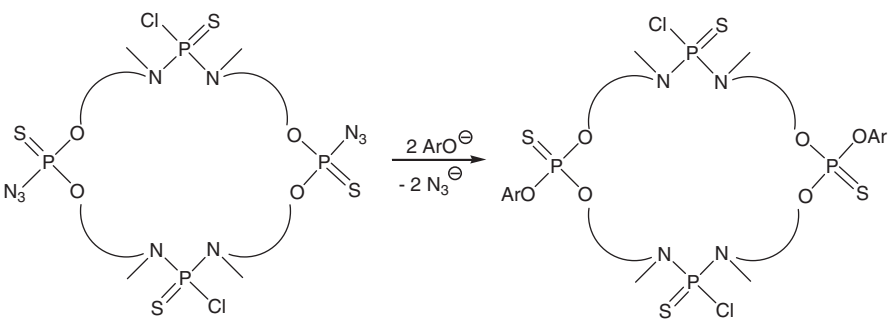
(159)

Figure 23



(160)

Figure 24



(161)

Scheme 48

2.3 Selected Biological Aspects. – Water soluble phosphate prodrugs of buparvaquinone (162) and (163) containing a hydroxynaphthoquinone structure, were synthesized and evaluated *in vitro* for improved topical and oral drug delivery against cutaneous and viscelar leishmaniasis. The investigation also showed that buparvaquinone permeation through human skin can be significantly improved by using phosphate prodrugs (Figure 25).[84]

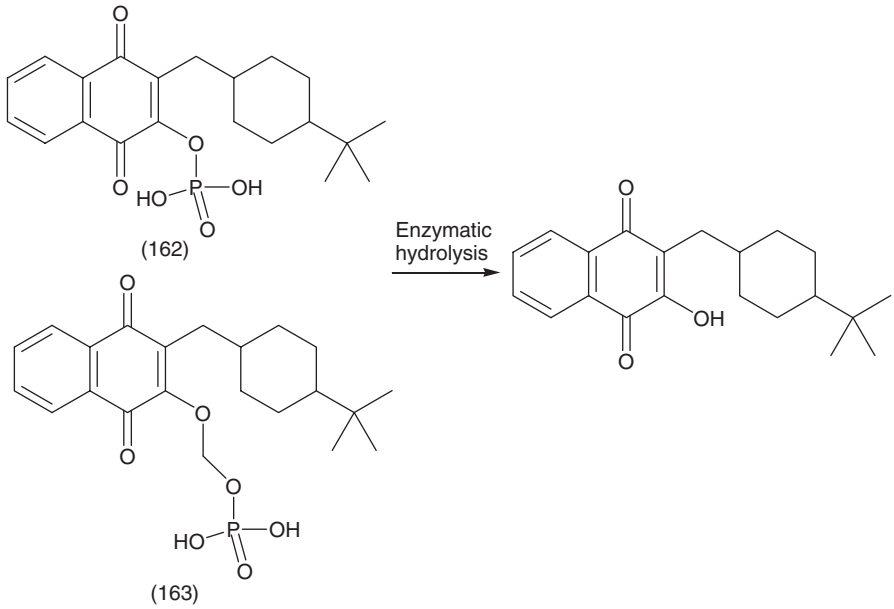


Figure 25

The physiochemical properties of noladin ether (164) were successfully improved by introducing a phosphate moiety to the structure. High water solubility and chemical stability, together with a rapid quantitative enzymatic hydrolysis *in vitro* and the ability to reduce IOP *in vivo*, prove that the phosphate esters (165) and (166) are promising prodrug candidates of endocannabinoid noladin ether (Figure 26).[85]

A superior class of nitroaryl phosphoroamides (167), (168) and (169) as potential prodrugs for nitroreductase-mediated enzyme-prodrug therapy has been developed. These nitroaryl phosphoroamides have low cytotoxicity before reduction and are converted to phosphoroamide mustard or similarly reactive species upon bioreduction. The excellent biological activity of these compounds correlates well with their substrate activity for E coli nitroreductase.[86] A novel series of phosphate esters (170), (171) and (172), small molecule tags with high affinity for serum albumin, reduce clearance and increase the circulating half life of bioactive peptides administered to rabbits (Figure 27) (Figure 28).[87]

A new enantioselective synthesis of both (2R)-OMPT (173) and (2S)-OMPT (174) has been described (Scheme 49). Calcium release assays in both LPA_3-transfected insect Sf9 and rat hapatoma Rh 7777 cells showed that (2S)-OMPT was 5- to 20-fold more active than (2R)-OMPT. Similar results were found for calcium release, MAPK and Akt activation, and IL-6 release in human OVCAR 3 ovarian cancer cell.[88]

Synthetic and biological evaluations of new diadenosine polyphosphate (175) analogues on blood platelet aggregation have been reported. The most active are compounds with sulphur replacing one or both non-bridging oxygens at

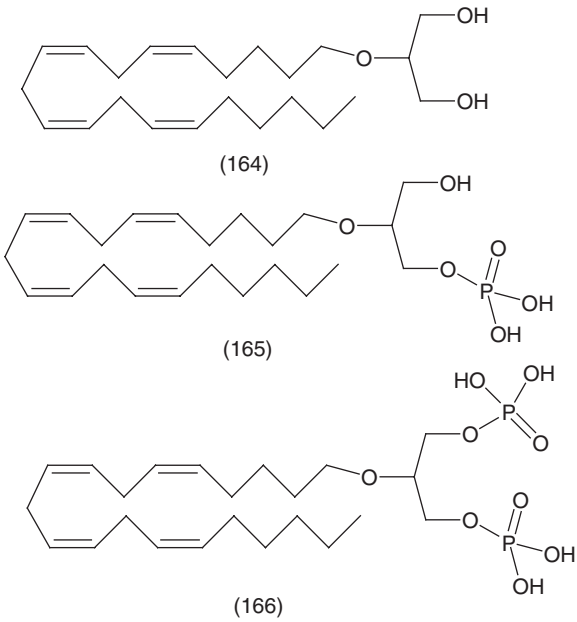


Figure 26

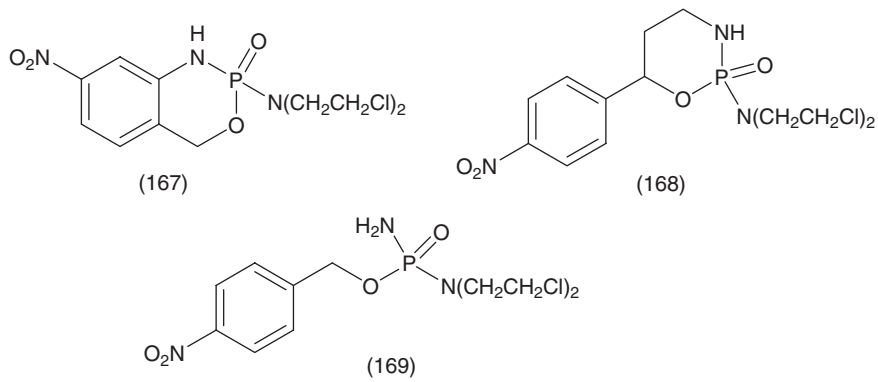


Figure 27

phosphorus bound to adenosyl residues and hydroxymethyl group of bis(hydroxymethyl)phosphinic acid (Figure 29).[89]

cyclo-Saligenyl-mannose-1-monophosphates (176), a new strategy in CDG-1a therapy, have been described.[90] The modified receptor antagonist (177) has been synthesized. This study has resulted also in the discovery of a high-affinity LPA/LPA_3 of (177), which exhibits a K_1 value of 18μM at the LPA_1 receptor and is significantly more potent than (178) at the LPA_3 receptor.[91] It was found that the Z-isomer of triphosphate (179) is a potent competitive inhibitor of

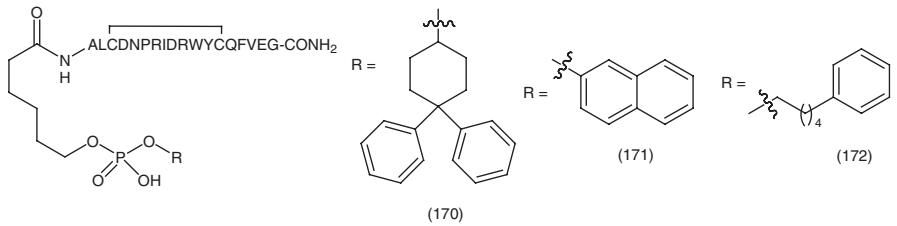


Figure 28

wild-type HIV-1 reverse transcriptase with K_i close to ddATP. The E-isomer (180) is about 30-times weaker (Figure 30) (Figure 31).[92]

A new and efficient route to enantiomerically homogenous lysophospholipid analogues from (S)-1,2,4-butanetriol (181) has given two 3-difluoromethyl substituted analogues of 2-acyl-sn-glycerol-3-phosphate (182). These compounds are migrated-blocked analogues of the labile sn-2 LPA species. It was shown that esters (182) are as fully active as natural LPA (Figure 32).[93]

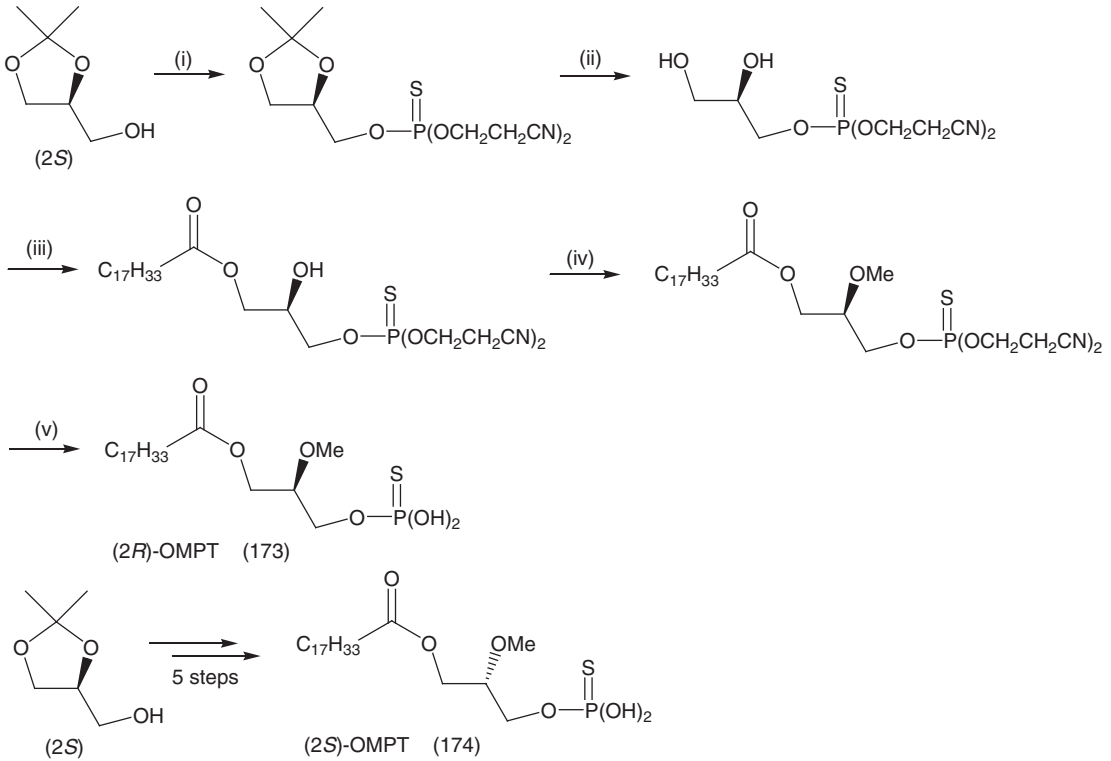
Potent and subtype-selective agonists (183), (184) and (185) for LPA_1 and LPA_3, were developed by using carbohydrates as a core structure.[94] Two fluorescently-labelled, activity-based probes, Probe A and Probe B have been successfully designed and synthesized. They were shown to label selectively different types of phosphatase over other enzymes (Figure 33) (Figure 34).[95]

For the purpose of cancer antineovascular therapy, a novel angiogenesis-targeted peptide, Ala-Pro-Arg-Pro-Gly (APRPG) was attached to hydrophobized polyethylene glycol (distearoylphosphatidylethanolamine [DSPE]-PEG). Liposomes modified (186) with this DSPE-PEG-APRPG conjugate strongly accumulate in tumors of tumour-bearing mice (Figure 35).[96]

3 Phosphonic and Phosphinic Acids

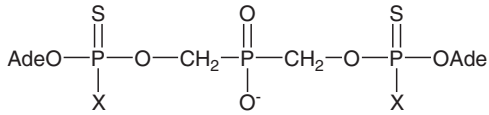
3.1 Synthesis of Phosphonic and Phosphinic Acids and Their Derivatives. – New synthetic approaches to phosphonic and phosphinic acids and their derivatives are still being developed because of their specific biological properties particularly as natural products and as analogues of phosphates, phosphono- and phosphino-peptides, amino-acid analogues and pro-drugs.

3.1.1 Alkyl, Cycloalkyl, Arylalkyl and Related Acids. New selenophosphates, selenophosphorothioates, selenophosphorodithioates and selenophosphorotrithioates are easily generated from readily available starting reagents, by a three or four-step sequence of reactions. These compounds (187) have been used as precursors of the corresponding phosphorus-centered radicals by homolytic cleavage of the P–Se bond. When radicals are produced in the presence of a range of alkenes (188) most of the expected adducts (189) are

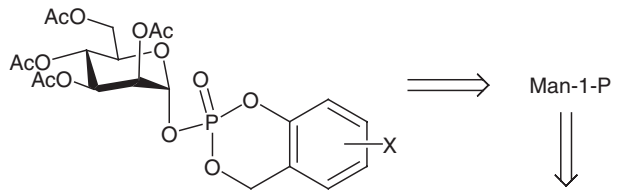


Reagents: (i) $(CNCH_2CH_2O)_2PN(Pr^i)_2$, 1*H*-tetrazole, S,CS_2/pyridine, 86%; (ii) *p*-TsOH, MeOH, 67%; (iii) oleoyl chloride, 2,4,6-collidine, -78 °C, 87%; (iv) $TMSCHN_2$, HBF_4, 58%; (v) Bu^tNH_2, BTMSA, 84%

Scheme 49

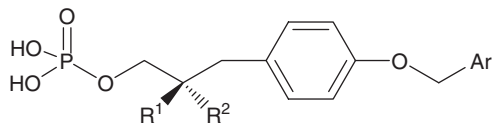


(175)



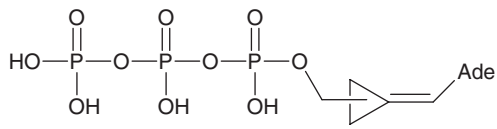
*cyclo*Sal-Man-1-P (176)

Figure 29



(178) R^1 = H; NHC(O)$C_{17}H_{33}$; Ar = Ph (K_i = 137 nM LPA_1)
(177) R^1 = NHC(O)$C_{17}H_{33}$; R^2 = H; Ar = 2-pyr (K_i = 18 nM LPA_1)

Figure 30



(179) *Z*-isomer
(180) *E*-isomer

Figure 31

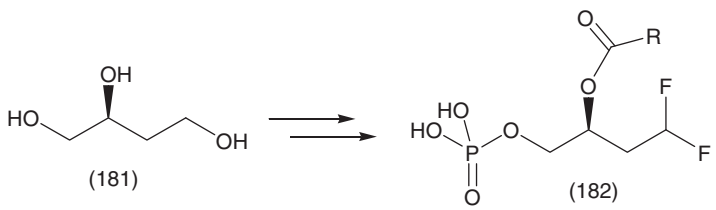


Figure 32

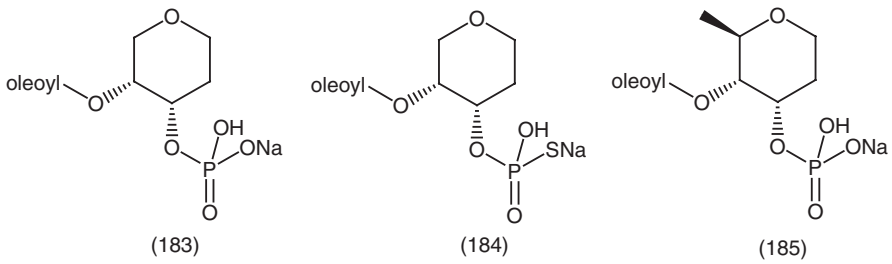


Figure 33

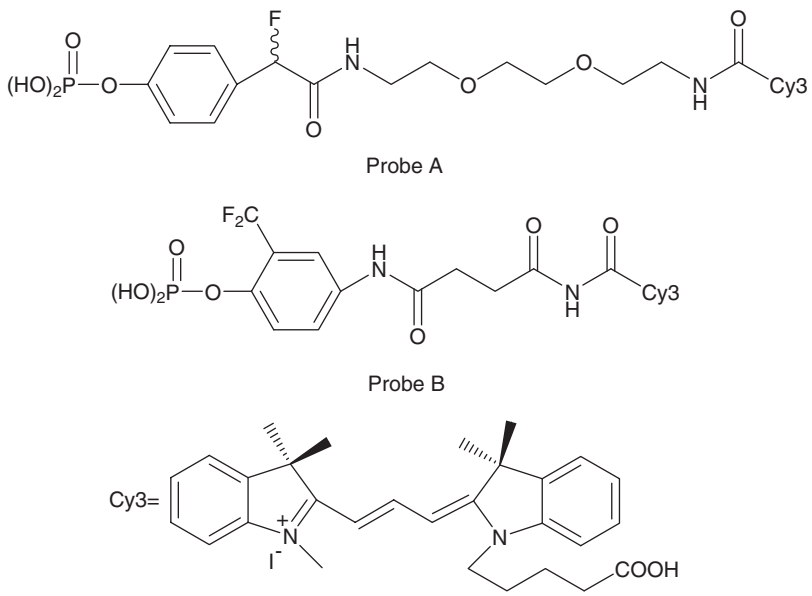


Figure 34

formed in high yields (Scheme 50).[97] AIBN-initiated free radical addition of dialkyl phosphites to various 1,6- and 1,7-dienes and heterodienes containing oxygen or nitrogen atoms (190) affords the corresponding 5- and 6-membered ring carbocyclic and heterocylic derivatives of dialkyl methylphosphonates (191) (Scheme 51).

Similar transformations using diphenylphosphine oxide and diethyl thiophosphite have also been performed.[98] Rhodium prolinate second generation complex Rh_2(S-TISP)$_2$ has been used as a very effective catalyst promoting conversion of dimethyl aryldiazomethyl phosphonates (192) into the stereochemically defined donor/acceptor substituted rhodium carbenoid intermediates. The latter are capable of cyclopropanation of various styrene derivatives affording cyclopropylphosphonates (193) in high yields (85–96%), diastereoselectivity (> 98% de), and enantioselectivity (76–92% ee) (Scheme 52).[99] A

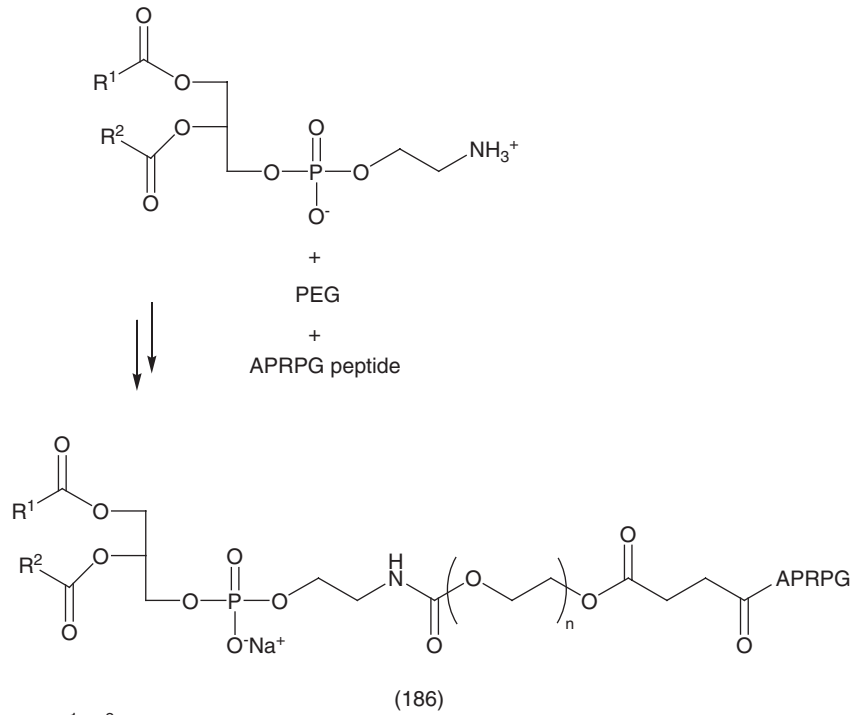
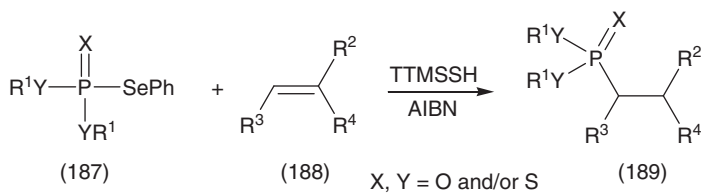
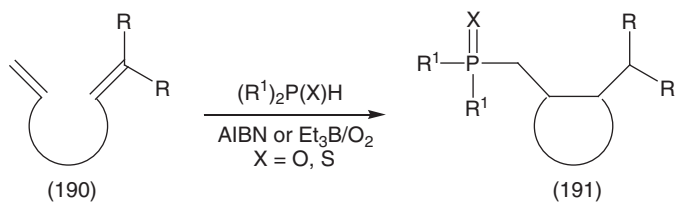


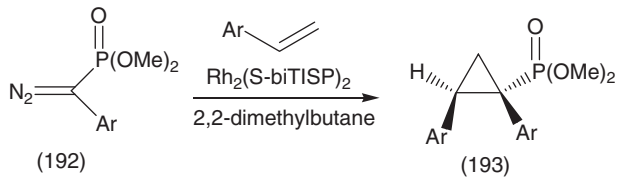
Figure 35



Scheme 50



Scheme 51



Scheme 52

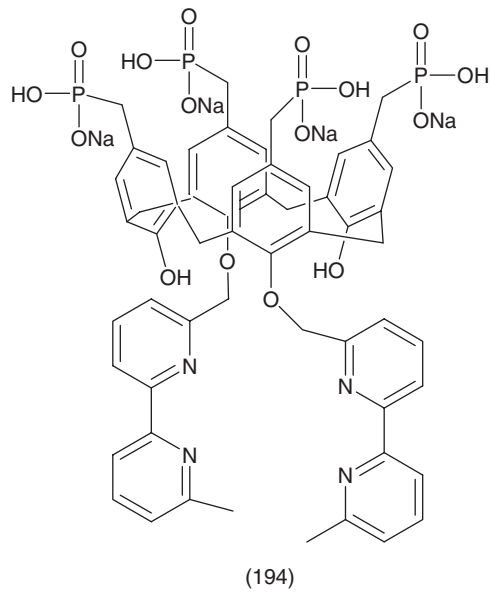


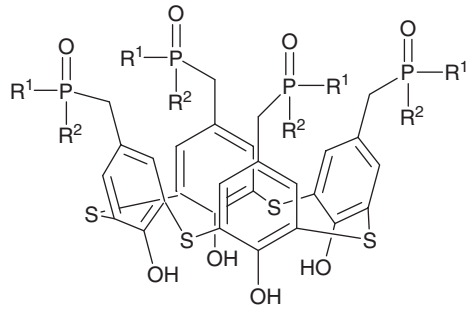
Figure 36

new water-soluble calix[4]-arene-based bipyridyl podand (194) has been elaborated by incorporation at the upper rim of four phosphonate groups. The association of its hydrophilic and chelating properties in the complexation of copper (I) in water is positively evaluated (Figure 36).[100]

A series of tetrahydroxythiacalix[4]arenes of the cone conformation with phosphonate and phosphine oxide groupings on the upper rim (195) has been synthesised (Figure 37).[101]

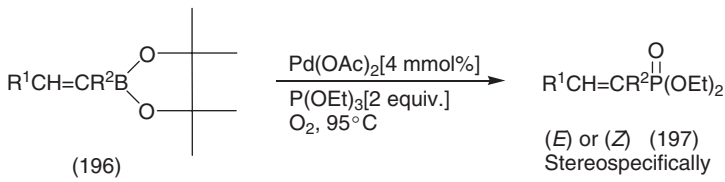
3.1.2 Alkenyl, Alkynyl, Aryl and Heteroaryl Acids. Treatment of readily accessible (E)- and (Z)-alkyl and aryl substituted vinyl boronates (196) with triethyl phosphite in the presence of lead diacetate results in their stereospecific transformation into (E)- and (Z)-vinylphosphonates (197) (Scheme 53).[102]

Palladium acetate catalysed Mizoroki-Heck reaction of arylboronic acids (198) with diethyl vinylphosphonates (199) is an effective synthetic approach to



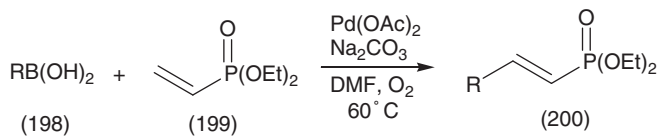
(195)

Figure 37



(196) (197)

Scheme 53



(198) (199) (200)

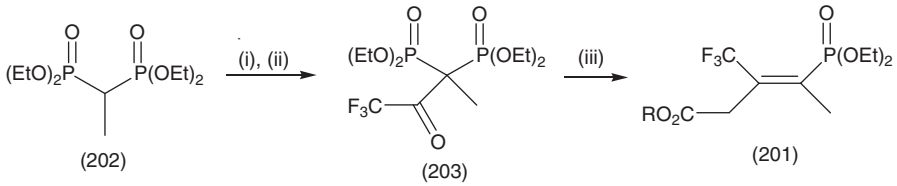
Scheme 54

aryl substituted α,β-unsaturated phosphonates (200) of (E) stereochemistry (Scheme 54).[103]

A simple procedure for the preparation of trifluoromethylated vinyl- and dienyl-phosphonates with γ-alkoxycarbonyl moiety of exclusively or predominantly (Z)-configuration (201) has been described. It involves acylation of ethyl-1,1-bisphosphonate (202) with trifluoroacetic anhydride, addition of selected Reformatsky reagents to the resulting 1-trifluoroacetyl-1,1-ethyl bisphosphonates (203) and finally spontaneous Horner-Wadsworth-Emmons (HWE) olefination of the adducts (Scheme 55).[104]

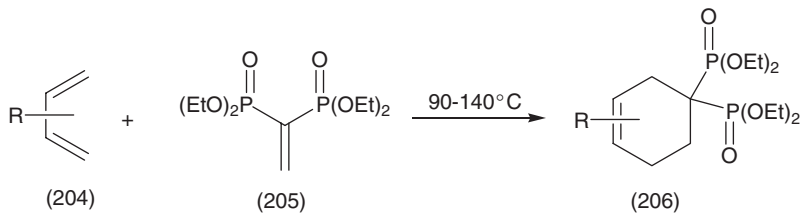
Differently substituted 1,3-dienes (204) readily add to vinylidene *bis*-phosphonate (205) to give the corresponding cyclohex-3-ene-1,1-bis-phosphonates (206). With unsymetrically substituted dienes mixture of regioisomers are obtained. In some cases migration of the double bond in the primary adducts is observed (Scheme 56).[105]

It has been demonstrated that under specially selected conditions the monoalkylation of triethyl phosphonocrotonate (207) with a number of halides or

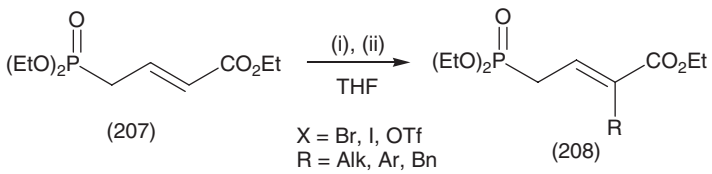


Reagents: (i) BuLi, (ii) $(CF_3CO_2)O$, (iii) $BrZnCH_2CO_2R$

Scheme 55

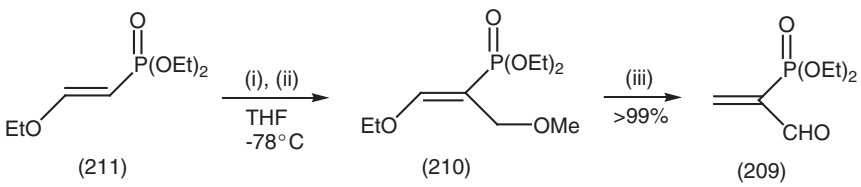


Scheme 56



Reagents: (i) LLiHMDS or NaHMDS, (ii) RX

Scheme 57



Reagents: (i) LDA, (ii) MOMCl, (iii) CF_3CO_2F

Scheme 58

triflates is an efficient method for the synthesis of α-substituted phosphonates (208). The alkylation is fully regio- and stereoselective (Scheme 57).[106]

The first synthesis of phosphonoacrolein (209) was achieved by acid decomposition of β-ethoxy-α-(methoxymethyl)vinylphosphonate (210) derived from lithiated phosphonate (211) and chloromethyl methyl ether (MOMCL) (Scheme 58). The phosphonoacrolein (209) appeared to be a particularly active heterodiene in the Diels-Alder additions with electron rich alkenes and alkynes.

New families of dihydropyrans (212), (213), (214) and pyranopyrans (215) have been obtained in this way (Figure 38).[107]

The preparation of a novel phosphonate containing 3,4-dihydro-2-H-pyrrole-1-oxide residue (216) has been reported. The synthesis of this solid and highly lipophilic spin trap is based on the addition of diethyl phosphite to pyrroline (217) and subsequent m-CPBA oxidation of phosphonate (218). (Scheme 59). The structure of the (218) was assigned using X-ray diffraction techniques. Its ability to react with different free radicals especially hydroxyl and superoxide was evaluated.[108]

Successive treatment of diethylphosphonylalkyl α-aminonitriles (219) with 1,1′-carbonylimidazole (CDI) or 1,1′-carbonyl-di-(1,2,4-triazole) (CDT) and O-substituted hydroxylamines has proven useful as a convenient protocol for the preparation of new 5-diethoxyphosphorylalkyl derivatives of 3-aralkoxy-4-imino-imidazolidine-2-ones (220) and 4-alkoxy (aralkoxy) imino-imidazoline-2-ones (221) (Scheme 60).[109]

A series of heterocycle derivatives of 1,1-bis-phosphonate (222), (223), (224) and (225) has been synthesized by Michael addition of 1,1-methylene bis-phosphonate to acceptors such as: 5-arylidene rhodamines, 5-benzylidene-2-thiohydantoin, benzylidene or 2(2′-furyliden)-cyanomethyl-1,3-benzothiazoles

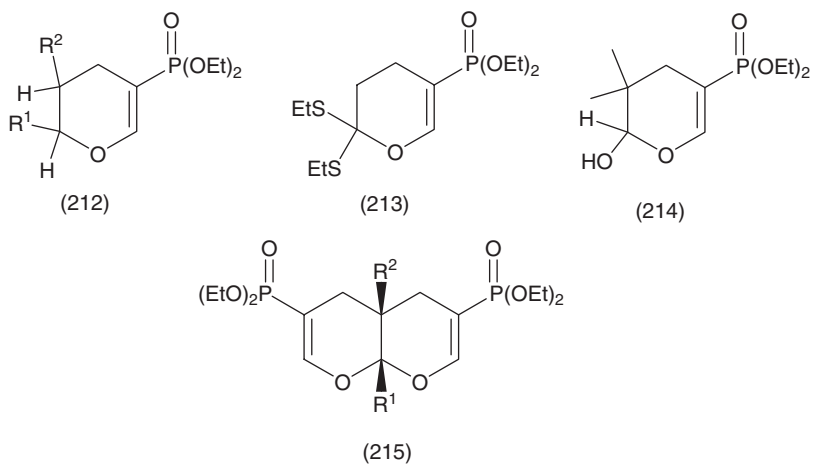
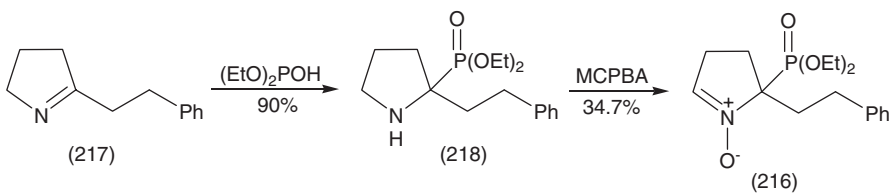
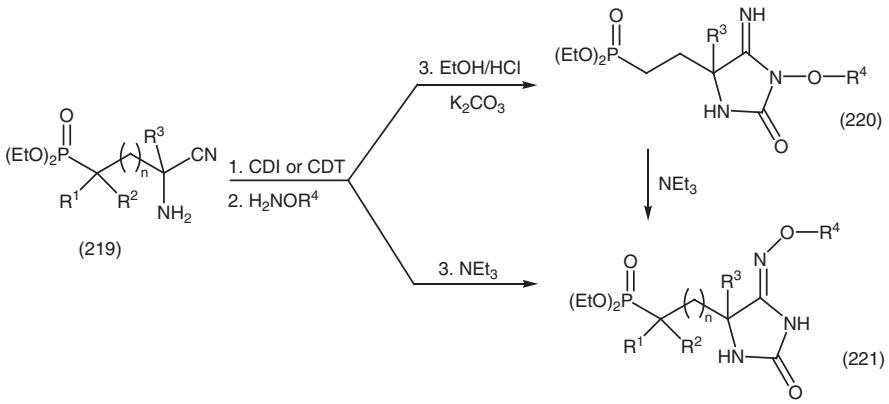


Figure 38



Scheme 59



Scheme 60

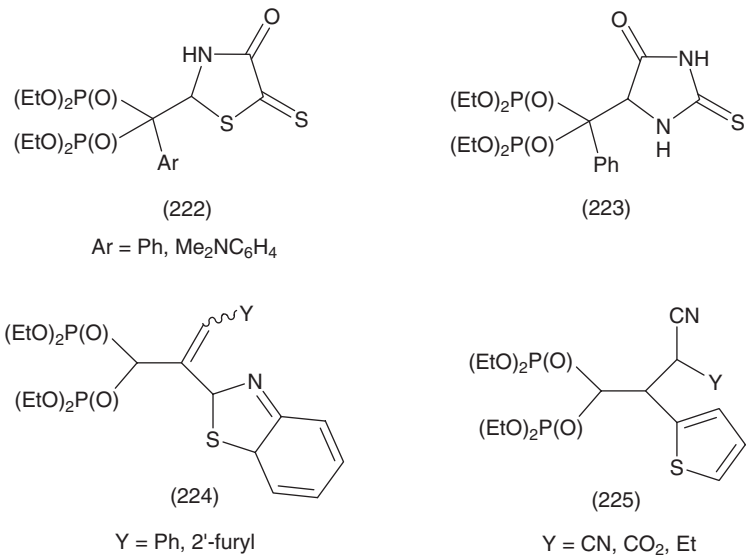
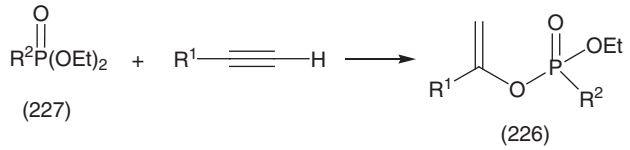


Figure 39

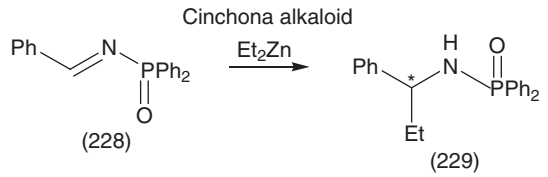
and ethyl 3-(2-thienyl)acrylocyanoacetate or related nitrile respectively (Figure 39).[110]

Alkenylphosphonates (226) can be prepared by regioselective addition of monoesters of phosphonic acid (227) to alkynes in the presence of $Hg(OAc)_2$/BF_3 OEt_2 (Scheme 61).[111]

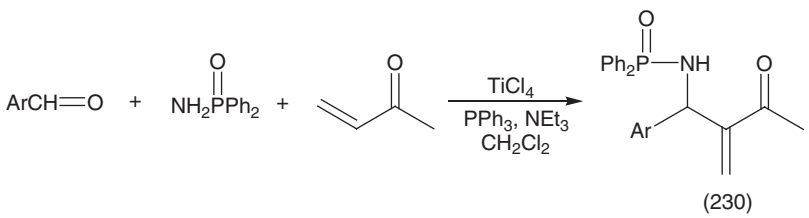
The cinchona alkaloids are particularly valuable ligands in asymmetric addition of diethylzinc to a N-diphenyl phosphinoylimine (228) leading to enantiomerically enriched (R)- and (S)-N-(1-phenylpropyl-diphenylphosphinic amide) (229). Cinchonine and cinchonidine were found to be the pseudo-enantiomeric pair which gave the adduct in highest enantiomeric excess (up to 93% ee) (Scheme 62).[112]



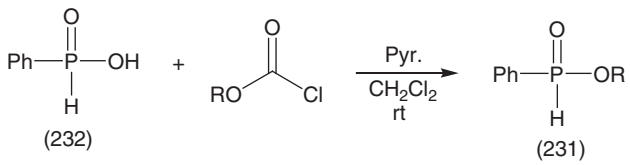
Scheme 61



Scheme 62



Scheme 63



Scheme 64

One pot, three component reactions of a variety of arylaldehydes, diphenylphosphinamide and methyl vinyl ketone catalysed by $TiCl_4$, PPh_3 and Et_3N have been found to give the aza-Baylis-Hillman adducts (230) (Scheme 63).[113]

Monoesters of phenylphosphinic acid (231) can be easily prepared in high yield from the reaction of phenylphosphinic acid (232) and the corresponding chloroformates (Scheme 64).[114]

3.1.3 Halogenoalkyl and Halogenocycloalkyl Acids. A couple of novel 6-(phosphonodifluoromethyl)-2-naphthoylosulfonamides (233) have been obtained in a conventional manner. The amides represent a structure-based extension in the design of inhibitors that may have broader utility in the development of protein-tyrosine phosphetase (PTB1B) inhibitors. The ability

of sulfonamido functionality to mimic carbonyl-H_2O motifs may be useful in other systems (Figure 40).[115]

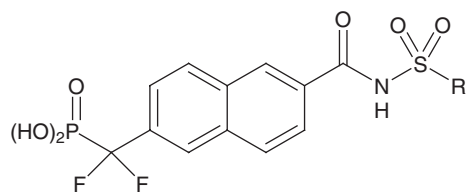
A series of (3-alkenylphenyldifluoromethyl)phosphonic acids (234), has been synthesized on non-crosslinked polystyrene (NCPS) support and examined for inhibition with protein tyrosine phosphatase 1B. Phosphonic acid (234) was the most potent of this series of compounds being a reversible, competitive inhibitor with a K_i of 8.0 1,4 μM (Figure 41).[116]

Diethyl difluoroalkylphosphonates (235), when subjected to chlorination by thionyl chloride, are smoothly transformed into difluoroalkylphosphonyl dichloride (236). Esterification of the latter with different thiols under basic conditions delivers new difluoroalkylphosphonodithioates (237) in good yield. Exposure of these compounds to Lawesson's reagent converts P=O into P=S giving new difluoroalkylphosphonotrithioates (238) (Scheme 65).[117]

Palladium catalysed cross-coupling reactions of α-phosphonylvinyl nonafluorobutanesulfonates (nonaflates Nf) (239) with dialkyl phosphite result in the formation of *gem*-bis(phosphono)ethylenes (240) (Scheme 66).

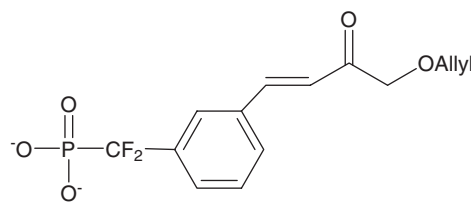
It was shown that (240) is a promising and versatile reagent for the synthesis of *gem*-bisphosphono substituted compounds (241),(242) and (243) expecting to exhibit not only biologically active but also other interesting properties (Figure 42) (Figure 43) (Figure 44).[118]

A convenient synthetic approach to highly reactive N-(arylsulfonyl)trichloro- and trifluoroacetimidoyl chlorides (244) by reacting the corresponding N-acylsulfonamides with PCl_5 has been elaborated. The interaction of (244) with phosphites proceeds through different pathways depending on the substituents in the reagents, and leads to compounds (245), (246), (247) and (248) (Figure 45).[119]



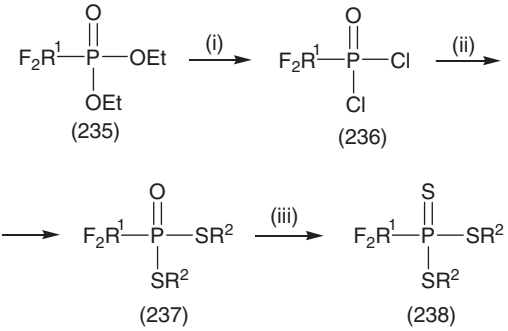
(233)

Figure 40



(234)

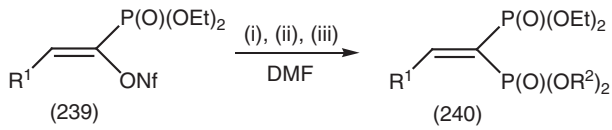
Figure 41



(235) (236) (237) (238)

Reagents: (i) $SOCl_2$, (ii) RSH, NEt_3, (iii) Lawesson's reagent

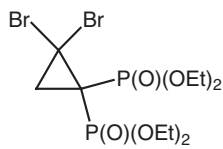
Scheme 65



(239) (240)

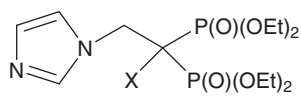
Reagents: (i) $HP(O)(OR^2)_2$, (ii) $Pd(PPh_3)$, (iii) $EtNPr^i_2$

Scheme 66



(241)

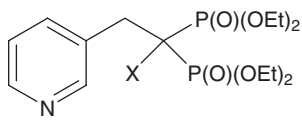
Figure 42



(242)

X = Cl, F

Figure 43



(243)

X = Cl, F

Figure 44

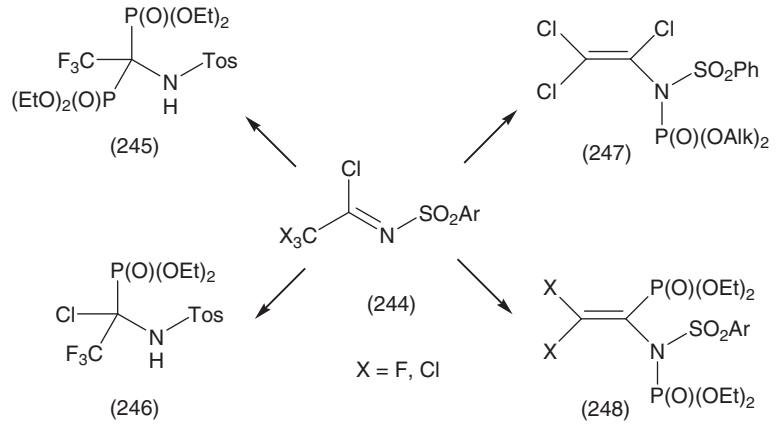


Figure 45

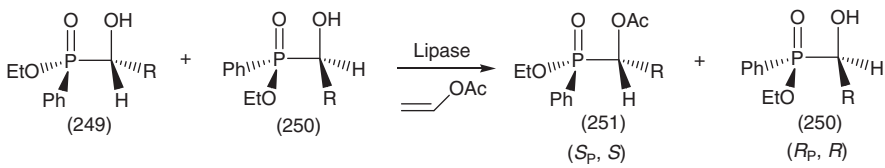


Figure 46

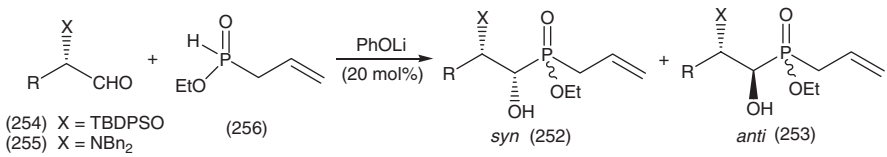


Figure 47

3.1.4 Hydroxyalkyl and Epoxyalkyl Acids. Lipase-catalysed acylation of ethyl(1-hydroxyalkyl)phenylphosphinates (249) and (250) afforded a single diastereoisomer of the corresponding acetates (251) in high enantiomeric excess (> 98%) (Figure 46).[120]

Diastereoselective synthesis of β-substituted α-hydroxyphosphinates (252) and (253) by hydroxyphosphinylation of α-silyloxy aldehydes (254) and α-amino aldehydes (255) with ethyl allylphosphinate (256), catalysed with lithium phenoxide, has been reported (Figure 47).[121]

Two methods for the first synthesis of partial amides (257), (258) and a partial amide ester (259) of etidronate have been developed (Figure 48).[122]

The preparation of 1,1-bisphosphonates from tris(trimethylsilyl)phosphite (260) and acid anhydrides (261) has been described. This synthesis allows a

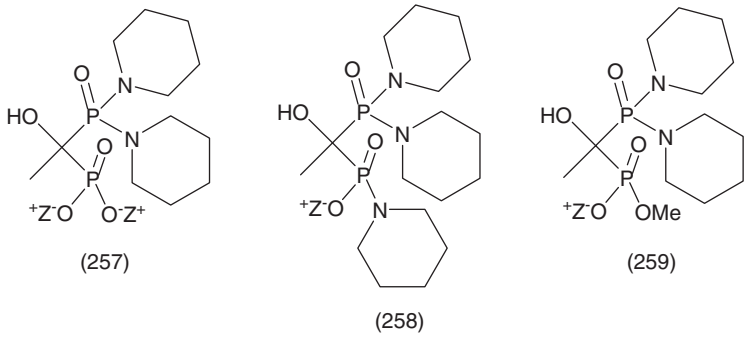
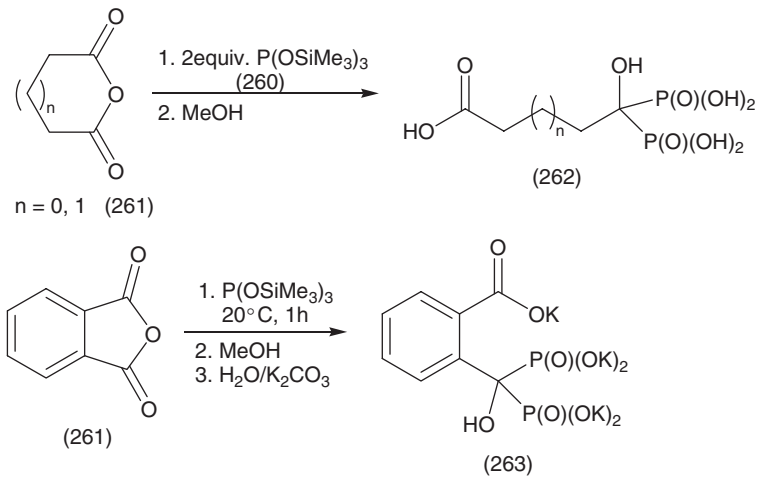


Figure 48



Scheme 67

direct access to 1-hydroxymethylene 1,1-bis(phosphonic) acids functionalyzed by a carboxylic function in the side chain (262) and (263) (Scheme 67).[123]

Alternative routes to acetylated etidronic acid derivatives have been investigated. (1-Acetoxyethylidene)-1,1-bisphosphonic acid (264) and its P,P-dimethyl (265), trimethyl-(266) and tetramethyl esters (267) were prepared (Figure 49).[124]

Candida antractica lipase B- and immobilised *Mucor miehei lipase*- catalysed alcoholysis and *C-rugosa lipase*- catalysed hydrolysis have been successfully used for the highly effective synthesis of optically active trifluoromethylated 1- and 2-hydroxyalkane-phosphonates (268) and (269) from their racemic O-acylated precursors (270) and (271) (Scheme 68).[125]

It has been found that reactions of diethyl mesyl- or tosyloxybenzyl-phosphonates (272) with sodium diethyl phosphite give the corresponding

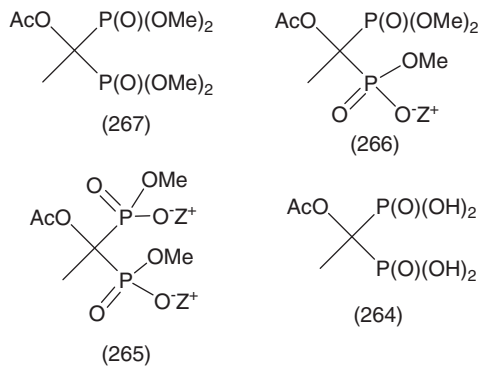
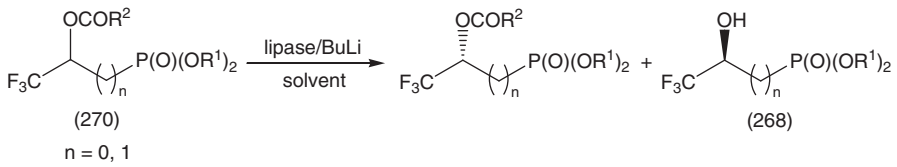
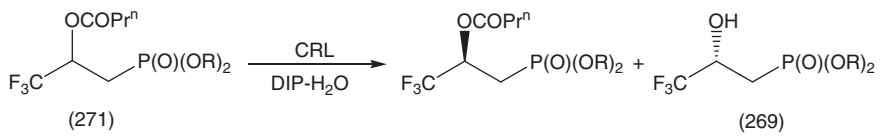
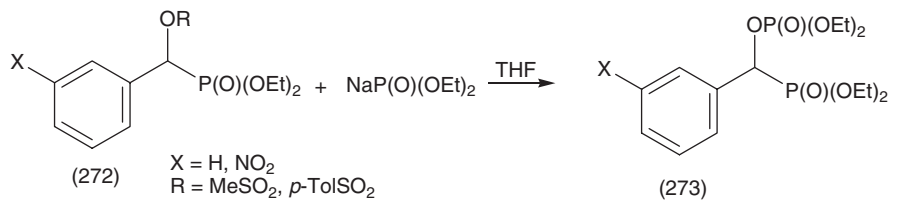


Figure 49





Scheme 68

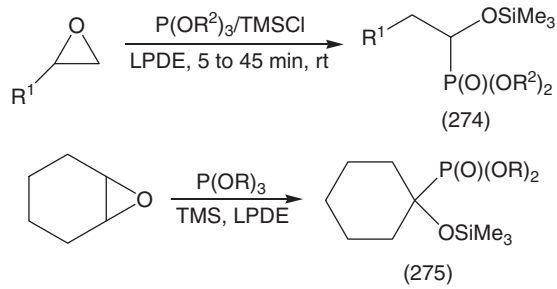


Scheme 69

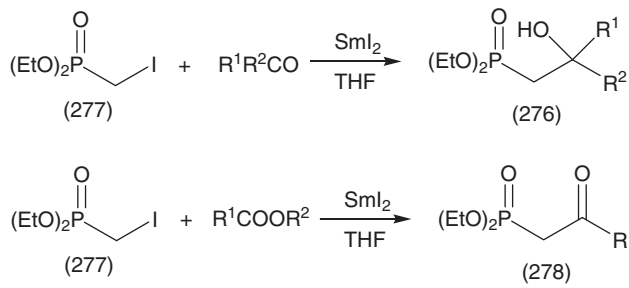
phosphono phosphates (273). Formation of the desired bisphosphonates was not observed (Scheme 69).[126]

A facile procedure for highly regioselective and efficient synthesis of α-hydroxyphosphonates (274) and (275) based on the reaction of trialkyl phosphites with epoxides in $LiClO_4/Et_2O$ has been presented (Scheme 70).[127]

β-Hydroxyalkylphosphonates (276) have been prepared under neutral conditions by reaction of diethyl iodomethylphosphonates (277) and carbonyl



Scheme 70



Scheme 71

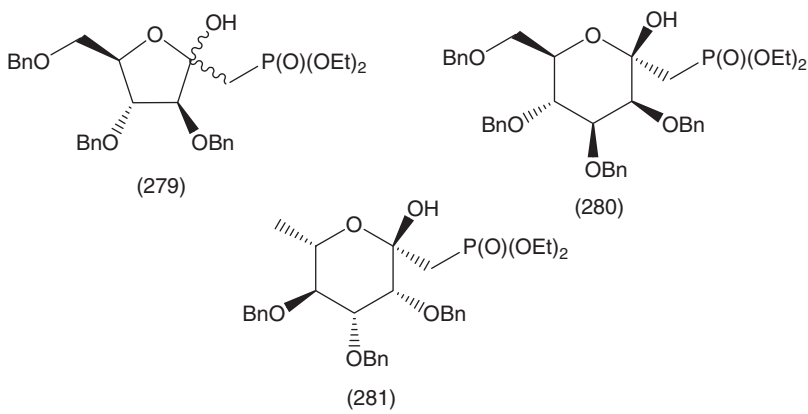


Figure 50

compounds (aldehydes and ketones) in the presence of samarium iodide. Similar reaction of iodomethylphosphonate (277) with esters leads stereoselectively to 2-oxoalkylphosphonates (278). The above protocol has also been applied to convert D-arabinonono-1,4-lactone, D-mannono-1,5-lactone and L-rhamnono-1,5-lactone into the 2-hydroxyphosphonates (279), (280) acid (281) respectively (Scheme 71) (Figure 50).[128,129]

(3R,4S)-3,4-Dihydroxy-5-oxohexylphosphonic acid (282), an isosteric analogue of 1-deoxy-D-xylulose-5-phosphate (DXP), the first C_5 intermediate in the MEP pathway for isoprenoid biosynthesis has been synthesized from (+)2,3-O-benzylidene-D-threitol (283) by a seven step reaction sequence. This phosphonate (282) was next enzymatically converted into (3R,4R)-3,4,5-trihydroxyphosphonic acid (284), an isosteric analogue of 2-C-methyl-D-erythritol-4-phosphate (Scheme 72).[130]

Enzymatic alcoholysis of 3-chloro-2-chloroacetoxy, 3-azido-2-chloroacetoxy and 1-chloro-2-chloroacetoxypropyl phosphonates (285), (286) and (287) catalysed by immobilized *mucor miehei lipase* (IM) and *candida antarectica lipase* B was a particularly effective method for the formation of the corresponding highly enriched enantiomerically chloroacetoxyphosphonates (288), (289) and (290). Kinetic resolution by specially selected reaction sequences led to phosphocarnitine (291), phosphogabob (292) and phosphomycin (293) respectively (Scheme 73).[131]

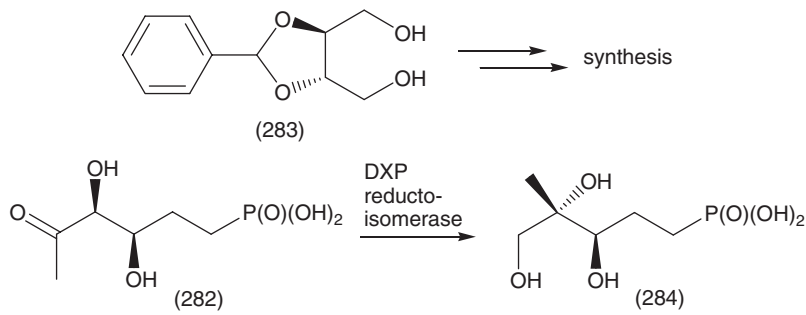
3.1.5 Oxoacids. It has been shown that Cobalt(0) or magnesium-mediated reactions of α-halomethylphosphonates (294) with esters constitute a novel approach to 2-oxoalkylphosphonates (295) (Scheme 74).[132]

A versatile method for the preparation of diverse range of α-ketophosphonates (296) involves the alkylation of 2-(diethoxyphosphonyl)- 1,3-dithiane (297) followed by hydrolysis of the resulting 2-alkyl-2-phosphonyl- 1,3-dithianes (298) (Scheme 75).[133]

Acylation of methythio-1-lithiomethylphosphonate (299) with 2′- and 3′-substituted benzoyl chlorides (300) constitutes an efficient synthesis of diethyl 1-methylthio-2-oxo-2-phenylethylphosphonates (301) (Scheme 76).[134]

Phosphonoformic acid (PFC) – amino acid P-N conjugates (302) have been obtained via coupling of C-methyl PFA dianion (303) with C-ethyl-protected amino acids which gave stable monoanionic intermediates (304) that resisted P-C cleavage during subsequent alkaline deprotection of the two carboxylate ester groups (Scheme 77).[135]

An α-phosphono lactone derivative of farnesol (305) has been prepared in both optically-inactive and -active forms to provide new analogues of farnesyl



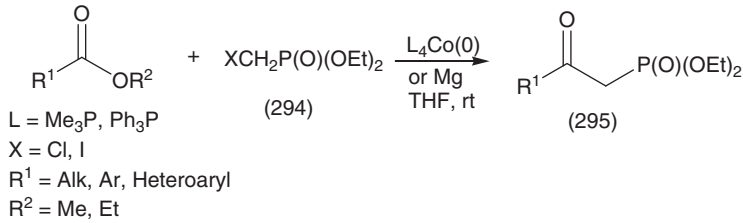
Scheme 72

Reagents: (i) K_2CO_3/MeOH, (ii) aq NMe_3/MeOH, (iii) Me_3SiBr/MeOH, dowex

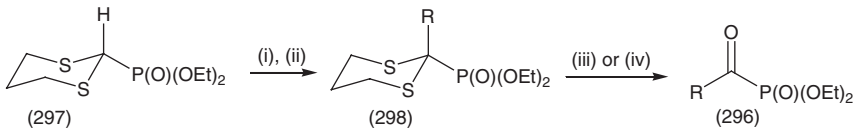
Reagents: (i) K_2CO_3/MeOH, (ii) Pd/C, (iii) Me_3SiBr/MeOH

Reagents: (i) K_2CO_3/MeOH, (ii) Me_3SiBr/MeOH, (iii) K_2CO_3/H_2O

Scheme 73

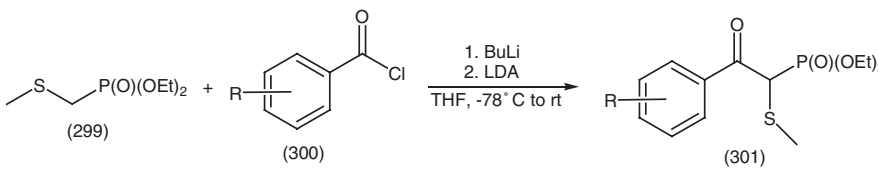


Scheme 74



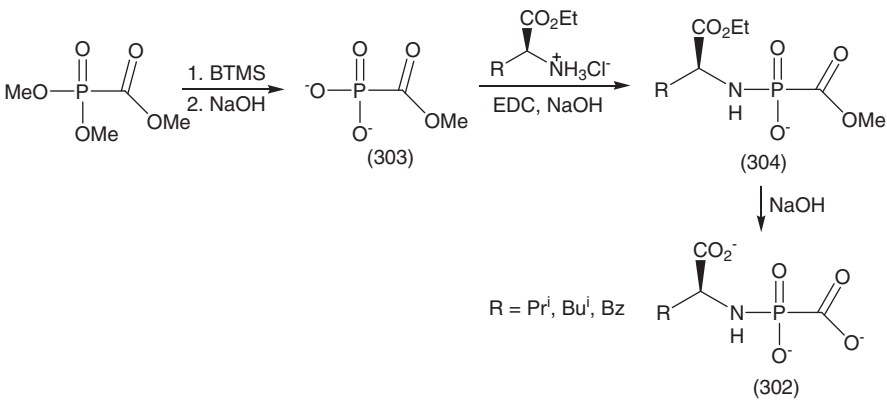
Reagents: (i) LDA, THF, -78°C, (ii) R-Hal, (iii) $AgNO_3$, Br_2, MeCN, H_2O or (iv) $AgNO_3$, NBS, MeCN/H_2O

Scheme 75



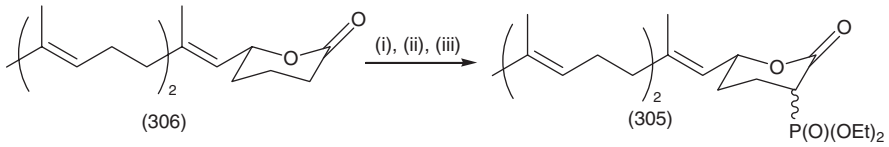
R = 2'-MeO, 2'-Me, 2-F, 2-Cl, 2-Br, 3-MeO, 3-Me, 3-F, 3-Cl, 3-Br, 3-NO_2

Scheme 76



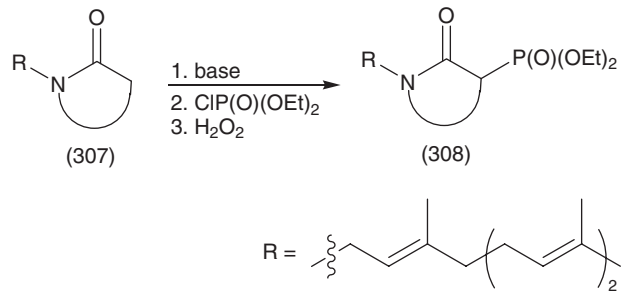
Scheme 77

pyrophosphate. The best of the examined synthetic strategies appeared to be that based on generation of enolate from racemic or enantiomerically enriched farnesyl lactone (306) followed by trapping the enolate with diethyl phosphonochloridate and oxidation (Scheme 78).[136]

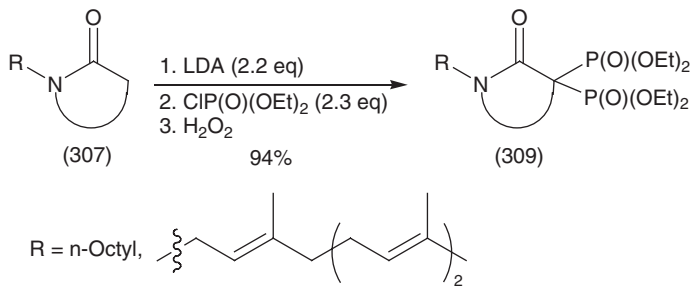


Reagents: (i) LDA, (ii) $ClP(OEt)_2$, (iii) [O]

Scheme 78



Scheme 79



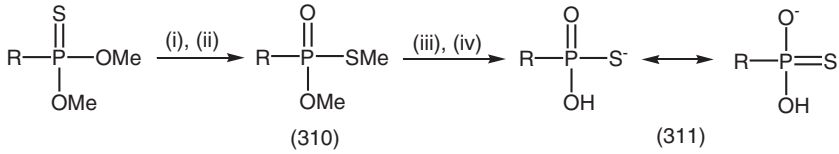
Scheme 80

It has been demonstrated that the reaction of a lactam enolate with diethyl phosphoro-chloridate and subsequent oxidation is an equally attractive method for transformation of different N-farnesyl lactams and imides (307) to the corresponding α-phosphono lactams (308) (Scheme 79).[137]

Analogous reaction sequences performed in the presence of excess base and phosphonylating reagent diethyl phosphorochloridate provided a series of new α,α-bisphosphonates (309) (Scheme 80).[138]

A method for the simple synthesis of phosphonothioates (310) or phosphonothioic acids (311) has been reported. It uses standard reagents and should be applicable to the preparation of phosphonothioic acids bearing a range of functional groups (Scheme 81).[139]

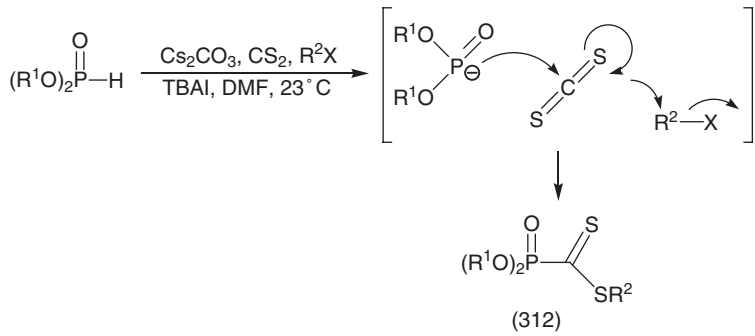
Catalysed by Cs_2CO_3 and TBAI a mild and efficient one pot three component coupling was performed using dialkylphosphite, CS_2 and alkyl halide leading to phosphonodithioformates (312) (Scheme 82).[140]



R = Pr, Bz, -$(CH_2)_5CO_2H$, -$(CH_2)_5CO_2Me$

Reagents: (i) NMe_3, (ii) MeI, (iii) Me_3SiI, (iv) H_2O/base

Scheme 81



Scheme 82

3.1.6 Aminoalkyl and Related Acids. Various 1-aminoalkylphosphonic acids (313) have been obtained in high yield by microwave assisted reaction of ammonium hypophosphites (314) with aldehydes (Scheme 83).[141]

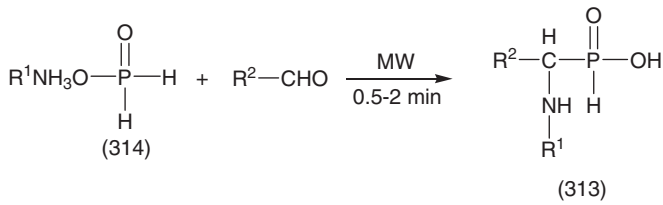
The same methodology has been successfully used in a simple synthesis of 1-aminoalkylphosphonates (315) from 1-hydroxyalkylophosphonates (316) and amines (Scheme 84).[142]

1,2-Diamino-, 1-amino-2-hydroxy and 1-amino-2-chloro-2-phenylphosphonates (317) have obtained in a stereo- and regio-selective manner from 2-amino-1-hydroxy-2-phenylethylphosphonate (318) through the intermediacy of an aziridinium ion (Scheme 85).[143]

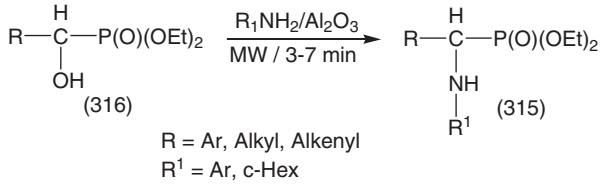
The first enantioselective synthesis of 1-aminoalkylphosphinic acids (319) based on the addition of phenylphosphinate (320) to chiral imines (321) and standard removal of protecting groups from the adducts (322) has been realized (Scheme 86).[144]

It has been found that addition of metalated isothiocyanomethylphosphonate (323) to aldehydes is a convenient route to diastereomeric, cis- and trans-5-substituted-(2-thio-oxazolidin-4-yl)phosphonates (324) which can be smoothly converted by a three step reaction sequence into syn- and anti- N-Boc 1-amino-2-hydroxyalkylphosphonates (325) respectively (Scheme 87).[145]

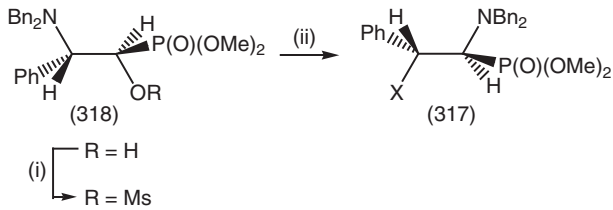
Condensation of the new pentacoordinate oxaphospholene (326) with azadicarboxylate, followed by reduction of the resultant ketone (327) produce cis- and/or trans-oxazolidones (328), potential precursors to phosphonate



Scheme 83



Scheme 84



Reagents: (i) MsCl, NEt_3, CH_2Cl_2, (ii) $BnNH_2$, NEt_3; or Bn_2NH, NEt_3; or $Et_4N^+Cl^-$; or H_2O-SiO_2

Scheme 85

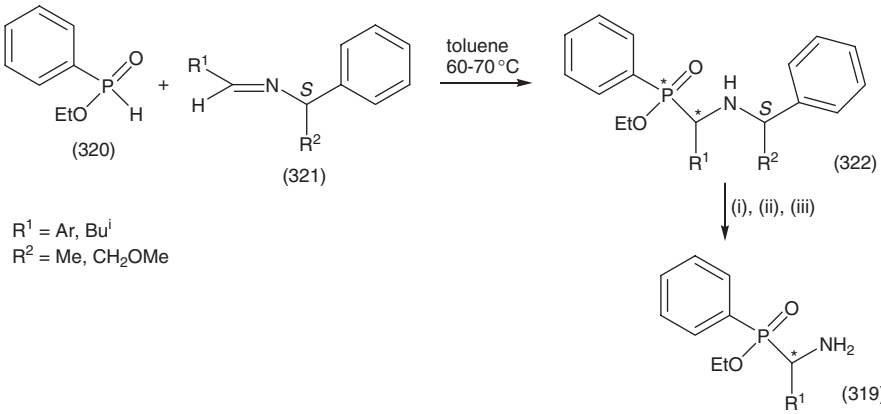
analogues of sphingomyelin, sphingosine 1-phosphate and ceramide 1-phosphate (Scheme 88).[146]

Catalytic hydrogenation of cis N-Boc aziridine 2-phosphonates (329) derived from 3-amino-2-hydroxyalkyl phosphonates affords N-Boc α-amino-2-phosphonic esters (330) regioselectively (Figure 51).[147]

The reaction of oxazolines (331) derived from L-serine with diethylphosphite leads to a mixture of racemic α- and β-phosphono alanines (332) and (333). This new reaction proceeds without the use of any halogenated intermediate, and offers a simple route for various phosphonoamino acids bearing suitable protecting groups (Scheme 89).[148]

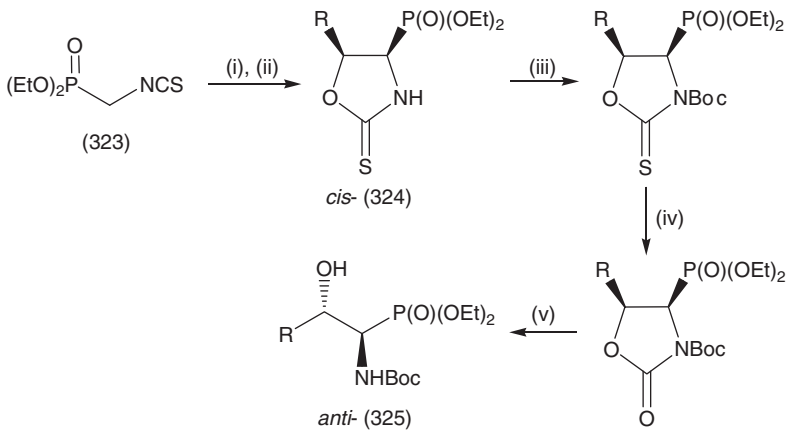
A modular method for the construction of polypeptides (334) containing the Phe-Arg phosphinic acid isostere has been reported (Figure 52).[149]

A new and facile synthesis of various 2[alkylamino(diethoxyphosphonyl)methyl] acrylic esters (335) has been developed. They constitute intermediates of choice to each α-methylene-β-functional azetidinones (336) through a tandem: hydrolysis-intramolecular lactamization (Figure 53).[150]



Reagents: (i) HBr-AcOH, (ii) propylene oxide, (iii) H_2, Pd/C

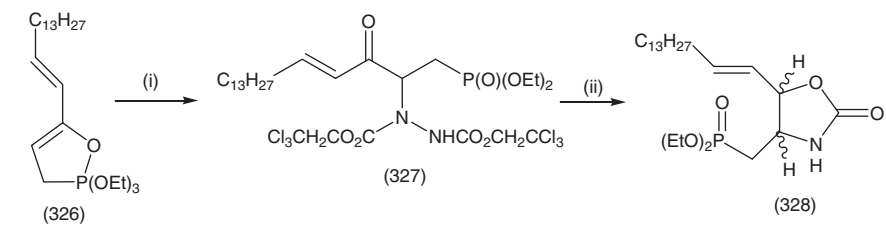
Scheme 86



R = Bu^t, Pr^i, Ph-CH=CH, 2-Furyl, Ph

Reagents: (i) NaH, (ii) RCHO, (iii) Boc_2O, DMAP, (iv) H_2O_2, HCO_2H, (v) Cs_2CO_3, MeOH/H_2O

Scheme 87



Reagents: (i) $Cl_3CCH_2CO_2N{=}NCO_2CH_2CCl_3$, ZnCl, (ii) [H], Zn/AcOH, [H] = $NaBH_4$, $ZnBH_4$, $LiBH_4$, BH_3-DMS

Scheme 88

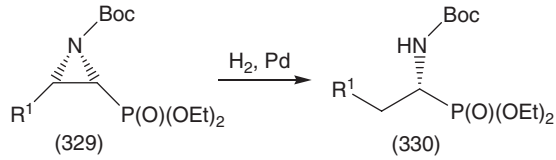
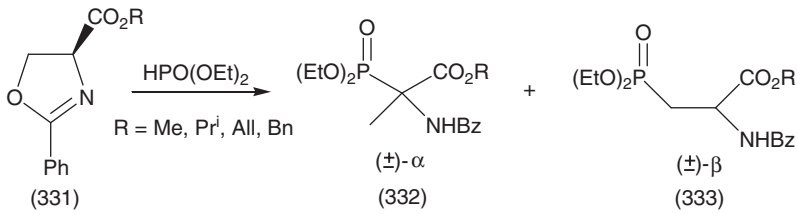


Figure 51



Isolated yields α+β: 46-77 %; Ratio α/β ~ 1:2

Scheme 89

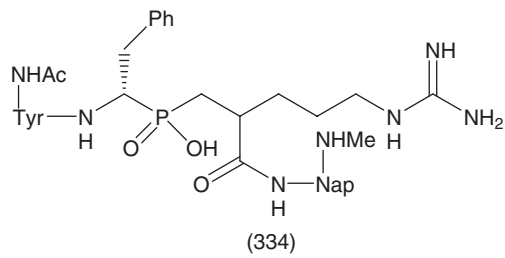


Figure 52

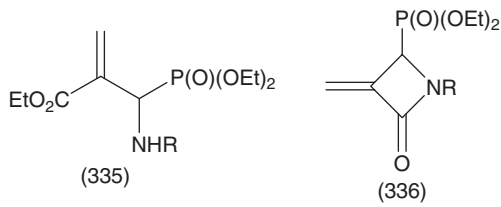
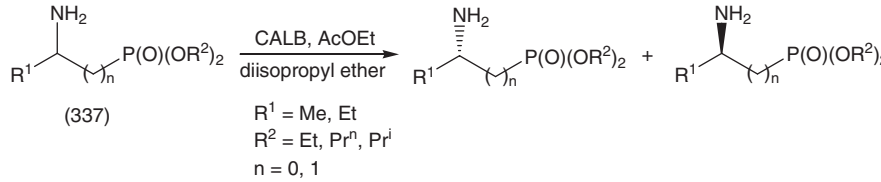
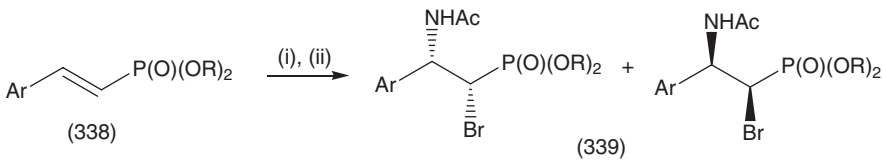


Figure 53

A number of 1- and 2-aminoalkanephosphonates (337) were successfully resolved by enzymatic, *Candida antractic lipase* B-catalysed acylation. The high enantioselectivity and preparative simplicity of these reactions makes them an attractive alternative for the preparation of optically pure aminoalkylphosphonates (Scheme 90).[151]

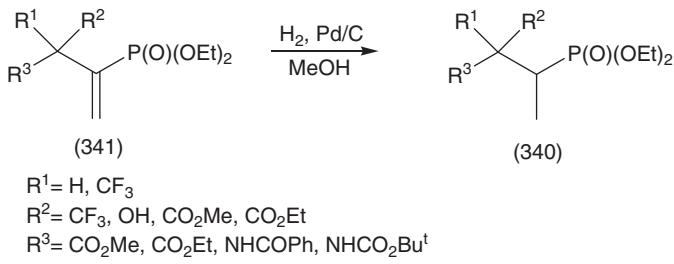


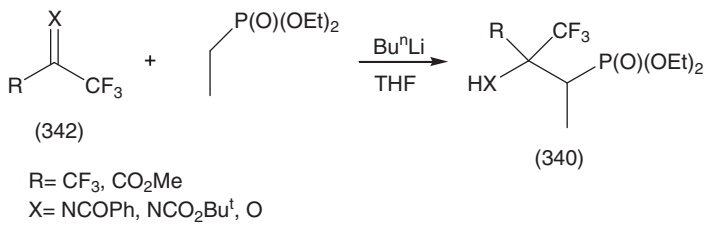
Scheme 90



Reagents: (i) BrNHCOMe (2.3 equiv.); 5% $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$; 4% $K_2OsO_2(OH)_4$; LiOH H_2O (1.02 equiv.), 0-4 °C; 71 mM in olefin; 1:1 $MeCN/H_2O$, (ii) Na_2SO_3, 1h

Scheme 91





Scheme 92

An original modification of the Sharpless AA reaction using excess of N-bromoacetamide as nitrogen/bromine source appeared particularly useful method for the transformation of 2-aryl-vinylphosphonates (338) into syn-2-aryl-2-amino-1-bromoethyl phosphonates (339) (Scheme 91).[152]

Two alternative routes to methyl- and trifluoromethyl- substituted β-amino and β-hydroxy phosphonates (340) via hydrogenation of vinylphosphonates (341) followed by aldol-type addition of ethylphosphonate to trifluoromethyl substituted imines (342) and carbonyl compounds have been elaborated (Scheme 92).[153]

Olefination of aldehydes with α-silyl- and α-stannyl-stabilized phosphonate carbanions derived from cyclo-[L-AP4-D-Val] allow a (Z)-selective access to α,β-substituted vinyl phosphonates (343) that have been transformed into enantiomerically pure 4-alkylidene 4PA derivatives (344) (Figure 54).[154]

Electrophilic fluorination of lithiated bis-lactim ethers derived from cyclo-[L-AP4-D Val] (345) with commercial NFSi allow direct access to α-monofluorinated phosphonate mimetics of naturally occurring phosphoserine (346) and phosphothreonine (347), in enantiomerically pure form and suitably protected for solid-phase peptide synthesis (Figure 55).[155]

A novel preparation of racemic and enantiopure forms of phosphocarnitine (348) from easily available 3-chloro-2-oxopropylphosphonate (349) has been accomplished. The Baker's yeast catalysed reduction of (349) followed by kinetic resolution of the reduction product using AH-S AMNO lipase-catalysed acylation and finally standard exchange of chlorine atom for trimethylamine group are the key steps in the synthesis of enantiomers of phosphocarnitine (Figure 56).[156]

A general method based on sequential reactivitives of bis-bromocycloalkenes (350) has been elaborated for the synthesis of phosphonocycloalkenes (351), the

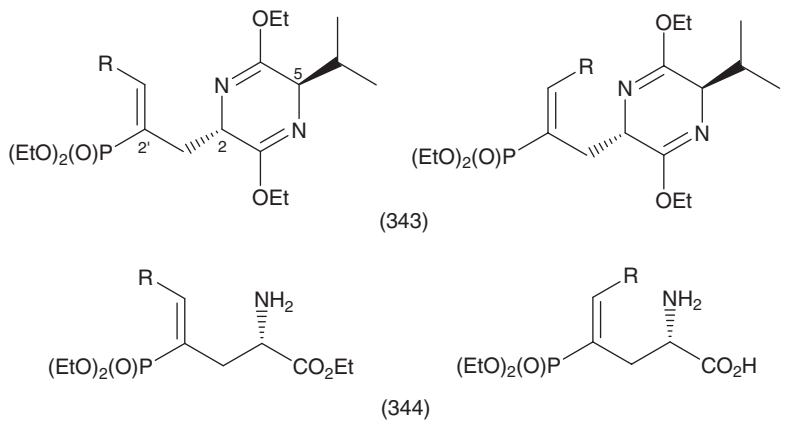


Figure 54

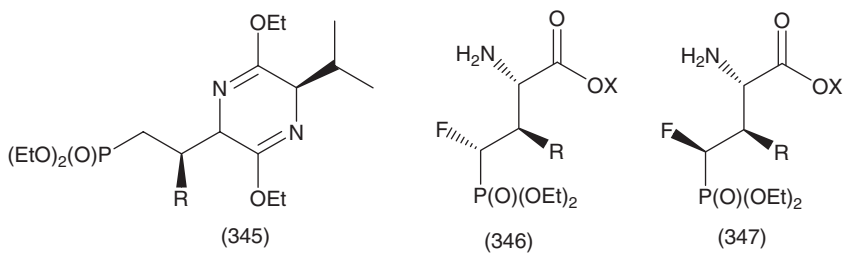


Figure 55

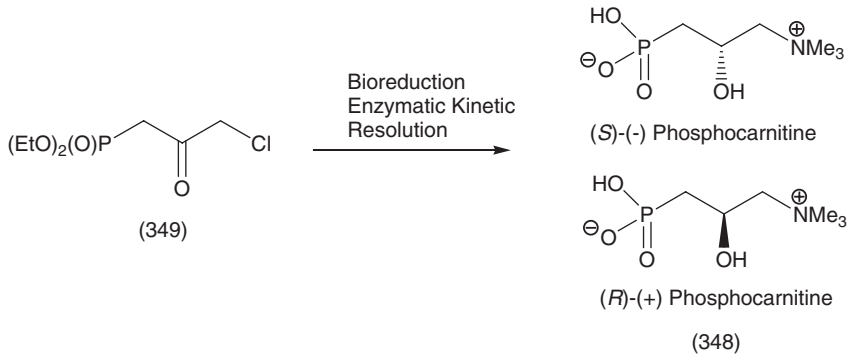
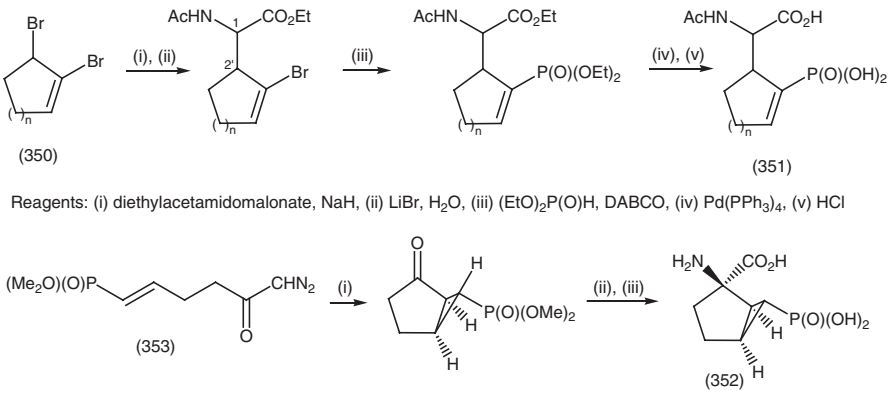


Figure 56



Scheme 93

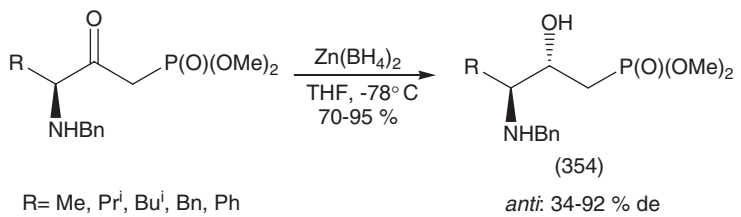


Figure 57

constrained analogues of AP4. An additional congested AP4 analogue (352) has also been obtained by a $Rh(OAc)_2$ catalysed intramolecular cyclopropanation of alkenylphosphonate (353) (Scheme 93).[157]

The reduction of N-benzylamino-β-ketophosphonates with $Zn(BH_4)_2$ shows excellent levels of anti-stereoselectivity to give preferentially anti- α-benzylamino-β-hydroxyphosphonates (354) (Figure 57).[158]

Palladium-catalysed addition of amines to 2-vinyl-1,1-cyclopropane bisphosphonate (355) has proven useful as a simple way to a new class of 5-amino-3-pentenyl-1,1-bisphosphonates (356) (Figure 58).[159]

An optimized protocol for the preparation of difluoromethylene phosphonate (357) an analogue of β-aspartyl phosphate based on the coupling of protected aspartic acid chloride (358) with difluoromethylphosphonate zinc reagent (359) has been described (Figure 59).[160]

A two step synthesis of the first β-aminophosphotyrosyl mimetic (360) was carried out. Addition of (−)(R)-tert-butanesulfinylamide to 4-phosphonomethyl benzaldehyde (361) gave chiral aldimine (362) which under treatment with the titanium enolate of methyl acetate produced the target compound with high diastereoselectivity (Figure 60).[161]

A convenient synthesis of new 2-substituted-2-(diethyl phosphono)-3-isopropenyl-2H-azirines (363) starting from phosphorylated allenes (364) has been developed (Figure 61a).[162]

Dimethyl thiophosphite was found to undergo diastereoselective addition to imines containing N-chiral auxiliaries derived from (S) and (R) phenylglycine and esters of different α-amino acids. This reaction gives ready access to a range of new α-aminophosphonothionates (365). Absolute stereochemistry of adducts resulting from the reaction conducted with (S)- and (R)-phenylglycine was unequivocally confirmed by conversion to known enantiomeric phosphonophenyl glycines (Figure 61b).[163]

New γ-ethoxycarbonyl- and α-amino-alkyl-hydroxyphosphinic acid derivatives (366) and (367) were conveniently prepared by Michael addition or Kabachnik-Fields reaction of a new precursor, benzyloxymethyl hydrogenphosphinate (368), with α,β-unsaturated esters or imines (Scheme 94).[164]

Phosphinic acid inhibitors (369) of Cathepsin C were synthesized by addition of methyl acrylate to the appropriate α-amino phosphinic acid and by

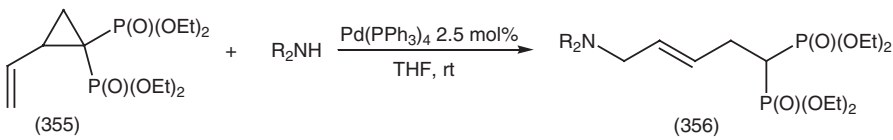


Figure 58

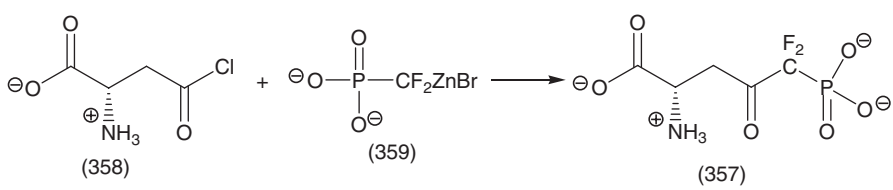


Figure 59

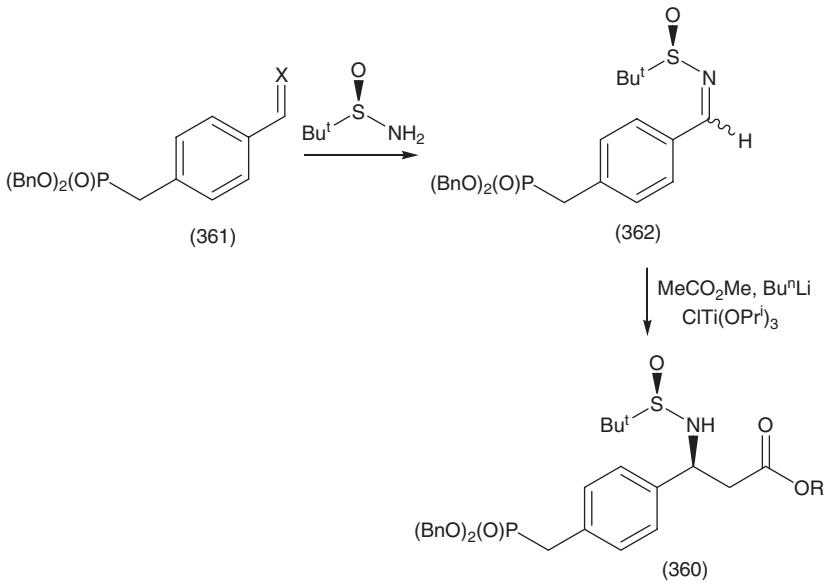
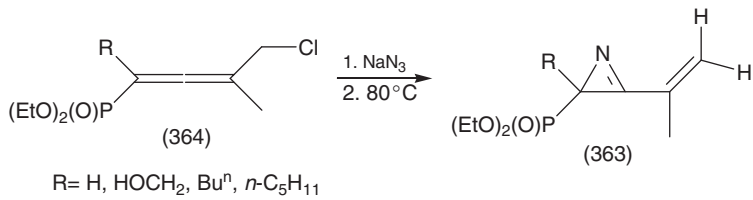


Figure 60



R= H, $HOCH_2$, Bu^n, *n*-C_5H_{11}

Figure 61a

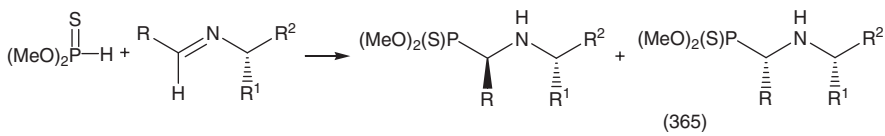
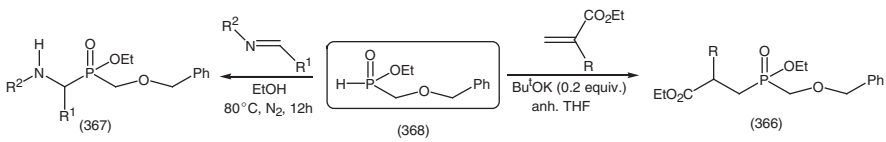
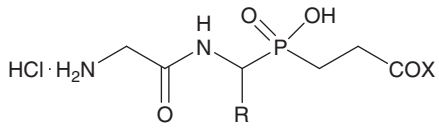


Figure 61b



Scheme 94

N-terminus elongation of the adduct using the mixed anhydride procedure. The latter step appeared to be a suitable method for N-terminal extension of phosphinic pseudopeptide analogues without rearrangement during the hydroxyphosphinyl protection (Figure 62).[165]

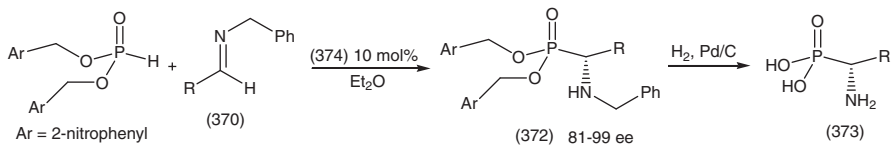


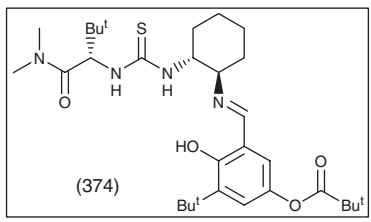
(369)

Non-competitive inhibitors

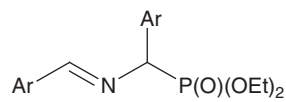
R= $CH_2CH(CH_3)_2$, Ph, Bz, $PhCH_2CH_2$
X= OH, OMe

Figure 62





Scheme 95



(375)

Figure 63

Thiourea-catalysed enantioselective hydrophosphonylation of imines (370) using phosphite (371) provides a general and convenient route to a wide range of highly enantiomerically enriched α-amino phosphonates (372). The deprotection of these products yields the corresponding α-amino phosphonic acids (373) (Scheme 95).[166]

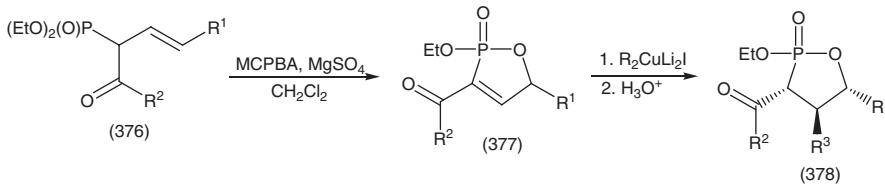
It has been reported that 1-arylidene-1-amino-1-arylmethylphosphonates (375) can be conveniently prepared by direct reaction of hydrobenzamides with diethyl phosphite (Figure 63).[166,167]

1.3.7 Phosphorus Containing Ring Systems. 1-Acyl allyl phosphonates (376) exposed to the action of m-CPBA in the presence of $MgSO_4$ are readily cyclized

to provide 3-acyl-1,2-oxaphosphol-3-enes (377). Addition of alkyl cuprates gives rise to the corresponding trans-3-acyl-4-1,2-oxaphospholanes (378) stereoselectively (Scheme 96).[168]

The first successful preparation of phosphorus-containing heterocyclic fatty acid derivatives has been presented. Reaction of α-keto allene (379) with trimethyl phosphite gave oxaphosphole derivative (380). Similar transformations with α-keto and α-chloro-α-ketoallenes (381) and (382) led to the formation of alkenylphosphonates (383) and (384), respectively (Figure 64).[169]

4-Iodophosphaisocoumarins (385) were obtained in good yields and with high regioselectivity by the reaction of 2-(1-alkynyl)phenylphosphonates (386) with I_2 or ICl. This reaction represents the first example of a phosphono iodocyclization onto a C-C triple bond (Figure 65).[170]



Scheme 96

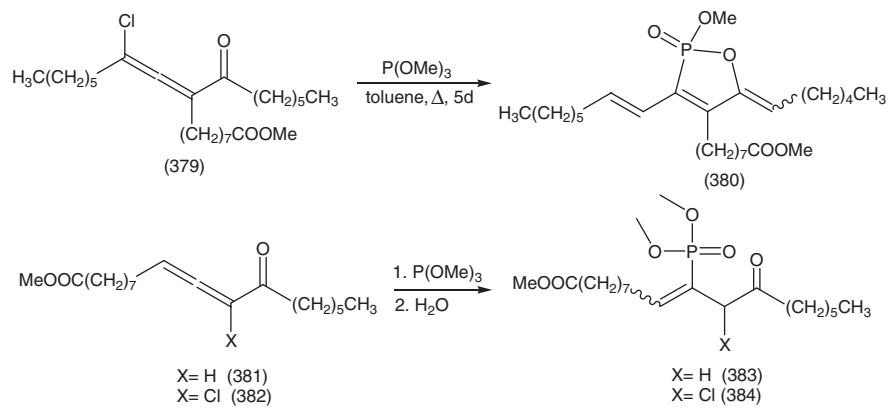


Figure 64

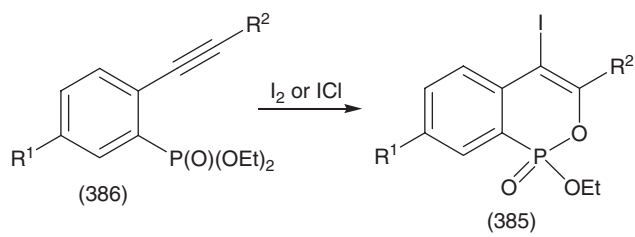


Figure 65

Conformationally constrained α-Boc-aminophosphonates (387), (388) (389), (390) and (391) were made via a transition metal catalysed Curtius rearrangement. The conformational constraint involved either a ring-closing metathesis reaction catalysed by the first generation Grubbs catalyst or intramolecular cyclopropanation mediated by $Rh_2(OAc)_4$ (Figure 66).[171]

A two step synthesis of 2-oxo-2-vinyl-1,3,2-dioxaphospholanes and dioxaphosphorinane (392) involves transesterification of diethyl phosphite with selected diols followed by palladium catalysed coupling of the resultant cyclic phosphites (393) with vinyl bromide (Figure 67).[172]

It has been observed that the reaction of methyl 2,3-di-O-benzyl-4,6-benzylidene-α(β)-D-glucopyranoside with triethyl phosphite and trimethylsilyl trifluoro-methanesulfonate leads unexpectively to seven-membered phostone (394). Removal of protecting groups from the phostone is also reported (Figure 68).[173]

The simple transformation of carbohydrate-derived γ-hydroxyphosphonic acids (395) into the corresponding phostones (396) using standard acylation conditions has been described (Scheme 97).[174]

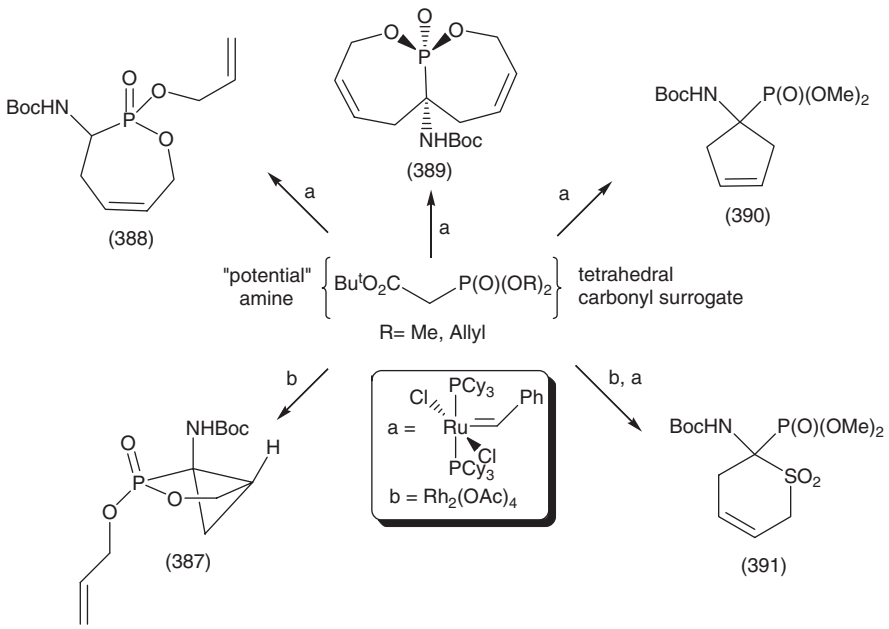


Figure 66

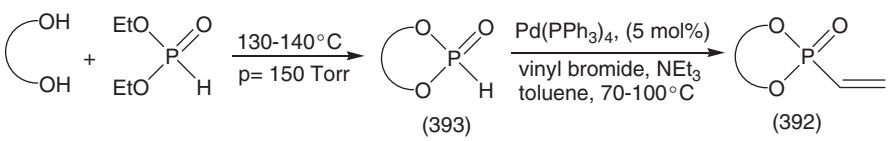
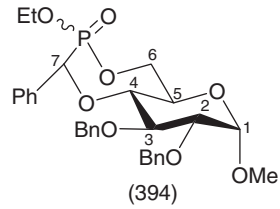
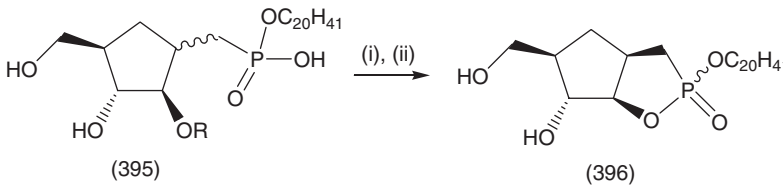


Figure 67



(394)

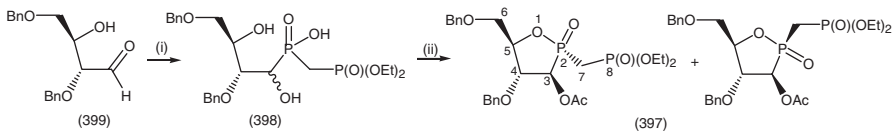
Figure 68



(395) (396)

Reagents: (i) NEt_3, (ii) Ac_2O, Py

Scheme 97



(399) (398) (397)

Reagents: (i) $(H)(OEt)P(O)CH_2P(O)(OEt)_2$, (ii) Ac_2O, Py

Scheme 98

The first synthesis of arabino-configured cyclic phosphonomethylphosphinates (397) has been accomplished. The crucial step of this synthesis consisted in the condensation of H-phosphinylphosphonate (398) with hydroxyaldehyde (399) derived from D-arabinol derivative followed by cyclization of (398) induced under acylation conditions (Scheme 98).[175]

Intramolecular transesterification of aminoalkylphosphinate (400) and direct intramolecular esterification of the related phosphinic acid (401) provided a simple route to a new 2-oxo-1,4,2-oxazephosphinane (402) (Figure 69).[176]

Dimethylsulfonium methylide opening of the oxirane ring of erythro-phospholane epoxides (403) constitutes a simple approach to the synthesis of one carbon atom homologated allylic alcohols of phospholane oxide (404) (Figure 70).[177]

A convenient preparation of a new class of 1-L-α-amino acid derivatives of 2-phospholene oxides (405) involves amination of (±) 1-chloro-2-phospholene oxides (406) with enantiomerically pure L-α-amino acid esters (407) (Figure 71).[178]

New phosphono containing pyrimidine analogues, diazaphosphinine oxides (408), were obtained by cyclization of metalated primary enamine phosphonates with nitriles (Figure 72).[179]

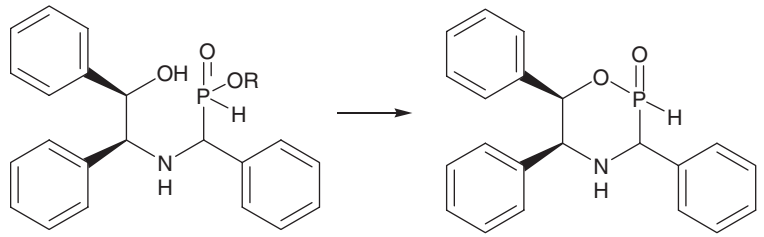


Figure 69

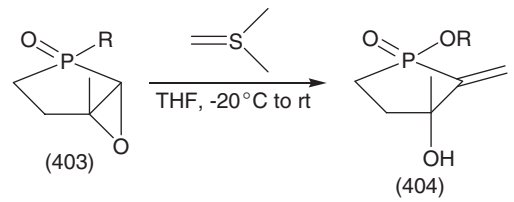


Figure 70

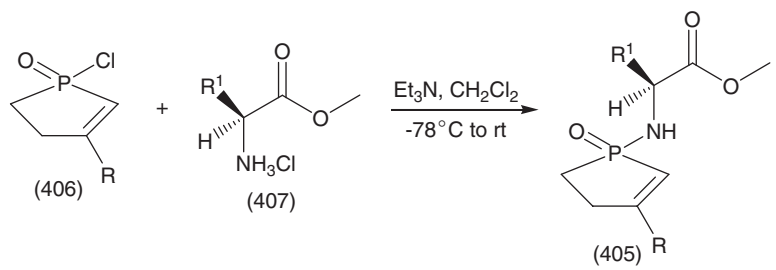


Figure 71

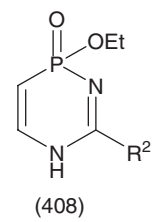
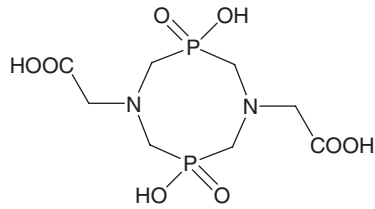


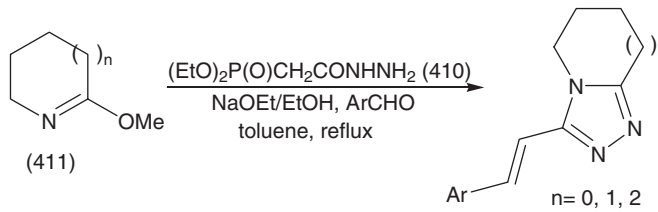
Figure 72

The eight membered 1,5,3,7-diazadiphosphocine-1,5-diacetic acid (409) was synthesized in a one pot reaction of glycine, formaldehyde and hypophosphorous acid in acidic aqueous medium (Figure 73).[180]



(409)

Figure 73



(411) (412)

Figure 74

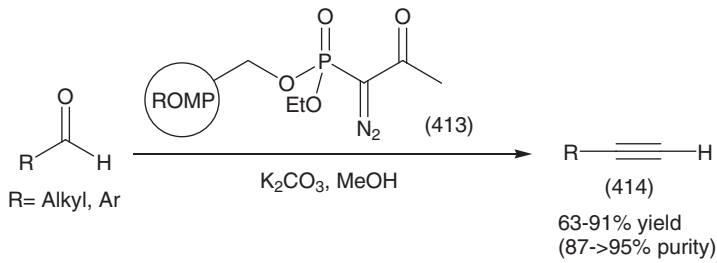


Figure 75

3.2 Reactions of Phosphonic and Phosphinic Acids and their Derivatives. – Diethoxyphosphinyl acetic acid (410) has been used as a unique reagent for a one-pot transformation of aldehydes and alkoxyimines (411) into fused [5,5]-[5,6]- and [5,7]-3[(E)-2-arylvinyl] 1,2,4-triazoles (412) (Figure 74).[181]

ROMP gel supported 1-azo-2-oxopropylphosphonate (413) has been synthesized and the immobilized reagent successfully employed to convert a number of aldehydes possessing different substitution patterns into the corresponding terminal alkynes (414) (Figure 75).[182]

The $[Rh_2(OAc)_4]$ catalysed cyclization of α-diazo-α-(diethoxyphosphonyl)acetamides (415) led to α- and γ-lactams (416) and (417). Conformational and electronic effects responsible for trans-stereochemistry of the γ-lactam ring

closure were studied. It was found that the steric effect exerted by the N-substituent of the amide determined the stereoselectivity of the β-lactam formation. A similar reaction of diazo-α-(dialkoxyphosphoryl)acetate was not so effective (Figure 76).[183]

The feasibility of the use of acylphosphonates as a carbonyl group radical acceptor have been demonstrated. Radical cyclization of the acylphosphonate (418) in the presence of hexamethylditin gave the cyclopentanone (419) in 91% yield. Additionally, various electrophilic alkyl radicals from activated olefins bearing α-electron-withdrawing groups smoothly reacted with alkenyl acylphosphonates (420). Furthermore, similar results were obtained with alkynylarylphosphonates (421) (Scheme 99).[184]

Arylphosphonic acids (422) have been discovered to react with a variety of alkenes in the presence of $Pd(OAc)_2$ and Me_3NO providing Heck-type adducts (423). The reaction requires TBAF as the activator (Figure 77).[185]

The first example of the $NaIO_4$ promoted oxidative C-P bond cleavage in α-aminophosphono acids has been observed. Strong evidence on its reaction mechanism was obtained from NMR, EPR and UVvis data collected by spectroscopic monitoring of the reaction.[186] It has been demonstrated that under treatment with EtSLi difluorophosphonomethyldithioacetate (424) undergoes clean monodefluorination. Thioacylation of amines, aminoesters and aminoalcohols of the resultant fluoromethyldithioacetate (425) led to fluorophosphonothioacetamides (426)-both potential HWE reagents (Scheme 100).[187]

Self-catalysed Michael Addition reactions of selected nitroalkanes (427) with dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate (428) afforded 4-nitroalkanoates (429) (Scheme 101). It was also demonstrated that the Nef reaction on the resulting primary and secondary 4-nitroalkanoates involved intramolecular catalysis by the carboxylic acid group.[188]

The conjugate addition of enolisable carbonyl compounds (430) to indoles appeared useful as a source of the phosphonates (431) and (432) (Figure 78).[189,190]

O-Phenylphosphonoamidates (433) including optically pure isomers were obtained according to a strategy based on hydrolytic removal of the phenoxy substituent from routinely accessible common precursor (434) and nucleophilic

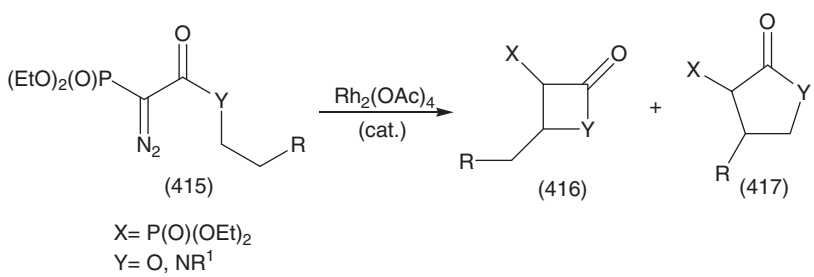
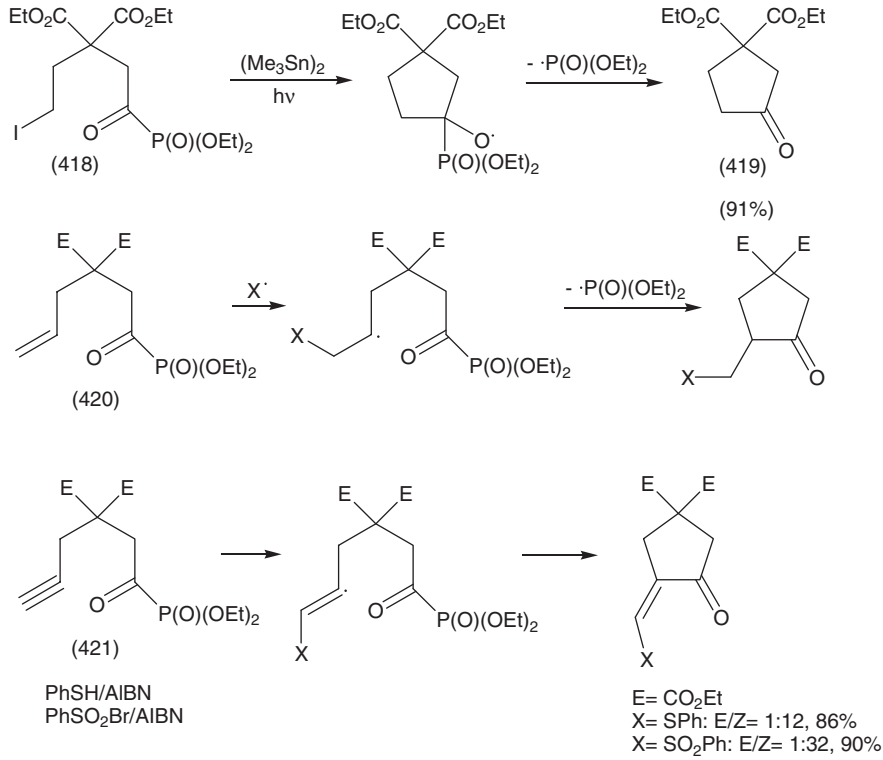


Figure 76



Scheme 99

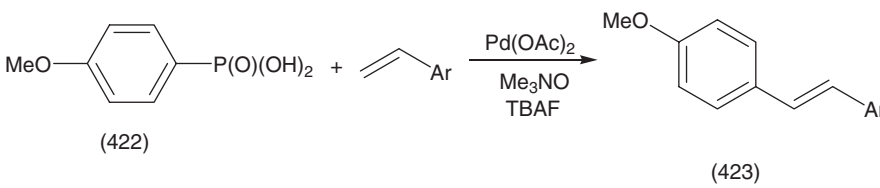
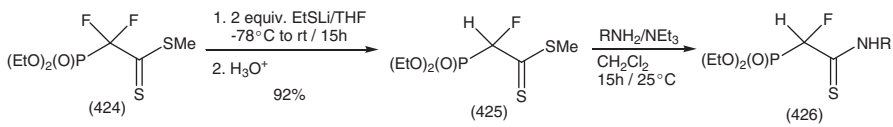
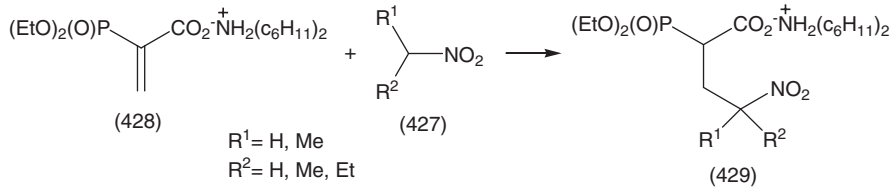


Figure 77



Scheme 100

exchange of a chlorine atom for the amine or amino acid ester moiety. (Scheme 102). The results of a study on the chemical behavior of (433) indicate that they may represent a new promising class of compounds useful for the design and construction of effective and specific inhibitors for serine protease family members.[191]



Scheme 101

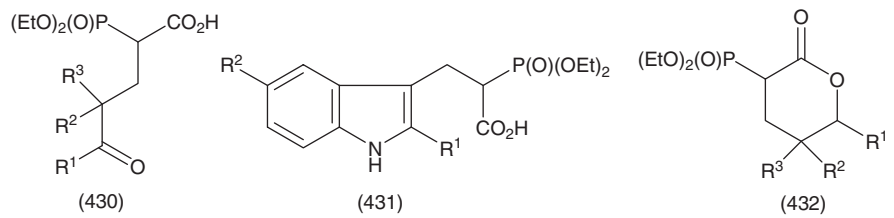
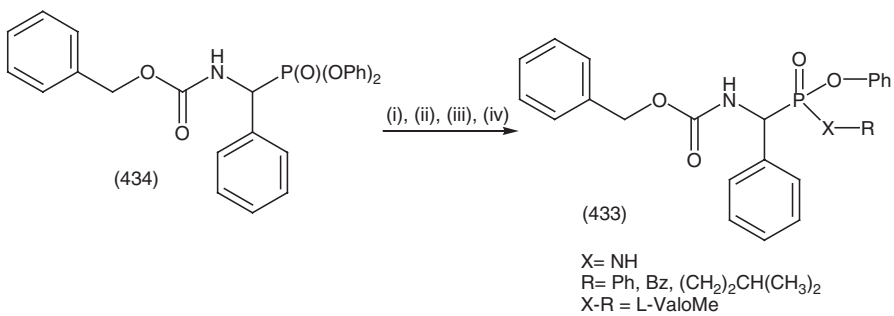


Figure 78



Reagents: (i) 1M NaOH/dioxane/KF, (ii) $SOCl_2$, (iii) nucleophile, NEt_3, (iv) pH1

Scheme 102

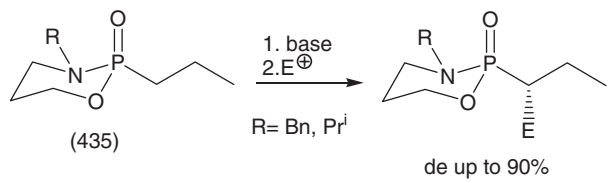


Figure 79

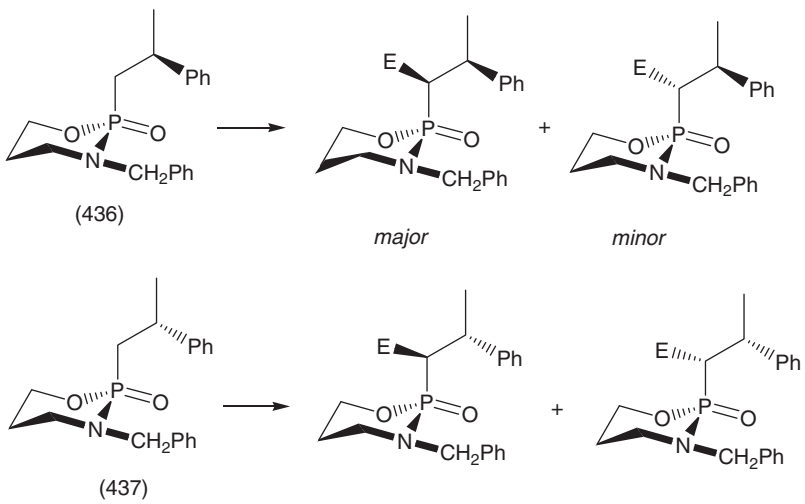
The diastereoselectivity in the alkylation of N-substituted 2-oxo-2-propyl-1,3,2-oxazaphosphorinanes (435) is influenced by the bulkiness of the nitrogen substituent. The α-carbanion derivatives of (435) when R = $CHPh_2$ and R = CPh_3 are unstable in the presence of DMPU and afford unexpected products (Figure 79).

Studies of structurally related phosphonoamidates possessing P- and C-stereogenic centers indicated that the alkylation of diastereoisomer (436) is mostly influenced by the chirality of the asymmetric phosphorus atom, while the alkylation of *l* diastereoisomer (437) depends on a combination of both the chirality of phosphorus and carbon atoms (Scheme 103).[192,193]

It has been demonstrated that methylsulfanyl difluoromethyl phosphonate (438) has an excellent potential as a freon-free source of phosphonodifluoromethyl carbanion. A simple preparative procedure involving sequential treatment of the former with butyl lithium and different electrophiles allowed the preparation of a wide range of new fluorinated building blocks (439) (Figure 80).[194]

Acylation of α-lithio-α-phosphonylalkyl sulfides (440) with carboxylic acid esters was utilized as a facile route to α-alkylsulfenyl substituted β-ketophosphonates (441). Keto-enol tautomerism of these new compounds in different solvents as well as regiochemistry of alkylation and acylation reactions and usefulness for HWE olefination reactions were studied (Scheme 104).[195]

It has been reported that xanthane derivatives of tetraalkylmethylene-1, 1-bisphosphonate (442) are smoothly added to different olefins to give various functionalised geminal bisphosphonates (443) via a radical chain reaction initiated by lauroyl peroxide (Figure 81).[196]



Scheme 103

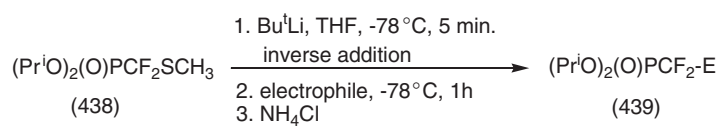
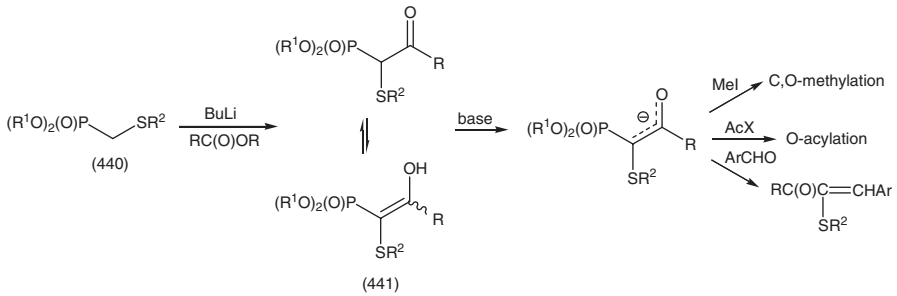
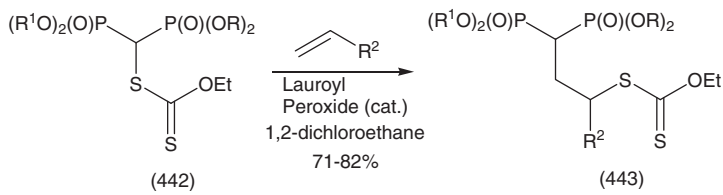


Figure 80



Scheme 104



R^1= Me, Et

R^2= $PivO(CH_2)_9$, $AcOCH_2$, $CH_3CO(CH_2)_2$, $TMSCH_2$, $NCCH_2$, 4-$ClC_6H_4OCH_2$, 4-$BrC_6H_4N(SO_2Me)CH_2$

Figure 81

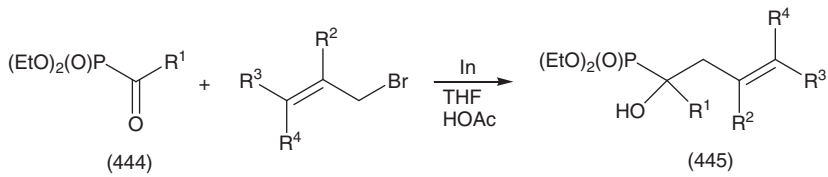


Figure 82

Acyl phosphonates (444) have been converted into tertiary α-hydroxy alkenylphosphonates (445) through an indium mediated allylation. The allylation proceeds equally well with different allylic bromides and does not appear to be sensitive to steric hindrance at the β-carbon atom (Figure 82).[197]

The particularly high reactivity of N-benzyloxycarbonyl α-aminophosphonochloridate (446) has been shown to arise from intramolecular catalysis by the carbonate group. This reactivity is not diminished when the hydrogen of the NH moiety is replaced by an alkyl group or when alkylation of α-carbon impedes intramolecular nucleophilic attack at the phosphoryl center (Figure 83).[198]

Bacterial phosphonotriesterase has proven to be a useful catalyst in enzymatic hydrolysis of (±) aryl methyl phenylphosphonates (447). Stereoselectivity of the natural phosphonotriesterase can be manipulated by alternation of the pKa value of the leaving phenol. For the wild-type enzyme the stereoselectivity has been enhanced in excess of 3 orders of magnitude (Figure 84).[199]

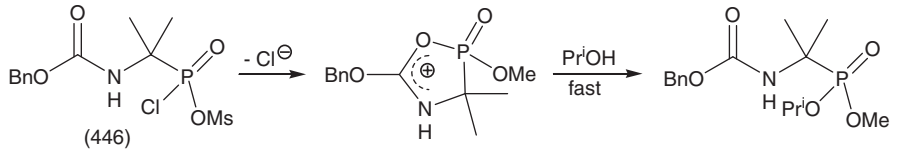


Figure 83

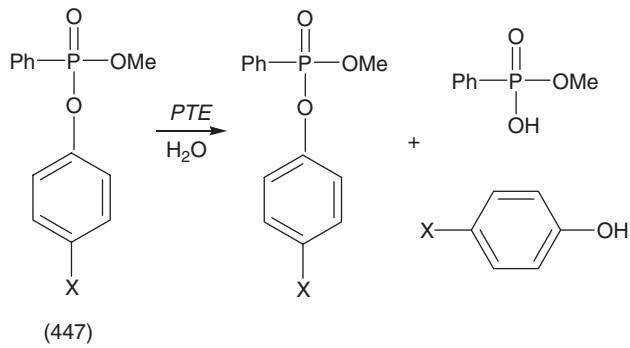


Figure 84

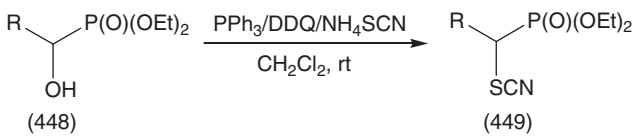
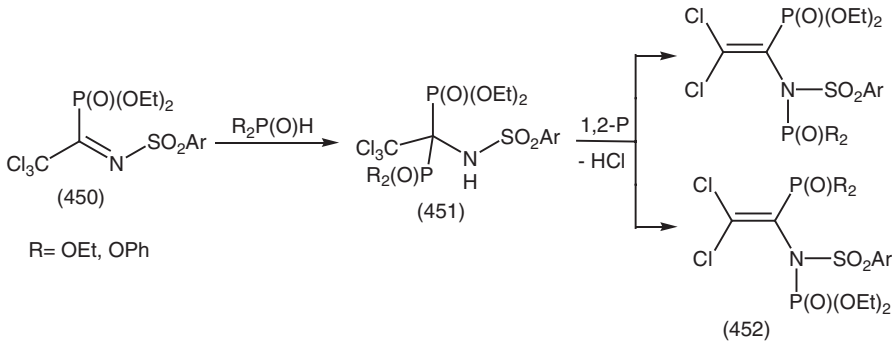


Figure 85

Diethyl α-hydroxyphosphonates (448) were converted into the corresponding α-thiocyanatophosphonates (449) using triphenyl phosphine, 2,3-dichloro-5,6-dicyanobenzoquinone and ammonium thiocyanate under neutral conditions (Figure 85).[200]

The first aza-Perkov reaction between N-sulfonyltrichloroacetimidoylphosphonates (450) and hydrophosphoryl nucleophilic reagents led to C,N-diphosphorylated dichlorovinylsulfonamides (452). Intermediacy of the bis-phosphonates (451) in this transformation has been unequivocally corroborated (Scheme 105).[201]

A concise and straightforward hydrolytic kinetic resolution of (±) 1,1-difluoro-3,4-epoxybutylphosphonate (453) using a chiral Salen-Co complex was employed as a key step to obtain enantiomeric diols in 99% ee as important intermediates. The enantiomerically homogenous 1,1-difluoro-2,3-dihydroxypropylphosphonates (454) and (455) were converted by stereoselective esterification and deprotection into the novel phosphatase resistant analogues of lysophosphatidic acid and phosphatidic acid (456) and (457), respectively (Figure 86).[202]



Scheme 105

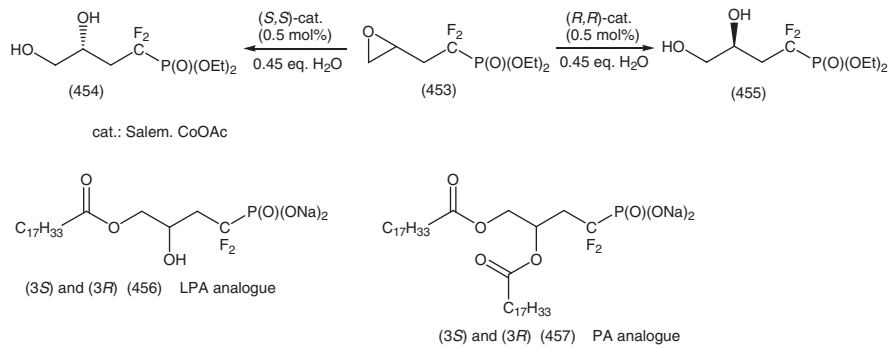
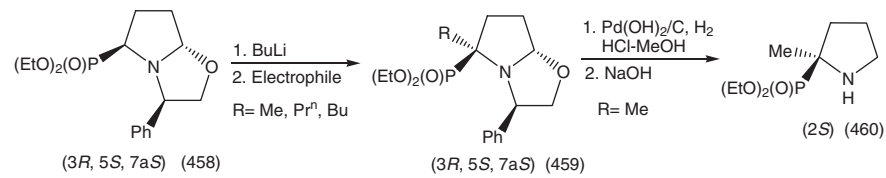


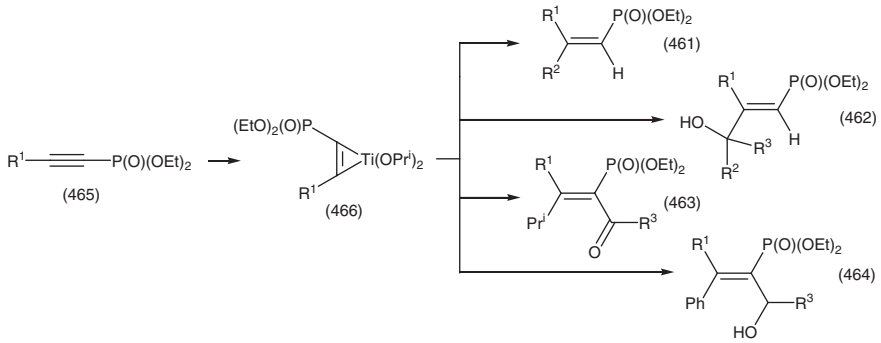
Figure 86



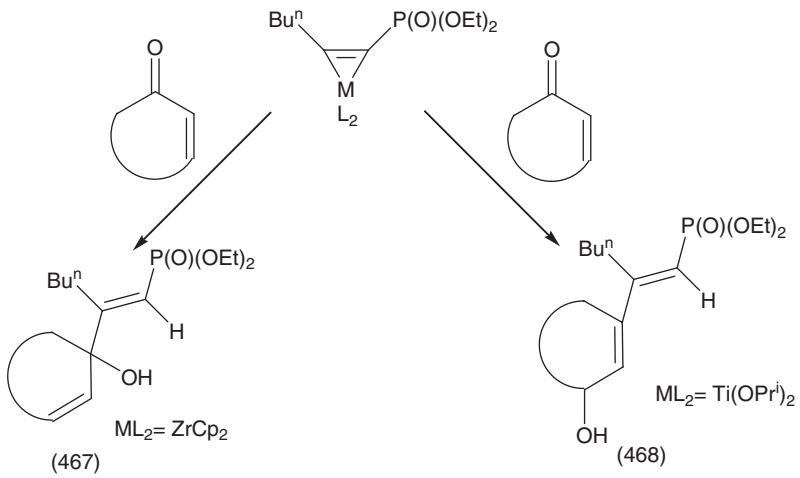
Scheme 106

Stereoselective alkylation of chiral oxazolopyrrolidine phosphonate (458) occurred with a complete retention of stereochemistry on the α-stereogenic center. Removal of the chiral auxiliary from the resultant diastereomerically pure phosphonates (459) by catalytic hydrogenolysis gave rise to enantiomerically homogenous α-substituted pyrrolidin-2-yl-phosphonates (460) (Scheme 106).[203]

Di- or tri-substituted vinylphosphonates (461), (462), (463) and (464) were selectively synthesized from 1-alkynylphosphonates (465) via intermediate phosphonates containing titanacycle (466), manipulated by $Ti(O\text{-}iPr)_4$/2i-Pr MgCl (Scheme 107).[204]



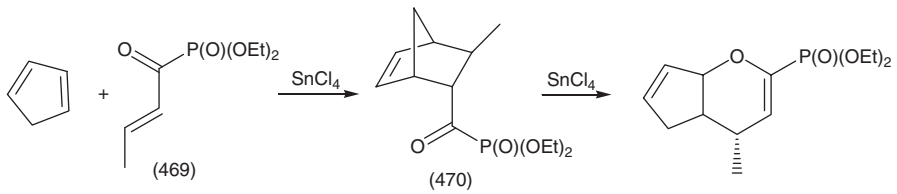
Scheme 107



Scheme 108

Addition of zircona- and titanacyclopropane metallocenes to conjugated enones was investigated. Analysis of the products shows that the reaction course is strongly controlled by both the metallocyclic and the enone moiety. The zirconacycle affords the rearranged (467). On the other hand, rearranged adducts, 1,3-butadienylphosphonates (468) are formed when titanacycles are used (Scheme 108).[205]

α-Keto-β,γ-unsaturated phosphonates (469) undergo Lewis acid catalysed cyclocondensation reactions to give hetero Diels-Alder products with cyclopentadiene, cyclohexadiene, dihydrofuran and dihydropyran with high endo stereoselectivity. Diels-Alder cycloadducts with cyclopentadiene (470) appear to be initially formed and undergo [3+3] Claisen rearrangement in the presence of Lewis acid. These cyclocondensations are further examples of inverse electron demand hetero Diels-Alder additions where the diene acts as a 2π component (e.g. Scheme 109).[206]



Scheme 109

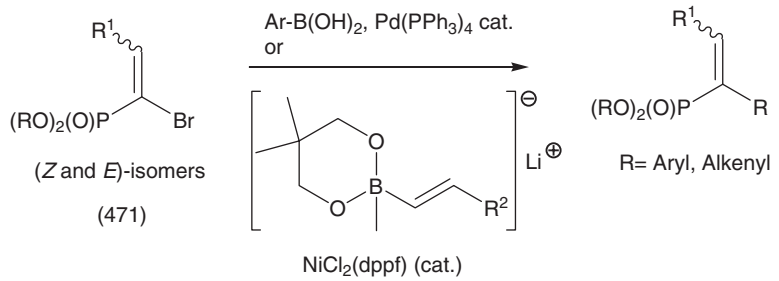


Figure 87

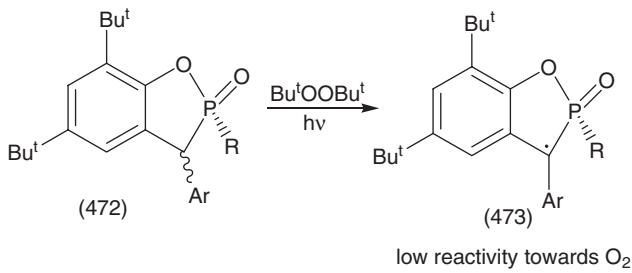


Figure 88

Synthetically attractive arylation and alkenylation of α-bromoalkenyl phosphonates (471) with organo-boranes and -borates have been performed. Arylation was successful with the aryl boronic acids and a palladium catalyst, while alkenylation proceeded best with alkenyl borates, and a nickel catalyst (Figure 87).[207]

Several benzo[d]-1,2-oxaphosphole 2-oxides (472) were examined as potential precursors of stabilized C-centered radicals (473) (Figure 88).[208]

The formation of phosphonates RP(X)(OH)OR′ (R = iPr, t-Bu, R′ = Me or i-Pr) from RP(X)(OH) NH t-Bu and R′OH in $CDCl_3$ is non-sensitive to steric effects when X = S but not when X = O (> 10^3 times slower with R = t-Bu, R′ = i-Pr than R = i-Pr, R′ = Me), pointing to a dissociative elimination – addition mechanism via metathiophosphonate intermediate (474) when X = S but the usual associative $S_N2(P)$ mechanism when X = O (Figure 89).[209]

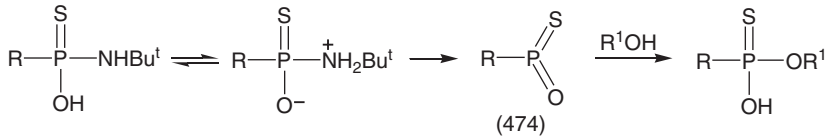


Figure 89

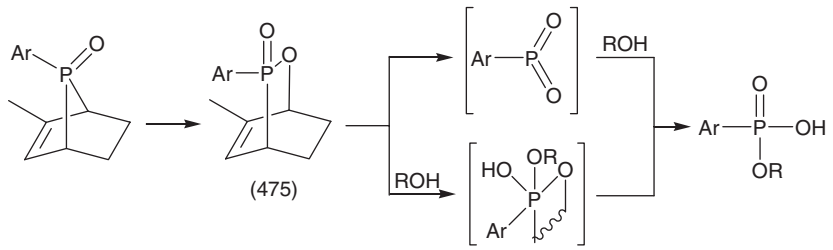
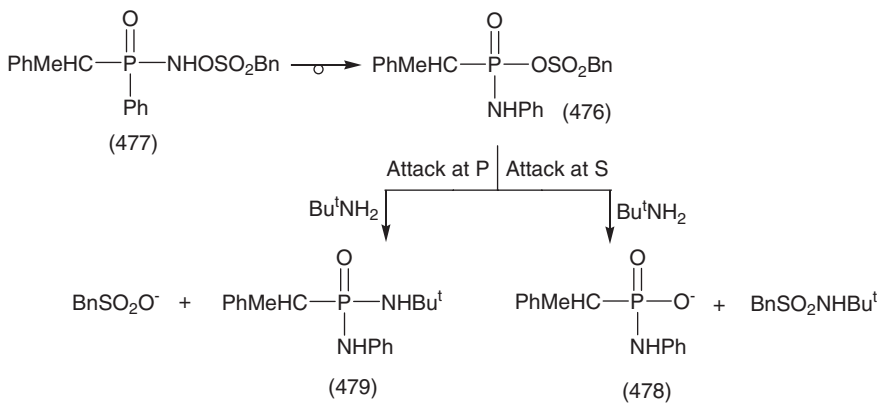


Figure 90



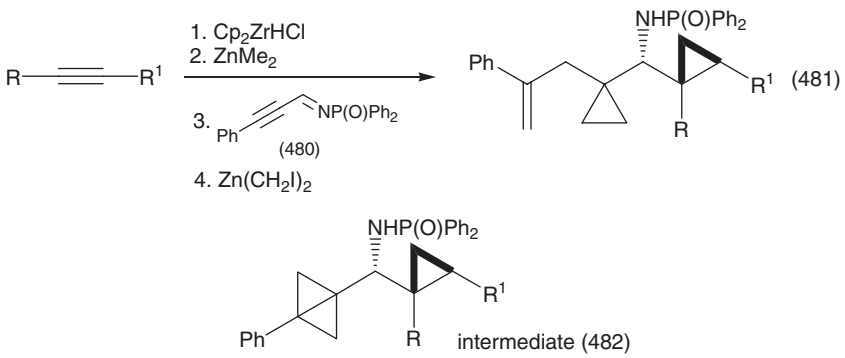
Scheme 110

Thermally induced and UV-light mediated alcoholysis reactions of 2,3-oxaphosphabicyclo [2.2.2] octenes bearing sterically demanding substituents at the P-atom (475) with different alcohols were studied. The observed sensitivity to steric effects suggests that phosphonylation of alcohols follows two parallel pathways which are consistent with EA and $S_N(2)P$ (or AE) mechanisms (Figure 90).[210]

The intermediacy of phosphonoamidic-sulfonic anhydride (476) in the rearrangement of O-sulfonyl-N-phosphinoylhydroxylamine (477) with tert-butylamine was confirmed. The observed products, phosphonoamidate anion (478) and phosphonic diamide (479) correspond to attack of tert-butylamine at sulphur and phosphorus atoms of the anhydride (Scheme 110).[211]

It has been discovered that the one-pot reaction of alkynylzirconocenes with alkynyl imines (480), dimethylzinc and a zinc carbenoid, leads to unprecedented C,C-dicyclopropylmethylamines (481) as single isomers. This reaction proceeds *via* the rare bicyclo[1.1.0]butane intermediates (482). This novel methodology tolerates a number of common protecting groups used in synthesis (Scheme 111).[212]

Both Me-DuPHOS (483) and Me-DuPHOS monoxide (484) have been successfully used as chiral ligands in the copper catalysed highly enantioselective addition of dialkylzinc to N-phosphinoyl imines (485). A simple deprotection of N-protecting group from (486) provided α-chiral amines (Figure 91).[213,214]



Scheme 111

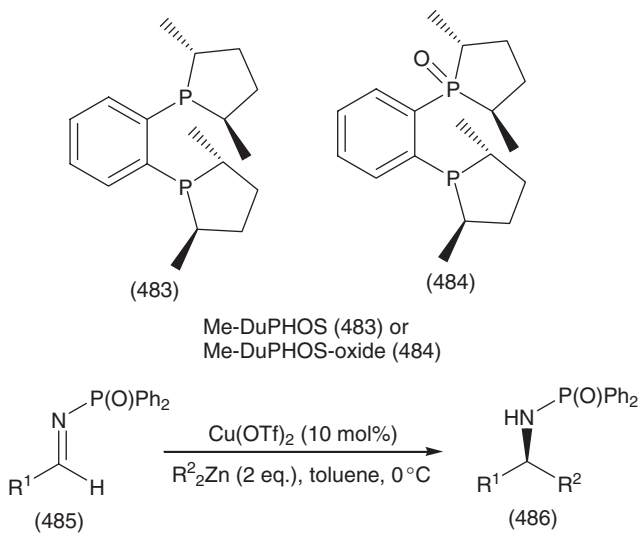


Figure 91

The highly enantioselective and diastereoselective asymmetric Mannich–type reaction of N-phosphinoylimines (487) with hydroxyketone (488) was catalysed by (S,S) linked BINOL, affording N-phosphinylated aminoalcohols (489). The observed complementary anti-selectivity, in combination with the facile removal of diphenylphosphinoyl group make this reaction synthetically attractive (Figure 92).[215]

Systematic studies on the asymmetric Strecker reaction of N-diphenylphosphinoyl imines (490) catalysed by $Gd(O\text{-}iPr)_3$ complexes with D-glucose derived ligands has been reported. A wide range of aliphatic, alicyclic, aromatic and heterocyclic imines were investigated. Particularly high enantioselectivity was obtained with the combined use of a catalytic amount of TMSCN and a stoichiometric amount of HCN as reagents and with a chiral gadolinium complex of (491) as the catalyst. The products were converted to disubstituted α-amino acids and their derivatives (Figure 93).[216–218]

The most effective route to aminoalcohol (493) was established by screening various stereochemically homogeneous N,N-disubstituted-, N-monosubstituted-amino alcohols and iminoalcohols as chiral additives to promote asymmetric addition of alkylzinc to N-diphenylphosphinoyl imine (492). The addition reactions that were performed in the presence of this compound resulted in excellent enantioselectivity (Figure 94a).[219]

Three deuterated analogues of 5-diethoxyphosphonyl-5-methyl-1-pyrrolidine N-oxide (DEPMPO) (494), (495) and (496) were synthesised and used to trap tert-butylperoxide radical (Figure 94b).[220]

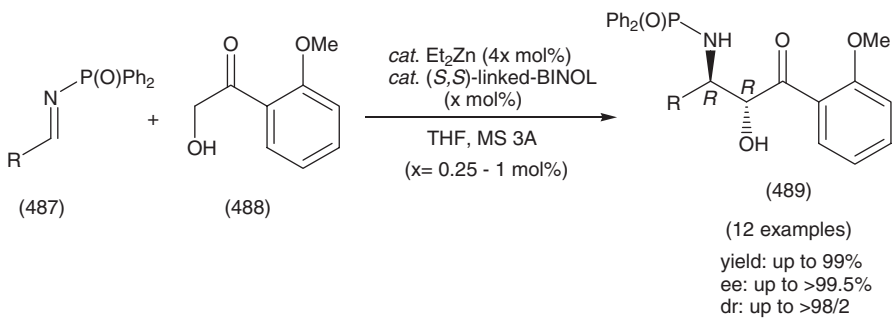


Figure 92

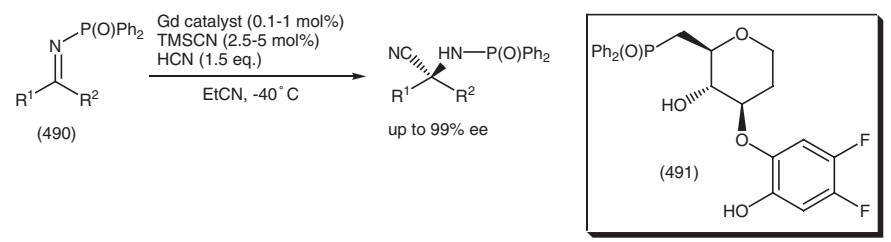


Figure 93

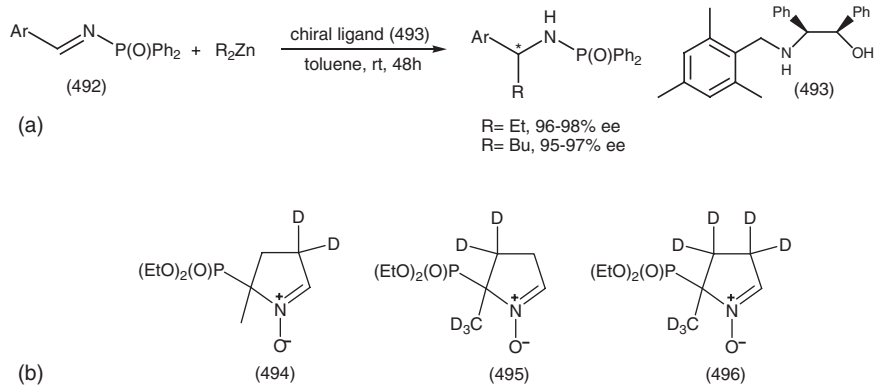


Figure 94

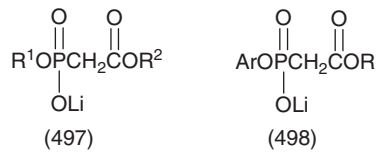


Figure 95

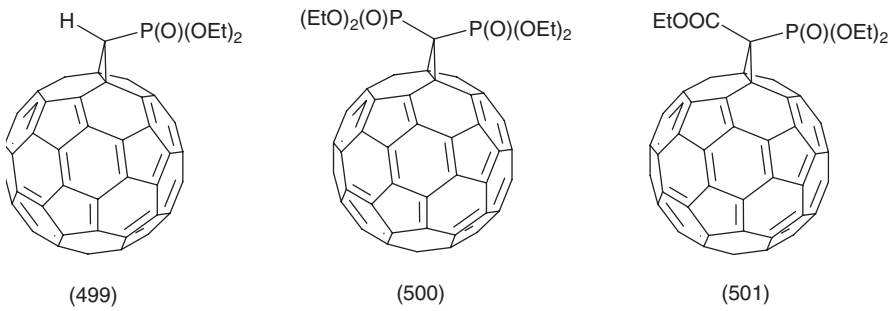
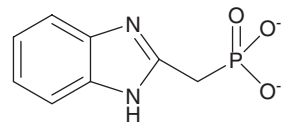


Figure 96

It has been observed that the lithium salts of phosphono acetates (497) and (498) undergo base catalysed D/H proton exchange and C-OR esterolysis as well as acidic hydrolysis mediated by Th^{4+} and Zn^{4+} (Figure 95).[221]

Three new phosphonate derivatives of C_{60} methanofullerenes (499), (500) and (501) were synthesized. Their electrochemical behavior and the pathways involved in the retrocyclopropanation reactions were also investigated (Figure 96).[222]

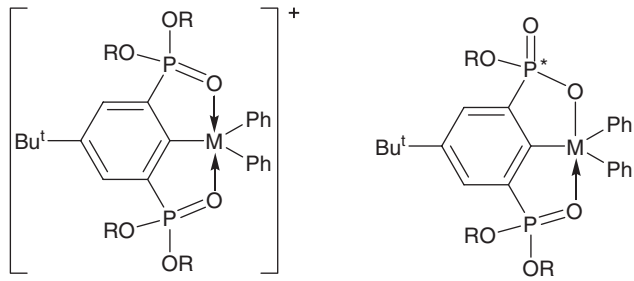
Acid-base properties of (^{1}H-benzimidazol-2-yl-methyl)phosphonate ($Bimp^{2-}$) (502) were investigated. Evidence for intramolecular hydrogen bond formation in aqueous solution between (N-1)H and the phosphonate group was presented (Figure 97).[223]



$Bimp^{2-}$

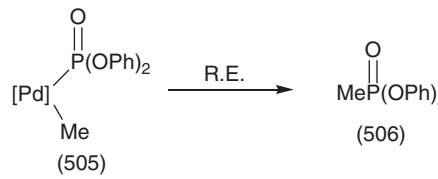
(502)

Figure 97



(503) M= Sn, Si R= Pr^i, Et (504)

Figure 98



(505) (506)

Figure 99

The cyclization reaction of organosilicon and organotin compounds containing the O–C–O coordinated Pincer-type ligand $\{4\text{-tertBu-2,6-}[P(O)(OR)_2]_2C_6H_2\}^-$ (R = i-Pr,Et) has been studied. O^{18}-labeling experiments revealed a mechanism according to which hypercoordinated trioganoelement cations (503) were transformed into benzoxaphosphastannols and benzoxaphosphasilole (504) respectively, depending on the identity of M (Figure 98).[224]

Transformation of intermediate complexes $L_2PdMe[P(O)(OPh)_2]$ (505) into diphenyl methylphosphonate (506) has been studied using discrete model substrates. The electronic and steric effects of the supporting ligands were characterized by measurements of the reductive elimination rates from a series of complexes containing nitrogen- or phosphine-based ligands (Figure 99).[225]

The cycloisomerization of various 1,6-enynes containing a modified chain has been investigated to provide cyclopentanes (507) with a great potential as novel conformationally – restricted analogues of farnesyl diphosphate FDP (508) (Figure 100).[226]

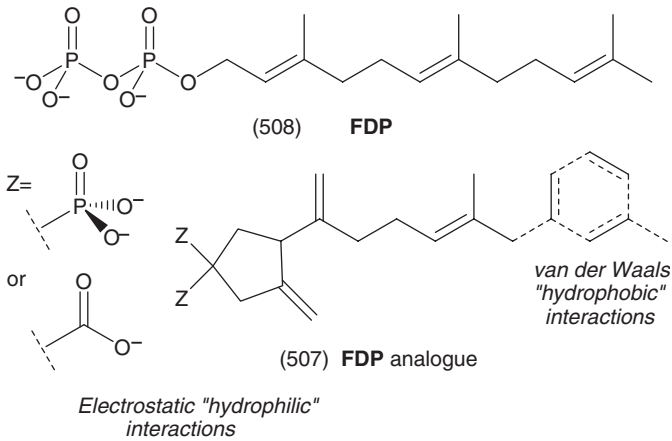


Figure 100

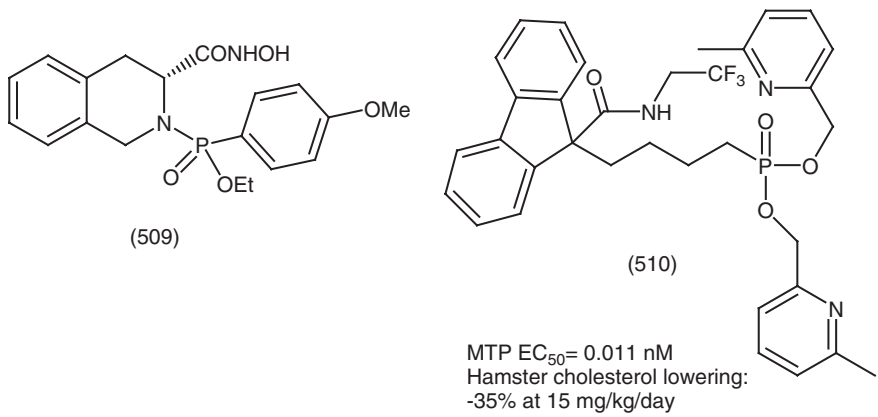


Figure 101

3.3 Selected Biological Aspects. – A novel series of phosphonamide based TACE inhibitors were discovered. The (S)- form of D-leucine derivative (509) showed potent inhibitory activity against TACE with a highly selective profile. The different binding mode of this type of compound is likely to enhance its selectivity for TACE. The study reveals the potential of the phosphonamide derivatives as a new type of MP inhibitor, and provides a novel concept for the design of selective inhibitors.[227] A number of newly synthesized (Figure 101) phosphonate esters were evaluated for their effects on microsomal triglyceride transfer protein activity (MTP) e.g. (510).[228] A series of phosphonothioic acids (511) and corresponding phosphonic acids (512) have been synthesized and their inhibitory properties were compared towards human placental and *E. coli* alkaline phosphatases, the protein-tyrosine phosphatase from Yersinia, and the serine/threonine protein phosphatases PP2C and lambda. It was found that,

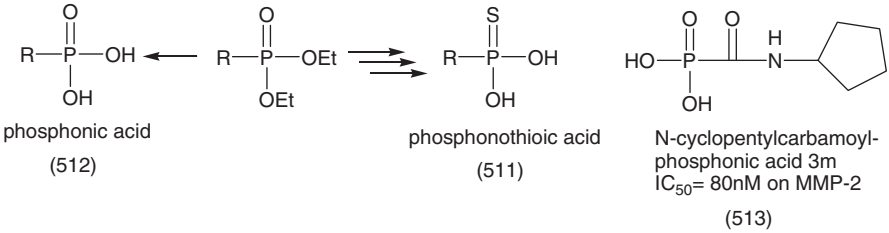


Figure 102

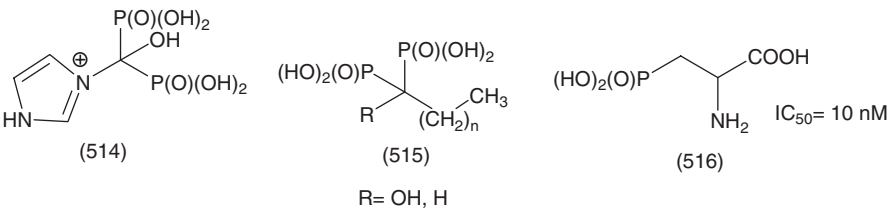


Figure 103

with some exceptions, differences in inhibitory properties were modest.[229] Several alkyl- and cycloalkylcarbamoylphosphonic acids have been obtained which (*in vitro*) inhibit selectively MMP-2 and are effective in preventing tumor cell dissemination *in vivo*. Further, some of these compounds showed enhanced anticancer properties. It was found that N-cyclopentylcarbamoylphosphonic acid (513) is the most active compound in the series studied (Figure 102).[230] The activities of bisphosphonates as inhibitors of the Leishmania major mevalonate/isoprene biosynthesis pathway enzyme, farnesyl pyrophosphate synthase, have been reported. The results obtained represent the first detailed quantitative structure-activity relationship study of the inhibition of an expressed farnesyl pyrophosphate synthase enzyme by bisphosphonate inhibitors and show that the activity of these inhibitors can be predicted within about a factor of 3 by using 3D-QSAR techniques.[231] The bisphosphonate (514) was the most active (Figure 103).[231–233] Bisphosphonates, e.g. (515), derived from fatty acids were shown to be potent inhibitors of Trypanosoma cruzi farnesyl pyrophosphate synthetase.[234] 2-Amino-3-phosphono propionic acid (AP3) (516) is a potent multisubstrate inhibitor of GFAT.[235] Phosphonate substrates (517) were prepared and shown to act as competitive inhibitors of IM Pase, while product mimics (518) showed various inhibitory modes of action (Figure 104).[236] The diastereoselective synthesis of a new class of potent phosphinic pseudopeptide metalloprotease inhibitors has been reported. A strategy to produce rapidly P'_1-deversified phosphinic pseudopeptides (519) led to the identification of inhibitors able to discriminate MMP-11 from other MMPS with a two-order magnitude of selectivity. This results confirm the efficiency of phosphinic peptide chemistry for the development of highly selective inhibitors of zinc-metalloproteases (Figure 104a).[237,238] The synthesis of phosphonate (520) and its use for

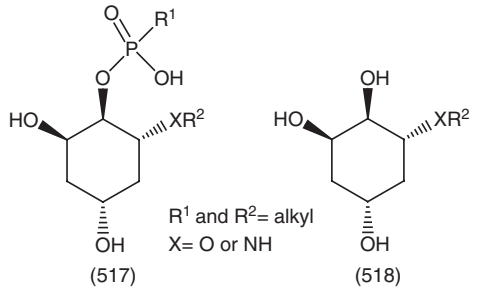


Figure 104

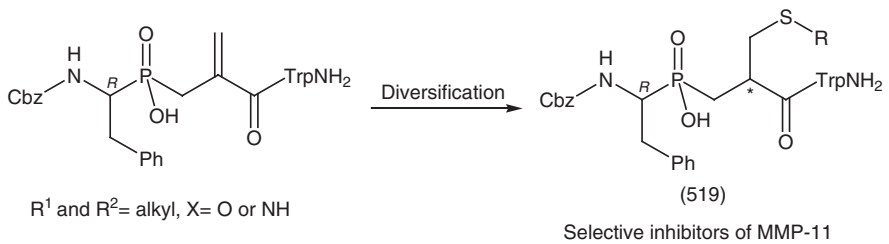


Figure 104a

the preparation of a Grb2 SH2 domain-directed tripeptide (521) has been reported. In extracellular ELISA-based assays (521), exhibits potent Grb2 SH2 domain binding affinity (IC_{50} = 8nM) (Figure 104) (Figure 105).[239]

The first Grb2 SH2 domain binding ligands derived from carboxamido-based macrocyclization of the pTyr mimetic β-position (522) have been presented (Figure 105a).[240]

The enantiomers of a novel unsaturated phosphonocholine antitumor ether lipid (523) were synthesized and found to have differential antiproliferative effects against epithelial cancer cell lines. The basis of the enantioselective effects on the cells was investigated in SK-N-MC and SK-N-SH neuroblastoma tumor cells (Figure 106).[241] The immunological characterization of (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) (Figure 106) (524) and its methylenediphosphonate analogue, HMB-PCP (525) has been described. With an EC_{50} of 0.1−0.2 μM, HMB-PP is significantly more potent in stimulating human Vγ9/Vδ2T cells than any other compound described so far. However, replacing the pyrophosphate by a P-CH_2-P function abrogates the bioactivity drastically, with HMB-PCP having a EC_{50} of only 5.3 μM (Figure 107).[242]

An antigenic peptide analogue consisting of HIV gp 120 residues 421–431 (an antigen recognition site probe) with diphenyl amino(4-amidinophenyl)- methanephosphonate located at the C-terminus (a catalytic site probe) (526) was synthesized and its trypsin and antibody reactivity characteristics were studied (Figure 108).[243]

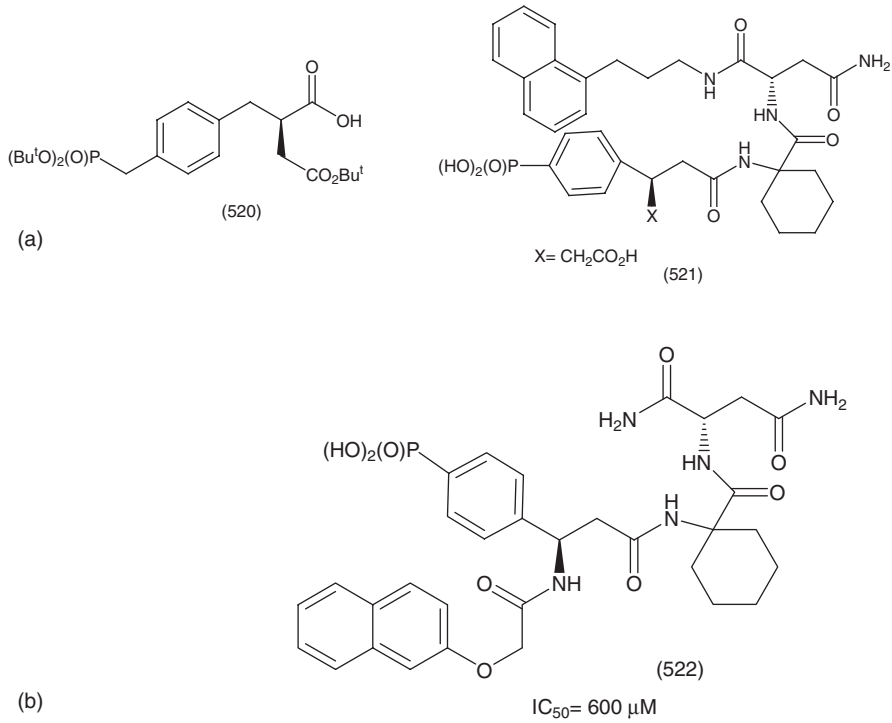


Figure 105

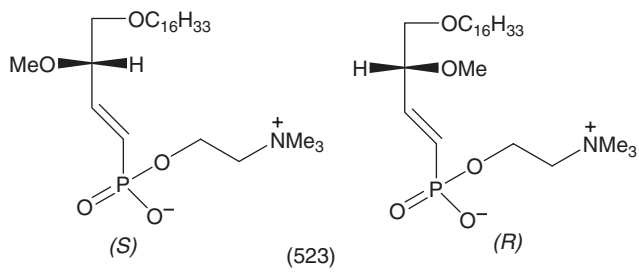
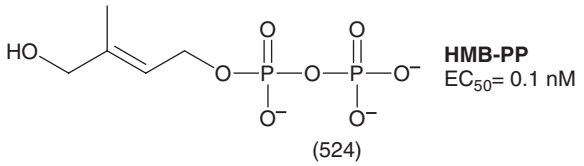


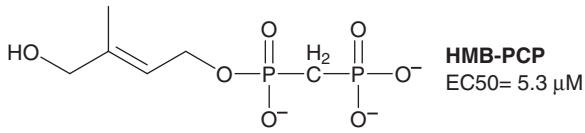
Figure 106

Prodrugs of FR900098 with increased oral anti-malarial efficacy were obtained by masking the polar phosphonate moiety as acyloxyalkyl esters. The acyloxyethyl ester (527), which is expected to release only acetic acid and acetaldehyde upon hydrolysis in addition to the active compound, was at least twice as active as FR900098 (Figure 109).[244]

The metabolically stabilized LPA analogue, 1-oleoyl-2-methyl-rac-glycerophosphothioate (OMPT) is a potent agonist for the LPA_3G-protein-coupled receptor. A new enantiospecific synthesis of both (2R)-OMPT and (2S)-OMPT has been described (Figure 109b).[245]

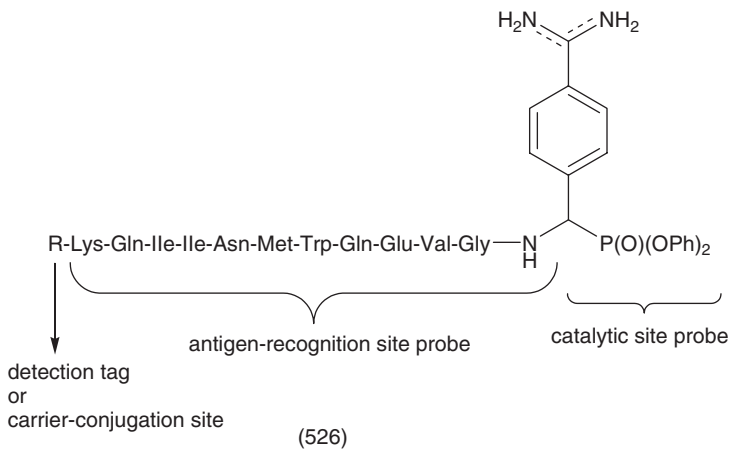


(524)



(525)

Figure 107



(526)

Figure 108

4 Structure

2-Ethoxy-2-oxo-1,4,2-oxazaphosphinanes (2S,5S)- and (2R,5S) (528) were synthesized. Both diastereomers were used in NMR and X-ray crystallographic studies that permitted unequivocal configurational assignment, as well as examination of the consequence of $n_O \rightarrow O^*_{P-O}$ stereoelectronic interactions on structural properties (Figure 110).[246]

1,3,2-Dioxaphosphorinane derivatives containing a substituent with different steric arrangement at the C5 position (529)–(532) have been prepared. Their conformations and configurations were determined by ^1H, ^{31}P NMR and X-ray crystallographic techniques. Both chair-twisted-chair and chair-boat equilibra were observed in solution. X-Ray analysis revealed in one case two independent molecules per asymmetric unit, one with chair and the other one with a boat conformation (Figure 111).[247]

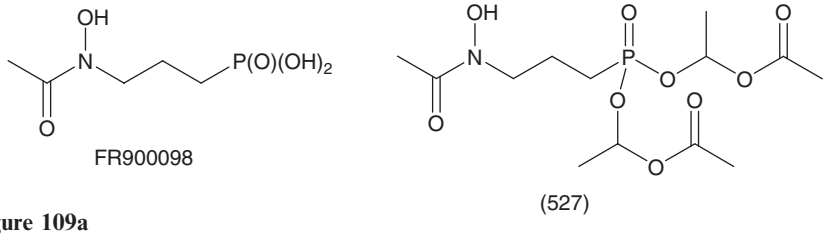


Figure 109a

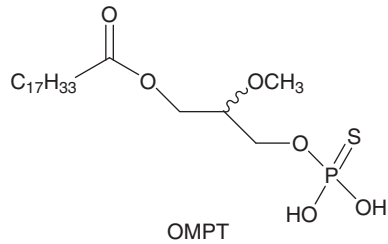


Figure 109b

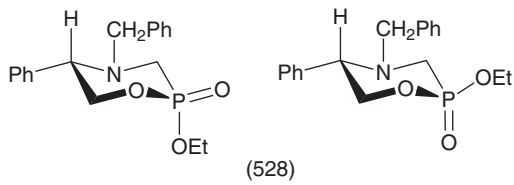


Figure 110

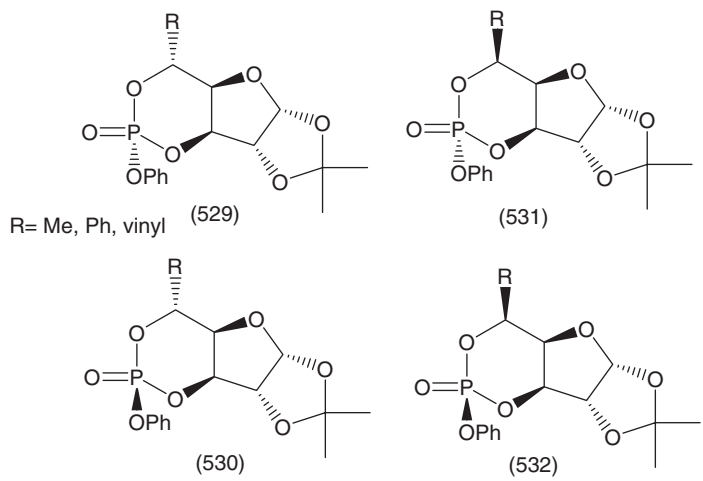
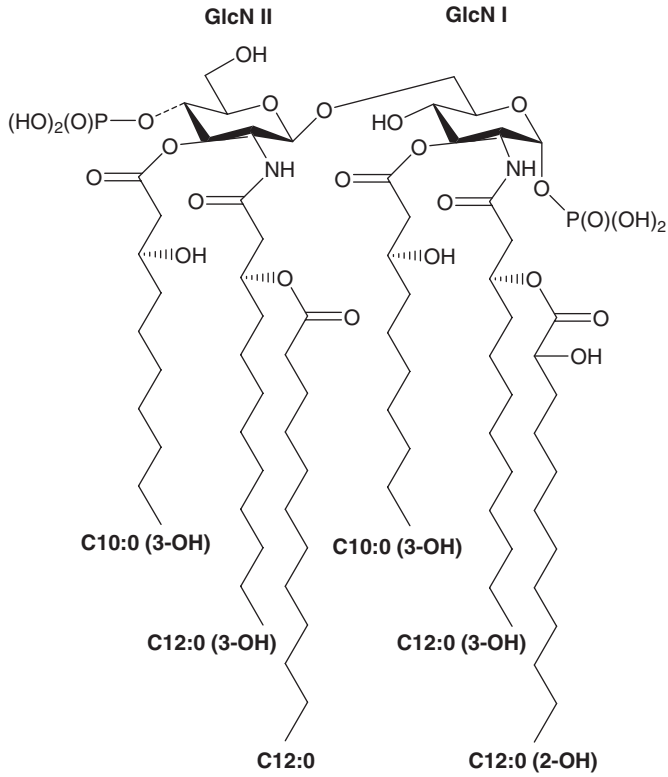


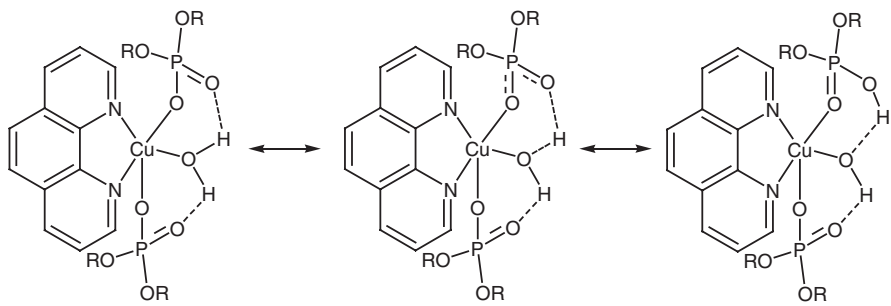
Figure 111

Diastereomeric 5-tert-butyl-4-methyl-2-phenoxy-2-oxo-1,3,2-dioxophosphorinanes were synthesized and studied by NMR and computational methods, assuming a novel criteria in which the conformations and configurations depend upon the conformation and configuration of the corresponding diol



(533)

Figure 112



(534)

Figure 113

precursors.[248] The chemical structure of lipid A from the lipopolysaccharide of the plant-associated bacterium *Pseudomonas cichorii* (533) was elucidated by compositional analysis and the spectroscopic methods MALDI-TOF and 2D NMR (Figure 112).[249]

The synthesis and structural elucidation of a copper mononuclear complex (534) at three different temperatures 293, 203 and 93 K provides evidence for the involvement of phosphoryl oxygen in the activation of the O–H bond of the coordinated water molecule through intramolecular hydrogen bonding while additional intermolecular C–H–O interactions shed light on the role of natural ligands in the activation of phosphate ester linkages and provide useful snap-shots of various steps in metal-catalysed phosphate ester hydrolysis (Figure 113).[250]

References

1. O. Molt and T. Schrader, *Synthesis*, 2002, 2633.
2. J.M. Kuiper, R. Hulst and J.B.N. Engberts, *Synthesis*, 2003, 695.
3. P. Rovnaňik and M. Černik, *J. Fluorine. Chem.*, 2004, **125**, 83.
4. Y. Hayakawa, M. Hyodo, K. Kimura and M. Kataoka, *Chem. Commun. (Cambridge)*, 2003, 1704.
5. E.J. Amigues and M.E. Migand, *Tetrahedron Lett.*, 2004, **45**, 887.
6. A. Whitehead, J.D. Moore and P.R. Hauson, *Tetrahedron Lett.*, 2003, **44**, 4275.
7. B. Kaboudin, *Tetrahedron Lett.*, 2002, **43**, 8713.
8. H. Oshida, A. Ishii and J. Nakayama, *Tetrahedron Lett.*, 2004, **45**, 1331.
9. Z. Zalán, T. Martinek, L. Lázár and F. Fülöp, *Tetrahedron*, 2003, **59**, 9117.
10. A. Jeziorna, J. Heliński and B. Krawiecka, *Tetrahedron Lett.*, 2003, **44**, 3239.
11. P.P. Onyśko, O.A. Suvalova, Y.V. Russukana, T.I. Chudakova and A.D. Simitsa, *Tetrahedron Lett.*, 2003, **44**, 1855.
12. Y. Hwang and P.A. Cole, *Organic Letters*, 2004, **6**, 1555.
13. L. Ma, J.C. Morgan, W.E. Stancill and W.E. Allen, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1075.
14. A. Maderna, R. Huertas, M.F. Hawthorne, R. Luguya and M.G.H. Vicente, *Chem. Commun. (Cambridge)*, 2002, 1784.
15. K. Fuji, K. Maki, M. Kanai and M. Shibuasaki, *Organic Letters*, 2003, **5**, 733.
16. J.-L. Giner, *Tetrahedron Lett.*, 2002, **43**, 5457.
17. D.S. Rawal and R.A. Gibbs, *Organic Letters*, 2002, **4**, 3027.
18. G. Soldaini, F. Cardona and A. Goti, *Tetrahedron Lett.*, 2003, **44**, 5589.
19. H. Bielawska and M. Michalska, *Tetrahedron Lett.*, 2004, **45**, 2263.
20. S.J. Mills, K. Backers, C. Erneux and B.V.L. Potter, *Organ. Biomol. Chem.*, 2003, **1**, 3546.
21. J. Lu, K.N. Jayaprakash, U. Schlueter and B. Fraser-Reid, *J. Am. Chem. Soc.*, 2004, **126**, 7540.
22. K. Pekan and R.R. Schmidt, *J. Org. Chem.*, 2003, **68**, 1295.
23. Y. Tanaka, Y.N. Nakahara, H. Hojo and Y. Nakahara, *Tetrahedron*, 2003, **59**, 4059.
24. P.W. Rzepecki and G.D. Prestwich, *J. Org. Chem.*, 2002, **67**, 5454.
25. J. Shin, O. Gerasimov and D.H. Thompson, *J. Org. Chem.*, 2002, **67**, 6503.
26. C.L. Franklin, H. Li and S.F. Martin, *J. Org. Chem.*, 2003, **68**, 7298.
27. L. Vares, A.V. Koulov and B.D. Smith, *J. Org. Chem.*, 2003, **68**, 10073.

28. Y.-A. Kim, H.-M. Chung, J.-S. Part, W. Choi, J. Min, N.-H. Park, K.A. Kim, G.-J. Jhon and S.-Y. Han, *J. Org. Chem.*, 2003, **68**, 10162.
29. H.-S. Lim, Y.-S. Oh, P.-G. Suh and S.-K. Chung, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 237.
30. H.-S. Lim, J.-J. Park, K. Ko, M.-H. Lee and S.-K. Chung, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2499.
31. X. Lu, S. Cseh, H.-S. Byun, G. Tigyi and R. Bittman, *J. Org. Chem.*, 2003, **68**, 7046.
32. G.A. Elsayed and G.-J. Bonns, *Synlett*, 2003, 1373.
33. D.M. Rothman, M.E. Vazquez, E.M. Vogel and B. Imperiali, *J. Org. Chem.*, 2003, **68**, 6795.
34. V. Maraval, J. Pyzowski, A.-M. Caminade and J.-P. Majoral, *J. Org. Chem.*, 2003, **68**, 6043.
35. V. Maraval, R. Laurent, B. Donnadieu, A.-M. Caminade and J.-P. Majoral, *Synthesis*, 2003, 389.
36. A. Núnez, D. Berroterán and O. Núnez, *Org. Biomol. Chem.*, 2003, **1**, 2283.
37. N. Asaad and A.J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1708.
38. A.J. Kirby, M.F. Lima, D. da Silva and F. Nome, *J. Am. Chem. Soc.*, 2004, **126**, 1360.
39. F. Caturla, J. Enjo, M.C. Bernabeu and St.Le. Serre, *Tetrahedron*, 2004, **60**, 1903.
40. I.K.-H. Um, S.-E. Jeon, M.-H. Baek and H.-R. Park, *Chem. Commun. (Cambridge)*, 2003, 3016.
41. J.S. Tsang, A.A. Neverov and R.S. Brown, *J. Am. Chem. Soc.*, 2003, **125**, 1559.
42. J.S. Tsang, A.A. Neverov and R.S. Brown, *J. Am. Chem. Soc.*, 2003, **125**, 7602.
43. F. Terrier, E. Le Guével, A.P. Chatrousse, G. Montiers and E. Buncel, *Chem. Commun. (Cambridge)*, 2003, 600.
44. D.N. Kevill and B. Miler, *J. Org. Chem.*, 2002, **67**, 7399.
45. J.B. Dominigos, E. Longhinotti, C.A. Bunton and F. Nome, *J. Org. Chem.*, 2003, **68**, 7051.
46. S. Jones and D. Selitsianos, *Organic Letters*, 2002, **4**, 3671.
47. S. Jones and C. Smammoo, *Tetrahedron Lett.*, 2004, **45**, 1585.
48. J. Baraniak, R. Kaczmarek, D. Korczyński and E. Wasilewska, *J. Org. Chem.*, 2002, **67**, 7267.
49. K. Zmudzka, B. Nawrot, T. Chojnacki and W.J. Stec, *Organic Letters*, 2004, **6**, 1385.
50. Hu Cheng, I. Nicolic-Hughes, J.A. Wang, H. Deng, P.J. O'Brien, L.W.Z.-Y. Zhang, D. Herschlag and R. Callender, *J. Am. Chem. Soc.*, 2002, **124**, 11295.
51. O. Iranzo, A.Y. Kovalevsky, J.R. Morrow and J.P. Richard, *J. Am. Chem. Soc.*, 2003, **125**, 1988.
52. J.C. Mareque-Rivas, R.T. Martin de Rosales and S. Parsons, *Chem. Commun. (Cambridge)*, 2004, 610.
53. F. Medrano, A. Calderón and A.K. Yatsimirsky, *Chem. Commun. (Cambridge)*, 2003, 1968.
54. S.L. Tobey and E.V. Anslyn, *J. Am. Chem. Soc.*, 2003, **125**, 14807.
55. T. Tsuda, S. Nakamura and S. Hashimoto, *Tetrahedron Lett.*, 2003, **44**, 6453.
56. L.A. Carpino, J. Xia and A. El-Faham, *J. Org. Chem.*, 2004, **69**, 62.
57. H. Matsuhashi and K. Shimada, *Tetrahedron*, 2002, **58**, 5619.
58. M. Pohlman and U. Kazmaier, *Organic Letters*, 2003, **5**, 2631.
59. U. Piarulli, Ch. Claverie, Ph. Daubos, C. Gennari, A.J. Minnaard and B.L. Feringa, *Organic Letters*, 2003, **5**, 4493.

60. D. Crich, M. Shirai and S. Rumthao, *Organic Letters*, 2003, **5**, 3767.
61. F. Sartillo-Piscil, M. Vargas, C.A. de Parrodi and L. Quinterro, *Tetrahedron Lett*., 2003, **44**, 3919.
62. R. Pedrosa, A. Maestro, A. Pérez-Encabo and R. Raliegos, *Synlett*, 2004, 1300.
63. E.E. Lee and R.A. Batey, *Angew. Chem. Int. Ed*., 2004, **43**, 1865.
64. B. Chen and A.K. Mapp, *J. Am. Chem. Soc*., 2004, **126**, 5364.
65. R.W. Kinas, A. Okruszek and W.J. Stec, *Tetrahedron Lett*., 2002, **43**, 7875.
66. K. Błażejewska and T. Gajda, *Tetrahedron*, 2003, **59**, 10249.
67. C. Grison, A. Thomas, F. Coutrot and Ph. Coutrot, *Tetrahedron*, 2003, **59**, 2101.
68. R.V. Smaliy, A.A. Chaikovskaya, A.M. Pinczuk and A.A. Tolmachov, *Synthesis*, 2003, 2525.
69. S.S. Kinderman, J.A. Maarseveen, H.E. Schoemaker, H. Hiemstra and F.P.J.T. Rutjes, *Synthesis*, 2004, 1413.
70. V.N. Yarovenko, A.V. Shirkov, J.V. Zawarzin, O.N. Krupinova, A.V. Ignatenko and M.M. Krayushkin, *Synthesis*, 2004, 17.
71. J.A. Miller, *Tetrahedron Lett*., 2002, **43**, 7111.
72. I. Maciągiewicz, P. Dybowski and A. Skowrońska, *Synthesis*, 2003, 723.
73. E. Krawczyk, K. Owsianik, A. Skowrońska, M. Wieczorek and W. Majzner, *New. J. Chem*., 2002, **26**, 1753.
74. I. Maciągiewicz, P. Dybowski and A. Skowrońska, *Tetrahedron*, 2003, **59**, 6057.
75. L.D.S. Yadov and R. Kapoor, *Synthesis*, 2002, 1502.
76. A. Chetia, A. Saikia, Ch.J. Saikia and R.C. Boruah, *Tetrahedron Lett*., 2003, **44**, 2741.
77. M. Stratakis, C. Rabalakos and N. Sofikiti, *Tetrahedron Lett*., 2003, **44**, 349.
78. Z. Li, Z. Zhou, K. Li, L. Wang, O. Zhou and Ch. Tang, *Tetrahedron Lett*., 2003, **43**, 7609.
79. P. Marchand, L. Griffe, A.-M. Caminade, J.-P. Majoral, M. Destarac and F. Leising, *Organic Letters*, 2004, **6**, 1309.
80. C.-O. Turrin, V. Maraval, J. Leclaire, E. Dantras, C. Lacabanne, A.-M. Caminade and J.-P. Majoral, *Tetrahedron*, 2003, **59**, 3965.
81. G.M. Salamończyk, *Tetrahedron Lett*., 2003, **44**, 7449.
82. A. Kanibolotsky, S. Roquet, M. Cariou, Ph. Lerche, C.-O. Turrin, R. de Bettignies, A.-M. Caminade, J.-P. Majoral, V. Khodorkovsky and A. Gorgues, *Organic Letters*, 2004, **6**, 2109.
83. G. Magro, A.-M. Caminade and J.-P. Majoral, *Tetrahedron Lett*., 2003, **44**, 7007.
84. A. Mäntyla, T. Garnier, J. Rautio, T. Navalainen, J. Vepsäläinen, A. Koskinen, S.L. Croft and T. Järvinen, *J. Med. Chem*., 2004, **47**, 188.
85. J. Juntunen, J. Vepsäläinen, R. Niemi, K. Laine and T. Järvinen, *J. Med. Chem*., 2003, **46**, 5083.
86. L. Hu, C. Yu, Y. Jiang, J. Han, Z. Li, P. Browne, P.R. Race, R.J. Knox, P.F. Searle and E.I. Hyde, *J. Med. Chem*., 2003, **46**, 4818.
87. K. Zobel, M.F.T. Koehler, M.H. Beresini, L.D. Caris and D. Combs, *Bioorg. Med. Chem. Lett*., 2003, **13**, 1513.
88. L. Qian, Y. Xu, Y. Hasegawa, J. Aoki, G.B. Mills and G.D. Prestwich, *J. Med. Chem*., 2003, **46**, 5575.
89. B. Walkowiak, J. Baraniak, Cz. Cierniewski and W.J. Stec, *Bioorg. Med. Chem. Lett*., 2002, **12**, 1959.
90. U. Muus, C. Kranz, T. Marquardt and C. Meier, *Eur. J. Org. Chem*., 2004, 1228.
91. B.H. Heasley, R. Jarosz, K.R. Lynch and T.L. Macdonald, *Bioorg. Med. Chem. Lett*., 2004, **14**, 2699.

92. R. Wang, S. Harada, H. Mitsuya and J. Zemlicka, *J. Med. Chem.*, 2003, **46**, 4799.
93. Y. Xu, L. Qian, A.V. Pontsler, T.M. McIntyre and G.D. Prestwich, *Tetrahedron*, 2004, **60**, 43.
94. Y. Tamaruya, M. Suzuki, C. Kamura, M. Karnai, K. Hama, K. Shimizu, J. Aoki, H. Arai and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2004, **43**, 2834.
95. Q. Zhu, X. Huang, G.Y.J. Chen and S.Q. Yao, *Tetrahedron Lett.*, 2003, **44**, 2669.
96. N. Maeda, Y. Takeuchi, M. Takada, Y. Namba and N. Oku, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1015.
97. C. Lopin, G. Gouhier, A. Gouhier and S.R. Piettre, *J. Org. Chem.*, 2003, **68**, 9916.
98. C.M. Jessop, A.F. Parsons, A. Routledge and D. Irvine, *Tetrahedron Lett.*, 2003, **44**, 479.
99. H.M.L. Davies and G.H. Lee, *Organic Letters*, 2004, **6**, 2117.
100. N. Psychogios and J.B. Regnouf-de-Vains, *Tetrahedron Lett.*, 2002, **43**, 7691.
101. O. Kasyan, D. Świerczyński, A. Drapailo, K. Suwińska, J. Lipkowski and V. Kalchenko, *Tetrahedron Lett.*, 2003, **44**, 7167.
102. G.W. Kabalka and S.K. Guchhait, *Organic Letters*, 2003, **5**, 729.
103. G.W. Kabalka, S.K. Guchhait and A. Naravane, *Tetrahedron Lett.*, 2004, **45**, 4685.
104. Y. Shen and P. Li, *J. Fluorine Chem.*, 2003, **125**, 63.
105. R. Ruzziconi, G. Ricci, A. Gioiello, H. Couthon-Gourves and J.-P. Gourves, *J. Org. Chem.*, 2003, **68**, 736.
106. G.F. Solberghe and J.E. Marko', *Tetrahedron Lett.*, 2002, **43**, 5061.
107. S. Arrimori, R. Kouno, T. Okauchi and T. Minami, *J. Org. Chem.*, 2002, **67**, 7303.
108. X.-K. Xu, Z.-W. Chen, J. Sun, K. Liu, W. Chen, W. Shi, H.-M. Wang and Y. Liu, *J. Org. Chem.*, 2002, **67**, 7624.
109. T. Kurz, D. Geffken and K. Widyan, *Tetrahedron*, 2004, **60**, 2409.
110. W.H. Abdou, N.A.F. Ganoub and Y.O. El Khoshnieh, *Synlett*, 2003, **785**.
111. A. Peng and Y. Ding, *Synthesis*, 2003, 205.
112. K.J.M. Bersford, *Tetrahedron Lett.*, 2002, **43**, 7175.
113. M. Shi and G.-L. Zhao, *Tetrahedron Lett.*, 2002, **43**, 9171.
114. K. Afarinkia and Hiu-wan Yu, *Tetrahedron Lett.*, 2003, **44**, 781.
115. D.G. Lou, Y. Gao, J.H. Voigt, K. Lee, M.C. Nicklaus, L. Wu, Z.-Y. Zhang and T.R. Burke Jr, *Bioorg. Med. Chem.*, 2003, **13**, 3005.
116. G. Hum, J. Lee and S.D. Taylor, *Bioorg. Med. Chem.*, 2002, **12**, 3471.
117. C. Lopin, G. Gouhier and S. Piettre, *Tetrahedron Lett.*, 2003, **44**, 8837.
118. S. Inoue, T. Okauchi and T. Minami, *Synthesis*, 2003, 1971.
119. Y.V. Rassukana, P.P. Onys'ko, A.G. Grechukha and A.D. Sinitsa, *Eur. J. Org. Chem.*, 2003, 4181.
120. K. Shioji, A. Tashiro, S. Shibata and K. Okuma, *Tetrahedron Lett.*, 2003, **44**, 403.
121. T. Yamagishi, T. Kusano, B. Kaboudin, T. Yokomatsu, C. Sakuma and S. Shibuya, *Tetrahedron*, 2003, **59**, 767.
122. P.A. Turhanen, R.N. Niemi, M. Peräkylä, T. Järvinen and J.J. Vepsäläinen, *Org. Biomol. Chem.*, 2003, **1**, 3223.
123. E. Guenin, E. Degache, J. Liquier and M. Lecouvey, *Eur. J. Org. Chem.*, 2004, 2983.
124. P. Turhabnen and J.J. Vepsäläinen, *Synthesis*, 2004, 992.
125. Y. Zhang, Jin.-feng Li and Cheng-ye Yuan, *Tetrahedron*, 2003, **59**, 473.
126. E. Årstad and L. Skattebøl, *Tetrahedron Lett.*, 2002, **43**, 8711.
127. N. Azizi and M.P. Saidi, *Tetrahedron Lett.*, 2003, **44**, 7933.
128. F. Orsini and A. Caselli, *Tetrahedron Lett.*, 2002, **43**, 7255.
129. F. Orsini and A. Caselli, *Tetrahedron Lett.*, 2002, **43**, 7259.

130. O. Meyer, C. Grosdemange-Billiard, D. Trisch and M. Rhomer, *Org. Biomol. Chem.*, 2003, 4367.
131. K. Wang, Y. Zhang and C. Yuan, *Org. Biomol. Chem.*, 2003, **1**, 3564.
132. F. Orsini, E. Di Teodoro and M. Ferrari, *Synthesis*, 2002, 1683.
133. K. Afarinkia, A. Faller and A.J. Twist, *Synthesis*, 2003, 357.
134. A. Rodrigues, E. Vinhato, R. Rittner and P.R. Olivato, *Synthesis*, 2003, 1248.
135. M.S. Marma, B.A. Kashemirov and C.E. Mc Kenno, *Biorg. Med. Chem. Lett.*, 2004, **14**, 1787.
136. Y. Du and D. Wiemer, *J. Org. Chem.*, 2002, **67**, 5701.
137. Y. Du and D. Wiemer, *J. Org. Chem.*, 2002, **67**, 5709.
138. Y. Du, K.-Y. Jung and D.F. Wiemer, *Tetrahedron Lett.*, 2002, **43**, 8665.
139. K. Swierczek, J.W. Peters and A.C. Hengge, *Tetrahedron*, 2003, **59**, 595.
140. D.L. Fox, N.R. Whitly, R.J. Cohen and R.N. Salvatore, *Synlett*, 2003, 2037.
141. B. Kaboudin and N. As-Habei, *Tetrahedron Lett.*, 2003, **44**, 4243.
142. B. Kaboudin, *Tetrahedron Lett.*, 2003, **44**, 1051.
143. D.G. Piotrowska and A. Wróblewski, *Tetrahedron*, 2003, **59**, 8405.
144. A. Szabo, Z.M. Jaszy, L. Hegedus, L. Töke and I. Pethenazy, *Tetrahedron Lett.*, 2003, **44**, 4603.
145. K. Błażewska, D. Sikora and T. Gajda, *Tetrahedron Lett.*, 2003, **44**, 4747.
146. C.K. Mc Clure and P.K. Mishra, *Tetrahedron Lett.*, 2002, **43**, 5249.
147. C. Pouset and M. Larchevêque, *Tetrahedron Lett.*, 2002, **43**, 5257.
148. F. Meyer, A. Laaziri, A.M. Papini, J. Uziel and S. Jugé, *Tetrahedron*, 2004, **60**, 3593.
149. A.S. Kende, H.-Q. Dong, X. Liu and F.H. Ebetino, *Tetrahedron Lett.*, 2002, **43**, 4979.
150. H. Kraiem, M.J. Abdullah and H. Amri, *Tetrahedron Lett.*, 2003, **44**, 553.
151. C. Yuan, C. Xu and Y. Zhang, *Tetrahedron*, 2003, **59**, 6095.
152. X. Qi, S.-H. Lee, J.Y. Kwon, Y. Kim, S.J. Kim, Y.-S. Lee and J. Yoon, *J. Org. Chem.*, 2003, **68**, 9140.
153. N.N. Serqeeva, A.S. Golubev, L. Henning and K. Burger, *Synthesis*, 2003, 915.
154. M.C. Fernandez, M. Ruiz, V. Ojea and J.M. Quintela, *Tetrahedron Lett.*, 2002, **43**, 5909.
155. M. Ruiz, V. Ojea, J.M. Quintela and J. Guillin, *Chem. Commun.*, 2002, 1600.
156. M. Mikołajczyk, J. Łuczak and P. Kiełbasiński, *J. Org. Chem.*, 2002, **67**, 7872.
157. B. Bessieres, A. Schoenfelder, C. Verrat, A. Mann, P. Ornstein and C. Pedregal, *Tetrahedron Lett.*, 2002, **43**, 7659.
158. M. Ordonez, R. de la Cruz-Cordero, C. Quinones and A. Gonzalez-Morales, *Chem. Commun.*, 2004, 672.
159. P. Moreau and M. Maffei, *Tetrahedron Lett.*, 2004, **45**, 743.
160. S. Han, R.A. Moore and R.E. Viola, *Synlett*, 2003, 845.
161. K. Lee, M. Zhang, D. Yang and T.R. Burke Jr., *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3399.
162. V.K. Brel, *Synthesis*, 2002, 1829.
163. P. Tongcharoensirikul, A.I. Suarez, T. Voelker and C.M. Thompson, *J. Org. Chem.*, 2004, **69**, 2322.
164. H.-J. Cristau, A.H. Herve and D. Virieux, *Tetrahedron*, 2004, **60**, 877.
165. A. Mucha, M. Pawełczak, J. Hurek and P. Kafarski, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3113.
166. G.D. Joly and E.N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 4102.
167. M. Soroka and K. Kołkodziejczyk, *Tetrahedron Lett.*, 2003, **44**, 1863.

168. J.H. Han, B. Sin, Lee, S.Y. Lee and H.Y. Lee, *Tetrahedron Lett*., 2003, **44**, 5811.
169. S. Fürmeier, M.M. Lau, M.S.F. Lie, A. Lützen and J.O. Metzger, *Eur. J. Org. Chem*., 2003, 4874.
170. Ai.-Yun Peng and Yi.-Xiang Ding, *Organic Letters*, 2004, **6**, 1119.
171. J.D. Moore, K.T. Sprott and P.R. Ranson, *J. Org. Chem*., 2002, **67**, 8123.
172. M. Maffei and G. Buono, *Tetrahedron*, 2003, **59**, 8821.
173. J. Moravcova, H. Heissigerova, P. Kocalka, A. Imberty, D. Sykora and M. Fris, *Tetrahedron Lett*., 2003, **44**, 8797.
174. M. Bosco, P. Bissere and J. Eustache, *Tetrahedron Lett*., 2003, **44**, 2347.
175. F. Bissert, J.-G. Boiteau and J. Eustache, *Tetrahedron Lett*., 2003, **44**, 2351.
176. H.J. Cristau, J. Monbrum, M. Tillard and J.-L. Pirat, *Tetrahedron Lett*., 2003, **44**, 3183.
177. V.K. Reddy, B. Harihata, T. Oshikawa and M. Yamashita, *Tetrahedron Lett*., 2004, **45**, 2851.
178. B. Haritha, V.K. Reddy, M. Takahashi and M. Yamashita, *Tetrahedron Lett*., 2004, **45**, 5339.
179. F. Palacios, A.M. Ochoa de Retana, S. Pacual and R. Lopez de Munain, *Tetrahedron Lett*., 2002, **43**, 5917.
180. S. Aime, C. Cavallotti, G. Gianolio, G.B. Giovenzana, G. Palmisano and M. Sisti, *Tetrahedron Lett*., 2002, **43**, 8387.
181. F. Liu, D.C. Palmer and K.L. Sorgi, *Tetrahedron Lett*., 2004, **45**, 1869.
182. A.G.M. Barret, B.T. Hopkins, A.C. Love and L. Tedeschi, *Org. Lett*., 2004, **6**, 835.
183. P.M.P. Gois and C.A.M. Afonso, *Eur. J. Org. Chem*., 2003, 379.
184. S. Kim, C. Ho Cho and C. Jo Lim, *J. Am. Chem. Soc*., 2003, **125**, 9574.
185. A. Inoue, H. Shinokubo and K. Oshima, *J. Am. Chem. Soc*., 2003, **125**, 1484.
186. A. Drąg, A. Jezierska and P. Kafarski, *Chem. Commun*., 2004, 1132.
187. E. Pfund, S. Masson, M. Vazeux and T. Lequeux, *J. Org. Chem*., 2004, **69**, 4670.
188. H. Krawczyk, W.M. Wolf and M. Śliwiński, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2794.
189. H. Krawczyk and M. Śliwiński, *Tetrahedron*, 2003, **59**, 9199.
190. H. Krawczyk and M. Śliwiński, *Synthesis*, 2002, 1351.
191. A. Mucha and P. Kafarski, *Tetrahedron*, 2002, **58**, 5855.
192. K. Afarinkia, L.C. Jones and H.W. Yu, *Synlett*, 2003, 509.
193. K. Afarinkia and C.L. Jones, *Synlett*, 2003, 513.
194. A. Henry-dit-Quesnel, L. Toupet, J.-C. Pommelet and T. Lequeux, *Org. Biol. Chem*., 2003, **1**, 2486.
195. M. Mikołajczyk, P. Bałczewski, H. Chewczyńska and A. Szadowiak, *Tetrahedron*, 2004, **60**, 3067.
196. F. Gagosz and S.Z. Zard, *Synlett*, 2003, 387.
197. D.Y. Kim and D.F. Wiemer, *Tetrahedron Lett*., 2003, **44**, 2803.
198. P.M. Cullis and M.J.P. Harger, *J. Chem. Soc. Perkin Trans. 2*, 2002, 1538.
199. Y. Li, S.D. Aubert and F.M. Raushel, *J. Am. Chem. Soc*., 2003, **125**, 7526.
200. H. Firouzabadi, N. Iranpoor and S. Sobhani, *Synthesis*, 2004, 290.
201. Y.V. Rassukana, P.P. Onys'ko, K.O. Davydova and A.D. Sinista, *Tetrahedron Lett*., 2004, **45**, 3899.
202. Y. Xu and D. Prestwich, *Org. Lett*., 2002, **4**, 4021.
203. M. Amedjkouh and K. Westerlund, *Tetrahedron Lett*., 2004, **45**, 5175.
204. A. Al Aziz Quntar and M. Srebnik, *Chem. Commun. (Cambridge)*, 2003, 58.
205. O. Baurm, A. Al Aziz Quntar, V.M. Dembitsky and M. Srebnik, *Tetrahedron*, 2004, **60**, 1359.

206. S. Hanessian and P. Compain, *Tetrahedron*, 2002, **58**, 6521.
207. Y. Kobayashi and A.D. William, *Org. Lett*., 2002, **4**, 4241.
208. J. Perez-Prieto, R.E. Galian, M.A. Miranda, F. CaFalinc, N. Martin-Vargas and F. Lopez-Ortiz, *Org. Lett*., 2004, **6**, 561.
209. (*a*) M.J. Harger and C. Preston, *Chem. Commun. (Cambridge)*, 2003, 2200; (*b*) M.J. Harger and C. Preston, *Org. Lett*., 2004, **4**, 561.
210. S. Jankowski, G. Keglevich, T. Nonas, H. Forintos, M. Główka and J. Rudziński, *Tetrahedron*, 2004, **60**, 2789.
211. M.J.P. Harger, *Org. Biomol. Chem*., 2003, **1**, 3390.
212. P. Wipf, C.R.J. Stephenson and K. Okumura, *J. Am. Chem. Soc*., 2003, **125**, 14694.
213. A.A. Boezio and A.B. Chavette, *J. Am. Chem. Soc*., 2003, **125**, 1692.
214. A. Boezio, J. Pytkowicz, A. Coté and A.B. Charatte, *J. Am. Chem. Soc*., 2003, **125**, 14260.
215. S. Matsunaga, N. Kumagai, S. Harada and M. Shibasaki, *J. Am. Chem. Soc*., 2003, **125**, 4712.
216. S. Masumoto, H. Usuda, M. Suzuki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc*., 2003, **125**, 5634.
217. N. Kato, M. Suzuki, M. Kanai and M. Shibasaki, *Tetrahedron Lett*., 2004, **45**, 3009.
218. N. Kato, M. Suzuki, M. Kanai and M. Shibasaki, *Tetrahedron Lett*., 2004, **45**, 3153.
219. H.-L. Zhang, F. Jiang, X.-M. Zhang, X. Cui, L.-Z. Gong, A.Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *Chem. Eur. J*., 2004, **10**, 1305.
220. J.-L. Clément, J.-P. Finet, C. Fréjaville and P. Tordo, *Org. Biomol. Chem*., 2003, **1**, 1591.
221. R.A. Moss and P. Gong, *Tetrahedron Lett*., 2003, **44**, 7845.
222. M. Ocafrain, M.A. Herranz, L. Marx, C. Thilgen, F. Diederich and L. Echegoyen, *Chem. Eur. J*., 2003, **9**, 4811.
223. M.J. Sanchez-Moreno, R.B. Gomez-Coca, A. Fernandez-Botello, J. Ochocki, A. Kotyński, R. Griesser and H. Sigel, *Org. Biomol. Chem*., 2003, **1**, 1819.
224. K. Peveling, M. Henn, C. Low, M. Mehrling, M. Schürmann, B. Costisella and K. Jurkschat, *Organometallics*, 2004, **23**, 1501.
225. R.A. Stockland, A.M. Levine, M.T. Giovine, J.A. Guzei and J.C. Cannistra, *Organometallics*, 2004, **23**, 647.
226. I.J.S. Fairlamb, A.C. Pike and S.P.C.P. Ribrioux, *Tetrahedron Lett*., 2002, **43**, 5327.
227. M. Sawa, K. Kurokawa, Y. Inoue, H. Kondo and K. Yoshino, *Biolog. Med. Chem. Lett*., 2003, **13**, 2021.
228. D.R. Magnin, S.A. Biller, J. Wetterau, J.A. Robel, K. Dickson Jr., P. Taunk, T.W. Harrity, R.M. Lawrence, C.-Q. Sun, T. Wang, J. Logan, O. Fryszman, F. Connolly, K. Jolibois and L. Kunselman, *Bioorg. Med. Chem. Lett*., 2003, **13**, 1337.
229. K. Swierczek, A.S. Pandey, J.W. Peters and A.C. Hengge, *J. Med. Chem*., 2003, **46**, 3703.
230. E. Breuer, C.J. Salomon, Y. Katz, W. Chen, S. Lu, G.-V. Röschenthaler, R. Hander and R. Reich, *J. Med. Chem*., 2004, **47**, 2826.
231. J.M. Sanders, A.O. Gomez, J. Mao, G.A. Meints, E.M. Van Brussel, A. Burzyńska, P. Kafarski, D. Gonzales-Pacanowska and E. Oldfield, *J. Med. Chem*., 2003, **46**, 5171.
232. E. Katsikorou and E. Oldfield, *J. Med. Chem*., 2003, **46**, 2932.

233. J.M. Sanders, S. Ghosh, J.M.W. Chan, A. Burzyńska, P. Kafarski, G.T. Morita and E. Oldfield, *J. Med. Chem.*, 2004, **47**, 375.
234. S.H. Szajmman, A. Montalvetti, Y. Wang and R. Docompo, JH.B. Rodriguez, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3231.
235. S.V. Chittur and R.K. Grifith, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2639.
236. D.J. Miller, M.B.-U. Sufraz, M. Akhtar, D. Gani and R.K. Allemann, *Org. Biomol. Chem.*, 2004, **2**, 671.
237. A. Makaritis, D. Georgiadis, V. Dive and A. Yiotakis, *Chem. Eur. J.*, 2003, **9**, 2079.
238. M. Matziari, F. Beau, F. Cinasse, V. Dive and A. Yiotakis, *J. Med. Chem.*, 2004, **47**, 325.
239. C.-Q. Wei, B. Li, R. Guo, D. Yang and T.R. Burke Jr., *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2781.
240. K. Lee, M. Zhang, H. Liu, D. Yang and T.R. Burke Jr, *J. Med. Chem.*, 2003, **46**, 2621.
241. P. Samadder, R. Bittman, H.-S. Byun and G. Arthur, *J. Med. Chem.*, 2004, **47**, 2710.
242. A. Reichenberg, M. Hintz, Y. Kletschek, T. Kuhl, Ch. Hang, R. Engel, J. Moll, D.N. Ostrovsky, H. Jomma and M. Eberl, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1257.
243. H. Taguchi, G. Burr, S. Karle, S. Planque, Y.-X. Zhou, S. Paul and Y.N. Shiyama, *Bioorg. Med. Chem. Lett.*, 2003, **12**, 3167.
244. R. Ortmann, J. Wiesner, A. Reichenberg, D. Henschker, E. Beck, H. Jom and M. Schlitzer, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2163.
245. L. Qian, Y. Xu, Y. Hasegawa, J. Aoki, G.B. Mills and G.D. Prestwich, *J. Med. Chem.*, 2003, **46**, 5575.
246. I. Linzaga, J. Escalante, M. Munoz and E. Juaristi, *Tetrahedron*, 2002, **58**, 8973.
247. F. Sartillo-Piscil, S. Cruz, H. Sánchez, H. Höpfl, G. Anaya de Parrodi and L. Quintero, *Tetrahedron*, 2003, **59**, 4077.
248. F. Sartillo-Piscil, M. Snachez, S. Cruz-Gregorio and L. Qintero, *Tetrahedron*, 2004, **60**, 3001.
249. A. Molinaro, A. Silipo, R. Lanzetta, M. Parrilli, P. Malvagna, A. Evidente and G. Surico, *Eur. J. Org. Chem.*, 2002, 3119.
250. R. Murugavel, M. Sathiyendiran, R. Pothiraja and R.J. Butcher, *Chem. Commun. (Cambridge)*, 2003, 2546.

Pentacoordinated and Hexacoordinated Compounds

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Summary

The three years since SPR 33 have seen considerable activity in the field of hypervalent phosphorus chemistry especially in the area of hexacoordinate and pseudo-hexacoordinate phosphorus compounds. In this respect, the Holmes' group have made further, substantial contributions to the subject of N, O and S donor interaction at hypervalent phosphorus and the relevance of such interactions to the mechanism of phosphoryl transfer enzymes. The utility of proazaphosphatranes as catalysts (or co-catalysts) has been established by Verkade *et al*. in an impressive range of synthetic procedures and both Kawashima and Akiba have reported outstanding work on bicyclic phosphorane systems, carbaphosphatranes and the relevance of anti-apicophilic phosphorane systems to the mechanism of the Wittig reaction. The Lacour group has detailed the use of C_2-symmetric hexacoordinated phosphate anions for enantiodifferentiation of organic and organometallic cations and last, but not least, Gillespie *et al*. have produced a thought-provoking review on bonding in penta- and hexacoordinated molecules.

Regrettably, this contribution must be my swan song. After 25 years, age, the call of the golf course, choral singing, bridge and a part-time involvement with the Katritzky group in Gainesville, Florida (home of the Gators) persuades me that it is time to hand over the reins to a younger, more perceptive mind. I should add, however, that it has been a great pleasure to work with a number of patient and highly dedicated senior reporters plus of course, the talented technical editing staff of the RSC. I am also indebted to Profesors Donald Denney and Alan Katritzky for reading and commenting on the manuscript. Finally, my sincere thanks are due to my wife, Jean Hall, who has typed all of these articles (and quite a few more over the years) without, as she plainly says, understanding a word. This, I am sure you will agree, is well above and beyond the call of duty.

Organophosphorus Chemistry, Volume 35

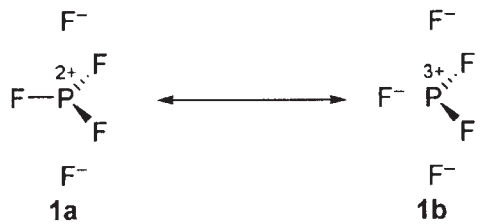
1 Introduction

The three years since June 2001 have seen a mini-revival of interest in penta- and hexacoordinated phosphorus chemistry. Several important reviews have appeared, the first of which by Gillespie and Silvi,[1] shows that there is no fundamental difference between bonds in hypervalent and non-hypervalent molecules and hence challenges the usefulness of the term ''hypervalency''. An accompanying paper by Gillespie *et al.*[2] emphasizes this point and shows that the total population of the valence shell in phosphorus compounds varies from 9.44 (PMe_5) through 7.15 (PCl_5) to 5.37 (PF_5) indicative of something close to five pure covalent bonds in PMe_5 but the equivalent of only *ca.* 2.5 covalent bonds in PF_5. Thus the latter molecule is largely ionic and could be represented approximately by two resonance structures (1a and 1b) with either three or two covalent bonds respectively. Group 16 (S, Se and Te) and Group 17 elements were subjected to the same topological analysis of the electron localization function (ELF) and although examples from the Group 17 elements were limited, similar overall conclusions were reached. These important papers make a substantial impact on the understanding of bonding in ''hypervalent'' molecules.

The synthetic utility of proazaphosphatranes, so admirably exploited by Verkade and co-workers (*vide infra*), is reported in three comprehensive reviews.[3–5] Overall they deal with the synthesis, structure and basicity/nucleophilicity of the proazaphosphatranes and then cover a wide range of synthetic applications including synthesis of heterocycles (e.g. oxazoles), ylid generation, cyclizations and base, nucleophilic or metal-catalyzed cross coupling (e.g. Suzuki) reactions. Holmes has provided another substantial review, this time on the role of hypervalent phosphorus chemistry in the mechanism of phosphoryl transfer enzymes and cAMP.[6] The article delineates the tendency of phosphorus to form the hexacoordinated state from a pentacoordinated one and the influence of such a change on the mechanism of phosphoryl transfer enzymes. Factors that are discussed include transition state or intermediate anionicity, hydrogen bonding, packing effects (van der Waals forces), the ease of formation of hexacoordinate phosphorus from lower coordination states and the problem of pseudorotation as part of the mechanistic process. The fact that X-ray crystallography of isolated intermediates in displacement reactions at phosphorus does not necessarily represent the situation in solution is emphasized and the author concludes that donor bonds are likely to play a significant role in determining active site interactions.

Density function calculations on metaphosphate, acyclic and cyclic phosphates and phosphoranes have been reported. Solvent effects calculated with three well established solvation models were also analyzed and compared. The results showed that microscopic solution pK_a values increased in the order, metaphosphates [$P(O)_2OH$] < phosphates [$P(O)(OH)_n(OR)_{3-n}$, n = 1–3, R=H or Me] < phosphoranes [$P(OH)_n(OR)_{5-n}$, n =1–5, R =H or Me] with values for cyclic phosphates and cyclic phosphoranes lower than the respective acyclic molecules. Furthermore protonation of the equatorial position in phosphoranes is about 4 pK_a units lower than that found for the axial positions. Finally in

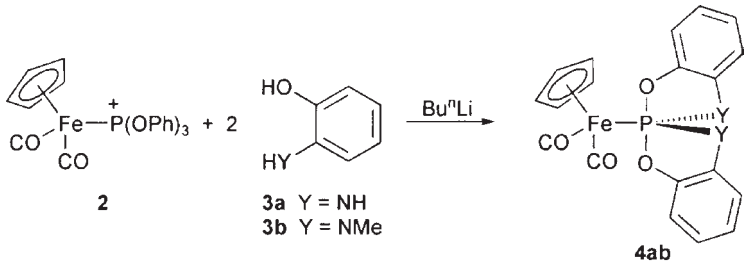
terms of bond energies, P–O single bonds in phosphates were found to be stronger than in phosphoranes, axial P–O bonds in phosphoranes were weaker than equatorial bonds by *ca.* 10 kcal mol^{-1} and P–OC bonds were more apicophilic than P–OH bonds. The authors anticipate that the results may afford quantitative insight into the structure and stability of phosphorus compounds relevant to RNA catalysis.[7]



An account has appeared on the preparation, structure and reactivity of a series of metallaphosphoranes.[8] For example, the transition metal complex (2) reacts with (3ab) to form (4ab). X-ray crystallographic analysis and spectroscopic data for these metallaphosphoranes reveal that the transition metal fragment serves as a strong π donor towards the phosphorane fragment. The account also reports the activation parameters for pseudorotation about phosphorus in several metallaphosphoranes with values ranging from 67.8 to 89.7 $kJmol^{-1}$ dependent upon the metal centre (Co, Ru or Fe) and the substituents in the Cp ring.

2 Acyclic Phosphoranes

Ab initio quantum calculations and ^{35}Cl NQR spectra show that chlorophosphoranes (5) and (6) have *tbp* structures with the pentafluorophenyl groups located in equatorial positions[9] consistent with the electronegativity of the respective groups but contrary to earlier claims regarding the same molecules.[10,11] The structure of Me_4PF has been investigated in the solid state, gas state and in solution.[12] In the solid state vibrational spectra (IR and Raman) and a single crystal X-ray structure show an ionic tetramethylphosphonium fluoride structure with the fluoride ion in an almost planar trigonal configuration surrounded by three Me_4P^+ cations. NMR spectra in a range of solvents (water-benzene) again show an ionic structure ($\delta^{31}P$ NMR, + 23.1 to + 31.3 dependent on solvent) with ^{19}F values matching those of tetramethylammonium fluoride. In the gas phase, however, vibrational spectra, quantum mechanical calculations using a variety of basis sets and gas electron diffraction (GED) studies reveal a *tbp* structure with one methyl group and the fluorine in apical positions. Thus in solution (e.g. in CH_3CN) the salt may serve as an excellent source of ''naked'' fluoride.



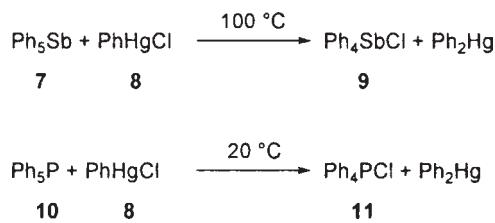
2 **3a** Y = NH **3b** Y = NMe **4ab**

$C_6F_5PCl_4$ $(C_6F_5)_2PCl_3$

5 **6**

The P–Cl^- bond strengths in hypervalent tetrahalophosphorus anions, $PF_2Cl_2^-$, $POCl_4^-$ and $PSCl_4^-$ (41–99 kJmol^{-1}) were determined by measuring thresholds for collision-induced dissociation in a flowing afterglow mass spectrometer and the differences attributed to rearrangement energies of the dissociation products. Computational results gave generally good agreement with experiment.[13]

Pentaphenylantimony (7) and pentaphenylphosphorus (10) react with phenylmercuric chloride (8) to form (9) and (11) respectively with diphenylmercury as the byproduct.[14] A similar but slightly more complex reaction occurs between (7) and ferrocenylmercuric chloride ($C_5H_5FeC_5H_4HgCl$).



7 **8** **9**

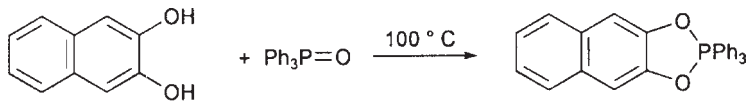
10 **8** **11**

The reaction of triphenylbismuth dichloride with sodium fluoride in acetone led to the formation of Ph_3BiF_2 and an X-ray crystal analysis of the product showed a *tbp* structure with both fluorines in axial positions.[15] It should be noted that the abstract in this paper states, erroneously, that the fluorine atoms are in equatorial positions. Gloede has shown that the reaction of 2,4,6-trichlorophenol with PCl_5 in CH_2Cl_2 gives a mixture of aryloxychlorophosphoranes $(C_6H_2Cl_3O)_nPCl_{5-n}$, n = 1–4) depending on the ratio of reactants.[16]

3 Monocyclic Phosphoranes

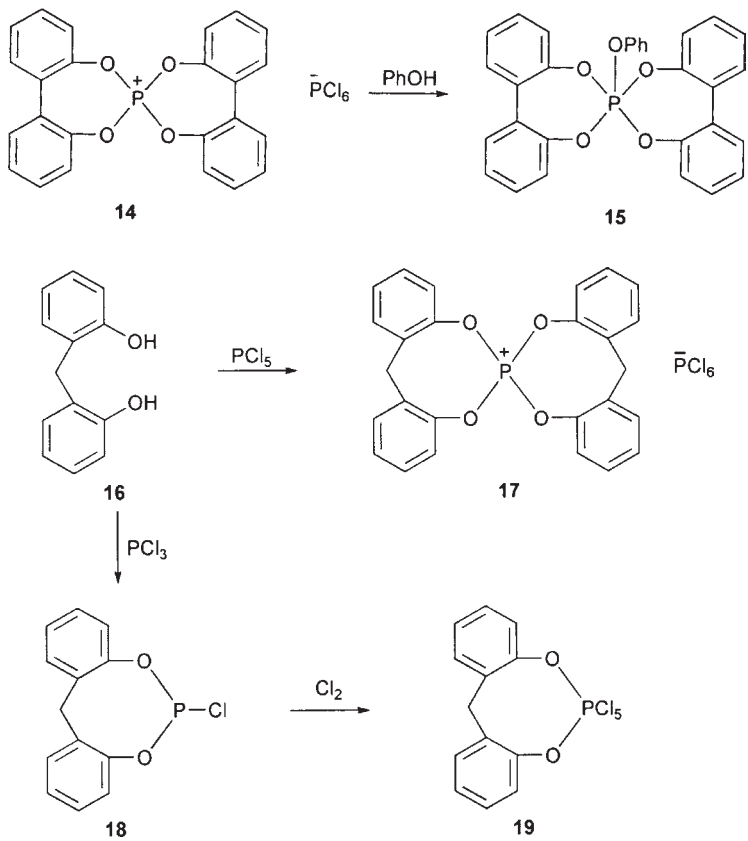
Triphenylphosphine oxide has been shown to react with *o*-dihydroxyaromatic compounds (e.g.12) to form (*o*-naphthalenedioxy)triphenylphosphorane (13) showing that the phosphoryl group is, in fact, quite reactive towards acidic

dihydroxy compounds probably as a result of the formation of a stable, five-membered ring within the pentacoordinate structure.[17]



12 **13**

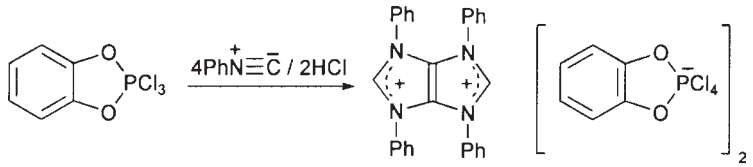
In a paper dealing with the reaction of dihydroxyarenes with PCl_5, Gloede *et al*. mention the formation of (15) from the reaction of (14) with phenol.[18] The compound was identified by its ^{31}P NMR signal at – 48 ppm. A companion paper[19] deals with the reaction of bis(2-hydroxyphenyl)methane (16) with PCl_5 and PCl_3 yielding (17) and (18) respectively, with the latter forming (19) on reaction with Cl_2. There was no mention of pentaoxy phosphoranes analogous to (15).



14 **15** **16** **17** **18** **19**

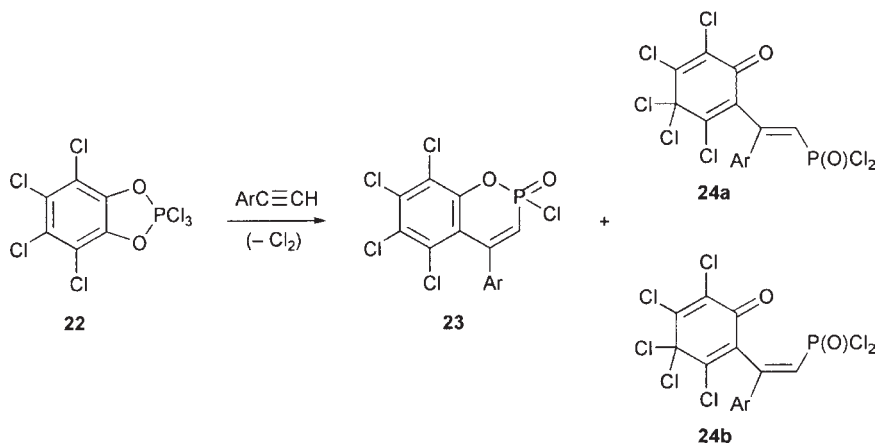
The phenylenedioxyphosphorane (20) does not react with benzonitrile but interestingly, reacts with benzoisonitrile in the presence of HCl, albeit in low

yield, to give a tetrameric dication (21) with two tetrachloro(phenylenedioxy)phosphorate counterions.[20] The structure of the product was established unequivocally by X-ray crystallography.



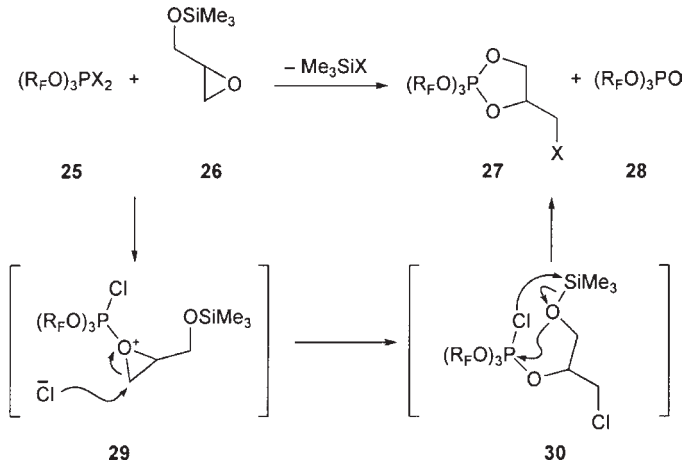
20 **21**

Further data has appeared on the reaction of arylenedioxy trihalogenophosphoranes (e.g. 20) with alkyl and aryl acetylenes.[21] To give but one example, (22) reacts with arylacetylenes to give a mixture of the expected product (23) and two quinonoid-type structures (24a, *cis*) and (24b, *trans*). The same products are obtained by the reaction of chloranil with PCl_3 and arylacetylenes. Full spectroscopic and X-ray crystallographic details of the products of these reactions have also been published.[22]



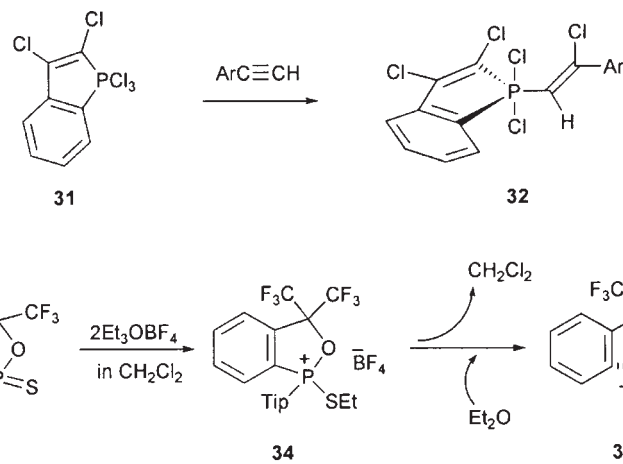
22 **23** **24a** **24b**

The reaction of fluorinated halogenophosphoranes (25) with the silyl epoxide (26) gives a mixture of (27, 70%) and (28, 15%) with X=Cl and a lower yield of (27, 27%) with X = Br. The products were characterized by ^{13}C and ^{31}P NMR and evidence is presented to suggest that the mechanism involves ring opening of the epoxide to give (30) *via* (29) followed by cyclisation to (27).[23]

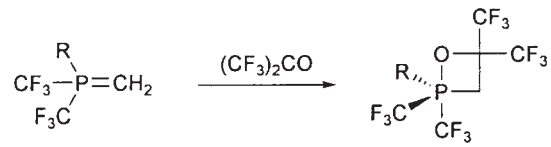


The reaction of 1-phosphaindene (31) with arylacetylenes leads to the formation of (32) and a single crystal X-ray diffraction study reveals an almost regular *tbp* with axial chlorines and the benzophosphole ring in a diequatorial configuration.[24]

Kawashima *et al*. have devised a new method for the synthesis of monocyclic phosphoranes by the reaction of the thiophosphinate (33) with triethyloxonium tetrafluoroborate to form the phosphonium salt (34) which, on exchange of the CH_2Cl_2 solvent for Et_2O, was converted quantitatively to (35) by fluoride abstraction from the counterion.[25]



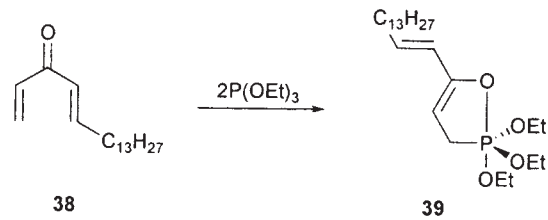
In a study of ylides containing bis(trifluromethyl) groups Röschenthaler *et al*. also reported an unusual method for the formation of monocyclic phosphoranes (37ab) by the reaction of ylide (36ab) with hexafluoroacetone.[26] The products were characterized by ^{1}H, ^{19}F, ^{31}P NMR, mass spectrometry and elemental analysis.



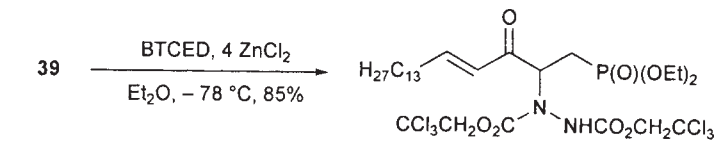
36a R = Me
36b R = Me_2N

37a δ^{31}P–60.7
37b δ^{31}P–51.5

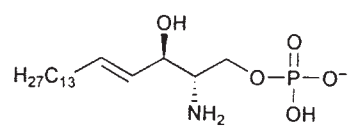
In an elegant extension of their pentacoordinate oxaphospholene methodology which uses the phosphorane as an enolate equivalent, McClure and Mishra synthesized (39) from (38) and triethyl phosphite and then proceeded to show that (39) could be converted to (40) a potential precursor to the biologically important sphingosine-1-phosphate (41).[27]



38 **39**

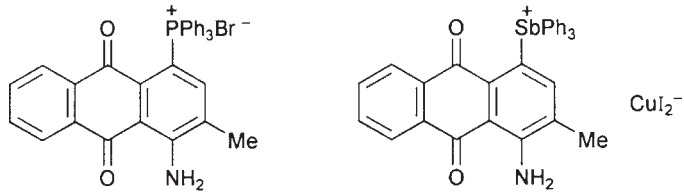


40



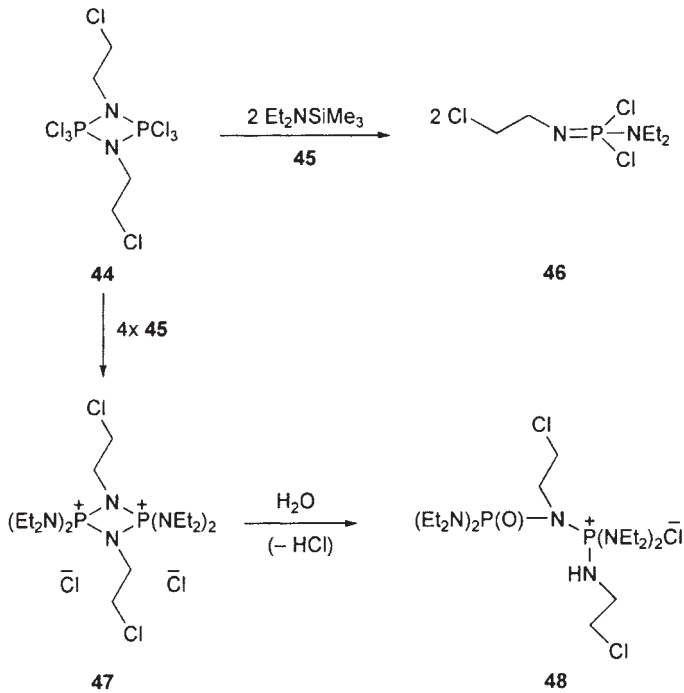
41

Allen *et al.* describe the synthesis and X-ray crystallographic studies of (42) and (43) in which there appears to be hypervalent interaction between the carbonyl oxygens and either the phosphonium or stibonium centres. The conclusion relies largely on the oxygen 'onium center bond distance at 2.661Å for (42) and 2.497Å for (43), both well within the respective van der Waals radii of 3.35Å and 3.75Å. In both structures, the Group 15 element and the carbonyl oxygen are bent out of the plane of the anthraquinone system but the extent of the deformation is less with (43) suggesting a genuine hypervalent interaction.[28]



42 **43**

The reaction of (44) with two equivalents of diethylaminotrimethylsilane (45) gave (46) whereas use of excess (45) gave (47) which was hydrolysed to (48) in the absence of base.[29] All the products were characterized by single crystal X-ray structure determinations.

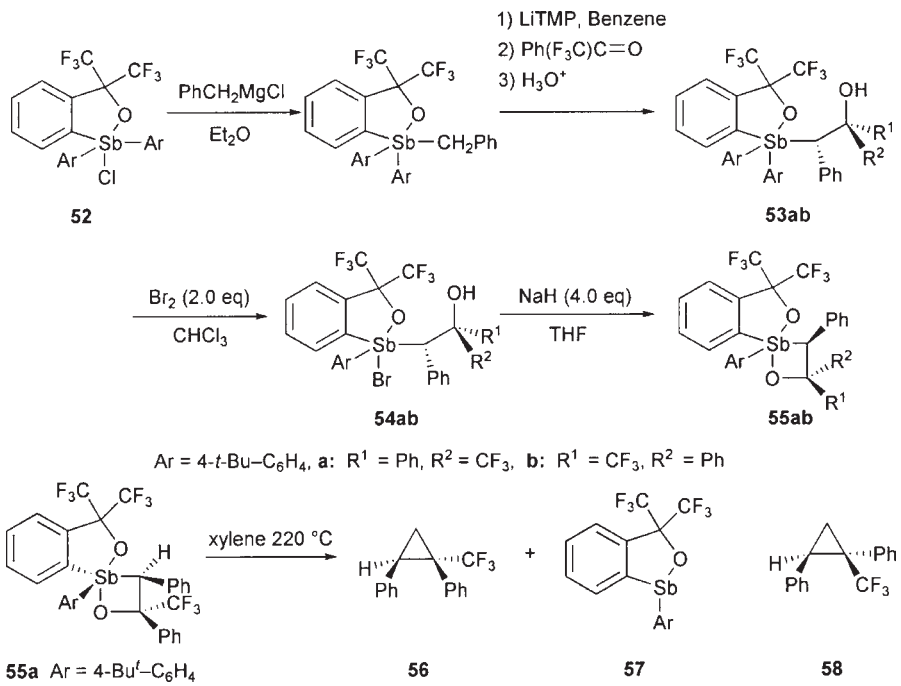


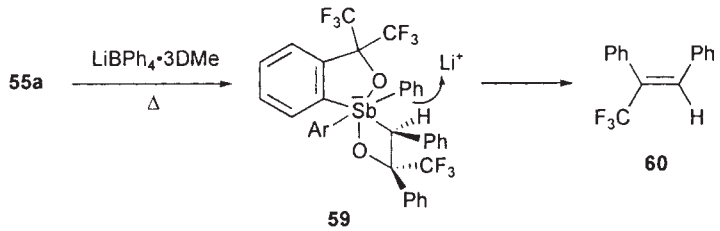
A series of tetracoordinate and pentacoordinate heterocyclic compounds containing P, S or Si within three-membered rings has been investigated by applying an electron-pair bond model for hypervalent molecules.[30] In the case of pentacoordinated phosphorus, axial-equatorial configuration of the three-membered ring (49a) is at a local minimum whereas the di-equatorial isomer (49b) is a T.S. on the pseudorotation pathway. The same holds true for (50) but with N in the three-membered ring, diequatorial disposition of the ring (as in 51) is preferred and the bond model analysis shows that the lone pairs on the N atom in the equatorial position delocalize more than those in the apical position into the equatorial P–F bonds. Hypervalent tetracoordinate three-membered heterocycles containing P, S and Si are also discussed within this paper.

49a **49b** **50** **51**

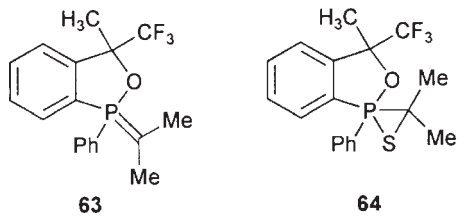
4 Bicyclic Phosphoranes

Although strictly outside the realm of phosphorus chemistry, reaction of (52) with benzylmagnesium bromide followed by treatment with lithium 2,2,6,6,tetramethylpyridine (LiTMP), trifluoroacetophenone and aqueous NH_4Cl gave (53ab) which reacted with bromine to form (54ab). The bromostiboranes were then cyclised to (55a) and (55b) and although (55b) was unstable to moisture, (55a) was isolated as a colourless crystals from hexane. X-ray crystallographic analysis of (55a) revealed a distorted *tbp* with both oxygen atoms in apical positions and the phenyl group at position 3 of the oxastibitane ring *cis* to both the aryl group on antimony and the phenyl group at position 4. Thermolysis of (55a) in *o*-xylene-d_{10} at 220°C gave (56) with retention of configuration plus the stibine (57) but there was no sign of the expected olefin (60). On the other hand, thermolysis of (55a) in the presence of LiBr in CD_3CN at 140°C gave a mixture of (56), (57) and (58). Interestingly, thermolysis of (55a) in the presence of lithium tetraphenylborate.3DME gave (60) in 85% yield together with trace amounts of (56–58). It was suggested that the reaction proceeded through a hexacoordinate antimonate (59) which collapsed to the olefinic product.[31,32]

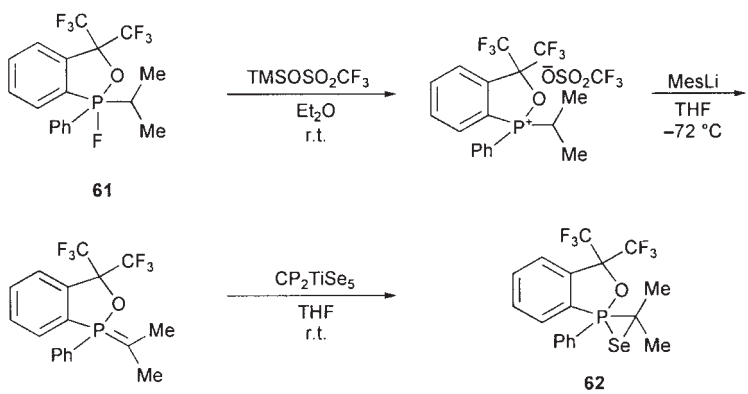




The utility of the Martin ligand has been exemplified once again in the synthesis of the first 1,2-σ^5-selenaphosphirane (62) from (61), Scheme 1,[33,34] and the first 1,2-σ^5-thiaphosphirane (64) from (63).[35] An X-ray crystallographic study of (62) showed a highly distorted *tbp* with O and Se in apical positions and an O1-P-Se bond angle of 155.82(6)° indicating a distortion from *tbp* to *sp* of 56%. In the solid state, (62) had δ^{31}P −26.1 but in solution the δ^{31}P value varied from −26.6 (C_6D_6) to −13.6 ($CDCl_3$) over a range of solvents and the values showed an approximate correlation with the acceptor number of the solvent used. A similar correlation was found with H^a of the phenyl ring and the ^{77}Se NMR signal moved to higher field in line with the acceptor number of the solvents. The results were consistent with increasing polarity of the P-Se bond with increasing solvent acceptor number.



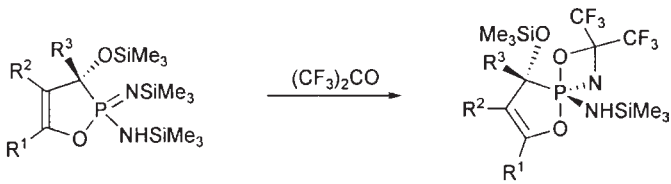
A very similar X-ray crystallographic structure was obtained for (64) with an O1-P-S angle of 155.60 (7)° indicating a highly distorted *tbp* and a P–S bond length of 2.2553 (13)Å, significantly longer than the sum of the corresponding covalent radii (2.14Å). Thus the P–S bond is also polar as reflected in the downfield shift of the H^a proton to 8.73 (cf 7.53 in 63) and a ^{31}P NMR signal



Scheme 1

which again responds to the acceptor number of the solvent from −48.8 in C_6D_6 to −40.4 in $CDCl_3$.

Iminooxaphospholens (65ab) can be stabilized by reaction with hexafluoroacetone to form (66ab).[36] X-ray crystallography of (66a) showed that both rings were disposed axial-equatorial with the oxygen atoms in axial positions within a slightly distorted *tbp*.



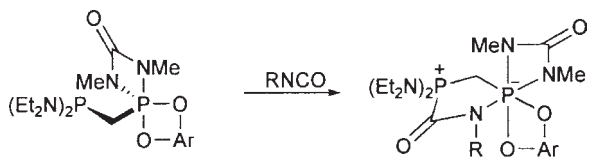
65a R^1, $R^2 = (CH_2)_3$; $R^3 = CF_3$
65b R^1, R^2 = Me; R^2 = H

66a δ^{31}P, −15.9
66b δ^{31}P, −22.2

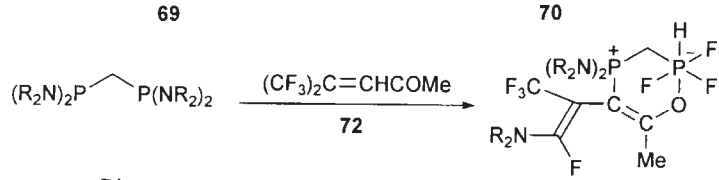
During a study of spirocyclotetraalkylphosphonium salts, Schmidbaur *et al.* reacted (67) with a series of organolithium reagents (RLi, with R = Me, Et, Bu^n, Vi (vinyl) and Ph) to form (68) in good (R = Me, Et, Bu^n) to low (R = Vi, Ph) yields Single crystal X-ray analysis of (68) with R = Me showed a *tbp* configuration with the rings axial-equatorial and the methyl group in an equatorial position. All the pentacoordinate structures showed fluxional behaviour in solution with a very low energy barrier to pseudorotation as evidenced by low temperature NMR.[37]

67 **68**

In a short review of compounds containing the P–CH_2–P fragment,[38] Shevchenko *et al.* mention the reaction of (69) with alkyl isocyanates,[39] azides[40] and hexafluoroacetone,[41] all of which give penta- or hexa-coordinate phosphorus compounds. (e.g.70). An unusual reaction of (71) with (72) gave a similar zwitterionic structure (73).[38]



69 **70**



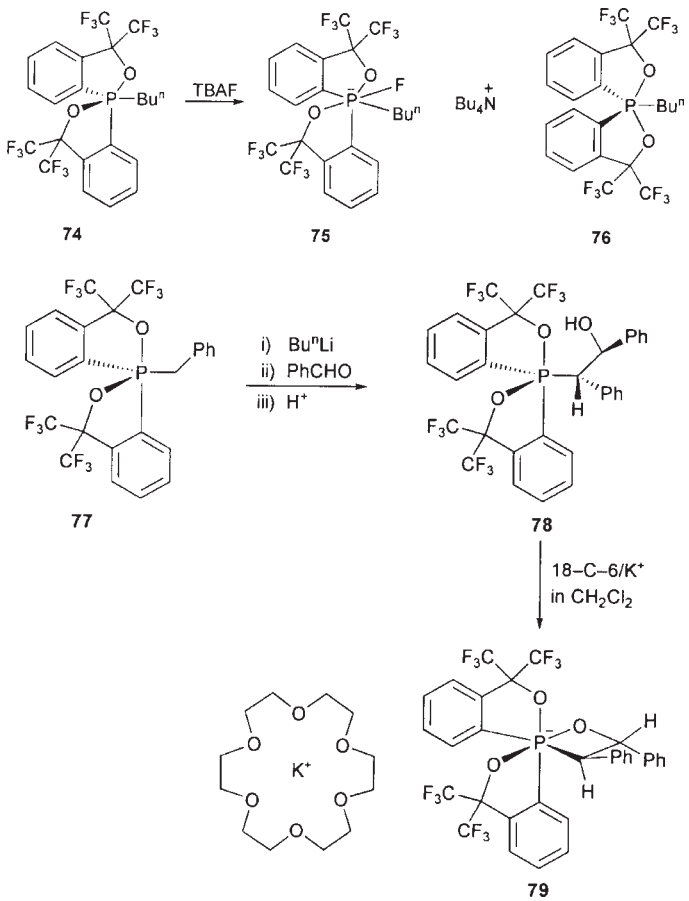
72

71
R = alkyl

73

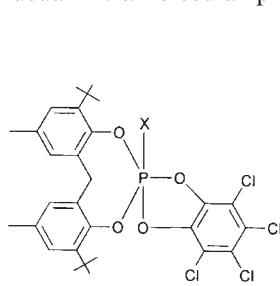
By further exploitation of the Martin ligand, Akiba *et al.*[42ab] have extended their work on the preparation of configurationally stable enantiomeric pairs of

optically active phosphoranes[43] and the isolation and characterization of an "anti-apicophilic" (O-*cis*) phosphorane[44] to explore the reactivity of O-*cis* phosphoranes. Thus the reaction of (74) with TBAF (Bu_4N^+ F^-) gave the hexacoordinate structure (75) presumably by attack of the fluoride anion anti to the P-O equatorial bond. Although the structure of (75) was not established unequivocally a parallel was drawn with the X-ray structure of the antimony analogue.[45] The O-*trans* isomer (76) did not react with TBAF thus enhancing the view that reaction with the fluoride ion occurs through the low lying O-*cis* σ* P–O orbital. Deprotonation of (77) followed by reaction with benzaldehyde over a prolonged period produced diastereomer (78) as the only product, presumably by equilibration of the stereoisomeric mixture and this, on reaction with KH in the presence of 18-C-6 gave the isolable phosphate (79) whose structure was determined by X-ray crystallography and shown to be the first phosphate bearing an oxaphosphetane ring system.[42a]Thermal decomposition of (79) to *trans* stilbene required 4 days at 60°C whereas decomposition of the O-*trans* isomer was shown to be very much faster.[42b]

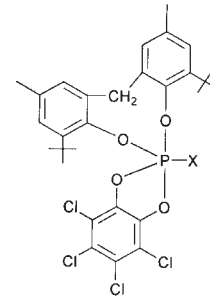


Several new spirocyclic phosphoranes (80a–e) have been isolated and examined by X-ray crystallography. For (80a–c), X was found to be apical but for

X = NH_2 or NHPh (80d,e) the equatorial position was preferred. The possible reasons for this are discussed and variable-temperature (^1H, ^{31}P) NMR spectra reveal some unusual intramolecular processes within these compounds.[46]

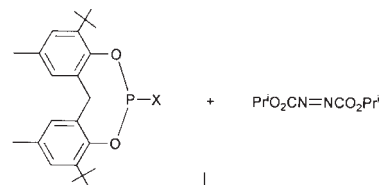


80a X = NMePh
80b X = $N(Pr^i)_2$
80c X = NCS

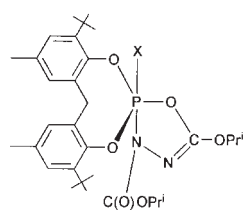


80d X = NH_2
80e X = NHPh

In a related paper, Swamy *et al*. report the reaction of (81a–e) with diisopropyl azodicarboxylate (DIAD) which in four of the five cases generates pentacoordinate structures (82a–d) with nitrogen, rather than the expected oxygen, in an apical position, *i.e*. a "reversed" apicophilicity. X-ray crystallography reveals that in (82a-c) the group X is apical but in (82d) the NHMe group is equatorial. In the case of (82e) oxygen is found in the expected apical position but now the phenyl group is forced into an apical position.[47]

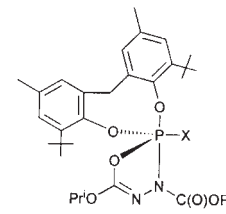


81a = X = NCS
81b = X = N_3
81c = X = Cl
81d = X = NHMe
81e = X = Ph



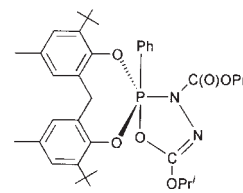
82a–c

or



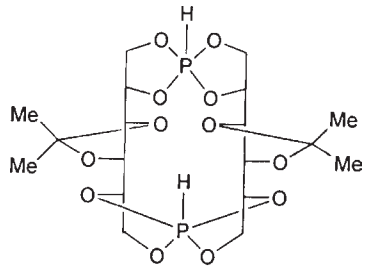
82d

or



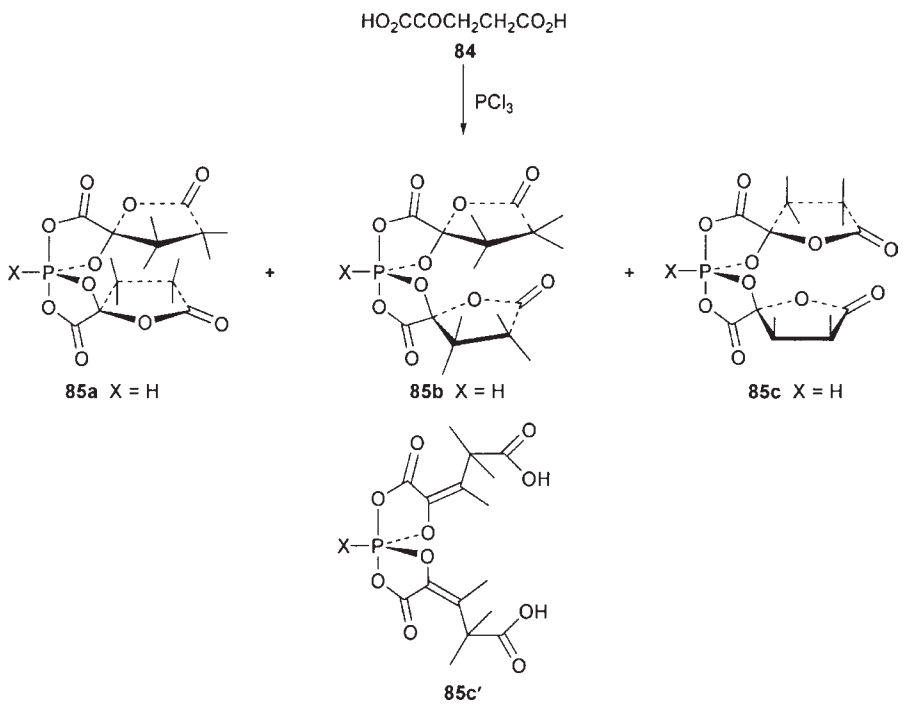
82e

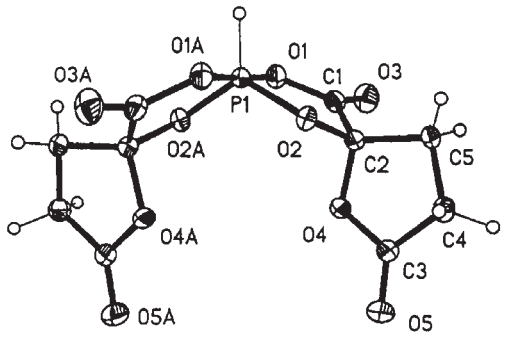
Several macrocyclic bisphosphoranes (e.g. 83) have been prepared by condensing tris(dimethylamino)phosphine with isopropylidene-mannitols and their structures determined by elemental analysis, MS, NMR, cryoscopy, polarimetry and AM1 calculations.[48]



83

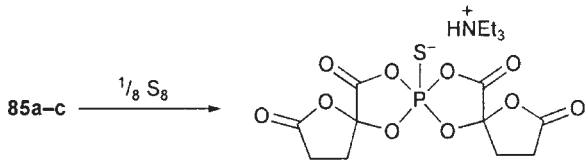
The reaction of 2-ketoglutaric acid (84) with phosphorus trichloride in THF gave a mixture of three enantiomeric pairs (85a–c), as evidenced by ^{1}H and ^{31}P NMR, which crystallized as (85c) identified by single-crystal X-ray analysis (Figure 1). After several hours in acetonitrile solution the crystals (with δ ^{31}P, −49.3) reverted to a mixture of the three isomers. The open enolate forms of the lactone rings (e.g. 85c′) were also detected in solution. The reaction of the spirophosphoranes with S_8 in the presence of triethylamine to form (86), was also described.[49]





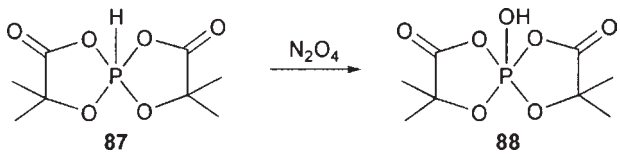
85c

Figure 1

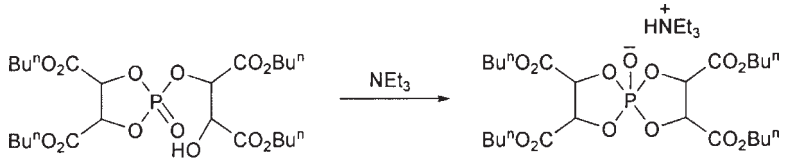


86

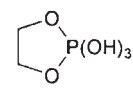
The crystal structure of the hydroxyphosphorane (88) prepared by N_2O_4 oxidation of (87) showed an almost perfect *tbp* structure with the unit cell containing two molecules of the same helicity connected by H-bonds between the P–OH and carbonyl groups.[50] The phosphorus ester (89), fashioned from two n-butyl tartrate moieties exists in solution due to intramolecular hydrogen bonds. On treatment with triethylamine, however, it forms the triethylammonium salt (90) of the corresponding hydroxyphosphorane. The pKa value of (89) was determined to be 7.7 in DMF and 4.4 in DMSO, similar to values for dichloroacetic acid in the same two solvents.[51]



87 **88**



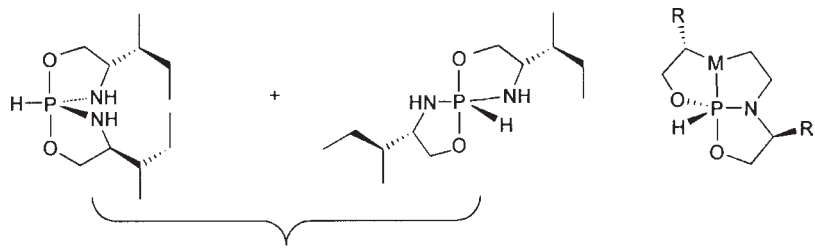
89 δ^{31}P, +146 **90** δ^{31}P, –33



91

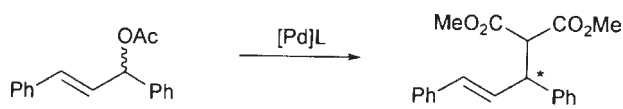
With trihydroxyethylenephosphorane (91) as a model for RNA hydrolysis, Karplus *et al*. developed a protocol for calculating the values of pK_a^1 and pK_a^2 of (91) based on estimates of the pK_a for phosphoric acid. The protocol used density functional theory to calculate gas-phase protonation energies and continuum dielectric methods to determine solvation corrections and arrived at values of 7.9 and 14.3 for pK_a^1 and pK_a^2 respectively.[52] These values are within the experimental ranges of 6.5–11.0 for pK_a^1 and 11.3–15.0 for pK_a^2 proposed for the molecules.[53]

Novel bicyclic (92) and tricyclic (93ab) hydrophosphoranes have been synthesized and shown to form complexes with $PdCl_2(COD)$, $PdCl_2(RCN)_2$, and $Pd(allyl)Cl_2$ containing an "open" form of the phosphoranes.[54] The Pd-catalyzed alkylation of 1,3-diphenylallyl acetate (94) with dimethyl malonate gave (95) in up to 74% ee using complexes of (92) or (93ab).[54]



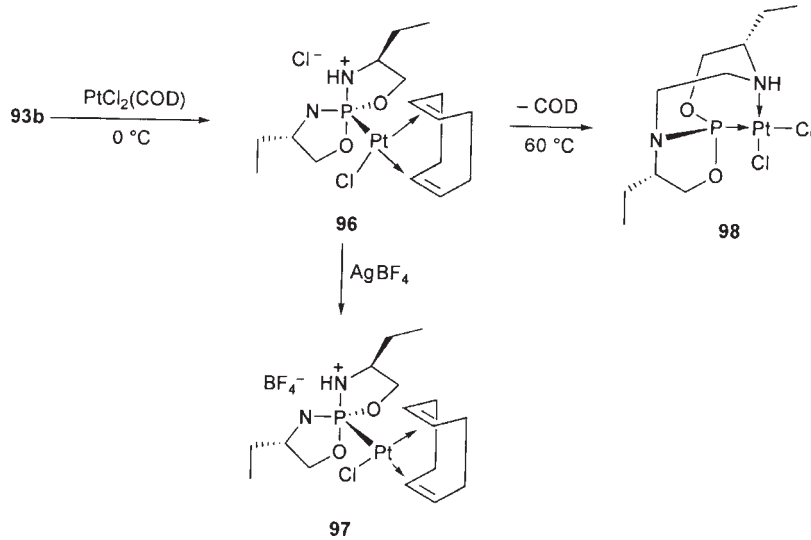
92 Ratio : 3:2

93a R = Bu^{Sec}
93b R = Et

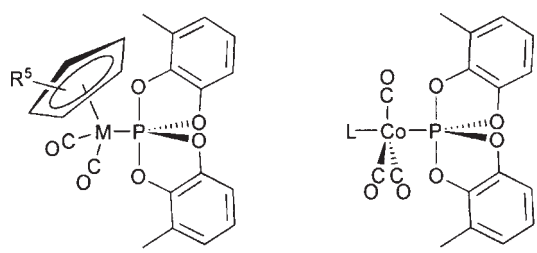


94 **95**

The reaction of (93b) with $Pt(COD)Cl_2$ gave (96) and when the reaction was carried out in the presence of silver tetrafluoroborate, the crystalline salt (97) was formed. An X-ray crystallographic structure determination of (97) showed a distorted *tbp* around phosphorus with the platinum fragment in an equatorial position and a near square-planar coordination geometry around the Pt atom.[55] On heating to 60°C, (97) lost cyclooctadiene to form (98). Variable temperature ^{31}P NMR studies were reported for (96) and (97). This work, using ligands (92) and (93a), was extended to complexes of Pt and Rh with similar results.[56]



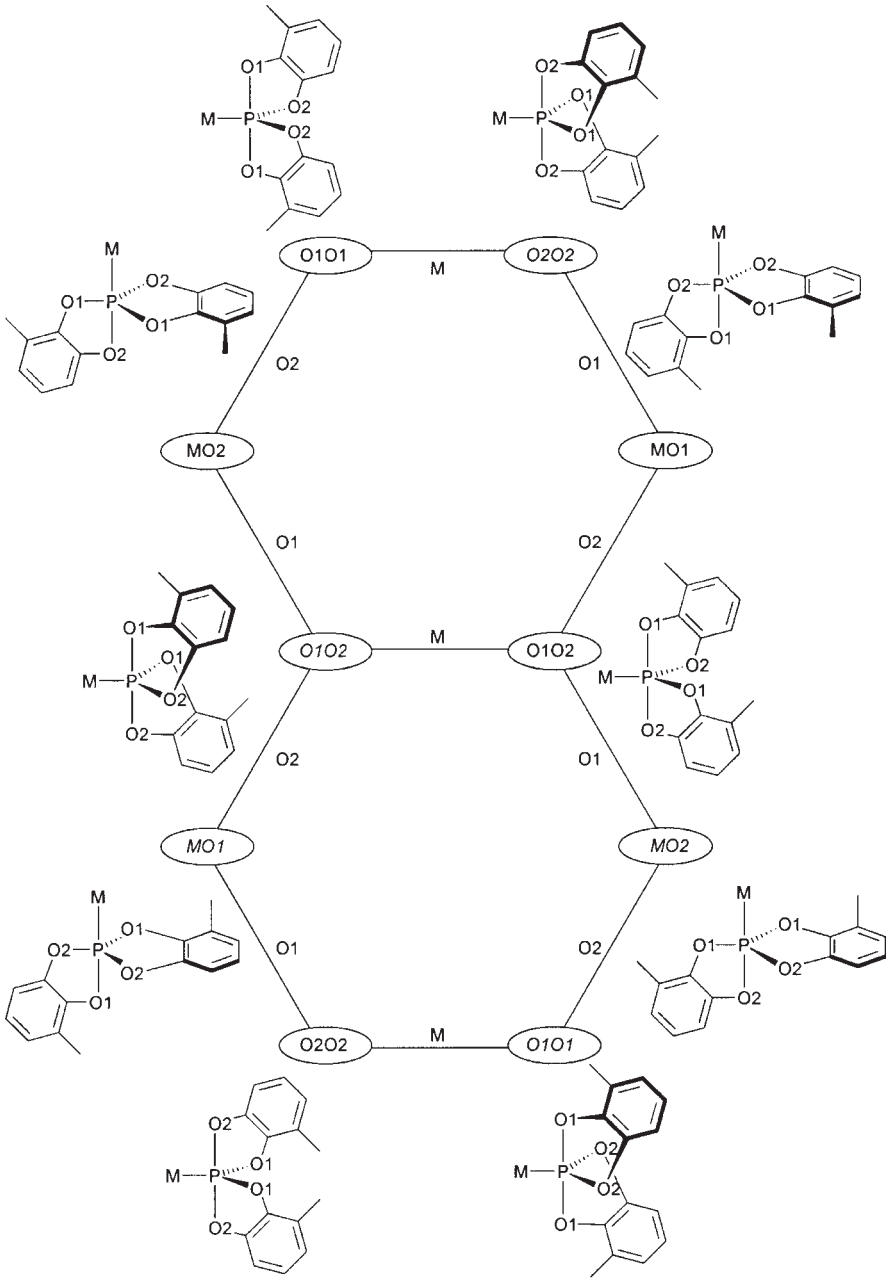
The influence of the transition metal fragment on the activation barriers for Berry pseudorotation have been determined for (99a–d) and (100ab).[57ab] Both the ^{31}P and ^{13}C NMR of (99b–d) showed that the metal fragment was in an equatorial position and the three possible pairs of enantiomers with the metal fragment equatorial (0101, *0101*, 0102, *0102*, and 0202, *0202*), were only interconvertible *via* high energy isomers (*MO1, MO2*) with the metal fragment apical (Scheme 2).[57b] The energy barriers ($\Delta G^{\#}$) for the interconversion in (99a), (99b) and (99c) were 84.2, 89.7 and 73.1 kJmol^{-1} respectively showing that changing the substituent from Cp to pentamethyl Cp (Cp*) increased the barrier. With (100ab), the $\Delta G^{\#}$ values were 67.8 and 67.9 kJmol^{-1} respectively.



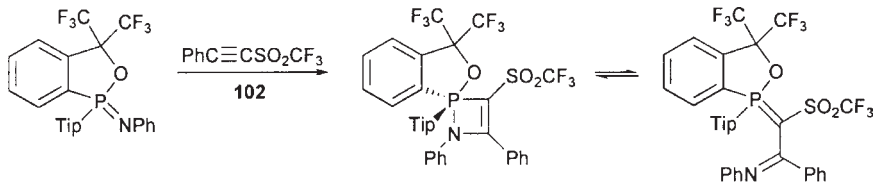
99a R = H; M = Fe
99b R = Me; M = Fe
99c R = H; M = Ru
99d R = Me; M = Ru

100a L = PPh_3
100b L = PPh_2Me

The cycloaddition of an alkyne (102) to the iminophosphorane (101) gave the first stable l,2-λ^5-azaphosphetene (103) whose structure, as determined by X-ray crystallography, showed a distorted *tbp* with N and O atoms at the apical positions.[58] The variable temperature ^{31}P NMR spectrum of (103) in C_7D_8 or CD_3CN showed a shift to lower field with decreasing temperature indicating that (103) was in equilibrium with the corresponding ylid structure (104).

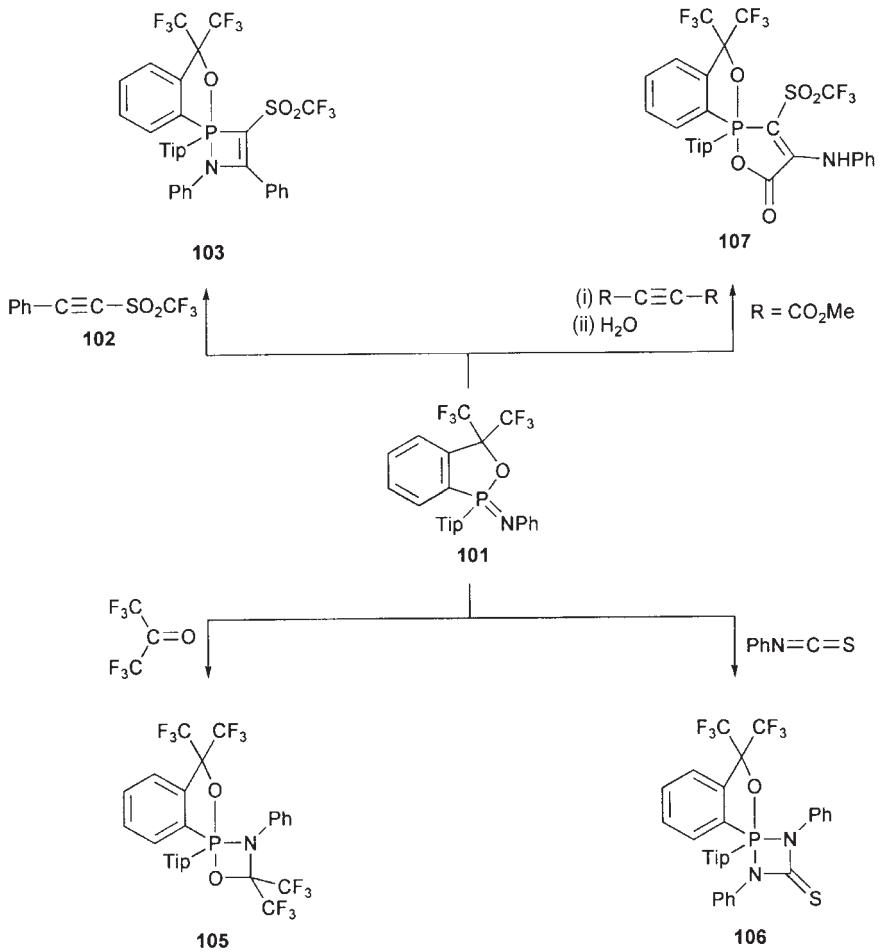


Scheme 2



101 **103** **104**

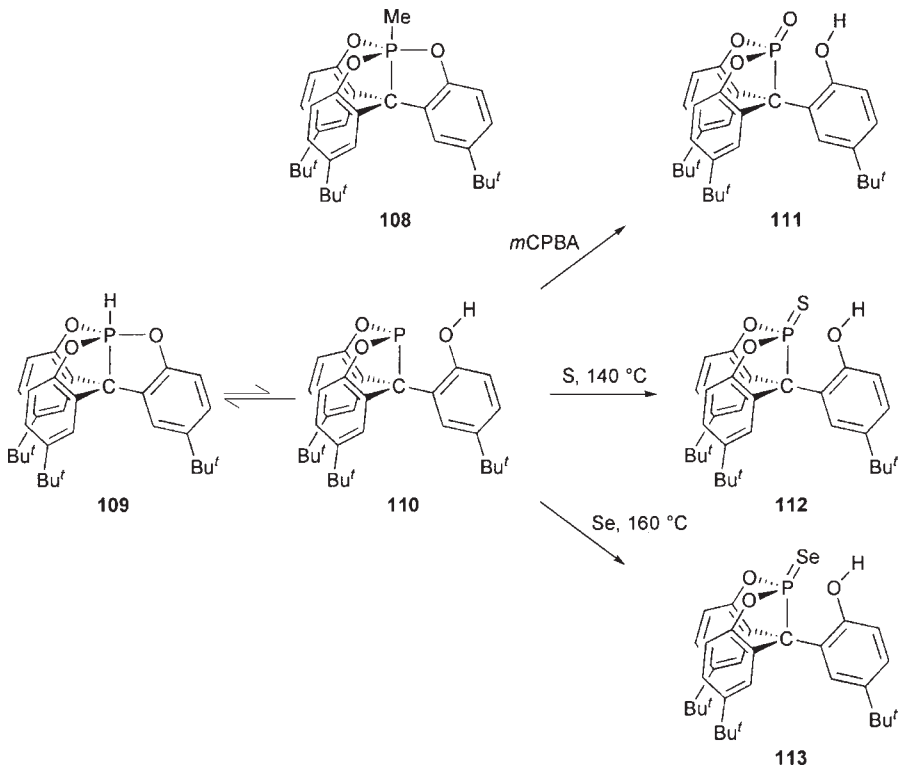
In a related study,[59] (101) was shown to give cycloadducts (103) when reacted with (102), and it gave (105) with hexafluoroacetone, (106) with phenylisothiocyanate and interestingly, (107) was obtained with dimethyl acetylene-dicarboxylate and water. The structures were all confirmed by X-ray crystallography.



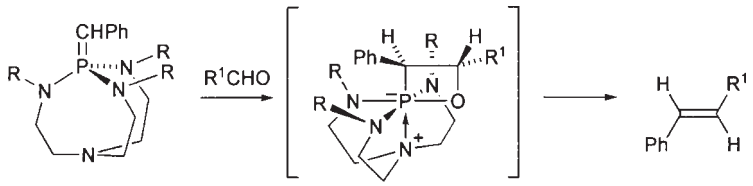
103 **107**

In a sequel to the synthesis of 5-carbaphosphatrane (108),[60] reported in SPR 33, Kawashima *et al.* described the oxidation, sulfurization and selenation of

(109) to give (111), (112) and (113) respectively.[61] The authors consider that the reactions occur through the tautomeric cyclic phosphonate (110) although the latter was not detectable by ^{31}P NMR.



There follows a section on the synthetic applications of proazaphosphatranes (PAP) developed extensively over the past few years by Verkade *et al*. The semi-stabilized ylid (114) reacts with aldehydes to give alkenes in high yield with quantitative selectivity despite changes in temperature, solvent polarity and the metal ion of the base used to generate (114).[62] It was suggested that the tricyclic cage structure of the ylid played a pivotal role in affording a dominant 1,2 interaction between the Ph and R^1 groups of the T.S. (or intermediate, 115) leading to the E olefin. Activated allylic compounds (116a-d) react with aromatic aldehydes in the presence of proazaphosphatranes, specifically $P(Pr^iNCH_2CH_2)_3N$, as catalyst at −93 to −63°C to give α addition products. When R = H and Z = CN, an allylic transposition occurs to give a Bayliss-Hillman adduct as the only product. (Scheme 3).[63]

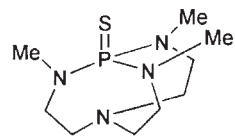


114 R = Me or Pr^i **115**

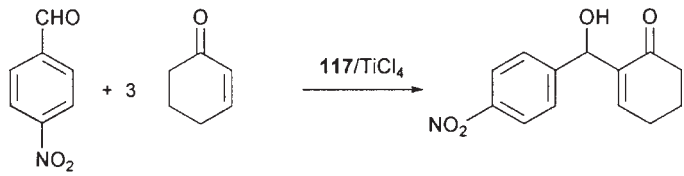
$RCH{=}CHCH_2Z$

116a R = H, Z = CN
116b R = Me, Z = CN
116c R = H, Z = CO_2Me
116d R = Me, Z = CO_2Me

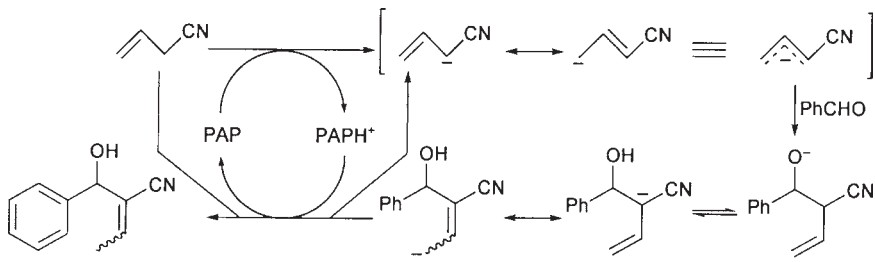
The proazaphosphatrane sulfide (117) has been shown to facilitate rapid and highly selective Bayliss-Hillman reactions between aromatic aldehydes and α,β-unsaturated ketones in the presence of suitable Lewis Acids, with $TiCl_4$ affording the best results. Thus *p*-nitrobenzaldehyde (118, 1mmol) reacted with cyclohexenone (3mmol) catalyzed by (117, 0.05 mmol) and $TiCl_4$ (1.0 mmol) in CH_2Cl_2 under argon at room temperature to give a 94% yield of (119).[64] The yields from a wide range of aromatic aldehydes and activated alkenes were in the region of 81-95% under extremely mild conditions.



117

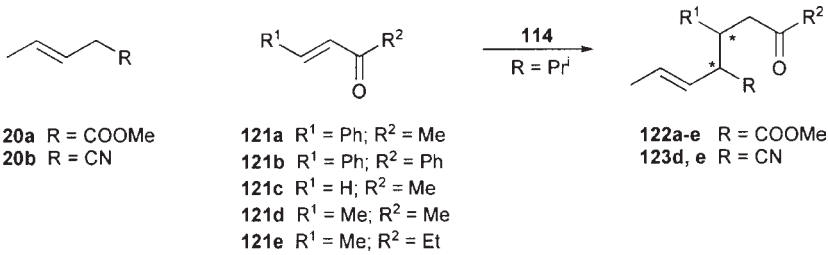


118 **119**



Scheme 3

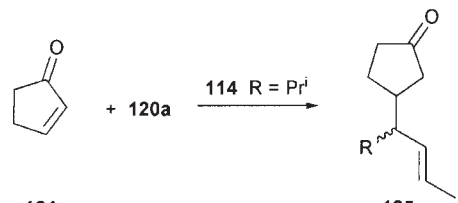
Michael additions of a β,γ-unsaturated ester (120a) or nitrile (120b) to α,β unsaturated ketones (121a–e) were also catalyzed by $P(Pr^iN\ CH_2CH_2)_3N$ to give (122a–e) or (123d,e) in high yield but low diastereomeric selectivity. In one case, however, using (120a) and (124) a diastereomeric ratio of 91: 9 was found in the product (125) by NMR.[65]



120a R = COOMe
120b R = CN

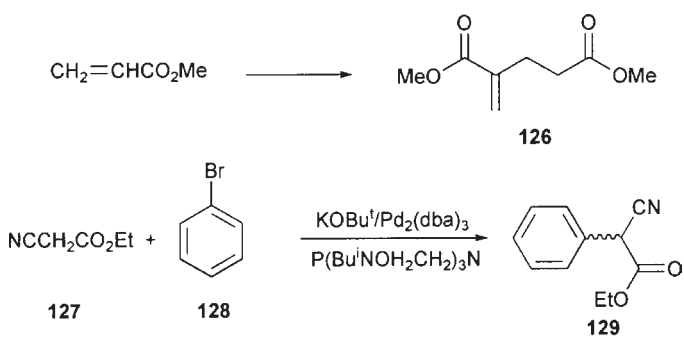
121a R^1 = Ph; R^2 = Me
121b R^1 = Ph; R^2 = Ph
121c R^1 = H; R^2 = Me
121d R^1 = Me; R^2 = Me
121e R^1 = Me; R^2 = Et

122a-e R = COOMe
123d, e R = CN



124 **125**

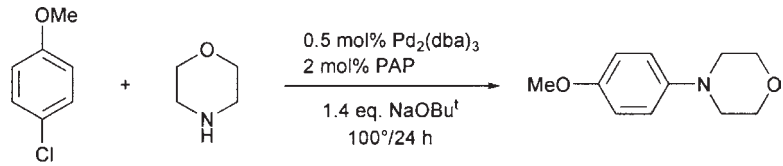
Head-to-tail dimerisation of methyl acrylate to the dimethyl ester of 2-methylenepentane-dioic acid (126) occurred in 82–85% yield in the presence of catalytic amounts of $P(RNCH_2CH_2)_3N$ with R = Pr^i, Bu^i, or Bz but the less sterically hindered proazaphosphatrane with R = Me, gave oligomer or polymer.[66] The proazaphosphatrane, $P(RNCH_2CH_2)_3N$ with R = Bu^i also acts as an effective ligand for the palladium-catalyzed direct arylation of ethyl cyanoacetate (127) with aryl bromides (e.g. 128) to form (129) in high yield.[67]



126

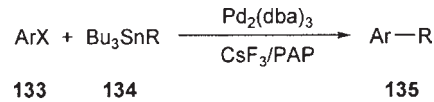
127 **128** **129**

Proazaphosphatrane ligands in combination with $Pd_2(dba)_3$ also generate highly active catalysts for Buchwald-Hartwig amination of aryl chlorides, e.g. (132) from (130) and (131). The PAP ligand with R = Bu^i was particularly effective and the catalyst performed extremely well with sterically hindered substrates.[68]



130 **131** dba = dibenzylideneacetone **132**, 88%

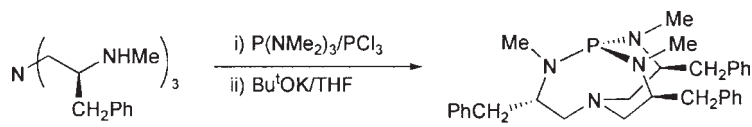
A family of proazaphosphatranes [$P(R^1NCH_2CH_2)_2N$ ($R^2NCH_2CH_2$)] with $R^1 = R^2 = Bu^i$, and $R^1 = Bz$, $R^2 = Bu^i$ and $R^1 = R^2 = Bz$ have also been shown to be effective ligands in the palladium-catalyzed Stille cross coupling of aryl halides (ArX, 133) with aryl-, vinyl- and allyl-tri-n-butyltin (Bu_3SnR,134) to give (135) thus illustrating, once again, the versatile synthetic utility of these powerful phosphorus ligands.[69,70]



133 **134** **135**

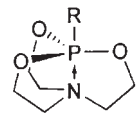
R = aryl, vinyl or allyl

The reaction of S,S,S-(136) with tris-dimethylaminophosphine/PCl_3 in CH_3CN at 0°C gave the chiral azaphosphatrane (137) in overall 56% yield. Unfortunately (137) did not induce asymmetry in mandelonitrile formed from the catalyzed reaction of Me_3SiCN with PhCHO. It was also inefficient in catalyzing the addition of alkyl cyanide to benzaldehyde, and was not sufficiently basic to effect rearrangement of cyclohexene oxide to 2-cyclohexenol.[71] Further experiments with analogues of (137) are promised for future publications.

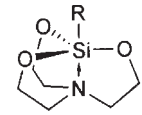


136 **137**

A new class of main group atranes has been afforded by the synthesis of carbophosphatranes (141) and (142) from (138) *via* (139) and (140),- Scheme 4.[72] X-ray crystallography of (141) reveals a typical *tbp* structure with hydrogen and carbon atoms in the apical positions and three oxygen atoms equatorial indicating that (141) is an example of an "anti-apicophilic" arrangement. The $^1J_{PH}$ of (141) and $^1J_{PC}$ values of (141) and (142) were 852 and 215 Hz respectively, large for apical coupling constants of phosphoranes in general but close to those reported for 5-azaphosphatranes (e.g. 143). Force constant calculations indicate that the transannular bond in (141) is about twice as strong as that in (143) and three times stronger than that of the silatrane (144) reflecting the difference between a substantially covalent C-P bond in (141) and the more ionic N-P and N-Si dative bonds.

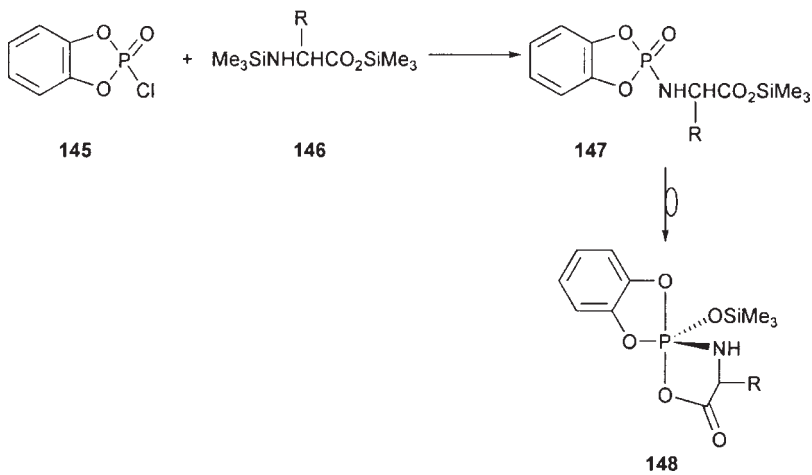


143



144

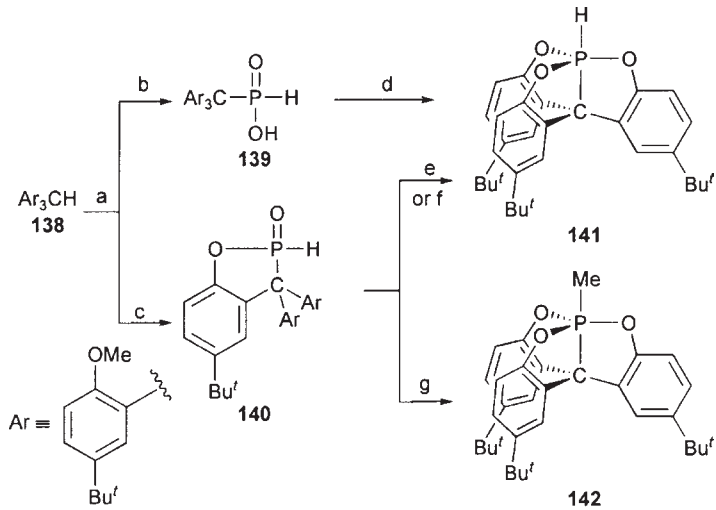
In a discussion of the role of pentacoordinate phosphorus compounds in biochemistry, Zhao *et al.* reported the isolation of a silicon-protected pentacoordinate phosphorus compound (148) by the cyclisation of (147) formed from (145) and (146). Phosphorane (148) was then discussed as a model for the involvement of pentacoordinate phosphorus in activating the formation of peptides from amino acids such as histidine, serine, threonine and α-alanine but not β- alanine.[73]



145 146 147

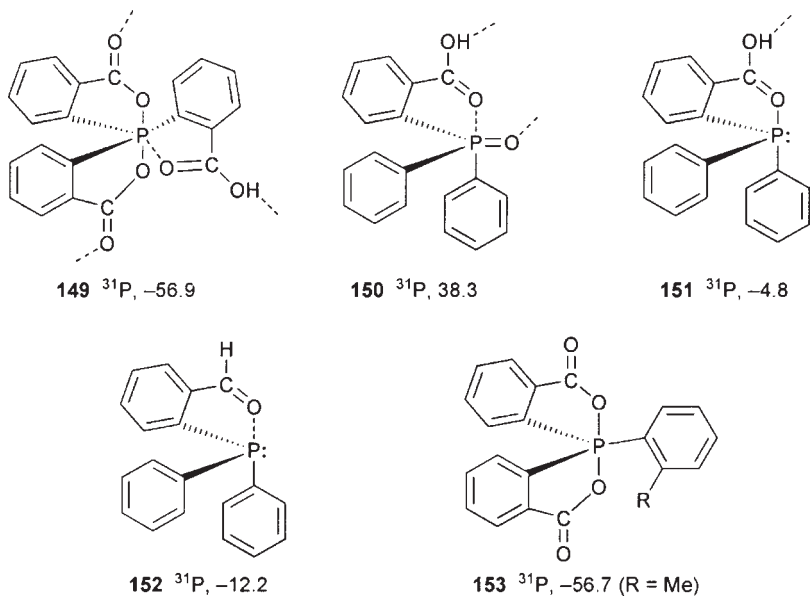
148

In an extension of their studies on oxygen donor action at phosphorus, Holmes *et al.* examined (149–153) as mimics for amino acid residues, especially those containing carbonyl (Asn, Gln) or carboxylate (Glu, Asp) groups. Phosphorane (153), without a donor group, was included for comparison purposes. The structures of all five compounds were determined by X-ray crystallography which revealed that P–O coordination occurred for (149–151) in the presence of H-bonding and also in (152) where H-bonding is not possible, leading to *tbp* geometry in all four cases. Evaluation of the energies associated with both bonding types indicated a range for P–O coordination above and below the hydrogen bond energy. It was concluded that phosphoryl transfer enzyme mechanisms should benefit by donor interaction at P and also by H-bonding interactions.[74]



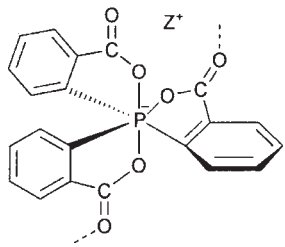
[a] Conditions: (a) *n*-BuLi; (b) PCl_3, room temperature, then H_2O, 11% (two steps); (c) PCl_3, 50 °C, then H_2O, 38% (two steps); (d) TMSI, room temperature, 38%; (e) TMSI, room temperature, 39%; (f) BBr_3, room temperature then aqueous $NaHCO_3$, 54%: (g) TMSI, 80 °C, in a sealed tube, 29%.

Scheme 4



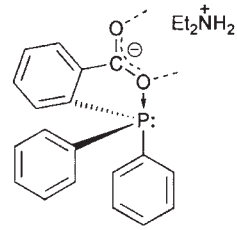
A similar conclusion was reached in a sequel to this paper in which (154ab, 155, and 156) were prepared from the respective neutral species by treatment with di- or triethylamine.[75] X-ray crystallography revealed hexacoordinated

anionic phosphoranates (154 ab), pseudo-*tbp* anionic phosphine (155) and *tbp* anionic phosphine oxide (156). All three had stronger P–O bond interactions than the corresponding neutral species as judged by P-O bond distances and all three showed the energy of donor interactions exceeding those of the H-bonds present. The basic coordination geometries were retained in solution as evidenced by ^{31}P data.

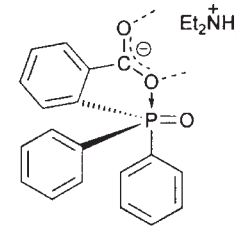


154a $\delta^{31}P$, –135.5
154b $\delta^{31}P$, –124.9

a $Z^+ = Et_2\overset{+}{N}H$
b $Z^+ = Et_3\overset{+}{N}H$



155 $\delta^{31}P$, –5.7

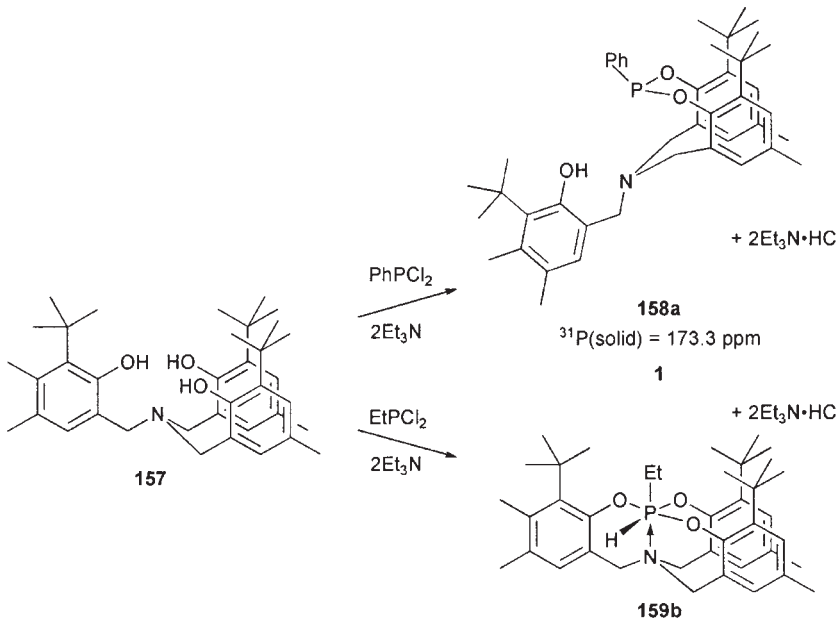


156 $\delta^{31}P$, 30.3

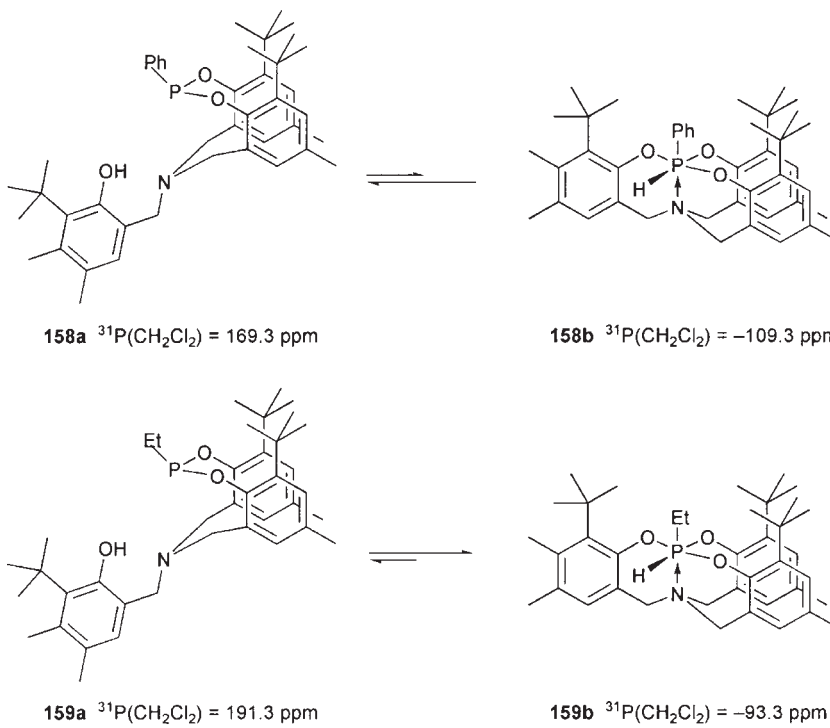
The whole concept of P-donor interaction in the presence of a H-bonding network and its relevance to the active site of phosphoryl transfer enzyme mechanisms was also discussed in two companion papers [76,77] which reached the conclusions that P-O donor interactions leading to hexacoordinate states, hydrogen bonding, and conformational distortions due to van der Waals forces, are all important in structuring the active site.

Reaction of $RPCl_2$ (R = Ph or Et) with (157) gave tricoordinate (158a) with R = Ph but hexacoordinate (159b) products with R = Et and both structures were confirmed by X-ray crystallography (Scheme 5). In addition, ^{31}P NMR showed that in solution the tricoordinate and hexacoordinate forms of both compounds existed in equilbrium, an unprecedented interchange between tricoordinate and hexacoordinate phosphorus (Scheme 6). Solid state ^{31}P NMR showed that (158) was in the tricoordinate state and (159) was hexacoordinate in agreement with the X-ray data.[78]

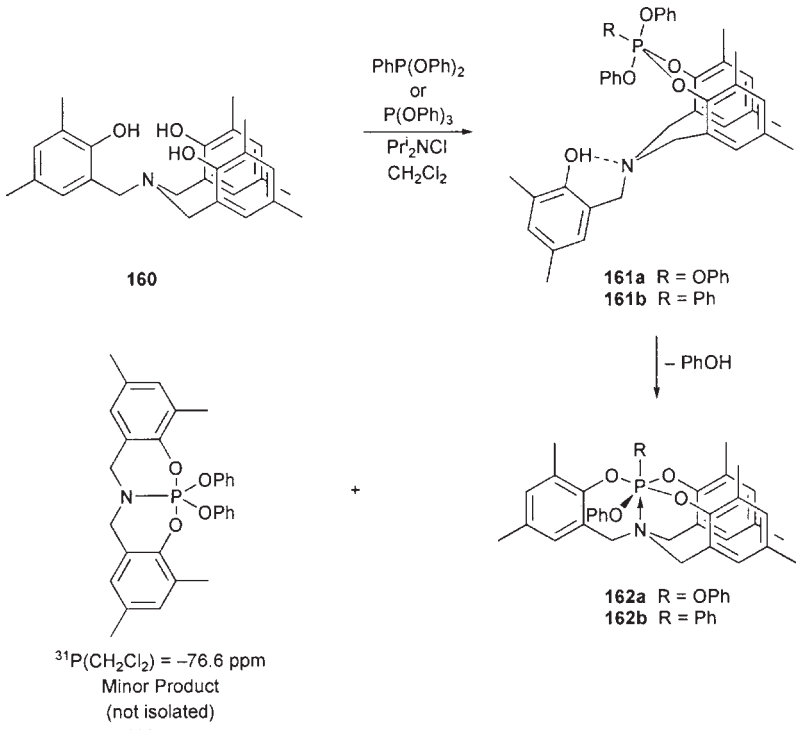
As part of a study of the reaction of aminotriphenols with phosphites or phosphonites, Holmes *et al.* reported the reaction of (160) with triphenyl phosphite or diphenoxyphenylphosphonite in the presence of N-chlorodiisopropylamine to give a mixture of (161a, isolated) or (161b, not isolated) both of which lost phenol to form (162a) or (162b) respectively with (163a) detected as a minor, unisolated product. X-ray crystallography and NMR data support the proposed structures and (162b) represents the first hexacoordinated tetraoxyazaphosphatrane; both (163a) and (163b) have pronounced P-N coordination.[79] The results were used yet again to support the concept of amino acid donor interaction at active sites of phosphoryl transfer enzymes.



Scheme 5



Scheme 6



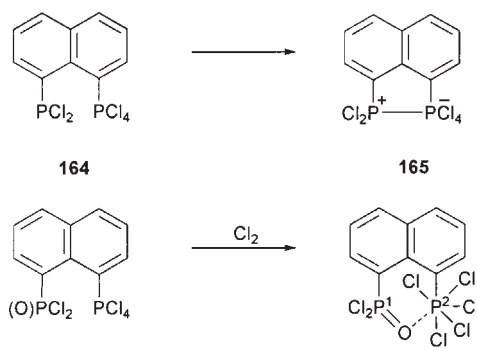
160

161a R = OPh
161b R = Ph

162a R = OPh
162b R = Ph

$^{31}P(CH_2Cl_2)$ = –76.6 ppm
Minor Product
(not isolated)
163a

Research on sterically imposed hypercoordination by Woollins *et al.* revealed that (164) collapsed its steric strain to form (165)[80], found in both the solid state and solution. Further to this work, (167) was prepared by the addition of chlorine to (166) and shown by X-ray crystallography to adopt a near perfect pseudo-octahedral coordination at P(2).[81] Despite the relatively long P(2)-O bond distance of 1.842Å, the data favour bonding in (167) as "sterically imposed interaction of peri-substituents *via* a bridging O atom." The interpretation is supported by $^{31}P\{^{1}H\}$ which shows $\delta^{31}P(1) = 63.5$ and $\delta^{31}P(2) = -182.7$ with $^{2}J_{PP} = 64$ Hz. The chemical shift of P(2) clearly belongs in the hexacoordinate region and the $^{2}J_{PP}$ value indicates significant electronic P–P interation in (167).



164

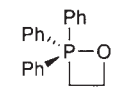
165

166

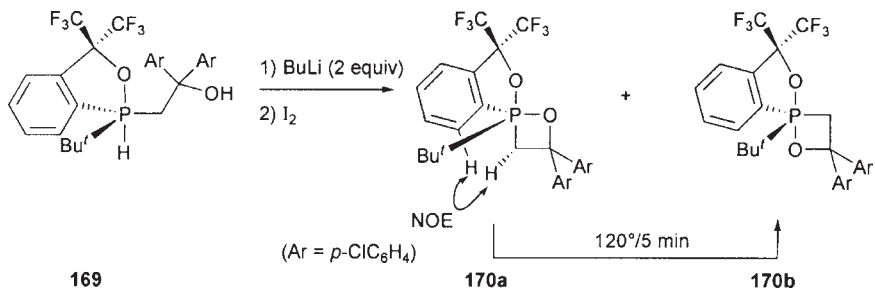
167

In an effort to determine whether apical oxygen or apical carbon (as represented by (168ab) is the reactive intermediate in the Wittig reaction, Akiba *et al*. synthesized and characterized (170a) by reaction of (169) with BuLi followed by I_2. The compound was formed as a mixture of (170a) and (170b) but (170a) crystallized from the reaction mixture and its structure was determined by X-ray crystallography. Heating a sample of (170a) at 120°C for 5 min. converted it to (170b, O-apical) whose structure was also defined by X-ray crystallography. Prolonged heating of (170b) at 140°C eventually gave olefin and phosphine oxide and and thus the strength of the apical P–C bond in (170a) makes bond cleavage a much higher energy process than stereomutation.[82]

168a apical oxygen



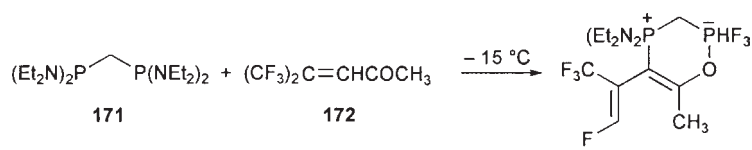
168b equatorial oxygen



169 **170a** **170b**

5 Hexacoordinate Phosphorus Compounds

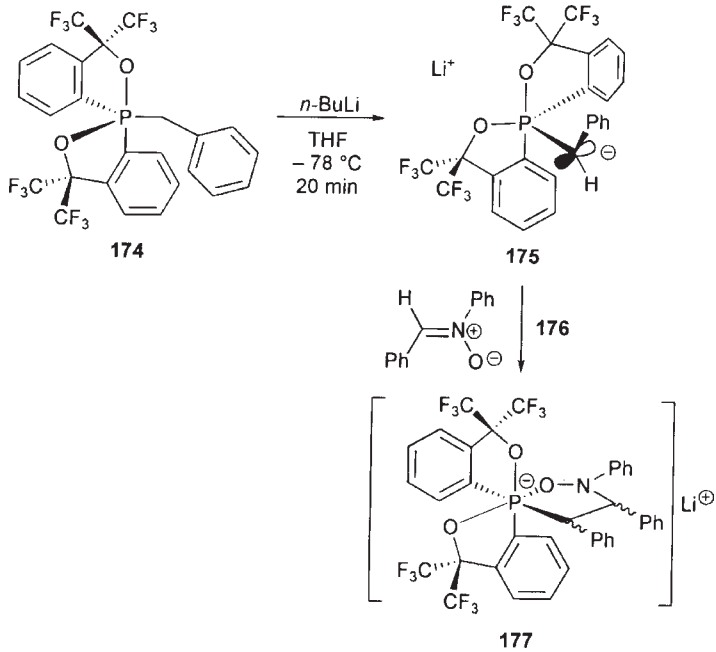
The oxidation of (171) with (172) gave the zwitterionic compound (173) that was analyzed by X-ray crystallography and shown to contain both λ^4P^+ and λ^6P^- atoms and a P–H bond. The $^{31}P\{^1H\}$ NMR data on (173) in $CDCl_3$ showed a high field doublet of triplets at −134.2 ppm, characteristic of hexacoordinate phosphorus with the splitting pattern due to one nonequivalent and two equivalent fluorines.[83]

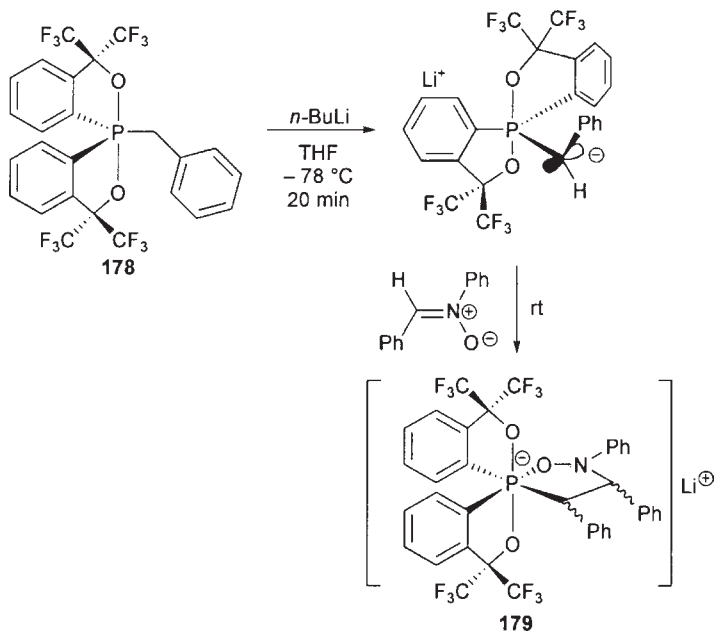


171 **172** **173**

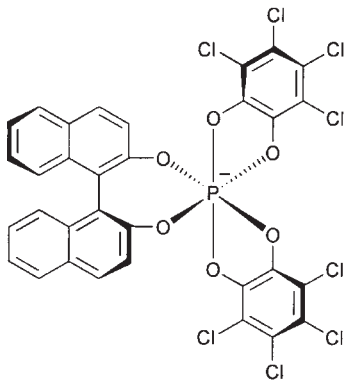
The benzylic anion (175) generated from (174) reacted with N-α-diphenylnitrone (176) to give the phosphorate (177), characterized by ^{31}P NMR, and subsequent protonolysis products. A similar reaction of the O-*trans* isomer of

(174), compound (178), led to the formation of the O-*trans* phosphorate (179) which proved to be less stable than (177) mainly due to the stabilizing influence of the σ* orbital of the *trans* P–O bond in (177)[84], c.f. reference 42ab.

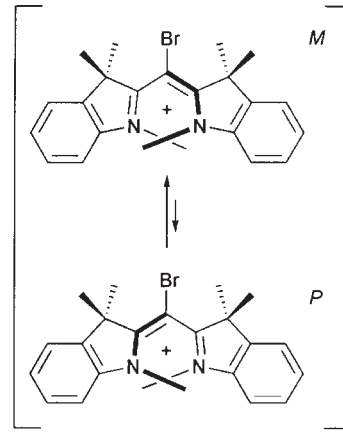




The work of Lacour *et al.* has focused attention on the use of C_2-symmetric hexacoordinated phosphate anions for enantio differentiation of chiral cationic dyes[85]and chiral quaternary ammonium cations.[86] Thus the BINPHAT anion (180) whose configuration is controlled by the BINOL ligand, behaves as an efficient NMR shift reagent and chiral inducer of monomethinium dyes (181) as determined by CD and ^{1}H NMR.[85]

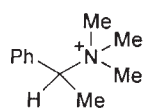


180 BINPHAT

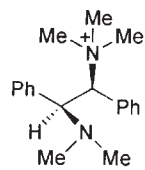


181

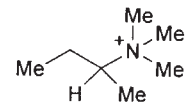
Likewise, the same BINPHAT anion acts as an efficient NMR shift reagent for quaternary ammonium cations (182–186) including the biologically active methacoline (187).[86,87] Furthermore, the BINPHAT anion has been shown to be an efficient NMR chiral shift reagent for triphenylphosphonium salts containing stereogenic centres on an aliphatic side chain, e.g. (188ab) and (189).[88]



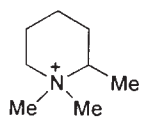
182



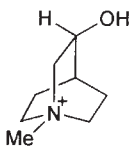
183



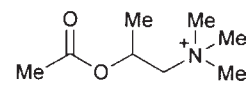
184



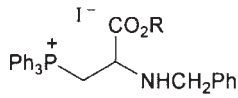
185



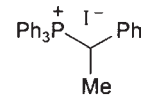
186



187



188a R = H
188b R = Me



189

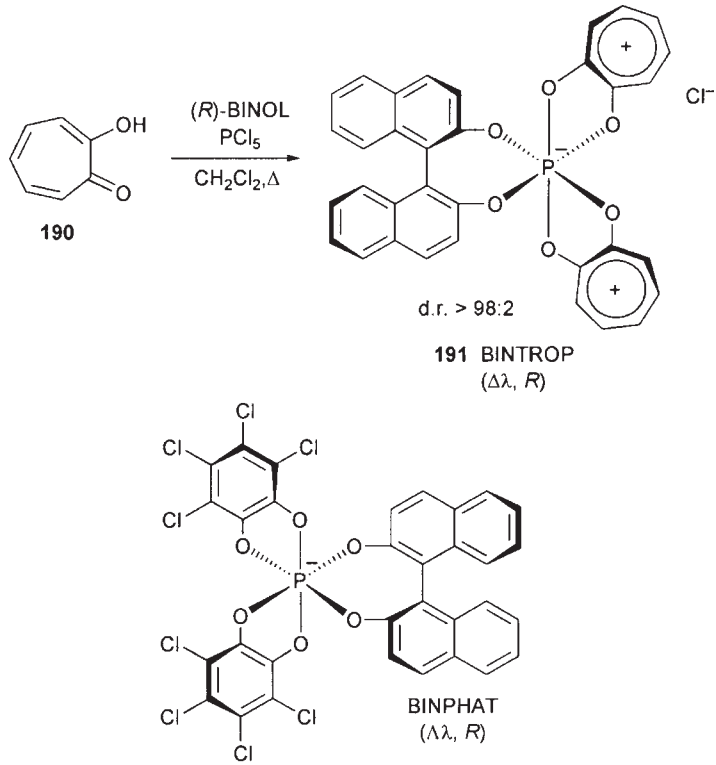
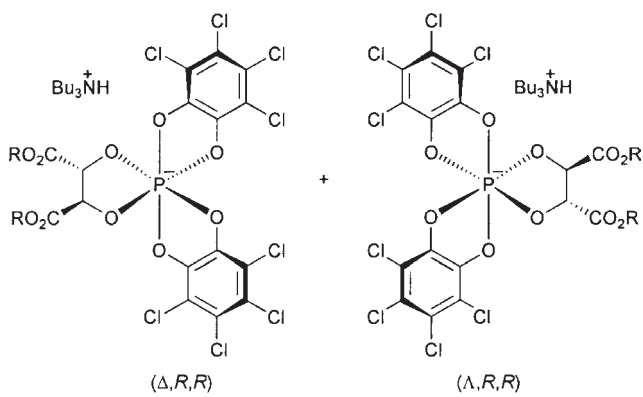


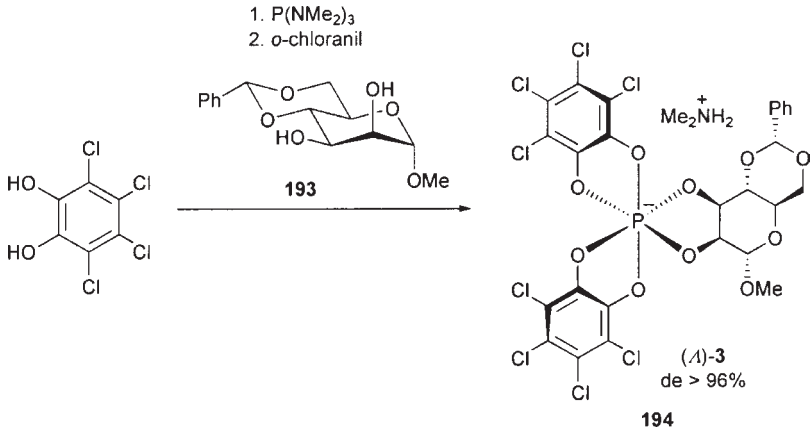
Figure 2

In a variation on the same theme, a novel C_2-symmetric hexacoordinated phosphorus cation (191) was synthesized from tropolone (190), R-BINOL and PCl_5 and shown to be an efficient NMR shift reagent for chiral anionic phosphate (e.g. BINPHAT, Figure 2) and borate anions.[89]

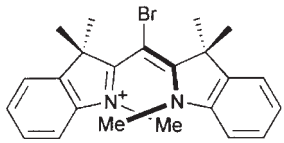


192a R = Me
192b R = Et
192c R = Pr^i
192d R = Bu^t

The one-pot synthesis of a series of C_2-symmetric hexacoordinated phosphate anions (192a–d, Δ or Λ isomers) containing tartrate esters as chiral auxiliaries, has been described.[90] The presence of the chiral tartrato ligands (usually 2R,3R) led to the formation of diastereomeric anions (Δ2R,3R/Λ2R,3R) with significant, but variable control over the Δ or Λ configuration depending on the nature of the ester chains and the solvent. The asymmetric induction improved with increasing size of the group R from a diastereomeric ratio of 65: 35 for Me to 84: 16 for Bu^t (Δ: Λ).



The search for an enantiopure hexacoordinated phosphorus anion that would be highly stable, easily and stereoselectively synthesized and asymmetrically efficient with both organic and organometallic cations was finally satisfied by the synthesis of (194) from tetrachlorocatehol and the α-D-mannopyranoside (193).[91] Multinuclear NMR data (^1H,^{13}C and ^{31}P) suggested the presence of only one diastereomer in the crystalline precipitate of the product and this was confirmed as the Λ isomer by X-ray crystallography and circular dichroism. The asymmetric efficiency of (194) was tested with organic (195) and organometallic (196) cations and compared with the asymmetric efficiency of Δ-1 TRISPHAT and Δ-2-BINPHAT. A modest diastereomeric excess of 34% was found with (195) by NMR and CD analysis, but better results were obtained with (196) for which the *de* varied from 89–30% as the polarity of the solvent was increased. A useful review on hexacoordinated phosphate anions as chiral auxiliaries has appeared recently.[92]



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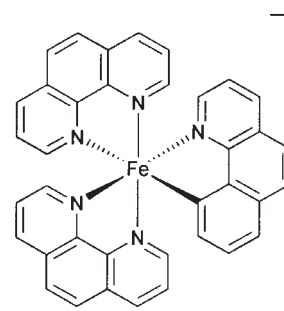
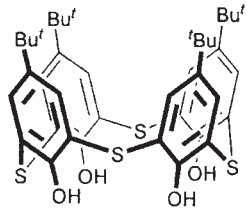
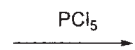
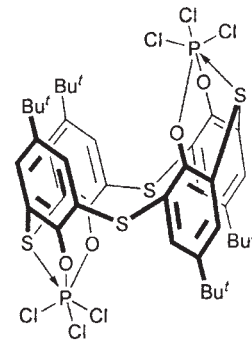


196

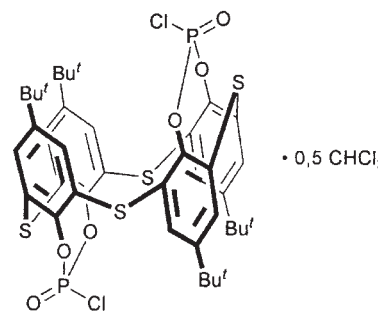


197





198



199

Reaction of the *p*-t-butylcalixarene (197) with PCl_5 forms the hexacoordinate structure (198) with two S–P donor bonds.[93,93] Although not isolated, the compound was characterized by a ^{31}P NMR signal at −133 ppm and by hydrolysis to (199).

A substantial paper by Akiba *et al*. describes the synthesis and characterization of a series of phosphorus (V) octaethylporphyrin derivatives of the type $[P(OEP)(X)(Y)]^+Z^-$where OEP = octaethylporphyrin; X = Me, Et, Ph or F; Y = Me, Et, OH, OMe, OEt, OPr, OPr^i, OBu^{sec}, NHBu, NEt_2, Cl, F, O^-; Z=ClO_4, PF_6. X-ray crystallographic analysis of eleven of these compounds revealed octahedral geometry about phosphorus, but a greater degree of ''ruffling'' in the porphyrin core coupled with shorter P–N bond distances as the electronegativity of X and Y increased. Comparison with arsenic analogous[95] showed a much smaller ring current in the phosphorus compounds due, at least in part, to the ruffling. Features of these unique hexacoordinate compounds were also investigated by density functional calculations on two models, (Por)P(Et)(O) and (Por)P(F)(O) where Por refers to unsubstituted porphyrin.

Ab initio density functional calculations afford theoretical evidence of hexacoordinate main group atoms, Si, P, and As centred in planar, hexagonal hydrocopper complexes, Cu_6H_6X where X = S, P or As.[96]

Finally, as a further contribution to understanding of bonding in hypervalent molecules, Sun has offered an alternative model of bonding in hexacoordinated molecules, eg SF_6 and PF_6^-, which does not involve d-orbital participation but employs the concept of the three center, four electron bond.[97] The model was supported by the use of a partial charge analysis using Allen's electronegativity approach.[98]

References

1. R.J. Gillespie and B. Silvi, *Coord. Chem. Rev*., 2002, **233–4**, 53.
2. S. Noury, B. Silvi and R.J. Gillespie, *Inorg. Chem*., 2002, **41**(8), 2164.
3. J.G. Verkade and P.B. Kisanga, *Tetrahedron*, 2003, **59**(40), 7819.
4. J.G. Verkade, *Topics in Curr. Chem*., 2003, **223**, 1.
5. J.G. Verkade and P.B. Kisanga, *Aldrichimica Acta*, 2004, **37**(1), 3.
6. R.R. Holmes, *Acc. Chem. Res*., 2004, **37**, 746.
7. K. Range, M.J. McGrath, X. Lopez and D.M. York, *J. Am. Chem. Soc*., 2004, **126**, 1654.
8. H. Nakazawa, K. Kubo and K. Miyoshi, *Bull. Chem. Soc. Jpn*., 2001, **74**(12), 2255.
9. G.B. Soifer, E.G. Kapustin and E.S. Kozlov, *Russ. J. Gen. Chem*., 2001, **71**(11), 1737.
10. K.B. Dillon and J. Lincoln, *Polyhedron*, 1985, **4**, 1333.
11. V.M. Vlasov and G.G. Yakobson, *Usp. Khim*., 1974, **43**(9), 1642.
12. A. Kornath, F. Neumann and H. Oberhammer, *Inorg. Chem*., 2003, **42**, 2894.
13. C.E. Check, K.C. Lobring, P.R. Keating, T.M. Gilbert and L.S. Sunderlin, *J. Phys. Chem. A*, 2003, **107**, 8961.
14. V.V. Sharutin, V.S. Senchurin, B.I. Petrov and O.K. Sharutina, *Russ. J. Gen. Chem*., 2003, **73**(8), 1322.
15. V.V. Sharutin, O.K. Sharutina, I.V. Egorova, T.K. Ivanenko and V.K. Bel'skii, *Russ. J. Gen. Chem*., 2002, **72**(1), 44.
16. J. Gloede, R. Waschke and U. Pieper, *Z. Anorg. Allg. Chem*., 2004, **630**(8-9), 1245.
17. T.A. Bidman, *Russ. J. Gen. Chem*., 2001, **71**(10), 1545.

18. J. Gloede, U. Pieper, W.D. Habicher and M. Schneider, *Z. Anorg. Allg. Chem.*, 2002, **628**(2), 480.
19. J. Gloede, U. Pieper and W.D. Habicher, *Z. Anorg. Allg. Chem.*, 2002, **628**(4), 877.
20. V.F. Mironov, R.R. Petrov, I.A. Litvinov, A.A. Shtyrlina, A.T. Gabaidullin and A.I. Konovalov, *Russ. J. Gen. Chem.*, 2001, **71**(10), 1662.
21. V.F. Mironov, A.A. Shtyrlina, R.R. Petrov, T.A. Baronova, F.F. Alekseev, E.N. Varaksina and A.I. Konovalov, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(6-7), 1381.
22. V.F. Mironov, A.T. Gubaidullin, A.A. Shtyrlina, I.A. Litvinov, R.R. Petrov, A.I. Konovalov, A.B. Dobrynin, T.A. Zyablikova, R.Z. Musin and V.I. Morozov, *Russ. J. Gen. Chem.*, 2002, **72**(11), 1764.
23. V.F. Mironov, A.A. Shtyrlina, R.F. Agzamov and A.I. Konovalov, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(8-9), 2033.
24. V.F. Mironov, A.A. Shtyrlina, F.F. Alekseev, I.A. Litvinov, A.T. Gubaidullin and A.I. Konovalov, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(8-9), 2035.
25. S. Sase, N. Kano and T. Kawashima, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(8-9), 2041.
26. U. Dieckbreder, G.-V. Röschenthaler and A.A. Kolomeitsev, *Heteroatom Chemistry*, 2002, **13**(7), 650.
27. C.K. McClure and P.K. Mishra, *Tetrahedron Lett.*, 2002, **43**(30), 5249.
28. D.W. Allen, J.S. Coles, M.B. Hursthouse and M.S. Khan, *Inorg. Chim. Acta*, 2004, **357**(1), 265.
29. H. Thoennessen, P.G. Jones and R. Schmutzler, *Z. Anorg. Allg. Chem.*, 2003, **629**(7-8), 1265.
30. H. Ikeda and S. Inagaki, *J. Phys. Chem. A*, 2001, **105**, 10711.
31. Y. Uchiyama, N. Kano and T. Kawashima, *J. Am. Chem. Soc.*, 2003, **125**, 13346.
32. T. Kawashima, Y. Uchiyama and N. Kano, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**(4-5), 849.
33. S. Sase, N. Kano and T. Kawashima, *J. Am. Chem. Soc.*, 2002, **124**, 9706.
34. S. Sase, N. Kano and T. Kawashima, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(8-9), 2039.
35. S. Sase, N. Kano and T. Kawashima, *Chem. Letters*, 2004, **33**(11), 1434.
36. D.V. Sevenard, E. Lork, K.I. Pashkevich and G.-V. Röschenthaler, *Heteroatom Chemistry*, 2002, **13**(2), 97.
37. U. Monkowius, N.W. Mitzel, A. Schier and H. Schmidbaur, *J. Am. Chem. Soc.*, 2002, **124**, 6126.
38. I. Shevchenko, V. Andrushko, R. Mikolenko, D. Shakhnin, H. Grützmacher and G.-V. Röschenthaler, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(6-7), 1413.
39. I. Shevchenko, *Tetrahedron Lett.*, 1995, **36**, 2021.
40. C. Widauer, H. Grützmacher, I. Shevchenko and V. Gramlich, *Eur. J. Org. Chem.*, 1999, 1659.
41. I. Shevchenko, *Chem. Commun.*, 1998, 1203.
42. (*a*) K.-y. Akiba, S. Matsukawa, K. Kajiyama, M. Nakamoto, S. Kojima and Y. Yamamoto, *Heteroatom Chem.*, 2002, **13**(5), 390; (*b*) S. Matsukawa, S. Kojima, K. Kajiyama, Y. Yamamoto, K.-y. Akiba, S. Re and S. Nagase, *J. Am. Chem. Soc.*, 2002, **124**, 13154.
43. (*a*) S. Kojima, K. Kajiyama and K.-y. Akiba, *Tetrahedron Lett.*, 1994, **35**, 7037; (*b*) S. Kojima, K. Kajiyama and K.-y. Akiba, *Bull. Chem. Soc., Jpn*, 1995, **68**, 1785.
44. S. Kojima, K. Kajiyama, M. Nakamoto and K.-y. Akiba, *J. Am. Chem. Soc.*, 1996, **118**, 12866.

45. S. Kojima, Y. Doi, M. Okuda and K.-y. Akiba, *Organometallics*, 1995, **14**, 1928.
46. P. Kommana, S. Kumaraswamy, J.J. Vittal and K.C. Kumara Swamy, *Inorg. Chem.*, 2002, **41**, 2356.
47. N.S. Kumar, P. Kommana, J.J. Vittal and K.C. Kumara Swamy, *J. Org. Chem.*, 2002, **67**, 6653.
48. A. Munoz and A. Rochal, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **174**, 177.
49. A. Munoz, H. Gornitzka and A. Rochal, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(5), 1255.
50. A. Munoz and H. Gornitzka, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**(1), 5.
51. D.G. Boyer, M-T. Boisdon, A. Rochal and A. Munoz, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**(10), 2117.
52. X. Lopez, M. Schaefer, A. Dejaegere and M. Karplus, *J. Am. Chem. Soc.*, 2002, **124**, 5010.
53. D.M. Perrault and E.V. Anslyn, *Angew Chem., Int. Ed.*, 1997, **36**, 432.
54. K.N. Gavrilov, A.I. Polosukhin, O.G. Bondarev, S.E. Lyubimov, K.A. Lyssenko, P. Petrovski and V.A. Davankov, *J. Mol. Cat. A: Chemical*, 2003, **196**(1-2), 39.
55. I.S. Mikhel, O.G. Bondarev, V.N. Tsarev, G.V. Grintselev-Knyazev, K.A. Lyssenko, V.A. Davankov and K.N. Gavrilov, *Organometallics*, 2003, **22**, 925.
56. O.G. Bondarev, I.S. Mikhel, V.M. Tsarev, P.V. Petrovskii, V.A. Davankov and K.N. Gavrilov, *Russ. Chem. Bull., Int. Ed.*, 2003, **52**(1), 116.
57. (*a*) H. Nakazawa, T. Ogawa, K. Kawamura and K. Miyoshi, *Phosphorus Sulfur Silicon Relat. Elem.*, 2002, **177**(8-9), 2163; (*b*) H. Nakazawa, K. Kawamura, T. Ogawa and K. Myoshi, *J. Organometallic Chem.*, 2002, **646**, 204.
58. N. Kano, A. Kikuchi and T. Kawashima, *Chem. Commun.*, 2001, 2096.
59. N. Kano, J.-H. Xing, A. Kikuchi, S. Kawa and T. Kawashima, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(6-7), 1685.
60. J. Kobayashi, K. Goto and T. Kawashima, *J. Am. Chem. Soc.*, 2001, **123**, 3387.
61. J. Kobayashi, K. Goto and T. Kawashima, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(6-7), 1405.
62. Z. Wang, G. Zhang, I. Guzei and J.G. Verkade, *J. Org. Chem.*, 2001, **66**(10), 3521.
63. P.B. Kisanga and J.G. Verkade, *J. Org. Chem.*, 2002, **67**, 426.
64. J. You, J. Xu and J.G. Verkade, *Angew. Chem. Int. Edn.*, 2003, **42**(41), 5054.
65. A.E. Wróblewski, V. Bansal, P. Kisanga and J.G. Verkade, *Tetrahedron*, 2003, **59**(4), 561.
66. W. Su, D. McLeod and J.G. Verkade, *J. Org. Chem.*, 2003, **68**(24), 9499.
67. J. You and J.G. Verkade, *J. Org. Chem.*, 2003, **68**(21), 8003.
68. S. Urgaonkar and J.G. Verkade, *J. Org. Chem.*, 2004, **69**(26), 9135.
69. W. Su, S. Urgaonkar and J.G. Verkade, *Organic Letters*, 2004, **6**(9), 1421.
70. W. Su, S. Urgaonkar, P.A. McLaughlin and J.G. Verkade, *J. Am. Chem. Soc.*, 2004, **126**(50), 16433.
71. J. You, A.E. Wróblewski and J.G. Verkade, *Tetrahedron*, 2004, **60**(36), 7877.
72. J. Kobayashi, K. Goto, T. Kawashima, M.W. Schmidt and S. Nagase, *J. Am. Chem. Soc.*, 2002, **124**, 3703.
73. Y.-F. Zhao, B. Han, J. Chen and Y. Jiang, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(6-7), 1391.
74. A. Chandrasekaran, R.O. Day and R.R. Holmes, *Inorg. Chem.*, 2001, **40**(24), 6229.
75. A. Chandrasekaran, R.O. Day and R.R. Holmes, *Inorg. Chem.*, 2002, **41**(6), 1645.
76. R.R. Holmes, A. Chandrasekaran, N.V. Timosheva and R.O. Day, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**(6–7), 1397.

77. A. Chandrasekaran, N.V. Timosheva, R.O. Day and R.R. Holmes, *Inorg. Chem.*, 2003, **42**, 3285.
78. N.V. Timosheva, A. Chandrasekaran, R.O. Day and R.R. Holmes, *J. Am. Chem. Soc.*, 2002, **124**(24), 7035.
79. N.V. Timosheva, A. Chandrasekaran and R.R. Holmes, *Inorg. Chem.*, 2004, **43**(23), 7403.
80. P. Kilian, D. Philip, A.M.Z. Slawin and J.D. Woollins, *Eur. J. Inorg. Chem.*, 2003, 249.
81. P. Kilian, A.M.Z. Slawin and D.J. Woollins, *Chem. Commun.*, 2003, 1174.
82. S. Kojima, M. Sugino, S. Matsukawa, M. Nakamoto and K.-y. Akiba, *J. Am. Chem. Soc.*, 2002, **124**, 7674.
83. I. Shevchenko, V. Andrushko, E. Lork and G.-V. Röschenthaler, *Chem.Commun.*, 2002, 120.
84. S. Matsukawa, Y. Yamamoto and K.-y. Akiba, *Heterocycles*, 2003, **59**(2), 707.
85. J. Lacour, A. Londez, C. Goujon-Ginglinger, V. Buss and G. Bernardinelli, *Org. Letters*, 2000, **2**(26), 4185.
86. J. Lacour, L. Vial and C. Herse, *Org. Letters*, 2002, **4**(8), 1351.
87. J. Lacour and A. Londez, *J. Organomet. Chem.*, 2002, **643–644**, 392.
88. V. Hebbe, A. Londez, C. Goujon-Ginglinger, F. Meyer, J. Uziel, S. Jugé and J. Lacour, *Tetrahedron Lett.*, 2003, **44**(12), 2467.
89. J. Lacour, L. Vial and G. Bernardinelli, *Org. Letters*, 2002, **4**(14), 2309.
90. J. Lacour, A. Londez, D.-H. Tran, V. Desvergnes-Breuil, S. Constant and G. Bernardinelli, *Helv. Chim. Acta.*, 2002, **85**, 1364.
91. C. Pérollier, S. Constant, J.J. Jodry, G. Bernardinelli and J. Lacour, *Chem. Commun.*, 2003, 2014.
92. J. Lacour and V. Helbe-Viton, *Chem. Soc. Rev.*, 2003, **32**(6), 373.
93. J. Gloede, S. Ozegowski, D. Weber and W.D. Habicher, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 923.
94. K.-y. Akiba, R. Nadano, W. Satoh, Y. Yamamato, S. Nagase, Z. Ou, X. Tan and K.M. Kadish, *Inorg. Chem.*, 2001, **40**(2), 5553.
95. W. Satoh, R. Nadano, G. Yamamoto, Y. Yamamoto and K.-y. Akiba, *Organometallics*, 1997, **16**, 3664.
96. S.-D. Li, G.-M. Ren and C.-Q. Miao, *Inorg. Chem.*, 2004, **43**, 6331.
97. X. Sun, *Chemical Educator*, 2002, **7**(5), 26l.
98. L.C. Allen, *J. Am. Chem. Soc.*, 1989, **111**, 9115.

Nucleic Acids and Nucleotides: Mononucleotides

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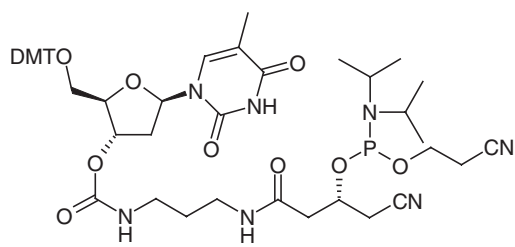
1 Introduction

Extensive work has been reported on the chemistry of polyphosphates, in particular that of dinucleoside and sugar nucleoside pyrophosphates. This reflects the reliability and flexibility of the phosphoramidate methods which have been developed over the past few years. Similarly, a wide range of oligonucleotide building blocks, incorporating extensive structural modifications when compared to the natural nucleoside structures, have been described.

2 Mononucleotides

2.1 Nucleoside Acyclic Phosphates. – *2.1.1 Methodologies*. A scaleable one-pot method to access *H*-phosphonate derivatives of 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) and AZT that employs PCl_3 as reagent and an acid catalysed Arbuzov dealkylation subsequent to a bis-alcoholysis, has been reported by Zhao.[1] While developing a method for the direct thiation of 2′-deoxy-5,6-dihydropyrimidine nucleosides with Lawesson's reagent, Clivio has identified a number of oxathiaphosphepane intermediates (1) which resulted from the heat reversible incorporation of an $AnPS_2$ moiety within the 2′-deoxyribose unit (Scheme 1).[2] Wolter reported the synthesis in four steps from 5′-*O*-DMT-thymidine of a "user-friendly" solid reagent, the phosphoramidite (2), that converts terminal hydroxyl groups of oligonucleotides into phosphate monoesters.[3]



(2)

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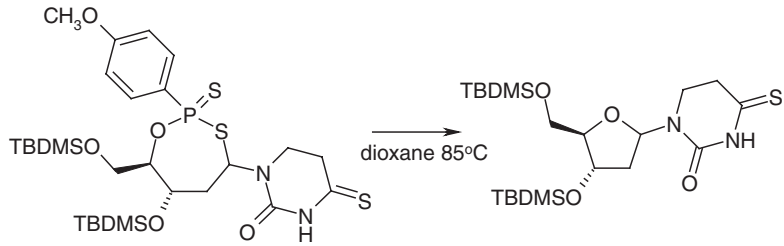
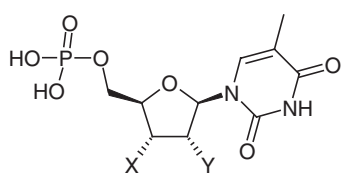


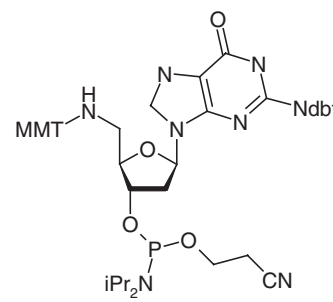
(1)

Scheme 1

2.1.2 Mononucleoside Phosphate Derivatives. To identify potential leads for new anti-mycobacterium tuberculosis treatment, Van Calenberg synthesized a number of 2′- and 3′-modified thymidine 5′-*O*-monophosphate analogues (3–6). These were evaluated amongst other known inhibitors of the mycobacterium thymidylate kinase.[4] Compound (7) was prepared in four steps from 2′-deoxyguanosine as a suitable building block for DNA synthesis.[5] Similarly, Beigelman reported the scaleable preparation of the 2′-deoxy-2′-*N*-phthaloyl nucleoside phosphoramidites (8–10) for use in oligonucleotide synthesis.[6] Eschenmoser described the synthesis of the α-threofuranosyl nucleoside phosphoramidites (11–14), starting either from 1,2,3-tri-*O*-acetyl erythrose or from α-L-threofuranosyl thymine.[7] 2′-Fluoro-L-uridine and 2′-fluoro-L-cytidine phosphoramidites, (15) and (16) respectively, were synthesized from L-arabinose and used as building blocks in the synthesis of 2′-fluoro-Spiegelmers binding to a D-neuropeptide.[8] To facilitate phase determination in X-ray crystallography and the 3-D-structure identification of nucleic acids, the selenium containing phosphoramidite (17) was prepared from the 2-Se-uridine and incorporated in DNA and RNA oligonucleotides.[9] Similarly, to further investigate the role played by the 2-hydroxyl group in RNA, the phosphoramidite derivative of 2′-deoxy-2′-C-β-methylcytidine (18) was prepared from 1,2,3,5-tetra-*O*-benzoyl-2-C-β-methylribofuranose.[10]



(3) X= Cl; Y= OH
(4) X= F; Y= OH
(5) X= OH; Y= NH_2
(6) X=NH_2; Y= OH



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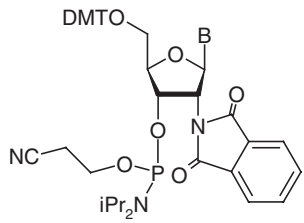
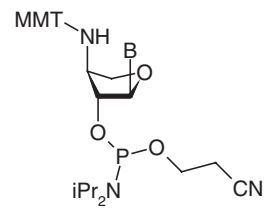
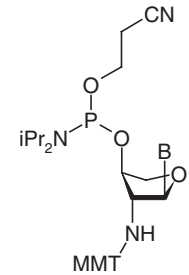


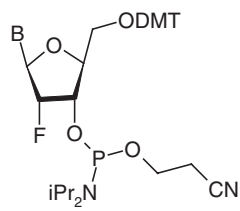
(8) B= Ura
(9) B= N4-Ac Cyt
(10) B= N-Bu, N-Bz Ade



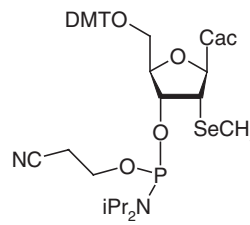
(11) B= T
(12) B= ABz



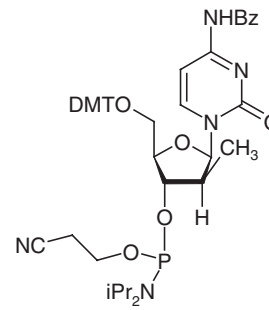
(13) B= T
(14) B= ABz



(15) B = Cyt
(16) B = N4-AcThy

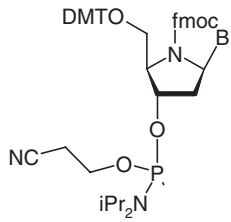


(17)

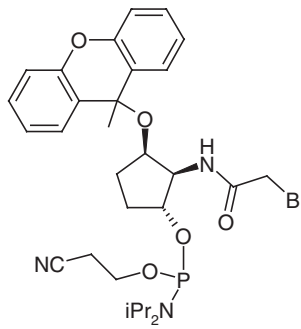


(18)

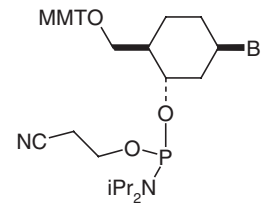
Leumann has reported the synthesis of various types of modified phosphoramidites. He described the synthesis of pyrrolidino-C-nucleoside phosphoramidites incorporating a pseudo-uracyl, pseudo-thymine or pseudo-isocytosine, (19), (20) and (21), respectively.[11] He also reported the preparation of the enantiomerically pure adenine and thymine cyclopentane amide phosphoramidites (22) and (23).[12] Herdewijn reported the use of lipases for the preparative scale resolution of (+/−) (4a*R*, 7*R*, 8a*S*)-2-phenyl-4a,7,8,8a,tetrahydro-4*H*-1,3-benzodioxine and the synthesis of eight enantiomerically pure phosphoramidites of D- and L-cyclohexyl nucleosides (24(+), 24(−), 25(+), 25(−), 26(+), 26(−), 27(+), 27(−)).[13] The phosphoramidite derivatives (28) and (29) were synthesized from 1-(5,6-di-*O*-acetyl-2,3-dideoxy-3-phthalimido-α-D-arabino-hexofuranosyl)thymine and incorporated into oligodeoxynucleotides as putative conformationally restricted acyclic nucleosides.[14] Starting from adenine β-D-nucleosides with ribo-, xylo- and arabino- configurations, the phosphonate derivatives (30-35) were synthesized after phosphonomethylation with diisopropyl tosylmethylphosphonate of the suitably protected nucleoside precursors. The phosphonomethyl derivatives were then incorporated into oligonucleotides using solid phase synthesis protocols.[15]



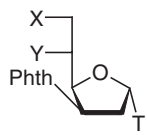
(19) B= pseudo-Ura
(20) B= pseudo-Thy
(21) B= pseudo-isocytosine



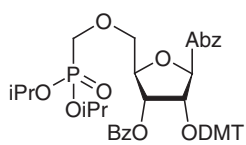
(22) B= Thy
(23) B= N6-anIsoyl-Ade



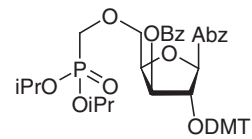
(24) (+) and (-) B= N6-Bz Ade
(25) (+) and (-) B= N2-iBu Gua
(26) (+) and (-) B= N4-Bz Cyt
(27) (+) and (-) B= Thy



(28) X= ODMT; Y= OP(NiPr$_2$)(OCH$_2$CH$_2$CN)
(29) X= OP(NiPr$_2$)(OCH$_2$CH$_2$CN); Y= ODMT



(30)



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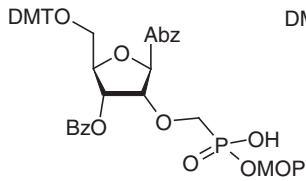

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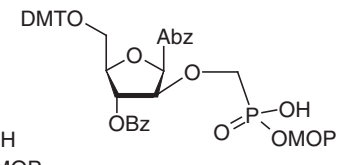

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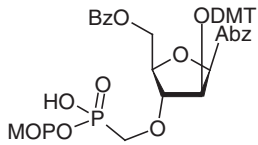

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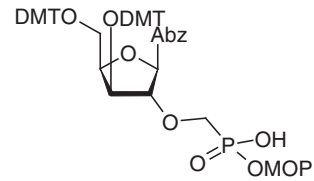
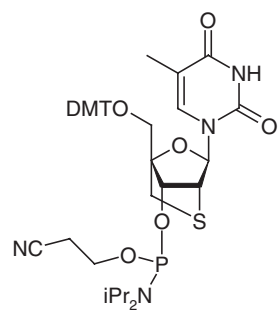


(35)

Extensive work has been reported with regard to the synthesis of phosphoramidites, building blocks for the synthesis of locked nucleic acids. For instance, Koch has developed a synthesis of the 2′-thio-LNA ribothymidine phosphoramidite (36), which is convergent with the previously reported procedures to access LNA and 2′-amino-LNA.[16] However, Wengel has been the most prolific in this area. He has reported the synthesis of four conformationally restricted bicyclic 2′-spiro nucleoside phosphoramidites (37–40). The nucleoside precursors showed no anti-viral activities and their introduction into oligonucleotides induced decreased duplex thermostabilities compared with the corresponding DNA:DNA and DNA:RNA duplexes.[17] He also described the syntheses and antiviral activities of conformationally locked 3′-deoxy and 3′-azido-3′-deoxynucleoside derivatives (41–46) as pro-drugs of potential 5′-*O*-triphosphorylated anti-HIV drugs.[18] In addition to reporting the syntheses of locked nucleosides based on natural nucleobases, he has described the synthesis of conformationally locked aryl C-nucleoside phosphoramidites, either in a D-ribo configuration (47–51)[19] or in a β-L-ribo configuration (52), (53).[20] He has also prepared the non-locked α-L-ribofuranosyl phosphoramidite (54) for incorporation in α-L-RNA/DNA; α-L-RNA/α-L-LNA chimeras.[21] Finally, he has described the synthesis of a methylphosphonamidite locked nucleic acid thymine derivative, (55). The two diastereoisomers of this phosphonamidite were obtained by treating the locked thymidine nucleoside suitably protected with bis(diisopropylamino)methylphosphine in the presence of 1*H*-tetrazole.[22]



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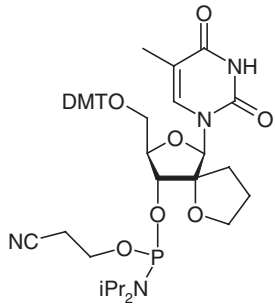

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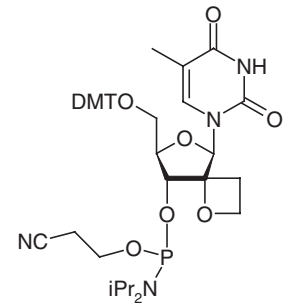

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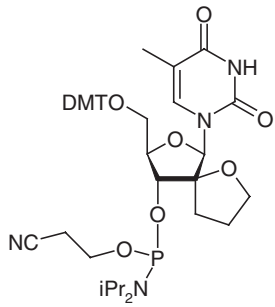

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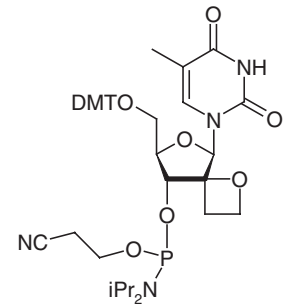

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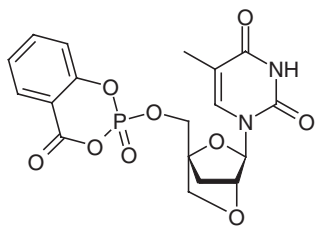
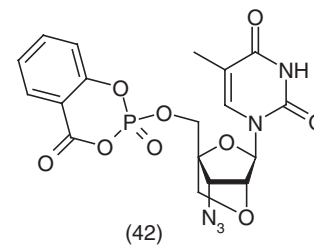


(41)



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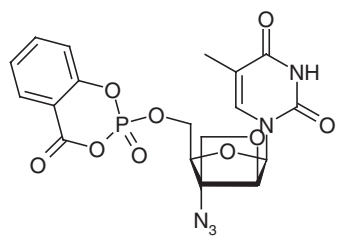

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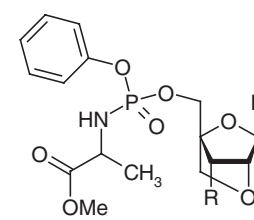
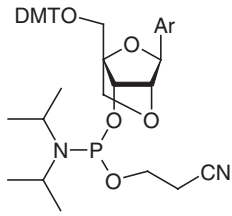
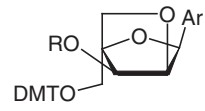


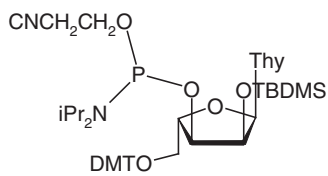
(44) B= Ade; R= N_3
(45) B= Ade; R= H
(46) B= Thy; R= N_3





(47) Ar= phenyl
(48) Ar= 4-fluoro-3-methylphenyl
(49) Ar= 1-naphthyl
(50) Ar= 1-pyrenyl
(51) Ar= 2,4,5-trimethylphenyl

(52) Ar= phenyl; R= $P(OCH_2CH_2CN)(NiPr_2)$
(53) Ar= 1-pyrenyl; R= $P(OCH_2CH_2CN)(NiPr_2)$



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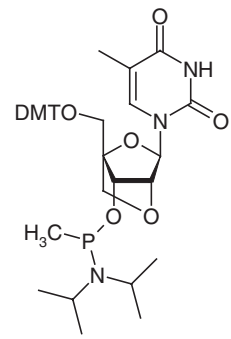
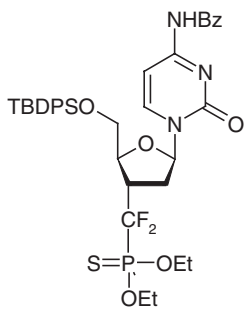


(55)

The Lewis acid-mediated *N*-glycosylation of 2,3-dideoxyribofuranosides having a (diethoxyphosphorothioyl)difluoromethyl group at the 3α-position with silylated nucleobases has been reported to be successful for the diastereoselective synthesis of β-*N*-pyrimidine-nucleotide analogues, (56–59).[23]



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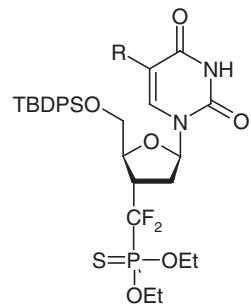
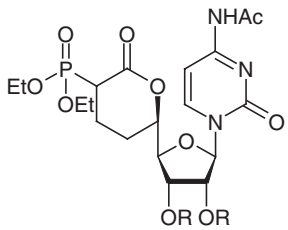


(57) R= H
(58) R= F
(59) R=CH_3

The α-phosphonolactones, (60) and (61), analogues of cytidine and cytosine arabinoside diphosphates, have been synthesized in an attempt to bypass

metabolic adaptations and resistance known to be occurring during the treatment of myeloid leukemias by cytosine arabinoside.[24] These phosphonates were prepared via ring closing metathesis on acrylate esters of homoallylic alcohols and reduction of the α,β-unsaturated lactones followed by a base-catalysed carbon-phosphorus bond formation using chlorodiethylphosphite. Chan has reported a novel class of tetrahydrofuran phosphonates with potential antiviral activity (62) and (63).[25] His work further extended to the preparation and evaluation of a series of substituted tetrahydrofuran derivatives (64–73).[26]



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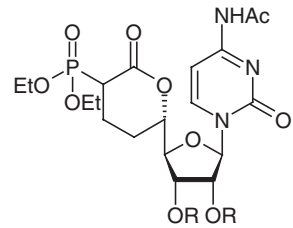
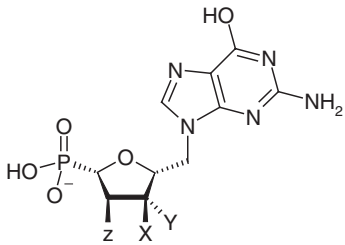
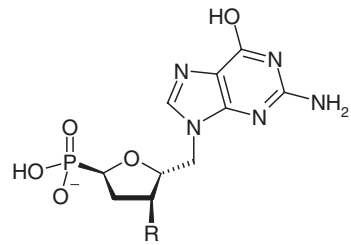


(61)

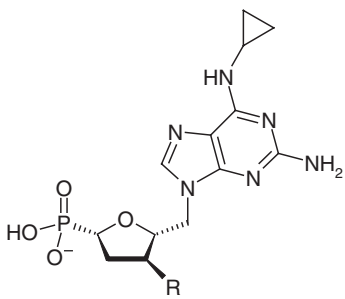
R= TBDMS



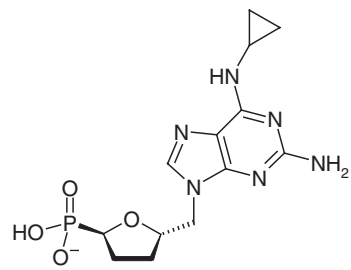
(62) X= Y= Z= H
(64) X= OH; Y= H; Z= H
(65) X= F; Y= H; Z= H
(66) X=H; Y= F; Z= H
(67) X=OCH_3; Y= Z= H
(68) X= OH; Y= H; Z= OH



(63) R= H
(69) R=OH



(70) R= H
(71) R= OH



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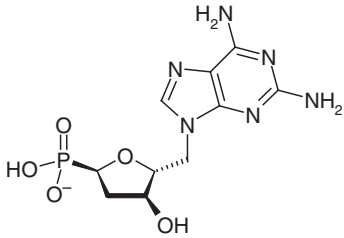
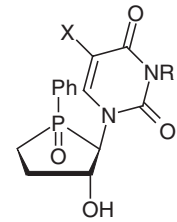
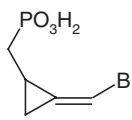


(73)

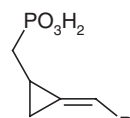


(74) X= CN; R= CH_3
(75) X= CN; R= p-Cl-Bn
(76) X= CN; R= H
(77) X= $COCH_3$; R= H
(78) X= COOEt; R= H
(79) X= CH_3; R= H
(80) X= H; R= H

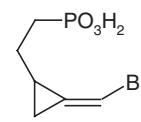
Oshikawa described an efficient method for the synthesis in racemic form of several deoxyphosphasugar pyrimidine nucleosides (74–80). The synthetic route involved the treatment of 2-aminophospholane 1-oxide with several α-cyano, acetyl, ethoxycarbonyl-β-ethoxy-*N*-ethoxycarbonylacrylamides, precursors of the substituted uracyl ring systems.[27] The phosphonate derivatives of methylenecyclopropane nucleoside analogues (81–92) have been synthesised by Zemlicka via an alkylation-elimination method.[28] Stec reported the synthesis of novel acyclic nucleosides (93–100) based on a bis(hydroxymethyl)phosphinic acid backbone and obtained by condensation of its bis-(4,4′-dimethoxytrityl) derivative with *N*-1 or *N*-3-(2-hydroxyethyl)thymine in the presence of 1-(2-mesitylensulfonyl)-3-nitro-1,2,4-triazole as activator.[29] Balzarini reported the synthesis and biological activity as antiproliferative agents of a series 2,4-diamino-6-[(2-phosphonomethoxy)ethoxy]pyrimidine derivatives (101–108).[30] Stang described the reaction of (1-chloro-4-diethoxyphosphonyl)alka-2,3-dienes with purine and pyrimidine heterocyclic bases in the presence of cesium carbonate. This afforded acyclic nucleoside analogues (109–120), containing a 1,2-alkadiene skeleton.[31]



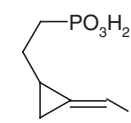
(81) B= Ade
(82) B= Gua
(83) B= Cyt



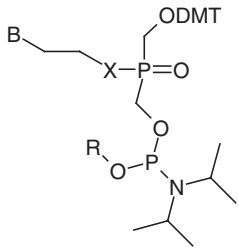
(84) B= Ade
(85) B= Gua
(86) B= Cyt



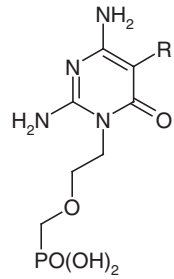
(87) B= Ade
(88) B= Gua
(89) B= Cyt



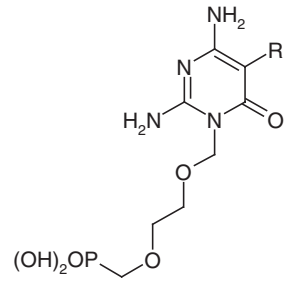
(90) B= Ade
(91) B= Gua
(92) B= Cyt



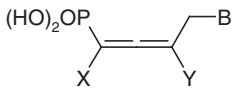
(93) R= CH_2CH_2CN; X= O; B= N1-Thy
(94) R= CH_3; X= O; B= N1-Thy
(95) R= CH_2CH_2CN; X= NH; B= N1-Thy
(96) R= CH2CH2CN; X= O; B= N3-Thy
(97) R= CH_3; X= O; B= N3-Thy
(98) R= CH_2CH_2CN; X= NH; B= N3-Thy



(101) R= Allyl
(102) R= Benzyl
(103) R= CH_2CN
(104) R= CH_2COOH

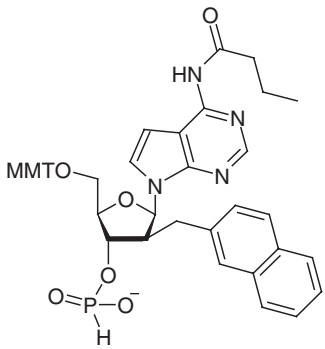


(105) R= Allyl
(106) R= Benzyl
(107) R= CH_2CN
(108) R= CH_2COOH

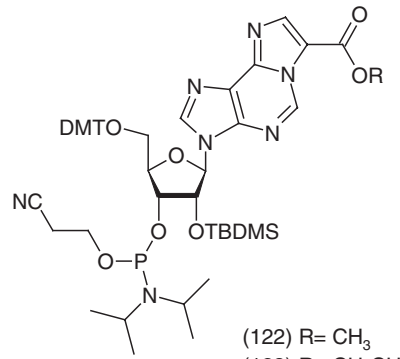


(109) X= Y= H; B= Ade
(110) X=H; Y= n-C_4H_9; B= Ade
(111) X=CH_3; Y= n-C_3H_7; B= Ade
(112) X=CH_3; Y= n-C_4H_9; B= Ade
(113) X= Y= H; B= Ura
(114) X=H; Y= n-C_4H_9; B= Ura
(115) X=CH_3; Y= n-C_3H_7; B= Ura
(116) X=CH_3; Y= n-C_4H_9; B= Ura
(117) X= Y= H; B= Thy
(118) X=H; Y= n-C_4H_9; B= Thy
(119) X=CH_3; Y= n-C_3H_7; B= Thy
(120) X=CH_3; Y= n-C_4H_9; B= Thy

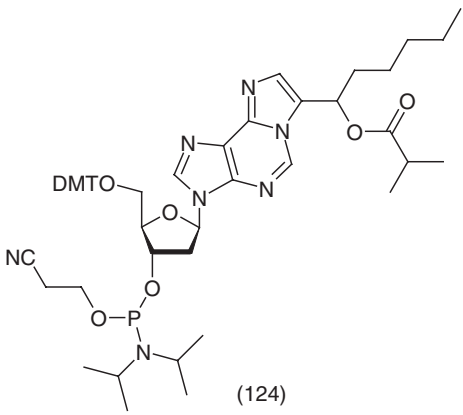
Extensive work has been reported on the synthesis of nucleoside phosphoramidite and *H*-phosphonate derivatives incorporating modified-nucleobases. To target the stabilization of RNA bulges, Stromberg synthesized the *H*-phosphonate derivative of 2′-naphthylmethyl-2′-deoxytubercidine, (121).[32] Lonnberg developed the synthesis of the phosphoramidites (122) and (123) to learn more about the effects that the *in vivo* base modification of adenosine to the 11-carboxy-1, *N*6-etheno adduct exerts on the duplex stability and coding properties of DNA.[33] To similar ends, Cadet synthesized the phosphoramidite derivative of 1-hexanol-1, *N*6-etheno-2′-deoxyadenosine, (124) and incorporated it into modified oligonucleotide chains.[34] Yaekura has shown that the treatment of guanine nucleotides with an excess of crotonaldehyde in pH 8 phosphate buffer containing an equimolar amount of arginine at 50°C for 2h resulted in the selective formation of the corresponding cyclic 1, *N*2-propano adducts (125–127).[35,36]



(121)



(122) R= CH_3
(123) R= CH_2CH_3



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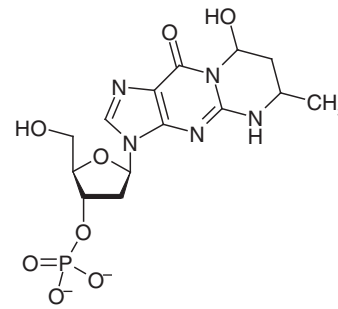

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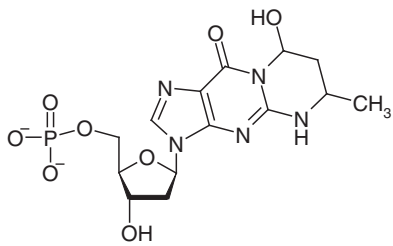

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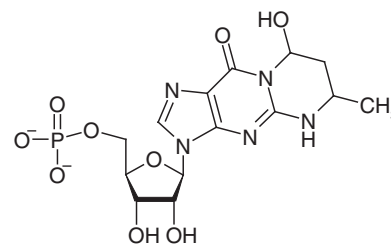
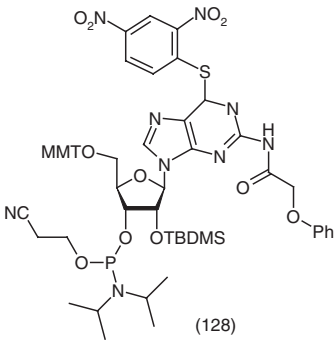


(127)

In order to expand on the number of thioguanosine-modified building blocks for the synthesis of RNA-type oligonucleotides, Zheng has developed a synthetic route to (128), which employs 2,4-dinitrophenyl as thiol protecting group for the starting material 6-thioguanosine. The 2,4-dinitrophenyl group was subsequently removed in high yield using mercaptoethanol under very mild alkaline conditions once the oligonucleotides had been synthesised.[37] Seela reported the syntheses of the phosphoramidites of 8-aza-7-deazaguanine *N*8-(2′-deoxy-β-D-ribofuranoside) (129),[38] the halogenated 7-deaza-2′-deoxyxanthosine derivatives (130–132)[39] and the *N*7-(2′-deoxy-β-D-erythro-pento-furanosyl) isoguanine (133).[40]



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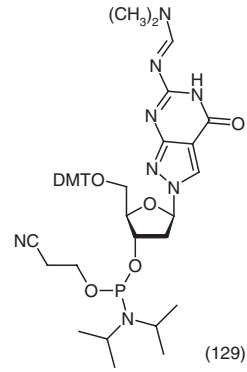

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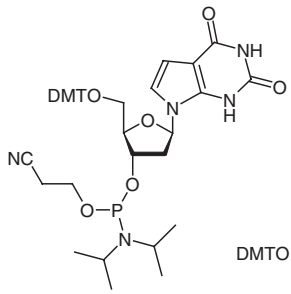

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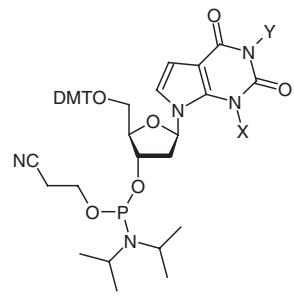
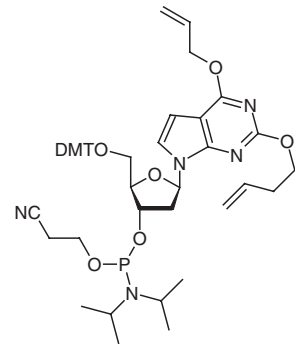


(131a) X= H; Y= DPCO
(131b) X=DPCO; Y=H



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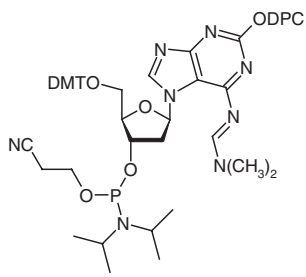
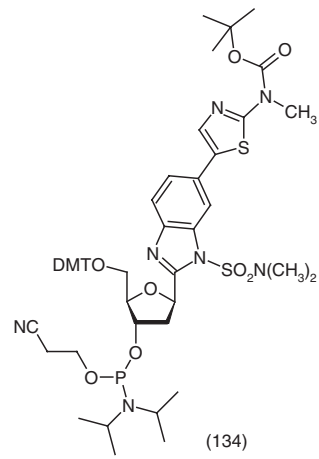
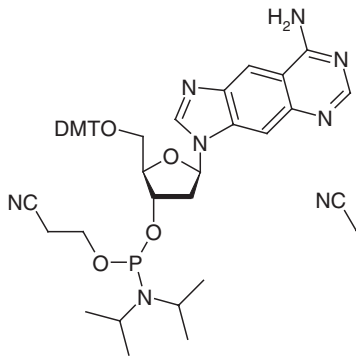


(133)

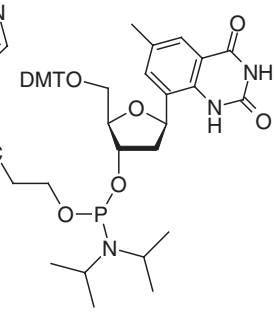


(134)

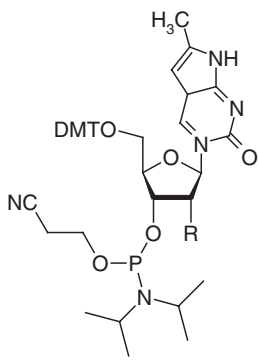
Benhida described the synthesis of a 2-deoxy-C-nucleoside analogue and its phosphoramidite derivative featuring 6-(thiazolyl-5)-α-benzimidazole nucleobase (134).[41] A more efficient route to the expanded adenosine analogue (135) was developed by Kool, who also described the synthesis of the expanded thymidine analogue (136) starting from 5-methylanthranilic acid. Both nucleosides were found to be efficient fluorophores.[42] 3′-Cyanoethyl phosphoramidites of 6-methyl-3-(2′-deoxy-β-D-ribofuranosyl)-3*H*-pyrrolo[2,3-d]pyrimidin-2-one (137) and of 6-methyl-3-(β-D-ribofuranosyl)-3*H*-pyrrolo[2,3-d]pyrimidin-2-one (138) were synthesized and used as fluorescent analogues for deoxycytidine and cytidine in oligonucleotides, respectively.[43]



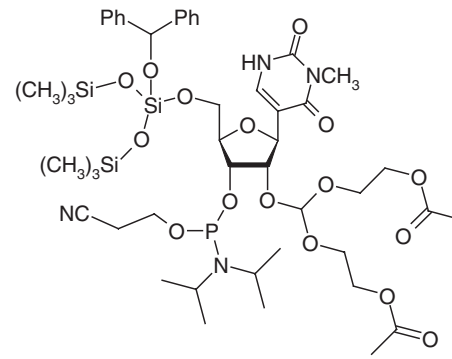
(135)



(136)



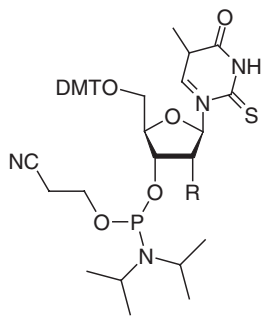
(137) R= H
(138) R= OTOM



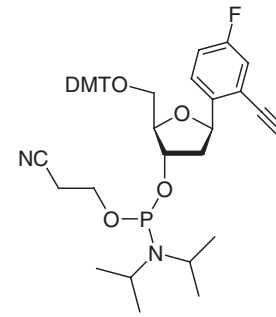
(139)

A selective method which involves the selective pivaloyloxymethyl protection of the N1 of pseudouridine followed by methylation at N3 was developed to prepare the 5-benzhydryloxybis(trimethylsilyloxy)silyl, bis(2-acetoxy-ethoxy)methyl- protected phosphoramidite derivative (139) of the nucleoside 3-methylpseudouridine. The methylated pseudouridine phosphoramidite was successfully used in oligonucleotide synthesis for the NMR study of helix 69 of *E. coli* 23S rRNA.[44] 2-Thiouridines incorporating 2′-modified nucleoside phosphoramidites

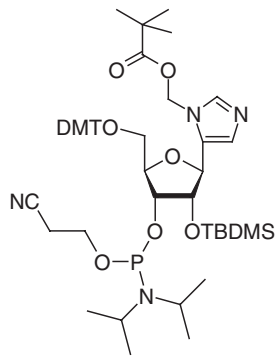
(140) and (141) have been synthesized from the 2′-modifed uridine via a 5-*O*-DMT-2-*O*-MOE-2-*O*-ethylthymidine prepared from a 5′-mesylate precursor.[45] Richert described the synthesis of the 5′-protected 3′-phosphoramidite of 1-(2′-deoxy-β-D-ribofuranosyl)-2-ethynyl-4-fluorobenzene, (142).[46] The C-nucleoside was obtained from the α-chlorosugar and a cadmium-activated arene anion as a mixture of α and β diastereoisomers, with the undesired α-anomer formed in excess. Harusawa reported the synthesis of the C4-linked imidazole ribonucleoside phosphoramidite (143). This C-nucleoside, prepared from tribenzylribofuranosylimidazole, was incorporated into an RNA sequence to study its capacity as a general acid and base catalyst of ribozymes.[47]



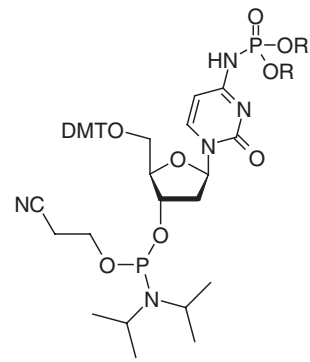
(140) R= $OCH_2CH_2OCH_3$
(141) R= F



(142)



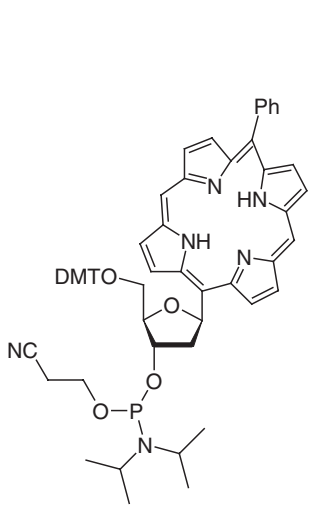
(143)



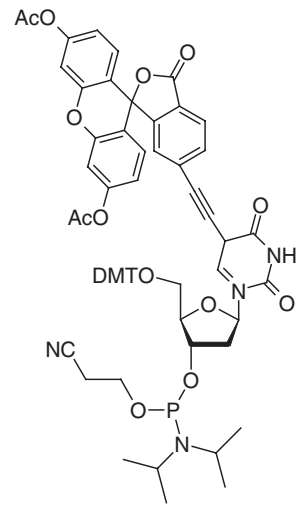
(144) R= CH_2CH_2CN
(145) R= CH_2CH_3

The synthesis and incorporation into oligonucleotides of the *N*-phosphorylated deoxycytidine 3′-phosphoramidites (144) and (145) obtained either from the *O*-protected 2′-deoxycytidine and bis(2-cyanoethyl) *N*,*N*-diisopropyl phosphoramidite or diethylphosphorochloridite, respectively, was described by Sekine.[48] Sekine also reported that the *N*-phosphorylated derivatives of 2′-deoxy adenosine decomposed readily and were unsuitable for incorporation into oligodeoxynucleotides.

Kool described the synthesis of the phosphoramidite derivative of a C-nucleoside incorporating a porphyrin moiety, (146).[49] His approach was to assemble the porphyrin de novo on the sugar moiety starting from 3,5-bis-*O*-toluoyl-protected deoxyribose-C1-carboxaldehyde, benzaldehyde and dipyrromethane under Lindsey conditions. Similarly, to fluorescently label oligonucleotides, Burgess reported the synthesis of phosphoramidite (147), for which the nucleoside precursor was prepared from 5-ethynyl thymidine and iodofluorescein via Sonogashira's coupling procedure.[50]



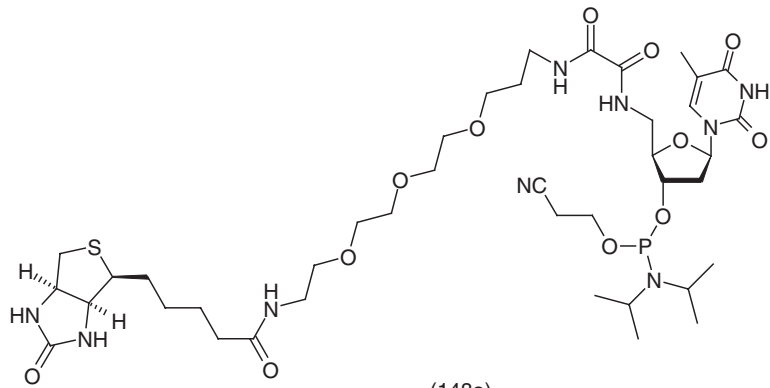
(146)



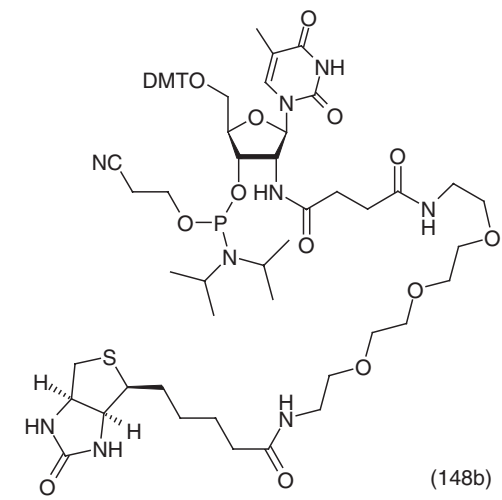
(147)

Methoxyoxalamido and succinimido precursors were used in conjunction with ETT as catalyst in the synthesis of the uridine phosphoramidites (148a) and (148b). Both compounds possess a biotin moiety linked via a long and uncharged tethering arm at the 2′-position.[51] The 3′-*O*-lysophosphatidyl-2′-nucleosides (149–152) were synthesized from the regioselective lipase-catalysed transacylation at the C1-hydroxyl of the glycerol moiety with activated palmitic acid ester in an organic solvent. The glycerol phosphate diester substrate was prepared from the protected nucleoside phosphoramidites and [(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol.[52] Shirokova reported the synthesis of uncharged 5′-aminocarbonyl and 5′-aminocarbonylmethylphosphonate derivatives of AZT and d4T, (153–162) and their activity in cell cultures infected with HIV-1. These compounds were prepared by treatment of the corresponding 5′-ethoxycarbonylphosphonyl nucleosides with primary amine followed by esterification.[53] Synthesis and cytotoxic activity of 1-dodecylthio-2-decyloxypropyl-3-phosphatidic acid conjugates of gemcitabine (163) and cytosine arabinoside (164) have been reported.[54] These compounds were prepared by direct conjugation of 1-S-dodecyl-2-*O*-decylthioglycero-3-phosphatidic acid to the 5′-OH of the nucleosides in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride in pyridine. Waldmann has developed a mild enzymatic deprotection method using penicillin G acylase for the synthesis of the nucleopeptides

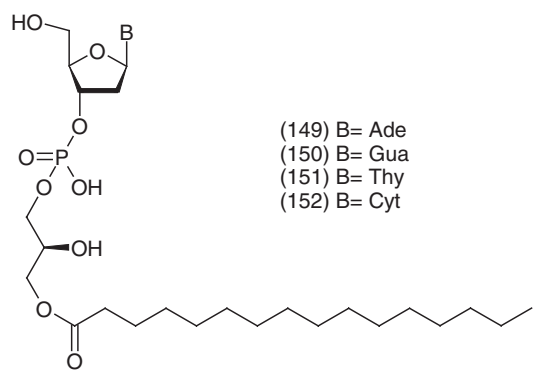
(165–168). This enzyme catalyses hydrolysis of the *N*-phenylacetoxybenzyloxycarbonyl group from the terminus amine.[55]



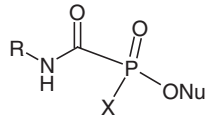
(148a)



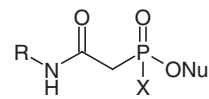
(148b)



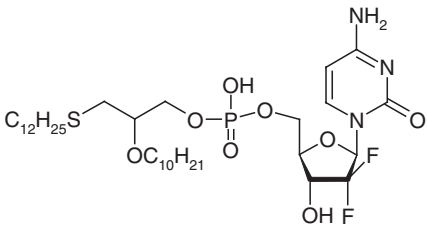
(149) B= Ade
(150) B= Gua
(151) B= Thy
(152) B= Cyt



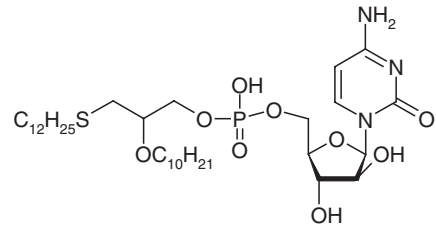
(153) R= H; X= OCH_2CH_3; Nu= AZT
(154) R= CH_3; X= OCH_2CH_3; Nu= AZT
(155) R= CH_2CH_2Ph; X= OCH_2CH_3; Nu= AZT
(156) R= H; X= OCH_2CH_3; Nu= d4T
(157) R= CH_3; X= OCH_2CH_3; Nu= d4T
(158) R= CH_2CH_2Ph; X= OCH_2CH_3; Nu= d4T



(159) R= H; X= OCH_2CH_3; Nu= AZT
(160) R= H X= OC_6H_{11}; Nu= AZT
(161) R= CH_3; X= OCH_2CH_3; Nu= AZT
(162) R= H; X= OCH_2CH_3; Nu= d4T



(163)



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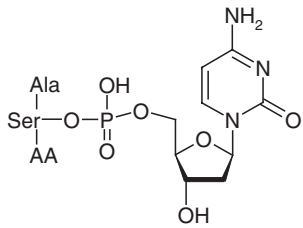
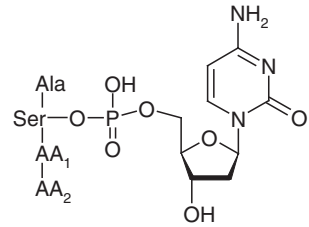
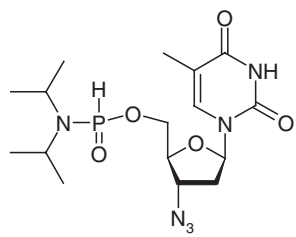


(165) AA= Val
(166) AA= Phe

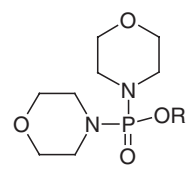


(167) AA_2-AA_1= Pro-Val
(168) AA_2-AA_1= Ala-Phe

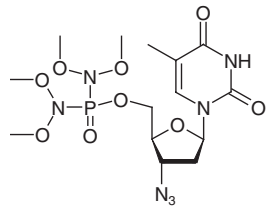
Perigaud reported the synthesis of the *H*-phosphonamidate of AZT (169). It was synthesized by the successive coupling of AZT to bis(diisopropylamino) chlorophosphine and *in situ* hydrolysis in the presence of tetrazole and water.[56] Phosphorodiamides (170–179) have also been reported as prodrugs for antiviral nucleosides.[57] These were prepared by quenching the reaction between phosphorus oxychloride and the nucleoside with an excess of amine in methanol or dioxane.



(169)



(170) R= AZT
(171) R= d4T
(172) R= d2T
(173) R= acyclovir
(174) R= ara-A
(175) R= ribo-A



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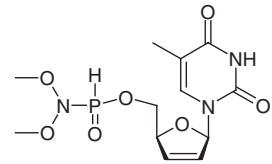
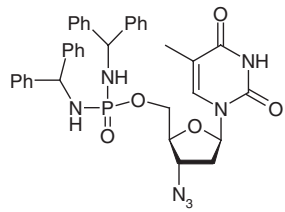
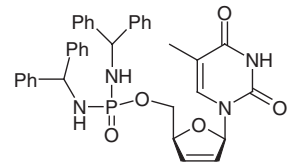


(178)

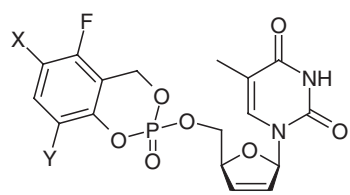


(177)

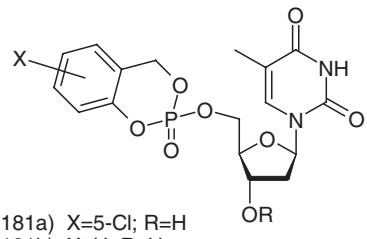


(179)

Meier reported two improved cycloSal-masking phosphate groups which once attached to the anti-HIV drug d4T (180a, 180b), possessed a reasonable chemical half-life and high cell selectivity, achieved TK-bypass and had no inhibitory effect on butyryl-cholinesterase.[58] He also described the synthesis, hydrolytic properties and biological activities of 3-unmodified and 3-*O*-esterified cycloSal-5-[(*E*)-2-bromovinyl]-2-deoxyuridine derivatives (181a–f), (182a–g) and (183a–g).[59] Other analogues containing benzyl-substituted monophosphates of cycloSal-d4T (184a–g) were prepared and evaluated for their ability to release d4T selectively and were found surprisingly stable.[60] Cyclosaligenyl-tiazofurin monophosphate (185) has also been synthesized and its biological activity as pronucleotide against human myologenous cell line has been confirmed despite being four-fold less active than its nucleotide parent.[61] However, it was also found to be A1 adenosine receptor agonist.

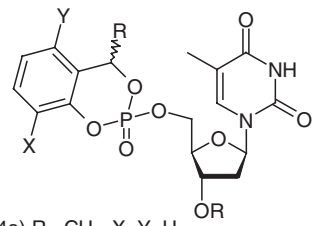


(180a) X=Y= H
(180b) X=Y=tBu

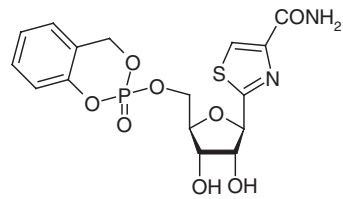


(181a) X=5-Cl; R=H
(181b) X=H; R=H
(181c) X=5-OMe; R=H
(181d) X=3-Me; R=H
(181e) X=3,5-diMe; R=H
(181f) X=3-tBu; R=H

(182a) X=3-Me; R=Ac
(182b) X=3-Me; R=C_2H_5CO
(182c) X=3-Me; R=i-C_3H_7CO
(182d) X=3-Me; R=t-C_4H_9CO
(182e) X=3-Me; R=$C_5H_{11}CO$
(182f) X=3-Me; R=$C_{10}H_{21}CO$
(182g) X=3-Me; R=Lev
(183a) X=3-Me; R=Gly
(+/-183b) X=3-Me; R=Ala
(+/- 183c) X=3-Me; R=Val
(+/- 183d) X=3-Me; R=Leu
(+/- 183e) X=3-Me; R=Ile
(+/- 183f) X=3-Me; R=Phe
(+/- 183g) X=3-Me; R=Pro

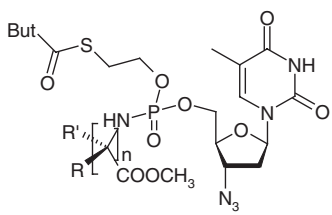


(184a) R= CH_3, X=Y=H
(184b) R= CH_3, X=CH_3; Y=H
(184c) R= CH_2Cl, X=Y=H
(184d) R= $CHCl_2$, X=Y=H
(184e) R= CCl_3, X=Y=H
(184f) R= CH_3, X=H; Y=Cl
(184g) R= H, X=H; Y=Cl

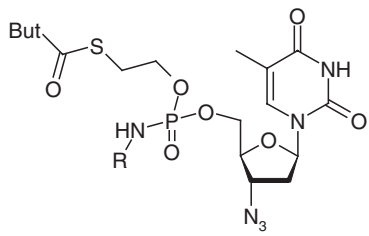


(185)

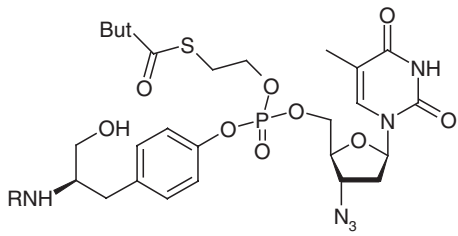
Perigaud reported an extensive amount of work on the synthesis of phosphodiester and triester derivatives and their ability to act as pro-drugs. For instance, the S-acyl-2-thioethyl phosphoramidate diesters of AZT (186a–m) were prepared by a one-pot procedure via the hydrogenphosphonates, which underwent oxidative coupling with the corresponding amines.[56] Similarly, he reported the synthesis, antiviral activity and stability study of phosphotriester derivatives of AZT bearing modified L-tyrosinyl residues where the carboxylate group of L-tyrosine has been replaced by an alcohol (187a,b) or an amide (187c–f) function.[62] They were synthesized via the phosphoramidite AZT derivative and showed potent antiviral activity in particular against TK-deficient cell lines. Mononucleoside SATE glucosyl phosphorothiolates (188a,b) were also found to be potent antiviral agents in TK-deficient cell lines.[63]



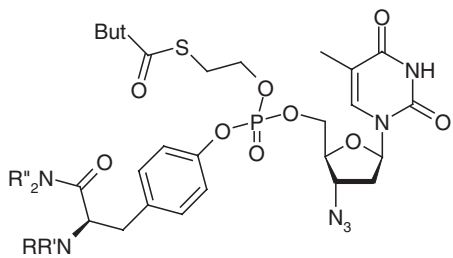
(186a) n=1 R=H, R'= CH_3
(186b) n=1 R=H, R'= H
(186c) n=1 R=H, R'= CH_2Ph
(186d) n=1 R=H, R'= CH_2PhOH
(186e) n=1 R=H, R'= $C_2OTBDMSH$
(186f) n=1 R=H, R'= CH_2OAc
(186g) n=1 R=CH_3, R'= H
(186h) n=1 R=CH_3, R'= CH_3
(186i) n=2 R=H, R'= H
(186j) n=3 R=H, R'= H



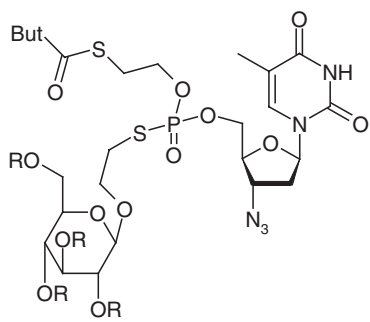
(186k) R=NHiPr
(186l) R= pyrimidine
(186m) R= CH_2Ph



(187a) R=tBoc
(187b) R=H

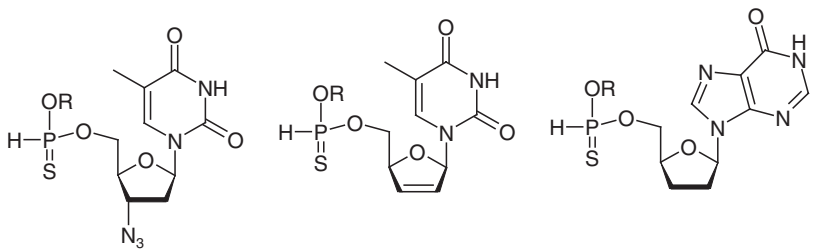


(187c) R=H; R'=R"=tBoc
(187d) R=Ac; R'=R"=tBoc
(187e) R=R'=R"=H
(187f) R=Ac; R'=R"=H



(188a) R=H
(188b) R=Ac

The syntheses of the 5′-hydrogenphosphonothioate derivatives of AZT, d4T and ddI (189a–i) have been reported.[64] They were prepared through sequential one-pot reactions, *i.e.* coupling of triethylammonium phosphinate with different alcohols in the presence of pivaloyl chloride, following oxidation with elemental sulfur and further condensation with the nucleoside analogues in the presence of pivaloyl chloride.

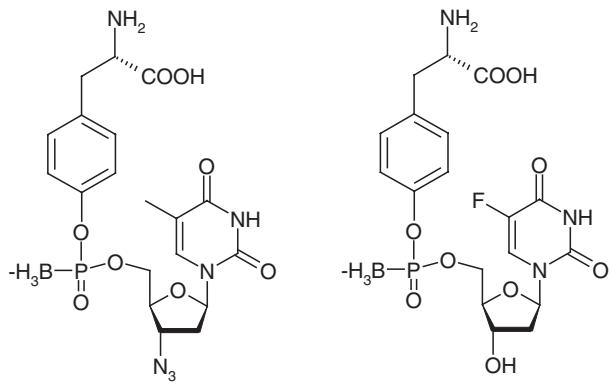


(189a) R=hexadecanyl
(189b) R= isopropyl
(189c) R=cyclohexyl

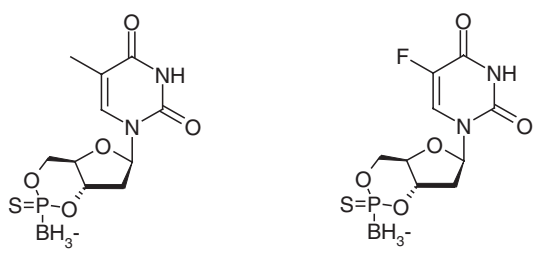
(189d) R=hexadecanyl
(189e) R= isopropyl
(189f) R=cyclohexyl

(189g) R=hexadecanyl
(189h) R= isopropyl
(189i) R=cyclohexyl

Shaw reported the synthesis of *P*-tyrosinyl-(*P*-*O*)-5-*P*-nucleosidyl boranophosphates (190a,b) obtained in a one-pot synthetic procedure via a phosphoramidite[65] and that of the nucleoside 3′,5′-cyclic boranophosphorothioates (191a,b) prepared from a cyclophosphoramidite intermediate.[66] The cyclophosphoramidite, obtained by heating the nucleoside with HMPA was transformed to the phosphite triester by reaction with 4-nitrophenol in the presence of 5-ethylthio-1*H*-tetrazole. The boranophosphite was oxidized with Li_2S after boronation with $BH_3.SMe_2$.



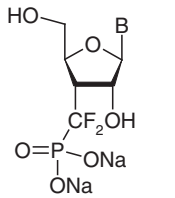
(190a) (190b)



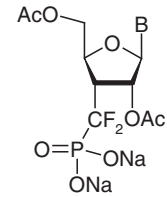
(191a) (191b)

3-Phosphonodifluoromethylene analogues of nucleoside 3′-phosphates (192a–e) were synthesized from readily available ketones. Their syntheses involve addition of the lithium salt of difluoromethylphosphonothioate. The beneficial presence of the sulfur atom in this reagent translates into increased

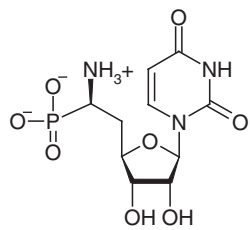
yields, reproducibilities, and ease of purification.[67] Wiemer reported the synthesis of the 5-amino-5-phosphonate analogues of uracyl, cytidine and cytosine arabinoside monophosphates, (193a–d).[68] These were synthesized via the addition of phosphite to an imine intermediate. He also reported the synthesis of the alcohol analogues of cytidine and cytosine arabinoside (194a–d), prepared via phosphite addition or a Lewis acid mediated hydrophosphorylation of the appropriately protected 5′-nucleoside aldehydes.[69]



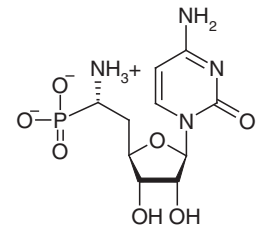
(192a) B=Thy
(192b) B=Ura
(192c) B=Cyt



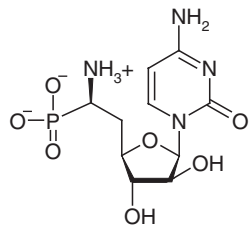
(192d) B=Ade
(192e) B=*N2*-Ac-*O6*-(Ph_2NCO)-Gua



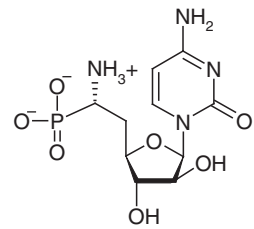
(193a)



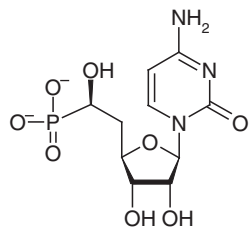
(193b)



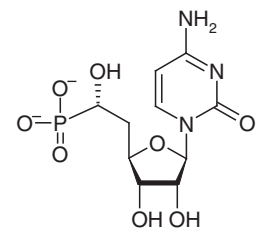
(193c)



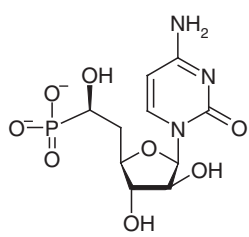
(193d)



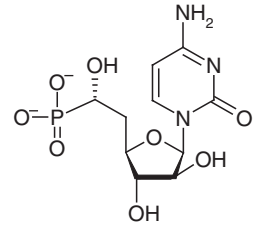
(194a)



(194b)

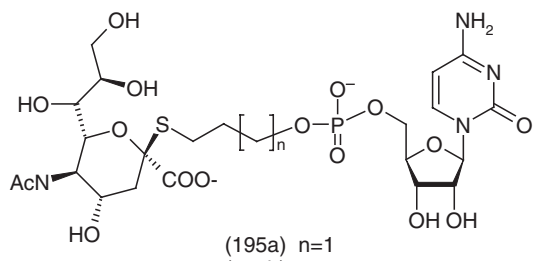


(194c)

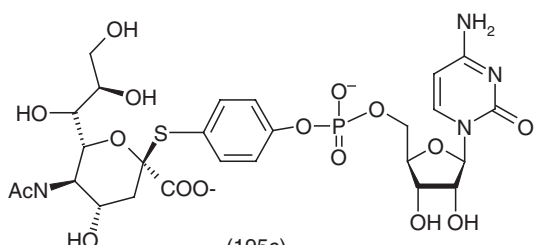


(194d)

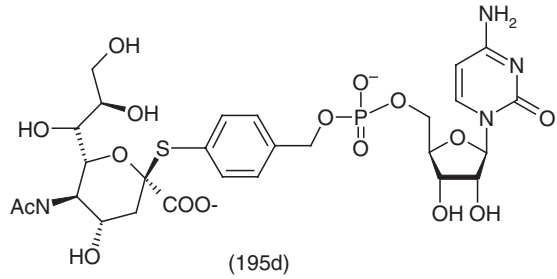
A procedure, which involved the highly β-stereoselective sialylation of the peracetylated sialic acid methyl ester with mercaptoalkyl- and mercaptoaryl-trichloroacetate, followed by removal of the trichloroacetate protecting group and phosphitylation of the 5′-nucleoside phosphoramidites, was developed to prepare cytosine monophosphate-*N*-Ac-neuramic acid derivatives containing tethered alkanes and arenes (195a–d).[70] Schmidt reported the asymmetric synthesis of the potent phosphoramidate α(2-6)sialyltransferase transition state analogue inhibitors, (196a,b). These were synthesized by condensation of cytidine phosphitamide with the non-racemic α-aminophosphonates, prepared by Mitsunobu azidation followed by Staudinger reduction of the corresponding chiral α-hydrophosphonates.[71] The bisubstrate-type inhibitors of sialyltransferases, (197a–c), reported by Ito, have CMP-NeuAc and lactose moieties connected by an alkanedithiol linker.[72] Sekine has furthered his work on phosmidosine by reporting the synthesis of chemically stabilized analogues (198a–c) and establishing phosmidosine's structure-activity relationship.[73]



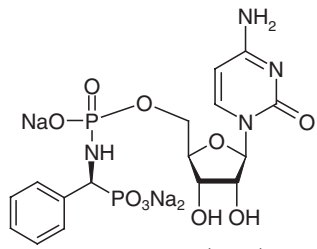
(195a) n=1
(195b) n=2



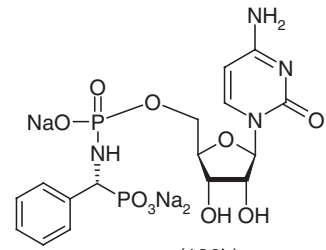
(195c)



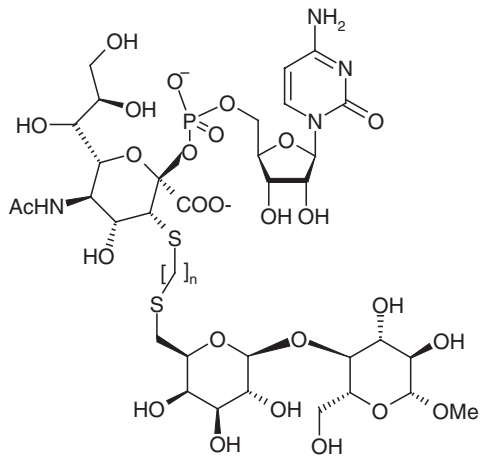
(195d)



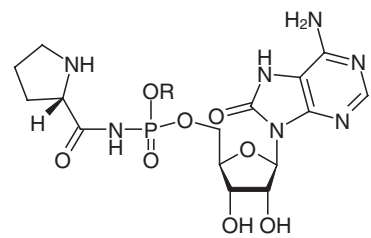
(196a)



(196b)

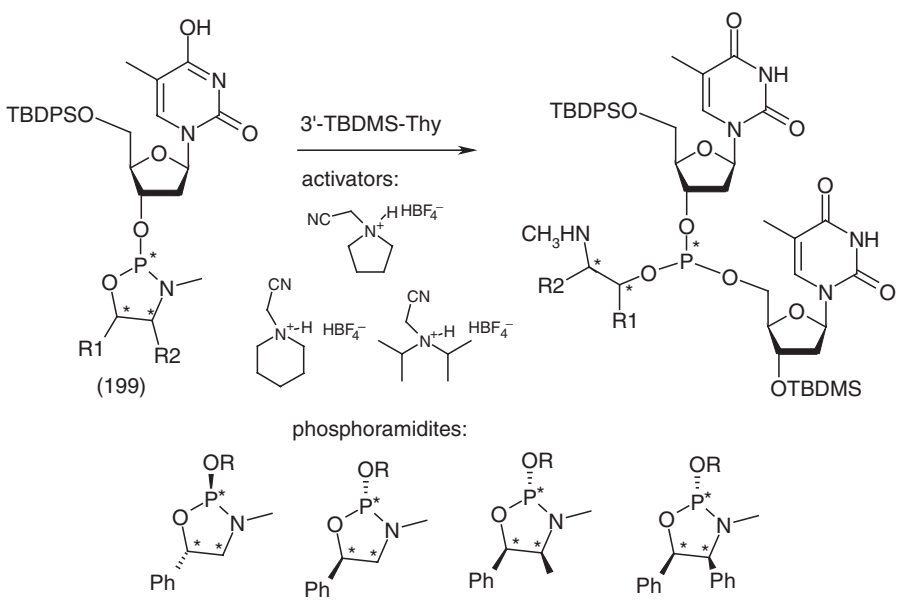


(197a) n= 1
(197b) n= 2
(197c) n= 3
(197d) n= 4
(197e) n= 5

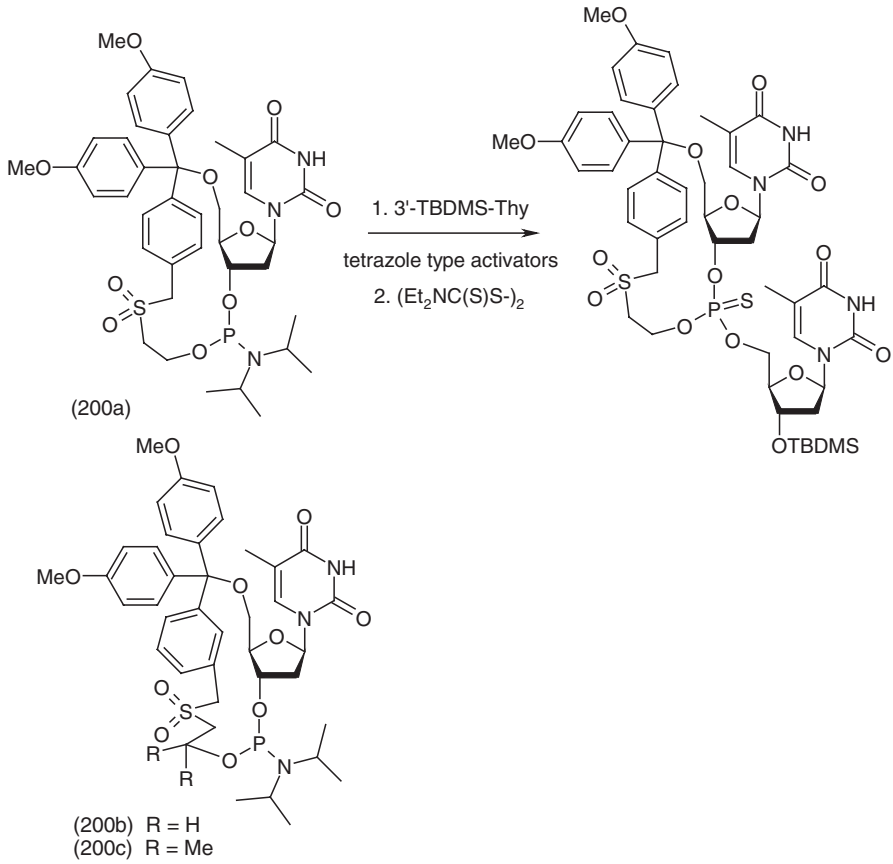


(198a) R= Et
(198b) R= iPr
(198c) R= Bu

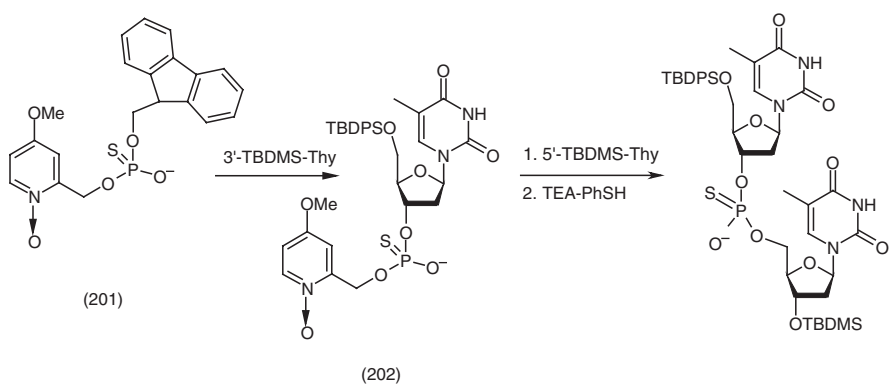
2.1.3 Polynucleoside Phosphate Derivatives. Saigo has developed novel dialkyl(cyanomethyl)-ammonium tetrafluoroborate activators to be used in the diastereocontrolled cyclic-phosphoramidite-based syntheses of oligodeoxyribonucleoside phosphorothioates (Scheme 2).[74] He further developed the stereocontrolled syntheses of such oligodeoxynucleotide derivatives by investigating the reaction conditions for the preparation of the 5′-TBDPS-thymidine-3-*O*-oxazaphospholidines (199) and proposed a mechanism for the diastereoselective formation of nucleoside 3-*O*-oxazaphospholidine derivatives on the basis of *ab initio* molecular orbital calculations.[75] To achieve best selectivity in the synthesis of thymidyl(5-3)thymidine phosphorothioate, Sekine developed new thymidine 3-phosphoramidite building blocks having a covalent linker between the trityl type 5′-hydroxyl protecting group and the phosphorus atom attached to the 3′-hydroxyl group of thymidine (Scheme 3). The ring structures were designed to reduce the conformational freedom around the phosphorus center (200a–c). The cyclic phosphoramidite gave preferentially the Rp diastereoisomer. This stereoselectivity was achieved without any chiral sources other than the 2-deoxyribose moiety itself.[76] Stawinski's approach to achieve diastereoselectivity was based on intramolecular nucleophilic catalysis. To this end, he developed the thiophosphorylating reagent (201), prepared by condensation of 9-fluorenemethyl phosphonate with 4-methoxy-2-pyridinemethanol 1-oxide followed by *in situ* sulfurisation with elemental sulfur. Compound (201) was then coupled to a 5′-protected thymidine in the presence of 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane (Scheme 4) and subsequent removal of the Fmoc group yielded (202) which was then coupled to a 3′-protected thymidine using the same coupling reagent.[77] Vigroux reported the synthesis of a diastereopure dinucleotide (203)



Scheme 2

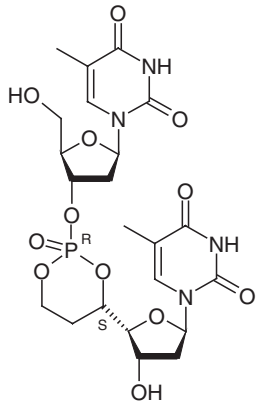


Scheme 3

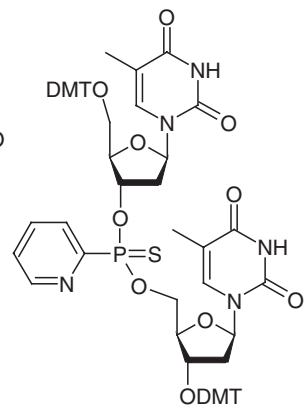


Scheme 4

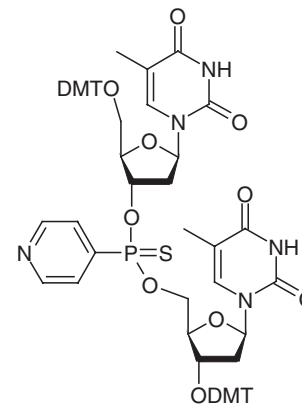
incorporating a 1,3,2-dioxaphosphorinane linkage in which two out of the six torsion angles of the natural phosphodiester backbone have been constrained.[78]



(203)



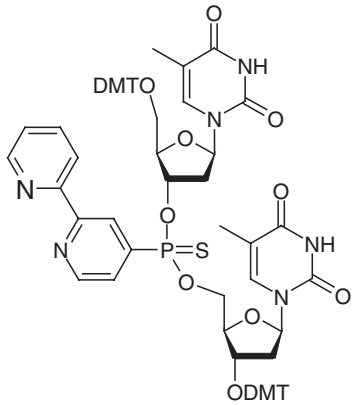
(204a)



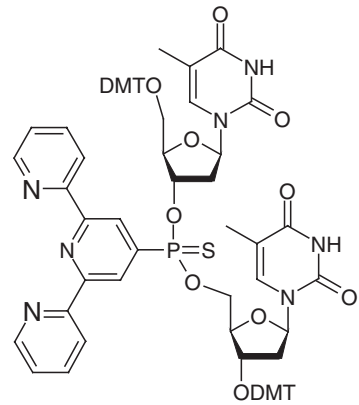
(204b)

Stromberg has reported a detailed kinetic study of the pivaloyl chloride-promoted nucleoside *H*-phosphonate condensation step with a suitably protected nucleoside in the presence of differently substituted pyridines.[79] He also investigated the stability of *H*-phosphonate nucleosidic dimers under various organic and aqueous basic conditions. Strong bases such as DBU and fluoride ions cleaved the dinucleoside *H*-phosphonates rapidly, as also did a combination of protic solvent and a base.[80]

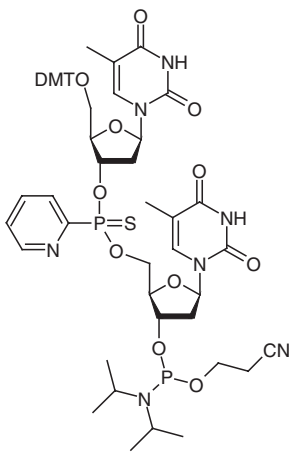
The base-promoted reaction of a suitably protected dithymidine *H*-phosphonothioate with *N*-methoxypyridinium tosylate in acetonitrile or with trityl chloride yielded the dithymidine analogues incorporating a 2-pyridyl or a 4-pyridyl moiety directly attached to the phosphorus center, (204a–b), after treatment with iodine.[81] Stawinski also described the synthesis of the arylphosphonates (204c,d) possessing metal complexing properties and prepared by palladium-catalysed coupling reaction between the bromopyridine derivatives and the dithymidine *H*-phosphonate precursor.[82] Nawrot reported the diastereoselective synthesis from the *H*-phosphonate dimer of the parent dinucleoside pyridinyl-phosphonates (205a–c) for use in oligonucleotide synthesis.[83] Meier used similar chemistry to synthesize a phthalidyl-phosphonate thymidine-thymidine dimer (206) and established its absolute P-configuration.[84] Saigo reported the use of the BH_3 group as an effective protecting group for phosphonic acid diesters. Starting from the dithymidine boranophosphate diester derivative, the dithymidine *H*-phosphonate was obtained by removal of the BH_3 group in the presence of triarylmethyl cations.[85] He also described the synthesis of compounds (207a–d) which were obtained from the appropriately protected nucleobases after condensation with dialkylboranophosphate in the presence of *N,N′*-bis-(2-oxo-3-oxazolidinyl) phosphinyl chloride, 3-nitro-1,2,4-triazole and Hunig's base.[86]



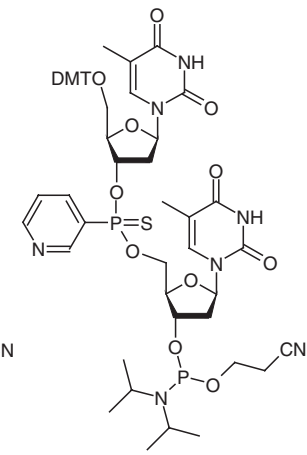
(204c)



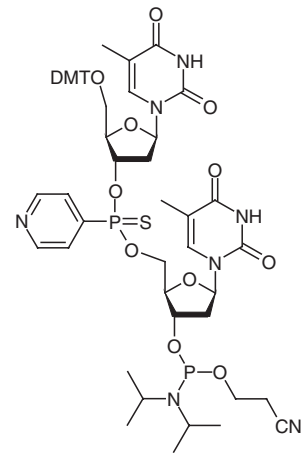
(204d)



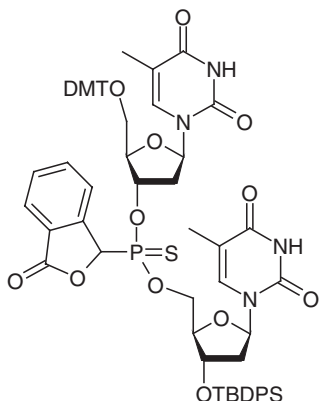
(205a)
Sp and Rp



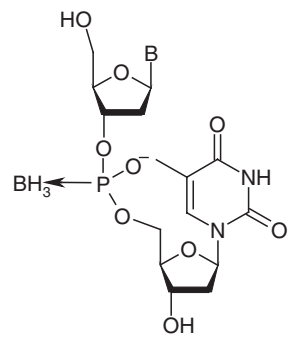
(205b)
Sp and Rp



(205c)
Sp and Rp

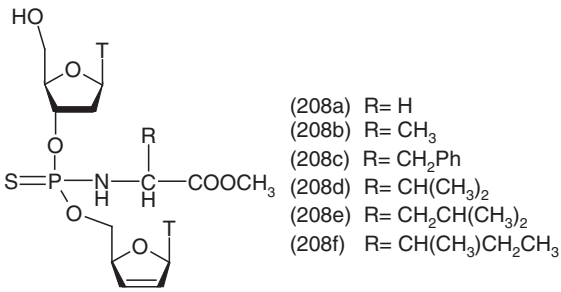


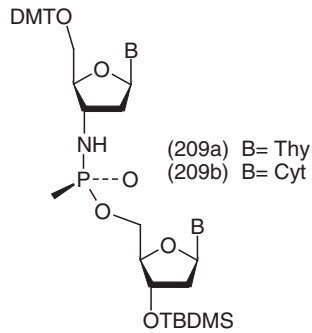
(206)



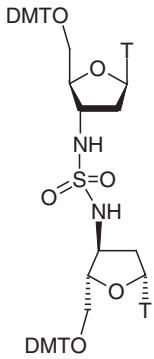
(207a) B= Ade
(207b) B= Gua
(207c) B= Thy
(207d) B= Cyt

Ora reported kinetic and mechanistic studies on hydrolytic reactions of di-ribonucleoside 3′,5′-(3′-*N*-phosphoramidates) and 3′,5′-(3′-*N*-thiophosphoramidates).[87,88] Sequential esterification of diphenylphosphite with 5′-O-DMT-thymidine and hydrogen sulfide yielded the *H*-thiophosphonate derivative of thymidine which was subsequently condensed with AZT or d4T in the presence of diphenyl chlorophosphate and offered compounds (208a–f) as new anti HIV-prodrugs after treatment with L-amino acid methyl esters.[89] Nawrot described the synthesis of the dinucleoside (N3′-MeP5′)-methanephosphonamidates (209a,b) starting from the appropriately protected amino-nucleobase and either dichloromethylphosphine or dichloromethanephosphonate.[90]

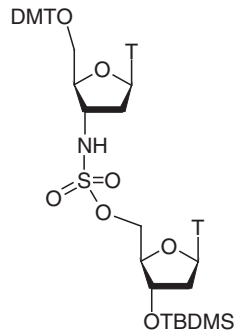




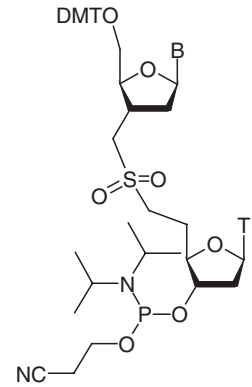
Mickelfield reported a new route to prepare sulfamide- (210a) and 3′-*N*-sulfamate- (210b) modified dinucleosides.[91] For this synthetic approach, the 4-nitrophenyl 3′- or 5′-sulfamates, prepared from 4-phenyl chlorosulfate, were coupled with alcohol and amine functionalities of other nucleosides. Benner reported the synthesis of two bis-methylene sulfone dinucleoside derivatives, (211a) and (211b).[92] These were synthesized from 3′-carboxaldehyde nucleoside starting materials, which after reduction to the corresponding alcohols, were thioacetylated under Mitsunobu conditions and hydrolysed to the corresponding thiols. These were then reacted with the 5′-monohalogenated thymidine and oxidized with Oxone®. The synthesis of thymidine dimers (212) in which the natural phosphodiester linkage has been replaced by a 2,5-disubstituted tetrazole ring has been described by Pedersen[93] while Vanek reported the synthesis of nucleotide analogues and the related dimers (213a,b), mimics of the α- and β-D-2′-deoxyadenosine 3′-phosphate, containing a pyrrolidine ring instead of the sugar unit.[94] Cyclic dinucleotides (214a–d), containing a butylene nucleobase-phosphotriester connection, synthesized by a tandem ring-closing metathesis and hydrogenation reaction, have been reported by Nielsen.[95,96] However, these cyclic dinucleotides are not compatible with standard solid phase oligonucleotide synthesis as they are reactive towards bases.



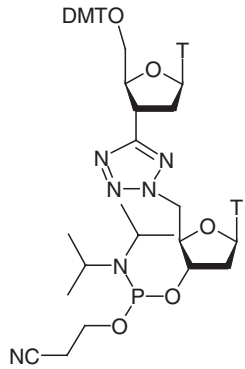
(210a)



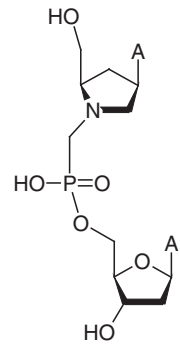
(210b)



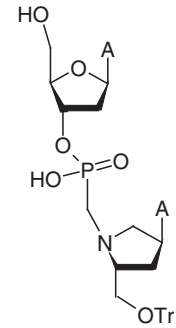
(211a) B= Thy
(211b) B= Ade



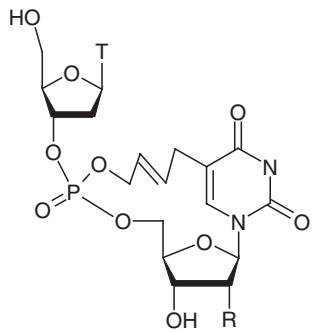
(212)



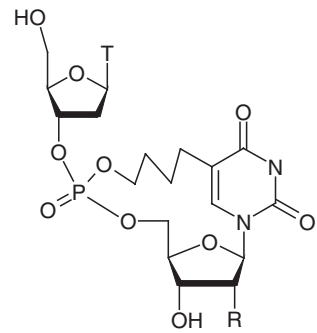
(213a)



(213b)



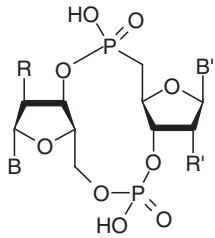
(214a) R=OH
(214b) R= H



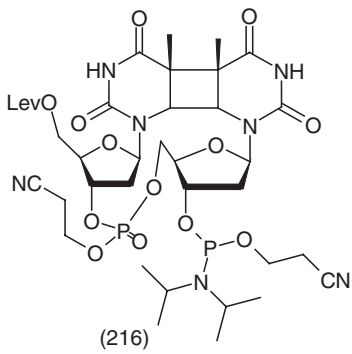
(214c) R=OH
(214d) R= H

Kool reported the synthesis of macrocyclic nucleotide-hybrid compounds (215a–h), putative inhibitors of the HCV polymerase, polymerase C NS5B. The compounds were prepared by solid phase synthesis on controlled pore glass.[97]

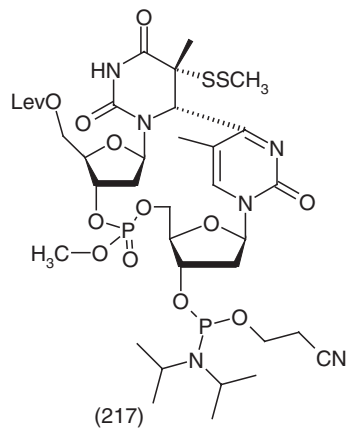
Clivio described the synthesis of an oligonucleotide building block containing a syn-cis thymine cyclobutane dimer photoproduct (216)[98] and that of the phosphoramidite (217), and the thio analogue at the 5,6-dihydropyrimidine C5 position of the thymidyl(3′-5′)thymidine (6–4) photoproduct (218).[99]



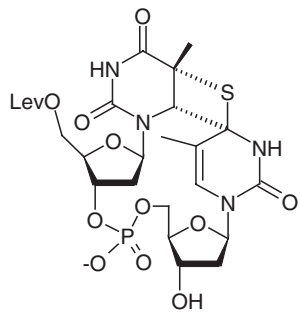
(215a) B=B'=H; R=R'= H
(215b) B=U; B'=T; R= OMe; R'=H
(215c) B=T; B'=U; R= H; R'=OMe
(215d) B=C; B'=C; R= OMe; R'=OMe
(215e) B=C; B'=U; R= OMe; R'=OMe
(215f) B=C; B'=G; R = OMe; R'=OMe
(215g) B=C; B'=A; R= OMe; R'=OMe
(215h) B=H; B'=C; R= H; R'=OMe



(216)



(217)

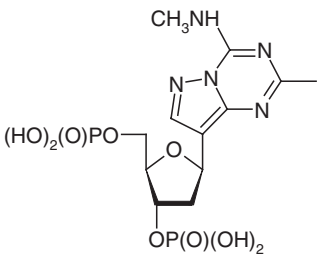


(218)

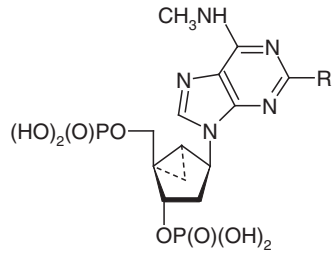
3 Nucleoside Polyphosphates

3.1 Polyphosphorylated Nucleosides. – The first C-nucleotide analogue (219) to be reported as displaying $P2Y_1$-receptor antagonist activity and being stable

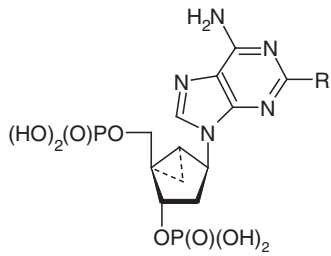
in vivo has been synthesized by Bourguignon. This compound is a C-nucleoside pyrazolo[1,5-a]-1,3,5-triazine 3′,5′-bisphosphate and its synthesis involved, amongst the crucial steps, a regio- and stereo-specific palladium-mediated coupling reaction of the unprotected glycal 1,4 anhydro-2-deoxy D-erythro-pent-1-enitol and the 8-iodo-2-methyl-4-(*N*-methyl-*N*-phenylamino)-pyrazolo-[1,5-*a*]-1,3,5-triazine.[100] Similarly, Jacobson reported the preparation of $P2Y_1$-receptor antagonists with enhanced potency, which incorporated substitution at the 2-position of the adenine ring of the parent nucleotide and contained a bicyclo[3.1.0]hexane ring system locked in a northern conformation, (220a–j).[101] Two cyclic nucleotide analogues of adenosine diphosphate, (221a–b), thought to be putative $P2Y_1$ antagonists, were reported by Shibuya and incorporated an isosteric difluoromethylene phosphonyl group.[102]



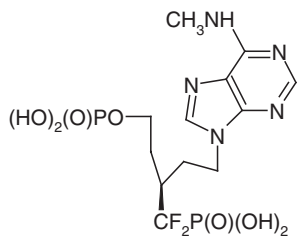
(219)



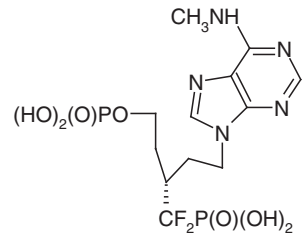
(220a) R= F
(220b) R= Br
(220c) R= I
(220d) R= CH_3
(220e) R= C_6H_{11}
(220f) R= 1-C_6H_9
(220g) R= 1-C_6H_7
(220h) R= SCH_3



(220i) R= I
(220j) R= SCH_3



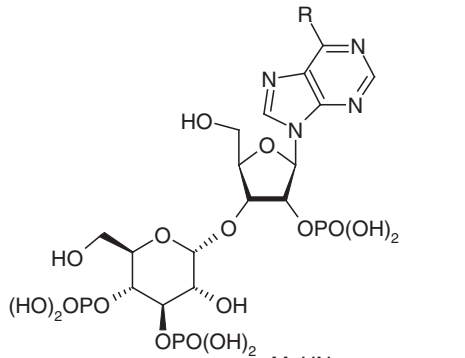
(221a)



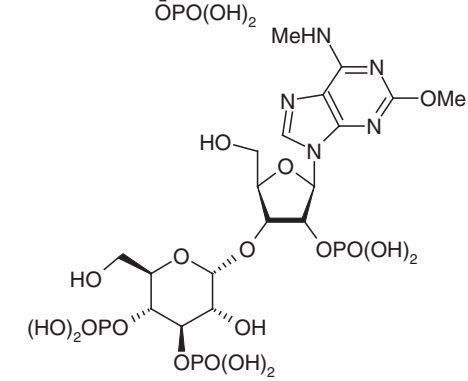
(221b)

Potter described the synthesis and Ca^{2+}-mobilizing activities of purine-modified mimics of adenophostin A incorporating modifications at the C-6

and C-2 of adenine, (222a–g).[103] These compounds were synthesized via a convergent route involving a modified Vórbrűggen condensation of either 6-chloropurine or 2,6-dichloropurine with a protected disaccharide.

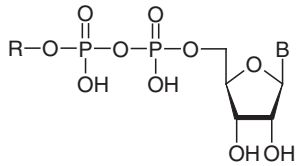


(222a) R= OMe
(222b) R= BNHcyclopentyl
(222c) R= NHMe
(222d) R= NMe_2
(222e) R= NHC_6H_{11}
(222f) R= NH-(3-noradamantantyl)

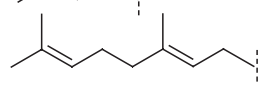


(222g)

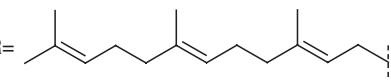
3.2 Nucleoside Pyrophosphates. – The reaction of ADP (disodium salt) with amino acid methyl esters mediated by trimethylsilyl chloride in pyridine produced adenosine 5′-phosphoramidates. This reaction was regiospecific, with the nucleophilic attack of the amino acid methyl esters only occurring on the α-phosphorus of ADP after silylation of all oxyanions.[104] Scott reported the one-pot synthesis of the isoprenoid conjugates (223a–c). These were obtained by nucleophilic displacement reactions of either isoprenyl chlorides or isopentenyl tosylate with nucleoside diphosphates.[105] Bertozzi described the synthesis of a bisubstrate analogue (224), targeting estrogen sulfotransferase.[106] This synthesis required the use of an orthogonally-protected 3′-phosphoradenosine 5′-phosphate derivative, allowing for the selective functionalisation of the 5′-phosphate with the sulfate acceptor mimic. The 2′- and 3′-deuteriocytidine 5′-diphosphates (225a,b) were synthesized from 5′-MMT-3′-OTBDMS and 2′,5′-*O*-diTBDMS cytidine derivatives, respectively, by oxidation followed by acidic removal of the 5′-protecting group, reduction with $NaBD(OAc)_3$ and finally displacement of a tosyl group by pyrophosphate.[107]



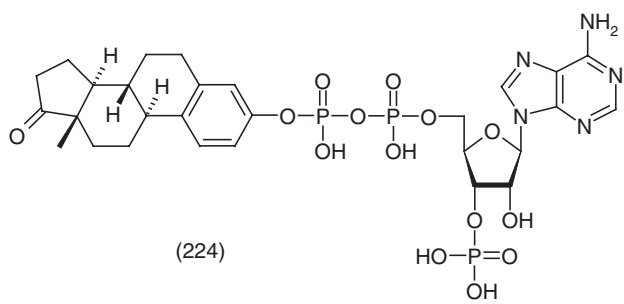
(223a) B= Gua, R=



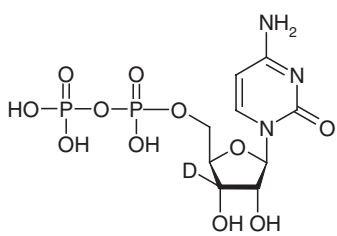
(223b) B= Ade, R=



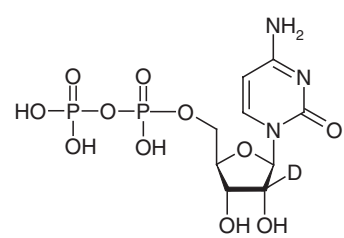
(223c) B= Gua, R=



(224)



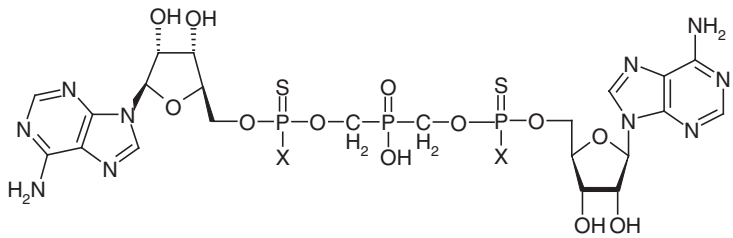
(225a)



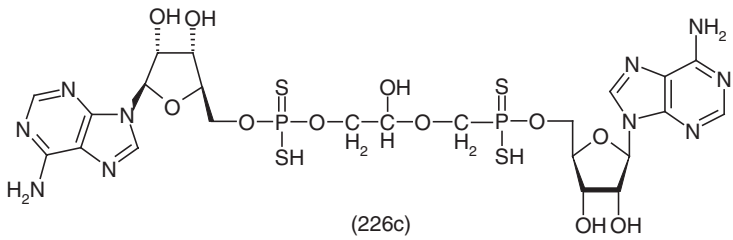
(225b)

Based on his study of hydrolytic reactions of diadenosine 5′,5′-triphosphate, Mikkola reported that Ap_3A was very resistant towards nucleophilic attack and that efficient hydrolysis was only observed under acidic conditions.[108] Stec described the synthesis of novel diadenosine polyphosphate analogues (226a–d) as putative inhibitors of ADP-triggered blood platelet aggregation. The most active compounds incorporated a sulfur atom replacing one or both non-bridging oxygens of the phosphorus bound to the adenosyl residues or with hydroxymethyl groups on the bis(hydroxymethyl)phosphinic acid moiety.[109] Pyrophosphonate analogues, the diaryl dinucleoside phosphonate-phosphate derivatives (227a–c), were synthesised by reacting arylnucleoside *H*-phosphonates and aryl nucleoside P-acylphosphonates generated *in situ* from

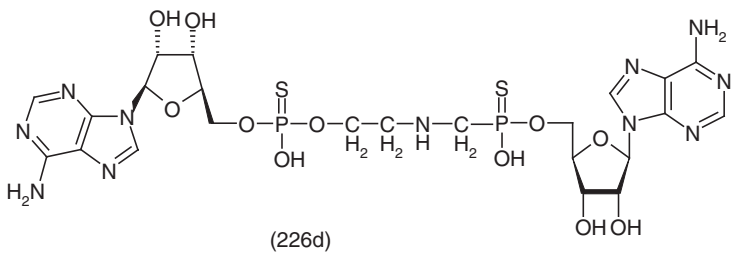
appropriate *H*-phosphonate and acylphosphonate monoester precursors, in the presence of a tertiary amine.[110] The syntheses of the polyphosphates (228a–h), linked by a 5′-5′ phosphate bridge and composed of modified 7-methylguanosine and guanosine, have been reported. These compounds were designed as tools for studying the mechanism of protein translation.[111] Franchetti reported the synthesis of two dinucleoside polyphosphate NAD analogues (229a–b), as putative NMN adenylyltransferase inhibitors. These were synthesised by coupling ATP (as a sodium salt) with nicotinamide riboside monophosphate imidazolide.[112] The synthesis of mycophenolic adenine biphosphonates, (230a,b), analogues of mycophenolic adenine dinucleotide, has been described by Pankiewicz.[113] These were prepared by diisopropylcarbodiimide coupling of 2′,3′-*O*-isopropylideneadenosine 5′-methylenebisphosphonate with mycophenolic alcohols.



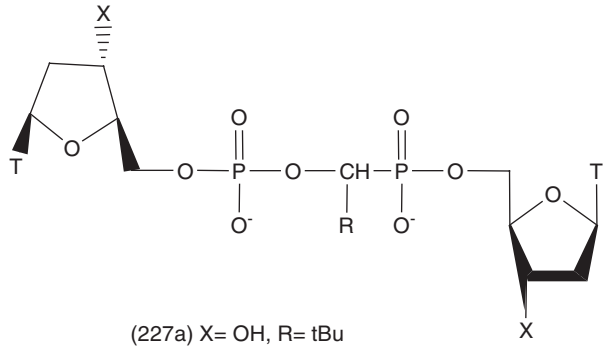
(226a) X= SH
(226b) X= OH



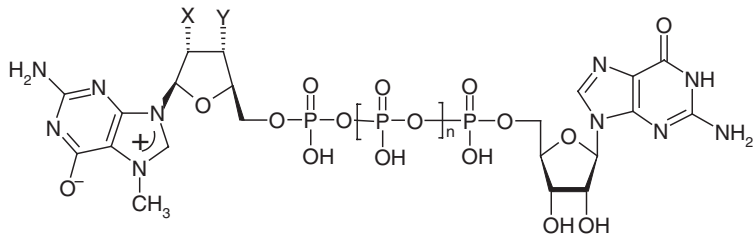
(226c)



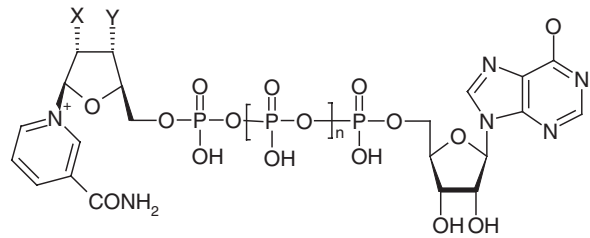
(226d)



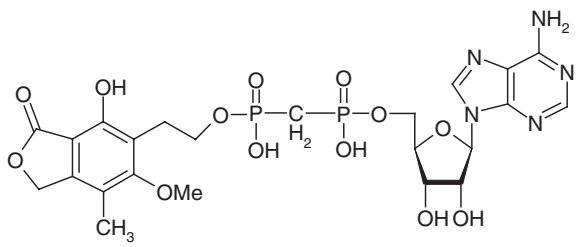
(227a) X= OH, R= tBu
(227b) X= N_3, R= tBu
(227c) X= N_3, R= Ph



(228a) X= OH; Y= OMe; n=1
(228b) X= OH; Y= H; n=1
(228c) X= H; Y= OMe; n=1
(228d) X= OMe; Y= OH; n=1
(228e) X= OH; Y= OMe; n=2
(228f) X= OMe; Y= OH; n=1
(228g) X= H; Y= OH; n=2
(228h) X= OH; Y= OMe; n=3

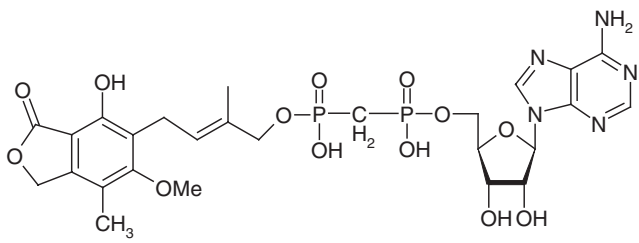


(229a) n=1
(229b) n=2

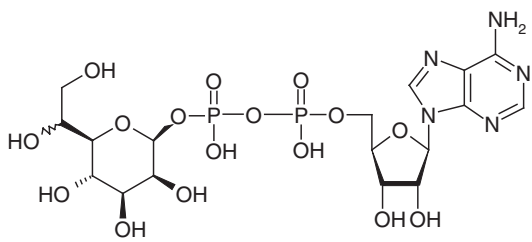


(230a)

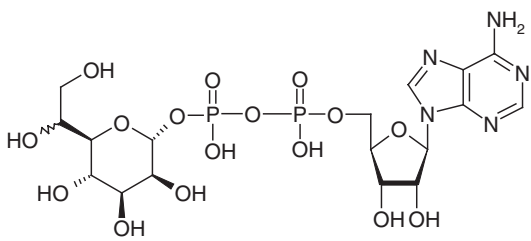
Klaffke developed a scaleable three step synthetic method to prepare uridine diphospho-D-xylose and UDP-L-arabinose from D-xylal and L-arabinal respectively and UDP.[114] The synthesis of ADP- L-*glycero*- and D-*glycero*-D-*manno*-heptopyranoses (231a,b) and of GDP- D-*glycero*-D-*manno*-heptopyranose (231c) has been reported by Kosma.[115,116] The α-anomers of the heptosyl phosphates were obtained using the phosphoramidite procedure, whereas the β-phosphates were formed by reacting diphenyl phosphorochloridate with the reducing heptoses. Schmidt reported the UDP-glycal derivatives (232a–d) as transition state analogues, inhibitors of UDP-GlcNAc 2-epimerase.[117] He also described the synthesis of UDP-C-glycosidic derivatives of 2-acetamidoglucal (232e) and of ketosides (232f–g). Three *O*-methylated UDP-GalNAc analogues (233a–c) have been synthesised from appropriate 3,6-dipivaloyl GlcNAc derivatives.[118] *N*-acylated UDP-GalNAc derivatives (234a–c) have been synthesised using Khorona's morpholidate coupling method, starting from D-galactosaminyl-1-phosphate after selective *N*-acylation of its amino group with appropriate *N*-acetyloxysuccinimides.[119] Rice reported the synthesis of 5′-(2,3,4-tri-*O*-acetyl-6-S-acetyl-6-thio-a-D-galactopyranosyl-uridine diphosphates (235)[120] while Palcic described the synthesis of GDP-5-thiosugars (236a–b) and their use as substrates for glycosyltransferases.[121]



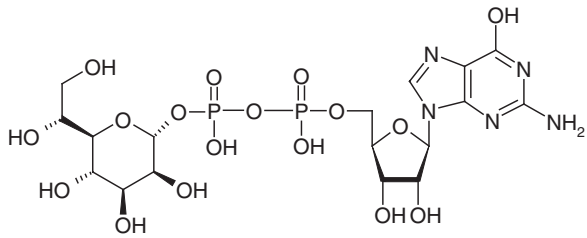
(230b)



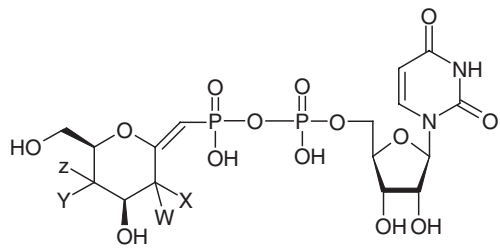
(231a)



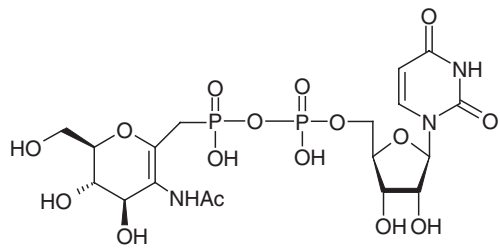
(231b)



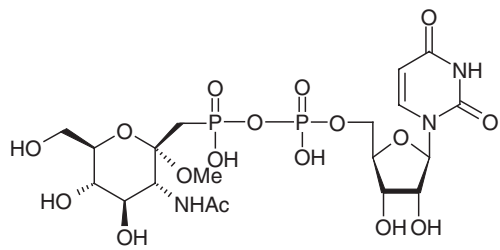
(231c)



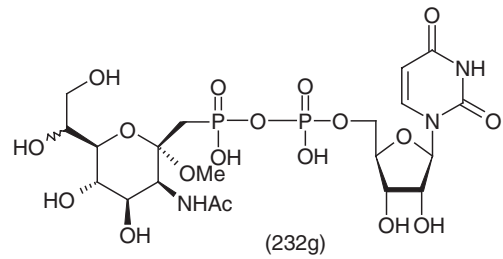
(232a) W=Y= OH, X=Z= H
(232b) X=Y= OH; W=Z= H
(232c) W=Z= OH; X=Y= H
(232d) W=NHAc, Y=OH; X=Z= H



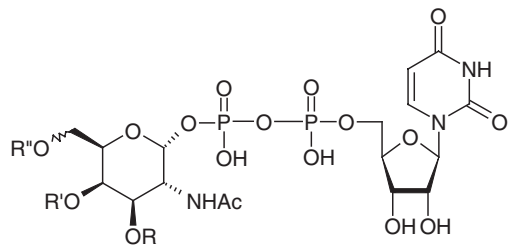
(232e)



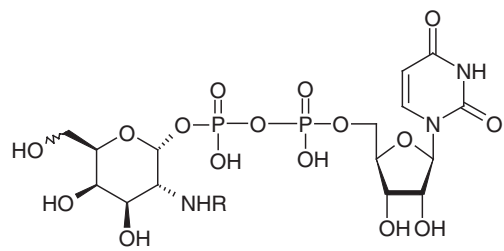
(232f)



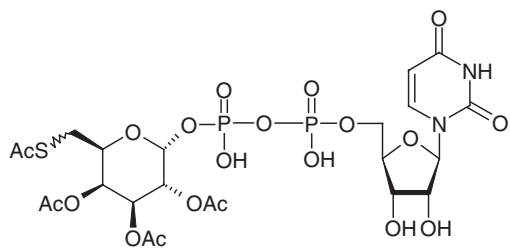
(232g)



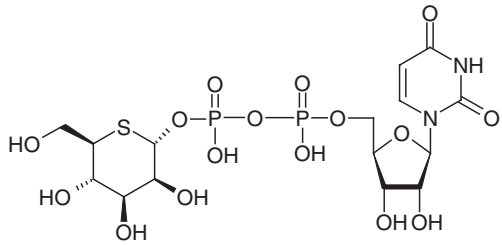
(233a) R=CH_3, R'=R"= H
(233b) R=R"= H; R'=CH_3
(233c) R=R'= H; R"= CH_3



(234a) R=$COCH_2CH_3$
(234b) R=$COCH_2CH_2CH_3$
(234c) R=$COCH_2Br$

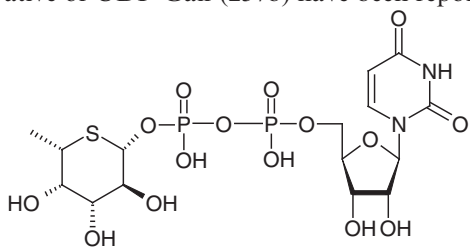


(235)

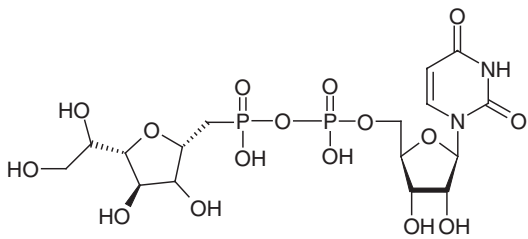


(236a)

Inhibition properties and the syntheses of a conformationally restricted probe for the mutase-catalysed UDP-galactose/furanose interconversion (237a) and of a C-glycoside derivative of UDP-Galf (237b) have been reported by Sinay.[122,123]

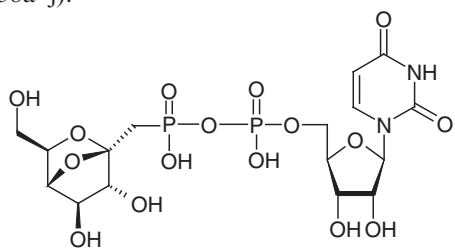


(236b)



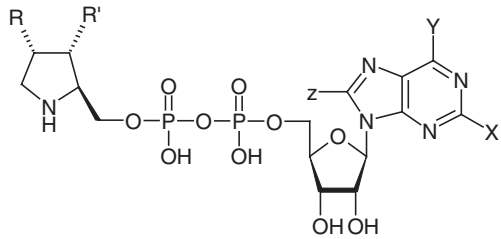
(237a)

To establish the SAR analysis of adenosine diphosphates (hydroxymethyl)pyrrolidinediol inhibition of poly(ADP-ribose) glycohydrolase, Jacobson has synthesised a series of guanosine- and adenosine-modified pyrrolidinediol pyrophosphates (238a–j).[124]

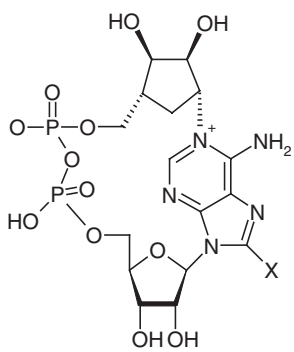


(237b)

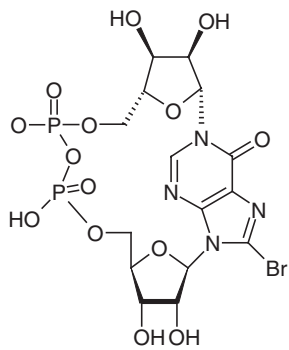
Much synthetic work has been reported by various groups on cyclic adenosine diphosphate ribose. Potter described the synthesis and biological evaluation of a series of 8-substituted analogues (239a–d) of cyclic ADP-carbocyclic ribose,[125] a stable mimic of cADPR, and also the first enzymatic synthesis of the N1-cyclic cADPR analogue (240) incorporating a hypoxanthine partial structure.[126] Another type of cADPR mimic, (241), incorporating a pyranose and a pyrimidine residue, was reported by Piccialli and was synthesized by a chemical strategy employing a Mitsunobu reaction for the condensation of the glucosyl moiety on the protected uridine and a Matsuda procedure for the cyclisation.[127] A similar cyclisation procedure was used by the same laboratory to prepare the *N1*-pentyl analogue of cyclic inosine diphosphate ribose, (242).[128]



(238a) X=Z=H; Y= NH_2; R=R'= OH
(238b) X=Z=H; Y= NH_2; R= OH; R'= H
(238c) X=Z= H; Y= NH_2; R=R'= H
(238d) X= H; Y= NH_2; Z=N_3; R=R'= OH
(238e) X= N_3; Y= NH_2; Z=H; R=R'= OH
(238f) X= H; Y= NH_2; Z=$NH(CH_2)_6NH_2$; R=R'= OH
(238g) X= H; Y= NH_2; Z=$NH(CH_2)_6NHCOCF_3$; R=R'= OH
(238h) X= H; Y= NH_2; Z=S-C_6H_5-*p*Cl; R=R'= OH
(238i) X= H; Y= $NHCH_2C_6H_5$; Z=H; R=R'= OH
(238j) X= H; Y= $NH(CH_2)_5$-CH_3; Z=H; R=R'= OH

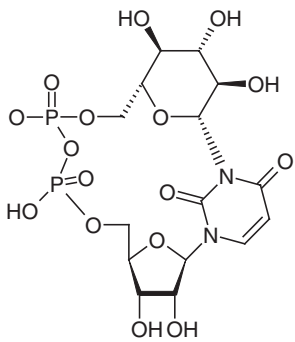


(239a) X=Cl
(239b) X= N_3
(239c) X= NH_2
(239d) X= SPh

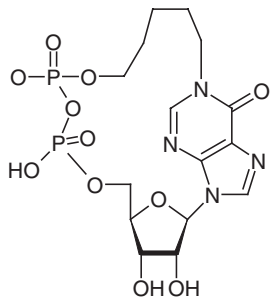


(240)

A synthetic method for the synthesis of 8-vinyl adenosine 5′-di and triphosphate (243a–b) has been developed. This procedure eliminates unwanted depurination side-reactions under acidic conditions by introduction of acetyl protecting groups at the 2′ and 3′ positions of adenosine. The di- and triphosphate esters were obtained by treatment of the adenylic acid with phosphate and pyrophosphate anions.[129] 6,6-Bicyclic pyrimidopyridazin-7-one nucleoside triphosphate (244) was synthesized by nucleophilic ring-opening and rearrangement of a furanopyridine nucleoside in the presence of anhydrous hydrazine.[130]

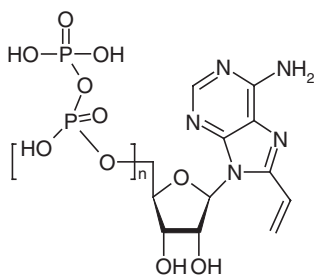


(241)

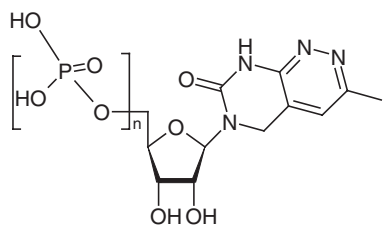


(242)

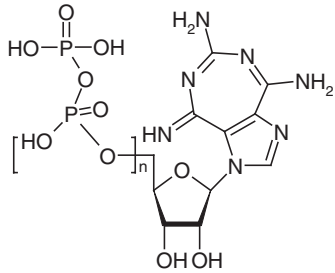
Borowski reported the synthesis of so called ''fat'' or ring expanded nucleoside triphosphates (245a,b) and evaluated these compounds and others previously synthesized in his laboratory against Flaviviridae NTPases and helicases.[131] 2-Deoxycytidine nucleoside triphosphates, (246a–c), bearing amino and thiol groups appended to the 5-position of the nucleobase have been chemically synthesized and enzymatically incorporated into oligodeoxynucleotides.[132] Kulikowski reported the synthesis of thiated analogues of 2′,3′-dideoxy-3′-fluorothimidine triphosphate, (247a–c).



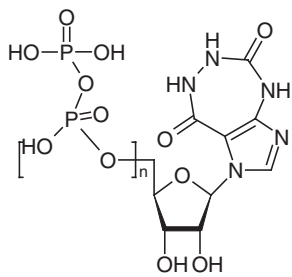
(243a) n=1
(243b) n=2



(244) n=3

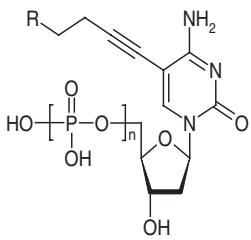


(245a) n=2

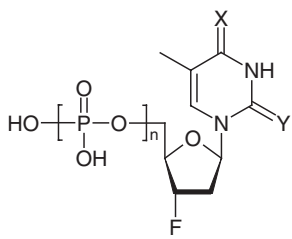


(245b) n=2

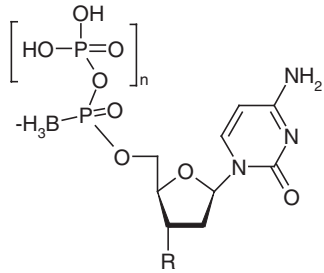
The nucleoside 5′-monophosphate was prepared by regioselective enzymatic phosphorylation of a nucleoside employing wheat shoot phosphotransferase while the triphosphates were obtained by a modification of the Ludwig procedure employing direct phosphorylation with $POCl_3$ and a tri-*N*-butylamine/bis-tri-*N*-butylammonium pyrophosphate mixture.[133] Shaw used the synthetic procedure well-established in her laboratory to achieve the synthesis of the Rp-stereoisomers of 5′-(α-*P*-borano)triphosphates of 2′-deoxycytidine and 2′,3′-dideoxycytidine, (248a) and (248b) respectively, and examined their incorporation into oligonucleotides by MMLV reverse transcriptase and *Taq* DNA polymerase.[134] She also reported the synthesis of an acyclonucleoside-(α-*P*-borano)triphosphate, (249), achieved via a phosphoramidite approach in a one-pot reaction. This compound was effectively incorporated by the MMLV retroviral reverse transcriptase.[135] Mikhailopulo used an enzymatic procedure to synthesize adenosine-5′-*O*-(1-thiotriphosphate), (250),[136] while Huang used the chemical approach based on the chemical synthesis of 5′-(α-*P*-thio)triphosphates to prepare nucleoside triphosphate analogues containing α-non-bridging selenium, (251).[137] Non-natural azole carboxamide nucleoside triphosphates (252a–c) have been synthesized as alternative substrates for DNA and RNA polymerases. Tosylate intermediates were employed to introduce the diphosphate ester which was subsequently enzymatically converted to the triphosphate ester as the conventional nucleoside triphosphate synthetic methods failed for non-purine and non-pyrimidine nucleosides.[138] A series of non-natural β-C-nucleoside triphosphates, (253a–e), bearing an aromatic nucleobase with phenolic hydroxy groups, has been synthesized by Shionoya and evaluated as inhibitors against DNA polymerase.[139]



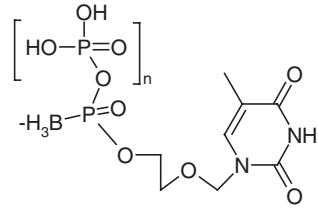
(246a) n=3; R= $NHCOCF_3$
(246b) n=3; R= $SSC(CH_3)_3$
(246c) n=3; R= NH_2



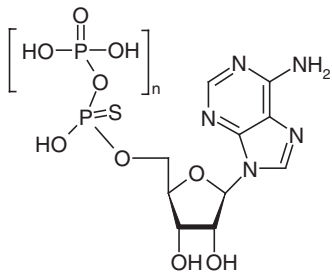
(247a) n=3; X=S; Y=O
(247b) n=3; X=S; Y=S
(247c) n=3; X=O; Y=S



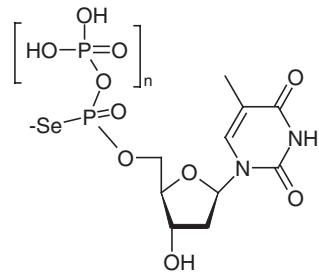
(248a) n= 2; R= OH
(248b) n= 2; R= H



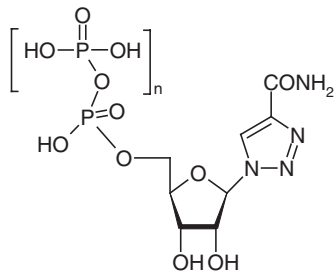
(249) n = 2



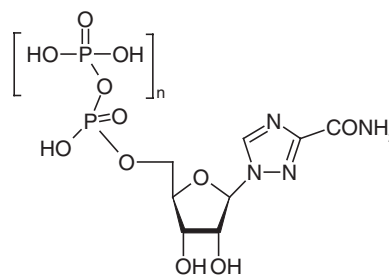
(250) n=2



(251) n= 2

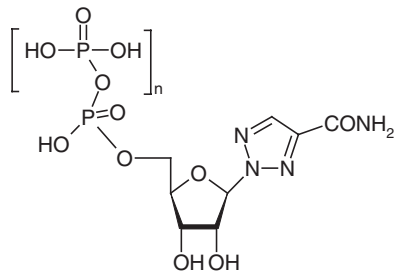


(252a) n=2

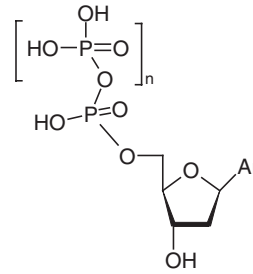


(252b) n=2

Burgess reported the synthesis of a set of energy transfer dye-labeled nucleoside triphosphates (254a–f). To achieve this synthesis, the coupling of the dye to the nucleosidic moiety had to be performed after formation of the triphosphate esters.[140]



(252c) n=2



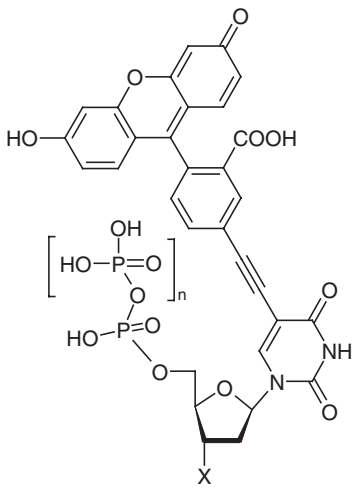
(253a) n= 2; Ar=

(253b) n= 2; Ar=

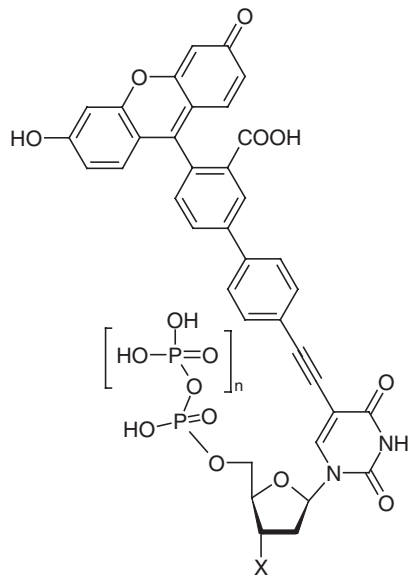
(253c) n= 2; Ar=

(253d) n= 2; Ar=

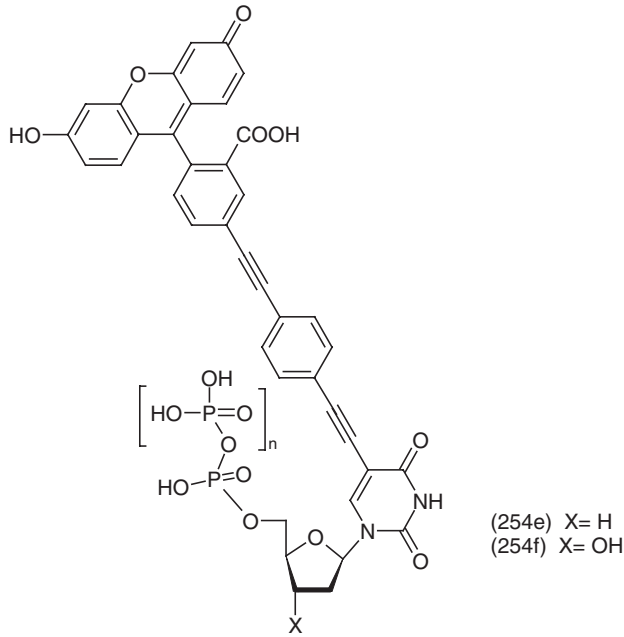
(253e) n= 2; Ar=



(254a) X= H
(254b) X= OH



(254c) X= H
(254d) X= OH



References

1. X.B. Sun, J.X. Kang and Y.F. Zhao, *Chem. Commun.*, 2002, 2414.
2. F. Peyrane, J.L. Fourrey and P. Clivio, *Chem. Commun.*, 2003, 736.
3. M. Leuck, K.E. Vagle, J.S. Roach and A. Wolter, *Tet. Let.*, 2004, **45**, 321.
4. V. Vanheusden, H. Munier-Lehmann, S. Pochet, P.V. Herdewijn and S. Van Calenbergh, *Bioorg. Med. Chem. Let.*, 2002, **12**, 2695.
5. J.A.R. Stutz and C. Richert, *Tet. Let.*, 2004, **45**, 509.
6. A. Karpeisky, D. Sweedler, P. Haeberli, J. Read, K. Jarvis and L. Beigelman, *Bioorg. Med. Chem. Let.*, 2002, **12**, 3345.
7. X. L. Wu, S. Guntha, M. Ferencic, R. Krishnamurthy and A. Eschenmoser, *Org. Let.*, 2002, **4**, 1279.
8. S. Helmling, E. Moyroud, W. Schroeder, I. Roehl, F. Kleinjung, S. Stark, G. Bahrenberg, C. Gillen, S. Klussmann and S. Vonhoff, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1035.
9. Y. Buzin, N. Carrasco and Z. Huang, *Org. Let.*, 2004, **6**, 1099.
10. N.S. Li and J.A. Piccirilli, *J. Org. Chem.*, 2003, **68**, 6799.
11. A. Haberli and C.J. Leumann, *Org. Let.*, 2001, **3**, 489.
12. D.R. Ahn, M. Mosimann and C.J. Leumann, *J. Org. Chem.*, 2003, **68**, 7693.
13. P. Gu, C. Griebel, A. Van Aerschot, J. Rozenski, R. Busson, H.J. Gais and P. Herdewijn, *Tetrahedron*, 2004, **60**, 2111.
14. V.V. Filichev and E.B. Pedersen, *Bioorg. Med. Chem. Let.*, 2004, **14**, 581.
15. O. Pav, M. Budesinsky and I. Rosenberg, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1053.
16. D.S. Pedersen and T. Koch, *Synthesis-Stuttgart*, 2004, 578.
17. B.R. Babu, L. Keinicke, M. Petersen, C. Nielsen and J. Wengel, *Org. Biomol. Chem.*, 2003, **1**, 3514.

18. T. Bryld, M.H. Sorensen, P. Nielsen, T. Koch, C. Nielsen and J. Wengel, *J. Chem. Soc. Perkin Trans. 1*, 2002, 1655.
19. B.R. Babu, A.K. Prasad, S. Trikha, N. Thorup, V.S. Parmar and J. Wengel, *J. Chem. Soc. Perkin Trans. 1*, 2002, 2509.
20. B.R. Babu, M.D. Sorensen, V.S. Parmar, N.H. Harrit and J. Wengel, *Org. Biomol. Chem.*, 2004, **2**, 80.
21. L. Keinicke, M.D. Sorensen and J. Wengel, *Bioorg. Med. Chem. Let.*, 2002, **12**, 593.
22. A. Lauritsen, B.M. Dahl, O. Dahl, B. Vester and J. Wengel, *Bioorg. Med. Chem. Let.*, 2003, **13**, 253.
23. T. Murano, S. Muroyama, T. Yokomatsu and S. Shibuya, *Synlett*, 2002, 1657.
24. X.M. Chen and D.F. Wiemer, *J. Org. Chem.*, 2003, **68**, 6597.
25. M. Bubenik, P. Preville, J. Dugas, G. Attardo and L. Chan, *Tet. Let.*, 2003, **44**, 8261.
26. M. Bubenik, R. Rej, N. Nguyen-Ba, G. Attardo, F. Ouellet and L. Chan, *Bioorg. Med. Chem. Let.*, 2002, **12**, 3063.
27. M. Yamashita, V.K. Reddy, P.M. Reddy, Y. Kato, B. Haritha, K. Suzuki, M. Takahashi and T. Oshikawa, *Tet. Let.*, 2003, **44**, 3455.
28. H.P. Guan, Y.L. Qiu, M.B. Ksebati, E.R. Kern and J. Zemlicka, *Tetrahedron*, 2002, **58**, 6047.
29. B. Nawrot, O. Michalak, M. Nowak, A. Okruszek, M. Dera and W.J. Stec, *Tet. Let.*, 2002, **43**, 5397.
30. D. Hockova, A. Holy, M. Masojidkova, G. Andrei, R. Snoeck, E. De Clercq and J. Balzarini, *J. Med. Chem.*, 2003, **46**, 5064.
31. V.K. Brel, V.K. Belsky, A.I. Stash, V.E. Zavodnik and P.J. Stang, *Org. Biomol. Chem.*, 2003, **1**, 4220.
32. A. Madder, R. Ehrl and R. Stromberg, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1289.
33. N. Koissi and H. Lonnberg, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1135.
34. V.M. Carvalho, D. Gasparutto, P. Di Mascio, M.H.G. Medeiros and J. Cadet, *Bioorg. Med. Chem.*, 2003, **11**, 2445.
35. M. Sako and I. Yaekura, *Tetrahedron*, 2002, **58**, 8413.
36. M. Sako, I. Yaekura and I. Deyashiki, *Tet. Lett.*, 2002, **43**, 6701.
37. Q.G. Zheng, Y. Wang and E. Lattmann, *Bioorg. Med. Chem. Let.*, 2003, **13**, 3141.
38. F. Seela and R. Kroschel, *Org. Biomol. Chem.*, 2003, **1**, 3900.
39. F. Seela, K. Shaikh and T. Wiglenda, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1239.
40. P. Leonard, P. Kroschel and F. Seela, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1235.
41. D. Guianvarc'h, J.L. Fourrey, R. Maurisse, J.S. Sun and R. Benhida, *Org. Let.*, 2002, **4**, 4209.
42. H.B. Liu, J.M. Gao, L. Maynard, Y.D. Saito and E.T. Kool, *J. Am. Chem. Soc.*, 2004, **126**, 1102.
43. D.A. Berry, K.Y. Jung, D.S. Wise, A.D. Sercel, W.H. Pearson, H. Mackie, J.B. Randolph and R.L. Somers, *Tet. Let.*, 2004, **45**, 2457.
44. H.M.P. Chui, J.P. Desaulniers, S.A. Scaringe and C.S. Chow, *J. Org. Chem.*, 2002, **67**, 8847.
45. K.G. Rajeev, T.P. Prakash and M. Manoharan, *Org. Let.*, 2003, **5**, 3005.

46. N. Griesang and C. Richert, *Tet. Lett.*, 2002, **43**, 8755.
47. L. Araki, S. Harusawa, M. Yamaguchi, S. Yonezawa, N. Taniguchi, D.M.J. Lilley, Z.Y. Zhao and T. Kurihara, *Tet. Let.*, 2004, **45**, 2657.
48. T. Moriguchi, T. Wada and M. Sekine, *Eur. J. Org. Chem.*, 2003, 2260.
49. H. Morales-Rojas and E.T. Kool, *Org. Let.*, 2002, **4**, 4377.
50. G.S. Jiao and K. Burgess, *Bioorg. Med. Chem. Let.*, 2003, **13**, 2785.
51. A.M. Morocho, V.N. Karamyshev, O.V. Shcherbinina, A.G. Malykh and N.N. Polushin, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1439.
52. R. Chillemi, D. Aleo, G. Granata and S. Sciuto, *Eur. J. Org. Chem.*, 2002, 3622.
53. E.A. Shirokova, M.V. Jasko, A.L. Khandazhinskaya, D.V. Yanvarev, Y.S. Skoblov, T.R. Pronayeva, N.V. Fedyuk, A.G. Pokrovsky and M.K. Kukhanova, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 981.
54. R.L. Alexander, S.L. Morris-Natschke, K.S. Ishaq, R.A. Fleming and Kucera, *J. Med. Chem.*, 2003, **46**, 4205.
55. D.A. Jeyaraj, H. Prinz and H. Waldmann, *Chem. Eur. J.*, 2002, **8**, 1879.
56. D. Egron, J.L. Imbach, G. Gosselin, A.M. Aubertin and C. Perigaud, *J. Med. Chem.*, 2003, **46**, 4564.
57. A.V. Shipitsyn, N.F. Zakirova, E.F. Belanov, T.R. Pronyaeva, N.V. Fedyuk, M.K. Kukhanova and A.G. Pokrovsky, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 963.
58. C. Ducho, S. Wendicke, U. Gorbig, J. Balzarini and C. Meier, *Eur. J. Org. Chem.*, 2003, 4786.
59. C. Meier, A. Lomp, A. Meerbach and P. Wutzler, *J. Med. Chem.*, 2002, **45**, 5157.
60. C. Meier, J.T. Renze, J. Balzarini and E. De Clercq, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 825.
61. L. Cappellacei, G. Barboni, P. Franchetti, C. Martini, H.N. Jayaram and M. Grifantini, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 869.
62. S. Peyrottes, G. Coussot, I. Lefebvre, J.L. Imbach, G. Gosselin, A.M. Aubertin and C. Perigaud, *J. Med. Chem.*, 2003, **46**, 782.
63. A. Jochum, N. Schfienger, G. Gosselin, J.L. Imbach, A.M. Aubertin and C. Perigaud, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 899.
64. Y. Jin, M. Sun, H. Fu and Y.F. Zhao, *Chem. Let.*, 2004, **33**, 116.
65. P. Li and B.R. Shaw, *Org. Let.*, 2002, **4**, 2009.
66. P. Li and B.R. Shaw, *Chem. Commun.*, 2002, 2890.
67. C. Lopin, A. Gautier, G. Gouhier and S.R. Piettre, *J. Am. Chem. Soc.*, 2002, **124**, 14668.
68. X.M. Chen and D.F. Wiemer, *J. Org. Chem.*, 2003, **68**, 6108.
69. X.M. Chen, A.J. Wiemer, R.J. Hohl and D.F. Wiemer, *J.Org. Chem.*, 2002, **67**, 9331.
70. K.H. Chang, Y.S. Tao and W.S. Li, *Synlett*, 2004, 37.
71. D. Skropeta, R. Schworer and R.R. Schmidt, *Bioorg. Med. Chem. Let.*, 2003, **13**, 3351.
72. H. Hinou, X.L. Sun and Y. Ito, *J. Org. Chem.*, 2003, **68**, 5602.
73. M. Sekine, K. Okada, K. Seio, H. Kakeya, H. Osada, T. Obata and T. Sasaki, *J. Org. Chem.*, 2004, **69**, 314.
74. N. Oka, T. Wada and K. Saigo, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1411.
75. N. Oka, T. Wada and K. Saigo, *J. Am. Chem. Soc.*, 2003, **125**, 8307.

76. K. Seio, K. Kumura, J.C. Bologna and M. Sekine, *J. Org. Chem.*, 2003, **68**, 3849.
77. H. Almer, T. Szabo and J. Stawinski, *Chem. Commun.*, 2004, 290.
78. I. Le Clezio, J.M. Escudier and A. Vigroux, *Org. Let.*, 2003, **5**, 161.
79. S. Sigurdsson and R. Stromberg, *J. Chem. Soc. Perkin Trans. 2*, 2002, 1682.
80. P. Heinonen, A. Winqvist, Y. Sanghvi and R. Stromberg, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1387.
81. T. Johansson and J. Stawinski, *Tetrahedron*, 2004, **60**, 389.
82. T. Johansson and J. Stawinski, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1459.
83. K. Zmudzka, T. Johansson, M. Wojcik, M. Janicka, M. Nowak, J. Stawinski and B. Nawrot, *New J. Chem.*, 2003, **27**, 1698.
84. W. Fendrich and C. Meier, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1127.
85. M. Shimizu, K. Tamura, T. Wada and K. Saigo, *Tet. Let.*, 2004, **45**, 371.
86. T. Wada, M. Shimizu, N. Oka and K. Saigo, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1171.
87. M. Ora, K. Mattila, T. Lonnberg, M. Oivanen and H. Lonnberg, *J. Am. Chem. Soc.*, 2002, **124**, 14364.
88. M. Ora, M. Murtola, S. Aho and M. Oivanen, *Org. Biomol. Chem.*, 2004, **2**, 593.
89. C.X. Lin, H. Fu, G.Z. Tu and Y.F. Zhao, *Synthesis-Stuttgart*, 2003, 1989.
90. B. Nawrot, M. Sobczak and S. Antoszczyk, *Org. Let.*, 2002, **4**, 1799.
91. K.J. Fettes, N. Howard, D.T. Hickman, S. Adah, M.R. Player, P.F. Torrence and J. Micklefield, *J. Chem. Soc. Perkin Trans. 1*, 2002, 485.
92. D. Hutter, M.O. Blaettler and S.A. Benner, *Helv. Chim. Acta*, 2002, **85**, 2777.
93. V.V. Filichev, A.A. Malin, V.A. Ostrovskii and E.B. Pedersen, *Helv. Chim. Acta*, 2002, **85**, 2847.
94. V. Vanek, M. Budesinsky, I. Kavenova, M. Rinnova and I. Rosenberg, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1065.
95. P. Borsting and P. Nielsen, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1139.
96. P. Borsting and P. Nielsen, *Chem. Commun.*, 2002, 2140.
97. M. Smietana, R.B. Johnson, Q.M. Wang and E.T. Kool, *Chem. Eur. J.*, 2004, **10**, 173.
98. J.U.O. Mayo, M. Thomas, C. Saintome and P. Clivio, *Tetrahedron*, 2003, **59**, 7377.
99. S.K.A. Matus, J.L. Fourrey and P. Clivio, *Org. Biomol. Chem.*, 2003, **1**, 3316.
100. P. Raboisson, A. Baurand, J.P. Cazenave, C. Gachet, D. Schultz, B. Spiess and J.J. Bourguignon, *J. Org. Chem.*, 2002, **67**, 8063.
101. H.S. Kim, M. Ohno, B. Xu, H.O. Kim, Y.S. Choi, X.D. Ji, S. Maddileti, V.E. Marquez, T.K. Harden and K.A. Jacobson, *J. Med. Chem.*, 2003, **46**, 4974.
102. T. Murano, Y. Yuasa, H. Kobayakawa, T. Yokomatsu and S. Shibuya, *Tetrahedron*, 2003, **59**, 10223.
103. H.J. Rosenberg, A.M. Riley, A.J. Laude, C.W. Taylor and B.V.L. Potter, *J. Med. Chem.*, 2003, **46**, 4860.
104. H. Fu, B. Han and Y.F. Zhao, *Chem. Commun.*, 2003, 134.
105. Y.H. Ryu and A.I. Scott, *Org. Let.*, 2003, **5**, 4713.
106. D.E. Verdugo and C.R. Bertozzi, *Anal. Biochem.*, 2002, **307**, 330.
107. J. Sandbrink and R. Stromberg, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1657.
108. S. Mikkola, *Org. Biomol. Chem.*, 2004, **2**, 770.

109. B. Walkowiak, J. Baraniak, C.S. Cierniewski and W. Stec, *Bioorg. Med. Chem. Let.*, 2002, **12**, 1959.
110. M. Szymczak, A. Szymanska, J. Stawinski, J. Boryski and A. Kraszewski, *Org. Let.*, 2003, **5**, 3571.
111. J. Jemielity, J. Stepinski, M. Jaremko, D. Haber, R. Stolarski, R.E. Rhoads and E. Darzynkiewicz, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 691.
112. P. Franchetti, L. Cappellacci, M. Pasqualini, M. Grifantini, T. Lorenzi, N. Raffaelli and G. Magni, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 865.
113. K.W. Pankiewicz, K.B. Lesiak-Watanabe, K.A. Watanabe, S.E. Patterson, H.N. Jayaram, J.A. Yalowitz, M.D. Miller, M. Seidman, A. Majumdar, G. Prehna and B.M. Goldstein, *J. Med. Chem.*, 2002, **45**, 703.
114. C. Ernst and W. Klaffke, *J. Org. Chem.*, 2003, **68**, 5780.
115. A. Zamyatina, S. Gronow, M. Puchberger, A. Graziani, A. Hofinger and P. Kosma, *Carbohyd. Res.*, 2003, **338**, 2571.
116. A. Graziani, A. Zamyatina and P. Kosma, *Carbohyd. Res.*, 2004, **339**, 147.
117. F. Stolz, M. Reiner, A. Blume, W. Reutter and R.R. Schmidt, *J. Org. Chem.*, 2004, **69**, 665.
118. P. Busca, W. Piller, F. Piller and O.R. Martin, *Bioorg. Med. Chem. Let.*, 2003, **13**, 1853.
119. D. Lazarevic and J. Thiem, *Carbohyd. Res.*, 2002, **337**, 2187.
120. J. Elhalabi and K.G. Rice, *Carbohyd. Res.*, 2002, **337**, 1935.
121. O. Tsuruta, H. Yuasa, H. Hashimoto, K. Sujino, A. Otter, H. Li and M.M. Palcic, *J. Org. Chem.*, 2003, **68**, 6400.
122. A. Caravano, S.P. Vincent and P. Sinay, *Chem. Commun.*, 2004, 1216.
123. A. Caravano, D. Mengin-Lecreulx, J.M. Brondello, S.P. Vincent and P. Sinay, *Chem. Eur. J.*, 2003, **9**, 5888.
124. D.W. Koh, D.L. Coyle, N. Mehta, S. Ramsinghani, H. Kim, J.T. Slama and M.K. Jacobson, *J. Med. Chem.*, 2003, **46**, 4322.
125. S. Shuto, M. Fukuoka, T. Kudoh, C. Garnham, A. Galione, B.V.L. Potter and A. Matsuda, *J. Med. Chem.*, 2003, **46**, 4741.
126. G.K. Wagner, S. Black, A. Guse and B.V.L. Potter, *Chem. Commun.*, 2003, 1944.
127. M. Cipolletta, M. de Champdore, L. De Napoli, G. Di Fabio, A. Messere, D. Montesarchio and G. Piccialli, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 663.
128. A. Galeone, L. Mayol, G. Oliviero, G. Piccialli and M. Varra, *Eur. J. Org. Chem.*, 2002, 4234.
129. P. Lang, C. Gerez, D. Tritsch, M. Fontecave, J.F. Biellmann and A. Burger, *Tetrahedron*, 2003, **59**, 7315.
130. D. Loakes, D.M. Brown, S.A. Salisbury, M.G. McDougall, C. Neagu, S. Nampalli and S. Kumar, *Tet. Let.*, 2003, **44**, 3387.
131. N. Zhang, H.M. Chen, V. Koch, H. Schmitz, C.L. Liao, M. Bretner, V.S. Bhadti, A.I. Fattom, R.B. Naso, R.S. Hosmane and P. Borowski, *J. Med. Chem.*, 2003, **46**, 4149.
132. A. Roychowdhury, H. Illangkoon, C.L. Hendrickson and S.A. Benner, *Org. Let.*, 2004, **6**, 489.
133. A. Miazga, K. Felczak, M. Bretner, M.A. Siwecka, A. Piasek and T. Kulikowski, *Nuc. Nuc. Nucleic Ac.*, 2003, **22**, 973.
134. M.I. Dobrikov, Z.A. Sergueeva and B.R. Shaw, *Nuc. Nuc. Nucleic. Ac.*, 2003, **22**, 1651.
135. P. Li, M. Dobrikov, H.Y. Liu and B.R. Shaw, *Org. Let.*, 2003, **5**, 2401.

136. V.N. Barai, A.I. Zinchenko, S.V. Kvach, O.I. Titovich, E.B. Rubinova, E.N. Kalinichenko and I.A. Mikhailopulo, *Helv. Chim. Acta*, 2003, **86**, 2827.
137. N. Carrasco and Z. Huang, *J. Am. Chem. Soc.*, 2004, **126**, 448.
138. W.D. Wu, D.E. Bergstrom and V.J. Davisson, *J. Org. Chem.*, 2003, **68**, 3860.
139. S. Aketani, K. Tanaka, K. Yamamoto, A. Ishihama, H.H. Cao, A. Tengeiji, S. Hiraoka, M. Shiro and M. Shionoya, *J. Med. Chem.*, 2002, **45**, 5594.
140. L.H. Thoresen, G.S. Jiao, W.C. Haaland, M.L. Metzker and K. Burgess, *Chem. Eur. J.*, 2003, **9**, 4603.

Nucleotides and Nucleic Acids; Oligo- and Poly-Nucleotides

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1 Introduction

Nucleic acid chemistry and biology has significantly advanced since the structure of DNA was solved just over 50 years ago. It is a constantly expanding area of research, and the applications of nucleic acids have become incredibly diverse. This review covers a two-year period (2002–2004) and is focussed on oligonucleotide modifications. The largest group of modifications involves novel nucleobases that are used not only for duplex stabilisation and tertiary structures, but find application in understanding the mode of action of other biological molecules, conjugation with small molecules as well as macromolecules and in nanotechnology devices. A number of advances have also been achieved with sugar and backbone modifications, especially LNA and PNA, and as in previous years, there have been a large number of structures solved for nucleic acids. There are also some noteworthy emerging areas of research, which includes templated organic synthesis, single molecule detection and, as noted above, nanodevices.

1.1 Oligonucleotide Synthesis. – *1.1.1 DNA Synthesis*. Whilst DNA synthesis has been routinely carried out for many years, there are still many reports on methods for improving synthesis. These range from new protecting group strategies and new solid support methodologies (which make up the majority of new reports), to new reagents for oligonucleotide synthesis. Possibly the most important paper in this field during this review period is a new synthesis strategy developed by Caruthers and co-workers. The method makes use of a 5′-aryloxycarbonyl group, the usual 5′-dimethoxytrityl protecting group being used instead to protect exocyclic amino groups. The internucleotide phosphite group is then oxidised by a buffered (pH 9.6) peroxy anion solution, which additionally removes the 5′-protecting group thus reducing the number of steps involved in the synthesis cycle.[1]

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A synthesiser has been developed which allows for the synthesis of 1536 oligonucleotides in parallel. Reactions are carried out in microwells, and oligonucleotides up to 119 nucleotides have been synthesised.[2] Various miscellaneous methods are reported for DNA synthesis. These include photosensitive nitrobenzyl esters which yield α-chloro-substituted acetic acid derivatives which may be used for 5′-deprotection with reduced depurination;[3] synthesis of 3′-modified oligonucleotides using reverse synthesis (*i.e.* in the 5′-3′ direction);[4] a method for the synthesis of H-phosphonate oligonucleotides using *N*,*N*-diisopropylamino-*p*-methoxybenzylphosphoramidites;[5] synthesis of phosphonoacetate and thiophosphonoacetate oligonucleotides using 3′-*O*-phosphinoamidite monomers[6] and a non-enzymatic chemical template synthesis of RNA using imidazole-activated 5′-monophosphates.[7] Non-enzymatic templated transcription of DNA may be carried out using monophosphates activated by 2-aminoimidazole. Using such transcription reactions, it has been shown that diaminopurine is a much better cognate base for 5-propynyluracil than adenine.[8] For large-scale oligonucleotide synthesis, solution phase is the preferred method. Two reports deal with solution phase synthesis, one using phosphotriester chemistry to synthesise a G-rich iso-oligonucleotide[9] the other H-phosphonate chemistry to synthesise a phosphorothioate oligonucleotide.[10]

A few new protecting group strategies have been reported. Methyl-SATE (2*S*-AcetylThioEthyl) pro-oligonucleotides can be prepared using fluoride-labile protecting groups.[11,12] SATE oligonucleotides have the advantage that their phosphate groups are fully protected and are therefore more readily taken up into cells where they may be hydrolysed. 6-(Levulinyloxymethyl)-3-methoxy-2-nitrobenzoyl has been introduced as a base-labile 5′-hydroxyl protecting group,[13,14] and 5′-hydroxyl protection has also been carried out using modified pixyl groups that are more acid-labile than dimethoxytrityl.[15] Dimethylacetamidine can be used as a selective protecting group for exocyclic amines in conjunction with other ultra-mild deprotection groups. It is stable to potassium carbonate in methanol, and is removed by methanolic ammonia.[16] Two alternative phosphate-protecting groups, 3-(*N*-*tert*-butylcarboxamido)-1-propyl[17] and 2-[*N*-methyl-*N*-(2-pyridyl)]aminoethyl-phosphates,[18] have been described, both protecting groups being removed thermolytically.

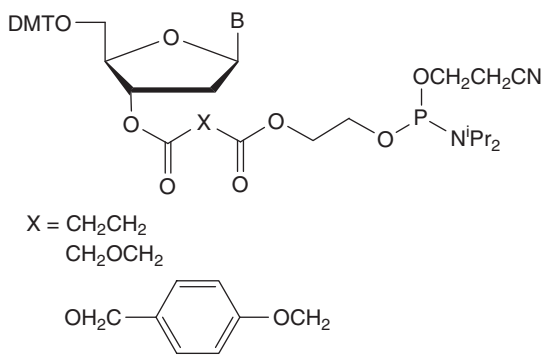
Terminal phosphate groups have been introduced via an oxime-derived solid support[19] and a phosphoramidite building block,[20] as well as for the introduction of phosphorothiolates.[21] New sulfurising agents have also been described such as dimethylthiuram disulfide[22] and diethyldithiodicarbonate[23] for introducing phosphorothioate linkages, and a novel solid support to allow the synthesis of 3′-phosphorothioate oligonucleotides.[24] Stereocontrolled synthesis of *R*p or *S*p phosphorothioates may be carried out using new oxazaphospholidine derivatives.[25] A method for desulfurisation of phosphorothioates has also been described.[26]

Sekine *et al*. have described the synthesis of oligonucleotides which does not require all protecting groups. Synthesis without exocyclic amino protecting groups involves protonation with 5-nitrobenzimidazolium triflate[27] whilst a novel HOBt-mediated coupling strategy reduces the phosphitylation at

exocyclic amino positions[28] and allows for no internucleotide phosphate protecting groups.[29]

New reagents useful during DNA synthesis include NBS in DMSO as a non-basic reagent for the oxidation of phosphite to phosphate triesters,[30] and a solution of CCl_4 and *N*-methylmorpholine in pyridine for the oxidation of H-phosphonate diesters to phosphates.[31] Removal of dimethoxytrityl protecting groups can be accompanied by depurination side-reactions, but the latter may be reduced by use of buffered (pH 3.0-3.2) sodium acetate solution.[32] 2-Methyl-5-*tert*-butylthiophenol and triethylamine in acetonitrile can be used to remove phosphate methyl protecting groups.[33] An on-column method for cross coupling of alkynylated nucleobases *via* a copper-catalysed oxidation reaction has also been described.[34]

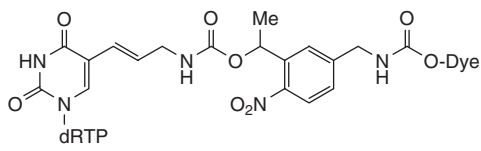
Various new solid supports have been used for oligonucleotide synthesis. Two *cis*-diol universal supports have been developed, one which is conformationally preorganised for more efficient oligonucleotide synthesis,[35] and one which is compatible with polyamine-assisted oligonucleotide deprotection,[36,37] as well as a photocleavable universal support which uses long wavelength UV light to avoid photolytic damage to the oligonucleotide.[38] A polymeric solid support has been described which has a 10-12 fold higher loading of functional groups for increased oligonucleotide loading.[39] It is reported that attachment of the dA to a solid support *via* its exocyclic amino group leads to reduction of (n-1)-mer formation.[40] Solid supports for 3′-modified oligonucleotides include a support that allows synthesis of 3′-amino-modified oligonucleotides[41] and a method for attachment of ligands *via* a 2′-succinyl linker.[42] Linker phosphoramidites, such as (1) are described which are suitable for attachment of the first nucleoside to underivatised solid supports.[43]



1

1.1.2 DNA Microarrays. The synthesis of DNA on microarrays is now an established procedure, but there are further developments in this field. There are methods for light-directed synthesis, one dealing with 5′→3′ synthesis,[44] and another with the effects of stray light on the fidelity of oligonucleotide

synthesis.[45] Methods for removal of contaminating fluorescence from DNA microarrays have also been described.[46] Triplet-sensitised deprotection of oligonucleotides bearing the photolabile 2-(2-nitrophenyl)propyl-protecting group has also been reported.[47] DNA sequencing on a chip has been demonstrated using photocleavable fluorescent nucleotides such as (2).[48] After incorporation of the fluorescent dNTP, the fluorescence signal was detected and then the fluorophore cleaved by 340 nm irradiation. The labelling of probes for microarray studies usually requires about 20 μg of total RNA. A method has been described which allows the synthesis of fluorescent probes using as little as 1 μg of RNA.[49] The method uses random DNA hexamers that have a free amino group at the 5′-terminus, which are then incorporated into cDNA using aminoallyl-dNTPs and fluorescent dyes are then attached to the free 5′-amino groups. Fluorescently-labelled cRNA libraries have also been produced by using Cy-modified aminoallyl-UTP.[50] Microarray-bound oligonucleotides can also be biotinylated using the aryldiazomethane reagent (3).[51–53]



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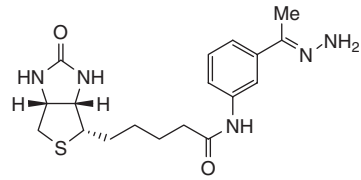
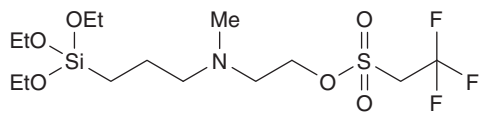


3

Analysis of microarrays is important for quality control of data obtained from hybridisation experiments. An analysis of probe density demonstrated its correlation to the efficiency of hybridisation and kinetics of capture.[54] The manufacture of microarrays from unpurified PCR products to aminated glass slides has been described which reports a signal intensity of 94% compared to that for purified PCR products.[55] The effects of linkage to solid support have been studied using C5-thymidine and N4-dC as the linkage point.[56] A three-colour cDNA array has been developed to allow for assay of the microarray, by using fluorescein-labelled probes which are compatible with Cy3 and Cy5 target labelling dyes,[57,58] whilst scanning electrochemical microscopy may be used as a label-free method for examining electrostatic interactions of DNA probes binding on a microarray.[59] A thin-film amorphous silicon photodetector has been used to quantify the density of both immobilised and hybridised oligonucleotides labelled with a fluorophore.[60]

There are a number of novel methods for the attachment of oligonucleotides to various solid surfaces. Oligonucleotides have been attached to glass surfaces coated with polycarbodiimide, and un-modified oligonucleotides may be attached by UV-irradiation, which increases coupling efficiency, and hence signal intensity.[61] A bifunctional reagent (NTMTA, 4) has been reported that reacts with the glass surface whilst the trifluoromethansulfonyl group reacts with aminoalkyl- or mercaptoalkyl-modified oligonucleotides.[62,63] Amino-modified glass surfaces can be functionalised with dendrimers bearing aldehyde groups

for the attachment of 5′-amino-oligonucleotides.[64] Commercial aldehyde-modified glass has also been used to attach oligonucleotides containing oxyamino groups by oxime bond formation.[65] High uniform loading of oligonucleotides to glass surfaces can be attained by functionalisation of the glass with γ-aminopropyltriethoxysilane or 3-glycidoxypropyltrimethoxysilane followed by a poly-L-lysine or polyacrylic acid polymer coating.[66,67] Following activation, amino-modified oligonucleotides may be attached. Zirconium phosphonate-derivatised glass surfaces allow for oligonucleotides with terminal phosphate groups to bind tightly to the organophosphonate groups.[68] Attachment of oligonucleotides has also been achieved using polylysine and other polyamine-modified oligonucleotides.[69]



4

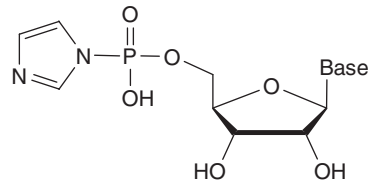
The functionalisation of poly(methyl methacrylate) (PMMA) using hexamethylene diamine generates an aminated surface suitable for the attachment of oligonucleotides.[70] A comparison of the oligonucleotide hybridisation signal with other PMMA-modified surfaces and silanised glass demonstrated that the new surface is highly robust. The impact of surface chemistry and blocking strategies on DNA microarrays has been studied in detail.[71,72]

Advances in applications of microarrays are varied and include SNP detection,[73,74] gene analysis,[75–78] DNA cleavage,[79] fingerprinting,[80] combinatorial decoding of nucleic acids,[81] nucleic acid quantification,[82] nucleic acid amplification[83] and purification.[84] Methods for the synthesis of PNA microarrays have also been reported.[85]

1.2 RNA Synthesis. – There are few reports concerning modifications to RNA synthesis. A new base-labile 5′-OH protecting group has been introduced, the (2-cyano-1-phenylethoxy)carbonyl group, which is removed 0.1M DBU.[86] ^{15}N-labelled uridine and cytidine {[(triisopropylsilyl)oxy]methyl} (tom)-protected phosphoramidites have been prepared for use in NMR studies,[87] and 2′-*Se*-methyl pyrimidines for X-ray crystallography.[88] The thermolabile 4-methylthio-1-butyl group has been introduced for protection of phosphate/thiophosphate groups during RNA synthesis,[89] and can be removed under neutral aqueous conditions. A pivaloyloxymethyl (POM)-protected C-linked imidazole ribonucleoside has been prepared to study its role as a general acid and base catalyst in ribozymes.[90]

RNA oligomers (35–40 mers) were formed within one day in a reaction catalysed by montmorillonite clay at 25°C in aqueous solution.[91,92] The reactions used imidazole-activated monophosphates (5), and gave ladders, which increased with increased reaction time. 5–17 Mers could be formed in ice

eutectic phases when dilute solutions of activated monomers (5) and Mg(II) and Pb(II) catalysts are maintained at −18°C for periods of up to 38 days.[93]



5

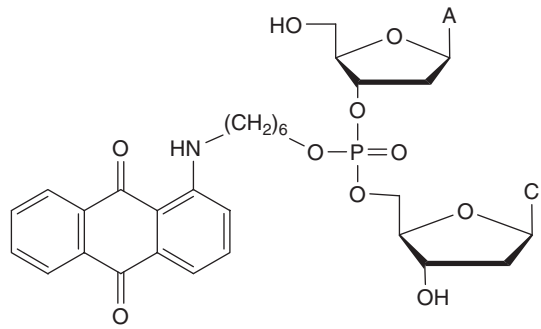
1.3 Synthesis of Modified Oligodeoxyribonucleotides and Modified Oligoribonucleotides. – *1.3.1 Oligonucleotides Containing Modified Phosphodiester Linkages*. A number of different internucleotide linkages have been examined for their effects in oligonucleotides. Of these, most reports are concerned with PNA or PNA analogues. Amongst oligonucleotide modifications, some reports are concerned with mixed DNA/RNA backbones but these are excluded from this review as this is such a common modification. Oligonucleotides containing 2-5 linkages are discussed in section 1.3.2.

Since introduced by Eckstein, probably the most widely studied modified phosphodiester linkage is the phosphorothioate.[94] Phosphorothioate-linked oligonucleotides are of significant interest because they have enhanced resistance to nuclease degradation, and have therefore been used in antisense,[95,96] siRNA[97] and enzyme studies.[98,99] A study of the effect of duplex stability of stereodefined phosphorothioate oligonucleotides[100] demonstrated that oligonucleotide stability is sequence-dependent, but *R*p linked DNA showed generally higher stability than *S*p with complementary RNA. Most phosphorothioate oligonucleotides involve substitution by sulfur of a non-bridging oxygen. However, replacement of the 3′-bridging oxygen has been shown to increase duplex stability, and induces a conformational shift as demonstrated by NMR studies.[101,102] Phosphorothioate oligonucleotides bearing an additional 3′-terminal phosphorothioate ester have been investigated for the effect of the additional negative charge, and has been shown that there was no effect for the recruitment of RNase H.[103]

Other phosphorothioate analogues that have been examined include methylthiophosphonate oligonucleotides,[104] and the biochemical properties of N3′-P5′ thiophosphoramidates[105] and thiophosphonoacetates.[106] Phosphoroselenoates have been used for heavy atom replacement for phase determination in X-ray crystallography.[107,108]

A few other reports describe oligonucleotides containing minor modifications to the internucleotide linkage. Oligonucleotides containing boranophosphate in place of a non-bridging oxygen are still able to induce RNase H activity.[109] DNA containing a single ethyl phosphotriester linkage was found to be a substrate for T4 DNA polymerase and *E. coli* DNA polymerase I.[110] The

replacement of a phosphate non-bridging oxygen by an alkyl group leads to neutralisation of charge on the phosphate backbone. Methyl phosphonates have previously been widely studied, but are used less frequently now. The effect of charge neutralisation in a DNA duplex has been studied using methylphosphonates where it was shown that the minor groove became narrower, particularly in GC rich regions.[111] The thermal stability of ODN duplexes containing various alkarylphosphonates has been measured. Short alkyl linkers gave higher stability with *R*p isomers, whilst this trend was reversed with longer linkers.[112] α-Hydroxyphosphonate linkages between thymidine dimers have similarly been examined for thermal and nuclease stability.[113] A phosphoramidite derivative of the dinucleotide (6) was incorporated into a TFO where one of the diastereoisomers strongly enhanced the triplex stability.[114]

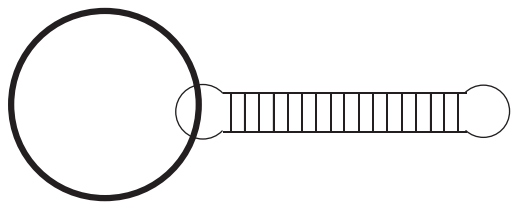


6

A popular strategy for triple helix formation is the use of an oligonucleotide that will hybridise to adjacent purine tracts by switching strands at the junction between an oligopurine-oligopyrimidine domain. In order to maintain the direction of hydrogen bonding (parallel or antiparallel) a 3′-3′ linkage is introduced. A number of examples of these alternate-strand TFOs have been examined,[115–117] including those in which an intercalating agent is introduced to aid thermal stability.[118–120] The immunostimulatory effect of oligonucleotides containing 3′-3′- or 5′-5′-linked CpG domains was found to enhance or suppress immunostimulation, respectively.[121,122]

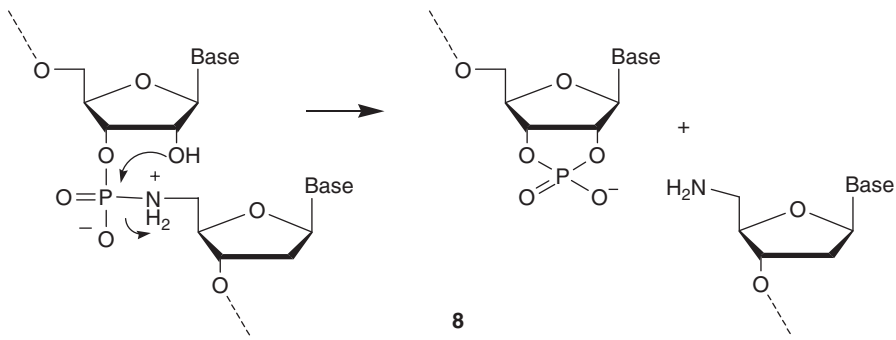
Cyclic and lariat oligonucleotides have attracted much attention since they were shown to be unusually good substrates for polymerases and as splicing intermediates, respectively, and a number of reports have dealt with their synthesis. A variety of methods have been used to cyclise oligonucleotides, the most common being a ligation method using linear templates.[123–125] Ligation methods have also been used for the synthesis of branched oligonucleotides.[126,127] Other methods of cyclisation use chemical ligation, for example ligation of a 5′-iodo-modified oligonucleotide to a 3′-phosphorothioate[128] and ligation of a 5′-oxyamino group to a 3′-aldehyde.[129] Branched RNA oligonucleotides have also been synthesised using the 2′-*O*- and 3′-*O*-positions as branching sites.[130]

Applications of cyclised oligonucleotides are varied. They have been used to produce artificial human telomeres by rolling circle DNA synthesis,[131] as inhibitors of viral replication in influenza virus[132] and as structural motifs for quadruplex formation.[133,134] A further form of 'cyclic' oligonucleotide figures in a recently described method in which a self-complementary oligonucleotide, e.g., a hairpin structure, is denatured and allowed to re-anneal in the presence of circular DNA such as a plasmid (7). The effect is that the short oligonucleotide traps the plasmid in what has been termed a padlock.[135] Such structures have been successfully used to inhibit transcription elongation reactions based on triple helix formation of the padlock structure.[136]



7

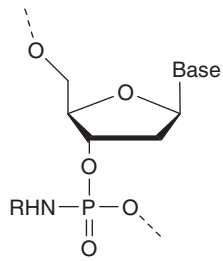
Phosphoramidates have received much attention, and a number of reports have dealt with this modification. The most widely studied modification has been the N3′-P5′ amidate linkage. This has recently been demonstrated to be effective in an antisense therapy as an inhibitor of human telomerase.[137] Substitution by nitrogen at the 5′-end, P3′-N5′ linkages, are less well studied, but oligonucleotides containing P3′-N5′ modified 2′-fluoroarabinonucleosides have been prepared and shown to be substrates for certain RNases.[138] A P3′-N5′ linkage has also been used to investigate cleavage reactions by an adjacent ribonucleotide (8). Upon protonation, the phosphoramidate linkage is attacked by the 2′-hydroxyl group to generate a 2′,3′-cyclic phosphate with cleavage of the amidate linkage.[139] Further substitution of phosphoramidate linkages by aminooxyethyl groups convey enhanced protection against exo- and endonucleases.[140]



8

The above phosphoramidates involve substitution of a bridging oxygen of the phosphate linkage. Examples have been reported in which the amino group replaces a non-bridging oxygen. Compound (9), in which the amidate contains

pendant groups with either terminal hydroxyl or amino functions, has been used to stabilise TFOs.[141] The *R*p modifications were found to exert the greatest stability, particularly with multiple substitutions. A method for post-synthesis modification to form cationic oligonucleotides has been described for the guanidine analogue (10).[142] The presence of a pendant imidazole group on a phosphoramidate-linked oligonucleotide improved affinity towards target nucleic acids.[143] Oligonucleotides containing the cationic amidate (11) efficiently target ssDNA and ssRNA, and have been shown to inhibit translation by Hepatitis C virus.[144]



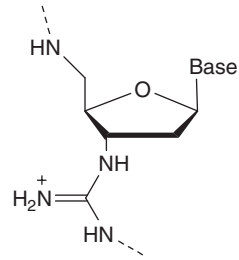
9 R = $(CH_2)_n(CH_2CH_2OH)_2$
or
$(CH_2)_n(CH_2CH_2NH_2)_2$

10 R = $(CH_2)_4NHC(NH_2)=NH_2^+$

11 R = $(CH_2)_3\overset{+}{N}(CH_3)_3$

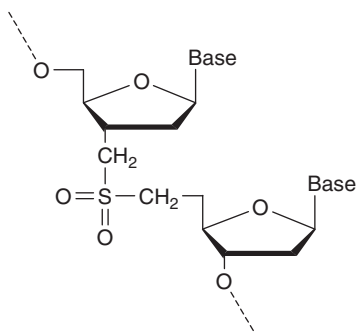
Alkyl linkers have been incorporated into oligonucleotides for a variety of uses. Incorporation of alkane-diol and hexaethylene glycol linkers to investigate stability of DNA quadruplexes demonstrated that the quadruplex stability increased with chain length.[145] The presence of an alkyl linker (C2-C12) within a CpG site neutralises the immunostimulatory effect of the CpG.[146] Phosphoramidate linkages containing pendant alkyl thiol groups form disulfide cross-linked duplexes, which may have application in nanostructures.[147–149] Likewise, calix[4]arene-linked nucleoside building blocks incorporated into oligonucleotides can be of use for the construction of oligonucleotide nanostructures.[150] Linkers have been used for the synthesis of branched[151,152] and dendritic[153,154] oligonucleotide structures.

Various other internucleotide linkages have been introduced into oligonucleotides. Bruice *et al.* examined oligonucleotides in which the internucleotide linkage is replaced by the guanidine linkage (12). The resulting oligonucleotide bound to complementary DNA with enhanced affinity for homopolymers, but with reduced affinity in mixed sequences,[155,156] in both duplex and triplex structures.[157] The replacement of the phosphate group by an amide linkage led to a slight increase in thermal stability towards an RNA target,[158] but the use of a tetrazole group as internucleotide linkage led to considerable duplex destabilisation.[159]



12

The neutral bis(methylene) sulfone internucleotide linkage (13) was introduced into oligonucleotides by solution phase synthesis, but was found to be considerably destabilising in duplexes and triplexes.[160,161] Replacement of the phosphate linkage by a squaryl diamide unit also caused duplex destabilisation, though NMR studies revealed that the overall structure of the duplex was largely unperturbed.[162,163] The presence of a single vinylphosphonate linkage within an oligonucleotide does not affect templating by a DNA polymerase, but multiple consecutive substitutions inhibits DNA synthesis. The presence of the vinylphosphonate linkage does not infer nuclease stability.[164] However, the incorporation of the disaccharide nucleoside linkage (14) into DNA does infer nuclease stability without loss of genetic information, whilst the modification can be used for chemical cleavage following an oxidation step.[165,166]



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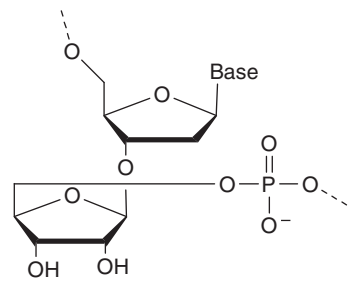


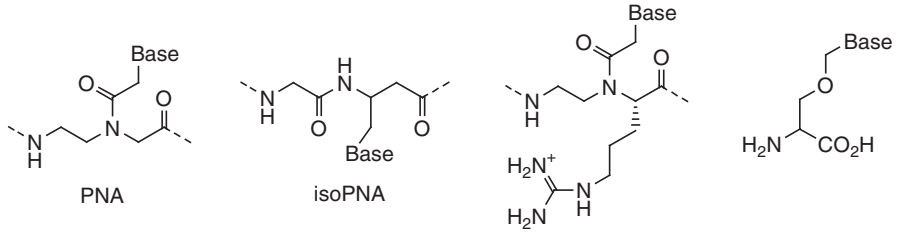
14

PNA, first introduced by Nielsen *et al.*[167], is able to form stable structures with either DNA or RNA, but has the unique property that it is able to strand-invade a DNA duplex, and is best accomplished with pyrimidine-rich PNA sequences. It has been reported that a pyrimidine hexamer of PNA combined with a mixed sequence decamer can strand-invade both duplex and triplex structures. Decreasing the pyrimidine region below six residues leads to a decrease in effectiveness of strand-invasion.[168] Two PNA strands connected by

a flexible linker forming a clamp structure (triplex) with DNA is known as bis-PNA. A bis-PNA conjugated to a 40 nucleotide DNA strand homologous to an adjacent region of the PNA clamp underwent site-directed recombination with a plasmid substrate in cell-free extracts.[169] Strand-invasion using PNA has also been used to initiate polymerase extension on dsDNA by opening the duplex structure to leave ssDNA primer binding sites.[170] PNA-DNA chimeras have been used to form stable duplexes[171] and TFOs[172] with DNA, which also exhibit enhanced protection against exonucleases. Chimeras of 2′-*O*-methyl RNA and PNA have similarly been used for enhanced binding towards complementary RNA.[173] PNA may be used for the detection of single-nucleotide polymorphisms (SNPs). When PNA binds to fully complementary ssDNA, the DNA is protected from restriction digestion, but in the presence of a DNA mismatch the DNA is digested.[174]

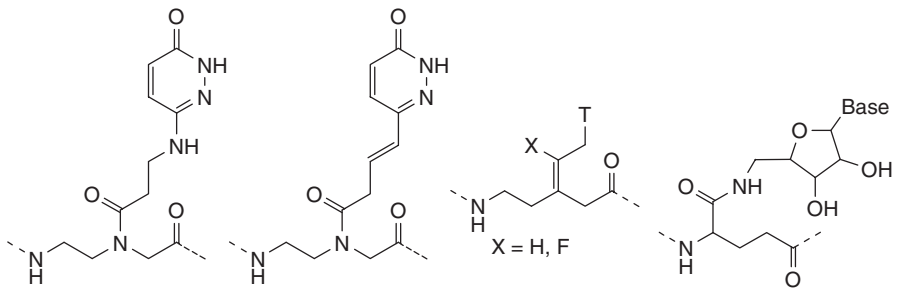
PNA is well known for stabilising duplex and triplex structures, and there are now reports of PNA involved in quadruplex structures. One report described the synthesis of four PNA-DNA chimeric quadruplexes, but concluded that the quadruplexes do not form well-defined structures as determined by NMR.[175] However, a second report describes a PNA-DNA chimeric structure studied by CD, UV and FRET in which the quadruplex adopts a parallel structure.[176] A four-stranded PNA quadruplex has also been reported in which an antiparallel structure is adopted, and the quadruplex exhibits many of the properties of a DNA quadruplex.[177] Cyclic PNA corresponding to the loop region of the TAR RNA of HIV-1 has been synthesised and examined as an inhibitor of the HIV-1 dimerisation process. The cyclic PNA was designed to form a kissing complex with the loop region of TAR RNA. In a preliminary report it was suggested that the cyclic RNA was able to inhibit HIV dimerisation,[178] but a later report claimed that no interaction occurred between the cyclic PNA and the RNA, though some interaction was observed with the linear form of the PNA.[179]

The original PNA consisted of an aminoethylglycine backbone (15) to which the nucleobases were attached. PNA has attracted much attention, and as a result many novel backbones have been reported. The analogue (16) has been used as a mimic of 2′,5′-RNA linkages.[180] However, PNAs derived from (16) were destabilising against both DNA and RNA compared to (15), and it was suggested that the glycylalanine backbone is not of optimal length for hybridisation. Replacement of glycine with arginine introduces a guanidinium group into the PNA backbone (17), which was developed to facilitate cellular uptake of the resultant PNA. This PNA was shown to preferentially form duplexes rather than triplexes, but enhanced cellular uptake was observed.[181] The use of ornithine in the PNA backbone has also been reported, and whilst there was no comparison with PNA it was reported that it formed more stable duplexes with DNA than DNA-DNA duplexes.[182] PNA derived from serine, (18), forms α-helical PNA structures composed of a repeating tetrapeptide unit.[183] These structures are able to hybridise to ssDNA, forming more stable parallel than antiparallel structures.



15 **16** **17** **18**

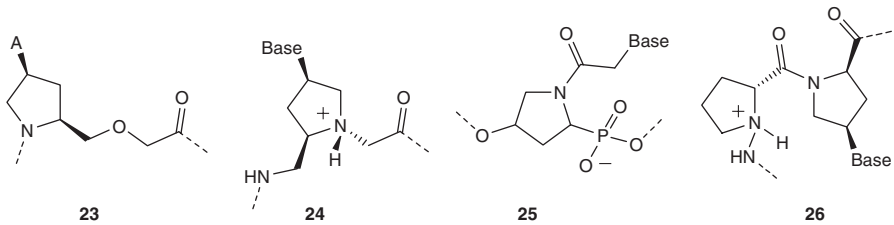
The previously described PNA analogue (19)[184] pairs with thymidine when in a Hoogsteen strand of a bis-PNA. The conformationally constrained analogue of (19, 20), was evaluated in bis-PNA, but there was no improvement of stability compared to (19).[185] The conformationally constrained PNA monomer (21, X=F) targeted towards DNA, formed stable structures, but was sequence dependent.[186,187] PNA containing (21, X=H) preferentially forms stable parallel duplexes with DNA rather than antiparallel.[188] PNA containing the peptide ribonucleic acid derivatives (22) are reported, but no additional data is provided.[189]

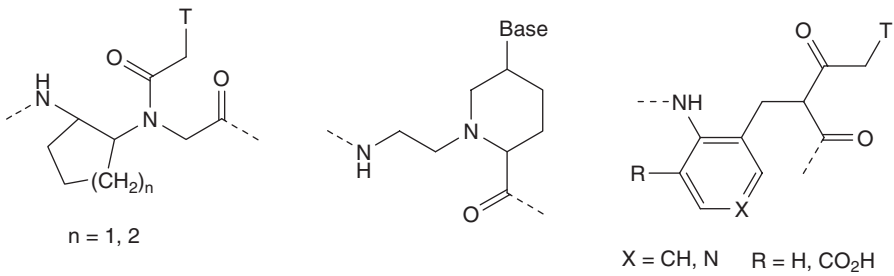


19 **20** **21** **22**

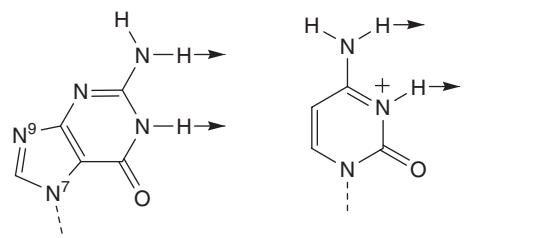
Various cyclic PNA analogues have been reported where a ring structure is incorporated to add conformational restraint. A number of pyrrolidine-based structures have been synthesised, but were found to be destabilising towards complementary DNA or RNA.[190–194] However, the pyrrolidine derivative (23, *cis*-L-derivative shown) demonstrated sharper melting profiles than (15),[195] whilst (24) exhibited unprecedented kinetic binding selectivity for ssRNA over DNA.[196] In an attempt to mimic the negative charge of the DNA backbone, phosphono derivatives of PNA have been examined. The phosphono-PNA derivative (25) derived from *trans*-4-hydroxy-L-proline was found to form exceptionally strong duplexes with either DNA or RNA.[197] The pyrrolidinyl-PNA (26) exhibits discrimination towards DNA in that when paired with a mismatch, the duplex is significantly destabilised compared to natural PNA.[198] Cyclopentane or cyclohexane modified PNA (27) show enhanced binding towards DNA and RNA.[199–202] Incorporation of pipecolyl (28) and piperidine units into the PNA backbone also enhance duplex stability with complementary DNA.[203–205] The incorporation of an aromatic ring into the backbone of

PNA (29), however, was destabilising towards complementary DNA, though inclusion of carboxyl groups improves the aqueous solubility of the PNA.[206]





As well as backbone modifications, a number of nucleobase modifications have been reported for PNA. 5-Propynyl- and 5-hexynyluracil have been incorporated into PNA where surprisingly it was found to be destabilising.[207] N7-substituted guanine (30) has been used as a mimic of protonated cytosine in a triplex with dsDNA.[208] A Janus-Wedge triple helix is a motif in which the incoming base from the third strand forms hydrogen bonds with the Watson-Crick faces of the target duplex.[209] 6-Amino-pseudocytidine forms a Janus-Wedge between a thymidine and cytidine in a bulge-loop.[210] A G-clamp PNA monomer (*cf* 106) has been incorporated into PNA and targeted towards both complementary DNA and RNA, where it was shown, as with the DNA/RNA G-clamp, to significantly enhanced duplex stability.[211]

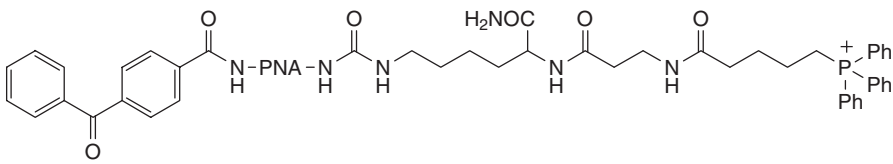


30

Demidov *et al.*[212–214] have described a method of DNA duplex recognition by modified PNA. Using strand-invading PNA containing diaminopurine and

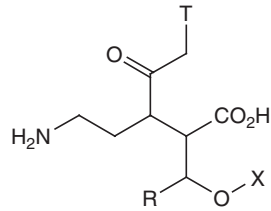
2-thiouracil in place of adenine and thymine, respectively, it was shown the PNA recognises its A-T or G-C counterpart, forming unstable duplexes due to steric interference with the modified nucleobases. The concept, known as pseudocomplementary-PNA, induces DNA bending at the target site and modifies protein activity of duplex DNA. A method for discriminating between dC and ^{Me}dC in DNA has been described.[215] The method involves using PNA to strand-invade the target sequence bearing dC or ^{Me}dC such that the target sequence binds to a further strand of DNA bearing a fluorophore. The complex is then digested and, if dC is in the target sequence, there is an enhancement of fluorescence as the fluorophore is released, but there is no increase in fluorescence from the ^{Me}dC containing complex. A similar system of using PNA to strand invade a DNA duplex was used to selectively cleave one strand of DNA at a designated site by a restriction enzyme.[216]

Various fluorinated aromatic nucleobases have been synthesised for PNA.[217] As is found with similar fluorinated aromatic bases in DNA (section 1.3.3), they behave as universal bases with complementary DNA. PNA with a terminal 9-aminoacridine has been prepared to examine binding of monovalent ions.[218] A T_{10} PNA oligomer was found to be sensitive to increasing the concentration of K(I) ions, but the presence of the terminal acridine significantly reduced the sensitivity. The incorporation of naphthalene diimide at the N-terminus of PNA stabilises DNA-PNA duplexes,[219,220] whilst the bis-functionalised PNA (31) not only stabilises the duplex with DNA but also can be used to photocrosslink to DNA.[221] The presence of the phosphonium ion in (31) aids mitochondrial location of the PNA.



31

PNA has been synthesised using an azido-group as a masking group for the terminal amine; mild deprotection is carried out with phosphines.[222] Various terminal-modification groups (aromatic, metal-binding and aliphatic) have been incorporated onto PNA to assess the thermal stability with complementary DNA.[223] PNA has also been synthesised bearing an N-terminal spin-label (*cf* 44) to investigate binding of PNA to DNA by EPR.[224] A series of trifunctional PNA conjugates has been examined for cellular uptake and ribonuclease activity.[225] The conjugates consist of PNA to target RNA, the ribonuclease unit diethylenetriamine (DETA) and a cell-penetrating peptide. Various length spacers were incorporated between the PNA and the peptide. The pharmacokinetic properties of PNA can be modulated by sugar residues. The galactose-modified PNA monomer (32) in PNA is slightly destabilising towards complementary DNA but was effectively targeted to the liver compared to the unmodified PNA.[226]

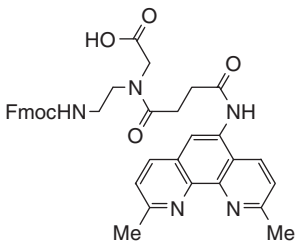


R = H, Me

X = tetra-*O*-acetyl-galactose-1-yl

32

PNA analogues have been designed for metal binding (see also section 3.3). The neocuproine-Zn PNA monomer (33) has been used to target the RNA component of human telomerase.[227] Incorporation of the Zn(II) binding units (34) and (35) at the termini of PNA substantially increases binding affinity towards DNA,[228,229] while (36) has been used to deliver radiometals, in particular ^{111}In.[230] The dioxime modification (37) was designed for chelation to metal ions. Synthesis was carried out using iron(II)-clathrochelates as protection for the dioxime unit, and the modified PNA was found to bind Cu(II) and Ni(II) at micromolar concentrations.[231]



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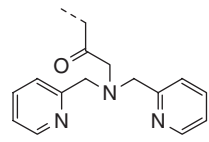

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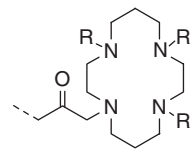
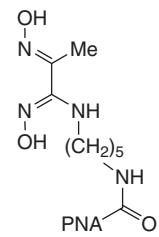


35 R = H

36 R = CH_2CO_2H



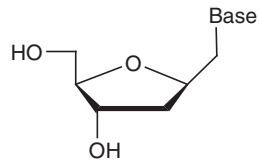
37

There are also reports in which PNA has been used in antisense. PNA has been targeted at the initiation codon of the p75 neutrophin receptor where it showed a dose-dependent inhibition,[232] for inhibition of murine CD40 expression by redirecting constitutive splicing,[233] and down-regulation of microsomal triglyceride transfer protein expression in hepatocytes.[234] A 13-mer antisense PNA was used to inhibit expression of the *bcr*/*abl* oncogene by binding to the junction of *bcr*/*abl* mRNA,[235,236] and, by targeting Ha-*ras* mRNA translation, elongation was arrested.[237] A 14-mer PNA was used to inhibit inducible nitric oxide synthase (iNOS) in macrophages.[238] PNA was used to inhibit the expression of human caveolin-1 and to discriminate between its α and β isoforms, selectively blocking the α isoform.[239]

The degradation of dsDNA by exonuclease III can be inhibited in specific and non-specific manners in the presence of PNA.[240] A promoter targeted PNA acted as a strong inhibitor of basal transcription in HeLa cells, but when

conjugated with a Gal80-binding peptide it activated transcription.[241] A Cy3-labeled PNA was targeted to telomeric DNA in living cells to observe the dynamics of telomers, where it was observed that a majority of telomers undergo constrained diffusive movement.[242] BisPNA has been used to target duplex DNA, where it was shown that it could inhibit transcription.[243,244]

1.3.2 Oligonucleotides Containing Modified Sugars. There are many new sugar derivatives, with modifications at each of the ribose carbon atoms, though 2′-modifications are the largest group. There is one 1′-modified analogue, the homo-*N*-oligonucleotide (38).[245] Oligonucleotides (38) can form duplexes with either (38) or natural oligomers. Duplex homo-*N*-oligonucleotides form left-handed helices, whilst with RNA they form right-handed helices.



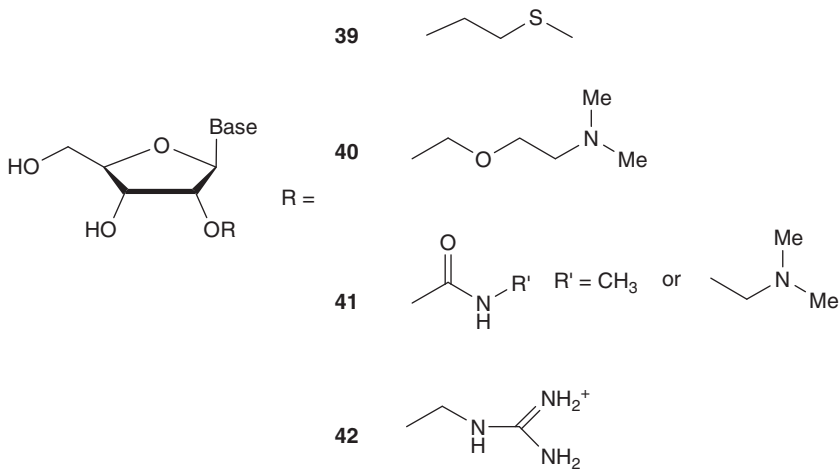
38

The most common C2′-modification is 2′-*O*-methyl, which has been widely used because 2′-*O*-methyl modified oligonucleotides are more thermally stable and nuclease resistant. For this reason they are widely used in oligonucleotides which need to be stable in cellular environments. This modification is so well known that reports which describe 2′-*O*-Me oligonucleotides are only included for completeness.[246–253] Polymerases have been evolved by directed evolution that can efficiently synthesise oligonucleotides using 2′-*O*-methyl 5′-triphosphates,[254] and 2′-*O*-methyl oligonucleotides conjugated to a phenanthroline derivative can cleave target complementary RNA sequences.[255]

2′-*O*-Alkyl-2-thiouridine-modified RNA duplexes were studied to show that the addition of an alkyl substituent to O-2′ of 2-thio-U gave higher Tms, though it was destabilising compared to 2-thio-U.[256] 2′-*O*-alkyl modifications in siRNA are generally tolerated at the 5′-end, especially 2′-*O*-allyl, but at the 3′-end low tolerance was exhibited.[257] 2′-*O*-(2-Methoxy)ethyl (2′-MOE) substituents in ODNs are known to give rise to higher duplex stability with complementary RNA.[258] The 2-MOE derivative of 2-thiothymidine in ODNs was therefore found to exhibit very high duplex stability with complementary RNA as well as enhanced resistance to nuclease degradation.[259] 2′-*O*-(2-methylthio)ethyl-modifications (39) also exhibited high binding to RNA targets, but are more susceptible to nuclease degradation.[260] The synthesis of 2′-MOE phosphorothioates has been studied and it has been shown that diastereomeric control may be achieved by varying activators and phosphate protecting groups.[261] 2′-MOE gapmers targeted towards telomerase were able to diffuse across cell membranes and inhibit telomerase without the use of a cationic lipid carrier.[262] A cytidine bearing a 2′-*O*-ribose sugar modification

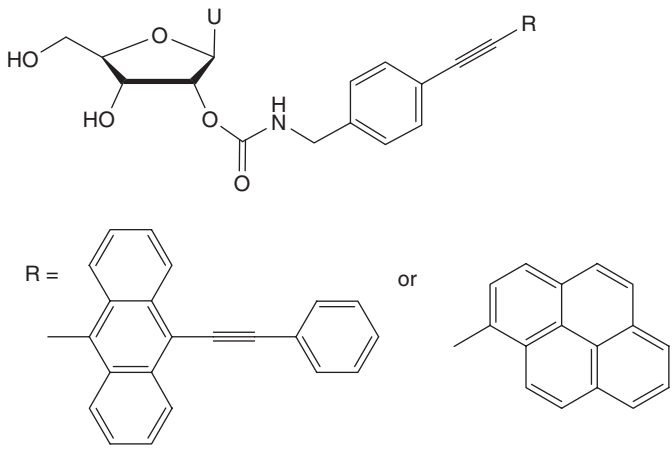
within an ODN has been oxidised to yield an aldehyde derivative that could then be used to crosslink to the methyltransferase *Eco*-RII.[263]

Many C2′-modifications have been examined for their potential use in antisense therapy. 2′-*O*-{2-[2-(*N*,*N*-Dimethylamino)ethoxy]ethyl} (2′-DMAOE) modified nucleosides (40), cationic analogues of 2′-MOE nucleosides, when incorporated into ODNs exhibit high binding to RNA but not DNA targets,[264,265] and are exceptionally stable towards nuclease degradation. Gapmer oligonucleotides with one or two regions of 2′-DMAOE modified nucleotides and a phosphorothioate DNA region were able to inhibit mRNA expression *in vitro* and *in vivo*.[266] A 2′-*O*-hydroxyethyl modified nucleoside also suppressed gene activity when incorporated into TFOs.[267] 2′-*O*-(2-Amino)-2-oxoethyl derivatives (41) considerably stabilise duplexes with RNA but not with DNA,[268] particularly (41, R=$CH_2CH_2N(CH_3)_2$). The guanidinium derivative (42), however, stabilises duplexes with both DNA and RNA, and has been used for triplex stabilisation.[269] Psoralen-linked 2′-*O*-(2-aminoethyl) oligonucleotides have been used in TFOs in a gene knockout assay, and maximum activity was achieved when four such modifications are clustered within the TFO.[270] ODNs have been prepared in which adenosine bearing a 2′-*O*-pyrrolepolyamide ligand was incorporated to aid duplex stability.[271]



There are a few reports detailing the use of 2′-5′ linked oligonucleotides, the best well known being 2′,5′-A which is associated with the antiviral effect of interferon. Antisense ODNs have been synthesised containing 2′-5′-A tetramers at the 5′-end and shown to have enhanced nuclease stability,[272–274] and were able to activate RNase L activity.[272,273] DNA containing 2-5 linked uridine can direct DNA synthesis with either Klenow fragment or HIV-RT polymerases.[275] 2-5 Linked xylose oligonucleotides shows a preference for base-pairing with RNA, and is unable to form a duplex with ssDNA.[276] A 2′,5′-oligoribonucleotide derived from 1-methyl-6-thioinosinic acid showed no organised secondary structure, but was found to be a potent inhibitor of HIV-1-RT.[277]

A method has been described which allows for post-synthesis modification of the 2′-hydroxyl group within an oligodeoxynucleotide. The silyl-protected 2′-hydroxyl group is deprotected prior to cleavage from the support, and then treated with carbonyl diimidazole followed by an amine.[278] The O2′-position has been used to attach a number of reporter groups. Highly conjugated pyrene and anthracene derivatives (43) have been attached via O2-carbamate linkages which show strong dye emissions at 401 and 485 nm respectively, but are not ideally suited for FRET analysis.[279] Pyrene, as its arabinoside, has been incorporated via a 2′-carbamate linkage and is a strong interstrand excimer in DNA duplexes.[280] Pyrene has also been used as a probe in RNA for acceptor sites by antisense.[281,282] A Dansyl fluorophore at the 2′-position of cytidine shows some quenching when base paired with guanosine.[283]



43

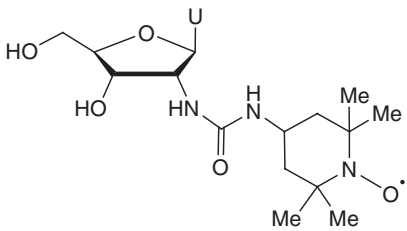
2′-Selenium modifications have been prepared as an aid to crystallography by multiple anomalous dispersion (MAD). The synthesis and incorporation into DNA of 2′-methylseleno-dC for this purpose has been described,[284,285] as have phosphoroselenates.[286]

The 5′-triphosphates of 2′-*C*-branched-uridine derivatives have been synthesised and examined as substrates for T7 RNA polymerase.[287] 2′-Hydroxymethyluridine-5′-triphosphate is a substrate and is specifically incorporated into short RNA transcripts, whilst the 2′-hydroxyethyl derivative is not.

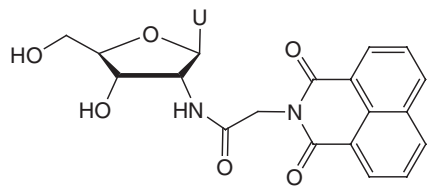
2′-Aminonucleosides are often used as a route for post-synthesis modification in oligonucleotides. Using this approach, RNA oligonucleotides were synthesised incorporating 2′-*N*-amido and 2′-*N*-ureido groups to assess them for thermal stability. All analogues were found to be destabilising in RNA duplexes, the 2′-*N*-ureido modification being the most stable.[288] A series of 2′-*N*-amido and 2′-*N*-ureido modifications were introduced into the hammerhead ribozyme to assess the affect of bulky residues on ribozyme activity.[289] A

number of such modifications were found that inhibited cleavage by preventing the formation of the active conformation. A method for the selective acylation of 2′-*N*-amino cytidine nucleotides at a nucleotide bulge site of an ODN was used to study the DNA flexibility. It was shown that a bulged (non-hydrogen bonded) 2′-*N*-amino dC was acylated 20 times faster than one involved in a hydrogen-bonded pair.[290] The synthesis of RNA with a 2′-cap at the 3′-end is reported,[291] where the incorporation of uridine bearing a 2′-*N*-aminoacyl anthraquinone significantly increases the Tm of short RNA duplexes.

Various reporter or reactive groups have been incorporated into oligonucleotides via 2′-*N*-amido or ureido linkages. The spin label (44) was incorporated into RNA duplexes to measure distances between labels by pulsed electron double resonance (PELDOR).[292] Two 2′-*N*-acylaminopyrene modified nucleosides were substituted into DNA duplexes to measure the formation rate of the pyrene dimer radical cation on one-electron oxidation.[293] Formation of the radical cation in less than 5 μs was observed. The synthesis of ODNs containing the naphthalimide nucleoside (45) as a fluorescent probe in DNA duplexes has been described.[294] The presence of the fluorophore did not significantly destabilise the duplex, and it is suggested that (45) could be used as an energy acceptor in FRET analysis. Arylazide-mediated photocrosslinking has been examined using the internally tethered derivative (46) in an RNA duplex. Crosslinking occurs broadly with functional groups in RNA, and is independent of the RNA local environment.[295]



44



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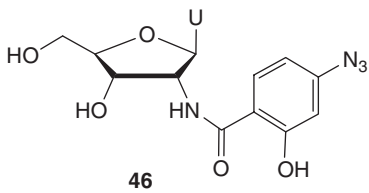


46

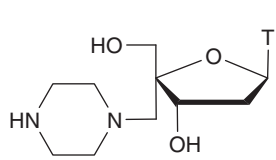
A 2′-deoxy-2′-fluoro-β-D-ribofuranoside can be considered a substitute for the natural β-D-ribose in RNA as it favors a C3′-*endo* sugar pucker and A-type conformation when hybridised with RNA. However, 2′-fluoro containing oligonucleotides are not substrates for RNase H,[296] and are inhibitors of human RNase L.[297] 2′-Deoxy-2′-fluoro-β-D-arabinonucleoside oligomers (2′-F-ANA) are substrates for RNase H, and oligonucleotides of alternating DNA and 2′-F-ANA nucleosides (altimers) have been shown to induce RNase H cleavage of complementary RNA.[298] Oligonucleotide gapmers, in which the

central portion is comprised of acyclic nucleoside residues and the termini from 2′-F-ANA, also induce RNase H activity[299] Oligonucleotides comprised of 2′-deoxy-2′,2″-difluoro-β-D-ribofuranosyl thymine as well as the α-D-analogue are destabilising in duplexes with RNA or DNA.[300] Various 2′-modifications, including amino, methylamino, thiol, *O*-methyl and fluoro, have been used to probe for exposed 2′-hydroxyl groups involved in solvation during group II intron catalysis.[301]

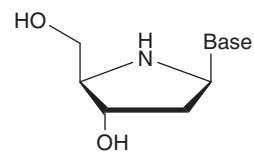
The synthesis of pyrimidine 3′-phosphorothioamidites has been carried out to prepare ODNs containing 3′-*S*-phosphorothiolate linkages for mechanistic studies.[302] The stereospecific synthesis of 3′-deuterated pyrimidine nucleosides for NMR studies of ODNs has also been reported.[303,304] The incorporation into DNA of a thymidine analogue bearing a 3′-methyl group was shown to be destabilising with both complementary DNA and RNA, though less so with RNA.[305]

Marx *et al.* reported a number of C4′-substituted alkyl-, alkenyl- and alkynyl-modified thymidine derivatives to investigate their effect on hybridisation and in primer extension reactions. In hybridisation studies, C4′-modified substituents caused some duplex destabilisation, increasingly with increasing size/chain length.[306,307] In a primer extension assay with various DNA polymerases, C4′-methyl TTP was found to be a slightly better substrate than TTP, but longer alkyl chains decreased incorporation efficiency.[308] Probes containing C4′-modified thymidine derivatives were used to detect SNPs, and it was shown that the use of C4′-vinyl thymidine gave enhanced SNP discrimination.[309,310]

The C4′-piperazinomethyl derivative (47), and its *N*-pyrenylcarbonyl derivative have been incorporated into DNA duplexes.[311] With complementary DNA, each stabilised the duplexes, particularly the pyrene derivative, but there was reduced stability towards RNA. Various C4′-alkylamino-modified 5-methyl-dC derivatives were used in TFOs to aid thermal and nuclease stability. Aminoethyl and aminopropyl linkers were found to stabilise triplexes, but other linkers were destabilising.[312] A range of other C4′-modifications, including 4′-N_3, 4′-MeO and 4′-$CH_3OCH_2CH_2O$, have also been used to aid stabilisation in TFOs.[313] The pyrrolidino nucleoside (48) was designed to introduce a positive charge within oligonucleotides for stabilisation in triplexes. Using pseudo-isocytosine as the nucleobase the analogue was stabilising in TFOs.[314]



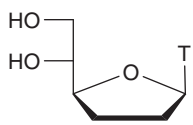
47



48

A few phosphoramidites have been used to prepare 5′-modified ODNs. The synthesis of a 5′-^{13}C-labeled ODN has been described to enable NMR analysis by 2D ^{1}H-^{13}C HMQC NOESY experiments.[315] A formamidine-protected

5′-amino-dG phosphoramidite was used to prepare 5′-acyl end-capped ODNs.[316] 5′-Iodo-dT-containing ODNs have been used in enzyme-less template-directed ligation reactions to a 3′-phosphorothioate-linked ODN.[317] The ligation was considerably enhanced in the presence of the intercalator proflavine. A trimethoxymethyl group was used to protect a 5′-thiol group during the synthesis of ODNs bearing 5′-thiol or thiol-modified groups.[318] The hexofuranosyl derivative (49) in ODNs causes a decrease in stability with complementary DNA or RNA, though a single substitution in a homopolymer showed a slight increase in stability against DNA.[319,320] The (5′*S*)-5′-*C*-modified nucleosides (50, R=H or CH_3) were incorporated into ODNs to explore alkyl-zipper formation between opposing alkyl groups in the minor groove, though both were destabilising in DNA duplexes.[321] The presence of 5′-chloro- and 5′-amino-dG modifications in RNA hairpin ribozyme structures inhibited hairpin-catalysed RNA-RNA ligation reactions.[322]



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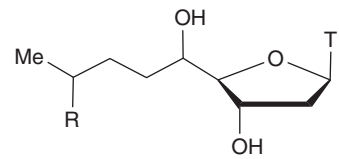
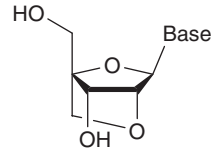


R = H or Me

50

There are two reports describing the use of nucleosides with other sugar conformations. A method for preparing internally ^{32}P-labelled L-DNA has been described using T4 polynucleotide kinase.[323] Chimeric DNA composed of tandem α- and β-anomeric strands have been used in TFOs and shown to have enhanced thermal stability compared to all α- or β-anomeric oligonucleotides.[324]

Locked Nucleic Acids (LNA) were first reported by the groups of Imanishi[325] and Wengel,[326] the Imanishi group terming the analogues as bridged nucleic acid (BNA). LNA (51) contains a methylene bridge between the 2′-oxygen and the C4′-carbon, which results in a locked 3′-*endo* conformation, reduced conformational flexibility of the ribose ring, and increasing the local organisation of the phosphate backbone. The entropic constraint in LNA leads to significantly enhanced binding of LNA to complementary DNA and RNA. LNA-modified oligonucleotides have enhanced resistance to nuclease degradation, and have proven to be effective in antisense strategies. The properties of LNA have been widely investigated, and in this review period, publications regarding LNA fall into three categories, new analogues of LNA, other locked nucleosides and the use of LNA oligonucleotides, including in antisense therapy.



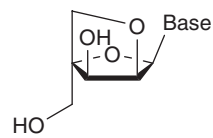
β-D-LNA

51

Analogues of LNA contain a methylene bridge between O2′ and C4′, but there have been modifications to the sugar, phosphate backbone and base modifications. The substitution of the phosphate group by a methylphosphonate still showed enhanced binding affinity towards DNA, but less so than normal LNA.[327] The 2′-amino analogue of LNA bearing an *N*-acyl group bound preferentially to RNA with higher affinity than DNA, but again less efficiently than LNA.[328] However, LNA bearing a P3′-N5′ phosphoramidate linkage exhibited slightly higher binding affinity towards DNA, RNA than LNA.[329]

The LNA derivatives of hypoxanthine, 2-aminopurine and diaminopurine have all been prepared and incorporated into oligonucleotides. As found with their DNA/RNA derivatives, each LNA analogue forms stable base pairs with their cognate nucleobase.[330,331] A series of aryl *C*-nucleoside derivatives of LNA were assessed for binding affinity towards both RNA and LNA. The analogues were generally destabilising, the pyrene analogue was the most stabilising where it behaved as a universal base.[332,333] As with DNA analogues there are base-modified LNA analogues for stabilising triplexes. 2-Pyridones[334,335] and 1-isoquinolone[336,337] have been used to stabilise CG interruptions in TFOs. Each analogue was found to have high selective binding to their target sequence.

The usual configuration of LNA is β-D-ribose, but other configurations of LNA have been examined. α-D-LNA and β-L-LNA nucleosides have very high affinity with complementary RNA in a parallel-stranded duplex.[338,339] Aryl *C*-nucleosides in the α-L-configuration (*cf* 52, base=aromatic residue) demonstrate preferential binding to DNA, with a pyrene derivative showing highest affinity and, as with the β-D-derivative[332] it behaves as a universal base.[340]

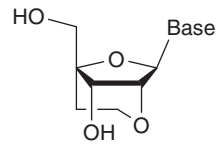


α-D-LNA

52

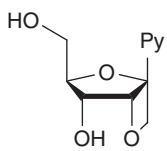
A number of other locked nucleosides have been studied, and Imanishi and Obika have reviewed a series of bridged nucleic acid analogues.[341] 2′-*O*,4′-*C*-ethylene (53) and propylene analogues also have C3′-*endo* conformations and

form duplexes and triplexes in the same way that LNA does. Oligonucleotides (53) have enhanced binding affinities towards RNA, with stability similar to LNA. However, the propylene analogue has decreased affinity towards RNA.[342] Oligonucleotides (53) also form stable triplexes at physiological pH.[343]



53

The C1′-O2′ locked pyrimidine analogues (54) also adopts a C3′-*endo* conformation. They have lower binding efficiency than their corresponding DNA analogues, but still elicit RNase H activity.[344] 2′-Spiro ribo- and arabino-nucleotides (etheno and propano rings) are also destabilising compared to DNA, and it is suggested that this is due to steric constraints.[345,346] The piperazine derivatives (55) and (56) were prepared to introduce basic functionality into the minor groove of DNA duplexes. Each analogue induced significant increase in thermal stability when in a DNA duplex.[347] Oligonucleotides containing the modified backbone bicyclo[3.2.1]amide-DNA (57) will form duplexes with DNA and RNA, but exhibit considerable destabilisation.[348–350] An anucleosidic analogue of (57) has also been used to study melting cooperativity in a helix-bulge-helix DNA model.[351] Tricyclo-DNA (58) exhibits significantly enhanced stability with complementary RNA, but it does not elicit RNase H cleavage. However, in an antisense assay compared to 2′-*O*-methylphosphorothioate oligonucleotides, tricyclo-DNA exhibited an antisense activity in the absence of lipofectamine.[352] The locked L-nucleoside derivatives, e.g., derived from thymine, (59), were destabilising in a duplex with DNA. However, the homo-uridine analogue showed enhanced binding with homo-rA compared to that formed with homo-dT.[353]



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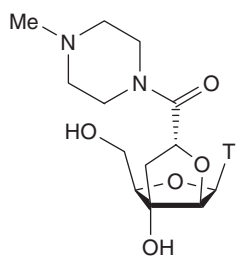

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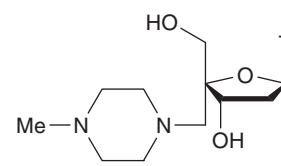

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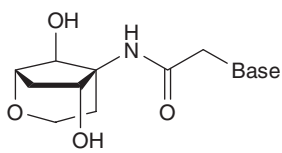

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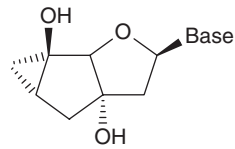

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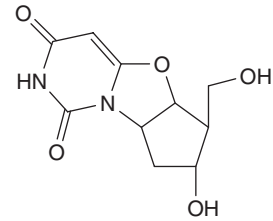


59

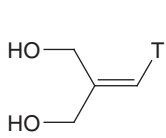
LNA has been used in a number of applications. As probes, the effect of incorporation of a single LNA into an ODN has been studied by thermal denaturation experiments.[354] LNA substitutions stabilise the duplex either by preorganisation or by improved stacking, but not both. The effects of mRNA target sequence and DNA-LNA chimera design have been examined,[355] and a method for the capture of poly(A)$^+$ RNA using oligo-LNA-thymidine has been reported.[356] LNA oligonucleotides also bind to plasmid DNA by strand displacement without interfering with plasmid conformation or gene expression.[357] LNA oligonucleotides are effective in the detection of SNPs[358,359] and have been used for SNP genotype analysis by real-time PCR.[360] The presence of LNA or α-L-LNA monomers stabilise duplexes towards endo- and exo-nucleases,[361] including resistance to DNA polymerase exonuclease activity.[362] DNA partially substituted by LNA has also been used to direct the repair of single base mutations in a yeast chromosomal gene.[363]

LNA has frequently been used to stabilise duplex structures, but in triplex structures the effect is mixed. Partial substitution of a DNA TFO by LNA increases triplex stability, whilst complete substitution leads to destabilisation.[364] Optimal stabilisation was found with substitution every 2-3 nucleotides of the TFO. The incorporation of LNA into a G-quadruplex structure was shown to alter the orientation of the quadruplex from antiparallel to parallel.[365]

The primary application of LNA has been in antisense therapy due to the aforementioned properties. It has been used to knock down human protein kinase C-α (PKC-α) with greater efficiency than the corresponding phosphorothioate ODN,[366] as an inhibitor of human telomerase,[367] to block the synthesis of RNA polymerase II[368] and to inhibit human vascular smooth muscle cell growth.[369] LNA-modified oligonucleotides have also been used in RNA interference (RNAi).[370,371]

Other locked nucleic acid derivatives have also been used in an antisense strategy. α-L-LNA chimeras with β-D-LNA are shown to be effective with enhanced nuclease stability and to recruit RNase H activity,[372] and are shown to be effective inhibitors of HIV-1 when targeted at TAR RNA.[373] α-L-LNA has also been used as a decoy for the transcription factor κB.[374] The tricyclo locked nucleic acid (58) has been used to target the splice sites of exon 4 of cyclophilin A (CyPA) pre-mRNA,[375] whilst the ethylene-bridged nucleic acids (53) have been targeted at VEGF mRNA[376] and rat organic anion-transporting polypeptide.[377]

Other sugar modifications include acyclic nucleoside analogues that have been incorporated into oligonucleotides. The analogues (60-62) were found to be destabilising towards DNA and RNA.[378–380] The hydroxymethylphosphinic acid analogues (63-64) have also been reported, though no data concerning their effects in oligonucleotides were reported.[381] An acyclic synthon for the introduction of a label or as a branching point for oligonucleotide synthesis[382] and one bearing two nucleobase units[383] have also been reported.



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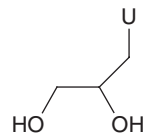

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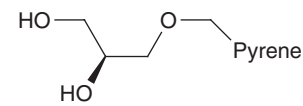

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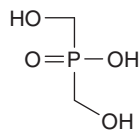

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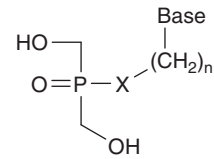
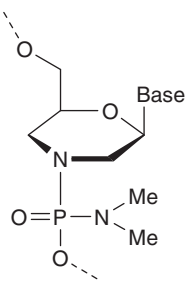


X = O or NH
n = 1 or 2

64

Various other sugars have also been incorporated into nucleosides. A method for the synthesis of arabinopyrimidine nucleosides has been described which are prepared from O^2,2′-anhydronucleosides.[384] The inclusion of arabinonucleosides into ODNs was shown to be slightly destabilising. Xylose-modified nucleosides (XNA), including a xylose locked nucleoside, when incorporated into DNA oligomers show a preference for pairing with complementary RNA rather than DNA. In homopolymers with either RNA or DNA, triplex structures are formed with two XNA strands[385,386] in which one XNA strand is parallel and the other antiparallel.[387] Phosphoramidate morpholino oligomers (65) have been used as antisense agents. Conjugation to arginine-rich peptides was found to significantly enhance cellular uptake.[388] Hexitol nucleic acids based on 1,5-anhydrohexitol as the sugar component have previously been studied as an alternative backbone system, and it has now been shown that methylation of the free hydroxyl groups (66) gives rise to a system which is an exceptionally good binder with RNA.[389]



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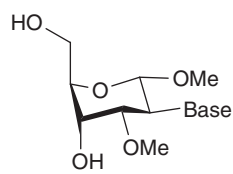
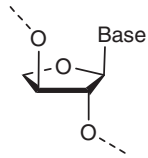


66

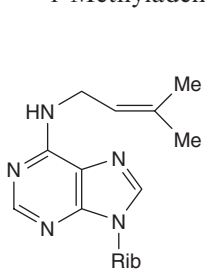
α-L-Threose nucleic acids, TNA, (67) is a nucleotide system built from sugar units with only four carbon atoms and therefore a shorter backbone. It efficiently forms Watson-Crick base pairs with TNA, RNA and DNA, and has been a topic of much investigation (for a review see Schöning *et al.*[390]). Recent developments with TNA have been polymerase recognition; the incorporation of the thymine derivative as its 3′-triphosphate into DNA with either Vent (exo-) DNA polymerase or HIV-RT was found to be quite efficient, comparing favourably with dTTP.[391] Various DNA polymerases were used to try to synthesise DNA on a TNA template.[392] Despite the differences in the sugar-phosphate backbone, several polymerases were able to copy limited stretches of a TNA template with good fidelity. TNA synthesis on a DNA template was also found to be efficient, with Deep Vent (exo-) DNA polymerase being the most efficient polymerase.[393]



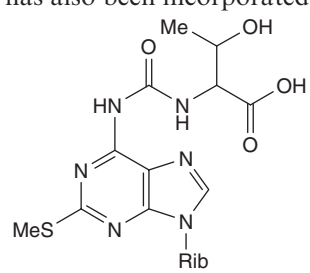
67

1.3.3 Oligonucleotides Containing Modified Bases. Oligonucleotides containing modified nucleobases represent the largest group of analogues. Purine and pyrimidine analogues are reviewed first, followed by a series of artificial nucleobases. There are then sections dealing with new base-pairs, universal base analogues, a number of aromatic nucleobases not dealt with within universal bases, and the final group are abasic sites, which can be considered as a nucleobase modification. In addition to the analogues discussed in this section there are also other nucleobase modifications covered in section 3, which deal with template-directed organic synthesis (3.2), metal-conjugates (3.3) charge transport analogues (3.4) and fluorescent analogues (3.5).

The synthesis and incorporation into RNA of three hypermodified tRNA nucleosides has been reported. The presence of the N^6-isopentyl modified adenosine (68, i^6A) in the anticodon stem-loop of *E.coli* $tRNA^{Phe}$ alters metal ion binding compared to the unmodified stem-loop sequence.[394] The presence of the N^6-lysine modified derivative (69), ms^2t^6A, found in $tRNA^{lys,3}$ of the specific RNA primer for HIV-1 RT has been shown to increase the stability of the hairpin.[395,396] 1-Methyladenosine has also been incorporated into RNA.[397]

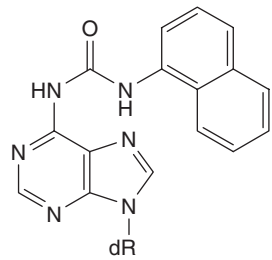


68 i^6A



69 ms^2t^6A

A number of analogues have been investigated for their ability to stabilise duplex or triplex structures. 8-Chloroadenosine was found to be destabilising in RNA duplexes, though the chloro group did not perturb the helical structure.[398] Various N6-alkyl adenosine derivatives were studied in RNA by a post-synthetic modification of 6-methylthiopurine.[399,400] For most of the modifications, it was found that the presence of alkyl groups was destabilising in duplexes and hairpins. However, the incorporation of various aromatic hydrocarbon groups via a urea linkage to C6, e.g., (70), lead to large stabilisation when in a duplex.[401]

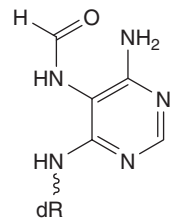


70

DNA polymerase incorporation of the mutagenic 2-hydroxy-dA has been examined and found to lead to GC→AT transition mutations.[402] The synthesis, incorporation and repair of etheno-dA adducts have been reported.[403–405] The use of a C2-alkaryl modified adenosine gave rise to enhanced stability towards a mutant U1A protein in which a conserved phenylalanine was substituted for alanine.[406] 2-Aminopurine (2-AP) has been widely used because of its fluorescent properties. However, 2-AP dinucleotide also exhibits a distinct positive CD band at 326 nm, and this property has been used to probe changes in local conformation of ODNs containing $(2\text{-AP})_2$ by CD measurements.[407]

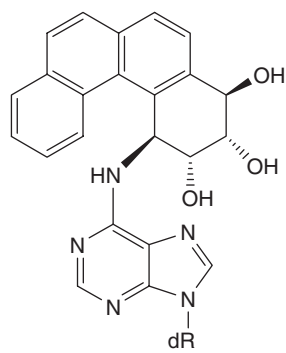
The effect of an 8-propynyl group on dA has been studied in quadruplex structures. The effect was to increase the stability of the quadruplex due to an increase in the *syn* glycosidic conformation.[408] An 8-histaminyl-dA phosphoramidite has been incorporated into DNA, where it was suggested it might be useful to probe nucleic acid structures.[409] 8-Chloro-dA has been examined as a substrate both as its 5′-triphosphate and in a template by the polymerase Klenow (exo-) fragment. Although it behaved as dA, incorporation efficiency was reduced.[410]

A series of adenosine derivatives have been reported which deal with damaged or adducted analogues. 8-Oxo-7,8-dihydroadenosine has been incorporated into DNA and its templating properties with three reverse transcriptases examined. It was shown that as well as directing the incorporation of TTP, dGTP was incorporated.[411] Another oxidative lesion of adenosine is formamidino-adenosine (Fapy-dA, 71). (71) and its C-nucleoside have been incorporated into DNA and its interaction with base excision repair enzymes assessed.[412] (5′*S*)-8, 5′-cyclo-dA is another oxidative lesion, and an assay to determine levels of this lesion in DNA by nuclease digestion has been reported.[413]



71

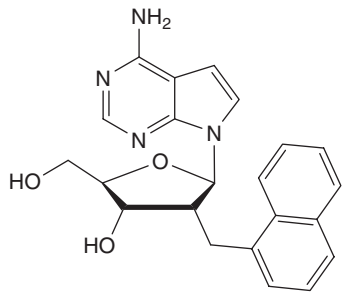
Polycyclic aromatic hydrocarbons (PAH) are a significant cause of tumorigenic lesions found in DNA, and purine analogues are particularly susceptible to adduction with PAHs. Two such analogues of dA have been reported, (+)-1*R*- or (-)-1*S*-*trans*-*anti*-[BPh]-N6-dA (72, (-)-1*S*- isomer shown) and the related 10*S* (+)- and 10*R* (-)-*trans*-*anti*-[BP]-N6-dA, derived from benzo[c]-phenanthrene diol and benzo[a]pyrene diol epoxides respectively. The presence of the lesion (72) in DNA was examined for its effect on transcription by human RNA Pol II, where it was found that the lesion caused polymerase stalling.[414] It was also assayed with mismatch repair (MMR) enzymes, where it was found that effective MMR enzymes caused cell apoptosis.[415] The translesion synthesis by human DNA polymerase ι was examined with (72) and its dG analogue. The dG analogue causes a strong block to Pol ι, but the dA analogue predominantly incorporated TTP opposite (72).[416] With human DNA polymerase γ, the dG analogue misincorporated dAMP and dGMP, whilst with the dA analogue, dTMP and dAMP was incorporated.[417] The presence of the benzo[a]pyrene diol epoxide adduct during DNA synthesis by T7 DNA polymerase also caused stalling at the lesion, but some incorporation of dATP occurred.[418] Interactions with nucleotide excision repair enzymes have also been reported.[419]



72

A few deaza- and aza-dA analogues are reported. 3′-Deaza-dA has been used to probe minor groove recognition contacts,[420,421] as well as its interactions in DNA curvature at A-tracts.[421] 1-Deaza-adenosine, tubercidin, purine and 4-methylindole deoxyribosides have all been used to probe for an essential

adenine in the U1A RNA complex.[422] An analogue of tubercidin, (73), which has a naphthylmethyl group at C2′, was shown to be slightly destabilising in a DNA duplex except at the terminal nucleotide where a slight stabilisation was observed. However, against an RNA target opposite a 2-3nt bulge, (73) stabilised the heteroduplex.[423,424] 7-Deaza-7-nitro-dA (74) and −dG with 5-hydroxy-dU and −dC have been used in a method for chemical cleavage of ODNs.[425] The method involves the use of their triphosphates incorporated into DNA by PCR. Treatment with an oxidant followed by an organic base results in cleavage of the DNA at all sites where the 7-nitropurine or 5-hydroxypyrimidine was incorporated. The use of the 7-deaza-8-aza-diaminopurine analogue (75) in a DNA duplex stabilises the A : T base pair, and the 7-bromo-derivative harmonised the stability of A : T with C : G base pairs.[426,427] Substitution of dA by 8-aza-dA accelerates the rate of adenosine deaminase reactions.[428] 7-Propynyl derivatives of 7-deaza-8-aza purines (dA, dG and diaminopurine) were all shown to give enhanced duplex stability.[429]



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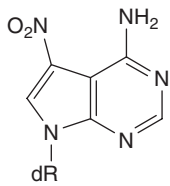

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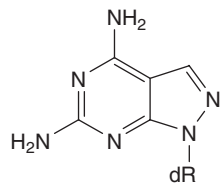
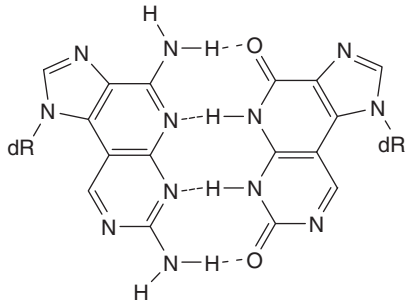
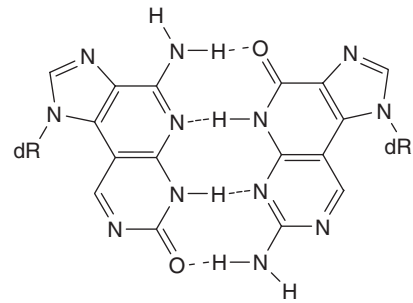


75

8-Amino- dA and dG derivatives have been used to aid stabilisation of TFOs. $G^{8A}G : C$ and $T^{8A}A : T$ triplets are significantly more stable than corresponding native triplets.[430,431] Other methods of stabilising duplex structures include the novel extended base pairs derived from imidazo[5′,4′:4,5]pyrido[2,3-*d*]pyrimidine nucleosides (76-79).[432] In these structures, (76 : 77) and (78 : 79) are base pairing nucleosides each of which present four hydrogen bonds. A single substitution of one of these pairs in the middle of a duplex was found to be destabilising, but three consecutive substitutions led to significantly higher duplex Tms.



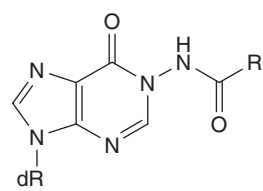
76 **77**



78 **79**

A set of six analogues (2-AP, 7-deaza-dG, pyrimidinone, 7-deaza-dA, 5-methylpyrimidinone and purine) were used to probe DNA recognition by the *Eco* RV restriction endonuclease.[433] Each of the analogues used has one or more hydrogen bonding functionality removed compared to native nucleosides, and hence gave useful information regarding hydrogen bond contacts between protein and DNA. Diaminopurine, purine, methylindole and an abasic site were each incorporated opposite dU in a DNA duplex to study their effects on base-flipping by uracil DNA glycosylase.[434]

A number of guanosine analogues have been investigated for their ability to stabilise duplex or higher structures. 8-Methylguanosine and 8-methyl-dG stabilise Z-DNA helical structures,[435,436] and the presence of 8-Me-G will convert a range of sequences from B- to Z-DNA.[435] The incorporation of L-nucleotides in a D-environment also leads to Z-form DNA duplexes.[436] The incorporation of 8-Br-G into RNA, which is in equilibrium between a hairpin and a duplex, shifts the equilibrium towards the hairpin structure by destabilisation of the duplex due to the preferred *syn*-conformation of 8-Br-G.[437] The use of N1-modified dI analogues (80) bearing pyrene or acridine were incorporated into ODNs where it was shown that the presence of the dangling aromatic group aided the stabilisation of both duplex and triplex structures.[438] Rapid reversible G-quadruplex hairpin dimer formation was reported for bis(oligonucleotide) conjugates containing stilbene diether linkages connecting the two poly(G) sequences.[439]

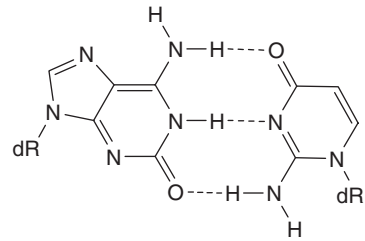


R = pyrenylmethyl
or acridine

80

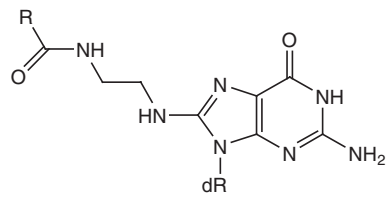
The genetic code only allows for two types of base-pair, A with T and G with C. There have been attempts to prepare nucleoside analogues to expand the

number of base pairs and hence the genetic code (a number of such analogues will be discussed later). One particular analogue that has been examined in detail is isoguanosine (81), which forms a base pair with isocytidine (82). (81) has been incorporated into ODNs both as phosphoramidite and H-phosphonate derivatives.[440] (81) and (82) have also been successfully used in PCR, confirming that they act as a third base pair.[441] Isoguanine adopts two tautomeric forms, and can form base pairs with isocytosine and thymine. These tautomeric properties have been examined theoretically,[442] and the effect of adjacent nucleosides examined in primer extension reactions with *Taq* DNA polymerase where it was shown that the 3′-neighbour has an effect on the tautomeric state and hence the templating properties of iso-dG.[443–445] The base pairing properties in parallel and antiparallel duplexes of ODNs containing 7-deaza-8-aza-iso-dG have also been examined.[446]



81 **82**

The incorporation of 6-thio-dI[447] and 6-thio-G[448] phosphoramidites into oligonucleotides has been reported. 6-Thio-G has also been used to introduce 6-thio-modified oligonucleotides using on-column conjugation. The 6-thio group is selectively deprotected, which then reacts with various alkyl iodides, followed by cleavage and deprotection with ammonia.[449] The incorporation of N2-benzyl-G into an Epstein-Barr virus encoded RNA sequence was shown to restrict the binding of protein kinase dependent on RNA (PKR).[450] A series of N1 alkylated inosine and guanosine analogues was incorporated into RNA as potential inhibitors of HIV-RT and HCMV. Of the analogues selected, an oligomer containing 1-propyl-6-thioinosine was found to be highly active.[451] An 8-ethylenediamine modified dG analogue (83) has been designed such that in the presence of a photosensitiser, such as riboflavin, a reporter group (e.g., TAMRA) is released on oxidation.[452]



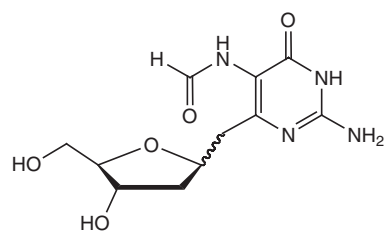
R = reporter group, e.g. TAMRA

83

Guanosine is particularly susceptible to damage, either oxidatively as it has the lowest oxidation potential, or by external mutagens. The main oxidative lesion is 8-oxo-guanosine, a known mutagenic lesion. The role of the translesion polymerase κ with a number of damaged bases has been examined, but opposite 8-oxo-dG, Pol κ is able to efficiently insert adenosine and then extend beyond it.[453] Ionising radiation leads to the formation of clustered DNA damage. When 8-oxo-dG is present within a clustered damaged site there is an enhanced mutagenic outcome with an increase in transversion mutations.[454] Proof-reading studies using Klenow fragment with 8-oxo-dG and a further oxidation product, guanidinohydantoin, were carried out in different sequence contexts.[455,456] It was shown that the presence of these lesions often led to primer slippage and therefore internal mismatches, but Klenow fragment was efficient at repairing these internal mismatch sites. Klenow fragment (exo-) incorporates both dATP and dGTP opposite guanidinohydantoin.[457] The synthesis of DNA containing the nitration product 5-guanidino-4-nitroimidazole has also been reported.[458]

The presence of 8-oxo-guanine residues within a recognition sequence has an effect on binding of proteins. Critical sites of the DNA sequence which binds to the p50 subunit of the NF-κB transcription factor were substituted with 8-oxo-dG, and the impact of these substitutions was assayed. Not every critical site was found to have an adverse affect on binding.[459] The binding capacity of the human Y box-binding protein 1 (YB-1) to RNA is enhanced when 8-oxo-G residues are present.[460] The interaction of the *E.coli* formamidopyrimidine DNA glycosylase with 8-oxo-G was examined using an oligonucleotide containing a photocrosslinking phenyl(trifluoromethyl)diazirine residue.[461]

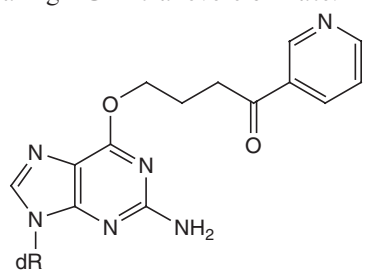
The repair of oligonucleotides containing 8-oxo-dG has been studied using eurkaryotic 8-oxoguanine glycosylases, which repaired the lesion 1000-fold faster when it was base paired with cytosine than with adenosine.[462,463] Repair was also studied using cellular extracts from human and rat testicular cells, though there was limited ability to repair the lesion.[464] The mechanism of repair with human 8-oxoguanine glycosylases was examined at lesions where 8-oxo-dG was opposed to an abasic site.[465] Further oxidation of 8-oxoguanine leads to the formamidopyrimidine derivative FapyG (84). (84) was incorporated into ODNs where its base pairing properties were compared with 8-oxo-dG. Whilst 8-oxo-dG pairs preferentially with dA and dC, (84) pairs with dT and dC.[466] The repair of (84) by various repair enzymes showed little difference in efficiency compared to that of 8-oxo-dG.[467] RNA containing the oxidised analogue 8-oxo-G may be cleaved at the 8-oxo-G site by ammonia in the presence of oxygen at 60°C.[468]



84

Another form of guanine lesion arises from alkylation leading to O^6-alkylguanine derivatives. The enzyme that is involved in the repair of such lesions is O^6-alkylguanine-DNA alkyltransferase (AGT), which also repairs O^4-alkylthymidine lesions. Using short ODN duplexes containing an O^6-methyl-dG : T(U) mispair, it has been shown that AGT has two repair mechanisms, one of which is an ATP-dependent efficient process. The other does not require ATP but is less efficient.[469] The repair of O^6-methyl-dG by two thermophilic AGTs has been assessed and found to be efficient, though less efficient in the repair of O^4-methyl thymidine lesions.[470] The repair of O^6-methyl-dG by human AGT has been shown to be 5-fold more efficient when up to 0.1M Zn(II) is present.[471] The mechanism by which AGTs work is not fully understood. Using alkylated nucleotides bearing an *O*-thiol tether, crosslinking between the ODN and protein occurs which demonstrates that the nucleotide is transiently extrahelical.[472] O^6-Benzyl guanine is an inhibitor of AGTs currently in clinical trials to enhance cancer chemotherapy. Short dG-rich ODNs containing one or more O^6-benzyl guanine residues are even more effective inhibitors of AGTs than O^6-benzyl guanine alone.[473]

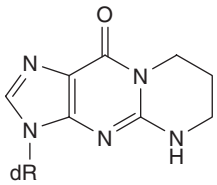
The presence of the lesion (85), believed to be involved in the initiation of lung cancer in smokers has been studied in ODNs to investigate 3′-exonuclease resistance. It was found to be resistant to a number of exonucleases unlike O^6-methyl-dG containing ODNs.[474] DNA Polymerases η and κ are highly expressed in the reproductive organs where steroid hormones are produced. N^2-dG and N^6-dA estrogen adducts have been identified, and translesion synthesis past them using a truncated human Pol κ has been examined. It was shown that translesion synthesis was efficient with a high incorporation of the correct nucleotide inserted opposite them.[475] Tamoxifen is used to treat breast cancer, but has been shown to cause liver cancer in rats. It forms adducts with N2 of dG, and the mutagenicity of the 4-hydroxytamoxifen adduct has been shown to lead to a high G-T transversion rate.[476]



85

Many other guanosine lesions have been investigated, the majority of which are those derived from polyaromatic hydrocarbons (PAHs), though adducts with smaller reactive species are also reported. Reaction with aldehydes, such as acrolein and crotonaldehyde leads to the formation of propano-dG adducts such as (86) and its α- and γ-hydroxy derivatives as well as ring-opened derivatives like (87). Derivatives (87) can further react with other nucleobases, particularly guanine, leading to crosslinking. The reaction with aldehydes is

accelerated by histones, and may therefore be linked to the mutagenic effects of these aldehydes.[477] The formation of a dG-dG crosslink with acrolein is accelerated when the ring-closed propano-dG is opposite dC, which causes the ring system to transiently open to the linear chain.[478,479] The α-hydroxy derivative of (86) acts as a strong block to DNA synthesis, and causes G-T transversions, whilst synthesis opposite the γ-hydroxy derivative was efficient and led to few mutagenic events.[480] The malondialdehyde adduct is also a strong block to synthesis by T7 RNA polymerase and mammalian RNA Pol II.[481] Propano-dG lesions derived from *trans*-4-hydroxynonenal have been shown to be repaired efficiently in human cell nuclear extracts by the nucleotide excision repair pathway.[482,483] They are destabilising in a DNA duplex, depending on the absolute stereochemistry of the adduct, and only one of the stereoisomers is able to form dG-dG crosslinks.[484]



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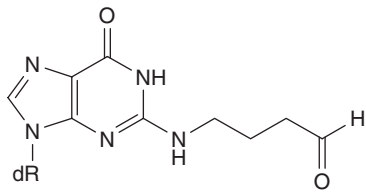
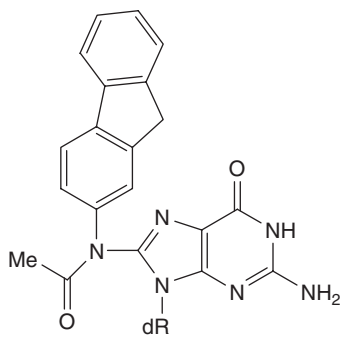


87

Translesion synthesis with DNA Pol ζ of the *N*-acetyl-2-aminofluorene adduct of guanosine (88) is inefficient with templates containing (88). In the presence of the Rev1 protein, translesion synthesis occurs and dCTP is the major nucleotide incorporated opposite it,[485] and studies with a mutant DNA Pol I gave similar results.[486] Benzo[a]pyrene is a potent environmental carcinogen, which when metabolised leads to *anti*-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (*anti*-BPDE). With dG, the major lesion is (+)-*trans*-*anti*-B[a]P-N^2-dG, (89), and is usually repaired by the nucleotide excision repair (NER) pathway. The translesion synthesis past (89) has been examined with a number of polymerases. With human RNA Pol II, (89) is a block to synthesis,[487] whilst DNA Pol κ preferentially incorporated the correct nucleotide.[488] In yeast cells, Pol ζ induced a large number of mutations involving Pol η, whilst Pol η alone contributed to 1-3 deletions or insertions.[489] The NER of (89) with UvrB proteins was also studied.[490]



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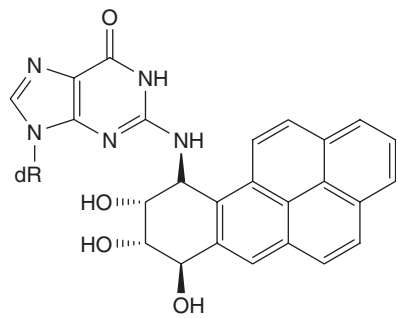
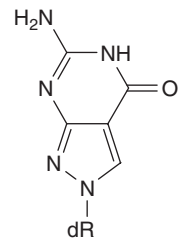


89

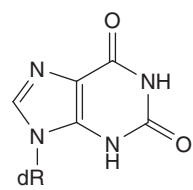
Deaza- and aza-analogues of guanosine have been examined primarily in hybridisation and primer extension studies. 1-Deaza-dG incorporated into ODN duplexes exhibited no preference for pairing with the natural nucleotides, and was more destabilising than a mismatch. In primer extension reactions it preferentially formed pairs with dC.[491] The importance of hydrogen bond recognition of the N3-nitrogen in guanosine was demonstrated by the incorporation of 3-deazaguanine into the hammerhead ribozyme. In most substitutions, catalytic activity was reduced except when a guanosine in the loop region was substituted when an increase in activity was observed.[492] The anti-HIV activity of quadruplexes containing 8-aza-3-deaza-dG demonstrated only moderate activity.[493]

A series of 7-alkynylamino-7-deaza-dG analogues was examined for their ability to stabilise DNA duplexes. As the length of the alkynyl chain increases, duplex stability decreases.[494,495] The incorporation of 7-deaza-8-aza-dG residues into guanine-rich sequences reduces the formation of guanine quartets due to the inability to form Hoogsteen base pairs.[496] The N^8-glycosylated 7-deaza-8-aza-dG derivative (90) forms stable base pairs with iso-dC in antiparallel duplexes and with dC in parallel duplexes, but does not form guanine quartet structures.[497]



90

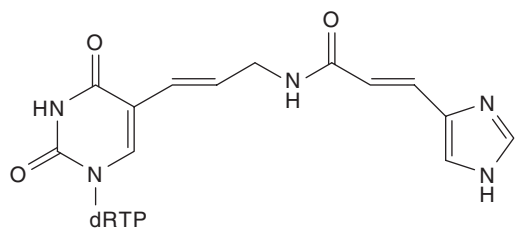
The deamination or action of nitric oxide on guanosine gives xanthine (X) (91), which is a mutagenic lesion. dX had been assumed to be an unstable lesion, but has been shown to be relatively stable when present in a duplex at pH 7,[498] though depurination occurs at pH < 4.[499] In a template, HIV-RT incorporated dCTP and dTTP opposite dX with equal efficiency, whilst Klenow fragment (exo-) preferentially incorporated dCTP.[499] 7-Deaza-dX has also been prepared and incorporated into ODNs.[500]



91

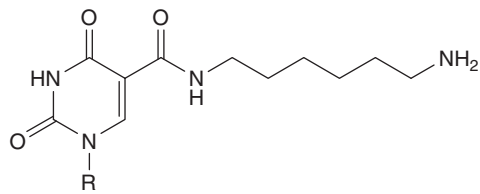
The following section deals with the pyrimidine analogues that have been reported during this review period. There are a number of positions at which pyrimidines can be modified, though C5 is the most common position. There are two reports of N3 dU-modified ODNs; the introduction of *N*-nitrothymidine into ODNs allows for the generation of various *N*3-thymine modified ODNs.[501] The base excision repair (BER) by *E.coli* GM31 extracts of etheno-dU and etheno-dC identified a new repair mechanism termed very-long patch BER that is dependent on DNA Pol I.[502] 4-Thiouridine has been used in RNA for photo-crosslinking to identify the active site of the VS ribozyme.[503] 4-Thiouridine has also been modified to incorporate a C5 spin label that was used to study RNA structure and dynamics.[504]

As the C5 position of dU is the easiest to modify, there are many new C5-substituted analogues. Analogues have been prepared for SELEX reactions. 5-Aminoallyl UTP and 5-aminoallyl-2′-fluoro-dUTP were both shown to be compatible with the enzymatic steps in SELEX.[505] dUTP and dCTP analogues bearing flexible and hydrophilic 7-amino-2,5-dioxaheptyl linker at C5 are also enzyme substrates.[506] The imidazole modified dUTP analogue (92) has been used with 3-(aminopropynyl)-7-deaza-dATP in SELEX reactions to evolve DNAzymes capable of cleaving RNA in the absence of divalent metal ions.[507]



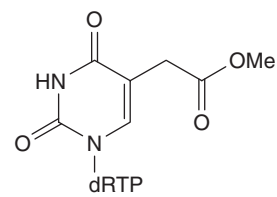
92

C5-Propynylated derivatives bearing terminal guanidinium groups have been prepared to examine duplex and triplex stability by introducing positive charges into the major groove.[508] The introduction of guanidinium groups stabilised both duplex and triplex structures, but there was little difference between the use of guanidinium and amino groups. Introducing C5-(3-aminopropyl) groups into duplexes induces bending into the helical structure, and this has been examined thermodynamically,[509] where the aminopropyl group induces a higher exposure of aromatic bases to the solvent. ODNs containing 5-(*N*-aminohexyl)carbamoyl dU derivatives (93) and (94) were prepared and the thermal and nuclease stability of duplexes containing them examined.[510] Duplexes containing the 2′-*O*-methyl analogue (94) gave higher duplex stability particularly towards RNA targets, and were also more resistant to SVPD.



93 R = 2'-deoxyribose
94 R = 2'-*O*-methylribose

5-(Methoxycarbonylmethyl)-dUTP (95) has been shown to be a good substrate for PCR, and, once incorporated, it can be reacted with a range of amine derivatives for post-synthetic modification.[511] The arabinoside derivative of (95) has also been incorporated into ODNs where it was post-synthetically modified,[512] and ODNs containing the arabinoside derivative induce RNase H cleavage as well as being more resistant to nuclease digestion. A cyanomethyl ester of (95) has also been used for post-synthesis modification by reaction with various amine nucleophiles.[513] 5-Carboxy-dU, a methyl oxidation product of thymidine, has been introduced into ODNs based on the hydrolysis of 5-trifluoromethyl-dU.[514] The mutagenic effect of the 5-formyl group has been examined. It was shown that it is sufficiently stable to allow for miscoding events to occur,[515] and the NER of ODNs containing it have been studied.[516] ODNs containing 5-formyl-dU are also able to form crosslinks to peptides by Schiff base formation.[517]



95

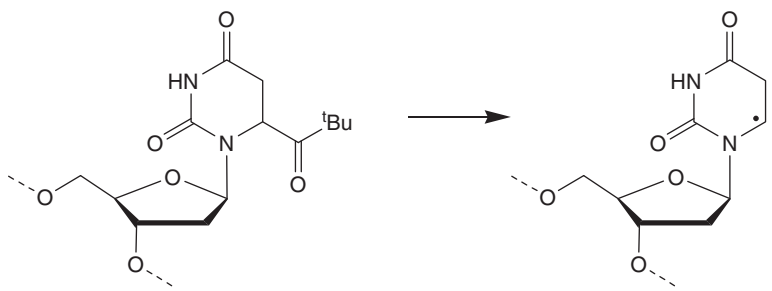
5-Hydroxymethyluracil (5 hmU) is another oxidative lesion, which is able to mispair with guanine. The excision repair of oligonucleotides containing 5 hmU has been examined.[518] 5 hmU is used in the synthesis of the naturally occurring glucopyranosylated nucleoside dJ, and improved synthetic yields have been reported.[519] Galactose-modified uridine oligonucleotides linked via a propynyl group have also been prepared.[520] In duplexes containing multiple substitutions it was shown that galactoside clusters were formed along the ODN.

A series of hapten-labelled (e.g., adamantane, dansyl) phosphoramidites has been prepared and incorporated into ODNs suitable for use in immunodetection assays.[521] EDTA has been conjugated to dU for the determination of protein binding by paramagnetic relaxation enhancement.[522] A spin label has

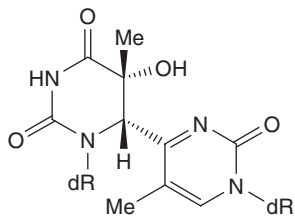
also been incorporated into TFOs for study by EPR spectroscopy.[523] A disulfide-protected thiol linker has been attached to C5 as its 5′-triphosphate, and its incorporation by several DNA polymerases reported.[524] A furan-linked phosphoramidite was used to prepare ODNs, which were then allowed to undergo Diels-Alder cycloaddition with fluorescent maleimides for the incorporation of fluorescent groups into DNA.[525]

5-Halo-dU derivatives have been used in DNA duplexes as they undergo photochemical crosslinking reactions. 5-Iodo-dU has been used in crosslinking reactions in Z-form DNA,[526] and 4-thio-5-bromo-dU has also been prepared and incorporated into ODNs where it was demonstrated that cells containing it became sensitive to UVA light.[527] The formation of a crosslink between Br-dC and dG has also been reported.[528] 5-Iodo pyrimidines as well as 7-iodotubercidin have been used for post-synthesis modification whilst on solid support for Pd-catalysed substitution by an alkynylated spin label.[529]

DNA damage caused by γ-radiolysis leads to the formation of lesions derived from the radical (97). The stable precursor (96), which leads to (97) on photolysis, has been introduced into ODNs and alkali-labile lesions generated on photolysis examined.[530] The BER of the thymidine oxidative damage lesion thymine glycol has been examined using chromatographically pure stereoisomers[531] opposite dA and as a mismatch with dG.[532] Two other thymidine-derived lesions are the thymidine dimer T(6-4)T (98) and *cis-syn* thymidine dimer (99), both of which are formed by photolysis. A C5 thiol-modified derivative of (98) has been prepared as its phosphoramidite and incorporated into ODNs for MALDI mass spectrometer studies.[533] The translesion synthesis past (98) by Pol η showed a high level of mutagenic bypass.[534] There are two reports of the *cis-syn* thymidine dimer phosphoramidite (99) and its incorporation into ODNs.[535,536] Translesion synthesis past the dimer by Pol η incorporated two adenylates,[536,537] though a further report states that there are higher error rates opposite the 3′-thymine than at the 5′-thymine.[538] The repair of thymine dimer (99) by DNA photylase[539] and an NMR study of DNA containing (99) with human replication protein A (RPA)[540] have also been described.

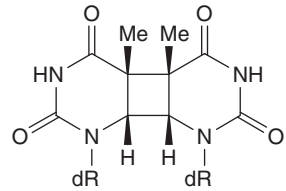


96 **97**



T(6-4)T

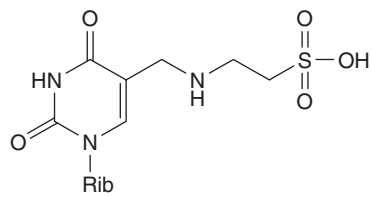
98



Cis-Syn thymine dimer

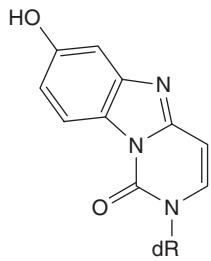
99

3-Methylpseudouridine ($m^3\psi$) has been synthesised and incorporated into RNA where it was found to be slightly destabilising compared to pseudouridine.[541] Psuedouridine can be selectively cyanoethylated with acrylonitrile, aiding its detection in tRNA by MALDI mass spectrometry.[542] The presence of pseudouridine in RNA has also been detected by NMR using chemical exchange spectroscopy as pseudouridine has an additional NH.[543] Another naturally occurring tRNA analogue found in mitochondrial tRNA is 5-taurinomethyluridine (100), as well as its 2-thio analogue.[544]



100

Few cytidine analogues are described. The *p*-benzoquinone adduct of dC gives rise to the etheno-derivative (101).[545] The introduction of a phosphate group to N^4 of dC causes destabilisation when in a DNA duplex.[546] Short duplexes have been prepared containing 1,3-N^4C-alkyl-N^4C interstrand linkages.[547] The introduction of the crosslink leads to more stable duplexes, and ethyl and butyl linkers causes helix bending. 2′-Deoxycytidine bearing C5-alkyne linked amino and thiol groups has been examined as 5′-triphosphates for incorporation by Vent (exo-) DNA polymerase.[548] The amino-modified analogue was found to be a suitable substrate, replacing dCTP in PCR reactions. The analogue (102) has been introduced into ODNs to probe DNA-protein interactions by forming crosslinks with target protein residues.[549] An N^4-modified-dC nucleoside bearing a *p*-azidotetrafluorobenzamide group has been incorporated into ODNs for photocrosslinking studies,[550] though the nature of the crosslink is unknown.



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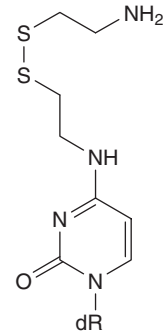
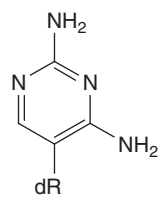


102

5-Aza-dC has been used to examine the role of methyltransferases,[551] where it was shown to be an inhibitor of *Hha*I DNA methyltransferase. Isonucleosides, e.g., isocytidine, can be used for new base-pair motifs. However, iso-dC is unstable to acidic conditions making ODN synthesis problematic. The substitution of iso-dC by 6-aza-iso-dC leads to more stable ODNs, though some duplex instability is introduced.[552] Various pyrimidine analogues, such as (103) and (104), have been used as substrates of modified HIV-RT polymerase in DNA containing non-standard base pairs with them.[553] Such new base pairs are of interest for expansion of the genetic code (see later).



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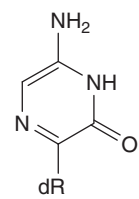
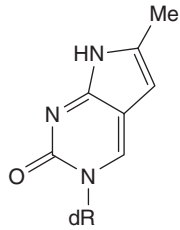


104

The bicyclic pyrrolo-dC (105) has been used as a fluorescent probe to study base-pair hybridisation in DNA/RNA duplexes and enzyme reactions using T7 RNA polymerase and HIV-RT.[554] The tricyclic G-clamp cytidine analogue[555] has been shown to endow ODNs with remarkably enhanced binding to RNA targets. The 2′-*O*-methyl analogue, (106), has been synthesised and shown that when in 2′-*O*-methyl oligonucleotides targeted towards TAR RNA there was significantly enhanced binding and a resultant marked decrease in *in vitro* transcription.[556,557]



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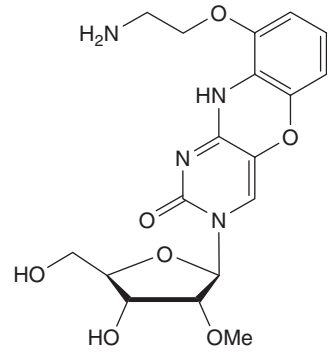
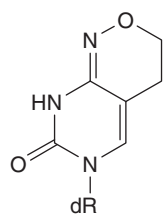


106

The analogue (107) has been previously described[558] and has been shown to behave as either a dC or a dU analogue as it exists as a mixture of amino and imino tautomers. The *N*1-methyl derivative was used to measure the tautomeric constant [imino:amino] that was found to be 11 : 1,[559] which correlates with the incorporation of the 5′-triphosphate of (107) by Klenow (exo-) DNA polymerase.[559,560] The 5′-triphosphate of (107) has also been used as a new method to sequence AT- and GC-rich sequences by introducing mutations into these intractable motifs.[561] The hydrazine derivative of (107, 108) has also been synthesised[562] and shown to exist as a dihydropyrimidopyridazine rather than as a pyrimidine, though biochemically it behaves as a thymidine analogue.[563] Pyrimidinones have been used in the third strand of TFOs as analogues for the recognition of CG pairs,[564–566] and as fluorescent probes in duplex DNA.[567]



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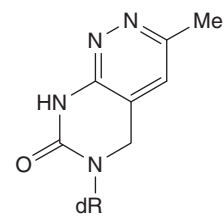
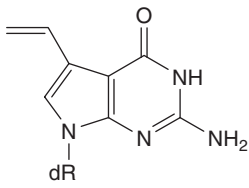


108

A variety of base analogues have been examined as new base pairs to expand the genetic code, including universal bases, aromatic analogues and abasic sites. Whilst certain analogues have been used to fulfil a specific task, most have been prepared primarily to see how they behave in oligonucleotides or to determine the range of an enzyme specificity, particularly of polymerases. The vinyl-dG derivative (109) has been incorporated into ODNs for post-synthetic modification to expand the functional diversity of DNA. Derivative (109) reacts with a maleimide through a Diels-Alder reaction, and can be used to introduce reporter groups, such as spin labels, fluorophores, biotin and active esters for further functionalisation.[568] The 6-vinyl-dG derivative (110) has been used in

TFOs where it has selectivity for recognition of dC of a G-C base pair.[569] The pteridine nucleoside 3-methyl isoxanthopterin (3-MI) is highly fluorescent and has been used as a probe for hybridisation. The probe is designed such that on hybridisation 3-MI forms a base-bulge whereupon fluorescence intensity increases.[570] The analogues (111), termed WNA, were designed with three parts, a benzene ring for stacking, a nucleobase for Hoogsteen base pairing and a bicyclo[3.3.0] skeleton to hold the structure in the correct conformation,. They were designed to form selective triplets in TFOs, including at TA or CG interruption sites.[571]



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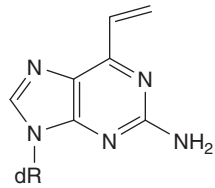

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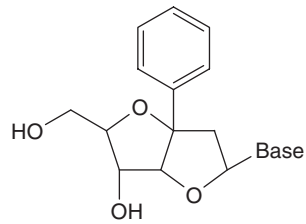
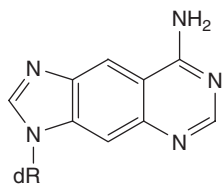


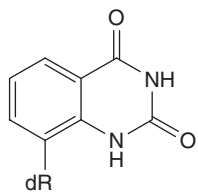
111

New genetic base pairing systems are of considerable interest, and potentially may be used to expand the genetic code for the ultimate purpose of introducing different amino acids into peptides/proteins. Ring-expanded nucleosides have been considered as a method to diversify genetic pairing. The ring expanded derivatives of dA, (112), and dT, (113), when incorporated separately into ODNs cause some destabilisation, but a 10-mer duplex comprised of only (112) and (113) showed considerable stability (55°C) compared to the natural AT duplex (21°C), probably due to enhanced stacking interactions. The duplex formed a right-handed helix, and was also highly fluorescent.[572]



dxA

112

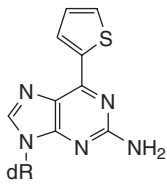


dxT

113

The groups of Hirao and Yokoyama have examined various new base pairs. Base-pairing partners for 6-thienylpurine nucleoside (114) have been examined. This does not form stable base pairs with thymidine as there is a steric clash between the thienyl group and the thymidine C4-oxo group, but specific base pairs are obtained with the pyridinone analogues (115). The 5′-triphosphates of the ribonucleoside derivatives (115) were incorporated specifically opposite (114) with T7 RNA polymerase.[573,574] In addition, (115, R=phenylethynyl) was shown to stabilise an internal loop of a theophylline-binding RNA aptamer.[574] Pyrrole-2-carbaldehyde derivatives (116) also form specific base pairs with the

imidazopyridine analogue (117). 5′-Triphosphate derivatives of (116) are specifically incorporated opposite (117) by Klenow fragment, (116, R=propynyl) being incorporated more efficiently.[575,576]



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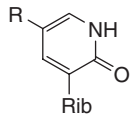

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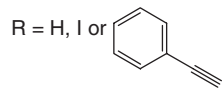
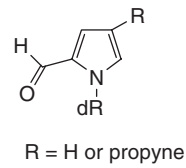
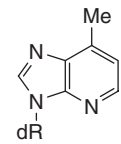


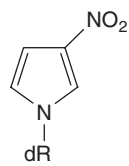


116



117

The previous class of analogues was defined as those that formed specific base pairing partners with nucleobases other than naturally occurring ones. Another class are those that are capable of forming base pairing partners with *each* of the naturally occurring nucleobases without discrimination, and are known as universal bases.[577] They are generally non-hydrogen bonding, planar aromatic analogues that primarily stabilise base pairs by stacking interactions. The first non-hydrogen-bonding analogue to be considered as a universal base was 3-nitropyrrole (118).[578] This has been used in sequence-specific oligonucleotide hybridisation (SSOH) probes to enhance mismatch discrimination to increase allelic differentiation.[579] The 5′-triphosphate of the ribosyl derivative of (118) was incorporated by polio-virus RNA polymerase opposite A and U only, and at a rate 100-fold lower than the structurally analogous ribavirin.[580] Acyclic nitroimidazole (119, *R*-isomer shown) and nitropyrazole (120) also behave as universal bases in duplex DNA and considering that they are acyclic derivatives, surprisingly high Tms were observed.[581] However, in TFOs each of these analogues is quite destabilising.



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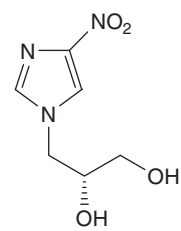
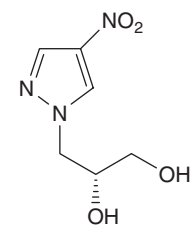


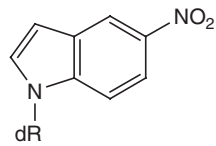
119



120

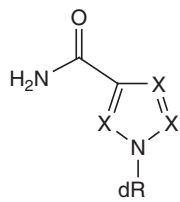
The 5-nitroindole (121), benzimidazole and 5-nitro- and 6-nitro-benzimidazole as their 5′-triphosphates are all incorporated opposite each of the natural nucleotides by DNA Pol α and Klenow fragment with efficiencies up to 4000-fold better than a natural mismatch.[582] Pol α preferentially incorporated each opposite pyrimidines, whilst Klenow preferentially incorporated them opposite purines. Both polymerases incorporated the triphosphates opposite an abasic site up to 140-fold more efficiently than dATP, whilst T4 DNA polymerase incorporated (121) 1000-fold more efficiently than dATP.[583] Incorporation of the 5′-triphosphate derivative of the related indole nucleoside opposite

an abasic site is 3600-fold reduced compared to (121).[584] Polymerases have been evolved to replicate oligonucleotides with very high specificity, and the introduction of modified nucleotides usually significantly reduces the polymerase efficiency and/or fidelity. Polymerase evolution has been used to identify novel enzymes with expanded substrate specificity. A polymerase engineered to extend 3′-mismatches was found to additionally amplify a range of modified nucleotides, including an abasic site, thymine dimer and (121).[585] 4-Nitroindazole derivatives glycosylated at N7 or N8 also behave as universal bases, though with lower Tms than (121).[586] Various fluorinated aromatic nucleobases also behave as universal bases, but will be dealt with separately.



121

Azole carboxamides were devised as analogues that could, in principle, behave as universal bases by presenting two alternative hydrogen-bonding faces, an inosine and an adenosine face. In practice, they exhibit more specific hydrogen-bonding preferences with, usually, two of the cognate bases. Ribavirin when incorporated as its 5′-triphosphate forms specific base pairs with the pyrimidines, though with reduced efficiency.[587] A series of five nitroazoles (122) was compared in both hybridisation studies and for polymerase recognition to determine their unique properties,[588] as was a set of imidazole-4-hydrazide derivatives.[589]

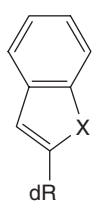


X = N or CH

122

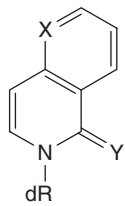
One of the notable features of these aromatic nucleobases is a preference for forming self-pairs. Romesberg *et al.* have prepared a range of analogues possessing minor groove hydrogen bond donor and acceptor sites to stabilise duplexes and as polymerase substrates. The benzofuran, benzothiophene, indole (123) and benzotriazole artificial bases all destabilised DNA duplexes, but when the analogue is self-paired, duplexes are significantly stabilised compared to the natural nucleosides.[590] Of these analogues, the benzothiophene analogue also behaved as a universal base. Klenow fragment was used to

extend a primer-template with an analogue self-pair at the 3′-end. Of the analogues described, only the benzotriazole self-pair was extended with any efficiency. Similar results were found for the analogues (124), and the best analogue was Y=S and X=N, with the highest Tm for a self-pair. It was also most efficiently extended from a 3′-self pair by Klenow fragment, and behaved as a universal base.[591] The analogues (125) and (126) were investigated in a similar manner, where again the self-pairing bases were the most stable.[592]



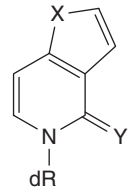
X = O, S or NH

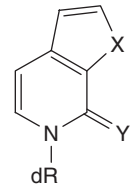
123



X = CH or N, Y = O or S

124

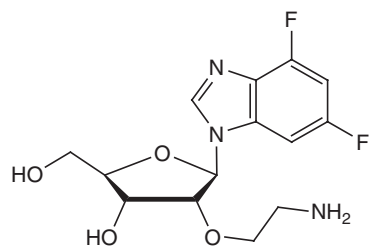




X = O or S, Y = O or S

125 **126**

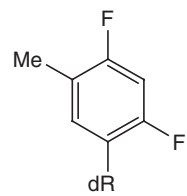
Fluorinated aromatic bases are widely used as artificial bases, and many behave as universal bases. The effect on duplex stability and polymerase recognition of fluorophenyl derivatives again demonstrated that self-pairs are more stable than those of the analogue with a cognate base, the best of which was 3-fluorobenzene.[593] Additionally, the stabilisation of a short duplex by a dangling fluorobenzene derivative as probes of electrostatic effects in DNA base stacking has been examined.[594,595] Dipole effects were shown to have a significant effect on DNA stabilisation due to base stacking as a result of dispersive induced-dipole attractions.[596,597] Various fluorinated phenyl and benzimidazole DNA analogues have been incorporated into RNA for structural investigations.[598] The fluorinated benzimidazole (127), incorporating a 2′-*O*-ethylamine group was found to be a universal base, and duplexes containing (127) were as stable as an unmodified duplex. Incorporation of (127) into the hammerhead ribozyme resulted in cleavage rates significantly higher than for the normal mismatch ribozyme.[599,600]



127

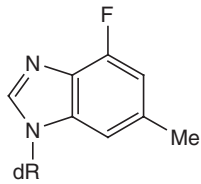
The final class of fluorinated artificial nucleobases are non-hydrogen-bonding isosteres of the natural bases, first described by Kool. The first such

analogue described was difluorotoluene (128), an isostere of thymidine. It was shown to have specific base pairing properties with adenosine, and the 5′-triphosphate of (128) was specifically incorporated opposite A by various polymerases. This led to the conclusion that base-pair recognition in oligonucleotides and enzymes does not require hydrogen bonding, but that the geometry of the base pair is important. The HIV-1 polypurine tract contains base pairs that deviate from the normal Watson-Crick base pairs. To investigate this, the non-hydrogen-bonding isosteres (128) and the cytosine isostere 2-fluoro-4-methylbenzene were incorporated into DNA and hybridised to polypurine tract containing RNA primers to disrupt the hydrogen bonded structure. Cleavage of these hybrids was examined with HIV-RT, where it was shown that cleavage still occurred but 3-4bp from the site of insertion.[601] A-tract containing duplexes exhibit curvature at the A-tract, and thymidines in an A-tract were substituted by the isostere (128) to determine the effect on the bend angle. The effect was variable, depending upon the position of the substitution, but the results support the view that A-tract bending arises as a result of localised electrostatic interactions.[602]



128

The effect of incorporating the non-hydrogen-bonding isosteres of thymidine (128) and adenosine, (117), in bacteria has been investigated. They were introduced into *E.coli* by insertion into a phage genome and transfected into bacteria. The two base mimics were bypassed with moderate efficiency in the cells and with very high efficiency under SOS induction conditions. Isostere (128) encoded genetic information in the bacteria as if it were thymine with high fidelity, whilst (117) directed incorporation of thymine opposite itself with high fidelity. Thus hydrogen bonding is not necessary for replication of a base pair *in vivo*.[603] The guanosine isostere (129) is shown to be more stabilising than the natural bases in a dangling end context, but is destabilising and non-selective when paired opposite itself. It forms a stable pair with (128) with stability approaching that of a GT mismatch.[604] The ethynylfluorobenzene derivative (130), an analogue of (128), has been shown to be more stable in DNA duplexes than (128).[605] A series of nonpolar adenine isosteres was examined to study the importance of hydrogen bonding functions in the repair of 8-oxo-dG by the *E.coli* repair enzymes Fpg and MutY. The absence of hydrogen bonding groups appeared to increase the rate of removal of analogue by the enzyme Fpg, but had a deleterious effect on repair by MutY.[606]



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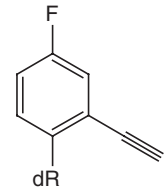
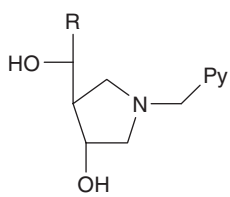


130

In addition to the fluorobenzene derivatives discussed above, a number of polycyclic aromatic nucleosides have been prepared to improve base stacking interactions. Perylene *C*-nucleoside was incorporated at either terminus of a DNA duplex where it stabilised the structure.[607] Binding studies of the methyltransferase M*Taq*I with duplexes in which pyrene, naphthyl, acenaphthyl or biphenyl *C*-nucleosides were opposite the M*Taq*I target adenosine showed enhanced binding compared to dA paired with any of the natural nucleosides, in particular, a 400-fold enhanced binding with pyrene *C*-nucleoside.[608] Uracil DNA glycosylase (UDG) is another enzyme that operates by first flipping a nucleobase out of the DNA duplex. The incorporation of pyrene *C*-nucleoside opposite the uracil in a DNA duplex increases the rate of recognition of the uracil by mutant UDGs, suggesting that the pyrene forces the uracil into an extrahelical position.[609] A similar outcome was observed for a DNA glycosylase engineered to site specifically remove cytosine bases in a duplex with pyrene *C*-nucleoside opposite to the target cytosine. The effect is to have a pre-flipped cytosine base that can then be recognised and excised by the modified glycosylase.[610]

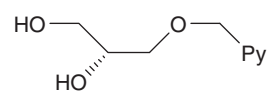
Two other pyrene nucleosides have been prepared attached to modified sugar residues. Pyrene attached to a pyrrolidine as modified sugar (131) was investigated as an intercalating agent where it was found to be slightly destabilising as a bulged nucleoside in DNA, but strongly destabilising with RNA. However, stabilisation was achieved when it was incorporated as a bulge in a three-way junction.[611] The acyclic pyrene derivative (132) aided stabilisation towards complementary DNA strands when present as a base bulge, and particularly when two residues are present. However, it is destabilising when partnered with RNA.[612] Two consecutive substitutions of (132) in a matched DNA duplex results in quenching of the excimer band at 480 nm, but in a mismatch environment the excimer band is present, and therefore can be used as a method to detect SNPs.[613]



R = H or CH_2OH

Py = pyrene

131

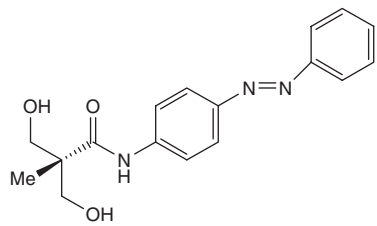


Py = pyrene

132

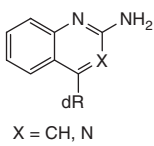
The 4-benzylmercaptophenyl *C*-nucleoside was designed such that when self-paired in a DNA duplex it could form a disulfide interstrand crosslink.[614] The presence of the crosslink considerably stabilised the duplex, but addition of a reducing agent led to duplex destabilisation. *N*-Methyl phenothiazine *C*-nucleoside was prepared as the terminal nucleoside in a DNA duplex, where it aided duplex stabilisation.[615] A free porphyrin *C*-nucleoside was substituted into DNA duplexes and was thermally and thermodynamically stabilising, particularly as a dangling nucleotide. Unlike other fluorophores, such as pyrene, porphyrin is not significantly affected by other nucleobases in ss- or dsDNA.[616]

A 2′-deoxyribosyl- and an acyclic phenanthridium artificial nucleoside were synthesised and incorporated into DNA duplexes as an intercalating agent to compare with the known DNA intercalator ethidium.[617] As expected the phenanthridium was shown to intercalate into DNA irrespective of the complementary nucleoside. Two diastereoisomers of a photoreactive *trans*-azobenzene derivative (133, *R* isomer shown) were incorporated into DNA via a diol linker. When in the *trans* conformation, the azobenzene intercalates into the duplex and stabilises it. However, irradiation at 300 nm caused the azobenzene to isomerise into the *cis* conformation, which destabilised the duplex. This was used as a "switching" mechanism to regulate transcription by T7 RNA polymerase by having (133) incorporated into the T7 primer.[618] Naphthyl Red is an azo dye, and has similarly been used as a visual probe for DNA hybridisation.[619]



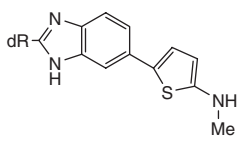
133

The analogues (134) were designed as nucleosides for TFOs to bind by Hoogsteen base pairing to an AT or CG pair respectively. The base pairing to the duplex is quite specific and they stabilise triplexes even at mixed purine/pyrimidine sequences.[620,621] A ureido isoquinoline homo-*N*-nucleoside was incorporated into TFOs to aid stabilisation of the third strand opposite each of the four base pairs, but was found to be destabilising.[622] The analogues (135) and (136) were also incorporated into TFOs targeted towards inverted AT duplex base pairs. Analogue (135) was found to be almost as stable as having a guanosine in the third strand,[623] whilst (136) was found to be very stabilising.[624,625] Other analogues were found to be destabilising.[626]

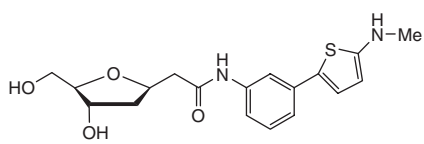


X = CH, N

134

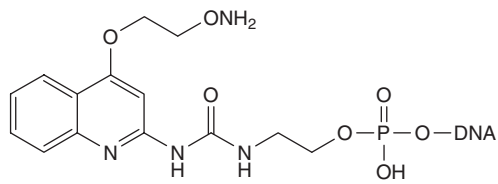


135



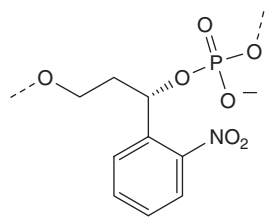
136

An acridine unit was incorporated either at the 5′-end or at internal sites of an ODN designed to affect cleavage of target RNA. The two phosphodiester linkages in front of the acridine are selectively cleaved in the presence of La(III).[627–629] Anthraquinone has been used in a TFO attached via a bis(hydroxymethyl)propionic acid linker and shown to facilitate triplex formation with pyrimidine-gapped polypurine sequences.[630] 8-Mer 2′-*O*-methylribonucleotides conjugated with the aminooxyethyl-2-(ethylureido)quinoline (137) bound to either complementary RNA or 2′-*O*-methyl RNA 9- or 10-mers with high binding affinity, whilst the absence of the conjugate (137) resulted in no duplex formation. The presence of the aminooxy group allowed for further conjugation with aldehydes or ketones and was used to attach short peptides via a terminal aldehyde group.[631] A variety of 5′-tethered stilbene derivatives were used to affect duplex stability. In a perfectly matched 5′-end the tethered stilbene derivatives significantly and selectively enhanced the melting temperature of the duplex.[632]

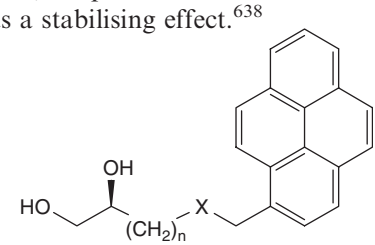


137

A three-carbon spacer group (C3) has the same framework as the backbone of a nucleoside, but does not contain a sugar or a base. The C3 spacer has been used to investigate the stability of tri- and tetra-loop hairpins in which there is a sheared GA base pair. The inclusion of the spacer at the various positions of the loop demonstrated that substitution at the first position of the loop (substituting the guanosine of the sheared pair) caused a large destabilisation supporting the presence of the sheared pair.[633] The *R* and *S* derivatives of a butane-1,3-diol spacer have been assayed in binding affinity studies, but it was found that there was no discrimination between the two isomers.[634] The photocleavable linker (138) has been incorporated into ODNs for allele-specific primer extension reactions and identification by MALDI-TOF mass spectroscopy after photocleavage.[635,636] A variety of different size linkers based on ethyleneglycol (e.g., TEG, HEG) have been shown to be destabilising when incorporated into a duplex.[637] However, the presence of an intercalating group such as (139) within a linker unit has a stabilising effect.[638]



138

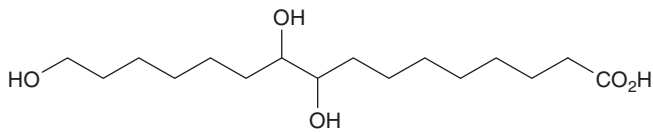


n = 1, 2
X = O, S

139

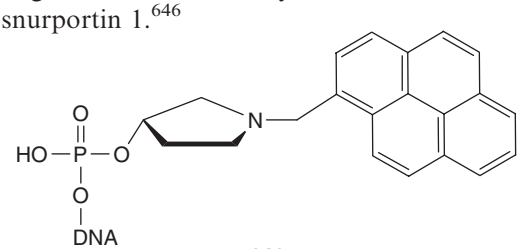
A series of 21 ODNs was prepared containing a core sequence comprising a CpG linkage, each ODN bearing a different modification to test for their immunostimulatory effect on murine macrophages. Many of the modifications failed to enhance immunostimulatory effects, but the presence of hexaethylene glycol linkers favouring nicked duplexes was found to enhance immunostimulatory effects.[639] Lesion bypass DNA polymerases of the Y superfamily are able to replicate across DNA containing C3 or C12 carbon spacers, even though it lacks all features of DNA. DNA Pol V is able to either completely bypass by ''hopping'' across the spacer or alternatively will insert one or two nucleotides opposite the bypass before synthesis continues on a nucleotide template beyond the spacer.[640]

Several methods for modifying the termini of oligonucleotides are described. Biotin phosphoramidites possessing exceptionally long and uncharged linkers are better polymerase substrates.[641] A biotinylated dUTP possessing a photocleavable linker has been prepared such that biotinylated DNA can be captured on streptavidin beads or surfaces, then cleaved by near UV irradiation.[642] A fluoride/amine-cleavable phosphoramidite designed for biotinylation, phosphorylation and affinity purification of oligonucleotides has also been reported.[643] A 5′-modifier prepared from aleuritic acid (140) attached to DNA via the terminal hydroxyl group during solid phase synthesis, followed by treatment with periodate, generates an aldehyde group which can then be reacted with amines and reduced.[644]

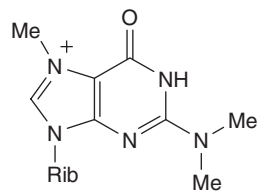


140

Duplexes are held together by a series of hydrogen bonds, but the termini are susceptible to ''breathing'' particularly if they are comprised of weak base pairs. The termini of duplexes have been stabilised by synthesising ODNs bearing 5′-amino groups (e.g., from 5′-amino-2′,5′-dideoxyadenosine) which can then be selectively acylated. A series of acyl end-caps have been examined and (*S*)-*N*-(pyren-1-ylmethyl)pyrrolidine-3-phosphate (141) was found to enhance the Tm of an 8-mer duplex by 11°C.[645] The synthesis of a 2,2,7-trimethylguanosine (142, TMG) capped DNA/RNA hybrid has been reported. The TMG-capped oligonucleotide is conveyed into the nucleus by the nuclear-transport protein snurportin 1.[646]

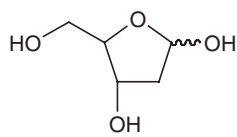


141



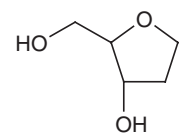
142

Abasic sites are a common lesion in oligonucleotides, and can arise for a number of reasons, such as depurination, γ-radiolysis and DNA damaging agents. There are four types of abasic sites that have been investigated, the most common abasic site, (143), often referred to as AP, and the chemically stable tetrahydrofuran abasic site analogous to (143), (144, or F). There are also oxidised abasic sites, namely the C1′-oxidised (145, L, or 2-deoxyribonolactone) and the C4′-oxidised abasic site caused by DNA damaging agents, (146, C4-AP). The difference between (143) and (144) abasic sites has been investigated *in vivo* for mutagenic response in yeast. Opposite (143), cytosine is most commonly incorporated, whilst for the stable abasic site (144) adenosine is most frequently incorporated.[647] The presence of the abasic site (144) in a DNA duplex opposite a natural DNA base has been detected using the naphthyridine (147) which in solution forms base pairs with the nucleoside opposite (144). Naphthyridine (147) forms particularly stable duplexes when there is a pyrimidine opposite (144).[648] The T4 DNA polymerase usually terminates replicative DNA synthesis at an abasic site, but deletion of the 3′-5′ exonuclease domain allows for translesion synthesis.[649]



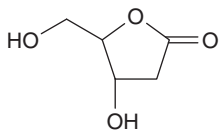
ap

143



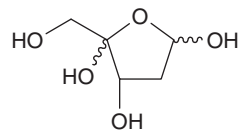
F

144



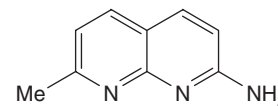
L

145



C4-AP

146



147

2′-Deoxyribonolactone lesions (145) are generated by DNA damaging agents and γ-radiolysis. To study (145) lesions in DNA, two modified nucleosides have been used which on photolysis generate the lesion. The incorporation of 5-iodo-dU in telomeric DNA quartets led to specific formation of the lesion (145) on photolysis at 302nm.[650] Similarly, irradiation at 360nm of DNA containing 7-nitroindole nucleosides led to (145) lesions.[651,652] Further studies with (145) lesions using the 7-nitroindole precursor in *E.coli* showed that (145) gave G → A mutations.[652] The SOS response in *E.coli* to plasmids containing (145) gave rise primarily to incorporation of dA and dG, the ratio of which depended on the sequence context of the lesion.[653] Lesion (145) may be further oxidised leading to strand cleavage and a terminal butenolide. The base excision repair of DNA containing (145) and the butenolide were studied by incorporation of a photolabile precursor (the uracil derivative of the analogue 164).[654]

The oxidised abasic site (146) was generated in ODNs by incorporation of 4′-azido-2′-dUTP. ssDNA containing 4′-azido-dU treated with uracil DNA glycosylase generates the lesion (146), and characterisation of DNA containing (146) has been carried out.[655] It has also been generated *in situ* by incorporation of a bis-*O*-veratryl modified nucleoside, which is then converted to (146) on photolysis.[656] The translesion synthesis of (146) by Klenow fragment demonstrated that, like the (145) lesion, dA and dG are principally incorporated opposite the C4′-oxidised lesion.[657]

2 Aptamers

Aptamers are single-stranded nucleic acid sequences isolated from random-sequence libraries by *in vitro* selection. The usual method of selection is SELEX (Systematic Evolution of Ligands by Exponential enrichment), and the method can be applied to DNA or RNA. There are essentially two types of aptamer, those that are designed for binding to a specific target, and those that bind and then carry out a pre-defined chemical reaction in a catalytic manner (known as deoxyribozymes or DNAzymes and ribozymes or RNAzymes). Each type of aptamer may also be allosteric or *trans*-acting, in that they require binding of a "co-factor" in order to either bind to their target sequence or to carry out their catalytic action. In the past few years, aptamer design has become an area of significant interest, and there are many reports concerning the selection and application of aptamers. In this review, DNA and RNA aptamers are discussed separately, but emphasis is made on aptamers designed using nucleoside analogues and on their applications. Little detail will be given for the selection of other aptamers.

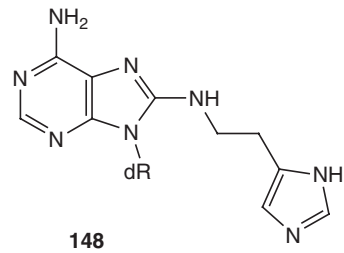
DNA-'binding' aptamers have been designed to bind to mRNA,[658] g-quadruplexes,[659] Tenascin-C, a protein found in the tumor matrix,[660] and to thrombin.[661] Aptamers have been selected as inhibitors of HIV-1 integrase,[662] human RNase H1,[663] human pro-urokinase[664] and for the design of molecular beacons.[665] An allosteric aptamer has been designed for binding as a colorimetric probe for cocaine.[666]

A greater number of aptamers with catalytic activity (DNAzymes) have been reported. Reactions include cleavage of RNA[667,668] including 2′-5′ linkages and L-RNA.[669] One DNAzyme designed for DNA cleavage was found to possess 2′-5′ RNA ligase activity.[670,671] Various other DNAzymes have been reported with ligase activity, ligating DNA,[672] RNA,[673] forming 2′-5′ linkages[674] and synthesising branched RNA.[675,676] Aptamers are often found to have a metal-dependence for functionality, and the metal-dependence of some DNAzymes is reported.[677–679]

Phosphorothioate-modified DNA aptamers have been selected for binding to NF-κB,[680–682] and phosphoramidate ODNs for binding to TAR to inhibit Tat-mediated transcription.[683] Deoxyribozymes that cleave RNA have been modified with 3′-3′ inverted linkages, phosphorothioate linkages, 2′*O*-methyl sugars and LNA in an attempt to enhance stability and cleavage activity.[684–687]

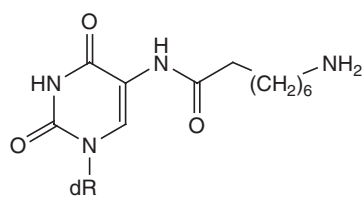
Aptamers incorporating 2′-fluoro-nucleoside from L-arabinose have also been selected that bind to neuropeptides.[688]

Various nucleobase modifications have been used to enhance functional groups available for catalytic aptamers, and imidazole has often been used as a general acid-base catalyst. Deoxyribozymes with RNA cleaving ability have been evolved in the presence of M^{2+} ions incorporating a C5-amino modified dT analogue and the imidazole-modified dA derivative (148). The aptamers showed activity in the presence of Pb(II) ions, and (148) is essential for activity.[689,690] The effects of incorporating a variety of nucleobase analogues into a Ca(II) dependent RNA-cleaving deoxyribozyme demonstrated that substitution of dC by C5-propynyl-dC in the catalytic site gave the highest increase in catalytic activity.[691] The effects of substituting a variety of purine nucleobase analogues into a thrombin-binding quadruplex aptamer have been examined by thermal denaturation experiments.[692] The attachment of spermine to the 5′-end of an RNA-cleaving ODN enhanced the cleavage reaction 40-fold compared to the unmodified ODN.[693]



148

Protein-nucleic acid cross-linking has been examined using a 5-bromo-dU-containing photoaptamer,[694] whilst a deoxyribozyme incorporating the thymine dimer (99) was evolved that was able to photo-repair the dimer in the presence of serotonin as a cofactor.[695] Aptamers have been modified by fluorescent dyes to study their mode of action. Fluorescent labelling was used to monitor switching from DNA-DNA duplex to DNA-target complexes[696] and the mode of action of a trifluorophore-labelled three-armed aptamer.[697] A hemin-binding aptamer has been hybridised to a gold surface-bound hemin in the presence of luminol which bioluminesces in the presence of hydrogen peroxide.[698] The amino-modified pyrimidine nucleoside (149) was used to develop cationic aptamers binding to sialyllactose. The strongest binding aptamer bound at 4.9 μM.[699]

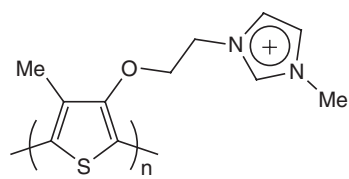


149

Previously, reports on aptamers have concentrated on evolution of structures for binding or catalytic activity. There are progressively more reports on methods for aptamer design and their applications. Murphy *et al.*[700] describe a method for evolution of aptamers used in enzyme-linked assays in the same manner as antibodies currently are. They offer the advantage of being easily reproduced and are more stable than antibodies. Evolution of aptamers by nonhomologous recombination (NRR) has been compared with SELEX and error-prone PCR.[701] NRR was shown to be able to generate aptamers binding to streptavidin with 15-20-fold higher binding than SELEX, and 27-46-fold better than error-prone PCR. *In vitro* selection of aptamers requires a separation of step-binding structures from non-binding ones. Capillary electrophoresis has been used to separate active from inactive aptamers as active sequences bind to a target and undergo a mobility shift allowing separation from unbound structures.[702]

Aptamers have been used for chiral HPLC separation. An aptamer binding to the D-enantiomer of arginine-vasopressin was immobilised on a solid support and the separation of D- and L-enantiomers of the target analysed under a variety of conditions. The L-enantiomer eluted in the void volume, whilst the D-enantiomer was strongly retained on the column.[703] Aptamers have also been applied to molecular-scale logic gates. Using three deoxyribozymes, a system that can add to single binary digits as measured by fluorescent output following cleavage reactions, has been described. The system uses two inputs and two outputs and is described as a half-adder.[704] A larger-scale system comprising 23 deoxyribozymes have been used to encode a version of the game tic-tac-toe.[705] It is claimed the system cannot be defeated because it implements a perfect strategy.

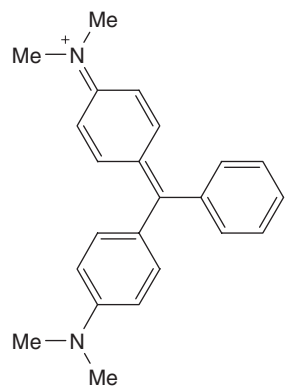
Aptamer-based technologies have also been used as sensors for a variety of applications. When an aptamer binds to its target it undergoes a conformational change, and this change may be detected using the cationic polythiophene (150). The resultant complex leads to the formation of a colorimetric signal, and has been used to detect human thrombin in the femtomole range.[706] FRET-labelled aptamers have been used to detect protein with aptamers binding to platelet-derived growth factor in the picomole range,[707] and lead-dependent aptamers for detecting Pb(II) in the nanomolar range.[708] A bis-pyrene labelled aptamer acted as a fluorescent detector for ATP in the millimolar range[709] whilst in a second report ATP detection in the micromolar range was detected using a 2′-amino-modified aptamer.[710]



150

Using a FRET-labelled DNAzyme that undergoes target-assisted self-cleavage a method for amplification-sensing has been reported. The probes undergo multiple-turnover upon binding to its target oligonucleotide sequence and fluorescence increase can be measured.[711] A further method of amplification uses circularised aptamers (deoxyribozymogens or pro-deoxyribozymes) which are inactive until linearised. When linearised they create a cascade in which the linear species accumulate, resulting in amplification of both function and selection.[712] Circular deoxyribozymes targeted towards β-lactamase mRNA have been cloned into bacteria where they were efficiently reproduced and exhibited high inhibition of β-lactamase and bacterial growth.[713] Bacterial cell division has also been inhibited by an aptamer binding to the cell division gene *fts*Z.[714]

A majority of RNA aptamers have been targeted towards protein binding. Aptamers have been selected that bind to human epidermal growth factor receptro-3 (HER3),[715] TATA-binding protein,[716] *E. coli* C5 protein,[717] peptide-acridine conjugates,[718] the antibacterial protein Colicin E3,[719] and the HIV-1 proteins RT[720] and TAR.[721] Aptamers designed against coagulation factor IXa have been shown to be effective anticoagulants,[722] and an allosteric aptamer targeted towards the repair enzyme formamidopyrimidine glycosylase (Fpg) could be regulated in the presence of neomycin.[723] RNA aptamers have also been selected for binding to nucleic acid, such as mutations in rRNA[724] and viral RNA.[725] Other binding aptamers are targeted towards small molecules, such as spectinomycin,[726] theophylline,[727] GTP[728,729] and the dye malachite green (151).[730,731]



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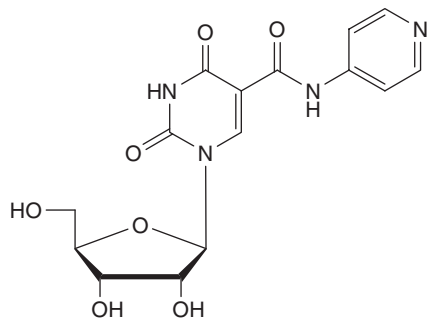
There are fewer catalytic ribozymes compared to deoxyribozymes. Examples include a *trans*-splicing ribozyme,[732] an alcohol dehydrogenase,[733] a ligase capable of functioning at low temperature,[734] a ribozyme that will ligate the 5′-terminus of RNA to a polypeptide,[735] a transcriptional activator[736] and a tRNA aminoacylation catalyst.[737] An RNA aptamer bearing 5′-CoA has been selected to catalyse thioester formation in the presence of biotin-AMP.[738] *In vitro* selection has also been used to identify allosteric hairpin ribozymes, activated in the presence of short oligonucleotides,[739] and a ribozyme that catalyses amide bond formation from a 2′-amino nucleotide.[740]

A few nucleoside analogues have been incorporated into RNA aptamers to provide additional functionality. The C5-modified uridine analogue (152) was incorporated randomly into RNA transcripts that were assayed for their ability to catalyse metal-metal bond formation.[741] After eight rounds of selection, aptamers were found that would mediate the growth of hexagonal palladium nanoparticles. Micrometer-sized particles were formed within minutes using 100 μM metal precursor and 1 μM ribozyme. The cationic 5-(3-aminopropyl)uridine was incorporated into a random RNA library to select an ATP-binding aptamer that operated under physiological conditions. The presence of the cationic analogue was shown to be essential for ATP binding as determined by mutagenesis studies.[742] 2′-Amino-modified RNA was used to select for a prion-protein specific aptamer.[743] In *in vitro* experiments, the presence of the aptamer demonstrated a marked reduction in the *de novo* synthesis of cellular prion protein within 16 hours.



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To test the hypothesis that early life could have been based on a simpler genetic system, ribozymes have been generated using only two nucleotides.[744] Using only diaminopurine and uracil ribonucleotides, a ribozyme capable of ligating two RNA molecules was evolved. The catalytic efficiency of the ribozyme was 36 000 fold faster than the uncatalysed reaction. Using RNA incorporating various anthracene dienes and maleimide dienophiles a Diels-Alderase ribozyme was developed. The ribozyme was further immobilised on an agarose matrix, and could be regenerated up to 40 times. Activity was only minimally reduced compared to the solution-phase ribozyme.[745]

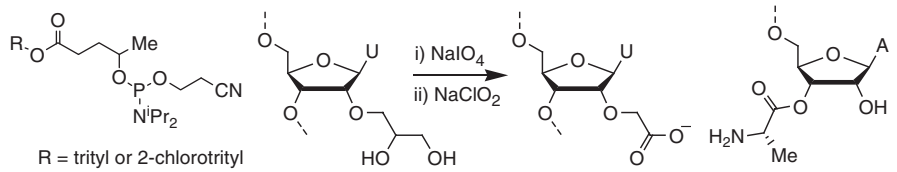
As with DNA aptamers, there is a trend towards applying RNA aptamers to a particular application. Allosteric ribozyme sensors have been developed which are specific for caffeine and aspartame.[746] Using a fluorescence-based assay, caffeine or aspartame may be detected in solution over a 0.5–5mM concentration range. Aptamers designed to malachite green (151) or other triphenylmethane dyes have been developed that enhance the fluorescence of the dye up to 2300-fold.[747] A further fluorescence-based assay has been

developed for the detection of microRNAs (miRNA). Hairpin ribozymes were selected that cleave short RNA substrates labelled with a 3′-fluorophore and a 5′-quencher. In the presence of miRNA the hairpin is cleaved and the resultant fluorescence activity may be measured in real-time.[748] Aptamers have also been used in *in vitro* applications. A *cis*-acting aptamer targeting the HCV NS3 proteases and HDV ribozyme-G9-II was shown to efficiently inhibit the protease,[749] and a method for the automated selection of aptamers binding to translated U1A protein has been described.[750]

3 Oligonucleotide Conjugates

There have been very many examples of chemical moieties being attached to oligonucleotides, and the purpose of these conjugates is just as varied. These range from the attachment of reporter groups to larger constructs, such as oligonucleotide-peptide conjugates. In this section the oligonucleotide conjugates are reviewed according to various specific applications. The first section deals with oligonucleotide-peptide conjugates, and then an exciting recent development is reviewed in which oligonucleotides are used as a template to direct various organic reactions. There are a number of examples of oligonucleotides that are conjugated to various metal ions, and a large number of references that deal with charge transport. Fluorescent labelling of oligonucleotides has been used in a number of applications including FRET and molecular beacons. Finally, there are a number of other miscellaneous conjugates that are dealt with as a group.

3.1 Oligonucleotide-Peptide Conjugates. – A number of developments for the synthesis of oligonucleotide-peptide conjugates have been reported. A method for condensing partially protected peptide fragments with oligonucleotides on a CPG support uses diisocyanatoalkane as linker between the fragments.[751,752] The novel phosphoramidite linker (153) and the *O*-2′-modified uridine (154) have been developed for solid phase synthesis of oligonucleotide conjugates;[753,754] peptide fragments are coupled to the linker through amide bond formation. Oligonucleotide-peptide conjugates are also synthesised using 2,2-dimethyl-3-hydroxypropionic acid as a linker via amide bond formation.[755] The uridine (154) may also be used to couple to hydroxylamino- and hydrazino-modified peptides through the intermediate 2′-*O*-aldehyde derivative.[756] Terminal linkers (5′- and 3′-) bearing *cis*-diols have been used, which after periodate oxidation leave aldehyde functions that react with hydroxylamine derivatives.[757,758] Miscellaneous other synthetic methods include synthesis on macroporous polystyrene,[759] a solution-phase synthesis in which oligonucleotide and peptide are linked through high molecular weight PEG,[760–762] and a method which uses conjugation of cysteine-modified oligonucleotides to the C-terminus of recombinant proteins.[763] 3′-Peptide conjugates have also been prepared by amide bond formation to the 2′-modified derivative (155).[764]



153 **154** **155**

Hybridisation properties of oligonucleotides are improved by conjugation to peptides. Short oligonucleotides conjugated to hydrophobic or cationic peptides improved duplex binding[765] whilst detection of hybridisation was observed by conjugation of oligonucleotides to the photoprotein aequorin.[766] Oligonucleotide-peptide conjugates are frequently used to aid cellular uptake. One report claims intracellular delivery has been improved by conjugation to signal peptides,[767] whilst another claims that conjugation to one or two NLS peptides had no effect on oligonucleotide uptake.[768] An antisense ODN targeted towards the 5′-non-coding region of HepC virus conjugated to recombinant *E.coli* RNase H was efficiently taken into cells where inhibition of HCV gene expression was observed.[769] Catalytically active oligonucleotide-peptide conjugates have been prepared targeted towards ssRNA where they induce RNase H activity.[770] tRNAs have been synthesised incorporating various unnatural acyl groups, which were added to a translation system where they were successfully incorporated into the new peptide chain.[771,772]

In addition to oligonucleotide-peptide conjugates, there are a few examples of PNA-peptide conjugates, which are easier to prepare as the two chemistries are compatible. A new chemistry using Fmoc and (1-(4,4-dimethyl-2,6-dioxacyclohexylidene)ethyl) (Dde) has been developed for the direct synthesis of PNA-peptide conjugates.[773] A native ligation method between a terminal cysteine peptide and a PNA thioester is reported which uses a cysteine-PEGA resin to capture excess peptide.[774] Like oligonucleotide-peptide conjugates, PNA-peptide conjugates are developed for antisense therapies. The conjugation of a cationic peptide derived from staphylococcal nuclease to a bisPNA resulted in enhanced strand invasion with the target DNA sequence.[775] The stable somatostatin-receptor octreotide has previously been used to internalise reagents for targeting tumor cells, and an octreotide-PNA conjugate has been reported for the delivery of PNA to target the *bcl*-2 gene.[776] BisPNAs have been tethered through variable amino acid linkers to target two DNA sequences. It was found that, provided the DNA sequences were of the same or longer length as the bisPNA sequences, efficient assembly occurred.[777]

3.2 DNA-Templated Organic Synthesis. – An exciting recent concept developed largely by Liu and co-workers is DNA-templated organic synthesis. DNA-templated synthesis generates products individually linked to ODNs that encode and direct their synthesis. DNA-templated synthesis is limited by the fact that DNA-linked reagents need to be prepared, reactions need to be

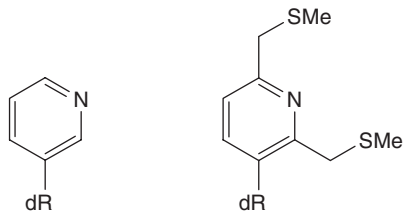
carried out in aqueous media, DNA-compatible chemistries are required and the scale of reactions and limitations for characterisation of products. Nevertheless, the range of reactions is increasing, and the methodology is ideal for the synthesis of large libraries. The range of suitable chemistries has expanded to include amine- and thiol-conjugate addition and nitro-Michael addition reactions,[778] synthesis of *N*-acyloxazolidines,[779] synthesis of PNA aldehydes,[780] assembly of metallosalen-DNA hairpin conjugates,[781] dimerization of hairpin polyamides[782] as well as multistep small molecule synthesis.[783] Stereoselective reactions have been performed,[784] as well as *in vitro* selections of small molecules with protein binding affinity.[785] DNA-templated reactions are mediated by particular architectures, and examples of such have been reported.[786] Diene- or dienophile-modified ODNs have been used for post-synthesis labelling or immobilisation.[787,788] PNA has also been used for DNA-templated synthesis to carry out metal catalysed DNA cleavage reactions.[789,790]

3.3 Oligonucleotide-Metal Conjugates. – There are a number of applications involving metal-oligonucleotide conjugates (see also section 1.3.1), the most common of which is attachment to a gold surface. The interactions of oligonucleotides on gold surfaces may be monitored by a number of physical methods, which makes Au-oligonucleotide interactions an attractive method of analysis. Scanning tunnelling microscopy has been widely used to study ssDNA,[791] dsDNA,[792] hybridisation,[793] mismatched duplexes[794] and to study the enzymatic formation of DNA nanoparticles.[795] X-ray photoelectron spectroscopy (XPS) and FTIR have been used to study ssDNA on gold surfaces,[796,797] whilst atomic force microscopy (AFM) has been used to study DNA nanoparticles[798] and surface plasmon resonance to examine Au-nanocrystals modified with PNA.[799]

More common methods of analysis are UV/visible spectroscopy, which have been used to study hybridisation,[800,801] triplexes[802] and nanoparticles.[803] Other methods include fluorescence to detect SNPs[804] and Raman to study dsDNA and DNA/RNA duplexes.[805] The detection of hybridisation has also been measured using a quartz crystal microbalance,[806] whilst a mixture of gold-DNA nanoparticles and DNA bound to magnetic particles, and magnetic particles with streptavidin-bound DNA via biotinylated DNA have been used to detect specific DNA sequences with very high sensitivity.[807,808] Oligonucleotide monolayers on gold surfaces have also been used as a method of nanolithography.[809,810] A number of methods of ultrasensitive electrical biosensing have been examined by attaching oligonucleotides either to quantum dots,[811–813] magnetic beads[814–816] or to electrodes,[817–820] including with PNA probes.[821]

Pyridine-based nucleobases have been used for silver(I) mediated base pairs. In one report[822] it was shown that the pyridine self-pair (156) was significantly destabilising in a duplex, but in the presence of Ag(I) only slightly destabilising compared to an AT pair. In a second report[823] the same pyridine self-pair was destabilising in the presence or absence of Ag(I), but the self-pair (157) was more stable than the corresponding CG duplex in the presence of Ag(I). A

bipyridyl nucleobase self-pair was shown to stabilise a DNA duplex, particularly with multiple consecutive substitutions, the self-pairs acting as a zip to stabilise the duplex.[824] However, the same bipyridyl self-pair was destabilising in the presence of metal ions (Mn(II), Cu(II), Zn(II) or Ni(II)).[825] A bipyridyl PNA analogue was found to be a selective binder to Ni(II).[826] Another self-pair derived from the hydroxypyridone nucleoside (158) is destabilising in the absence of metal ions compared to the corresponding AT duplex, but stabilising in the presence of Cu(II) ions.[827,828] Two azacrown ethers (159) and (160) have been incorporated into oligonucleotides as a method for delivering metal ions.[829–831]



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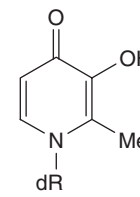

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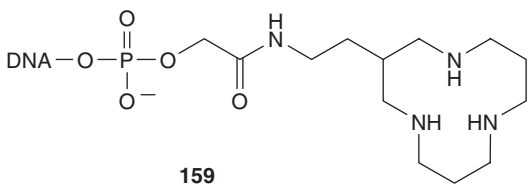

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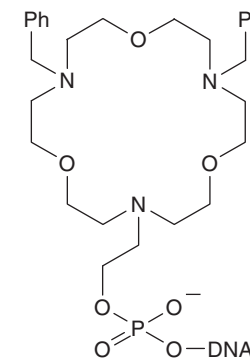

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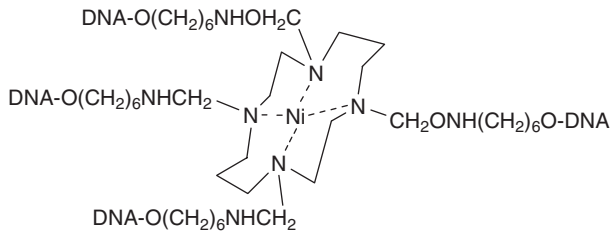
Two different terpyridine-modified dU nucleosides have been incorporated into a 2′-*O*-methyl modified oligonucleotide antisense to an RNA target.[832] In the presence of Cu(II) ions the terpyridine modified oligonucleotide cleaved the target RNA in a site-specific manner. Copper(I)-adenylates have also been shown to cleave DNA,[833] and a europium complex conjugated at the end of a uniformly modified 2′-*O*-methoxyethyl oligonucleotide cleaved an RNA target in a site-specific manner.[834]

Ruthenium has been incorporated into ODNs, via an oxime conjugate,[835] or through an amide linker.[836] In the latter case, the ruthenium conjugate was used to photo-crosslink with a G residue on a complementary strand. Ruthenium and osmium have been incorporated into ODNs via a C5-phenanthroline dU amidite[837] to study photoinduced energy transfer, and metallocarboranes have been used as redox labels by attachment to O4 of dT.[838] Ferrocene has

similarly been used as a redox label for electrochemical detection by cyclic voltametry,[839] incorporated as a C5-modified dUTP analogue,[840,841] as a C5-modified phosphoramidite,[842] as a 5′-modifier[843] and as a tag via a 3′-thiol linkage.[844]

Metal ions have also been used to assist hybridisation. Using two 9-mer ODNs, which bind to adjacent sites on a complementary target, one with a 3′-imidoacetic acid terminus, the other with a 5′-amino modified terminus,[845] in the presence of Gd(III), significantly stronger binding of the two 9-mers to the target was observed compared to no metal ions. Similar results were observed with terpyridine-modified short ODNs in the presence of Zn(II).[846] The multi-arm metal-centred cyclam (161) has been used to prepare supramolecular DNA structures.[847] The structure is stabilised in the presence of Ni(II).



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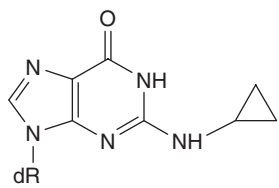
The final class of metal-oligonucleotide conjugates are those involving platinum. Platinum has been introduced into ODNs via a 2-(2-aminoethylamino)ethanol-phosphoramidite followed by complexation with Pt(II).[848] Site-specific platination has also been carried out during DNA synthesis.[849] *Cis*-platin is widely used for the treatment of various cancers, and its mode of action is widely understood. *Cis*-platin is involved in intrastrand crosslinking, primarily between two guanosine residues, but also between G and A. It has been shown that GG crosslinks causes DNA bending and unwinding independent of flanking bases.[850] When crosslinks are present in nucleosomes, the nucleosome significantly inhibits nucleoside excision repair.[851] It has been shown that a highly conserved non-histone DNA-binding protein (HMGB1) and YB-1, a multifunctional protein, bind to *cis*-platin-modified DNA.[852–854] The proteins that interact with *cis*-platin-modified DNA have been probed using a photoreactive *cis*-platin analogue.[855] The effect of Mn(II) on the replication of *cis*-platin-modified DNA by the herpes simplex virus type-1 DNA polymerase has also been investigated.[856]

The crosslinking of purines in human telomere sequences by *cis*- and *trans*-platin reagents have been examined[857] and it was suggested that crosslinking of telomere sequences could be used to inhibit telomerase. Crosslinking by *trans*-platin reagents has been studied with RNA oligomers[858] and it was suggested that this might be a method of trapping naturally occurring RNA tertiary structures. *Trans*-platination has also been used to generate novel quartet structures.[859] Crosslinking of DNA and PNA has been demonstrated with

trans-Pt(II) PNA derivatives.[860] The translesion synthesis by DNA polymerases β and μ past *cis*-, *trans*- and oxaliplatin adducts has also been examined.[861,862]

3.4 Charge Transport. – As guanine has the lowest ionisation potential, one electron oxidation of DNA leads to a guanine radical cation ($G^{\cdot+}$), which then migrates along the DNA duplex via hopping steps. The guanine radical cation can be detected using pulse radiolysis.[863] There have been two principal areas in which electron transport in DNA has been studied, the use of base analogues and the charge donor/acceptor. A number of base analogues have been explored in electron transport where they can act as radical traps. The oxidation of 8-oxo-dG has been used to probe the interaction of MutY, the enzyme that repairs 8-oxo-G:A mismatches.[864,865] Charge transfer to 8-oxo-dG has also been used to probe the effects of C5 cytidine substituents,[866] where the direction of transfer may be controlled by the introduction of C5 methyl or bromo groups. By using 8-bromo-dG, electron transport through B- and Z-DNA was studied,[867] where it was shown that the reactivity of 8-Br-dG is greater in Z- than in B-DNA. 8-Methyl-dG and 8-methoxy-dG have also been used to study electron transfer to a 5-bromo-dU residue in both B- and Z-DNA.[868] Again, transport was more efficient in Z-DNA.

A number of adenine analogues have also been used to study charge transfer. 2-Aminopurine (2-AP) is widely used as a fluorescent analogue, and it has been shown that, in its photoexcited state, it initiates hole transfer through duplex DNA.[869] In this case the guanosine analogue (162) was used as a radical trap, but N6-cyclopropyl-dA may also be used.[870] Photoexcited 2-AP has also been used to study the efficiency of charge transfer in terms of direction and near-neighbour base coupling,[871] and the role of temperature.[872] 2-Amino-7-deazaadenine (163) has also been shown to be an efficient radical trap during electron transfer.[873]



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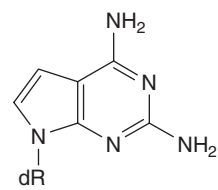

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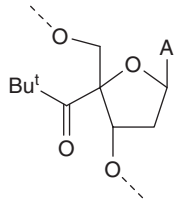
The redox potential of adenosine lies between that of thymidine and guanosine, and electron transfer to adenosine does occur. The adenosine derivative (164) has been used as the radical that is formed results in strand cleavage.[874,875] The purine analogue 4-methylindole, which has a lower redox potential than dG, has been shown to be particularly effective in studying charge transfer because the 4-methylindole radical cation has a strong absorption at 600 nm. It has therefore been monitored by transient absorption and by EPR.[876,877] The dA analogue (165) has lower oxidation potential than dA and a wider stacking area, but is not decomposed during charge transport, and has been used as a DNA wire, as it is more stable to oxidative damage.[878]



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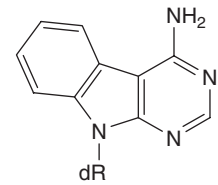

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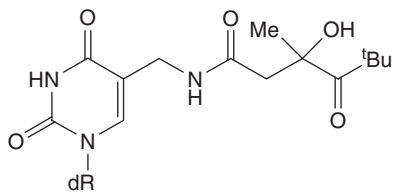
2′-Deoxyuridine analogues have also been studied in electron transfer, though usually as electron donor or acceptor. The dU analogue (166) acts as a radical donor upon photolysis.[879] Excess electron transfer occurs on photolysis of duplexes containing 5-Br-dU which are internally conjugated to an aromatic amine.[880,881] The effect of helical order in charge transport has been examined using duplexes containing the LNA-T.[882] Here it was shown that charge transfer was more efficient in duplexes containing the LNA-T derivative with complementary RNA whilst with complementary DNA, where there is helical perturbation, then charge transfer efficiency is reduced. Excess electron transfer has also been studied using a flavin-capped hairpin with a thymine dimer that acts as the electron acceptor,[883–885] including in DNA:PNA duplexes.[886]



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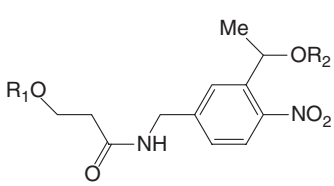
A number of modifications have been introduced into duplexes as charge donors. A C5 pyrene-modified dU[887–889] and a 2′-*N* pyrene-modified dU[890,891] have both been used as photochemical electron donors, as has the ethidium derivative phenanthridinium,[892] which acts as an artificial base as well as charge donor. The mechanism of charge hopping has been studied using anthraquinone,[893–897] (including the effect of mismatches[898]) naphthaldiimide (NDI),[899–901] stilbene dicarboxamide[902–906] and flavin.[907,908] Electron transfer through DNA with ferrocene at either 5′- or 3′-terminus showed little difference in the rate of transfer.[909] The incorporation of a ruthenium-phenanthrene crosslinking agent at the end of a duplex was used to demonstrate that the yield of crosslinking is higher when there are guanosine residues close to the 3′-end of the complementary strand.[910]

Electron transfer has primarily been studied with DNA duplexes, but there are higher order structures that have been examined. Triplexes have been studied[911,912] where it was shown that transfer to the third strand occurs. In quadruplex structures more damage occurs at the external tetrads, and quadruplex guanines are more effective traps than when in a duplex.[913] Charge transfer has also been examined with three-way[914] and four-way junctions.[915] DNA bound to electrode surfaces has been used to study the electrochemical

reduction of methylene blue to probe base pair stacking in different DNA conformations. Both A- (as a DNA/RNA duplex) and B-form DNA support efficient charge transport as measured by methylene blue reduction, but Z-form DNA supports charge transport much less efficiently.[916] Electron transfer has also been studied in PNA oligonucleotides.[917]

3.5 Fluorescence. – There have been many publications regarding the use of fluorescently-labelled nucleotides and oligonucleotides. The major use is to be able to detect an oligonucleotide, and a fluorescent label has many advantages. There are more specific applications that will also be covered which include fluorescence resonance energy transfer (FRET), molecular beacons (including TaqMan probes) and the emerging area of single molecule detection. Finally, there are some applications applied to nano-devices.

Many different fluorophores have been incorporated into oligonucleotides, covering applications such as sequencing, fluorescence detection and FRET dyes. Several sets of dideoxynucleoside triphosphates have been reported for sequencing applications[918–924] and FRET.[925] A photocleavable linker for attachment of dyes to oligonucleotides has been reported.[926,927] The linker (167) may be incorporated as a 5′-triphosphate (R2 is attachment to C5 of dUTP via a linker) or to the 5′-end of an oligonucleotide (R2 is attachment via phosphate). UV irradiation at 340 nm cleaves the linker, and releases the dye. A method for introducing the fluorophore (168) onto an oligonucleotide using a synthetic cofactor for DNA methyltransferases has been examined.[928] The fluorophore is ''alkylated'' onto the N6-amino group of adenines according to the specificity of the methyltransferase.



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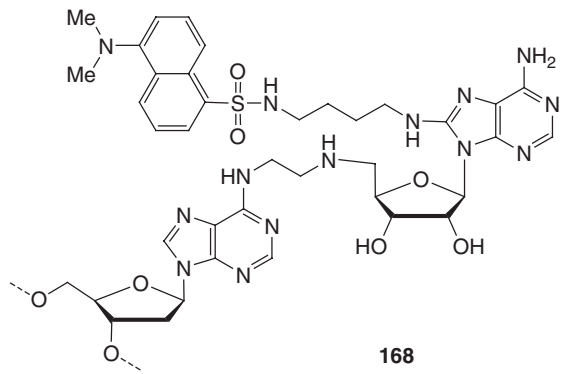
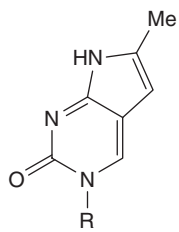


168

A number of reports describe the use of pyrene as a fluorophore, and there are methods for attaching fluorophores to nucleosides. It has been attached to C5 of pyrimidines,[929–931] C8 of purines,[931] N3 of thymidine,[932] at the O2′ position of the sugar,[933] as a *C*-nucleoside[933,934] and has been incorporated as a phosphoramidite without being attached to a nucleoside.[935,936] Pyrene has also been attached via an azido group to the 5′-end of an oligonucleotide using a Staudinger ligation reaction.[937] A number of other dyes have been attached directly to nucleosides for incorporation into oligonucleotides. Burgess *et al.*

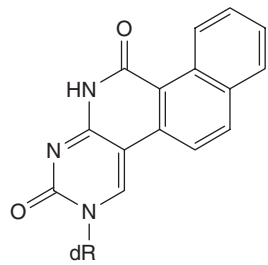
examined dyes that are π-conjugated to the nucleobase.[938,939] Coumarin has been attached via a linker to C5 of dU,[940] and fluorescein has been attached to the amino groups of nucleosides via carbamoyl linkers.[941] Nile Red, a benzophenoxazine dye, has been attached to oligonucleotides via a 2′-carbamate linkage[942] where the dye fluorescence is quenched in oligonucleotide conjugates. DABCYL has also been attached to the 3′- or 5′-OH groups of dT.[943]

Another class of analogues are those which are inherently fluorescent due to their extended ring structure, and which retain hydrogen-bonding group capability. These analogues are useful for detection of change in the microenvironment of DNA. Examples of such analogues are pyrrolo-dC (169)[944] and a series of analogues from the group of Saito *et al* which include benzopyridopyrimidine,[945] naphthopyridopyrimidine (170)[946] and the purine derivatives methoxybenzodeaza-inosine (171) and adenosine.[947]



R = dR or ribose

169



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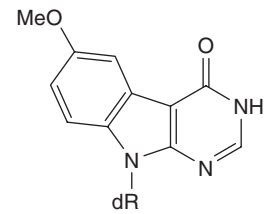


171

Other dyes include Methyl Red, as a phosphoramidite, for incorporation into ODNs, where it was used to generate aggregates when multiple consecutive residues are incorporated into ssDNA.[619,948] A benzotriazole azo dye has been used for immobilisation of oligonucleotides onto metal surfaces[949] and the coenzyme flavin has been used as a fluorophore and for electron exchange in ODNs.[950] A probe termed MagiProbe has been designed which incorporates a fluorophore and an intercalator that on hybridisation emits enhanced fluorescence.[951] Water soluble phthalocyanine dyes have been used which are suitable for conjugation to 5′-amino-modified oligonucleotides[952] and phthalocyanine-conjugated oligonucleotides have been used to aid duplex and triplex stabilisation.[953]

Finally, there have been reports that deal with other forms of spectral detection. A platinum (II)-coproporphyrin reagent has been evaluated for phosphorescent labelling of oligonucleotides.[954] The presence of the label had little effect on conjugation, and labelled primers were effective in PCR reactions. A silicon nanoparticle conjugated to ODNs acted as a luminescent label,[955] and a molecular beacon (see later) has been prepared which contains a photoluminescent dye ($Ru(II)(bpy)_3$) and the luminescent quencher Black Hole Quencher-2™.[956]

Although there are some specific applications of fluorescent analogues (FRET, molecular beacons, single-molecule detection described below) there are many reports that use fluorescence as a means of detection and monitoring

of biomolecules. One of the most widely used analogues in this area is 2-aminopurine (2-AP), which emits fluorescence when excited between 310–320 nm and is most often used to replace adenine where there is little perturbation caused by the substitution. Its fluorescent properties within oligonucleotides have been further examined[957] and fluorescence is strongly influenced by an electron transfer quenching process from guanine and 7-deazaguanine.[958]

2-AP has been used to examine conformational changes in telomeric sequences,[959] in AT sequences[960–962] and to monitor conformational changes during nucleotide incorporation by Klenow fragment[963] and by DNA Pol β by monitoring fluorescence of 2-AP in conjunction with tryptophan fluorescence.[964] Fluorescently-labelled dNTPs have similarly been used to monitor nucleotide incorporation by Klenow fragment.[965] 2-AP is an effective analogue to monitor methyltransferase reactions where its environment is disturbed by base flipping.[966,967] It has been used to monitor changes in rRNA binding to antibiotics,[968] to monitor the formation of an intramolecular triplex[969] and probing of RNA-protein interactions.[970]

Another common fluorophore is fluorescein, which has been used to monitor siRNA expression in cells,[971] to visualise hybridisation on the surface of a liposome,[972] interaction of UvrB protein with damaged DNA[973] and as a sensor on 3-way junctions.[974] A method for colorimetric gene detection involves using the aggregation of ODNs immobilized onto organic nanospheres impregnated with fluorescent dyes. Addition of complementary ssDNA causes the spheres to produce aggregates by cross-linked networking. The colours of the aggregates, which depend on the added fluorophore, were observed using an ordinary fluorescence microscope. FRET between the particles also provided information about point mutations on added DNA.[975]

The effect of temperature on fluorescence has been studied,[976] as has the effect of salt concentration[977] and water-soluble conjugated polymers.[978] A method for the quantification of ssDNA:dsDNA is described,[979] as well as kinetics of mismatch hybridization[980] and the kinetics of collision in short ss-nucleic acids.[981] Fluorescence quenching of Cy-5 labelled oligonucleotides by poly(phenylene ethynylene) particles has been shown to be a more sensitive method than excitation of the Cy-5 fluorophore.[982] An ultrasensitive method for the detection of DNA uses highly fluorescent conjugated nanoparticles, and detection limits below 1fM were achieved.[983] DNA transport through a carbon nanotube has also been observed using fluorescence microscopy.[984]

Fluorescence resonance energy transfer (FRET) involves the non-radiative transfer of energy from a fluorophore in an excited state to a nearby acceptor fluorophore. FRET has proven to be a useful tool for measuring distances of 10–100 Å, and for monitoring conformational changes as a consequence of oligonucleotide- or protein-induced bending. A series of dye-conjugated pyrimidine nucleosides with differing linkers between the nucleoside and dye were evaluated for FRET.[985,986] Whilst no conclusions were drawn as to the nature of the linker, it was noted that N4-dC-modified nucleosides did not perform as well as C5-dU analogues. Multi-step FRET has been reported between eosin (donor), TexasRed (acceptor) and tetramethylrhodamine

(mediator),[987] and has been used for high-throughput screening of small molecule inhibitors of a ribosome assembly.[988]

FRET has found many applications including measuring distances between species,[989] measuring DNA bending on binding to proteins,[990,991] actions of enzymes such as helicase unwinding,[992,993] RNA degradation,[994] catalytic folding of a ribozyme,[995] monitoring hybridisation,[282,996–998] PNA hybridisation,[999] quadruplexes,[1000,1001] interactions with proteins,[1002] and the interactions of FRET dyes with other intercalated agents.[1003]

Molecular beacons (MB) are stem-loop hairpin oligonucleotide structures that have a fluorescent dye at one end and a fluorescence quencher at the other. In the hairpin state, the quencher and fluorophore are in close proximity and therefore there is no fluorescence from the probe. However, when the MB binds to a complementary oligonucleotide as a duplex then the fluorophore and quencher are separated and the fluorophore can emit fluorescence. They are particularly useful in monitoring reactions with time, e.g., in PCR,[1004] rolling circle amplification,[1005] hybridisation,[1006–1008] telomerase activity,[1009] ligation reactions[1010] and DNA-photolyase activity.[1011] MBs may be used attached to solid supports, e.g., gold surfaces,[1012] and have been used to deliver drugs (biotin) by a photocleavage reaction when the MB is in a duplex form.[1013] They have been used *in vitro* to detect delivery of peptides into cells[1014] and nuclear mRNA export.[1015,1016] A number of fluorophores and quenchers that have specific use in MBs, TaqMan probes and Scorpion primers have been examined.[1017–1023]

With the advent of the confocal fluorescence microscope it became possible to detect single molecules containing fluorophores, allowing the monitoring of individual events. There are now a growing number of studies of biochemical reactions on a single molecule level using fluorescently labelled reagents or by FRET. Using a single-molecule manipulation procedure, the real-time decatenation of two mechanically braided DNA molecules by *Drosophila melanogaster* topoisomerase (Topo) II and *E.coli* Topo IV were monitored.[1024,1025] The equilibrium folding of the catalytic domain of *Bacillus subtilis* RNase P RNA has been investigated by single-molecule FRET. Histogram analysis of the Mg(II)-dependent single-molecule FRET efficiency revealed two previously undetermined folding intermediates.[1026] Using single-molecule FRET, an in-depth characterisation of the transition-state of a model two-state folding reaction of the hairpin ribozyme, where two RNA helical domains dock to make specific tertiary contacts, was studied.[1027,1028]

Single-molecule FRET has been used to study the kinetics of unfolding of the human telomeric intramolecular G-quadruplex,[1029,1030] the DNA-binding orientation of an *E.coli* REP monomer to a ss/ds DNA junction,[1031] four-way junctions[1032] and to study pre-mRNA splicing[1033] and gene expression.[1034] The synthesis and study of multicolor quenched autoligating (QUAL) probes for identification and discrimination of closely related RNA and DNA sequences in solution and in bacteria has been reported. A dabsyl quencher doubles as an activator in the oligonucleotide-joining reaction. The ODNs remain dark until they bind at adjacent sites, and fluoresce on nucleophilic displacement of the

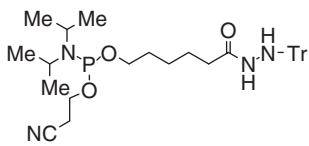
dabsyl quencher.[1035,1036] Many areas of biomedical research depend on the analysis of uncommon variations in individual genes or transcripts. A method has been developed that can quantify such variation. Each DNA molecule in a collection is conjugated to a single magnetic particle to which many copies of DNA, identical in sequence to the original are bound. This population of beads corresponds to a one-to-one representation of the starting DNA molecules. Counting fluorescently labelled particles via flow cytometry can then assess variation within the population.[1037]

As a step towards single-molecule sequencing there have been attempts to prepare DNA that is fluorescently labelled at every nucleobase. A total of 30 different dNTPs labelled with various reporter groups (fluorescent or non-fluorescent) were evaluated in the synthesis of labelled DNA. Using Vent (exo-) DNA polymerase a 300bp product was prepared using dNTPs fully labelled with biotin.[1038,1039] Another group has demonstrated that DNA fully labelled with tetramethylrhodamine and rhodamine-green could be digested using *E.coli* Exonuclease III.[1040] Naturally occurring DNA polymerases do not readily accept dye-terminators, and mutant polymerases are being developed that will accept them more readily.[1041] In another report,[1042] several different propynyl modified (C5 for pyrimidines, C7-deaza-C7-propynylated for purines) were assessed for their ability to be used in PCR, both as 5′-triphosphates and in a template. A set of four such modified nucleosides was found to be effective, but synthesis of fully modified DNA using these analogues was unsuccessful.

Nanotechnology has become an area of intense research, and oligonucleotides have various roles in this developing field. A number of nanodevices have been reported (see section 3.6) and there are reports concerned with monitoring of such devices. A molecular thermometer based on the change in π-stacks on converting from B- to Z-DNA has been described where the equilibrium between the Z- and B-conformations can be controlled by temperature. At low temperature the proportion of the Z-conformation is high due to lower entropy. An increase in temperature increases the proportion of the B-conformation. 2-AP was incorporated into the duplex and the fluorescence intensity was reported to be a measure of temperature.[1043] A novel molecular machine based on a four-stranded DNA structure called the i-motif, is formed from sequences containing series of cytosine residues. Protonated C forms a non-canonical base pair with an unprotonated C ($C:C^+$), and this structure can interconvert to form a quadruplex that is stable under slightly acidic conditions. Using FRET, in the i-motif form, the fluorophore and quencher are in close proximity, and there is no fluorescence. At high pH, the i-motif collapses, and the oligonucleotide can be captured by a complementary strand as a duplex whereupon the fluorophore fluoresces.[1044]

Fluorescent-labelled oligonucleotides have been applied to the development of photonic logic gates,[1045] which may have application in molecular computation. A machine which undergoes extension-contraction motion is described, which is monitored by FRET, between a duplex and a quadruplex structure.[1046] The motion is driven by the addition of single-stranded oligonucleotide that causes the quadruplex to collapse and leads to a duplex structure.

3.6 Miscellaneous Conjugates. – A number of new conjugation chemistries have been described for the synthesis of oligonucleotide-peptide conjugates (section 3.1) and surprisingly few for other oligonucleotide conjugates. The phosphoramidites (172) and (173) have been developed for enhanced attachment of oligonucleotides to surfaces.[1047] 5′- and 3′-amino-modified TFOs bearing the alkylating agent (174) has been used as gene therapy agents targeting HER-2 expression.[1048] On binding to its target sequence the mustard alkylated target N7-residues of guanine.



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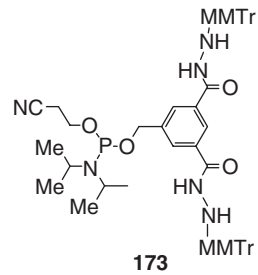

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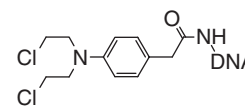
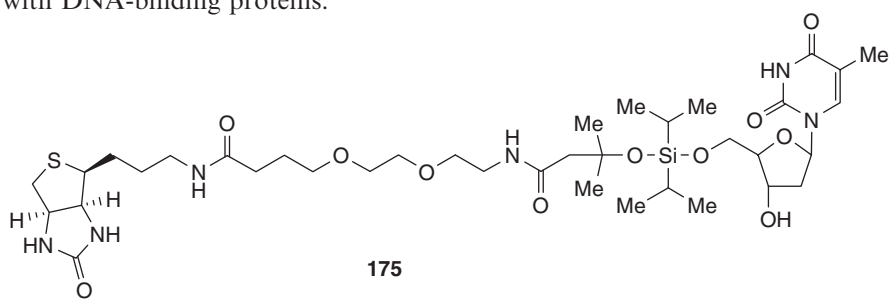


174

Biotin is a common reagent for labelling oligonucleotides, and a new amidite (175) has been prepared for biotinylated oligonucleotides, but the biotin group may be removed by fluoride treatment.[1049] Biotinylated ddNTPs have been used for single base extension for multiplex genotyping by mass spectroscopy.[1050] The binding of biotin to streptavidin has also been used for the self-assembly of DNA-templated protein arrays,[1051] and solid-support-bound biotinylated oligonucleotides have been used to detect motion and interactions with DNA-binding proteins.[1052]

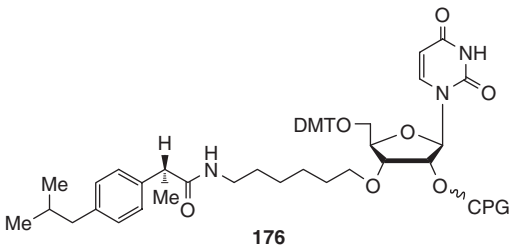


175

Oligonucleotides have been used as a platform for generating carbohydrate clusters. Various carbohydrates were attached to aminoalkylated oligonucleotide quadruplex structures to afford DNA-assisted tetrasaccharide cluster motifs.[1053] Similar clusters have been used as a delivery system for oligonucleotides into cells for antisense therapy.[1054] Oligonucleotides have been modified at both termini by glucose residues also for antisense delivery, though only hybridisation data are supplied.[1055] A phosphoramidite for the introduction of a 5′-*N*-acetyl glucosamine unit onto oligonucleotides is reported as a substrate for glycosyl transferase enzymes.[1056]

Various drugs have been conjugated to oligonucleotides to target the drug to a specific site. The ibuprofen modified nucleoside (176) has been incorporated into ODNs to aid binding to human serum albumin,[1057] whilst the DNA

cleaving agents camptothecin and bleomycin have been conjugated to ODNs to direct cleavage to a specific RNA sequence.[1058,1059] The DNA-binding agent daunomycin has been conjugated to DNA in an attempt to aid stabilisation of triplexes by intercalation,[1060] and distamycin-based peptides have been used to aid stabilisation of DNA in a DNA duplex at A/T rich sequences.[1061] A reagent for ^{18}F-labelling of oligonucleotides for use in radiopharmaceuticals has been described.[1062] The reagent is introduced as a bromoacetamide derivative that reacts with a terminal phosphorothioate to yield (177). The synthesis of the labelled ODN, including preparation of the ^{18}F-reagent, was carried out in less than three hours. The conjugation of minor groove binders to TFO oligonucleotides gave rise to much more stable triplex structures.[1063,1064]



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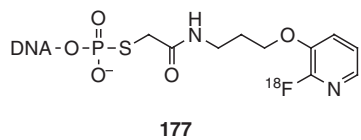

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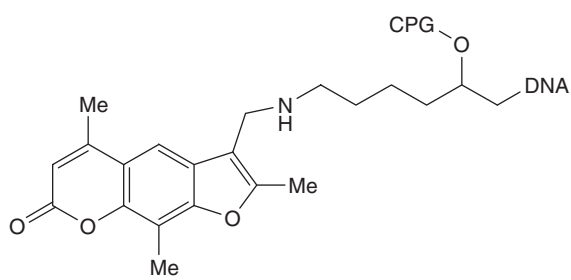
Conjugates containing stilbene diether linkages form the most stable DNA hairpin structures reported to date. Hairpins with as few as two A-T base pairs or four non-canonical G-C base pairs are stable with stilbene linkages.[1065] Similar results were found when pyrene is used in the loop of the hairpin structure.[1066] Stilbene diether and related analogues have also been used to construct linear and branched conjugated nanostructures, modified stilbene units being used to introduce further strands of oligonucleotides.[1067] Aromatic residues have been conjugated to oligonucleotides to aid duplex stability using phenanthrene[1068,1069] and triplex stability using benzopyridoindoles[1070] and benzoquinoquinoxaline conjugates.[1071] Oligonucleotides that contain multiple (non-consecutive) substitutions of perylene are able to fold into structured species in which the perylene units pair by hydrophobic effects or π-conjugation.[1072] Various aromatic and aliphatic linkers have been used to bind two oligonucleotides into a hairpin structure; the aromatic units gave rise to particularly stable hairpin structures.[1073] Oligonucleotides conjugated to psoralen via various length linkers, e.g., (178), were tested for their ability to form triplex-directed psoralen photoproducts with the Sickle cell β-globin gene.[1074–1076]



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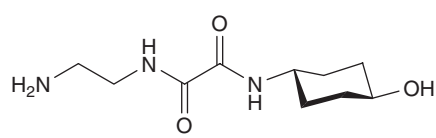
Oligonucleotides have frequently been used in the construction of nanodevices where they are used as a means of detection, as electrical 'wires' or as a scaffold (see also section on nanodevices in section 3.5). A real-time DNA detection method using ssDNA-modified nanoparticles and micropatterned chemoresponsive diffraction gratings has been reported that allows hybridisation detection of 40-900 femtomoles of surface-bound DNA.[1077] Carbon nanotubes are widely used for the construction of nanodevices, and DNA-functionalised carbon surfaces and nanotubes have been reported as platforms for electrochemical detection of hybridisation.[1078,1079] PNA-modified carbon nanotubes have similarly been used for the detection of hybridisation with DNA.[1080] DNA conjugated to carbon and other solid surfaces may additionally be used as molecular wires,[1081–1084] and carbon-modified nanotubes have been developed that act as a field-effect transistor.[1085]

Oligonucleotides may be deposited onto solid surfaces in defined patterns, and this has been utilised to use oligonucleotide conjugates for a variety of applications. A widely used application is lithography that takes advantage of the fact that DNA interacts with various metals, and various new lithographic methods have been reported.[1086–1089] A method for templated replication of DNA nanoscaffolds has also been developed.[1090,1091]

Oligonucleotides have been conjugated to various polymeric reagents, for example polyethylene glycol (PEG)[1092] and poly(*N*-isopropylacrylamide)[1093] as a method for delivery of antisense reagents. Polyethylene glycol (PEG) is often used as a linking agent in oligonucleotides. It has been used to link an oligonucleotide and biotin to observe motion of the oligonucleotide through the α-HL transmembrane pore[1094] and as a linker between two oligonucleotides.[1095] A series of spacer/linker phosphoramidites derived from, e.g., (179), have been prepared using methoxyoxalamido (MOX) chemistry, with linker length of up to 56 atoms.[1096,1097] Dendrimers have been used as a method for generating self-assembled structures,[1098,1099] as has nylon.[1100]



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4 Nucleic Acid Structures

As in previous years, there is a growing number of nucleic acid structures reported. Advances in X-ray and NMR methodologies means that more complex structures are now being studied. However, in addition to these more traditional methods of structure analysis there are also other techniques emerging, and these are discussed at the end of this section.

There has been a number of complex crystal structures reported that are beyond the scope of this review, but are included for completeness. RNA

structures include ribosomal RNA,[1101–1107] tRNA,[1108–1111] ribozymes,[1112,1113] siRNA,[1114–1116] the *trp* RNA-binding attenuation protein (TRAP) bound to RNA containing UAG triplets,[1117] the Rho transcription terminator bound to mRNA,[1118] a zinc-finger-RNA complex[1119] and NF-κB bound to an RNA aptamer.[1120] DNA structures are more diverse, and include glia cell missing (GCM) domain bound to DNA,[1121] endonuclease-DNA covalent intermediate,[1122,1123] nucleosome DNA,[1124,1125] transcription factors bound to DNA,[1126–1129] *myc* protein bound to DNA,[1130] telomeric DNA[1131] and TraR bound to DNA.[1132] A number of crystal structures of DNA and RNA polymerases or repair enzymes have been reported. For RNA polymerases there are structures for T7 RNA polymerase,[1133–1135] RNA polymerase II,[1136,1137] reovirus polymerase λ3[1138] and for HIV-1 RT.[1139–1141] There are also structures for DNA polymerases[1142–1146] and DNA repair enzymes.[1147–1150]

A crystal structure of the duplex r(GUAUACA) which forms six base pairs and 3′-dangling adenosine ends was determined at 2.0 Å where it was shown that the structure forms two types of duplex. The first duplex stacks to form a pseudo-continuous column typical of RNA, whilst the second duplex is in an A-DNA conformation with its termini in abutting interactions.[1151] A study of the binding of 13 different metal ions to the HIV-1 RNA dimerisation initiation site showed that divalent metal ions bind almost exclusively at Hoogsteen sites of guanine residues. Cobalt hexamine was unable to displace magnesium hexahydrate, raising questions about the use of cobalt hexamine as a magnesium mimetic.[1152] The 1.25 Å structure of the ribosomal frameshifting RNA pseudoknot from beet western yellow virus uses both H-π and lone-pair-π interactions between water and functionally important unstacked residues.[1153,1154]

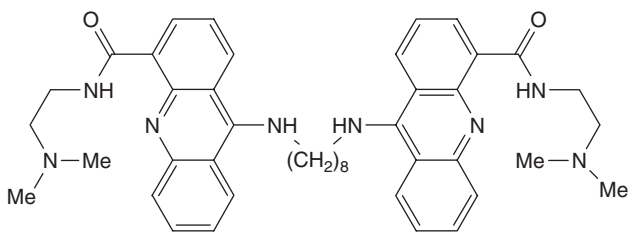
Retroviral conversion of ssRNA to dsDNA requires priming for each strand, and the viral polypurine tract (PPT) is the primer for one of these strands. A crystal structure of a 10-mer RNA from the PPT sequence bound to DNA shows a region similar to domain swapping in proteins, denoted as base-pair swapping, involving a highly mobile CA step. All sugars are C2′-*endo* except one, which is C3′-*endo* as in B-DNA, and this A→B conversion affects the pattern of hydrogen bonding interactions.[1155,1156] The mechanism by which the adenine DNA glycosylase MutY repairs 8-oxo-dG mispairs has been investigated by the determination of a crystal structure of MutY with a DNA duplex containing an 8-oxo-dG:dA base pair. It interacts with the strand containing the adenine residue, which is completely extruded from the DNA helix and is inserted into an extrahelical pocket in the catalytic domain. MutY directly contacts the backbone of the complementary 8-oxo-dG-containing strand, and bends the DNA substrate 55°, which is localized to the lesion.[1157]

An aptamer that site-specifically cleaves RNA in the presence of Pb(II) has been determined at 1.8 Å using Sr(II), which mimics binding of Pb(II) but not cleavage. Binding of Sr(II) induces local structural changes that align the catalytic 2′-hydroxyl group with the scissile bond for cleavage.[1158] An RNA aptamer for binding the antibiotic streptomycin has been solved at 2.9 Å. The structure shows that streptomycin is encapsulated by a stacked array of bases from two asymmetric internal loops.[1159]

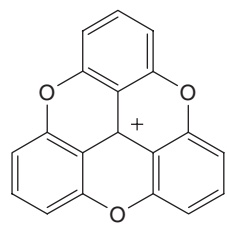
Of the DNA crystal structures, only three duplexes have been reported with the majority of structures involving higher order structures or analogues. The structure of the self-complementary duplex d(CATGGGCCCATG) shows a conformation between A- and B-DNA, with different hydration patterns for the GC and AT pairs providing the basis for the A → B-form transition.[1160] A DNA duplex region of the HIV-1 polypurine tract has been solved which contains three separate A-tract regions, with each A-tract region showing marked similarities.[1161] The sequence d(GCGAAAGCT) forms a mini hairpin in solution, but the X-ray crystal structure showed a short parallel-stranded duplex with homo base pairs between the CGAA residues, with the remainder of the residues splitting away in separate directions.[1162]

The sequence d(GCGAGAGC) has been determined at differing salt concentrations. At low potassium concentrations it forms a G-quartet structure between two duplexes, but at higher potassium concentrations it exists as a duplex.[1163] The sequence $d(TGGGGT)_4$ forms thymine tetrads that are stabilised by either Na^+ or Tl^+ ions.[1164] The sequence d(GCATGCT) also exists as a quadruplex structure through G-C intrastrand hydrogen bonding.[1165] Two DNA four-way junctions are reported in which the distortion of the junctions perturbs the conformational features of the duplex regions, and hydration pattern consequences are discussed.[1166] A 1.7 Å structure of the excisionase (Xis) protein from the bacteriophage λ with its DNA-binding site has been reported.[1167]

A number of DNA crystal structures involving intercalating reagents have been reported. The bis-acridine derivative (180) has been reported to be a intercalating threading agent by solution studies, but in the duplex d(CGTACG) it undergoes terminal base exchange with a cytosine residue to yield a guanine quadruplex intercalation site.[1168] In the G-quadruplex structure d(GGGGTTTTGGGG) a single modified acridine residue also binds at the end of a G-quartet within a thymine loop.[1169] However, an acridine-tetraarginine intercalator stacks within an AA/TT step rather than a CG/CG step in the duplex sequence d(CGCGAATTCGCG).[1170] The trioxatriangulenium ion ($TOTA^+$, 181) intercalates in GC base pairs in DNA duplexes, and can be used to inject a radical cation into DNA. The structure of the duplex d(CGATCG) with bound TOTA reveals considerable distortion of the DNA at the intercalation site, and orientation of (181) is sensitive to hydrogen bonding interactions with the phosphate backbone.[1171]



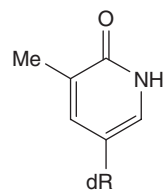
180



181

Various DNA-drug interactions have been examined by crystallography. The structure of actinomycin D binding to its GpC site revealed that it binds preferentially when there is a T:T mismatch flanking the GpC site.[1172] The structure of a DNA hexamer duplex with a disaccharide anthracycline antibiotic showed two different binding modes giving rise to two duplex structures. In one, the disaccharide lies in the minor groove, whereas in the other it protrudes out of the helix.[1173] The binding of the anticancer drug chromomycin A3 shows a marked preference for binding at GGCC sites in the presence of Mg(II) ions.[1174] The anticancer drug daunomycin interacts with telomeric DNA, and a crystal structure has been reported which shows daunomycin binding to telomeric G-quartets in parallel stranded DNA.[1175]

The remaining DNA crystal structures involve base or sugar analogues. The replacement of a thymine base by the C-nucleobase (182) demonstrated that the analogue was able to effectively base pair with adenine, but the spine of hydration was destabilised compared to a normal AT base pair.[1176] Two crystal structures involving the *cis-syn*-thymine dimer (99) are reported. A duplex structure incorporating (99) is bent towards the major groove with a slight unwinding of the helix. At the lesion site there is considerable distortion from the usual B-form DNA.[1177] The second structure involves DNA containing (99) within the active site of a DNA polymerase (Pol η). The 3′-thymine forms normal Watson-Crick base pairs with the incoming ddATP, but the 5′-thymine forms Hoogsteen base pairs with ddATP in a *syn* conformation.[1178]

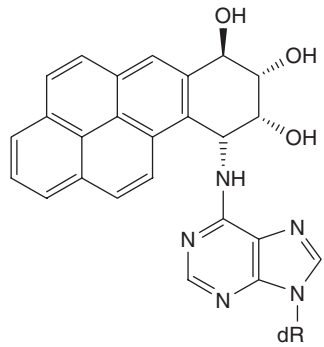


182

The Dickerson dodecamer in which an internal dC is replaced by the adduct N^4-etheno-dC opposed to dG has been reported.[1179] Minor perturbations are found local to the lesion, but the structure shows very similar features to that found for a T:G wobble pair. The structure of a duplex containing the 2′-dC analogue of (106) bearing a guanidinium group in place of the amino group has been solved and shows additional hydrogen bonds to O6 and N7 of guanosine.[1180]

A 3.1 Å crystal structure of human topoisomerase I in complex with DNA containing 8-oxo-dG at the +1 position in the scissile strand shows the enzyme active site to be rearranged into an inactive conformation.[1181] A primer-template duplex in complex with the lesion-bypass polymerase Dpo4 is studied in which there is a benzo[a]pyrene diol epoxide adduct of dA (183) base paired with thymidine in the enzyme active site. Two conformations of the adduct are observed, one in which it is intercalated between base pairs, and the other in

which it is solvent exposed, appears to be a more favourable conformation for lesion bypass.[1182] A benzo[a]pyrene adduct with dG in a duplex showed that the dG does not base pair with either the adduct or other nucleobases.[1183] A DNA hairpin containing a stilbene diether linkage forming the hairpin loop has been determined at 1.5 Å, and shows two structures in the crystal unit.[1184] One shows a planar stilbene unit stacking on the adjacent G-C base pair. In the other the stilbene is rotated to give edge-to-face orientation of the stilbene and the base pair.



183

A duplex containing the 2′-*O*-modified guanidinium nucleoside (42) has been studied by crystallography and shown that the guanidinium group forms hydrogen bonds with the phosphate group of the adjacent 3′-nucleotide.[269] Crystal structures have been solved for DNA duplexes containing one[1185] or two[1186] TNA nucleoside (67) derivatives. With one TNA analogue it was found that there was very little disruption of the normal B-form DNA helix. With two TNA substitutions it was found that the intranucleotide phosphorus-phosphorus distance was shorter than in B-form DNA, and was more like that found in RNA, which may explain why TNA base pairs with RNA better than DNA.

There is one crystal structure involving PNA.[1187] A PNA decamer with its complementary DNA has been solved at 1.66 Å, and the heteroduplex adopts a P-helix conformation. The conformational rigidity and the presence of chiral centres limit PNA from adopting other conformations.

There is a larger number of solution structures reported. The self-complementary RNA duplex r(GGCAAGCCU) has been examined to determine the effect of A:A mismatch within the duplex. The duplex has sheared A_{anti}:A_{anti} base pairs, in which only the exocyclic amino group of one of the pair is involved in hydrogen bonding. Replacement of the other amino group by hydrogen stabilises the base pair.[1188,1189] The structure of a branched oligonucleotide has been studied where the solution structure was determined using ^{13}C-isotopically-labelled nucleotides.[1190]

A number of stem-loop structures have been examined. The *Bacillus subtilis* T-box antiterminator RNA containing a UUCG stem-loop,[1191] UACG loop structure of SL1 RNA in HIV-1[1192] and the 3′-stem-loop from human U4

snRNA[1193] have each been determined. The CACG tetraloop that forms part of the cloverleaf structure of the 5′-UTR of coxsackievirus B3 is involved extensive stacking and hydrogen bonding interactions, with the loop closed by a U:G wobble base pair.[1194] Another stable loop structure is GNRA, where R is a purine. The structures of the pyrimidine-rich internal loop in the poliovirus 3′-UTR[1195] and ψ-RNA stem-loop SL1 of HIV-1[1196,1197] belonging to this GNRA family have been reported. Other stem-loop structures reported include an essential stem-loop of human telomerase RNA (UGG) closed off by a U:G wobble base pair,[1198] the HIV-1 frameshift inducing stem-loop (ACAA),[1199] stem-loop IV domain of the *Enterovirus* internal ribosome entry site (UCCC)[1200] and a family of stem-loop RNAs which bind to the N-terminal RNA-binding domains of nucleolin (UCCC).[1201] Larger loop structures (CAG-UGC) and (GCAUA) have also been reported in the iron-responsive element from the non-coding regions of mRNAs of proteins involved in iron regulation[1202] and U6 RNA,[1203] respectively.

Three ribozyme structures have been studied; domain 5 of a group II intron ribozyme,[1204] a hammerhead ribozyme[1205] and the cleavage site from the Varkud satellite ribozyme,[1206] each with particular reference to their metal binding sites. The structure of the group II intron ribozyme also revealed a novel RNA motif. The oligonucleotide r(GGAGGUUUUGGAGG) forms a quadruplex structure even in the absence of potassium ions, and at low potassium concentrations an unusually stable dimeric quadruplex forms.[1207,1208] Two complex RNA structures are reported; the 101-nucleotide core of the encapsidation signal of MMLV[1209] and the luteoviral P1-P2 frameshifting mRNA pseudoknot.[1210]

Only a few RNA structures involving modifications have been reported. A study of the hammerhead ribozyme with phosphorothioate modifications has been carried out, the aim being to determine the metal-binding site. Cd(II) binds not at the scissile bond but at another known metal-binding site.[1211] An RNA-DNA duplex in which the pyrimidines in the DNA strand are modified with C5-propynyl groups has been compared to C5-methyl modified DNA. The propynylated structure was much more stable, with the propynyl groups occupying the major groove, making van der Waals interactions with their nearest neighbours.[1212] Stem-loop structures of the form UUCG are more stable with 2′,5′-linkages in the loop structure compared to the usual 3′,5′-linked RNA. The NMR of such a 2′,5′-linked stem-loop structure revealed a novel fold in the loop region involving a U:G wobble-pair in which the nucleobases adopt an *anti*-conformation.[1213,1214]

NMR has been used to study the binding of various phenothiazine analogues, which have been identified as promising ligands for binding to HIV-1 TAR RNA.[1215] RNA interference (RNAi) is a rapidly developing field of research for gene regulation. The mechanism by which RNAi works is complex, and involves a number of proteins leading to the eventual cleavage of target RNA. NMR has been used to study some of these protein-RNA interactions, in particular the binding of RNA to the complex Argonaut 2 PAZ.[1216–1218] Other RNA-protein interactions that have been examined are the N-terminal domain

of nucleolin binding to pre-rRNA[1219] and Rnt1p RNase III binding to dsRNA.[1220]

NMR structures of DNA containing non-canonical base pairs are reported, including an I-motif structure of $d(^{Me}CCTC_nTCC)_4$, where n=1–3, in which the two parallel duplexes are associated by hemi-protonated $C–C^+$ pairs. The structure is revealed as an interconversion of a symmetric and an asymmetric structure, where the asymmetric structure involves a T–T base pair.[1221] A stable loop structure has been investigated at low salt concentration where a closing G-C pair in the loops adopts a rare sheared G_{anti}-C_{syn} base pair.[1222] A study of the kinetics of imino proton exchange in 9-mer duplexes containing different mismatches revealed that different mismatches have different lifetimes,[1223] for example, a T-T mismatch has a shorter lifetime than a G-G mismatch. The effect of the mismatch was observed up to two nucleotides away, indicating that the disruption to the duplex structure is localised. A A_{syn}-T_{anti} Hoogsteen base pair has been observed in an otherwise undistorted B-DNA duplex in the MATα2 homoeodomain.[1224]

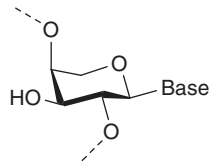
d(ATATAT) has been studied by both X-ray and NMR where different structures were observed.[1225] By X-ray the base pairing is of Hoogsteen form with the adenines flipped over such that the features of both grooves are changed. In solution, the structure adopts a B-form duplex. DNA sequences containing short adenine tracts often cause bending in DNA duplexes. It is reported that ApT steps exhibit a large negative roll, and the curvature is a result of in-phase negative roll and positive roll at the 5′-end of the duplex.[1226,1227] The binding of Mn(II) ions in A-tract duplexes demonstrated that Mn(II) binds in the minor groove, though the position of the ion is dependent upon both the duplex sequence and length.[1228]

The solution structure of three-way junctions has been reported in an attempt to establish empirical stacking interactions of the helical arms.[1229] A variety of quadruplex structures have also been examined. Telomeric sequences from *Tetrahymena* and human sequences have been solved by NMR,[1230,1231] as well as the structures $d(G_4T_4G_3)_2$ and $d(G_3T_4G_4)_2$, each of which consist of three G-quartets.[1232,1233] The telomeric sequences $d(TTAGGGT)_4$ and $d(GGAGG)_4$ each form quadruplex structures involving both G- and A-tetrads,[1234,1235] whilst $d(GCGGTGGAT)_4$ forms tetrads involving G : C : G : C as well as an A-A mismatch.[1236]

The largest number of solution structures reported involves modified DNA structures, including a number of duplexes binding to small molecules. A number of structures are reported complexed to various antibiotics, including actinomycin D,[1237] distamycin,[1238] phleomycin[1239] and nogalamycin.[1240–1242] Structures are solved for DNA-binding to the alkaloid berberine,[1243] the telomerase inhibitor RHPS4,[1244] a DNA binding cyclic polyamide[1245] and a spirocylic agent that modulates DNA strand slippage by DNA polymerase I.[1246,1247] There are also structures reported for DNA binding to DNA-binding proteins.[1248–1250]

Of the DNA solution structures, there is a small number involving modifications to the internucleotide linkage or sugar residues. The cyclic

oligonucleotide d(pCGCTCATT) forms a symmetric dimer that involves two GCAT tetrads[1251] that are stabilised by sodium ions. The solution structure of the self-pairing duplex α-L-arabinopyranosyl-(4′→2′)-(CGAATTCG) (184) revealed that the structure adopts an antiparallel duplex with a strong propensity for interstrand base stacking.[1252] A DNA duplex containing a single α-anomeric adenosine, which is a substrate for endonuclease IV, reveals that the α-A stacks intrahelically by reverse Watson-Crick base pairing.[1253]

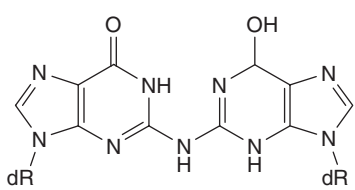


α-L-arabinopyranosyl (4'→2')

184

The majority of DNA solution structures involve a nucleobase modification. 6-Thioguanosine (^{6S}dG) opposite dT and dC adopts the usual B-form duplex, though ^{6S}dG-dT is a wobble base pair.[1254] The structures of quadruplexes in which individual guanine residues are replaced by 8-bromoguanosine (^{8Br}G) reveal that the ^{8Br}G adopts the anticipated *syn* conformation, thus affecting the quadruplex stability but retaining the parallel orientation of the unmodified quadruplex.[1255] A duplex incorporating an 8-oxo-dG:G mismatch is reported where the 8-oxo-dG is inserted into the helix, forming a Hoogsteen base pair with the guanosine on the opposite strand.[1256]

A number of guanosine crosslinked structures are reported. A duplex containing the G-G crosslink (185) formed between adjacent CpG steps by the action of nitrous acid is reported.[1257,1258] The crosslinked guanines form an almost planar G:G base pair, whilst the cytosine partners are flipped out of the helix into the minor groove. Using the stabilised analogue (186), it was shown that malondialdehyde crosslinking forms a G:G base pair that is not planar, but skewed about the trimethylene linker.[1259] The action of *trans*-platin reagents revealed that an interstrand crosslink is formed in preference to an intrastrand crosslink. The structure exhibits significant distortion at residues adjacent to the crosslink.[1260]



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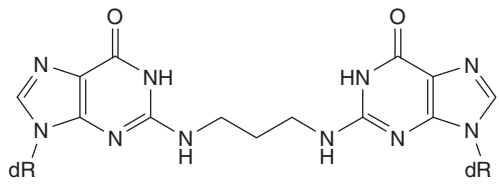
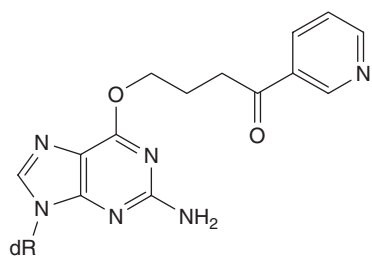


186

The pyridyloxybutyl derivative (187), derived from tobacco-specific nitrosamines, forms O^6-adducts of guanosine. A solution structure of a duplex containing (187) showed the adduct in the major groove of the duplex, and the modified G:C in a wobble base pair.[1261] Benz[a]anthracene forms adducts with the exocyclic amino groups of nucleobases (*cf* 72) and a duplex containing a guanosine adduct of benz[a]anthracene showed the anthracene residue located in the minor groove.[1262] The aflatoxin adduct (188) intercalates into duplexes,[1263] without significant disruption of the overall duplex structure.[1264] The adenine adduct of the (+)-CPI-indole (189), related to the daunomycin antitumor agents, was examined to compare with other daunomycin agents. It was shown that the indole resides in the minor groove, and that there was a local perturbation of the duplex, which was restricted to the modified base pair.[1265] A duplex consisting of the ring expanded adenine base (190) paired with thymidine showed that whilst the base pairs are 2.4 Å longer than a canonical A:T pair, the structure largely resembles that of a regular B-form duplex.[1266]



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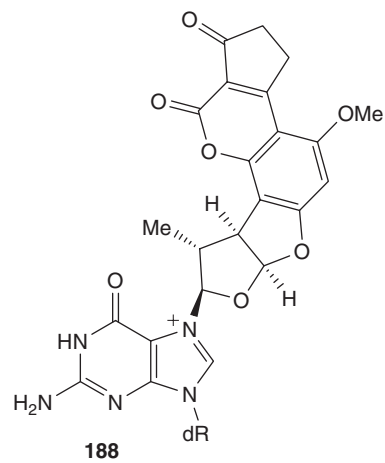

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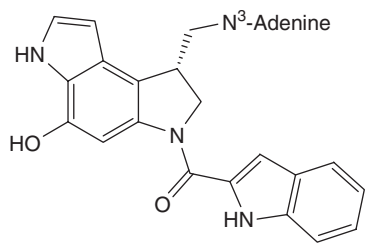

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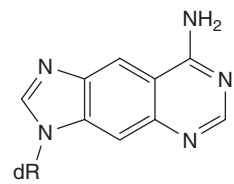
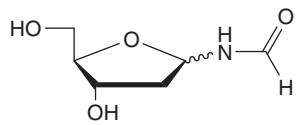


190

There are a few pyrimidine-modified DNA structures. 5-(2-Hydroxyethyl)-dU was substituted for thymidines in a quadruplex structure.[1267] The presence of the hydroxyethyl groups allows for additional hydrogen bonding within the expected tetrads. A study of the effect of introducing C5-propyne groups showed that the propyne groups stack on the aromatic ring of the

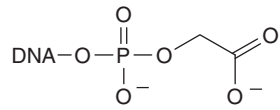
5′-nucleobases, and extend into the major groove. The results suggest that propynylated oligonucleotides are more stable due to pre-organisation of the propynylated ssDNA strands.[1268] The presence of a 5-(3-aminopropyl)-modified dU has little effect on overall duplex structure, the aminopropyl unit extending towards the 3′-direction from the modification site in the major groove.[1269] A self-complementary duplex with an opposed N^4C-ethyl-N^4C crosslink was studied as a model for crosslinking agents in cancer therapy. The ethyl crosslink extends within the major groove, and there is a widening of the groove at the crosslink site, resulting from underwinding at that base pair step.[1270] NMR structures of duplexes containing *cis-syn* cyclobutane pyrimidine dimers (99) and up to two T:G wobble base pairs have been examined. The overall structures were similar to the usual B-form duplex except when two T:G base pairs were present, where significant duplex distortion was observed.[1271]

Other modifications include a formamide residue (191), a ring fragmentation product of thymine, which exists as either a *cis* or a *trans* conformer. Both isomers are rotated out of the helix, and the bases on either side of (191) occupy the space vacated by it.[1272] A pyrene:abasic site base pair in DNA duplexes adopts the usual B-form duplex, with the pyrene residue within the duplex stacking on adjacent nucleobases. The abasic site folds back over the opposite strand to shelter the hydrophobic base from exposure to water.[1273,1274] The photoresponsive azobenzene analogues (133, *R*- and *S*-forms) have been incorporated into DNA for NMR analysis. Both isomers intercalate between neighbouring base pairs, and the *S*-isomer exhibits more disturbance in its duplex structure which is reflected in lower Tms compared to the *R*-isomer.[1275]



191

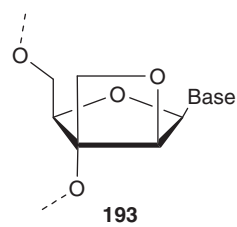
The self-complementary hexamer d(TGCGCA) modified to incorporate cholesterol attached via a 5′-amine modification showed that the duplex was stabilised by the stacking of the steroid on the terminal A:T base pair through van der Waals interactions.[1276] Bleomycins damage DNA by 4′-hydrogen abstraction resulting in the formation of base-propenal adducts and 3′-phosphoglycolate (192) modifications. The NMR structure of a duplex containing (192) at the 3′-end with a 5′-phosphate revealed a regular B-form duplex, both terminal modifications being extrahelical.[1277] DNA containing the intercalating nucleic acid modification (139) has been studied by NMR, in a duplex with two (139) opposing modifications.[1278] The two modifications caused significant unwinding of the overall duplex structure, leading to a ladder-like structure.



192

The solution structure of the first fully modified LNA oligonucleotide with its complementary RNA is described.[1279] The duplex adopts a canonical A-form duplex, and the helix is almost straight. The LNA oligonucleotide TGGGT forms a parallel stranded quadruplex structure with right-handed helicity.[1280] α-L-LNA has also been incorporated into a DNA oligonucleotide with complementary DNA and RNA.[1281–1283] Opposite DNA, it adopts a B-form duplex, with the backbone rearranged in the vicinity of the substitutions to accommodate them. Opposite RNA, the structure is a hybrid between A- and B-form with the phosphate groups of the LNA nucleotide rotated into the minor groove.

The locked nucleic acid [3.2.0]bcANA (193) with an *arabino*-configuration is fixed in an O4′-*endo* conformation. The solution structure of DNA containing a single substitution of (193) showed a B-form duplex with stacking of the nucleobases unperturbed.[1284] The 2′-*O*,3′-*C*-methylene bridge is located in the major groove and is accommodated by the B-form duplex. The O4′-*endo* conformation of the sugar causes a local disruption in the backbone angle. A PNA-DNA chimera $^{5\prime}$TGGG$^{3\prime}$-t forms a regular parallel duplex as determined by NMR,[1285] whereas $^{5\prime}$TGG$^{3\prime}$-gt does not form well-defined species.



193

As well as investigating structures by crystallography and NMR, there are other techniques that have been used. Electron microscopy has been used to study nucleoprotein RNA structures of measles virus.[1286] Cryoelectron microscopy has been used to visualise tmRNA (RNA that acts as both messenger and transfer RNA) entry into the ribosome and ribosomal motion,[1287–1290] and visualisation of a 1.7 kb ssDNA structure.[1291] Atomic force microscopy (AFM) was used to visualise a DNA hemiknot structure,[1292] four-arm DNA structures[1293] and DNA hybridisation in the absence of a DNA label.[1294] A surface plasmon diffraction sensor has also been used to study oligonucleotide hybridisation.[1295] Other more established methods have also been used, such as footprinting to determine the binding of T7 endonuclease I to a Holliday junction[1296] and the investigation of Holliday junctions using gel electrophoresis.[1297]

References

1. A.B. Sierzchala, D.J. Dellinger, J.R. Betley, T.K. Wyrzykiewicz, C.M. Yamada and M.H. Caruthers, *J. Am. Chem. Soc.*, 2003, **125**, 13427.
2. J.-Y. Cheng, H.-H. Chen, Y.-S. Kao and K. Peck, *Nucl. Acids Res.*, 2002, **30**, e93.
3. P.J. Serafinowski and P.B. Garland, *J. Am. Chem. Soc.*, 2003, **125**, 962.
4. C.D. Claeboe, R. Gao and S.M. Hecht, *Nucl. Acids Res.*, 2003, **31**, 5685.
5. A. Meyer, F. Morvan and J.-J. Vasseur, *Tetrahedron Lett.*, 2004, **45**, 3745.
6. D.J. Dellinger, D.M. Sheehan, N.K. Christensen, J.G. Lindberg and M.H. Caruthers, *J. Am. Chem. Soc.*, 2003, **125**, 940.
7. M. Hey, C. Hartel and M.W. Göbel, *Helv. Chim. Acta*, 2003, **86**, 844.
8. J.C. Chaput, S. Sinha and C. Switzer, *Chem. Commun.*, 2002, 1568.
9. J. Chen, L.R. Zhang, J.M. Min and L.H. Zhang, *Nucl. Acids Res.*, 2002, **30**, 3005.
10. C.B. Reese and H. Yan, *J. Chem. Soc. Perkin Trans. I*, 2002, 2619.
11. T. Guerlavais-Dagland, A. Meyer, J.-L. Imbach and F. Morvan, *Eur. J. Org. Chem.*, 2003, 2327.
12. J.-C. Brès, J.-L. Imbach and F. Morvan, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1243.
13. K. Kamaike, T. Namiki and E. Kawashima, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 469.
14. K. Kamaike, T. Namiki and E. Kawashima, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1011.
15. C.B. Reese and H. Yan, *Tetrahedron Lett.*, 2004, **45**, 2567.
16. U.M. Lindström and E.T. Kool, *Nucl. Acids Res.*, 2002, **30**, e101.
17. A. Wilk, M.K. Chmielewski, A. Grajkowski, L.R. Phillips and S.L. Beaucage, *J. Org. Chem.*, 2002, **67**, 6430.
18. J. Cieslak and S.L. Beaucage, *J. Org. Chem.*, 2003, **68**, 10123.
19. S.M. Langenegger, L. Moesch, F. Natt, J. Hall and R. Häner, *Helv. Chim. Acta*, 2003, **86**, 3476.
20. M. Leuck, K.E. Vagle, J.S. Roach and A. Wolter, *Tetrahedron Lett.*, 2004, **45**, 321.
21. S. Battaggia and J.S. Vyle, *Tetrahedron Lett.*, 2003, **44**, 861.
22. Q. Song, Z. Wang and Y.S. Sanghvi, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 629.
23. Z.S. Cheruvallath, R.K. Kumar, C. Rentel, D.L. Cole and V.T. Ravikumar, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 461.
24. Z.S. Cheruvallath, D.L. Cole and V.T. Ravikumar, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 281.
25. N. Oka, T. Wada and K. Saigo, *J. Am. Chem. Soc.*, 2003, **125**, 8307.
26. C.B. Reese and H. Yan, *Tetrahedron Lett.*, 2003, **44**, 2501.
27. M. Sekine, A. Ohkubo and K. Seio, *J. Org. Chem.*, 2003, **68**, 5478.
28. A. Ohkubo, K. Seio and M. Sekine, *Tetrahedron Lett.*, 2004, **45**, 363.
29. M. Ushioda, M. Kadokura, T. Moriguchi, A. Kobori, M. Aoyagi, K. Seio and M. Sekine, *Helv. Chim. Acta*, 2002, **85**, 2930.
30. M.C. Uzagare, K.J. Padiya, M.M. Salunkhe and Y.S. Sanghvi, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3537.
31. N.U. Mohe, K.J. Padiya and M.M. Salunkhe, *Bioorg. Med. Chem.*, 2003, **11**, 1419.
32. A.H. Krotz, D.L. Cole and V.T. Ravikumar, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 129.

33. R.K. Kumar, D.L. Cole and V.T. Ravikumar, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 453.
34. N. Minakawa, Y. Ono and A. Matsuda, *J. Am. Chem. Soc.*, 2003, **125**, 11545.
35. A.P. Guzaev and M. Manoharan, *J. Am. Chem. Soc.*, 2003, **125**, 2380.
36. P. Kumar, G. Dhawan, R. Chandra and K.C. Gupta, *Nucl. Acids Res.*, 2002, **30**, e130.
37. P. Kumar and K.C. Gupta, *Helv. Chim. Acta*, 2003, **86**, 59.
38. E. Anderson, T. Brown and D. Picken, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1403.
39. R. Manchanda, S.K. Agarwal, P. Kumar, A.K. Sharma and K.C. Gupta, *Helv. Chim. Acta*, 2002, **85**, 2754.
40. V.T. Ravikumar, R.K. Kumar, D.C. Capaldi and D.L. Cole, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1421.
41. M. Leuck, R. Giare, M. Paul, N. Zien and A. Wolter, *Tetrahedron Lett.*, 2004, **45**, 317.
42. J. Winkler, E. Urban, D. Losert, V. Wacheck, H. Pehamberger and C.R. Noe, *Nucl. Acids Res.*, 2004, **32**, 710.
43. R.T. Pon and S. Yu, *Nucl. Acids Res.*, 2004, **32**, 623.
44. T.J. Albert, J. Norton, M. Ott, T. Richmond, K. Nuwaysir, E.F. Nuwaysir, K.-P. Stengele and R.D. Green, *Nucl. Acids Res.*, 2003, **31**, e35.
45. P.B. Garland and P.J. Serafinowski, *Nucl. Acids Res.*, 2002, **30**, e99.
46. M.J. Martinez, A.D. Aragon, A.L. Rodriguez, J.M. Weber, J.A. Timlin, M.B. Sinclair, D.M. Haaland and M. Werner-Washburne, *Nucl. Acids Res.*, 2003, **31**, e18.
47. D. Wöll, S. Walbert, K.-P. Stengele, T.J. Albert, T. Richmond, J. Norton, M. Singer, R.D. Green, W. Pfleiderer and U.E. Steiner, *Helv. Chim. Acta*, 2004, **87**, 28.
48. T.S. Seo, X. Bai, H. Ruparel, Z. Li, N.J. Turro and J. Ju, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5488.
49. C.C. Xiang, O.A. Kozhich, M. Chen, J.M. Inman, Q.N. Phan, Y. Chen and M.J. Brownstein, *Nat. Biotechnol.*, 2002, **20**, 738.
50. P.A.C. 't Hoen, F. de Kort, G.J.B. van Ommen and J.T. den Dunnen, *Nucl. Acids Res.*, 2003, **31**, e20.
51. A. Laayoun, M. Kotera, I. Sothier, E. Trévisiol, E. Bernal-Méndez, C. Bourget, L. Menou, J. Lhomme and A. Troesch, *Bioconjugate Chem.*, 2003, **14**, 1298.
52. A. Laayoun, I. Sothier, L. Menou, E. Bernal-Méndez, M. Kotera, C. Bourget, E. Trévisiol, J. Lhomme and A. Troesch, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 649.
53. E. Bernal-Méndez, C. Tora, I. Sothier, M. Kotera, A. Troesch and A. Laayoun, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1647.
54. A.W. Peterson, L.K. Wolf and R.M. Georgiadis, *J. Am. Chem. Soc.*, 2002, **124**, 14601.
55. F. Diehl, B. Beckmann, N. Kellner, N.C. Hauser, S. Diehl and J.D. Hoheisel, *Nucl. Acids Res.*, 2002, **30**, e79.
56. K. Ketomäki, H. Hakala, O. Kuronen and H. Lönnberg, *Bioconjugate Chem.*, 2003, **14**, 811.
57. M.J. Hessner, X. Wang, K. Hulse, L. Meyer, Y. Wu, S. Nye, S.-W. Guo and S. Ghosh, *Nucl. Acids Res.*, 2003, **31**, e14.
58. M.J. Hessner, X. Wang, S. Khan, L. Meyer, M. Schlicht, J. Tackes, M.W. Datta, H.J. Jacob and S. Ghosh, *Nucl. Acids Res.*, 2003, **31**, e60.

59. F. Turcu, A. Schulte, G. Hartwich and W. Schuhmann, *Angew. Chem. Int. Ed.*, 2004, **43**, 3482.
60. F. Fixe, V. Chu, D.M.F. Prazeres and J.P. Conde, *Nucl. Acids Res.*, 2004, **32**, e70.
61. N. Kimura, R. Oda, Y. Inaki and O. Suzuki, *Nucl. Acids Res.*, 2004, **32**, e68.
62. P. Kumar, J. Choithani and K.C. Gupta, *Nucl. Acids Res.*, 2004, **32**, e80.
63. P. Kumar and K.C. Gupta, *Bioconj. Chem.*, 2003, **14**, 507.
64. V. Le Berre, E. Trévisiol, A. Dagkessamanskaia, S. Sokol, A.-M. Caminade, J.P. Majoral, B. Meunier and J. François, *Nucl. Acids Res.*, 2003, **31**, e88.
65. E. Defrancq, A. Hoang, F. Vinet and P. Dumy, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2683.
66. C. Consolandi, B. Castiglioni, R. Bordoni, E. Busti, C. Battaglia, L.R. Bernardi and G. De Bellis, *Nucleosides, Nucleotides & Nucl. Acids*, 2002, **21**, 561.
67. S.-K. Chiu, M. Hsu, W.-C. Ku, C.-Y. Tu, Y.-T. Tseng, W.-K. Lau, R.-Y. Yan, J.-T. Ma and C.-M. Tzeng, *Biochem. J.*, 2003, **374**, 625.
68. G. Nonglaton, I.O. Benitez, I. Guisle, M. Pipelier, J. Léger, D. Dubreuil, C. Tellier, D.R. Talham and B. Bujoli, *J. Am. Chem. Soc.*, 2004, **126**, 1497.
69. A. Levina, E. Mikhaleva and V. Zarytova, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 931.
70. F. Fixe, M. Dufva, P. Telleman and C.B.V. Christensen, *Nucl. Acids Res.*, 2004, **32**, e9.
71. S. Taylor, S. Smith, B. Windle and A. Guiseppi-Elie, *Nucl. Acids Res.*, 2003, **31**, e87.
72. A.W. Machl, C. Schaab and I. Ivanov, *Nucl. Acids Res.*, 2002, **30**, e127.
73. X.-b. Zhong, R. Reynolds, J.R. Kidd, K.K. Kidd, R. Jenison, R.A. Marlar and D.C. Ward, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 11559.
74. K. Lindroos, S. Sigurdsson, K. Johansson, L. Rönnblom and A.-C. Syvänen, *Nucl. Acids Res.*, 2002, **30**, e70.
75. H.A. Behrensdorf, M. Pignot, N. Windhab and A. Kappel, *Nucl. Acids Res.*, 2002, **30**, e64.
76. R. Grifantini, E. Bartolini, A. Muzzi, M. Draghi, E. Frigimelica, J. Berger, G. Ratti, R. Petracca, G. Galli, M. Agnusdei, M.M. Giuliani, L. Santini, B. Brunelli, H. Tettelin, R. Rappuoli, F. Randazzo and G. Grandi, *Nat. Biotechnol.*, 2002, **20**, 914.
77. J. Banér, A. Isaksson, E. Waldenström, J. Jarvius, U. Landegren and M. Nilsson, *Nucl. Acids Res.*, 2003, **31**, e103.
78. A.J. Flavell, V.N. Bolshakov, A. Booth, R. Jing, J. Russell, T.H.N. Ellis and P. Isaac, *Nucl. Acids Res.*, 2003, **31**, e115.
79. M. Lu, J.G. Hall, M.R. Shortreed, L. Wang, W.T. Berggren, P.W. Stevens, D.M. Kelso, V. Lyamichev, B. Neri, J.L. Skinner and L.M. Smith, *J. Am. Chem. Soc.*, 2002, **124**, 7924.
80. M.Á. Reyes-López, A. Méndez-Tenorio, R. Maldonado-Rodríguez, M.J. Doktycz, J.T. Fleming and K.L. Beattie, *Nucl. Acids Res.*, 2003, **31**, 779.
81. J.R. Epstein, J.A. Ferguson, K.-H. Lee and D.R. Walt, *J. Am. Chem. Soc.*, 2003, **125**, 13753.
82. A. Vainrub and B.M. Pettitt, *J. Am. Chem. Soc.*, 2003, **125**, 7798.
83. T.T. Goodrich, H.J. Lee and R.M. Corn, *J. Am. Chem. Soc.*, 2004, **126**, 4086.
84. J.W. Hong, V. Studer, G. Hang, W.F. Anderson and S.R. Quake, *Nature Biotech.*, 2004, **22**, 435.
85. O. Brandt, J. Feldner, A. Stephan, M. Schröder, M. Schnölzer, H.F. Arlinghaus, J.D. Hoheisel and A. Jacob, *Nucl. Acids Res.*, 2003, **31**, e119.

86. U. Münch and W. Pfleiderer, *Helv. Chim. Acta*, 2003, **86**, 2546.
87. P. Wenter and S. Pitsch, *Helv. Chim. Acta*, 2003, **86**, 3955.
88. C. Höbartner and R. Micura, *J. Am. Chem. Soc.*, 2004, **126**, 1141.
89. J. Cieslak, A. Grajkowski, V. Livengood and S.L. Beaucage, *J. Org. Chem.*, 2004, **69**, 2509.
90. L. Araki, S. Harusawa, M. Yamaguchi, S. Yonezawa, N. Taniguchi, D.M.J. Lilley, Z.-y. Zhao and T. Kurihara, *Tetrahedron Lett.*, 2004, **45**, 2657.
91. W. Huang and J.P. Ferris, *Chem. Commun.*, 2003, 1458.
92. S. Miyakawa and J.P. Ferris, *J. Am. Chem. Soc.*, 2003, **125**, 8202.
93. P.-A. Monnard, A. Kanavarioti and D.W. Deamer, *J. Am. Chem. Soc.*, 2003, **125**, 13734.
94. F. Eckstein, *Ann. Rev. Biochem.*, 1985, **54**, 367.
95. V.T. Ravikumar, D.C. Capaldi, W.F. Lima, E. Lesnik, B. Turney and D.L. Cole, *Bioorg. Med. Chem.*, 2003, **11**, 4673.
96. Z. Zhang, M. Li, H. Wang, S. Agrawal and R. Zhang, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 11636.
97. D.A. Braasch, Z. Paroo, A. Constantinescu, G. Ren, O.K. Öz, R.P. Mason and D.R. Corey, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1139.
98. R. Gao, C.D. Claeboe, B.M. Eisenhauer and S.M. Hecht, *Biochemistry*, 2004, **43**, 6167.
99. D. Di Giusto and G.C. King, *Nucl. Acids Res.*, 2003, **31**, e7.
100. M. Boczkoswa, P. Guga and W.J. Stec, *Biochemistry*, 2002, **41**, 12483.
101. A.P.G. Beevers, K.J. Fettes, I.A. O'Neil, S.M. Roberts, J.R.P. Arnold, R. Cosstick and J. Fisher, *Chem. Commun.*, 2002, 1458.
102. A.P.G. Beevers, K.J. Fettes, G. Sabbagh, F.K. Murad, J.R.P. Arnold, R. Cosstick and J. Fisher, *Org. Biomol. Chem.*, 2004, **2**, 114.
103. V.T. Ravikumar, W.F. Lima, K. Van Sooy and B. Turney, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 149.
104. S. Olejniczak, M.J. Potrzebowski and L.A. Wozniak, *Eur. J. Org. Chem.*, 2004, 1958.
105. S. Gryaznov, A. Asai, Y. Oshima, Y. Yamamoto, K. Pongracz, R. Pruzan, E. Wunder, K. Piatyszek, S. Li, A. Chin, C. Harley, S. Akinaga and Y. Yamashita, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 577.
106. D. Sheehan, B. Lunstad, C.M. Yamada, B.G. Stell, M.H. Caruthers and D.J. Dellinger, *Nucl. Acids Res.*, 2003, **31**, 4109.
107. N. Carrasco and Z. Huang, *J. Am. Chem. Soc.*, 2004, **126**, 448.
108. G.A. Holloway, C. Pavot, S.A. Scaringe, Y. Lu and T.B. Rauchfuss, *Chem. Bio. Chem.*, 2002, **3**, 1061.
109. X. Wang, M. Dobrikov, D. Sergueev and B.R. Shaw, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1151.
110. L. Tsujikawa, M. Weinfield and L.J. Reha-Krantz, *Nucl. Acids Res.*, 2003, **31**, 4965.
111. D. Hamelberg, L.D. Williams and W.D. Wilson, *Nucl. Acids Res.*, 2002, **30**, 3615.
112. S. Amberg and J.W. Engels, *Helv. Chim. Acta*, 2002, **85**, 2503.
113. S. Králíková, M. Budesínsky and I. Rosenberg, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1061.
114. T. Miyashita, N. Matsumoto, T. Moriguchi and K. Shinozuka, *Tetrahedron Lett.*, 2003, **44**, 7399.
115. S. Hoshika, Y. Ueno and A. Matsuda, *Bioconj. Chem.*, 2003, **14**, 607.
116. S. Hoshika, Y. Ueno, H. Kamiya and A. Matsuda, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3333.

117. Y. Ueno, A. Shibata, A. Matsuda and Y. Kitade, *Bioconj. Chem.*, 2003, **14**, 684.
118. V. Esposito, A. Galeone, L. Mayol, G. Oliviero, A. Randazzo and M. Varra, *Eur. J. Org. Chem.*, 2002, 4228.
119. B. Catalanotti, C. Fattorusso, L. Mayol, G. Oliviero, G. Piccialli and M. Varra, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1069.
120. J. Amato, A. Galeone, G. Oliviero, L. Mayol, G. Piccialli and M. Varra, *Eur. J. Org. Chem.*, 2004, 2331.
121. D. Yu, E.R. Kandimalla, L. Bhagat, J.-Y. Tang, Y. Cong, J. Tang and S. Agrawal, *Nucl. Acids Res.*, 2002, **30**, 4460.
122. E.R. Kandimalla, L. Bhagat, D. Yu, Y. Cong, J. Tang and S. Agrawal, *Bioconj. Chem.*, 2002, **13**, 966.
123. S. Carriero and M.J. Damha, *Org. Lett.*, 2003, **5**, 273.
124. S. Carriero and M.J. Damha, *J. Org. Chem.*, 2003, **68**, 8328.
125. Y. Zhang and D.M. Crothers, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 3161.
126. S. Carriero and M.J. Damha, *Nucl. Acids Res.*, 2003, **31**, 6157.
127. M. Mendel-Hartvig, A. Kumar and U. Landegren, *Nucl. Acids Res.*, 2004, **32**, e2.
128. M. Smietana and E.T. Kool, *Angew. Chem. Int. Ed.*, 2002, **41**, 3704.
129. O.P. Edupuganti, E. Defrancq and P. Dumy, *J. Org. Chem.*, 2003, **68**, 8708.
130. S. Carriero, M.M. Mangos, K.A. Agha, A.M. Noronha and M.J. Damha, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1599.
131. U.M. Lindström, R.A. Chandrasekaran, L. Orbai, S.A. Helquist, G.P. Miller, E. Oroudjev, H.G. Hansma and E.T. Kool, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 15953.
132. H. Hamazaki, T. Abe, H. Yamakawa, T. Yokota, S. Shigeta and H. Takaku, *Helv. Chim. Acta*, 2002, **85**, 2183.
133. J. Chen, D. Liu, A.H.F. Lee, J. Qi, A.S.C. Chan and T. Li, *Chem. Commun.*, 2002, 2686.
134. D. Liu, J. Chen, A.H.F. Lee, L.M.C. Chow, A.S.C. Chan and T. Li, *Angew. Chem. Int. Ed.*, 2003, **42**, 797.
135. T. Roulon, C. Hélène and C. Escudé, *Bioconj. Chem.*, 2002, **13**, 1134.
136. M. Bello-Roufaï, T. Roulon and C. Escudé, *Chem. Biol.*, 2004, **11**, 509.
137. K. Pongracz, S. Li, B.-S. Herbert, R. Pruzan, E. Wunder, A. Chin, M. Piatyszek, J. Shay and S.M. Gryaznov, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1627.
138. E. Viazovkina, K.-L. Min, A. Galarneau and M.J. Damha, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1335.
139. J.L. Wolfe, B.H. Wang, T. Kawate and V.P. Stanton, *J. Am. Chem. Soc.*, 2003, **125**, 10500.
140. A.M. Awad, M. Sobkowski and H. Seliger, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 777.
141. U. Asseline, M. Chassignol, J. Draus, M. Durand and J.-C. Maurizot, *Bioorg. Med. Chem.*, 2003, **11**, 3499.
142. T. Michel, F. Debart and J.-J. Vasseur, *Tetrahedron Lett.*, 2003, **44**, 6579.
143. T. Michel, L. Mouls, F. Debart and J.-J. Vasseur, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1263.
144. T. Michel, C. Martinand-Mari, F. Debart, B. Lebleu, I. Robbins and J.-J. Vasseur, *Nucl. Acids Res.*, 2003, **31**, 5282.
145. A. Risitano and K.R. Fox, *Nucl. Acids Res.*, 2004, **32**, 2598.
146. D. Yu, E.R. Kandimalla, Y. Cong, J. Tang, J.-Y. Tang, Q. Zhao and S. Agrawal, *J. Med. Chem.*, 2002, **45**, 4540.

147. M. Endo and T. Majima, *Angew. Chem. Int. Ed.*, 2003, **42**, 5744.
148. M. Endo and T. Majima, *J. Am. Chem. Soc.*, 2003, **125**, 13654.
149. M. Endo and T. Majima, *Chem. Commun.*, 2004, 1308.
150. S.J. Kim and B.H. Kim, *Nucl. Acids Res.*, 2003, **31**, 2725.
151. M.G. Grimau, D. Iacopino, A. Aviñó, B.G. de la Torre, A. Ongaro, D. Fitzmaurice, J. Wessels and R. Eritja, *Helv. Chim. Acta*, 2003, **86**, 2814.
152. A. Aviñó, M.G. Grimau, M. Frieden and R. Eritja, *Helv. Chim. Acta*, 2004, **87**, 303.
153. G. Oliviero, N. Borbone, A. Galeone, M. Varra, G. Piccialli and L. Mayol, *Tetrahedron Lett.*, 2004, **45**, 4869.
154. M. Nielsen, A.H. Thomsen, E. Cló, F. Kirpekar and K.V. Gothelf, *J. Org. Chem.*, 2004, **69**, 2240.
155. P.M. Reddy and T.C. Bruice, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1281.
156. H. Challa and T.C. Bruice, *Bioorg. Med. Chem.*, 2004, **12**, 1475.
157. P.M. Reddy and T.C. Bruice, *J. Am. Chem. Soc.*, 2004, **126**, 3736.
158. E. Rozners, D. Katkevica, E. Bizdena and R. Strömberg, *J. Am. Chem. Soc.*, 2003, **125**, 12125.
159. V.V. Filichev, A.A. Malin, V.A. Ostrovskii and E.B. Pedersen, *Helv. Chim. Acta*, 2002, **85**, 2847.
160. D. Hutter, M.O. Blaettler and S.A. Benner, *Helv. Chim. Acta*, 2002, **85**, 2777.
161. B. Eschgfäller, J.G. Schmidt, M. König and S.A. Benner, *Helv. Chim. Acta*, 2003, **86**, 2959.
162. K. Sato, K. Seio and M. Sekine, *J. Am. Chem. Soc.*, 2002, **124**, 12715.
163. K. Sato, R. Tawarada, K. Seio and M. Sekine, *Eur. J. Org. Chem.*, 2004, 2142.
164. Z.A. Doddridge, R.D. Bertram, C.J. Hayes and P. Soultanas, *Biochemistry*, 2003, **42**, 3239.
165. K. Nauwelaerts, K. Vastmans, M. Froeyen, V. Kempeneers, J. Rozenski, H. Rosemeyer, A. Van Aerschot, R. Busson, J.C. Lacey, E. Efimtseva, S. Mikhailov, E. Lescrinier and P. Herdewijn, *Nucl. Acids Res.*, 2003, **31**, 6758.
166. S.N. Mikhailov, E.V. Efimtseva, B.S. Ermolinsky, G.V. Bobkov, O.I. Andreeva, A.S. Golubeva, S.N. Kochetkov, A. Van Aerschot, G. Schepers and P. Herdewijn, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1117.
167. P.E. Nielsen, M. Egholm, R.H. Berg and O. Buchardt, *Science*, 1991, **254**, 1487.
168. T. Bentin, H.J. Larsen and P.E. Nielsen, *Biochemistry*, 2003, **42**, 13987.
169. F.A. Rogers, K.M. Vasquez, M. Egholm and P.M. Glazer, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 16695.
170. I.V. Smolina, V.V. Demidov and M.D. Frank-Kamenetskii, *J. Mol. Biol.*, 2003, **326**, 1113.
171. Z. Bajor, G. Sági, Z. Tegyey and L. Ötvös, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1215.
172. G. Barone, L. De Napoli, G. Di Fabio, E. Erra, C. Giancola, A. Messere, D. Montesarchio, L. Petraccone and G. Piccialli, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1089.
173. B. Greiner, G. Breipohl and E. Uhlmann, *Helv. Chim. Acta*, 2002, **85**, 2619.
174. M. Komiyama, S. Ye, X. Liang, Y. Yamamoto, T. Tomita, J.-M. Zhou and H. Aburatani, *J. Am. Chem. Soc.*, 2003, **125**, 3758.
175. V. Esposito, A. Randazzo, A. Messere, A. Galeone, L. Petraccone, C. Giancola, G. Piccialli and L. Mayol, *Eur. J. Org. Chem.*, 2003, 3364.
176. B. Datta, C. Schmitt and B.A. Armitage, *J. Am. Chem. Soc.*, 2003, **125**, 4111.
177. Y. Krishnan-Ghosh, E. Stephens and S. Balasubramanian, *J. Am. Chem. Soc.*, 2004, **126**, 5944.

178. C. Schwergold, G. Depecker, C. Di Giorgio, N. Patino, F. Jossinet, B. Ehresmann, R. Terreux, D. Cabrol-Bass and R. Condom, *Tetrahedron*, 2002, **58**, 5675.
179. G. Depecker, N. Patino, C. Di Giorgio, R. Terreux, D. Cabrol-Bass, C. Bailly, A.-M. Aubertin and R. Condom, *Org. Biomol. Chem.*, 2004, **2**, 74.
180. M. Abdel-Aziz, T. Yamasaki and M. Otsuka, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1041.
181. P. Zhou, M. Wang, L. Du, G.W. Fisher, A. Waggoner and D.H. Ly, *J. Am. Chem. Soc.*, 2003, **125**, 6878.
182. N. Sumbatyan, A. Maksimenko, M. Gottikh, C. Malvy and G. Korshunova, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1077.
183. Y. Huang, S. Dey, X. Zhang, F. Sönnichsen and P. Garner, *J. Am. Chem. Soc.*, 2004, **126**, 4626.
184. A.B. Eldrup, O. Dahl and P.E. Nielsen, *J. Am. Chem. Soc.*, 1997, **119**, 11116.
185. A.G. Olsen, O. Dahl and P.E. Nielsen, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1551.
186. M. Hollenstein and C.J. Leumann, *Org. Lett.*, 2003, **5**, 1987.
187. M. Hollenstein, D. Gautschi and C.J. Leumann, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1191.
188. D. Gautschi and C.J. Leumann, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1211.
189. H. Sato, Y. Hashimoto, T. Wada and Y. Inoue, *Tetrahedron*, 2003, **59**, 7871.
190. Meena and V.A. Kumar, *Bioorg. Med. Chem.*, 2003, **11**, 3393.
191. A. Slaitas and E. Yeheskiely, *Eur. J. Org. Chem.*, 2002, 2391.
192. T. Vilaivan, C. Suparpprom, P. Duanglaor, P. Harnyuttanakorn and G. Lowe, *Tetrahedron Lett.*, 2003, **44**, 1663.
193. N.K. Sharma and K.N. Ganesh, *Chem. Commun.*, 2003, 2484.
194. V.A. Kumar and Meena, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1101.
195. M. Kitamatsu, M. Shigeyasu, T. Okada and M. Sisido, *Chem. Commun.*, 2004, 1208.
196. D.T. Hickman, T.H.S. Tan, J. Morral, P.M. King, M.A. Cooper and J. Micklefield, *Org. Biomol. Chem.*, 2003, **1**, 3277.
197. V.A. Efimov, V.N. Klykov and O.G. Chakhmakhcheva, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 593.
198. T. Vilaivan and G. Lowe, *J. Am. Chem. Soc.*, 2002, **124**, 9326.
199. M.C. Myers, M.A. Witschi, N.V. Larionova, J.M. Franck, R.D. Haynes, T. Hara, A. Grajkowski and D.H. Appella, *Org. Lett.*, 2003, **5**, 2695.
200. T. Govindaraju, R.G. Gonnade, M.M. Bhadbhade, V.A. Kumar and K.N. Ganesh, *Org. Lett.*, 2003, **5**, 3013.
201. T. Govindaraju, V.A. Kumar and K.N. Ganesh, *Chem. Commun.*, 2004, 860.
202. T. Govindaraju, V.A. Kumar and K.N. Ganesh, *J. Org. Chem.*, 2004, **69**, 1858.
203. P.S. Shirude, V.A. Kumar and K.N. Ganesh, *Tetrahedron Lett.*, 2004, **45**, 3085.
204. P. Lonkar and V.A. Kumar, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1105.
205. P.S. Lonkar and V.A. Kumar, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2147.
206. L.D. Fader, E.L. Myers and Y.S. Tsantrizos, *Tetrahedron*, 2004, **60**, 2235.
207. Z. Bajor, G. Sági, Z. Tegyey and F. Kraicsovits, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1963.
208. M. D'Costa, V.A. Kumar and K.N. Ganesh, *J. Org. Chem.*, 2003, **68**, 4439.
209. N. Branda, G. Kurz and J.M. Lehn, *Chem. Commun.*, 1996, 2443.
210. D. Chen, Meena, S.K. Sharma and L.W. McLaughlin, *J. Am. Chem. Soc.*, 2004, **126**, 70.

211. K.G. Rajeev, M.A. Maier, E.A. Lesnik and M. Manoharan, *Org. Lett*., 2002, **4**, 4395.
212. I.V. Smolina and V.V. Demidov, *Chem. Biol*., 2003, **10**, 591.
213. E. Protozanova, V.V. Demidov, P.E. Nielsen and M.D. Frank-Kamenetskii, *Nucl. Acids Res*., 2003, **31**, 3929.
214. H. Kuhn, D.I. Cherny, V.V. Demidov and M.D. Frank-Kamenetskii, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 7548.
215. A. Okamoto, K. Tanabe and I. Saito, *J. Am. Chem. Soc*., 2002, **124**, 10262.
216. H. Kuhn, Y. Hu, M.D. Frank-Kamenetskii and V.V. Demidov, *Biochemistry*, 2003, **42**, 4985.
217. K.A. Frey and S.A. Woski, *Chem. Commun*., 2002, 2206.
218. T. Bentin and P.E. Nielsen, *J. Am. Chem. Soc*., 2003, **125**, 6378.
219. A.A. Mokhir and R. Kraemer, *Bioconjugate Chem*., 2003, **14**, 877.
220. H. Ikeda, Y. Nakamura and I. Saito, *Tetrahedron Lett*., 2002, **43**, 5525.
221. G.F. Ross, P.M. Smith, A. McGregor, D.M. Turnbull and R.N. Lightowlers, *Bioconjugate Chem*., 2003, **14**, 962.
222. F. Debaene and N. Winssinger, *Org. Lett*., 2003, **5**, 4445.
223. A. Mokhir, B. Zohm, A. Fuessl and R. Kraemer, *Bioorg. Med. Chem. Lett*., 2003, **13**, 2489.
224. A. Cerasi, E. Millo, M.F. Ottaviani, G. Damonte, M. Cangiotti, U. Benatti and L. Chiarantini, *Tetrahedron Lett*., 2003, **44**, 8701.
225. L. Petersen, M.C. de Koning, P. van Kuik-Romeijn, J. Weterings, C.J. Pol, G. Platenburg, M. Overhand, G.A. van der Marel and J.H. van Boom, *Bioconjugate Chem*., 2004, **15**, 576.
226. R. Hamzavi, F. Dolle, B. Tavitian, O. Dahl and P.E. Nielsen, *Bioconjugate Chem*., 2003, **14**, 941.
227. A. Whitney, G. Gavory and S. Balasubramanian, *Chem. Commun*., 2003, 36.
228. A. Mokhir, R. Krämer and H. Wolf, *J. Am. Chem. Soc*., 2004, **126**, 6208.
229. A. Mokhir, R. Stiebing and R. Kraemer, *Bioorg. Med. Chem. Lett*., 2003, **13**, 1399.
230. F. Gallazzi, Y. Wang, F. Jia, N. Shenoy, L.A. Landon, M. Hannink, S.Z. Lever and M.R. Lewis, *Bioconjugate Chem*., 2003, **14**, 1083.
231. A. Mokhir, R. Krämer, Y.Z. Voloshin and O.A. Varzatskii, *Bioorg. Med. Chem. Lett*., 2004, **14**, 2927.
232. I.K. Cheah, S.S. Cheema, S.J. Langford, E.C. Lopes, K.J. Macfarlane, S. Petratos and B.J. Turner, *Bioorg. Med. Chem. Lett*., 2003, **13**, 2377.
233. A.M. Siwkowski, L. Malik, C.C. Esau, M.A. Maier, E.V. Wancewicz, K. Albertshofer, B.P. Monia, C.F. Bennett and A.B. Eldrup, *Nucl. Acids Res*., 2004, **32**, 2695.
234. S.M.W. van Rossenberg, K.M. Sliedregt-Bol, P. Prince, T.J.C. van Berkel, J.H. van Boom, G.A. van der Marel and E.A.L. Biessen, *Bioconjugate Chem*., 2003, **14**, 1077.
235. V. Rapozzi, B.E.A. Burm, S. Cogoi, G.A. van der Marel, J.H. van Boom, F. Quadrifoglio and L.E. Xodo, *Nucl. Acids Res*., 2002, **30**, 3712.
236. S. Cogoi, V. Rapozzi and L. E. Xodo, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1615.
237. N. Dias, C. Sénamaud-Beaufort, E. le Forestier, C. Auvin, C. Hélène and T.E. Saison-Behmoaras, *J. Mol. Biol*., 2002, **320**, 489.
238. L. Chiarantini, A. Cerasi, A. Fraternale, F. Andreoni, S. Scarí, M. Giovine, E. Clavarino and M. Magnani, *Biochemistry*, 2002, **41**, 8471.

239. Y. Liu, D.A. Braasch, C.J. Nulf and D.R. Corey, *Biochemistry*, 2004, **43**, 1921.
240. A. Slaitas, C. Ander, Z. Földes-Papp, R. Rigler and E. Yeheskiely, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1603.
241. B. Liu, Y. Han, A. Ferdous, D.R. Corey and T. Kodadek, *Chem. Biol.*, 2003, **10**, 909.
242. C. Molenaar, K. Wiesmeijer, N.P. Verwoerd, S. Khazen, R. Eils, H.J. Tanke and R.W. Dirks, *EMBO J.*, 2003, **22**, 6631.
243. K. Kaihatsu, R.H. Shah, X. Zhao and D.R. Corey, *Biochemistry*, 2003, **42**, 13996.
244. X. Zhao, K. Kaihatsu and D.R. Corey, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 535.
245. K. Ishiyama, G.E. Smyth, T. Ueda, Y. Masutomi, T. Ohgi and J. Yano, *J. Am. Chem. Soc.*, 2004, **126**, 7476.
246. F. Darfeuille, A. Arzumanov, M.J. Gait, C. Di Primo and J.-J. Toulmé, *Biochemistry*, 2002, **41**, 12186.
247. D. Yu, E.R. Kandimalla, Q. Zhao, L. Bhagat, Y. Cong and S. Agrawal, *Bioorg. Med. Chem.*, 2003, **11**, 459.
248. T. Hamma, A. Saleh, I. Huq, T.M. Rana and P.S. Miller, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1845.
249. R.A. Cassidy, N. Puri and P.S. Miller, *Nucl. Acids Res.*, 2003, **31**, 4099.
250. C.E. Prater and P.S. Miller, *Bioconjugate Chem.*, 2004, **15**, 498.
251. B.H. Yoo, E. Bochkareva, A. Bochkarev, T.-C. Mou and D.M. Gray, *Nucl. Acids Res.*, 2004, **32**, 2008.
252. E. Rozners and J. Moulder, *Nucl. Acids Res.*, 2004, **32**, 248.
253. D.S. Novopashina, A.N. Sinyakov, V.A. Ryabinin, A.G. Venyaminova, L. Perroualt, E. Brunet, C. Giovannangeli and A.S. Boutorine, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 1015.
254. M. Fa, A. Radeghieri, A.A. Henry and F.E. Romesberg, *J. Am. Chem. Soc.*, 2004, **126**, 1748.
255. H. Åström, N.H. Williams and R. Strömberg, *Org. Biomol. Chem.*, 2003, **1** 1461.
256. I. Okamoto, K.-i. Shohda, K. Seio and M. Sekine, *J. Org. Chem.*, 2003, **68**, 9971.
257. M. Amarzguioui, T. Holen, E. Babaie and H. Prydz, *Nucl. Acids Res.*, 2003, **31**, 589.
258. M. Polak, M. Manoharan, G.B. Inamati and J. Plavec, *Nucl. Acids Res.*, 2003, **31**, 2066.
259. K.G. Rajeev, T.P. Prakash and M. Manoharan, *Org. Lett.*, 2003, **5**, 3005.
260. T.P. Prakash, M. Manoharan, A.M. Kawasaki, A.S. Fraser, E.A. Lesnik, N. Sioufi, J.M. Leeds, M. Teplova and M. Egli, *Biochemistry*, 2002, **41**, 11642.
261. V.T. Ravikumar and D.L. Cole, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1639.
262. Z. Chen, B.P. Monia and D.R. Corey, *J. Med. Chem.*, 2002, **45**, 5423.
263. O.M. Gritsenko, E.V. Koudan, S.N. Mikhailov, B.S. Ermolinsky, A. Van Aerschot, P. Herdewijn and E. S. Gromova, *Nucleosides, Nucleotides & Nucl. Acids*, 2002, **21**, 753.
264. M. Prhavc, T.P. Prakash, G. Minasov, P.D. Cook, M. Egli and M. Manoharan, *Org. Lett.*, 2003, **5**, 2017.
265. T.P. Prakash, A.M. Kawasaki, E.A. Lesnik, N. Sioufi and M. Manoharan, *Tetrahedron*, 2003, **59**, 7413.
266. T.P. Prakash, J.F. Johnston, M.J. Graham, T.P. Condon and M. Manoharan, *Nucl. Acids Res.*, 2004, **32**, 828.

267. M. Kundu, F. Nagatsugi, A. Majumdar, P.S. Miller and M.M. Seidman, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1927.
268. T.P. Prakash, A.M. Kawasaki, E.A. Lesnik, S.R. Owens and M. Manoharan, *Org. Lett.*, 2003, **5**, 403.
269. T.P. Prakash, A. Püschl, E. Lesnik, V. Mohan, V. Tereshko, M. Egli and M. Manoharan, *Org. Lett.*, 2004, **6**, 1971.
270. N. Puri, A. Majumdar, B. Cuenoud, P.S. Miller and M.M. Seidman, *Biochemistry*, 2004, **43**, 1343.
271. E. Kawashima, D. Itoh, K. Kamaike, Y. Terui and T. Oshima, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1309.
272. Y. Ueno, S. Okatani, Y. Yamada and Y. Kitade, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3959.
273. Y. Ueno, Y. Kato, S. Okatani, N. Ishida, M. Nakanishi and Y. Kitade, *Bioconj. Chem.*, 2003, **14**, 690.
274. H. Sawai, A. Hirano, H. Mori, K. Shinozuka, B. Dong and R.H. Silverman, *J. Med. Chem.*, 2003, **46**, 4926.
275. S. Sinha, P.H. Kim and C. Switzer, *J. Am. Chem. Soc.*, 2004, **126**, 40.
276. K.A. Agha and M.J. Damha, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1175.
277. T. Aboul-Fadl, V.K. Agrawal, R.W. Buckheit and A.D. Broom, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 545.
278. K. Sasaki, T. Kubo, R. Ueki, M. Yano, Y. Anno, H. Ohba and M. Fujii, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1447.
279. N.N. Dioubankova, A.D. Malakhov, Z.O. Shenkarev and V.A. Korshun, *Tetrahedron*, 2004, 4617.
280. N.N. Dioubankova, A.D. Malakhov, D.S. Stetsenko, M.J. Gait, P.E. Volynsky, R.G. Efremov and V.A. Korshun, *Chem. Bio. Chem.*, 2003, **4**, 841.
281. A. Mahara, R. Iwase, T. Sakamoto, K. Yamana, T. Yamaoka and A. Murakami, *Angew. Chem. Int. Ed.*, 2002, **41**, 3648.
282. A. Mahara, R. Iwase, T. Sakamoto, T. Yamaoka, K. Yamana and A. Murakami, *Bioorg. Med. Chem.*, 2003, **11**, 2783.
283. A. Misra, S. Mishra and K. Misra, *Bioconjugate Chem.*, 2004, **15**, 638.
284. Y. Buzin, N. Carrasco and Z. Huang, *Org. Lett.*, 2004, **6**, 1099.
285. N. Carrasco, Y. Buzin, E. Tyson, E. Halpert and Z. Huang, *Nucl. Acids Res.*, 2004, **32**, 1638.
286. C.J. Wilds, R. Pattanayek, C. Pan, Z. Wawrzak and M. Egli, *J. Am. Chem. Soc.*, 2002, **124**, 14910.
287. J.B.J. Pavey, A.J. Lawrence, I.A. O'Neil, S. Vortler and R. Cosstick, *Org. Biomol. Chem.*, 2004, **2**, 869.
288. J.W. Pham, I. Radhakrishnan and E.J. Sontheimer, *Nucl. Acids Res.*, 2004, **32**, 3446.
289. K.F. Blount, N.L. Grover, V. Mokler, L. Beigelman and O.C. Uhlenbeck, *Chem. Biol.*, 2002, **9**, 1009.
290. D.M. John, E.J. Merino and K.M. Weeks, *J. Mol. Biol.*, 2004, **337**, 611.
291. W.H. Connors, S. Narayanan, O.P. Kryatova and C. Richert, *Org. Lett.*, 2003, **5**, 247.
292. O. Schiemann, A. Weber, T.E. Edwards, T.F. Prisner and S.T. Sigurdsson, *J. Am. Chem. Soc.*, 2003, **125**, 3434.
293. K. Kawai, K. Miyamoto, S. Tojo and T. Majima, *J. Am. Chem. Soc.*, 2003, **125**, 912.

294. K. Kawai, K. Kawabata, S. Tojo and T. Majima, *Bioorg. Med. Chem. Lett*., 2002, **12**, 2363.
295. K.L. Buchmueller, B.T. Hill, M.S. Platz and K.M. Weeks, *J. Am. Chem. Soc*., 2003, **125**, 10850.
296. D.R. Yazbeck, K.-L. Min and M.J. Damha, *Nucl. Acids Res*., 2002, **30**, 3015.
297. Y. Ueno, Y. Yamada, M. Nakanishi and Y. Kitade, *Bioorg. Med. Chem*., 2003, **11**, 5069.
298. K.-L. Min, E. Viazovkina, A. Galarneau, M.A. Parniak and M.J. Damha, *Bioorg. Med. Chem. Lett*., 2002, **12**, 2651.
299. M.M. Mangos, K.-L. Min, E. Viazovkina, A. Galarneau, M.I. Elzagheid, M.A. Parniak and M.J. Damha, *J. Am. Chem. Soc*., 2003, **125**, 654.
300. E. Viazovkina, M.M. Mangos and M.J. Damha, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1251.
301. P.M. Gordon, R. Fong, S.K. Deb, N.-S. Li, J.P. Schwans, J.-D. Ye and J.A. Piccirilli, *Chem. Biol*., 2004, **11**, 237.
302. G. Sabbagh, K.J. Fettes, R. Gosain, I.A. O'Neil and R. Cosstick, *Nucl. Acids Res*., 2004, **32**, 495.
303. P. Chirakul and S.T. Sigurdsson, *Org. Lett*., 2003, **5**, 917.
304. D. MacDonald and P. Lu, *J. Am. Chem. Soc*., 2002, **124**, 9722.
305. D. Lindegaard and J. Wengel, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1159.
306. I. Detmer, D. Summerer and A. Marx, *Chem. Commun*., 2002, 2314.
307. I. Detmer, D. Summerer and A. Marx, *Eur. J. Org. Chem*., 2003, 1837.
308. M. Strerath, J. Cramer, T. Restle and A. Marx, *J. Am. Chem. Soc*., 2002, **124**, 11230.
309. M. Strerath and A. Marx, *Angew. Chem. Int. Ed*., 2002, **41**, 4766.
310. M. Strerath, J. Gaster, D. Summerer and A. Marx, *Chem. Bio. Chem*, 2004, **5**, 333.
311. T. Bryld, T. Højland and J. Wenger, *Chem. Commun*., 2004, 1064.
312. N. Atsumi, Y. Ueno, M. Kanazaki, S. Shuto and A. Matsuda, *Bioorg. Med. Chem*., 2002, **10**, 2933.
313. R. Liboska, M. Budesínsky, I. Dvoráková-Kavenová, O. Páv and I. Rosenberg, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1057.
314. A. Häberli, A. Mayer and C.J. Leumann, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1187.
315. E. Kawashima, T. Sekine, K. Umabe, K. Kamaike, T. Mizukoshi, N. Shimba, E.-i. Suzuki and C. Kojima, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 255.
316. J.A.R. Stütz and C. Richert, *Tetrahedron Lett*., 2004, **45**, 509.
317. S.S. Jain, F.A.L. Anet, C.J. Stahle and N.V. Hud, *Angew. Chem. Int. Ed*., 2004, **43**, 2004.
318. Z. Kupihár, G. Kovács, Z. Kele, Z. Darula and L. Kovács, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1297.
319. V.V. Filichev and E.B. Pedersen, *Bioorg. Med. Chem. Lett*., 2004, **14**, 581.
320. V.V. Filichev, B. Vester and E.B. Pedersen, *Bioorg. Med. Chem*., 2004, **12**, 2843.
321. H. Trafelet, S.P. Parel and C.J. Leumann, *Helv. Chim. Acta*, 2003, **86**, 3671.
322. A.P. Massey and S.T. Sigurdsson, *Nucl. Acids Res*., 2004, **32**, 2017.
323. C. Frauendorf, F. Hausch, I. Röhl, A. Lichte, S. Vonhoff and S. Klussmann, *Nucl. Acids Res*., 2003, **31**, e34.
324. K. Shinozuka, N. Matsumoto, H. Suzuki, T. Moriguchi and H. Sawai, *Chem. Commun*., 2002, 2712.

325. S. Obika, D. Nanbu, Y. Hari, K. Morio, Y. In, T. Ishida and T. Imanishi, *Tetrahedron Lett*., 1997, **38**, 8735.
326. S.K. Singh, P. Nielsen, A.A. Koshkin and J. Wengel, *Chem. Commun*., 1998, 455.
327. A. Lauritsen, B.M. Dahl, O. Dahl, B. Vester and J. Wengel, *Bioorg. Med. Chem. Lett*., 2003, **13**, 253.
328. M.D. Sørensen, M. Petersen and J. Wengel, *Chem. Commun*., 2003, 2130.
329. S. Obika, O. Nakagawa, A. Hiroto, Y. Hari and T. Imanishi, *Chem. Commun*., 2003, 2202.
330. C. Rosenbohm, D.S. Pedersen, M. Frieden, F.R. Jensen, S. Arent, S. Larsen and T. Koch, *Bioorg. Med. Chem*., 2004, **12**, 2385.
331. A.A. Koshkin, *J. Org. Chem*., 2004, **69**, 3711.
332. B.R. Babu, A.K. Prasad, S. Trikha, N. Thorup, V.S. Parmar and J. Wengel, *J. Chem. Soc. Perkin Trans. I*, 2002, 2509.
333. B.R. Babu and J. Wengel, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1317.
334. S. Obika, Y. Hari, M. Sekiguchi and T. Imanishi, *Chem. Eur. J*., 2002, **8**, 4796.
335. H. Torigoe, Y. Hari, S. Obika and T. Imanishi, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1097.
336. Y. Hari, S. Obika, M. Sekiguchi and T. Imanishi, *Tetrahedron*, 2003, **59**, 5123.
337. H. Torigoe, Y. Hari, S. Obika and T. Imanishi, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1571.
338. N.K. Christensen, M. Petersen, B. Vester and P. Nielsen, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1143.
339. N.K. Christensen, T. Bryld, M.D. Sørensen, K. Arar, J. Wengel and P. Nielsen, *Chem. Commun*., 2004, 282.
340. Raunak, B.R. Babu, M.D. Sørensen, V.S. Parmar, N.H. Harrit and J. Wengel, *Org. Biomol. Chem*., 2004, **2**, 80.
341. T. Imanishi and S. Obika, *Chem. Commun*., 2002, 1653.
342. K. Morita, M. Takagi, C. Hasegawa, M. Kaneko, S. Tsutsumi, J. Sone, T. Ishikawa, T. Imanishi and M. Koizumi, *Bioorg. Med. Chem*., 2003, **11**, 2211.
343. M. Koizumi, K. Morita, M. Daigo, S. Tsutsumi, K. Abe, S. Obika and T. Imanishi, *Nucl. Acids Res*., 2003, **31**, 3267.
344. P.I. Pradeepkumar, N.V. Amirkhanov and J. Chattopadhyaya, *Org. Biomol. Chem*., 2003, **1**, 81.
345. B.R. Babu, L. Keinicke, M. Petersen, C. Nielsen and J. Wengel, *Org. Biomol. Chem*., 2003, **1**, 3514.
346. B.R. Babu, L. Keinicke and J. Wengel, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1313.
347. M. Raunkjær, T. Bryld and J. Wengel, *Chem. Commun*., 2003, 1604.
348. D.-R. Ahn, A. Egger, C. Lehmann, S. Pitsch and C.J. Leumann, *Chem. Eur. J*., 2002, **8**, 5312.
349. D.-R. Ahn, M. Mosimann and C.J. Leumann, *J. Org. Chem*., 2003, **68**, 7693.
350. D.-R. Ahn, M. Mosimann and C.J. Leumann, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1207.
351. J. Becaud, I. Pompizi and C.J. Leumann, *J. Am. Chem. Soc*., 2003, **125**, 15338.
352. D. Renneberg, E. Bouliong, U. Reber, D. Schümperli and C.J. Leumann, *Nucl. Acids Res*., 2002, **30**, 2751.
353. H. Urata, H. Miyagoshi, T. Kumashiro, T. Yumoto, K. Mori, K. Shoji, K. Gohda and M. Akagi, *Org. Biomol. Chem*., 2004, **2**, 183.
354. P.M. McTigue, R.J. Peterson and J.D. Kahn, *Biochemistry*, 2004, **43**, 5388.
355. D.A. Braasch, Y. Liu and D.R. Corey, *Nucl. Acids Res*., 2002, **30**, 5160.

356. N. Jacobsen, P.S. Nielsen, D.C. Jeffares, J. Eriksen, H. Ohlsson, P. Arctander and S. Kauppinen, *Nucl. Acids Res.*, 2004, **32**, e64.
357. K.M.L. Hertoghs, J.H. Ellis and I.R. Catchpole, *Nucl. Acids Res.*, 2003, **31**, 5817.
358. N. Jacobsen, J. Bentzen, M. Meldgaard, M.H. Jakobsen, M. Fenger, S. Kauppinen and J. Skouv, *Nucl. Acids Res.*, 2002, **30**, e100.
359. A. Simeonov and T.T. Nikiforov, *Nucl. Acids Res.*, 2002, **30**, e91.
360. M.P. Johnson, L.M. Haupt and L.R. Griffiths, *Nucl. Acids Res.*, 2004, **32**, e55.
361. M. Frieden, H.F. Hansen and T. Koch, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1041.
362. D.A. Di Giusto and G.C. King, *Nucl. Acids Res.*, 2004, **32**, e32.
363. H. Parekh-Olmedo, M. Drury and E.B. Kmiec, *Chem. Biol.*, 2002, **9**, 1073.
364. B.-W. Sun, B.R. Babu, M.D. Sørensen, K. Zakrzewska, J. Wengel and J.-S. Sun, *Biochemistry*, 2004, **43**, 4160.
365. P.K. Dominick and M.B. Jarstfer, *J. Am. Chem. Soc.*, 2004, **126**, 5050.
366. J.B. Hansen, M. Westergaard, C.A. Thrue, B. Giwercman and H. Oerum, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1607.
367. A.N. Elayadi, D.A. Braasch and D.R. Corey, *Biochemistry*, 2002, **41**, 9973.
368. K. Fluiter, A.L.M.A. ten Asbroek, M.B. de Wissel, M.E. Jakobs, M. Wissenbach, H. Olsson, O. Olsen, H. Oerum and F. Baas, *Nucl. Acids Res.*, 2003, **31**, 953.
369. R.G. Fahmy and L.M. Khachigian, *Nucl. Acids Res.*, 2004, **32**, 2281.
370. D.A. Braasch, S. Jensen, Y. Liu, K. Kaur, K. Arar, M.A. White and D.R. Corey, *Biochemistry*, 2003, **42**, 7967.
371. A. Grünweller, E. Wyszko, B. Bieber, R. Jahnel, V.A. Erdmann and J. Kurreck, *Nucl. Acids Res.*, 2003, **31**, 3185.
372. M. Frieden, S.M. Christensen, N.D. Mikkelsen, C. Rosenbohm, C.A. Thrue, M. Westergaard, H.F. Hansen, H. Ørum and T. Koch, *Nucl. Acids Res.*, 2003, **31**, 6365.
373. J. Wengel, B. Vester, L.B. Lundberg, S. Douthwaite, M.D. Sørensen, B.R. Babu, M.J. Gait, A. Arzumanov, M. Petersen and J.T. Nielsen, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 601.
374. R. Crinelli, M. Bianchi, L. Gentilini, L. Palma, M.D. Sørensen, T. Bryld, R.B. Babu, K. Arar, J. Wengel and M. Magnani, *Nucl. Acids Res.*, 2004, **32**, 1874.
375. D. Ittig, S. Liu, D. Renneberg, D. Schümperli and C.J. Leumann, *Nucl. Acids Res.*, 2004, **32**, 346.
376. K. Morita, K. Yamate, S. Kurakata, K. Watanabe, T. Imanishi and M. Koizumi, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1619.
377. M. Takagi, K. Morita, D. Nakai, R. Nakagomi, T. Tokui and M. Koizumi, *Biochemistry*, 2004, **43**, 4501.
378. T. Boesen, D.S. Pedersen, B.M. Nielsen, A.B. Petersen, U. Henriksen, B.M. Dahl and O. Dahl, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 847.
379. H. Hakala, P. Ollikka, J. Degerholm and J. Hovinen, *Tetrahedron*, 2002, **58** 8771.
380. V.V. Filichev, K.M.H. Hilmy, U.B. Christensen and E.B. Pedersen, *Tetrahedron Lett.*, 2004, **45**, 4907.
381. B. Nawrot, O. Michalak, M. Nowak, A. Okruszek, M. Dera and W.J. Stec, *Tetrahedron Lett.*, 2002, **43**, 5397.
382. N.N. Dioubankova, A.D. Malakov, D.S. Stetsenko, V.A. Korshun and M.J. Gait, *Org. Lett.*, 2002, **4**, 4607.
383. T. Wu, M. Froeyen, G. Schepers, K. Mullens, J. Rozenski, R. Busson, A. Van Aerschot and P. Herdewijn, *Org. Lett.*, 2004, **6**, 51.

384. H. Ozaki, K. Nakajima, K. Tatsui, C. Izumi, M. Kuwahara and H. Sawai, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2441.
385. N.E. Poopeiko, B.M. Dahl and J. Wengel, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1147.
386. N.E. Poopeiko, M. Juhl, B. Vester M.D. Sørensen and J. Wengel, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2285.
387. S. Ivanov, Y. Alekseev, J.-R. Bertrand, C. Malvy and M.B. Gottikh, *Nucl. Acids Res.*, 2003, **31**, 4256.
388. H.M. Moulton, M.H. Nelson, S.A. Hatlevig, M.T. Reddy and P.L. Iversen, *Bioconjugate Chem.*, 2004, **15**, 290.
389. A. Van Aerschot, A. Marchand, G. Schepers, W. Van den Eynde, J. Rozenski, R. Busson and P. Herdewijn, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1227.
390. K.-U. Schöning, P. Scholz, X. Wu, S. Guntha, G. Delgado, R. Krishnamurthy and A. Eschenmoser, *Helv. Chim. Acta*, 2002, **85**, 4111.
391. V. Kempeneers, K. Vastmans, J. Rozenski and P. Herdewijn, *Nucl. Acids Res.*, 2003, **31**, 6221.
392. J.C. Chaput, J.K. Ichida and J.W. Szostak, *J. Am. Chem. Soc.*, 2003, **125**, 856.
393. J.C. Chaput and J.W. Szostak, *J. Am. Chem. Soc.*, 2003, **125**, 9274.
394. J. Cabello-Villegas, I. Tworowska and E.P. Nikonowicz, *Biochemistry*, 2004, **43**, 55.
395. A.C. Bajji and D.R. Davis, *J. Org. Chem.*, 2002, **67**, 5352.
396. A.C. Bajji, M. Sundaram, D.G. Myszka and D.R. Davis, *J. Am. Chem. Soc.*, 2002, **124**, 14302.
397. E.V. Efimtseva, S.N. Mikhailov, J. Rozenski, R. Busson, A. Van Aerschot and P. Herdewijn, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1113.
398. L.S. Chen and T.L. Sheppard, *Nucleosides, Nucleotides & Nucl. Acids*, 2002, **21**, 599.
399. E. Kierzek and R. Kierzek, *Nucl. Acids Res.*, 2003, **31**, 4461.
400. E. Kierzek and R. Kierzek, *Nucl. Acids Res.*, 2003, **31**, 4472.
401. S.-i. Nakano, Y. Uotani, S. Nakashima, Y. Anno, M. Fujii and N. Sugimoto, *J. Am. Chem. Soc.*, 2003, **125**, 8086.
402. K. Satou, H. Harashima and H. Kamiya, *Nucl. Acids Res.*, 2003, **31**, 2570.
403. V.M. Carvalho, D. Gasparutto, P. Di Mascio, M.H.G. Medeiros and J. Cadet, *Bioorg. Med. Chem.*, 2003, **11**, 2445.
404. N. Koissi and H. Lönnberg, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1135.
405. A.B. Guliaev, B. Hang and B. Singer, *Nucl. Acids Res.*, 2002, **30**, 3778.
406. Y. Zhao and A.M. Baranger, *J. Am. Chem. Soc.*, 2003, **125**, 2480.
407. N.P. Johnson, W.A. Baase and P.H. von Hippel, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 3426.
408. V. Esposito, A. Randazzo, A. Galeone, M. Varra and L. Mayol, *Bioorg. Med. Chem.*, 2004, **12**, 1191.
409. L. Lermer, J. Hobbs and D.M. Perrin, *Nucleosides, Nucleotides & Nucl. Acids*, 2002, **21**, 651.
410. L.S. Chen, M.H. Bahr and T.L. Sheppard, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1509.
411. S.K. Kim, J.Y. Kim, A.K. Baek and B.J. Moon, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1977.
412. C.J. Wiederholt, M.O. Delaney and M.M. Greenberg, *Biochemistry*, 2002, **41**, 15838.

413. P. Jaruga, J. Theruvathu, M. Dizdaroglu and P.J. Brooks, *Nucl. Acids Res.*, 2004, **32**, e87.
414. T.M. Schinecker, R.A. Perlow, S. Broyde, N.E. Geacintov and D.A. Scicchitano, *Nucl. Acids Res.*, 2003, **31**, 6004.
415. J. Wu, B.-B. Zhu, J. Yu, H. Zhu, L. Qiu, M.S. Kindy, L. Gu, A. Seidel and G.-M. Li, *Nucl. Acids Res.*, 2003, **31**, 6428.
416. E.G. Frank, J.M. Sayer, H. Kroth, E. Ohashi, H. Ohmori, D.M. Jerina and R. Woodgate, *Nucl. Acids Res.*, 2002, **30**, 5284.
417. M.A. Graziewicz, J.M. Sayer, D.M. Jerina and W.C. Copeland, *Nucl. Acids Res.*, 2004, **32**, 397.
418. S.F. Yan, M. Wu, N.E. Geacintov and S. Broyde, *Biochemistry*, 2004, **43**, 7750.
419. S. Yan, M. Wu, T. Buterin, H. Naegeli, N.E. Geacintov and S. Broyde, *Biochemistry*, 2003, **42**, 2339.
420. C.L. Hendrickson, K.G. Devine and S.A. Benner, *Nucl. Acids Res.*, 2004, **32**, 2241.
421. A.S. Maki, T. Kim and E.T. Kool, *Biochemistry*, 2004, **43**, 1102.
422. J.B. Tuite, J.C. Shiels and A.M. Baranger, *Nucl. Acids Res.*, 2002, **30**, 5269.
423. A. Madder, R. Ehrl and R. Strömberg, *Chem. Bio. Chem.*, 2003, **4**, 1194.
424. A. Madder, R. Ehrl and R. Strömberg, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1289.
425. J.L. Wolfe, T. Kawate, D.A. Sarracino, M. Zillmann, J. Olson, V.P. Stanton and G.L. Verdine, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 11073.
426. J. He, G. Becher, S. Budow and F. Seela, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 573.
427. J. He and F. Seela, *Org. Biomol. Chem.*, 2003, **1**, 1873.
428. E.A. Véliz, L.M. Easterwood and P.A. Beal, *J. Am. Chem. Soc.*, 2003, **125**, 10867.
429. J. He and F. Seela, *Nucl. Acids Res.*, 2002, **30**, 5485.
430. A. Aviñó, E. Cubero, C. González, R. Eritja and M. Orozco, *J. Am. Chem. Soc.*, 2003, **125**, 16127.
431. A. Aviñó, M. Frieden, J.C. Morales, B.G. de la Torre, R. Güimil-Garciá, M. Orozco, C. González and R. Eritja, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 645.
432. N. Minakawa, N. Kojima, S. Hikishika, T. Sasaki, A. Kiyosue, N. Atsumi, Y. Ueno and A. Matsuda, *J. Am. Chem. Soc.*, 2003, **125**, 9970.
433. D. Parry, S.A. Moon, H.-H. Liu, P. Heslop and B.A. Connolly, *J. Mol. Biol.*, 2003, **331**, 1005.
434. D.J. Krosky, F.P. Schwarz and J.T. Stivers, *Biochemistry*, 2004, **43**, 4188.
435. Y. Xu, R. Ikeda and H. Sugiyama, *J. Am. Chem. Soc.*, 2003, **125**, 13519.
436. I. Cherrak, O. Mauffret, F. Santamaria, A. Hocquet, M. Ghomi, B. Rayner and S. Fermandjian, *Nucl. Acids Res.*, 2003, **31**, 6986.
437. D.J. Proctor, E. Kierzek, R. Kierzek and P.C. Bevilacqua, *J. Am. Chem. Soc.*, 2003, **125**, 2390.
438. M. Kubota and A. Ono, *Tetrahedron Lett.*, 2004, **45**, 1187.
439. F.D. Lewis, Y. Wu and L. Zhang, *Chem. Commun.*, 2004, 636.
440. P. Leonard, R. Kröschel and F. Seela, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1235.
441. S.C. Johnson, C.B. Sherrill, D.J. Marshall, M.J. Moser and J.R. Prudent, *Nucl. Acids Res.*, 2004, **32**, 1937.
442. J.R. Blas, F.J. Luque and M. Orozco, *J. Am. Chem. Soc.*, 2004, **126**, 154.
443. A.M. Maciejewska, K.D. Lichota and J.T. Kusmierek, *Biochem. J.*, 2003, **369**, 611.

444. C.B. Sherrill, D.J. Marshall, M.J. Moser, C.A. Larsen, L. Daudé-Snow and J.R. Prudent, *J. Am. Chem. Soc.*, 2004, **126**, 4550.
445. M.J. Moser and J.R. Prudent, *Nucl. Acids Res.*, 2003, **31**, 5048.
446. F. Seela and R. Kröschel, *Nucl. Acids Res.*, 2003, **31**, 7150.
447. C. Beuck and E. Weinhold, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 635.
448. Q. Zheng, Y. Wang and E. Lattmann, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3141.
449. Q. Zheng, Y. Wang and E. Lattmann, *Tetrahedron*, 2003, **59**, 1925.
450. S. Puthenveetil, E.A. Véliz and P.A. Beal, *Chem. Bio. Chem.*, 2004, **5**, 383.
451. R.M. Hyde, A.D. Broom and R.W. Buckheit, *J. Med. Chem.*, 2003, **46**, 1878.
452. A. Okamoto, K. Tanaka and I. Saito, *J. Am. Chem. Soc.*, 2004, **126**, 416.
453. L. Haracska, L. Prakash and S. Prakash, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 16000.
454. C.G. Pearson, N. Shikazono, J. Thacker and P. O'Neill, *Nucl. Acids Res.*, 2004, **32**, 263.
455. O. Kornyushyna and C.J. Burrows, *Biochemistry*, 2003, **42**, 13008.
456. P.T. Henderson, J.C. Delaney, J.G. Muller, W.L. Neeley, S.R. Tannenbaum, C.J. Burrows and J.M. Essigman, *Biochemistry*, 2003, **42**, 9257.
457. O. Kornyushyna, A.M. Berges, J.G. Muller and C.J. Burrows, *Biochemistry*, 2002, **41**, 15304.
458. W.L. Neeley, P.T. Henderson and J.M. Essigmann, *Org. Lett.*, 2004, **6**, 245.
459. M.K. Hailer-Morrison, J.M. Kotler, B.D. Martin and K.D. Sugden, *Biochemistry*, 2003, **42**, 9761.
460. H. Hayakawa, T. Uchiumi, T. Fukuda, M. Ashizuka, K. Kohno, M. Kuwano and M. Sekiguchi, *Biochemistry*, 2002, **41**, 12739.
461. M.V. Taranenko, N.V. Sumbatyan, M.T. Mtchedlidze and S.A. Kuznetsova, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1505.
462. M.D. Leipold, H. Workman, J.G. Muller, C.J. Burrows and S.S. David, *Biochemistry*, 2003, **42**, 11373.
463. T. Morales-Ruiz, M. Birincioglu, P. Jaruga, H. Rodriguez, T. Roldan-Arjona and M. Dizdaroglu, *Biochemistry*, 2003, **42**, 3089.
464. A.-K. Olsen, N. Duale, M. Bjørås, C.T. Larsen, R. Wiger, J.A. Holme, E.C. Seeberg and G. Brunborg, *Nucl. Acids Res.*, 2003, **31**, 1351.
465. F. Barone, E. Dogliotti, L. Cellai, C. Giordano, M. Bjørås and F. Mazzei, *Nucl. Acids Res.*, 2003, **31**, 1897.
466. M. Ober, U. Linne, J. Gierlich and T. Carell, *Angew. Chem. Int. Ed.*, 2003, **42**, 4947.
467. C.J. Wiederholt, M.O. Delaney, M.A. Pope, S.S. David and M.M. Greenberg, *Biochemistry*, 2003, **42**, 9755.
468. C. Meyer, D. Meyer, T.A. Bickle and B. Giese, *Chem. Bio. Chem.*, 2003, **4**, 610.
469. S.-U. Lari, F. Al-Khodairy and M.C. Paterson, *Biochemistry*, 2002, **41**, 9248.
470. S. Kanugula and A.E. Pegg, *Biochem. J.*, 2003, **375**, 449.
471. J.J. Rasimas, S. Kanugula, P.M. Dalessio, I.J. Ropson, M.G. Fried and A.E. Pegg, *Biochemistry*, 2003, **42**, 980.
472. E.M. Duguid, Y. Mishina and C. He, *Chem. Biol.*, 2003, **10**, 827.
473. K.X. Luu, S. Kanugula, A.E. Pegg, G.T. Pauly and R.C. Moschel, *Biochemistry*, 2002, **41**, 8689.
474. S. Park, M. Seetharaman, A. Ogdie, D. Ferguson and N. Tretyakova, *Nucl. Acids Res.*, 2003, **31**, 1984.
475. N. Suzuki, S. Itoh, K. Poon, C. Masutani, F. Hanaoka, H. Ohmori, I. Yoshizawa and S. Shibutani, *Biochemistry*, 2004, **43**, 6304.

476. K.I.E. McLuckie, M.N. Routledge, K. Brown, M. Gaskell, P.B. Farmer, G.C.K. Roberts and E.A. Martin, *Biochemistry*, 2002, **41**, 8899.
477. M. Sako, S. Inagaki, Y. Esaka and Y. Deyashiki, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3497.
478. H.-Y.H. Kim, M. Voehler, T.M. Harris and M.P. Stone, *J. Am. Chem. Soc.*, 2002, **124**, 9324.
479. I.D. Kozekov, L.V. Nechev, M.S. Moseley, C.M. Harris, C.J. Rizzo, M.P. Stone and T.M. Harris, *J. Am. Chem. Soc.*, 2003, **125**, 50.
480. I.-Y. Yang, G. Chan, H. Miller, Y. Huang, M.C. Torres, F. Johnson and M. Moriya, *Biochemistry*, 2002, **41**, 13826.
481. S.D. Cline, J.N. Riggins, S. Tornaletti, L.J. Marnett and P.C. Hanawalt, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 7275.
482. S. Choudhury, J. Pan, S. Amin, F.-L. Chung and R. Roy, *Biochemistry*, 2004, **43**, 7514.
483. Z. Feng, W. Hu, S. Amin and M.-S. Tang, *Biochemistry*, 2003, **42**, 7848.
484. H. Wang, I.D. Kozekov, T.M. Harris and C.J. Rizzo, *J. Am. Chem. Soc.*, 2003, **125**, 5687.
485. D. Guo, Z. Xie, H. Shen, B. Zhao and Z. Wang, *Nucl. Acids Res.*, 2004, **32**, 1122.
486. S. Lone and L.J. Romano, *Biochemistry*, 2003, **42**, 3826.
487. R.A. Perlow, A. Kolbanovskiy, B.E. Hingerty, N.E. Geacintov, S. Broyde and D.A. Scicchitano, *J. Mol. Biol.*, 2002, **321**, 29.
488. X. Huang, A. Kolbanovskiy, X. Wu, Y. Zhang, Z. Wang, P. Zhuang, S. Amin and N.E. Geacintov, *Biochemistry*, 2003, **42**, 2456.
489. Z. Xie, E. Braithwaite, D. Guo, B. Zhao, N.E. Geacintov and Z. Wang, *Biochemistry*, 2003, **42**, 11253.
490. Y. Zou, H. Ma, I.G. Minko, S.M. Shell, Z. Yang, Y. Qu, Y. Xu, N.E. Geacintov and R.S. Lloyd, *Biochemistry*, 2004, **43**, 4196.
491. N. Kojima, K. Inoue, R. Nakajima-Shibata, S.-i. Kawahara and E. Ohtsuka, *Nucl. Acids Res.*, 2003, **31**, 7175.
492. F. Seela, H. Debelak, L. Andrews and L. Beigelman, *Helv. Chim. Acta*, 2003, **86**, 2726.
493. S. Jaksa, B. Kralj, C. Pannecouque, J. Balzarini, E. De Clercq and J. Kobe, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 77.
494. H. Rosemeyer, N. Ramzaeva, E.-M. Becker, E. Feiling and F. Seela, *Bioconj. Chem.*, 2002, **13**, 1274.
495. H. Rosemeyer, N. Ramzaeva, E.-M. Becker, E. Feiling and F. Seela, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1231.
496. I.V. Kutyavin, S.G. Lokhov, I.A. Afonina, R. Dempcy, A.A. Gall, V.V. Gorn, E. Lukhtanov, M. Metcalf, A. Mills, M.W. Reed, S. Sanders, I. Shishkina and N.M.J. Vermeulen, *Nucl. Acids Res.*, 2002, **30**, 4952.
497. F. Seela and R. Kröschel, *Org. Biomol. Chem.*, 2003, **1**, 3900.
498. V. Vongchampa, M. Dong, L. Gingipalli and P. Dedon, *Nucl. Acids Res.*, 2003, **31**, 1045.
499. G.E. Wuenschell, T.R. O'Connor and J. Termini, *Biochemistry*, 2003, **42**, 3608.
500. F. Seela, K. Shaikh and T. Wiglenda, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1239.
501. O. Gorchs, A. Grandas and J. Farràs, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1081.
502. J.-S. Sung and D.W. Mosbaugh, *Biochemistry*, 2003, **42**, 4613.
503. S.L. Hiley, V.D. Sood, J. Fan and R.A. Collins, *EMBO J.*, 2002, **21**, 4691.

504. P.Z. Qin, K. Hideg, J. Feigon and W.L. Hubbell, *Biochemistry*, 2003, **42**, 6772.
505. T. Schoetzau, J. Langner, E. Moyroud, I. Roehl, S. Vonhoff and S. Klussmann, *Bioconjugate Chem.*, 2003, **14**, 919.
506. M. Kuwahara, Y. Takahata, A. Shoji, A.N. Ozaki, H. Ozaki and H. Sawai, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3735.
507. A.V. Sidorov, J.A. Grasby and D.M. Williams, *Nucl. Acids Res.*, 2004, **32**, 1591.
508. V. Roig and U. Asseline, *J. Am. Chem. Soc.*, 2003, **125**, 4416.
509. A.M. Soto, B.I. Kankia, P. Dande, B. Gold and L.A. Marky, *Nucl. Acids Res.*, 2002, **30**, 3171.
510. T. Ito, Y. Ueno, Y. Komatsu and A. Matsuda, *Nucl. Acids Res.*, 2003, **31**, 2514.
511. M.M. Masud, A. Ozaki-Nakamura, M. Kuwahara, H. Ozaki and H. Sawai, *Chem. Bio. Chem.*, 2003, **4**, 584.
512. H. Ozaki, K. Nakajima, M. Kuwahara and H. Sawai, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1115.
513. H. Ozaki, M. Mine, K. Shinozuka and H. Sawai, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 339.
514. V. Guerniou, D. Gasparutto, S. Sauvaigo, A. Favier and J. Cadet, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1073.
515. D.K. Rogstad, J. Heo, N. Vaidehi, W.A. Goddard, A. Burdzy and L.C. Sowers, *Biochemistry*, 2004, **43**, 5688.
516. K. Kino, Y. Shimizu, K. Sugasawa, H. Sugiyama and F. Hanaoka, *Biochemistry*, 2004, **43**, 2682.
517. T. Sugiyama, A. Kittaka, H. Takayama, M. Tomioka, Y. Ida and R. Kuroda, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2847.
518. M. Hori, S. Yonei, H. Sugiyama, K. Kino, K. Yamamoto and Q.-M. Zhang, *Nucl. Acids Res.*, 2003, **31**, 1191.
519. J.J. Turner, N.J. Meeuwenoord, A. Rood, P. Borst, G. van der Marel and J.H. van Boom, *Eur. J. Org. Chem.*, 2003, 3832.
520. K. Matsuura, M. Hibino, T. Ikeda, Y. Yamada and K. Kobayashi, *Chem. Eur. J.*, 2004, **10**, 352.
521. M. Adamczyk, S.R. Akireddy, P.G. Mattingly and R.E. Reddy, *Tetrahedron*, 2003, **59**, 5749.
522. J. Iwahara, D.E. Anderson, E.C. Murphy and G.M. Clore, *J. Am. Chem. Soc.*, 2003, **125**, 6634.
523. P.M. Gannett, E. Darian, J. Powell, E.M. Johnson, C. Mundoma, N.L. Greenbaum, C.M. Ramsey, N.S. Dalal and D.E. Budil, *Nucl. Acids Res.*, 2002, **30**, 5328.
524. H.A. Held and S.A. Benner, *Nucl. Acids Res.*, 2002, **30**, 3857.
525. D. Graham, A. Grondin, C. McHugh, L. Fruk and W.E. Smith, *Tetrahedron Lett.*, 2002, **43**, 4785.
526. T. Oyoshi, K. Kawai and H. Sugiyama, *J. Am. Chem. Soc.*, 2003, **125**, 1526.
527. Y.-Z. Xu, X. Zhang, H.-C. Wu, A. Massey and P. Karran, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 995.
528. Y. Zeng and Y. Wang, *J. Am. Chem. Soc.*, 2004, **126**, 6552.
529. N. Piton and J.W. Engels, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1661.
530. K.N. Carter and M.M. Greenberg, *J. Am. Chem. Soc.*, 2003, **125**, 13376.
531. H. Miller, A.S. Fernandes, E. Zaika, M.M. McTigue, M.C. Torres, M. Wente, C.R. Iden and A.P. Grollman, *Nucl. Acids Res.*, 2004, **32**, 338.
532. J.-H. Yoon, S. Iwai, T.R. O'Connor and G.P. Pfeifer, *Nucl. Acids Res.*, 2003, **31**, 5399.

533. V. Guérineau, S.K.A. Matus, F. Halgand, O. Laprévote and P. Clivio, *Org. Biomol. Chem.*, 2004, **2**, 899.
534. A. Bresson and R.P.P. Fuchs, *EMBO J.*, 2002, **21**, 3881.
535. J.U.O. Mayo, M. Thomas, C. Saintomé and P. Clivio, *Tetrahedron*, 2003, **59**, 7377.
536. K. Takasawa, C. Masutani, F. Hanaoka and S. Iwai, *Nucl. Acids Res.*, 2004, **32**, 1738.
537. M.T. Washington, L. Prakash and S. Prakash, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 12093.
538. S.D. McCulloch, R.J. Kokoska, C. Masutani, S. Iwai, F. Hanaoka and T.A. Kunkel, *Nature*, 2004, **428**, 97.
539. A.W. Macfarlane and R.J. Stanley, *Biochemistry*, 2003, **42**, 8558.
540. J.-H. Lee, C.-J. Park, A.I. Arunkumar, W.J. Chazin and B.-S. Choi, *Nucl. Acids Res.*, 2003, **31**, 4747.
541. H.M.-P. Chui, J.-P. Desaulniers, S.A. Scaringe and C.S. Chow, *J. Org. Chem.*, 2002, **67**, 8847.
542. J. Mengel-Jørgensen and F. Kirpekar, *Nucl. Acids Res.*, 2002, **30**, e135.
543. M.I. Newby and N.L. Greenbaum, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 12697.
544. T. Suzuki, T. Suzuki, T. Wada, K. Saigo and K. Watanabe, *EMBO J.*, 2002, **21**, 6581.
545. A.B. Guliaev, B. Hang and B. Singer, *Nucl. Acids Res.*, 2004, **32**, 2844.
546. T. Moriguchi, T. Wada and M. Sekine, *Eur. J. Org. Chem.*, 2003, **2260**.
547. A.M. Noronha, C.J. Wilds and P.S. Miller, *Biochemistry*, 2002, **41**, 8605.
548. A. Roychowdhury, H. Illangkoon, C.L. Hendrickson and S.A. Benner, *Org. Lett.*, 2004, **6**, 489.
549. C. He and G.L. Verdine, *Chem. Biol.*, 2002, **9**, 1297.
550. M. Repkova, M. Meshchaninova and A. Venyaminova, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 969.
551. A.S. Brank, R. Eritja, R.G. Garcia, V.E. Marquez and J.K. Christman, *J. Mol. Biol.*, 2003, **323**, 53.
552. F. Seela and Y. He, *J. Org. Chem.*, 2003, **68**, 367.
553. A.M. Sismour, S. Lutz, J.-H. Park, M.J. Lutz, P.L. Boyer, S.H. Hughes and S.A. Benner, *Nucl. Acids Res.*, 2004, **32**, 728.
554. C. Dash, J.W. Rausch and S.F.J. Le Grice, *Nucl. Acids Res.*, 2004, **32**, 1539.
555. K.-Y. Lin and M. Matteucci, *J. Am. Chem. Soc.*, 1998, **120**, 8531.
556. S.C. Holmes and M.J. Gait, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1259.
557. S.C. Holmes, A.A. Arzumanov and M.J. Gait, *Nucl. Acids Res.*, 2003, **31**, 2759.
558. P. Kong Thoo Lin and D.M. Brown, *Nucl. Acids Res.*, 1989, **17**, 10373.
559. V.H. Harris, C.L. Smith, W.J. Cummins, A.L. Hamilton, H. Adams, M. Dickman, D.P. Hornby and D.M. Williams, *J. Mol. Biol.*, 2003, **326**, 1389.
560. V.H. Harris, C.L. Smith, W.J. Cummins, A.L. Hamilton, D.P. Hornby and D.M. Williams, *Org. Biomol. Chem.*, 2003, **1**, 2070.
561. J.M. Keith, D.A.E. Cochran, G.H. Lala, P. Adams, D. Bryant and K.R. Mitchelson, *Nucl. Acids Res.*, 2004, **32**, e35.
562. D. Loakes, D.M. Brown, S.A. Salisbury, M.G. McDougal, C. Neagu, S. Nampalli and S. Kumar, *Tetrahedron Lett.*, 2003, **44**, 3387.
563. D. Loakes, D.M. Brown, S.A. Salisbury, M.G. McDougal, C. Neagu, S. Nampalli and S. Kumar, *Helv. Chim. Acta*, 2003, **86**, 1193.
564. S. Buchini and C.J. Leumann, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1199.

565. S. Buchini and C.J. Leumann, *Tetrahedron Lett*., 2003, **44**, 5065.
566. J. Robles, A. Grandas and E. Pedroso, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1085.
567. D.N. Kaluzhny, S.N. Mikhailov, E.V. Efimtseva, O.F. Borisova, V.L. Florentiev, A.K. Shchyolkina and T.M. Jovin, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1499.
568. A. Okamoto, T. Taiji, K. Tainaka and I. Saito, *Bioorg. Med. Chem. Lett*., 2002, **12**, 1895.
569. F. Nagatsugi, S. Sasaki, P.S. Miller and M.M. Seidman, *Nucl. Acids Res*., 2003, **31**, e31.
570. M.E. Hawkins and F.M. Balis, *Nucl. Acids Res*., 2004, **32**, e62.
571. S. Sasaki, Y. Taniguchi, R. Takahashi, Y. Senko, K. Kodama, F. Nagatsugi and M. Maeda, *J. Am. Chem. Soc*., 2004, **126**, 516.
572. H. Liu, J. Gao, S.R. Lynch, Y.D. Saito, L. Maynard and E.T. Kool, *Science*, 2003, **302**, 868.
573. M. Kimoto, M. Endo, T. Mitsui, T. Okuni, I. Hirao and S. Yokoyama, *Chem. Biol*., 2004, **11**, 47.
574. M. Endo, T. Mitsui, T. Okuni, M. Kimito, I. Hirao and S. Yokoyama, *Bioorg. Med. Chem. Lett*., 2004, **14**, 2593.
575. T. Mitsui, A. Kitamura, M. Kimoto, T. To, A. Sato, I. Hirao and S. Yokoyama, *J. Am. Chem. Soc*., 2003, **125**, 5298.
576. T. Mitsui, M. Kimito, A. Sato, S. Yokoyama and I. Hirao, *Bioorg. Med. Chem. Lett*., 2003, **13**, 4515.
577. D. Loakes, *Nucl. Acids Res*., 2001, **29**, 2437.
578. R. Nichols, P.C. Andrews, P. Zhang and D.E. Bergstrom, *Nature*, 1994, **369**, 492.
579. D. Burgner, M. D'Amato, D.P. Kwiatkowski and D. Loakes, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 755.
580. D.A. Harki, J.D. Graci, V.S. Korneeva, S.K.B. Ghosh, Z. Hong, C.E. Cameron and B.R. Peterson, *Biochemistry*, 2002, **41**, 9026.
581. K. Walczak, M. Wamberg and E.B. Pedersen, *Helv. Chim. Acta*, 2004, **87**, 469.
582. M. Chiaramonte, C.L. Moore, K. Kincaid and R.D. Kuchta, *Biochemistry*, 2003, **42**, 10472.
583. E.Z. Reineks and A.J. Berdis, *Biochemistry*, 2004, **43**, 393.
584. X. Zhang, I. Lee and A.J. Berdis, *Org. Biomol. Chem*., 2004, **2**, 1703.
585. F.J. Ghadessy, N. Ramsay, F. Boudsocq, D. Loakes, A. Brown, S. Iwai, A. Vaisman, R. Woodgate and P. Holliger, *Nature Biotech*., 2004, **22**, 755.
586. F. Seela and A. Jawalekar, *Helv. Chim. Acta*, 2002, **85**, 1857.
587. N.V. Vo, K.-C. Young and M.M.C. Lai, *Biochemistry*, 2003, **42**, 10462.
588. N. Paul, V.C. Nashine, G. Hoops, P. Zhang, J. Zhou, D.E. Bergstrom and V.J. Davisson, *Chem. Biol*., 2003, **10**, 815.
589. S. Pochet, L. Dugué and H. Strobel, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1665.
590. S. Matsuda, A.A. Henry, P.G. Schultz and F.E. Romesberg, *J. Am. Chem. Soc*., 2003, **125**, 6134.
591. C. Yu, A.A. Henry, F.E. Romesberg and P.G. Schultz, *Angew. Chem. Int. Ed*., 2002, **41**, 3841.
592. A.A. Henry, C. Yu and F.E. Romesberg, *J. Am. Chem. Soc*., 2003, **125**, 9638.
593. A.A. Henry, A.G. Olsen, S. Matsuda, C. Yu, B.H. Geierstanger and F.E. Romesberg, *J. Am. Chem. Soc*., 2004, **126**, 6923.
594. J.S. Lai, J. Qu and E.T. Kool, *Angew. Chem. Int. Ed*., 2003, **42**, 5973.

595. J.S. Lai and E.T. Kool, *J. Am. Chem. Soc.*, 2004, **126**, 3040.
596. G. Mathis and J. Hunziker, *Angew. Chem. Int. Ed.*, 2002, **41**, 3203.
597. G. Mathis, R. Schütz and J. Hunziker, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1183.
598. A. Zivkovic and J.W. Engels, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1167.
599. A.E. Klöpffer and J.W. Engels, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1347.
600. A.E. Klöpffer and J.W. Engels, *Chem. Bio. Chem.*, 2004, **5**, 707.
601. J.W. Rausch, J. Qu, H.Y. Yi-Brunozzi, E.T. Kool and S.F.J. Le Grice, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 11279.
602. A. Maki, F.E. Brownewell, D. Liu and E.T. Kool, *Nucl. Acids Res.*, 2003, **31**, 1059.
603. A.C. Delaney, P.T. Henderson, S.A. Helquist, J.C. Morales, J.M. Essigmann and E.T. Kool, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 4469.
604. B.M. O'Neill, J.E. Ratto, K.L. Good, D.C. Tahmassebi, S.A. Helquist, J.C. Morales and E.T. Kool, *J. Org. Chem.*, 2002, **67**, 5869.
605. N. Griesang and C. Richert, *Tetrahedron Lett.*, 2002, **43**, 8755.
606. A.W. Francis, S.A. Helquist, E.T. Kool and S.S. David, *J. Am. Chem. Soc.*, 2003, **125**, 16235.
607. Y. Aubert and U. Asseline, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1223.
608. C. Beuck, I. Singh, A. Bhattacharya, W. Hecker, V.S. Parmar, O. Seitz and E. Weinhold, *Angew. Chem. Int. Ed.*, 2003, **42**, 3958.
609. Y.L. Jiang, J.T. Stivers and F. Song, *Biochemistry*, 2002, **41**, 11248.
610. K. Kwon, Y.L. Jiang and J.T. Stivers, *Chem. Biol.*, 2003, **10**, 351.
611. V.V. Filichev and E.B. Pedersen, *Org. Biomol. Chem.*, 2003, **1**, 100.
612. U.B. Christensen and E.B. Pedersen, *Nucl. Acids Res.*, 2002, **30**, 4918.
613. U.B. Christensen and E.B. Pedersen, *Helv. Chim. Acta*, 2003, **86**, 2090.
614. A. Hatano, S. Makita and M. Kirihara, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2459.
615. S.A.N. Hashmi, X. Hu, C.E. Immoos, S.J. Lee and M.W. Grinstaff, *Org. Lett.*, 2002, **4**, 4571.
616. H. Morales-Rojas and E.T. Kool, *Org. Lett.*, 2002, **4**, 4377.
617. R. Huber, N. Amann and H.-A. Wagenknecht, *J. Org. Chem.*, 2004, **69**, 744.
618. H. Asanuma, D. Tamaru, A. Yamazawa, M. Liu and M. Komiyama, *Chem. Bio. Chem.*, 2002, **3**, 786.
619. H. Asanuma, H. Kashida, X. Liang and M. Komiyama, *Chem. Commun.*, 2003, **1536**.
620. J.-S. Li, Y.-H. Fan, Y. Zhang, L.A. Marky and B. Gold, *J. Am. Chem. Soc.*, 2003, **125**, 2084.
621. J.-S. Li, R. Shikiya, L.A. Marky and B. Gold, *Biochemistry*, 2004, **43**, 1440.
622. E. Mertz, S. Mattei and S.C. Zimmerman, *Bioorg. Med. Chem.*, 2004, **12**, 1517.
623. D. Guianvarc'h, J.-L. Fourrey, R. Maurisse, J.-S. Sun and R. Benhida, *Org. Lett.*, 2002, **4**, 4209.
624. D. Guianvarc'h, J.-L. Fourrey, R. Maurisse, J.-S. Sun and R. Benhida, *Bioorg. Med. Chem.*, 2003, **11**, 2751.
625. M. Jazouli, D. Guianvarc'h, K. Bougrin, M. Soufiaoui, P. Vierling and R. Benhida, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1277.
626. F. Lecubin, M. Devys, J.-L. Fourrey, J.-S. Sun and R. Benhida, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1281.
627. A. Kuzuya, K. Machida and M. Komiyama, *Tetrahedron Lett.*, 2002, **43**, 8249.

628. A. Kuzuya, R. Mizoguchi, T. Sasayama, J.-M. Zhou and M. Komiyama, *J. Am. Chem. Soc.*, 2004, **126**, 1430.
629. Y. Shi, A. Kuzuya, K. Machida and M. Komiyama, *Tetrahedron Lett.*, 2004, **45**, 3703.
630. M. Sato, T. Moriguchi and K. Shinozuka, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1305.
631. T. Hamma and P.S. Miller, *Bioconj. Chem.*, 2003, **14**, 320.
632. Z. Dogan, R. Paulini, J.A.R. Stütz, S. Narayanan and C. Richert, *J. Am. Chem. Soc.*, 2004, **126**, 4762.
633. E.M. Moody and P.C. Bevilacqua, *J. Am. Chem. Soc.*, 2003, **125**, 2032.
634. S.J. Kim and B.H. Kim, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 2003.
635. T. Wenzel, T. Elssner, K. Fahr, J. Bimmler, S. Richter, I. Thomas and M. Kostrzewa, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1579.
636. S. Sauer, H. Lehrach and R. Reinhardt, *Nucl. Acids Res.*, 2003, **31**, e63.
637. I.A. Pyshnaya, D.V. Pyshnyi, A.A. Lomzov, V.F. Zarytova and E.M. Ivanova, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 1065.
638. U.B. Christensen, M. Wamberg, F.A.G. El-Essawy, A.E.-H. Ismail, C.B. Nielsen, V.V. Filichev, C.H. Jessen, M. Petersen and E.B. Pedersen, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 207.
639. S. Narayanan, A.H. Dalpke, K. Siegmund, K. Heeg and C. Richert, *J. Med. Chem.*, 2003, **46**, 5031.
640. A. Maor-Shoshani, V. Ben-Ari and Z. Livneh, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 14760.
641. A.M. Morocho, V.N. Karamyshev, O.V. Shcherbinina, A.G. Malykh and N.N. Polushin, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1439.
642. X. Bai, S. Kim, Z. Li, N.J. Turro and J. Ju, *Nucl. Acids Res.*, 2004, **32**, 535.
643. S. Fang and D.E. Bergstrom, *Bioconj. Chem.*, 2003, **14**, 80.
644. Z. Skrzypczynski and S. Wayland, *Bioconj. Chem.*, 2003, **14**, 642.
645. S. Narayanan, J. Gall and C. Richert, *Nucl. Acids Res.*, 2004, **32**, 2901.
646. M. Sekine, M. Ushioda, T. Wada and K. Seio, *Tetrahedron Lett.*, 2003, **44**, 1703.
647. C. Otsuka, S. Sanadai, Y. Hata, H. Okuto, V.N. Noskov, D. Loakes and K. Negishi, *Nucl. Acids Res.*, 2002, **30**, 5129.
648. K. Yoshimoto, S. Nishizawa, M. Minagawa and N. Teramae, *J. Am. Chem. Soc.*, 2003, **125**, 8982.
649. N.T. Le Gac, E. Delagoutte, M. Germain and G. Villani, *J. Mol. Biol.*, 2004, **336**, 1023.
650. Y. Xu and H. Sugiyama, *J. Am. Chem. Soc.*, 2004, **126**, 6274.
651. Y. Roupioz, J. Lhomme and M. Kotera, *J. Am. Chem. Soc.*, 2002, **124**, 9129.
652. V. Faure, J.-F. Constant, P. Dumy and M. Saparbaev, *Nucl. Acids Res.*, 2004, **32**, 2937.
653. K.M. Kroeger, Y.L. Jiang, Y.W. Kow, M.F. Goodman and M.M. Greenberg, *Biochemistry*, 2004, **43**, 6723.
654. K.M. Kroeger, M. Hashimoto, Y.W. Kow and M.M. Greenberg, *Biochemistry*, 2003, **42**, 2449.
655. J. Chen and J. Stubbe, *Biochemistry*, 2004, **43**, 5278.
656. J. Kim, J.M. Gil and M.M. Greenberg, *Angew. Chem. Int. Ed.*, 2003, **42**, 5882.
657. M.M. Greenberg, Y.N. Weledji, K.M. Kroeger, J. Kim and M.F. Goodman, *Biochemistry*, 2004, **43**, 2656.
658. M. Kuznetsova, A. Fokina, M. Lukin, M. Repkova, A. Venyaminova and V. Vlassov, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1521.

659. J.-D. Wen and D.M. Gray, *Biochemistry*, 2004, **43**, 2622.
660. D.A. Daniels, H. Chen, B.J. Hicke, K.M. Swiderek and L. Gold, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 15416.
661. M. Vairamani and M.L. Gross, *J. Am. Chem. Soc.*, 2003, **125**, 42.
662. V.R. de Soultrait, P.-Y. Lozach, R. Altmeyer, L. Tarrago-Litvak, S. Litvak and M.L. Andréola, *J. Mol. Biol.*, 2002, **324**, 195.
663. F. Pileur, M.-L. Andreola, E. Dausse, J. Michel, S. Moreau, H. Yamada, S.A. Gaidamakov, R.J. Crouch, J.-J. Toulmé and C. Cazanave, *Nucl. Acids Res.*, 2003, **31**, 5776.
664. N.A. Skrypina, L.P. Savochkina and R.S. Beabealashvilli, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 891.
665. M. Rajendran and A.D. Ellington, *Nucl. Acids Res.*, 2003, **31**, 5700.
666. M.N. Stojanovic and D.W. Landry, *J. Am. Chem. Soc.*, 2002, **124**, 9678.
667. S.H. J. Mei, Z. Liu, J.D. Brennan and Y. Li, *J. Am. Chem. Soc.*, 2003, **125**, 412.
668. R.P.G. Cruz, J.B. Withers and Y. Li, *Chem. Biol.*, 2004, **11**, 57.
669. P. Ordoukhanian and G.F. Joyce, *J. Am. Chem. Soc.*, 2002, **124**, 12499.
670. A. Flynn-Charlebois, T.K. Prior, K.A. Hoadley and S.K. Silverman, *J. Am. Chem. Soc.*, 2003, **125**, 5346.
671. A. Flynn-Charlebois, Y. Wang, T.K. Prior, I. Rashid, K.A. Hoadley, R.L. Coppins, A.C. Wolf and S.K. Silverman, *J. Am. Chem. Soc.*, 2003, **125**, 2444.
672. A. Sreedhara, Y. Li and R.R. Breaker, *J. Am. Chem. Soc.*, 2004, **126**, 3454.
673. R.L. Coppins and S.K. Silverman, *Nature Struct. Mol. Biol.*, 2004, **11**, 270.
674. B.L. Ricca, A.C. Wolf and S.K. Silverman, *J. Mol. Biol.*, 2003, **330**, 1015.
675. Y. Wang and S.K. Silverman, *J. Am. Chem. Soc.*, 2003, **125**, 6880.
676. Y. Wang and S.K. Silverman, *Biochemistry*, 2003, **42**, 15252.
677. J.P. May, R. Ting, L. Lerner, J.M. Thomas, Y. Roupioz and D.M. Perrin, *J. Am. Chem. Soc.*, 2004, **126**, 4145.
678. Z. Liu, S.H.J. Mei, J.D. Brennan and Y. Li, *J. Am. Chem. Soc.*, 2003, **125**, 7539.
679. A.K. Brown, J. Li, C.M.-B. Pavot and Y. Lu, *Biochemistry*, 2003, **42**, 7152.
680. X. Yang, S.E. Bassett, X. Li, B.A. Luxon, N.K. Herzog, R.E. Shope, J. Aronson, T.W. Prow, J.F. Leary, R. Kirby, A.D. Ellington and D.G. Gorenstein, *Nucl. Acids Res.*, 2002, **30**, e132.
681. X. Yang, X. Li, T.W. Prow, L.M. Reece, S.E. Bassett, B.A. Luxon, N.K. Herzog, J. Aronson, R.E. Shope, J.F. Leary and D.G. Gorenstein, *Nucl. Acids Res.*, 2003, **31**, e54.
682. D.J. King, S.E. Bassett, X. Li, S.A. Fennewald, N.K. Herzog, B.A. Luxon, R. Shope and D.G. Gorenstein, *Biochemistry*, 2002, **41**, 9696.
683. F. Darfeuille, A. Arzumanov, S. Gryaznov, M.J. Gait, C. Di Primo and J.-J. Toulmé, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 9709.
684. S. Schubert, D.C. Gül, H.-P. Grunert, H. Zeichhardt, V.A. Erdmann and J. Kurreck, *Nucl. Acids Res.*, 2003, **31**, 5982.
685. A.A. Fokina, M.A. Kuznetsova, M.N. Repkova and A.G. Venyaminova, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 1031.
686. F. Darfeuille, J.B. Hansen, H. Orum, C. Di Primo and J.-J. Toulmé, *Nucl. Acids Res.*, 2004, **32**, 3101.
687. B. Vester, L.B. Lundberg, M.D. Sørensen, B.R. Babu, S. Douthwaite and J. Wengel, *J. Am. Chem. Soc.*, 2002, **124**, 13682.
688. S. Helmling, E. Moyroud, W. Schroeder, I. Roehl, F. Kleinjung, S. Stark, G. Bahrenberg, C. Gillen, S. Klussmann and S. Vonhoff, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1035.

689. L. Lermer, Y. Roupioz, R. Ting and D.M. Perrin, *J. Am. Chem. Soc*., 2002, **124**, 9960.
690. J.M. Thomas, R. Ting and D.M. Perrin, *Org. Biomol. Chem*., 2004, **2**, 307.
691. Y. Okumoto, Y. Tanabe and N. Sugimoto, *Biochemistry*, 2003, **42**, 2158.
692. H. Rosemeyer, V. Mokrosch, A. Jawalekar, E.-M. Becker and F. Seela, *Helv. Chim. Acta*, 2004, **87**, 536.
693. T. Kubo, K. Yokoyama, R. Ueki, M. Yano, Y. Anno, K. Sasaki, H. Ohba and M. Fujii, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1359.
694. R.H. Koch, D. Smith, E. Tabacman and D.A. Zichi, *J. Mol. Biol*., 2004, **336**, 1159.
695. D.J.-F. Chinnapen and D. Sen, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 65.
696. R. Nutiu and Y. Li, *J. Am. Chem. Soc*., 2003, **125**, 4771.
697. J. Liu and Y. Lu, *J. Am. Chem. Soc*., 2002, **124**, 15208.
698. Y. Xiao, V. Pavlov, R. Gill, T. Bourenko and I. Willner, *Chem. Bio. Chem*., 2004, **5**, 374.
699. M.M. Masud, M. Kuwahara, H. Ozaki and H. Sawai, *Bioorg. Med. Chem*., 2004, **12**, 1111.
700. M.B. Murphy, S.T. Fuller, P.M. Richardson and S.A. Doyle, *Nucl. Acids Res*., 2003, **31**, e110.
701. J.A. Bittker, B.V. Le and D.R. Liu, *Nat. Biotechnol*., 2002, **20**, 1024.
702. S.D. Mendonsa and M.T. Bowser, *J. Am. Chem. Soc*., 2004, **126**, 20.
703. M. Michaud, E. Jourdan, A. Villet, A. Ravel, C. Grosset and E. Peyrin, *J. Am. Chem. Soc*., 2003, **125**, 8672.
704. M.N. Stojanovic and D. Stefanovic, *J. Am. Chem. Soc*., 2003, **125**, 6673.
705. M.N. Stojanovic and D. Stefanovic, *Nature Biotech*., 2003, **21**, 1069.
706. H.-A. Ho and M. Leclerc, *J. Am. Chem. Soc*., 2004, **126**, 1384.
707. X. Fang, A. Sen, M. Vicens and W. Tan, *Chem. Bio. Chem*., 2003, **4**, 829.
708. J. Liu and Y. Lu, *J. Am. Chem. Soc*., 2003, **125**, 6642.
709. K. Yamana, Y. Ohtani, H. Nakano and I. Saito, *Bioorg. Med. Chem. Lett*., 2003, **13**, 3429.
710. E.J. Merino and K.M. Weeks, *J. Am. Chem. Soc*., 2003, **125**, 12370.
711. S. Sando, T. Sasaki, K. Kanatani and Y. Aoyama, *J. Am. Chem. Soc*., 2003, **125**, 15720.
712. M. Levy and A.D. Ellington, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 6416.
713. F. Chen, R. Wang, Z. Li, B. Liu, X. Wang, Y. Sun, D. Hao and J. Zhang, *Nucl. Acids Res*., 2004, **32**, 2336.
714. X.-X. Tan, K. Rose, W. Margolin and Y. Chen, *Biochemistry*, 2004, **43**, 1111.
715. C.-h.B. Chen, G.A. Chernis, V.Q. Hoang and R. Landgraf, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9226.
716. X. Fan, H. Shi, K. Adelman and J.T. Lis, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 6934.
717. J.H. Lee, H. Kim, J. Ko and Y. Lee, *Nucl. Acids Res*., 2002, **30**, 5360.
718. C.B. Carlson, M. Vuyisich, B.D. Gooch and P.A. Beal, *Chem. Biol*., 2003, **10**, 663.
719. I. Hirao, Y. Harada, T. Nojima, Y. Osawa, H. Masaki and S. Yokoyama, *Biochemistry*, 2004, **43**, 3214.
720. L. Chaloin, M.J. Lehmann, G. Sczakiel and T. Restle, *Nucl. Acids Res*., 2002, **30**, 4001.
721. F. Beaurain, C. Di Primo, J.-J. Toulmé and M. Laguerre, *Nucl. Acids Res*., 2003, **31**, 4275.
722. C.P. Rusconi, E. Scardino, J. Layzer, G.A. Pitoc, T.L. Ortel, D. Monroe and B.A. Sullenger, *Nature*, 2002, **419**, 90.

723. M. Vuyisich and P.A. Beal, *Chem. Biol*., 2003, **9**, 907.
724. L. Cochella and R. Green, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 3786.
725. K. Kossen, N.K. Vaish, V.R. Jadhav, C. Pasko, H. Wang, R. Jenison, J.A. McSwiggen, B. Polisky and S.D. Seiwert, *Chem. Biol*., 2004, **11**, 807.
726. J.M. Zimmerman and L.J. Maher, *Nucl. Acids Res*., 2002, **30**, 5425.
727. F.M. Jucker, R.M. Phillips, S.A. McCallum and A. Pardi, *Biochemistry*, 2003, **42**, 2560.
728. J.H. Davis and J.W. Szostak, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 11616.
729. J.M. Carothers, S.C. Oestreich, J.H. Davis and J.W. Szostak, *J. Am. Chem. Soc*., 2004, **126**, 5130.
730. D.H. Nguyen, S.C. DeFina, W.H. Fink and T. Dieckmann, *J. Am. Chem. Soc*., 2002, **124**, 15081.
731. J. Flinders, S.C. DeFina, D.M. Brackett, C. Baugh, C. Wilson and T. Dieckmann, *Chem. Bio. Chem*., 2004, **5**, 62.
732. B.G. Ayre, U. Köhler, R. Turgeon and J. Haseloff, *Nucl. Acids Res*., 2002, **30**, e141.
733. S. Tsukiji, S.B. Pattnaik and H. Suga, *Nature Struct. Biol*., 2003, **10**, 713.
734. A.V. Vlassov, B.H. Johnston, L.F. Landweber and S.A. Kazakov, *Nucl. Acids Res*., 2004, **32**, 2966.
735. S. Baskerville and D.P. Bartel, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 9154.
736. A.R. Buskirk, P.D. Kehayova, A. Landrigan and D.R. Liu, *Chem. Biol*., 2003, **10**, 533.
737. H. Murakami, H. Saito and H. Suga, *Chem. Biol*., 2003, **10**, 655.
738. T.M. Coleman and F. Huang, *Chem. Biol*., 2002, **9**, 1227.
739. Y. Komatsu, K. Nobuoka, N. Karino-Abe, A. Matsuda and E. Ohtsuka, *Biochemistry*, 2002, **41**, 9090.
740. S.I. Chamberlin, E.J. Merino and K.M. Weeks, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 14688.
741. L.A. Gugliotti, D.L. Feldheim and B.E. Eaton, *Science*, 2004, **304**, 850.
742. N.K. Vaish, R. Larralde, A.W. Fraley, J.W. Szostak and L.W. McLaughlin, *Biochemistry*, 2003, **42**, 8842.
743. D. Proske, S. Gilch, F. Wopfner, H.M. Schätzl, E.-L. Winnacker and M. Famulok, *Chem. Bio. Chem*., 2002, **3**, 717.
744. J.S. Reader and G.F. Joyce, *Nature*, 2002, **420**, 841.
745. J.C. Schlatterer, F. Stuhlmann and A. Jäschke, *Chem. Bio. Chem*., 2003, **4**, 1089.
746. A. Ferguson, R.M. Boomer, M. Kurz, S.C. Keene, J.L. Diener, A.D. Keefe, C. Wilson and S.T. Cload, *Nucl. Acids Res*., 2004, **32**, 1756.
747. J.R. Babendure, S.R. Adams and R.Y. Tsien, *J. Am. Chem. Soc*., 2003, **125**, 14716.
748. J.S. Hartig, I. Grüne, S.H. Najafi-Shoushtari and M. Famulok, *J. Am. Chem. Soc*., 2004, **126**, 722.
749. F. Nishikawa, N. Kakiuchi, K. Funaji, K. Fukuda, S. Sekiya and S. Nishikawa, *Nucl. Acids Res*., 2003, **31**, 1935.
750. J.C. Cox, A. Hayhurst, J. Hesselberth, T.S. Bayer, G. Georgiou and A.D. Ellington, *Nucl. Acids Res*., 2002, **30**, e108.
751. T. Kubo, M. Morikawa, H. Ohba and M. Fujii, *Org. Lett*., 2003, **5**, 2623.
752. Y. Anno, T. Kubo, R. Ueki, M. Yano, K. Sasaki, H. Ohba and M. Fujii, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1451.
753. A.V. Kachalova, D.S. Stetsenko, E.A. Romanova, V.N. Tashlitsky, M.J. Gait and T.S. Oretskaya, *Helv. Chim. Acta*, 2002, **85**, 2409.

754. A.V. Kachalova, D.S. Stetsenko, M.J. Gait and T.S. Oretskaya, *Bioorg. Med. Chem. Lett*., 2004, **14**, 801.
755. C.-P. Chen, L.-R. Zhang, Y.-F. Peng, X.-B. Wang, S.-Q. Wang and L.-H. Zhang, *Bioconj. Chem*., 2003, **14**, 532.
756. T.S. Zatsepin, D.S. Stetsenko, A.A. Arzumanov, E.A. Romanova, M.J. Gait and T.S. Oretskaya, *Bioconj. Chem*., 2002, **13**, 822.
757. D. Forget, D. Boturyn, O. Renaudet, E. Defrancq and P. Dumy, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1427.
758. O.P. Edupuganti, O. Renaudet, E. Defrancq and P. Dumy, *Bioorg. Med. Chem. Lett*., 2004, **14**, 2839.
759. D.S. Stetsenko, A.D. Malakov and M.J. Gait, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1379.
760. S. Drioli, I. Adamo, M. Ballico, F. Morvan and G.M. Bonora, *Eur. J. Org. Chem*., 2002, **9**, 3473.
761. G.M. Bonora, M. Ballico, P. Campaner, S. Drioli and I. Adamo, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1255.
762. I. Adamo, M. Ballico, P. Campaner, S. Drioli and G.M. Bonora, *Eur. J. Org. Chem*., 2004, 2603.
763. S. Takeda, S. Tsukiji and T. Nagamune, *Bioorg. Med. Chem. Lett*., 2004, **14**, 2407.
764. S. Terenzi, E. Biala, N.Q. Nguyen-Trung and P. Strazewski, *Angew. Chem. Int. Ed*., 2003, **42**, 2909.
765. V. Marchán, L. Debéthune, E. Pedroso and A. Grandas, *Tetrahedron*, 2003, **60**, 5461.
766. K. Glynou, P.C. Ioannou and T.K. Christopoulos, *Bioconjugate Chem*., 2003, **14**, 1024.
767. M. Yano, T. Kubo, K. Yokoyama, R. Ueki, K. Sasaki, Y. Anno, H. Ohba and M. Fujii, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1367.
768. M. Tanimoto, H. Kamiya, N. Minakawa, A. Matsuda and H. Harashima, *Bioconjugate Chem*., 2003, **14**, 1197.
769. T. Fukuma, C.M. Walton, C.H. Wu and G.Y. Wu, *Bioconj. Chem*., 2003, **14**, 295.
770. N.L. Mironova, D.V. Pyshnyi, E.M. Ivanova, M.A. Zenkova, H.J. Gross and V.V. Vlassov, *Nucl. Acids Res*., 2004, **32**, 1928.
771. A. Frankel, S.W. Millward and R.W. Roberts, *Chem. Biol*., 2003, **10**, 1043.
772. K. Tamura and P. Schimmel, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 8666.
773. J.J. Díaz-Mochón, L. Bialy and M. Bradley, *Org. Lett*., 2004, **6**, 1127.
774. M.C. de Koning, D.V. Filippov, G.A. van der Marel, J.H. van Boom and M. Overhand, *Eur. J. Org. Chem*., 2004, 850.
775. K. Kaihatsu, D.A. Braasch, A. Cansizoglu and D.R. Corey, *Biochemistry*, 2002, **41**, 11118.
776. W. Mier, R. Eritja, A. Mohammed, U. Haberkorn and M. Eisenhut, *Angew. Chem. Int. Ed*., 2002, **42**, 1968.
777. C.J. Nulf and D.R. Corey, *Nucl. Acids Res*., 2002, **30**, 2782.
778. C.T. Calderone, J.W. Puckett, Z.J. Gartner and D.R. Liu, *Angew. Chem. Int. Ed*., 2002, **41**, 4104.
779. X. Li, Z.J. Gartner, B.N. Tse and D.R. Liu, *J. Am. Chem. Soc*., 2004, **126**, 5090.
780. D.M. Rosenbaum and D.R. Liu, *J. Am. Chem. Soc*., 2003, **125**, 13924.
781. J.L. Czlapinski and T.L. Sheppard, *Chem. Bio. Chem*., 2004, **5**, 127.
782. A.T. Poulin-Kerstien and P.B. Dervan, *J. Am. Chem. Soc*., 2003, **125**, 15811.
783. Z.J. Gartner, M.W. Kanan and D.R. Liu, *J. Am. Chem. Soc*., 2002, **124**, 10304.
784. X. Li and D.R. Liu, *J. Am. Chem. Soc*., 2003, **125**, 10188.

785. J.B. Doyon, T.M. Snyder and D.R. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 12372.
786. Z.J. Gartner, R. Grubina, C.T. Calderone and D.R. Liu, *Angew. Chem. Int. Ed.*, 2003, **42**, 1370.
787. L. Fruk, A. Grondin, W.E. Smith and D. Graham, *Chem. Commun.*, 2002, **2100**.
788. H.A. Latham-Timmons, A. Wolter, J.S. Roach, R. Giare and M. Leuck, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1495.
789. J. Brunner, A. Mokhir and R. Kraemer, *J. Am. Chem. Soc.*, 2003, **125**, 12410.
790. F.H. Zelder, J. Brunner and R. Krämer, *Chem. Commun.*, 2004, 902.
791. H. Wackerbarth, M. Grubb, J. Zhang, A.G. Hansen and J. Ulstrup, *Angew. Chem. Int. Ed.*, 2004, **43**, 198.
792. Y. Liu, W. Meyer-Zaika, S. Franzka, G. Schmid, M. Tsoli and H. Kuhn, *Angew. Chem. Int. Ed.*, 2003, **42**, 2853.
793. A.G. Kanaras, Z. Wang, A.D. Bates, R. Cosstick and M. Brust, *Angew. Chem. Int. Ed.*, 2003, **42**, 191.
794. D.M. Ceres and J.K. Barton, *J. Am. Chem. Soc.*, 2003, **125**, 14964.
795. C.S. Yun, G.A. Khitrov, D.E. Vergona, N.O. Reich and G.F. Strouse, *J. Am. Chem. Soc.*, 2002, **124**, 7644.
796. H. Kimura-Suda, D.Y. Petrovykh, M.J. Tarlov and L.J. Whitman, *J. Am. Chem. Soc.*, 2003, **125**, 9014.
797. D.Y. Petrovykh, H. Kimura-Suda, L.J. Whitman and M.J. Tarlov, *J. Am. Chem. Soc.*, 2003, **125**, 5219.
798. F. Patolsky, Y. Weizmann, O. Lioubashevski and I. Willner, *Angew. Chem. Int. Ed.*, 2002, **41**, 2323.
799. R. Chakrabarti and A.M. Klibanov, *J. Am. Chem. Soc.*, 2003, **125**, 12531.
800. K. Sato, K. Hosokawa and M. Maeda, *J. Am. Chem. Soc.*, 2003, **125**, 8102.
801. C.M. Niemeyer, B. Ceyhan and P. Hazarika, *Angew. Chem. Int. Ed.*, 2003, **42**, 5766.
802. D. Murphy, R. Eritja and G. Redmond, *Nucl. Acids Res.*, 2004, **32**, e65.
803. R. Jin, G. Wu, Z. Li, C.A. Mirkin and G.C. Schatz, *J. Am. Chem. Soc.*, 2003, **125**, 1643.
804. D.J. Maxwell, J.R. Taylor and S. Nie, *J. Am. Chem. Soc.*, 2002, **124**, 9606.
805. Y.C. Cao, R. Jin and C.A. Mirkin, *Science*, 2002, **297**, 1536.
806. F. Patolsky, A. Lichtenstein and I. Willner, *Chem. Eur. J.*, 2003, **9**, 1137.
807. J.-M. Nam, S.I. Stoeva and C.A. Mirkin, *J. Am. Chem. Soc.*, 2004, **126**, 5932.
808. Y. Weizmann, F. Patolsky, O. Lioubashevski and I. Willner, *J. Am. Chem. Soc.*, 2004, **126**, 1073.
809. A. Bruckbauer, L. Ying, A.M. Rothery, D. Zhou, A.I. Shevchuk, C. Abell, Y.E. Korchev and D. Klenerman, *J. Am. Chem. Soc.*, 2002, **124**, 8810.
810. J. Hyun, J. Kim, S.L. Craig and A. Chilkoti, *J. Am. Chem. Soc.*, 2004, **126**, 4770.
811. F. Patolsky, R. Gill, Y. Weizmann, T. Mokari, U. Banin and I. Willner, *J. Am. Chem. Soc.*, 2003, **125**, 13918.
812. J. Wang, G. Liu and A. Merkoçi, *J. Am. Chem. Soc.*, 2003, **125**, 3214.
813. B.G. de la Torre, J.C. Morales, A. Aviñó, D. Iacopino, A. Ongaro, D. Fitzmaurice, D. Murphy, H. Doyle, G. Redmond and R. Eritja, *Helv. Chim. Acta*, 2002, **85**, 2594.
814. J. Wang, G. Liu and M.R. Jan, *J. Am. Chem. Soc.*, 2004, **126**, 3010.
815. F. Patolsky, Y. Weizmann, E. Katz and I. Willner, *Angew. Chem. Int. Ed.*, 2003, **42**, 2372.
816. Y. Weizmann, F. Patolsky, E. Katz and I. Willner, *J. Am. Chem. Soc.*, 2003, **125**, 3452.

817. P. Hou, M. Ji, C. Ge, J. Shen, S. Li, N. He and Z. Lu, *Nucl. Acids Res.*, 2003, **31**, e92.
818. M. Fojta, L. Havran, M. Vojtiskova and E. Palecek, *J. Am. Chem. Soc.*, 2004, **126**, 6532.
819. R. Meunier-Prest, S. Raveau, E. Finot, G. Legay, M. Cherkaoui-Malki and N. Latruffe, *Nucl. Acids Res.*, 2003, **31**, e150.
820. L.A. Thompson, J. Kowalik, M. Josowicz and J. Janata, *J. Am. Chem. Soc.*, 2003, **125**, 324.
821. A. Macanovic, C. Marquette, C. Polychronakos and M.F. Lawrence, *Nucl. Acids Res.*, 2004, **32**, e20.
822. K. Tanaka, Y. Yamada and M. Shionoya, *J. Am. Chem. Soc.*, 2002, **124**, 8802.
823. N. Zimmermann, E. Meggers and P.G. Schultz, *J. Am. Chem. Soc.*, 2002, **124**, 13684.
824. C. Brotschi and C.J. Leumann, *Angew. Chem. Int. Ed.*, 2003, **42**, 1655.
825. C. Brotschi and C.J. Leumann, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1195.
826. D.-L. Popescu, T.J. Parolin and C. Achim, *J. Am. Chem. Soc.*, 2003, **125**, 6354.
827. K. Tanaka, A. Tengeiji, T. Kato, N. Toyama, M. Shiro and M. Shionoya, *J. Am. Chem. Soc.*, 2002, **124**, 12494.
828. K. Tanaka, A. Tengeiji, T. Kato, N. Toyama and M. Shionoya, *Science*, 2003, **299**, 1212.
829. T. Niitymäki, U. Kaukinen, P. Virta, S. Mikkola and H. Lönnberg, *Bioconjugate Chem.*, 2004, **15**, 174.
830. S. Vogel, K. Rohr, O. Dahl and J. Wengel, *Chem. Commun.*, 2003, **9**, 1006.
831. S. Vogel, K. Rohr, O. Dahl and J. Wengel, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1039.
832. S. Sakamoto, T. Tamura, T. Furukawa, Y. Komatsu, E. Ohtsuka, M. Kitamura and H. Inoue, *Nucl. acids Res.*, 2003, **31**, 1416.
833. S. Verma, S.G. Srivatsan, C.A. Claussen and E.C. Long, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2501.
834. L. Canaple, D. Hüsken, J. Hall and R. Häner, *Bioconj. Chem.*, 2002, **13**, 945.
835. S. Deroo, E. Defrancq, C. Moucheron, A. Kirsch-De Mesmaeker and P. Dumy, *Tetrahedron Lett.*, 2003, **44**, 8379.
836. D. Ossipov, S. Gohil and J. Chattopadhyaya, *J. Am. Chem. Soc.*, 2002, **124**, 13416.
837. D.J. Hurley and Y. Tor, *J. Am. Chem. Soc.*, 2002, **124**, 13231.
838. A.B. Olejniczak, J. Plesek, O. Kriz and Z.J. Lesnikowski, *Angew. Chem. Int. Ed.*, 2003, **42**, 5740.
839. A. Anne, A. Bouchardon and J. Moiroux, *J. Am. Chem. Soc.*, 2003, **125**, 1112.
840. D.A. Di Giusto, W.A. Wlassoff, S. Giesebrecht, J.J. Gooding and G.C. King, *Angew. Chem. Int. Ed.*, 2004, **43**, 2809.
841. D.A. Di Giusto, W.A. Wlassoff, S. Giesebrecht, J.J. Gooding and G.C. King, *J. Am. Chem. Soc.*, 2004, **126**, 4120.
842. A.R. Pike, L.C. Ryder, B.R. Horrocks, W. Clegg, M.R.J. Elsegood, B.A. Connolly and A. Houlton, *Chem. Eur. J.*, 2002, **8**, 2891.
843. A.-E. Navarro, N. Spinelli, C. Chaix, C. Moustrou, B. Mandrand and H. Brisset, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2439.
844. C. Fan, K.W. Plaxco and A.J. Heeger, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9134.
845. I. Horsey, Y. Krishnan-Ghosh and S. Balasubramanian, *Chem. Commun.*, 2002, **1950**.

846. L. Zapata, K. Bathany, J.-M. Schmitter and S. Moreau, *Eur. J. Org. Chem.*, 2003, **1022**.
847. K.M. Stewart and L.W. McLaughlin, *J. Am. Chem. Soc.*, 2004, **126**, 2050.
848. S.K. Sharma and L.W. McLaughlin, *J. Am. Chem. Soc.*, 2002, **124**, 9658.
849. R.J. Heetebrij, M. de Kort, N.J. Meeuwenoord, H. den Dulk, G.A. van der Marel, J. van Boom and J. Reedijk, *Chem. Eur. J.*, 2003, **9**, 1823.
850. K. Stehlikova, H. Kostrhunova, J. Kasparkova and V. Brabec, *Nucl. Acids Res.*, 2002, **30**, 2894.
851. D. Wang, R. Hara, G. Singh, A. Sancar and S.J. Lippard, *Biochemistry*, 2003, **42**, 6747.
852. Y. Jung and S.J. Lippard, *Biochemistry*, 2003, **42**, 2664.
853. J. Kasparkova, O. Delalande, M. Stros, M.-A. Elizondo-Riojas, M. Vojtiskova, J. Kozelka and V. Brabec, *Biochemistry*, 2003, **42**, 1234.
854. I. Gaudreault, D. Guay and M. Lebel, *Nucl. Acids Res.*, 2004, **32**, 316.
855. C.X. Zhang, P.V. Chang and S.J. Lippard, *J. Am. Chem. Soc.*, 2004, **126**, 6536.
856. G. Villani, N.T. Le Gac, L. Wasungu, D. Burnout, R.P. Fuchs and P.E. Boehmer, *Nucl. Acids Res.*, 2002, **30**, 3323.
857. S. Redon, S. Bombard, M.-A. Elizondo-Riojas and J.-C. Chottard, *Nucl. Acids Res.*, 2003, **31**, 1605.
858. M. Escraffre, J.-C. Chottard and S. Bombard, *Nucl. Acids Res.*, 2002, **30**, 5222.
859. E. Freisinger, I.B. Rother, M.S. Lüth and B. Lippert, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 3748.
860. K.S. Schmidt, M. Boudvillain, A. Schwartz, G.A. van der Marel, J.H. van Boom, J. Reedijk and B. Lippert, *Chem. Eur. J.*, 2002, **8**, 5566.
861. J.M. Havener, S.A.N. McElhinny, E. Bassett, M. Gauger, D.A. Ramsden and S.G. Chaney, *Biochemistry*, 2003, **42**, 1777.
862. E. Bassett, A. Vaisman, J.M. Havener, C. Masutani, F. Hanaoka and S.G. Chaney, *Biochemistry*, 2003, **42**, 14197.
863. K. Kobayashi and S. Tagawa, *J. Am. Chem. Soc.*, 2003, **125**, 10213.
864. E.M. Boon, M.A. Pope, S.D. Williams, S.S. David and J.K. Barton, *Biochemistry*, 2002, **41**, 8464.
865. E.M. Boon, A.L. Livingston, N.H. Chmiel, S.S. David and J.K. Barton, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 12543.
866. K. Kawai, T. Takada, S. Tojo and T. Majima, *Tetrahedron Lett.*, 2002, **43**, 8083.
867. T. Kimura, K. Kawai, S. Tojo and T. Majima, *J. Org. Chem.*, 2004, **69**, 1169.
868. R. Tashiro and H. Sugiyama, *J. Am. Chem. Soc.*, 2003, **125**, 15282.
869. M.A. O'Neill, C. Dohno and J.K. Barton, *J. Am. Chem. Soc.*, 2004, **126**, 1316.
870. C. Dohno, A. Ogawa, K. Nakatani and I. Saito, *J. Am. Chem. Soc.*, 2003, **125**, 10154.
871. M.A. O'Neill and J.K. Barton, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 16543.
872. M.A. O'Neill, H.-C. Becker, C. Wan, J.K. Barton and A.H. Zewail, *Angew. Chem. Int. Ed.*, 2003, **42**, 5896.
873. A. Okamoto, K. Tanaka and I. Saito, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3641.
874. T. Kendrick and B. Giese, *Chem. Commun.*, 2002, 2016.
875. E. Furrer and B. Giese, *Helv. Chim. Acta*, 2003, **86**, 3623.
876. J. Yoo, S. Delaney, E.D.A. Stemp and J.K. Barton, *J. Am. Chem. Soc.*, 2003, **125**, 6640.
877. M. Pascaly, J. Yoo and J.K. Barton, *J. Am. Chem. Soc.*, 2002, **124**, 9083.
878. A. Okamoto, K. Tanaka and I. Saito, *J. Am. Chem. Soc.*, 2003, **125**, 5066.
879. B. Giese, B. Carl, T. Carl, T. Carell, C. Behrens, U. Hennecke, O. Schiemann and E. Feresin, *Angew. Chem. Int. Ed.*, 2004, **43**, 1848.

880. T. Ito and S.E. Rokita, *J. Am. Chem. Soc.*, 2003, **125**, 11480.
881. T. Ito and S.E. Rokita, *Angew. Chem. Int. Ed.*, 2004, **43**, 1839.
882. E.M. Boon, J.K. Barton, P.I. Pradeepkumar, J. Isaksson, C. Petit and J. Chattopadhyaya, *Angew. Chem. Int. Ed.*, 2002, **41**, 3402.
883. C. Behrens and T. Carell, *Chem. Commun.*, 2003, 1632.
884. C. Haas, K. Kräling, M. Cichon, N. Rahe and T. Carell, *Angew. Chem. Int. Ed.*, 2004, **43**, 1842.
885. S. Breeger, U. Hennecke and T. Carell, *J. Am. Chem. Soc.*, 2004, **126**, 1302.
886. M.K. Cichon, C.H. Haas, F. Grolle, A. Mees and T. Carrell, *J. Am. Chem. Soc.*, 2002, **124**, 13984.
887. N. Amann, E. Pandurski, T. Fiebig and H.-A. Wagenknecht, *Chem. Eur. J.*, 2002, **8**, 4877.
888. N. Amann, E. Pandurski, T. Fiebig and H.-A. Wagenknecht, *Angew. Chem. Int. Ed.*, 2002, **41**, 2978.
889. M. Rist, N. Amann and H.-A. Wagenknecht, *Eur. J. Org. Chem.*, 2003, 2498.
890. T. Takada, K. Kawai, S. Tojo and T. Majima, *Tetrahedron Lett.*, 2003, **44**, 3851.
891. K. Kawai, T. Takada, S. Tojo and T. Majima, *J. Am. Chem. Soc.*, 2003, **125**, 6842.
892. N. Amann, R. Huber and H.-A. Wagenknecht, *Angew. Chem. Int. Ed.*, 2004, **43**, 1845.
893. C.-S. Liu, R. Hernandez and G.B. Schuster, *J. Am. Chem. Soc.*, 2004, **126**, 2877.
894. U. Santhosh and G.B. Schuster, *J. Am. Chem. Soc.*, 2002, **124**, 10986.
895. C.-S. Liu and G.B. Schuster, *J. Am. Chem. Soc.*, 2003, **125**, 6098.
896. S. Kanvah and G.B. Schuster, *J. Am. Chem. Soc.*, 2002, **124**, 11286.
897. S. Kanvah and G.B. Schuster, *J. Am. Chem. Soc.*, 2004, **126**, 7341.
898. N.W. Schlientz and G.B. Schuster, *J. Am. Chem. Soc.*, 2003, **125**, 15732.
899. T. Takada, K. Kawai, X. Cai, A. Sugimoto, M. Fujitsuka and T. Majima, *J. Am. Chem. Soc.*, 2004, **126**, 1125.
900. K. Kawai, T. Takada, T. Nagai, X. Cai, A. Sugimoto, M. Fujitsuka and T. Majima, *J. Am. Chem. Soc.*, 2003, **125**, 16198.
901. K. Kawai, X. Cai, A. Sugimoto, S. Tojo, M. Fujitsuka and T. Majima, *Angew. Chem. Int. Ed.*, 2004, **43**, 2406.
902. F.D. Lewis, J. Liu, X. Zuo, R.T. Hayes and M.R. Wasielewski, *J. Am. Chem. Soc.*, 2003, **125**, 4850.
903. F.D. Lewis, X. Liu, S.E. Miller, R.T. Hayes and M.R. Wasielewski, *J. Am. Chem. Soc.*, 2002, **124**, 11280.
904. F.D. Lewis, X. Liu, Y. Wu and X. Zuo, *J. Am. Chem. Soc.*, 2003, **125**, 12729.
905. F.D. Lewis, X. Liu, S.E. Miller, R.T. Hayes and M.R. Wasielewski, *J. Am. Chem. Soc.*, 2002, **124**, 14020.
906. F.D. Lewis, J. Liu, W. Weigel, W. Rettig, I.V. Kurnikov and D.N. Beratan, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 12536.
907. N. Rahe, C. Rinn and T. Carell, *Chem. Commun.*, 2003, 2120.
908. C. Behrens, M. Ober and T. Carell, *Eur. J. Org. Chem.*, 2002, 3281.
909. Y.-T. Long, C.-Z. Li, T.C. Sutherland, M. Chahma, J.S. Lee and H.-B. Kraatz, *J. Am. Chem. Soc.*, 2003, **125**, 8724.
910. O. Lentzen, J.-F. Constant, E. Defrancq, M. Prévost, S. Schumm, C. Moucheron, P. Dumy and A. Kirsch-De Mesmaeker, *Chem. Bio. Chem.*, 2003, **4**, 195.
911. C. Dohno, K. Nakatani and I. Saito, *J. Am. Chem. Soc.*, 2002, **124**, 14580.
912. F.D. Lewis, Y. Wu, R.T. Hayes and M.R. Wasielewski, *Angew. Chem. Int. Ed.*, 2002, **41**, 3485.

913. S. Delaney and J.K. Barton, *Biochemistry*, 2003, **42**, 14159.
914. U. Santhosh and G.B. Schuster, *Nucl. Acids Res.*, 2003, **31**, 5692.
915. R.P. Fahlman, R.D. Sharma and D. Sen, *J. Am. Chem. Soc.*, 2002, **124**, 12477.
916. E.M. Boon and J.K. Barton, *Bioconjugate Chem.*, 2003, **14**, 1140.
917. D. Weicherding, W.B. Davis, S. Hess, T. von Feilitzsch, M.E. Michel-Beyerle and U. Diederichsen, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1629.
918. P.J. Finn, M.G. Bull, H. Xiao, P.D. Phillips, J.R. Nelson, G. Grossman, S. Nampalli, B.F. McArdle, J.A. Mamone, P.K. Flick, C.W. Fuller and S. Kumar, *Nucl. Acids Res.*, 2003, **31**, 4769.
919. P.J. Finn, L. Sun, S. Nampalli, H. Xiao, J.R. Nelson, J.A. Mamone, G. Grossman, P.K. Flick, C.W. Fuller and S. Kumar, *Nucl. Acids Res.*, 2002, **30**, 2877.
920. R.S. Duthie, I.M. Kalve, S.B. Samols, S. Hamilton, I. Livshin, M. Khot, S. Nampalli, S. Kumar and C.W. Fuller, *Bioconj. Chem.*, 2002, **13**, 699.
921. T.S. Rao, W. Zhang, H. Xiao, P. Flick, S. Kumar and S. Nampalli, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1443.
922. S. Nampalli, P.J. Finn, L. Sun, H. Xiao, J.R. Nelson, G. Grossmann, P.K. Flick, C.W. Fuller and S. Kumar, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1471.
923. S. Kumar, S. Nampalli, P.J. Finn, T.S. Rao, C.-Y. Chen, P.K. Flick and C.W. Fuller, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1595.
924. L.H. Thoresen, G.-S. Jiao, W.C. Haaland, M.L. Metzker and K. Burgess, *Chem. Eur. J.*, 2003, **9**, 4604.
925. K. Takatsu, T. Yokomaku, S. Kurata and T. Kanagawa, *Nucl. Acids Res.*, 2004, **32**, e60.
926. Z. Li, X. Bai, H. Ruparel, S. Kim, N.J. Turro and J. Ju, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 414.
927. X. Bai, Z. Li, S. Jockusch, N.J. Turro and J. Ju, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 409.
928. G. Pljevaljcic, M. Pignot and E. Weinhold, *J. Am. Chem. Soc.*, 2003, **125**, 3486.
929. A. Okamoto, K. Kanatani and I. Saito, *J. Am. Chem. Soc.*, 2004, **126**, 4820.
930. G.T. Hwang, Y.J. Seo, S.J. Kim and B.H. Kim, *Tetrahedron Lett.*, 2004, **45**, 3543.
931. R. Huber, T. Fiebig and H.-A. Wagenknecht, *Chem. Commun.*, 2003, 1878.
932. M. Kosuge, M. Kubota and A. Ono, *Tetrahedron Lett.*, 2004, **45**, 3945.
933. K.F. Blount and Y. Tor, *Nucl. Acids Res.*, 2003, **31**, 5490.
934. J. Gao, C. Strässler, D. Tahmassebi and E.T. Kool, *J. Am. Chem. Soc.*, 2002, **124**, 11590.
935. A.D. Malakhov, M.V. Skorobogatyi, I.A. Prokhorenko, S.V. Gontarev, D.T. Kozhich, D.S. Stetsenko, I.A. Stepanova, Z.O. Shenkarev, Y.A. Berlin and V.A. Korshun, *Eur. J. Org. Chem.*, 2004, **9**, 1298.
936. K. Yamana, T. Iwai, Y. Ohtani, S. Sato, M. Nakamura and H. Nakano, *Bioconj. Chem.*, 2002, **13**, 1266.
937. C.C.-Y. Wang, T.S. Seo, Z. Li, H. Ruparel and J. Ju, *Bioconj. Chem.*, 2003, **14**, 697.
938. G.-S. Jiao, T.G. Kim, M.R. Topp and K. Burgess, *Org. Lett.*, 2004, **6**, 1701.
939. G.-S. Jiao and K. Burgess, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2785.
940. H. Ozaki, H. Kobari, K. Takagi and H. Sawai, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1219.
941. H. Sigmund and W. Pfleiderer, *Helv. Chim. Acta*, 2003, **86**, 2299.
942. I.A. Prokhorenko, N.N. Dioubankova and V.A. Korshun, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 509.

943. T. Gunnlaugsson, J.M. Kelly, M. Nieuwenhuyzen and A.M.K. O'Brien, *Tetrahedron Lett*., 2003, **44**, 8571.
944. D.A. Berry, K.-Y. Jung, D.S. Wise, A.D. Sercel, W.H. Pearson, H. Mackie, J.B. Randolph and R.L. Somers, *Tetrahedron Lett*., 2004, **45**, 2457.
945. A. Okamoto, K. Tainaka and I. Saito, *J. Am. Chem. Soc*., 2003, **125**, 4972.
946. A. Okamoto, K. Tainaka and I. Saito, *Tetrahedron Lett*., 2003, **44**, 6871.
947. A. Okamoto, K. Tanaka, T. Fukuta and I. Saito, *J. Am. Chem. Soc*., 2003, **125**, 9296.
948. H. Asanuma, K. Shirasuka, T. Takarada, H. Kashida and M. Komiyama, *J. Am. Chem. Soc*., 2003, **125**, 2217.
949. R. Brown, W.E. Smith and D. Graham, *Tetrahedron Lett*., 2003, **44**, 1339.
950. A. Mees, C. Behrens, A. Schwögler, M. Ober and T. Carell, *Eur. J. Org. Chem*., 2003, **9**, 2670.
951. A. Yamane, *Nucl. Acids Res*., 2002, **30**, e97.
952. R.P. Hammer, C.V. Owens, S.-H. Hwang, C.M. Sayes and S.A. Soper, *Bioconj. Chem*., 2002, **13**, 1244.
953. A.A. Chernonosov, N.A. Kuznetsov, V.V. Koval, D.V. Pyshnyi, N.M. Derkacheva, E.A. Lukyanets and O.S. Fedorova, *Nucleosides, Nucleotides & Nucl. Acids*, 2004, **23**, 983.
954. P.J. O'Sullivan, M. Burke, A.E. Soini and D.B. Papkovsky, *Nucl. Acids Res*., 2002, **30**, e114.
955. L. Wang, V. Reipa and J. Blasic, *Bioconjugate Chem*., 2004, **15**, 409.
956. R. Wilson and M.K. Johansson, *Chem. Commun*., 2003, 2710.
957. J.M. Jean and K.B. Hall, *Biochemistry*, 2002, **41**, 13152.
958. T. Kimura, K. Kawai and T. Majima, *Chem. Commun*., 2004, 268.
959. T. Kimura, K. Kawai, M. Fujitsuka and T. Majima, *Chem. Commun*., 2004, 1438.
960. P. Rai, T.D. Cole, E. Thompson, D.P. Millar and S. Linn, *Nucl. Acids Res*., 2003, **31**, 2323.
961. M.A. O'Neill and J.K. Barton, *J. Am. Chem. Soc*., 2002, **124**, 13053.
962. S.K. Pal, L. Zhao, T. Xia and A.H. Zewail, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 13746.
963. V. Purohit, N.D.F. Grindley and C.M. Joyce, *Biochemistry*, 2003, **42**, 10200.
964. C.A. Dunlap and M.-D. Tsai, *Biochemistry*, 2002, **41**, 11226.
965. A. Krieg, S. Laib, T. Ruckstuhl and S. Seeger, *Chem. Bio. Chem*., 2003, **4**, 589.
966. T.-J. Su, B.A. Connolly, C. Darlington, R. Mallin and D.T.F. Dryden, *Nucl. Acids Res*., 2004, **32**, 2223.
967. C. Beck and A. Jeltsch, *Biochemistry*, 2002, **41**, 14103.
968. M. Kaul, C.M. Barbieri and D.S. Pilch, *J. Am. Chem. Soc*., 2004, **126**, 3447.
969. A.K. Shchyolkina, D.N. Kaluzhny, O.F. Borisova, M.E. Hawkins, R.L. Jernigan, T.M. Jovin, D.J. Arndt-Jovin and V.B. Zhurkin, *Nucl. Acids Res*., 2004, **32**, 432.
970. T. Xia, H.-C. Becker, C. Wan, A. Frankel, R.W. Roberts and A.H. Zewail, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 8119.
971. M. Taki, Y. Kato, M. Miyagashi, Y. Takagi and K. Taira, *Angew. Chem. Int. Ed*., 2004, **43**, 3160.
972. K.-i. Shohda, T. Toyota, T. Yomo and T. Sugawara, *Chem. Bio. Chem*., 2003, **4**, 778.
973. H. Ma and Y. Zou, *Biochemistry*, 2004, **43**, 4206.
974. M.N. Stojanovic, E.G. Green, S. Semova, D.B. Nikic and D.W. Landry, *J. Am. Chem. Soc*., 2003, **125**, 6085.
975. T. Ihara, Y. Chikaura, S. Tanaka and A. Jyo, *Chem. Commun*., 2002, **9**, 2152.

976. S. Jeon, J. Turner and S. Granick, *J. Am. Chem. Soc.*, 2003, **125**, 9908.
977. L.A. Gearheart, M.M. Somoza, W.E. Rivers, C.J. Murphy, R.S. Coleman and M.A. Berg, *J. Am. Chem. Soc.*, 2003, **125**, 11812.
978. B.S. Gaylord, A.J. Heeger and G.C. Bazan, *J. Am. Chem. Soc.*, 2003, **125**, 896.
979. L. Beach, C. Schweitzer and J.C. Scaiano, *Org. Biomol. Chem.*, 2003, **1**, 450.
980. K. Tawa and W. Knoll, *Nucl. Acids Res.*, 2004, **32**, 2372.
981. X. Wang and W.M. Nau, *J. Am. Chem. Soc.*, 2004, **126**, 808.
982. J.H. Moon, R. Deans, E. Krueger and L.F. Hancock, *Chem. Commun.*, 2003, 104.
983. X. Zhao, R. Tapec-Dytioco and W. Tan, *J. Am. Chem. Soc.*, 2003, **125**, 11474.
984. T. Ito, L. Sun and R.M. Crooks, *Chem. Commun.*, 2003, 1482.
985. M.H. Lyttle, T.A. Walton, D.J. Dick, T.G. Carter, J.H. Beckman and R.M. Cook, *Bioconj. Chem.*, 2002, **13**, 1146.
986. T.A. Walton, M.H. Lyttle, D.J. Dick and R.M. Cook, *Bioconj. Chem.*, 2002, **13**, 1155.
987. Y. Ohya, K. Yabuki, M. Hashimoto, A. Nakajima and T. Ouchi, *Bioconjugate Chem.*, 2003, **14**, 1057.
988. D. Klostermeier, P. Sears, C.-H. Wong, D.P. Millar and J.R. Williamson, *Nucl. Acids Res.*, 2004, **32**, 2707.
989. C.M. Soto, A. Srinivasan and B.R. Ratna, *J. Am. Chem. Soc.*, 2002, **124**, 8508.
990. K. Wojtuszewski and I. Mukerji, *Biochemistry*, 2003, **42**, 3096.
991. D.A. Hiller, J.M. Fogg, A.M. Martin, J.M. Beechem, N.O. Reich and J.J. Perona, *Biochemistry*, 2003, **42**, 14375.
992. H.Q. Xu, A.H. Zhang, C. Auclair and X.G. Xi, *Nucl. Acids Res.*, 2003, **31**, e70.
993. A.L. Lucius, C.J. Wong and T.M. Lohman, *J. Mol. Biol.*, 2004, **339**, 731.
994. S.A. Uhler, D. Cai, Y. Man, C. Figge and N.G. Walter, *J. Am. Chem. Soc.*, 2003, **125**, 14230.
995. R.A. Tinsley, D.A. Harris and N.G. Walter, *J. Am. Chem. Soc.*, 2003, **125**, 13972.
996. B. Liu, S. Baudrey, L. Jaeger and G.C. Bazan, *J. Am. Chem. Soc.*, 2004, **126**, 4076.
997. W.J. Kim, T. Akaike and A. Maruyama, *J. Am. Chem. Soc.*, 2002, **124**, 12676.
998. L. Feng, S.H. Park, J.H. Reif and H. Yan, *Angew. Chem. Int. Ed.*, 2003, **42**, 4342.
999. A. Karadag, M. Riminucci, P. Bianco, N. Cherman, S.A. Kuznetsov, N. Nguyen, M.T. Collins, P.G. Robey and L.W. Fisher, *Nucl. Acids Res.*, 2004, **32**, e63.
1000. A. Risitano and K.R. Fox, *Biochemistry*, 2003, **42**, 6507.
1001. H. Ueyama, M. Takagi and S. Takenaka, *J. Am. Chem. Soc.*, 2002, **124**, 14286.
1002. J.S. Hartig and M. Famulok, *Angew. Chem. Int. Ed.*, 2002, **41**, 4263.
1003. S. Wang, B.S. Gaylord and G.C. Bazan, *J. Am. Chem. Soc.*, 2004, **126**, 5446.
1004. D. Summerer and A. Marx, *Angew. Chem. Int. Ed.*, 2002, **41**, 3620.
1005. M. Nilsson, M. Gullberg, F. Dahl, K. Szuhai and A.K. Raap, *Nucl. Acids Res.*, 2002, **30**, e66.
1006. K. Fujimoto, H. Shimizu and M. Inouye, *J. Org. Chem.*, 2004, **69**, 3271.
1007. G. Yao, X. Fang, H. Yokota, T. Yanagida and W. Tan, *Chem. Eur. J.*, 2003, **9**, 5686.
1008. A. Tsourkas, M.A. Behlke and G. Bao, *Nucl. Acids Res.*, 2002, **30**, 5168.
1009. Y. Xiao, V. pavlov, T. Niazov, A. Dishon, M. Kotler and I. Willner, *J. Am. Chem. Soc.*, 2004, **126**, 7430.
1010. Z. Tang, K. Wang, W. Tan, J. Li, L. Liu, Q. Guo, X. Meng, C. Ma and S. Huang, *Nucl. Acids Res.*, 2003, **31**, e148.
1011. L.M. Kundu, L.T. Burgdorf, O. Kleiner, A. Batschauer and T. Carell, *ChemBioChem*, 2002, **3**, 1053.
1012. H. Du, M.D. Disney, B.L. Miller and T.D. Krauss, *J. Am. Chem. Soc.*, 2003, **125**, 4012.

1013. A. Okamoto, K. Tanabe, T. Inasaki and I. Saito, *Angew. Chem. Int. Ed.*, 2003, **42**, 2502.
1014. N. Nitin, P.J. Santangelo, G. Kim, S. Nie and G. Bao, *Nucl. Acids Res.*, 2004, **32**, e58.
1015. R.H. Kehlenbach, *Nucl. Acids Res.*, 2003, **31**, e64.
1016. P.J. Santangelo, B. Nix, A. Tsourkas and G. Bao, *Nucl. Acids Res.*, 2004, **32**, e57.
1017. D.-M. Kong, L. Gu, H.-X. Shen and H.-F. Mi, *Chem. Commun.*, 2002, 2584.
1018. N. Dobson, D.G. McDowell, D.J. French, L.J. Brown, J.M. Mellor and T. Brown, *Chem. Commun.*, 2003, 1234.
1019. J.P. May, L.J. Brown, I. Rudloff and T. Brown, *Chem. Commun.*, 2003, 970.
1020. R. Nutiu and Y. Li, *Nucl. Acids Res.*, 2002, **30**, e94.
1021. C.M. McKeen, L.J. Brown, J.T.G. Nicol, J.M. Mellor and T. Brown, *Org. Biomol. Chem.*, 2003, **1**, 2267.
1022. E. Mayer, L. Valis, C. Wagner, M. Rist, N. Amann and H.-A. Wagenknecht, *Chem. Bio. Chem.*, 2004, **5**, 865.
1023. G.T. Hwang, Y.J. Seo and B.H. Kim, *J. Am. Chem. Soc.*, 2004, **126**, 6528.
1024. G. Charvin, D. Bensimon and V. Croquette, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9820.
1025. N.H. Dekker, T. Viard, C. Bouthier de la Tour, M. Duguet and V. Croquette, *J. Mol. Biol.*, 2003, **329**, 271.
1026. Z. Xie, N. Srividya, T.R. Sosnick, T. Pan and N.F. Scherer, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 534.
1027. G. Bokinsky, D. Rueda, V.K. Misra, M.M. Rhodes, A. Gordus, H.P. Babcock, N.G. Walter and X. Zhuang, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9302.
1028. E. Tan, T.J. Wilson, M.K. Nahas, R.M. Clegg, D.M.J. Lilley and T. Ha, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9308.
1029. L. Ying, J.J. Green, H. Li, D. Klenerman and S. Balasubramanian, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 14629.
1030. J.J. Green, L. Ying, D. Klenerman and S. Balasubramanian, *J. Am. Chem. Soc.*, 2003, **125**, 3763.
1031. I. Rasnik, S. Myong, W. Cheng, T.M. Lohman and T. Ha, *J. Mol. Biol.*, 2004, **336**, 395.
1032. S. Hohng, T.J. Wilson, E. Tan, R.M. Clegg, D.M.J. Lilley and T. Ha, *J. Mol. Biol.*, 2004, **336**, 69.
1033. J. Zhu, J. Shendure, R.D. Mitra and G.M. Church, *Science*, 2003, **301**, 836.
1034. K. Korn, P. Gardellin, B. Liao, M. Amacker, Å. Bergström, H. Björkman, A. Camacho, S. Dörhöfer, K. Dörre, J. Enström, T. Ericson, T. Favez, M. Gösch, A. Honegger, S. Jaccoud, M. Lapczyna, E. Litborn, P. Thyberg, H. Winter and R. Rigler, *Nucl. Acids Res.*, 2003, **31**, e89.
1035. S. Sando and E.T. Kool, *J. Am. Chem. Soc.*, 2002, **124**, 9686.
1036. S. Sando, H. Abe and E.T. Kool, *J. Am. Chem. Soc.*, 2004, **126**, 1081.
1037. D. Dressman, H. Yan, G. Traverso, K.W. Kinzler and B. Vogelstein, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 8817.
1038. G. Giller, T. Tasara, B. Angerer, K. Mühlegger, M. Amacker and H. Winter, *Nucl. Acids Res.*, 2003, **31**, 2630.
1039. T. Tasara, B. Angerer, M. Damond, H. Winter, S. Dörhöfer, U. Hübscher and M. Amacker, *Nucl. Acids Res.*, 2003, **31**, 2636.
1040. S. Brakmann and S. Löbermann, *Angew. Chem. Int. Ed.*, 2002, **41**, 3215.
1041. B. Arezi, C.J. Hansen and H.H. Hogrefe, *J. Mol. Biol.*, 2002, **322**, 719.
1042. S. Jäger and M. Famulok, *Angew. Chem. Int. Ed.*, 2004, **43**, 3337.

1043. R. Tashiro and H. Sugiyama, *Angew. Chem. Int. Ed.*, 2003, **42**, 6018.
1044. D. Liu and S. Balasubramanian, *Angew. Chem. Int. Ed.*, 2003, **42**, 5734.
1045. A. Saghatelian, N.H. Völcker, K.M. Guckian, V.S.-Y. Lin and M.R. Ghadiri, *J. Am. Chem. Soc.*, 2003, **125**, 346.
1046. P. Alberti and J.-L. Mergny, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 1569.
1047. S. Raddatz, J. Mueller-Ibeler, J. Kluge, L. Wäß, G. Burdinski, J.R. Havens, T.J. Onofrey, D. Wang and M. Schweitzer, *Nucl. Acids Res.*, 2002, **30**, 4793.
1048. A.J. Ziemba, M.W. Reed, K.D. Raney, A.B. Byrd and S.W. Ebbinghaus, *Biochemistry*, 2003, **42**, 5013.
1049. S. Fang and D.E. Bergstrom, *Nucl. Acids Res.*, 2003, **31**, 708.
1050. S. Kim, J.R. Edwards, L. Deng, W. Chung and J. Ju, *Nucl. Acids Res.*, 2002, **30**, e85.
1051. H. Li, S.H. Park, J.H. Reif, T.H. LaBean and H. Yan, *J. Am. Chem. Soc.*, 2004, **126**, 418.
1052. N. Pouget, C. Dennis, C. Turlan, M. Grigoriev, M. Chandler and L. Salomé, *Nucl. Acids Res.*, 2004, **32**, e73.
1053. S. Sando, K. Matsui, Y. Niinomi, N. Sato and Y. Aoyama, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2633.
1054. M.A. Maier, C.G. Yannopoulos, N. Mohamed, A. Roland, H. Fritz, V. Mohan, G. Just and M. Manoharan, *Bioconj. Chem.*, 2003, **14**, 18.
1055. M. Adinolfi, L. De Napoli, G. Di Fabio, A. Ladonisi, D. Montesarchio and G. Piccialli, *Tetrahedron*, 2002, **58**, 6697.
1056. Y. Wang and T.L. Sheppard, *Bioconjugate Chem.*, 2003, **14**, 1314.
1057. M. Manoharan, G.B. Inamati, E.A. Lesnik, N. Sioufi and S.M. Freier, *Chem. Bio. Chem.*, 2002, **3**, 1257.
1058. P.B. Arimondo, S. Angenault, L. Halby, A. Boutorine, F. Schmidt, C. Monneret, T. Garestier, J.-S. Sun, C. Bailly and C. Hélène, *Nucl. Acids Res.*, 2003, **31**, 4031.
1059. P.E. Vorobjev, J.B. Smith, I.A. Pyshnaya, A.S. Levina, V.F. Zarytova and E. Wickstrom, *Bioconjugate Chem.*, 2003, **14**, 1307.
1060. G.M. Carbone, E. McGuffie, S. Napoli, C.E. Flanagan, C. Dembech, U. Negri, F. Arcamone, M.L. Capobianco and C.V. Catapano, *Nucl. Acids Res.*, 2004, **32**, 2396.
1061. S. Ghosh, E. Defrancq, J.H. Lhomme, P. Dumy and S. Bhattacharya, *Bioconjugate Chem.*, 2004, **15**, 520.
1062. B. Kuhnast, B. de Bruin, F. Hinnen, B. Tavitian and F. Dollé, *Bioconjugate Chem.*, 2004, **15**, 617.
1063. A.S. Bouterine, V.A. Ryabinin, D.S. Novopashina, A.G. Venyaminova, C. Hélène and A.S. Sinyakov, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1267.
1064. D. Novopashina, A. Sinyakov, V. Ryabinin, A. Venyaminova and A. Bouterine, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1179.
1065. F.D. Lewis, Y. Wu and X. Liu, *J. Am. Chem. Soc.*, 2002, **124**, 12165.
1066. J. Michel, K. Bathany, J.-M. Schmitter, J.-P. Monti and S. Moreau, *Tetrahedron*, 2002, **58**, 7975.
1067. K.V. Gothelf, A. Thomsen, M. Nielsen, E. Cló and R.S. Brown, *J. Am. Chem. Soc.*, 2004, **126**, 1044.
1068. S.M. Langenegger and R. Häner, *Helv. Chim. Acta*, 2002, **85**, 3414.
1069. A. Stutz, S.M. Langenegger and R. Häner, *Helv. Chim. Acta*, 2003, **86**, 3156.
1070. S. Vinogradov, V. Roig, Z. Sergueeva, C.H. Nguyen, P. Arimondo, N.T. Thuong, E. Bisagni, J.-S. Sun, C. Hélène and U. Asseline, *Bioconj. Chem.*, 2003, **14**, 120.

1071. R. Zain, D. Polverari, C.-H. Nguyen, Y. Blouquit, E. Bisagni, T. Garestier, D. S. Grierson and J.-S. Sun, *Chem. Bio. Chem.*, 2003, **4**, 856.
1072. W. Wang, W. Wan, H.-H. Zhou, S. Niu and A.D. Q. Li, *J. Am. Chem. Soc.*, 2003, **125**, 5248.
1073. P.-S. Ng, M.R. Pingle, G. Balasundarum, A. Friedman, X. Zu and D.E. Bergstrom, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1635.
1074. O. Amosova, S.L. Broitman and J.R. Fresco, *Nucl. Acids Res.*, 2003, **31**, 4673.
1075. S.L. Broitman, O. Amosova and J.R. Fresco, *Nucl. Acids Res.*, 2003, **31**, 4682.
1076. F. Guillonneau, A.L. Guieysse, S. Nocentini, C. Giovannangeli and D. Praseuth, *Nucl. Acids Res.*, 2004, **32**, 1143.
1077. R.C. Bailey, J.-M. Nam, C.A. Mirkin and J.T. Hupp, *J. Am. Chem. Soc.*, 2003, **125**, 13541.
1078. A. Ruffien, M. Dequaire and P. Brossier, *Chem. Commun.*, 2003, 912.
1079. P. He and L. Dai, *Chem. Commun.*, 2004, 348.
1080. K.A. Williams, P.T.M. Veenhuizen, B.G. de la Torre, R. Eritja and C. Dekker, *Nature*, 2002, **420**, 761.
1081. R. Iwaura, K. Yoshida, M. Masuda, M. Ohnishi-Kameyama, M. Yoshida and T. Shimizu, *Angew. Chem. Int. Ed.*, 2003, **42**, 1009.
1082. A.-H. Bae, T. Hatano, N. Nakashima, H. Murakami and S. Shinkai, *Org. Biomol. Chem.*, 2004, **2**, 1139.
1083. H. Yan, S.H. Park, G. Finkelstein, J.H. Reif and T.H. LaBean, *Science*, 2003, **301**, 1882.
1084. D. Liu, S.H. Park, J.H. Reif and T.H. LaBean, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 717.
1085. K. Keren, R.S. Berman, E. Buchstab, U. Sivan and E. Braun, *Science*, 2003, **302**, 1380.
1086. G.-J. Zhang, T. Tanii, T. Funatsu and I. Ohdomari, *Chem. Commun.*, 2004, 786.
1087. H. Nakao, M. Gad, S. Sugiyama, K. Otobe and T. Ohtani, *J. Am. Chem. Soc.*, 2003, **125**, 7162.
1088. K. Keren, M. Krueger, R. Gilad, G. Ben-Yoseph, U. Sivan and E. Braun, *Science*, 2002, **297**, 72.
1089. H. Yan, T.H. LaBean, L. Feng and J.H. Reif, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 8103.
1090. L.H. Eckardt, K. Naumann, W.M. Pankau, M. Rein, M. Schweitzer, N. Windhab and G. von Kiedrowski, *Nature*, 2002, **420**, 286.
1091. J. Wang, G. Liu, B. Munge, L. Lin and Q. Zhu, *Angew. Chem. Int. Ed.*, 2004, **43**, 2158.
1092. J.H. Jeong, S.W. Kim and T.G. Park, *Bioconj. Chem.*, 2003, **14**, 473.
1093. M. Murata, W. Kaku, T. Anada, Y. Sato, T. Kano, M. Maeda and Y. Katayama, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3967.
1094. J. Sánchez-Quesada, A. Saghatelian, S. Cheley, H. Bayley and M.R. Ghadiri, *Angew. Chem. Int. Ed.*, 2004, **43**, 3063.
1095. E.A. Fogleman, W.C. Yount, J. Xu and S.L. Craig, *Angew. Chem. Int. Ed.*, 2002, **41**, 4026.
1096. A.M. Morocho, V.N. Karamyshev and N.N. Polushin, *Bioconjugate Chem.*, 2004, **15**, 569.
1097. A.M. Morocho, V.N. Karamyshev and N.N. Polushin, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1407.
1098. S.L. Goh, M.B. Francis and J.M.J. Fréchet, *Chem. Commun.*, 2002, **9**, 2954.

1099. S.A. Bell, M.E. McLean, S.-K. Oh, S.E. Tichy, W. Zhang, R.M. Corn, R.M. Crooks and E.E. Simanek, *Bioconj. Chem.*, 2003, **14**, 488.
1100. L. Zhu, P.S. Lukeman, J.W. Canary and N.C. Seeman, *J. Am. Chem. Soc.*, 2003, **125**, 10178.
1101. A. Nikulin, I. Eliseikina, S. Tishchenko, N. Nevskaya, N. Davydova, O. Platonova, W. Piendl, M. Selmer, A. Liljas, D. Drygin, R. Zimmermann, M. Garber and S. Nikonov, *Nature Struct. Biol.*, 2003, **10**, 104.
1102. A. Vila-Sanjurjo, W.K. Ridgeway, V. Seymaner, W. Zhang, S. Santoso and K. Yu, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 8682.
1103. J.L. Hansen, P.B. Moore and T.A. Steitz, *J. Mol. Biol.*, 2003, **330**, 1061.
1104. Q. Vicens and E. Westhof, *J. Mol. Biol.*, 2003, **326**, 1175.
1105. R.J.M. Russell, J.B. Murray, G. Lentzen, J. Haddad and S. Mobashery, *J. Am. Chem. Soc.*, 2003, **125**, 3410.
1106. M. Halic, T. Becker, M.R. Pool, C.M.T. Spahn, R.A. Grassucci, J. Frank and R. Beckmann, *Nature*, 2004, **427**, 808.
1107. M.R. Sharma, E.C. Koc, P.P. Datta, T.M. Booth, L.L. Spremulli and R.K. Agrawal, *Cell*, 2003, **115**, 97.
1108. S. Gutmann, P.W. Haebel, L. Metzinger, M. Sutter, B. Felden and N. Ban, *Nature*, 2003, **424**, 699.
1109. W. Xie, X. Liu and R.H. Huang, *Nature Struct. Biol.*, 2003, **10**, 781.
1110. H. Pan, S. Agarwalla, D.T. Moustakas, J. Finer-Moore and R.M. Stroud, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 12648.
1111. C. Mazza, A. Segref, I.W. Mattaj and S. Cusack, *EMBO J.*, 2002, **21**, 5548.
1112. C.M. Dunham, J.B. Murray and W.G. Scott, *J. Mol. Biol.*, 2003, **332**, 327.
1113. P.B. Rupert, A.P. Massey, S.T. Sigurdsson and A.R. Ferré-D'Amaré, *Science*, 2002, **298**, 1421.
1114. J.M. Vargason, G. Szittya, J. Burgyán and T.M. T. Hall, *Cell*, 2003, **115**, 799.
1115. J.-B. Ma, K. Ye and D.J. Patel, *Nature*, 2004, **429**, 318.
1116. J.-J. Song, J. Liu, N.H. Tolia, J. Schneiderman, S.K. Smith, R.A. Martienssen, G.J. Hannon and L. Joshua-Tor, *Nature Struct. Biol.*, 2003, **10**, 1026.
1117. N.H. Hopcroft, A. Manfredo, A.L. Wendt, A.M. Brzozowski, P. Gollnick and A.A. Antson, *J. Mol. Biol.*, 2004, **338**, 43.
1118. E. Skordalakes and J.M. Berger, *Cell*, 2003, **114**, 135.
1119. D. Lu, M.A. Searles and A. Klug, *Nature*, 2003, **426**, 96.
1120. D.-B. Huang, D. Vu, L.A. Cassiday, J.M. Zimmerman, L.J. Maher and G. Ghosh, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9268.
1121. S.X. Cohen, M. Moulin, S. Hashemolhosseini, K. Kilian, M. Wegner and C. W. Müller, *EMBO J.*, 2003, **22**, 1835.
1122. J.C. Fromme and G.L. Verdine, *EMBO J.*, 2003, **22**, 3461.
1123. C.M. Moure, F.S. Gimble and F.A. Quiocho, *Nature Struct. Biol.*, 2002, **9**, 764.
1124. T.J. Richmond and C.A. Davey, *Nature*, 2003, **423**, 145.
1125. R.K. Suto, R.S. Edayathumangalam, C.L. White, C. Melander, J.M. Gottesfeld, P.B. Dervan and K. Luger, *J. Mol. Biol.*, 2003, **326**, 371.
1126. L. Jin, P. Sliz, L. Chen, F. Macián, A. Rao, P.G. Hogan and S.C. Harrison, *Nature Struct. Biol.*, 2003, **10**, 807.
1127. J.C. Stroud and L. Chen, *J. Mol. Biol.*, 2003, **334**, 1009.
1128. J.S. Lamoureux, D. Stuart, R. Tsang, C. Wu and J.N.M. Glover, *EMBO J.*, 2002, **21**, 5721.
1129. K.K. Swinger, K.M. Lemberg, Y. Zhang and P.A. Rice, *EMBO J.*, 2003, **22**, 3749.

1130. S.K. Nair and S.K. Burley, *Cell*, 2003, **112**, 193.
1131. M. Lei, E.R. Podell, P. Baumann and T.R. Cech, *Nature*, 2003, **426**, 198.
1132. A. Vannini, C. Volpari, C. Gargioli, E. Muraglia, R. Cortese, R. De Francesco, P. Neddermann and S. Di Marco, *EMBO J.*, 2002, **21**, 4393.
1133. T.H. Tahirov, D. Temlakov, M. Anikin, V. Patian, W.T. McAllister, D.G. Vassylyev and S. Yokoyama, *Nature*, 2002, **420**, 43.
1134. Y.W. Yin and T.A. Steitz, *Cell*, 2004, **116**, 393.
1135. Y.W. Yin and T.A. Steitz, *Science*, 2002, **298**, 1387.
1136. K.D. Westover, D.A. Bushnell and R.D. Kornberg, *Science*, 2004, **303**, 1014.
1137. D.A. Bushnell, K.D. Westover, R.E. Davis and R.D. Kornberg, *Science*, 2004, **303**, 983.
1138. Y. Tao, D.L. Farsetta, M.L. Nibert and S.C. Harrison, *Cell*, 2002, **111**, 733.
1139. S.G. Sarafianos, A.D. Clark, K. Das, S. Tuske, J.J. Birktoft, P. Ilankumaran, A.R. Ramesha, J.M. Sayer, D.M. Jerina, P.L. Boyer, S.H. Hughes and E. Arnold, *EMBO J.*, 2002, **21**, 6614.
1140. M.J. Griffin, J.C. Stroud, D.L. Bates, K.D. von Koenig, J. Hardin and L. Chen, *Nature Struct. Biol.*, 2003, **10**, 800.
1141. S. Tuske, S.G. Sarafianos, A.D. Clark, J. Ding, L.K. Naeger, K.L. White, M.D. Miller, C.S. Gibbs, P.L. Boyer, P. Clark, G. Wang, B.L. Gaffney, R.A. Jones, D.M. Jerina, S.H. Hughes and E. Arnold, *Nature Struct. Mol. Biol.*, 2004, **11**, 469.
1142. M. Hogg, S.S. Wallace and S. Doublié, *EMBO J.*, 2004, **23**, 1483.
1143. F. Li, Y. Xiong, J. Wang, H.D. Cho, K. Tomita, A.M. Weiner and T.A. Steitz, *Cell*, 2002, **111**, 815.
1144. G.D. Bowman, M. O'Donnell and J. Kuriyan, *Nature*, 2004, **429**, 724.
1145. E. Freisinger, A.P. Grollman, H. Miller and C. Kisker, *EMBO J.*, 2004, **23**, 1494.
1146. D. Temiakov, V. Patlan, M. Anikin, W.T. McAllister, S. Yokoyama and D.G. Vassylyev, *Cell*, 2004, **116**, 381.
1147. J.C. Fromme and G.L. Verdine, *Nature Struct. Biol.*, 2002, **9**, 544.
1148. S.J. Johnson and L.S. Beese, *Cell*, 2004, **116**, 803.
1149. B.R. Chapados, D.J. Hosfield, S. Han, J. Qiu, B. Yelent, B. Shen and J.A. Tainer, *Cell*, 2004, **116**, 39.
1150. P.J. O'Brien and T. Ellenberger, *Biochemistry*, 2003, **42**, 12418.
1151. K. Shi, B. Pan and M. Sundaralingam, *Nucl. Acids Res.*, 2003, **31**, 1392.
1152. E. Ennifar, P. Walter and P. Dumas, *Nucl. Acids Res.*, 2003, **31**, 2671.
1153. S. Sarkhel, A. Rich and M. Egli, *J. Am. Chem. Soc.*, 2003, **125**, 8998.
1154. M. Egli, S. Sarkhel, G. Minasov and A. Rich, *Helv. Chim. Acta*, 2003, **86**, 1709.
1155. G.W. Han, M.L. Kopka, D. Langs, M.R. Sawaya and R.E. Dickerson, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9214.
1156. M.L. Kopka, L. Lavelle, G.W. Han, H.-L. Ng and R.E. Dickerson, *J. Mol. Biol.*, 2003, **334**, 653.
1157. J.C. Fromme, A. Banerjee, S.J. Huang and G.L. Verdine, *Nature*, 2004, **427**, 652.
1158. J.E. Wedekind and D.B. McKay, *Biochemistry*, 2003, **42**, 9554.
1159. V. Tereshko, E. Skripkin and D.J. Patel, *Chem. Biol.*, 2003, **10**, 175.
1160. H.-L. Ng and R.E. Dickerson, *Nucl. Acids Res.*, 2002, **30**, 4061.
1161. M.L. Coté, M. Pflomm and M.M. Georgiadis, *J. Mol. Biol.*, 2003, **330**, 57.
1162. T. Sunami, J. Kondo, T. Kobuna, I. Hirao, K. Watanabe, K. Miura and A. Takénaka, *Nucl. Acids Res.*, 2002, **30**, 5253.
1163. J. Kondo, W. Adachi, S.-i. Umeda, T. Sunami and A. Takénaka, *Nucl. Acids Res.*, 2004, **32**, 2541.

1164. S. Cáceres, G. Wright, C. Gouyette, G. Parkinson and J.A. Subirana, *Nucl. Acids Res.*, 2004, **32**, 1097.
1165. J.H. Thorpe, S.C.M. Teixeira, B.C. Gale and C.J. Cardin, *Nucl. Acids Res.*, 2003, **31**, 844.
1166. B.F. Eichman, M. Ortiz-Lombardía, J. Aymamí, M. Coll and P.S. Ho, *J. Mol. Biol.*, 2002, **320**, 1037.
1167. M.D. Sam, D. Cascio, R.C. Johnson and R.T. Clubb, *J. Mol. Biol.*, 2004, **338**, 229.
1168. S.C.M. Teixeira, J.H. Thorpe, A.K. Todd, H.R. Powell, A. Adams, L.P.G. Wakelin, W.A. Denny and C.J. Cardin, *J. Mol. Biol.*, 2002, **323**, 167.
1169. S.M. Haider, G.N. Parkinson and S. Neidle, *J. Mol. Biol.*, 2003, **326**, 117.
1170. L. Malinina, M. Soler-López, J. Aymamí and J.A. Subirana, *Biochemistry*, 2002, **41**, 9341.
1171. J. Reynisson, G. B. Schuster, S. B. Howerton, L. D. Williams, R.N. Barnett, C.L. Cleveland, U. Landman, N. Harrit and J.B. Chaires, *J. Am. Chem. Soc.*, 2003, **125**, 2072.
1172. M.-H. Hou, H. Robinson, Y.-G. Gao and A.H.-J. Wang, *Nucl. Acids Res.*, 2002, **30**, 4910.
1173. C. Temperini, L. Messori, P. Orioli, C. Di Bugno, F. Animati and G. Ughetto, *Nucl. Acids Res.*, 2003, **31**, 1464.
1174. M.-H. Hou, H. Robinson, Y.-G. Gao and A.H.-J. Wang, *Nucl. Acids Res.*, 2004, **32**, 2214.
1175. G.R. Clark, P.D. Pytel, C.J. Squire and S. Neidle, *J. Am. Chem. Soc.*, 2003, **125**, 4066.
1176. K.K. Woods, T. Lan, L.W. McLaughlin and L.D. Williams, *Nucl. Acids Res.*, 2003, **31**, 1536.
1177. H. Park, K. Zhang, Y. Ren, S. Nadji, N. Sinha, J.-S. Taylor and C. Kang, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 15965.
1178. H. Ling, F. Boudsocq, B.S. Plosky, R. Woodgate and W. Yang, *Nature*, 2003, **424**, 1083.
1179. E. Freisinger, A. Fernandes, A.P. Grollman and C. Kisker, *J. Mol. Biol.*, 2003, **329**, 685.
1180. C.J. Wilds, M.A. Maier, M. Manoharan and M. Egli, *Helv. Chim. Acta*, 2003, **86**, 966.
1181. D.-T.T. Lesher, Y. Pommier, L. Stewart and M.R. Redinbo, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 12102.
1182. H. Ling, J.M. Sayer, B.S. Plosky, H. Yagi, F. Boudsocq and R. Woodgate, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 2265.
1183. I.L. Karle, H. Yagi, J.M. Sayer and D.M. Jerina, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 1433.
1184. M. Egli, V. Tereshko, G.N. Mushudov, R. Sanishvili, X. Liu and F.D. Lewis, *J. Am. Chem. Soc.*, 2003, **125**, 10842.
1185. C.J. Wilds, Z. Wawrzak, R. Krishnamurthy, A. Eschenmoser and M. Egli, *J. Am. Chem. Soc.*, 2002, **124**, 13716.
1186. P.S. Pallan, C.J. Wilds, Z. Wawrzak, R. Krishnamurthy, A. Eschenmoser and M. Egli, *Angew. Chem. Int. Ed.*, 2003, **42**, 5893.
1187. V. Menchise, G. De Simone, T. Tedeschi, R. Corradini, S. Sforza, R. Marchelli, D. Capasso, M. Saviano and C. Pedone, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 12021.
1188. B.M. Znosko, M.E. Burkard, S.J. Schroeder, T.R. Krugh and D.H. Turner, *Biochemistry*, 2002, **41**, 14969.

1189. B.M. Znosko, M.E. Burkard, T.R. Krugh and D.H. Turner, *Biochemistry*, 2002, **41**, 14978.
1190. B.N.M. van Buuren, J. Schleucher, V. Wittmann, C. Griesinger, H. Schwalbe and S.S. Wijmenga, *Angew. Chem. Int. Ed.*, 2004, **43**, 187.
1191. M.S. Gerdeman, T.M. Henkin and J.V. Hines, *J. Mol. Biol.*, 2003, **326**, 189.
1192. Y. Yuan, D.J. Kerwood, A.C. Paoletti, M.F. Shubsda and P.N. Borer, *Biochemistry*, 2003, **42**, 5259.
1193. L.R. Comolli, N.B. Ulyanov, A.M. Soto, L.A. Marky, T.L. James and W.H. Gmeiner, *Nucl. Acids Res.*, 2002, **30**, 4371.
1194. Z. Du, J. Yu, R. Andino and T.L. James, *Biochemistry*, 2003, **42**, 4373.
1195. E.M.H.P. Lescrinier, M. Tessari, F.J.M. van Kuppeveld, W.J.G. Melchers, C.W. Hilbers and H.A. Heus, *J. Mol. Biol.*, 2003, **331**, 759.
1196. D.C. Lawrence, C.C. Stover, J. Noznitsky, Z. Wu and M.F. Summers, *J. Mol. Biol.*, 2003, **326**, 529.
1197. J. Greatorex, J. Gallego, G. Varani and A. Lever, *J. Mol. Biol.*, 2002, **322**, 543.
1198. T. Leeper, N. Leulliot and G. Varani, *Nucl. Acids Res.*, 2003, **31**, 2614.
1199. D.W. Staple and S.E. Butcher, *Nucl. Acids Res.*, 2003, **31**, 4326.
1200. Z. Du, N.B. Ulyanov, J. Yu, R. Andino and T.L. James, *Biochemistry*, 2004, **43**, 5757.
1201. L.D. Finger, L. Trantirek, C. Johansson and J. Feigon, *Nucl. Acids Res.*, 2003, **31**, 6461.
1202. S.A. McCallum and A. Pardi, *J. Mol. Biol.*, 2003, **326**, 1037.
1203. D.G. Sashital, A.M. Allmann, S.R. Van Doren and S.E. Butcher, *Biochemistry*, 2003, **42**, 1470.
1204. R.K.O. Sigel, D.G. Sashital, D.L. Abramovitz, A.G. Palmer, S.E. Butcher and A.M. Pyle, *Nature Struct. Mol. Biol.*, 2004, **11**, 187.
1205. Y. Tanaka, Y. Kasai, S. Mochizuki, A. Wakisaka, E.H. Morita, C. Kojima, A. Toyozawa, Y. Kondo, M. Taki, Y. Takagi, A. Inoue, K. Yamasaki and K. Taira, *J. Am. Chem. Soc.*, 2004, **126**, 744.
1206. B. Hoffmann, G.T. Mitchell, P. Gendron, F. Major, A.A. Andersen, R.A. Collins and P. Legault, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 7003.
1207. H. Liu, A. Matsugami, M. Katahira and S. Uesugi, *J. Mol. Biol.*, 2002, **322**, 955.
1208. H. Liu, A. Kugimiya, T. Sakurai, M. Katahira and S. Uesugi, *Nucleosides, Nucleotides & Nucl. Acids*, 2002, **21**, 785.
1209. V. D'Souza, A. Dey, D. Habib and M.F. Summers, *J. Mol. Biol.*, 2004, **337**, 427.
1210. P.L. Nixon, A. Rangan, Y.-G. Kim, A. Rich, D.W. Hoffman, M. Hennig and D.P. Giedroc, *J. Mol. Biol.*, 2002, **322**, 621.
1211. K.-i. Suzumura, K. Yoshinara, Y. Tanaka, Y. Takagi, Y. Kasai, M. Warashina, T. Kuwabara, M. Orita and K. Taira, *J. Am. Chem. Soc.*, 2002, **124**, 8230.
1212. J.I. Gyi, D. Gao, G.L. Conn, J.O. Trent, T. Brown and A.N. Lane, *Nucl. Acids Res.*, 2003, **31**, 2683.
1213. A.Y. Denisov, R.N. Hannoush, K. Gehring and M.J. Damha, *J. Am. Chem. Soc.*, 2003, **125**, 11525.
1214. R.N. Hannoush, A.Y. Denisov, K. Gehring and M.J. Damha, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1687.
1215. M. Mayer and T.L. James, *J. Am. Chem. Soc.*, 2004, **126**, 4453.
1216. A. Lingel, B. Simon, E. Izaurraide and M. Sattler, *Nature*, 2003, **426**, 465.
1217. K.S. Yan, S. Yan, A. Farooq, A. Han, L. Zeng and M.-M. Zhou, *Nature*, 2003, **426**, 469.

1218. A. Lingel, B. Simon, E. Izaurralde and M. Sattler, *Nature Struct. Mol. Biol.*, 2004, **11**, 576.
1219. C. Johansson, L.D. Finger, L. Trantirek, T.D. Mueller, S. Kim, I.A. Laird-Offringa and J. Feigon, *J. Mol. Biol.*, 2004, **337**, 799.
1220. H. Wu, A. Henras, G. Chanfreau and J. Feigon, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 8307.
1221. J.L. Leroy, *J. Mol. Biol.*, 2003, **333**, 125.
1222. K.-H. Chin and S.-H. Chou, *J. Mol. Biol.*, 2003, **329**, 351.
1223. P.K. Bhattacharya, J. Cha and J.K. Barton, *Nucl. Acids Res.*, 2002, **30**, 4740.
1224. J. Aishima, R.K. Gitti, J.E. Noah, H.H. Gan, T. Schlick and C. Wolberger, *Nucl. Acids Res.*, 2002, **30**, 5244.
1225. N.G.A. Abrescia, C. González, C. Gouyette and J.A. Subirana, *Biochemistry*, 2004, **43**, 4092.
1226. R. Stefl, H. Wu, S. Ravindranathan, V. Sklenár and J. Feigon, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 1177.
1227. A. Barbic, D.P. Zimmer and D.M. Crothers, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 2369.
1228. N.V. Hud and J. Feigon, *Biochemistry*, 2002, **41**, 9900.
1229. B. Wu, F. Girard, B. van Buuren, J. Schleucher, M. Tessari and S. Wijmenga, *Nucl. Acids Res.*, 2004, **32**, 3228.
1230. A.T. Phan and D.J. Patel, *J. Am. Chem. Soc.*, 2003, **125**, 15021.
1231. A.T. Phan, Y.S. Modi and D.J. Patel, *J. Mol. Biol.*, 2004, **338**, 93.
1232. M. Crnugelj, N.V. Hud and J. Plavec, *J. Mol. Biol.*, 2002, **320**, 911.
1233. M. Crnugelj, P. Sket and J. Plavec, *J. Am. Chem. Soc.*, 2003, **125**, 7866.
1234. E. Gavathiotis and M.S. Searle, *Org. Biomol. Chem.*, 2003, **1**, 1650.
1235. M.S. Searle, H.E.L. Williams, C.T. Gallagher, R.J. Grant and M.F.G. Stevens, *Org. Biomol. Chem.*, 2004, **2**, 810.
1236. M.W. da Silva, *Biochemistry*, 2003, **42**, 14356.
1237. K.-H. Chin, F.-M. Chen and S.-H. Chou, *Nucl. Acids Res.*, 2003, **31**, 2622.
1238. G.L. Olsen, E.A. Louie, G.P. Drobny and S.T. Sigurdsson, *Nucl. Acids Res.*, 2003, **31**, 5084.
1239. W. Wu, D.E. Vanderwall, C.J. Turner, S. Hoehn, J. Chen, J.W. Kozarich and J. Stubbe, *Nucl. Acids Res.*, 2002, **30**, 4881.
1240. M.L. Colgrave, H.E.L. Williams and M.S. Searle, *Angew. Chem. Int. Ed.*, 2002, **41**, 4754.
1241. C.T. Gallagher and M.S. Searle, *Chem. Commun.*, 2003, 1814.
1242. M.S. Searle, A.J. Maynard and H.E.L. Williams, *Org. Biomol. Chem.*, 2003, **1**, 60.
1243. S. Mazzini, M.C. Bellucci and R. Mondelli, *Bioorg. Med. Chem.*, 2003, **11**, 505.
1244. E. Gavathiotis, R.A. Heald, M.F.G. Stevens and M.S. Searle, *J. Mol. Biol.*, 2003, **334**, 25.
1245. Q. Zhang, T.J. Dwyer, V. Tsui, D.A. Case, J. Cho, P.B. Dervan and D.E. Wemmer, *J. Am. Chem. Soc.*, 2004, **126**, 7958.
1246. G.-S. Hwang, G.B. Jones and I.H. Goldberg, *Biochemistry*, 2003, **42**, 8472.
1247. G.-S. Hwang, G.B. Jones and I.H. Goldberg, *Biochemistry*, 2004, **43**, 641.
1248. D.T. Braddock, J.L. Baber, D. Levens and G.M. Clore, *EMBO J.*, 2002, **21**, 3476.
1249. C. Laguri, M.K. Phillips-Jones and M.P. Williamson, *Nucl. Acids Res.*, 2003, **31**, 6778.
1250. M.D. Gearhart, S.M.A. Holmbeck, R.M. Evans, H.J. Dyson and P.E. Wright, *J. Mol. Biol.*, 2003, **327**, 819.

1251. N. Escaja, J.L. Gelpí, M. Orozco, M. Rico, E. Pedroso and C. González, *J. Am. Chem. Soc.*, 2003, **125**, 5654.
1252. M.-O. Ebert, A. Luther, H.K. Huynh, R. Krishnamurthy, A. Eschenmoser and B. Jaun, *Helv. Chim. Acta*, 2002, **85**, 4055.
1253. J.M. Aramini, S.H. Cleaver, R.T. Pon, R.P. Cunningham and M.W. Germann, *J. Mol. Biol.*, 2004, **338**, 77.
1254. J. Bohon and C.R. de los Santos, *Nucl. Acids Res.*, 2003, **31**, 1331.
1255. V. Esposito, A. Randazzo, G. Piccialli, L. Petraccone, C. Giancola and L. Mayol, *Org. Biomol. Chem.*, 2004, **2**, 313.
1256. V. Thiviyanathan, A. Somasunderam, T.K. Hazra, S. Mitra and D.G. Gorenstein, *J. Mol. Biol.*, 2003, **325**, 433.
1257. N.B.F. Edfeldt, E.A. Harwood, S.T. Sigurdsson, P.B. Hopkins and B.R. Reid, *Nucl. Acids Res.*, 2004, **32**, 2785.
1258. N.B.F. Edfeldt, E.A. Harwood, S.T. Sigurdsson, P.B. Hopkins and B.R. Reid, *Nucl. Acids Res.*, 2004, **32**, 2795.
1259. P.A. Dooley, M. Zhang, G.A. Korbel, L.V. Nechev, C.M. Harris, M.P. Stone and T.M. Harris, *J. Am. Chem. Soc.*, 2003, **125**, 62.
1260. S.J. Berners-Price, M.S. Davies, J.W. Cox, D.S. Thomas and N. Farrell, *Chem. Eur. J.*, 2003, **9**, 713.
1261. L.A. Peterson, C. Vu, B.E. Hingerty, S. Broyde and M. Cosman, *Biochemistry*, 2003, **42**, 13134.
1262. H.-Y.H. Kim, A.S. Wilkinson, C.M. Harris, T.M. Harris and M.P. Stone, *Biochemistry*, 2003, **42**, 2328.
1263. I. Giri and M.P. Stone, *Biochemistry*, 2003, **42**, 7023.
1264. D.E. Volk, V. Thiviyanathan, J.S. Rice, B.A. Luxon, J.H. Shah, H. Yagi, J.M. Sayer, H.J.C. Yeh, D.M. Jerina and D.G. Gorenstein, *Biochemistry*, 2003, **42**, 1410.
1265. C. Bassarello, P. Cimino, G. Bifulco, D.L. Boger, J.A. Smith, W.J. Chazin and L. Gomez-Paloma, *Chem. Bio. Chem.*, 2003, **4**, 1188.
1266. H. Liu, S.R. Lynch and E.T. Kool, *J. Am. Chem. Soc.*, 2004, **126**, 6900.
1267. L. Petraccone, E. Erra, L. Nasti, A. Galeone, A. Randazzo, V. Esposito, L. Mayol, G. Barone and C. Giancola, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1677.
1268. B.M. Znosko, T.W. Barnes, T.R. Krugh and D.H. Turner, *J. Am. Chem. Soc.*, 2003, **125**, 6090.
1269. Z. Li, L. Huang, P. Dande, B. Gold and M.P. Stone, *J. Am. Chem. Soc.*, 2002, **124**, 8553.
1270. M.W. da Silva, A.M. Noronha, D.M. Noll, P.S. Miller, O.M. Colvin and M.P. Gamcsik, *Biochemistry*, 2002, **41**, 15181.
1271. J.-H. Lee, C.-J. Park, J.-S. Shin, T. Ikegami, H. Akutsu and B.-S. Choi, *Nucl. Acids Res.*, 2004, **32**, 2474.
1272. C. Maufrais, G.V. Fazakerley, J. Cadet and Y. Boulard, *Nucl. Acids Res.*, 2003, 5930.
1273. S. Smirnov, T.J. Matray, E.T. Kool and C. de los Santos, *Nucl. Acids Res.*, 2002, **30**, 5561.
1274. G. Cui and C. Simmerling, *J. Am. Chem. Soc.*, 2002, **124**, 12154.
1275. X. Liang, H. Asanuma, H. Kashida, A. Takasu, T. Sakamoto, G. Kawai and M. Komiyama, *J. Am. Chem. Soc.*, 2003, **125**, 16408.
1276. J. Tuma and C. Richert, *Biochemistry*, 2003, **42**, 8957.
1277. H.-D. Junker, S.T. Hoehn, R.C. Bunt, V. Marathius, J. Chen, C.J. Turner and J. Stubbe, *Nucl. Acids Res.*, 2002, **30**, 5497.

1278. C.B. Nielsen, M. Petersen, E.B. Pedersen, P.E. Hansen and U.B. Christensen, *Bioconjugate Chem*., 2004, **15**, 260.
1279. K.E. Nielsen, J. Rasmussen, R. Kumar, J. Wengel, J.P. Jacobsen and M. Petersen, *Bioconjugate Chem*., 2004, **15**, 449.
1280. A. Randazzo, V. Esposito, O. Ohlenschläger, R. Ramachandran and L. Mayol, *Nucl. Acids Res*., 2004, **32**, 3083.
1281. K.M.E. Nielsen, M. Petersen, A.E. Håkansson, J. Wengel and J.P. Jacobsen, *Chem. Eur. J*., 2002, **8**, 3001.
1282. M. Petersen, J.T. Nielsen, K. Bondensgaard, J. Wengel and J.P. Jacobsen, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1691.
1283. J.T. Nielsen, P.C. Stein and M. Petersen, *Nucl. Acids Res*., 2003, **31**, 5858.
1284. H.V. Tømmerholt, N.K. Christensen, P. Nielsen, J. Wengel, P.C. Stein, J.P. Jacobsen and M. Petersen, *Org. Biomol. Chem*., 2003, **1**, 1790.
1285. V. Esposito, A. Galeone, L. Mayol, A. Messere, G. Piccialli and A. Randazzo, *Nucleosides, Nucleotides & Nucl. Acids*, 2003, **22**, 1681.
1286. G. Schoehn, M. Mavrakis, A. Albertini, R. Wade, A. Hoenger and R.W.H. Ruigrok, *J. Mol. Biol*., 2004, **339**, 301.
1287. M. Valle, A. Zavialov, J. Sengupta, U. Rawat, M. Ehrenberg and J. Frank, *Cell*, 2003, **114**, 123.
1288. M. Valle, R. Gillet, S. Kaur, A. Henne, V. Ramakrishnan and J. Frank, *Science*, 2003, **300**, 127.
1289. F. Tama, M. Valle, J. Frank and C.L. Brooks, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 9319.
1290. M. Valle, A. Zavialov, W. Li, S.M. Stagg, J. Sengupta, R.C. Nielsen, P. Nissen, S.C. Harvey, M. Ehrenberg and J. Frank, *Nature Struct. Biol*., 2003, **10**, 899.
1291. W.M. Shih, J.D. Quispe and G.F. Joyce, *Nature*, 2004, **427**, 618.
1292. Y.L. Lyubchenko, L.S. Shlyakhtenko, M. Binus, C. Gaillard and F. Strauss, *Nucl. Acids Res*., 2002, **30**, 4902.
1293. D. Liu, M. Wang, Z. Deng, R. Walulu and C. Mao, *J. Am. Chem. Soc*., 2004, **126**, 2324.
1294. D. Zhou, K. Sinniah, C. Abell and T. Rayment, *Angew. Chem. Int. Ed*., 2003, **42**, 4934.
1295. F. Yu, D. Yao and W. Knoll, *Nucl. Acids Res*., 2004, **32**, e75.
1296. A.-C. Déclais, J.M. Fogg, A.D.J. Freeman, F. Coste, J.M. Hadden, S.E.V. Phillips and D.M.J. Lilley, *EMBO J*., 2003, **22**, 1398.
1297. T.A. Goody, D.M.J. Lilley and D.G. Norman, *J. Am. Chem. Soc*., 2004, **126**, 4126.

Phosphazenes

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1 Introduction

This review covers phosphazene literature over the period January 2003 to June 2004 (*Chemical Abstracts* Vols. 138, 139 and 140), and discusses linear phosphazenes including compounds derived thereof (Section 2), cyclophosphazenes (Section 3) and polyphosphazenes (Section 4). Structural data have been summarized in Section 5. It is worthy to note that this period has seen a considerable growth in contributions from Chinese investigators. However, many of these papers are only accessible in English *via Chemical Abstracts*.

Two books have appeared covering the present state of the phosphazene chemistry, *viz*. *Chemistry and Applications of Polyphosphazenes*[1], and a three-volume edition entitled *Phosphazenes, A Worldwide Insight*.[2]

2 Linear Phosphazenes

Interest continues in linear (acyclic) phosphazenes, resulting in a considerable number of papers. *N*-arylphosphoranimines ArN = PPh_3 have been prepared in excellent yields by refluxing phosphorus ylides $MeO_2CCH(NHAr)CO_2Me$ = PPh_3 in xylene or toluene. The ylides can be easily synthesized by the addition reaction of a primary aromatic amine and triphenylphosphine with dimethyl acetylenedicarboxylate (DMAD).[3] The Staudinger procedure, involving a phosphine and an azide, forms a part of many multi-step organic syntheses,[4] and plays an important role in the preparation of nucleosides[5] and nucleotides[6,7] and in carbohydrate chemistry[8]. An intramolecular Staudinger reaction has been proposed for one of the reaction steps of the conversion of the 4-azido-4-deoxy-D-galactoside (1) into the 4-deoxy-D-*erythro*-hexose-3-ulose (2) using $MeOP(OBn)NPr^i_2$ (Bn = $CH_2C_6H_5$) and tetrazole.[9]

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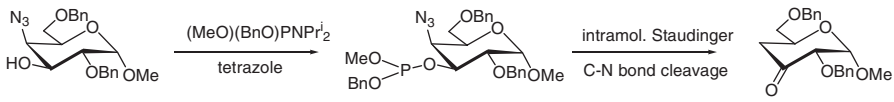
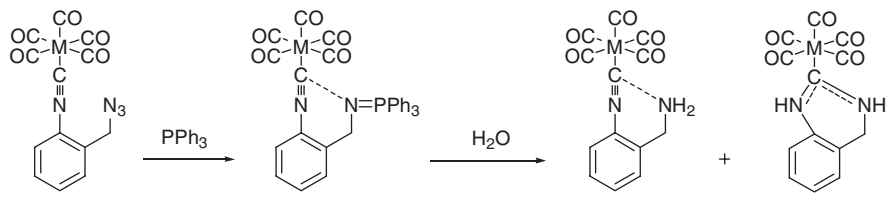
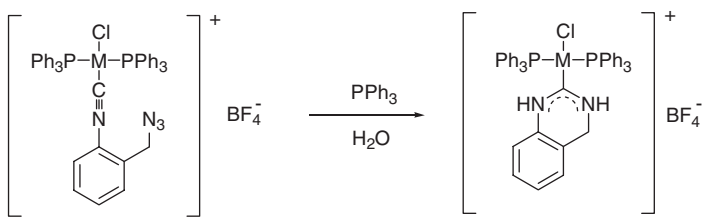


The azidomethylphenyl complexes (3a-b) react with triphenylphosphine according to the Staudinger scheme to yield the products (4a-b). Upon hydrolysis, (4b) has been transformed into (5) and (6). The absence of a displacement of the isocyanide group by a PPh_3 group has been explained by the fact that the isocyanide group is connected to a coordinatively saturated metal complex.[10] A similar reaction mode has been found for complexes (7a–b) leading to heterocyclic carbene complexes (8a–b). In this case steric hindrance has been put forward to explain the preference for the Staudinger mode.[11]

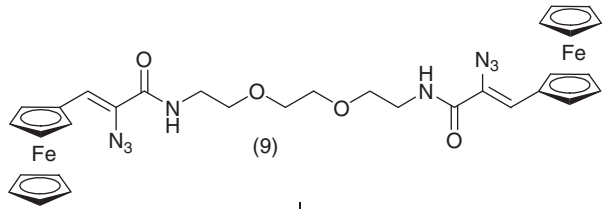


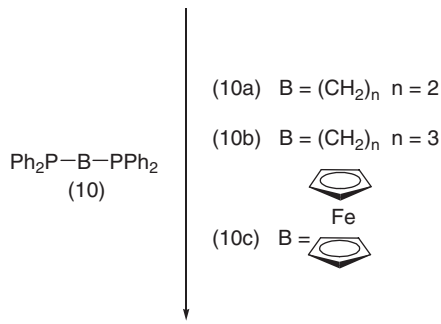
(3a) M = W
(3b) M = Cr
(4a) M = W
(4b) M = Cr
(5) M =Cr
(6) M = Cr

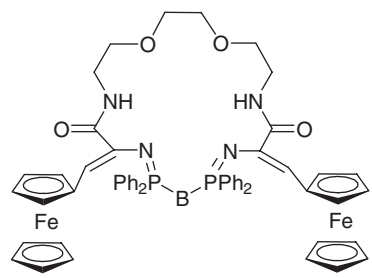


(7a) M = Pt
(7b) M = Pd
(8a) M = Pt
(8b) M = Pd

Heteromacrocycles (11a–c) have been synthesized from the bis(azido) compound (9) and the diphosphines (10a–c).[12]

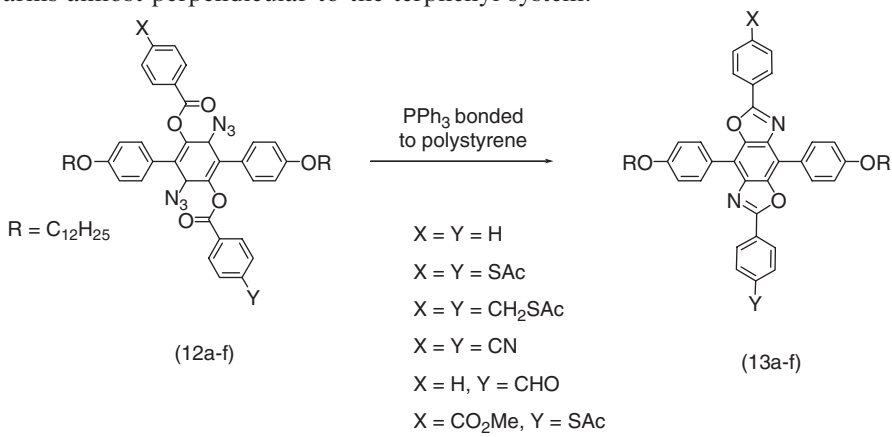






(11a-c)

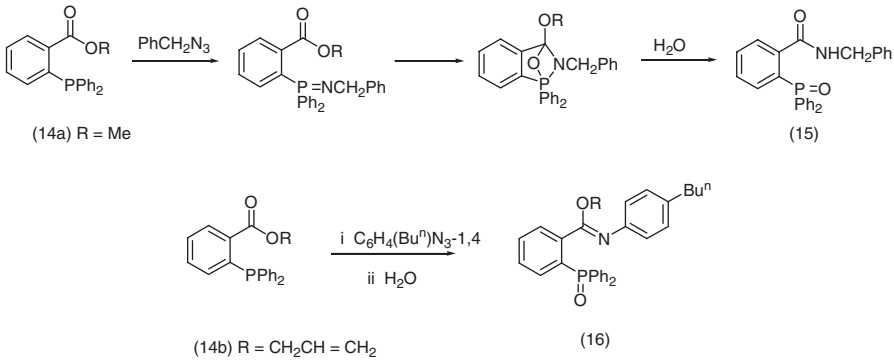
A new class of compounds (13a-f) has been prepared from (12a–f) by a Staudinger reaction with Ph_3P followed by an intramolecular aza-Wittig cyclization. Compounds (13) are cruciform π-systems with the phenyloxazole arms almost perpendicular to the terphenyl system.[13]



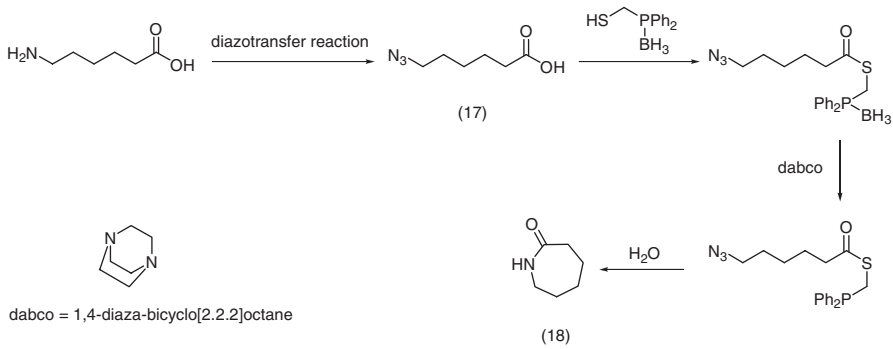
(12a-f)

(13a-f)

The pathway of the Staudinger ligation of alkylazides and *o*-carboalkoxy triarylphosphines (*e.g.* 14a) has been established by NMR analysis of the intermediates and leads to the formation of compounds with amide bonds (15).[14] In contrast, the Staudinger ligation of aryl azides with *o*-carboalkoxy triarylphosphines (*e.g.* 14b) has been reported to give products (16) with an *o*-alkyl imidate linkage.[15]



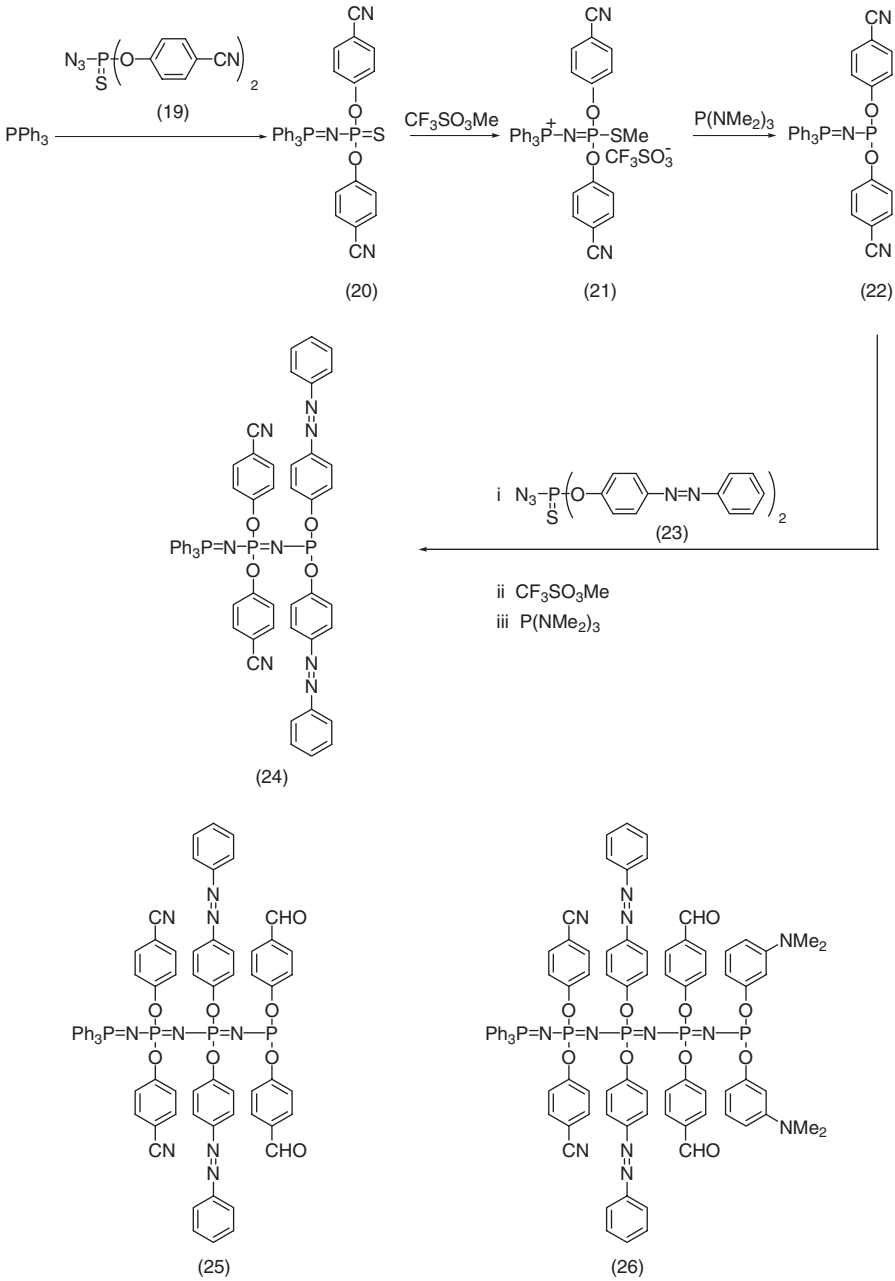
The ligation methodology has been successfully applied to attaching various moieties to cell surfaces [14,16,17], to fluorescent labeling of DNA fragments [18] and to probing glycosyltransferase activities.[19] The aforementioned ligation has also been used for the activation of a coumarin–phosphine dye.[20] Staudinger ligation involving peptides with a *C*-terminal phosphanylthioester and peptides having a *N*-terminal azido group has been used for assembling proteins.[21] The same method can be used to immobilize proteins.[22] An elegant way for the synthesis of medium-sized lactams from ω-amino acids has been described, by making use of an intramolecular Staudinger ligation.[23] This method is exemplified by the conversion of (17) into (18).



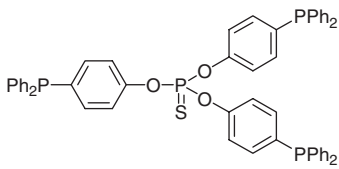
The synthesis of phosphinoalkanethiol-borane complexes for use in the formation of amide bonds has been covered by a patent.[24]

The Staudinger reaction forms also the basis for the preparation of linear oligophosphazenes. The reaction of triphenylphosphine with (19) affords the thiophosphazene (20), which can be converted *via* (21) into phosphine (22) by subsequent reactions with CF_3SO_3Me and $P(NMe_2)_3$. Compound (22) can be

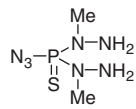
converted into (24) using (23) following the same reaction sequence. It has been demonstrated that this combination of three reactions can be extended with other thiophosphinoazides such as $N_3P(S)(OC_6H_4CHO\text{-}4)_2$ and $N_3P(S)(OC_6H_4NMe_2\text{-}3)_2$ affording the oligomers (25) and (26), consecutively. The presence of the CHO group offers the possibility for grafting reactions giving dendrimeric structures.[25]



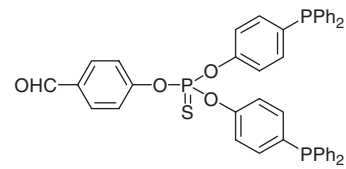
Ongoing research on the preparation of phosphazene dendrimers has led to the use of branched monomers in order to reduce the number of reaction steps. An example is the preparation of a dendrimer with 48 phosphine end groups by four consecutive reactions starting from $S = P[OC_6H_4(PPh_2\text{-}4)]_3$ (27), and using $N_3P(S)[N(Me)NH_2]_2$ (28) and $S = P[OC_6H_4(PPh_2\text{-}4)]_2(OC_6H_4CHO\text{-}4)$ (29) as reagents.[26]



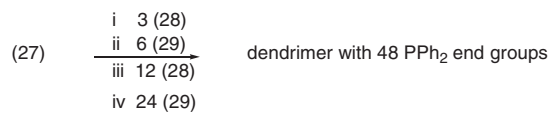
(27)



(28)



(29)

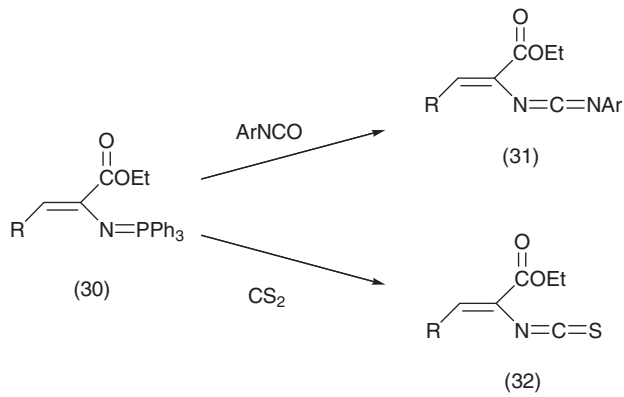


Phosphazene dendrimers having a P = S or P = O core possess high thermal stability up to about 380°C, which depends on the nature of end groups but little on the generation number.[27] The molecular mobility around the glass transition of these phosphorus dendrimers has been investigated by dielectric techniques.[28]

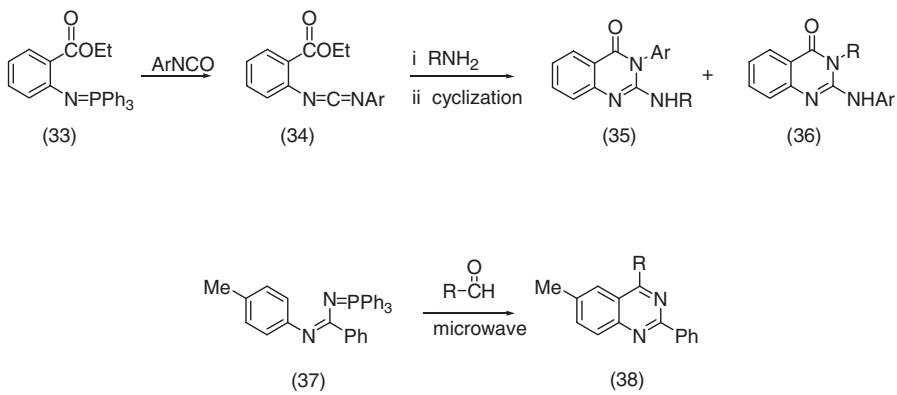
In addition to the well-known Staudinger reaction, a new high-yield method for the preparation of phosphoranimines has been presented involving a reaction of aminophosphanes $R^1{}_2PNHR^2$ and reactive alkyl halides.[29]

A review has appeared on the use of phosphoranimines in aza-Wittig reactions for the preparation of a wide variety of natural products.[30] *Ab initio* calculations regarding the formation of iminoacetic acid $HN = CHCO_2H$ by the aza-Wittig reaction of $O = CHCO_2H$ with $HN = PPh_3$ reveal the existence of low energy barriers.[31] In continuation of an earlier theoretical study it has been shown that the aza-Wittig reaction of $X_3P = NH$ and $H_2C = O$ in the gas phase proceeds more easily when X = H or Me than for X = Cl.[32] Calculations with respect to the substituent effect of X on the negative charge of the NH moiety in $X_3P = NH$ suggest a similar result.[33]

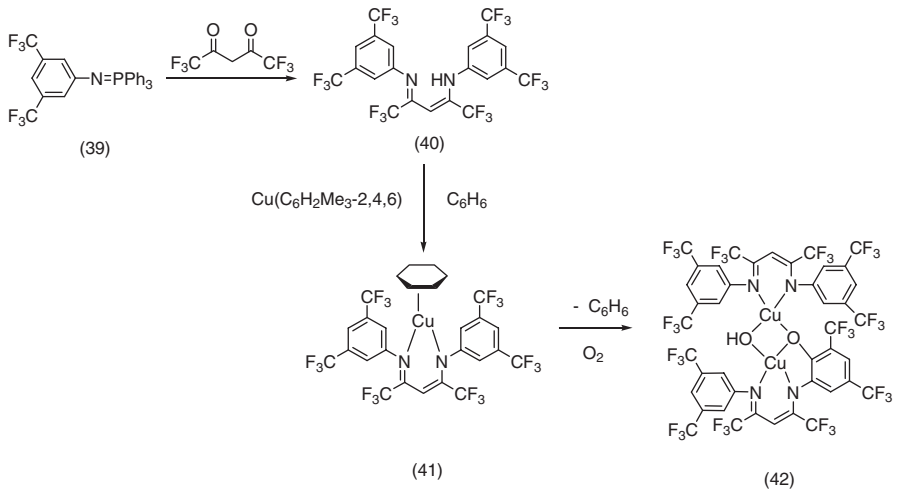
Carbodiimides (31) have been synthesized by the aza-Wittig reaction of vinylphosphoranimines (30) and aryl isocyanates. In their turn, compounds (31) form excellent starting materials for the preparation of 1*H*-imidazol-5(4H)-ones.[34] The sulfur analogue (32) has been prepared by the reaction of (30) with CS_2, and can be used for the synthesis of 2-thioxoimidazolidin-4-ones.[35]



Ethyl-2-(triphenylphosphoraniminato)benzoate (33) reacts with aryl isocyanate to give ethyl-2-[(arylimino)methyleneamino]benzoate (34), which is an excellent precursor for the formation of quinazolin-4(3*H*)-ones (35) and (36).[36] Quinazolines (38) have been produced in high yields by heating a mixture of a *N*-imidoyliminophosphorane (37) and an aldehyde in a 300 watt domestic microwave oven.[37]

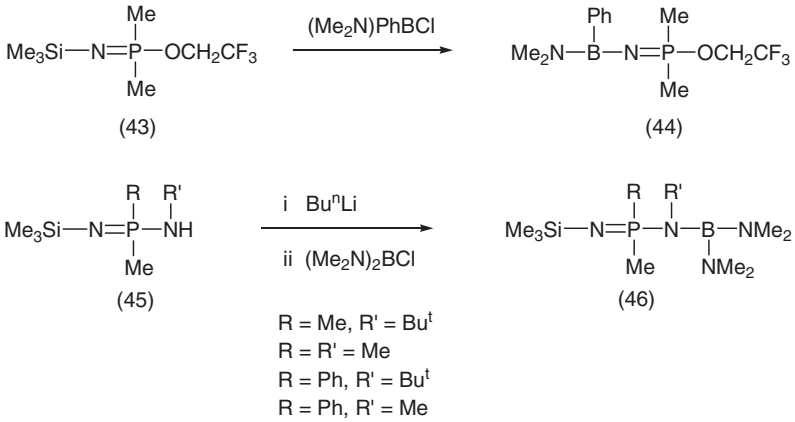


Without giving further details it has been stated that reactions of aryl isocyanates with the N = PPh_3 group form the basis of various heteroaromatic compounds.[38–40] The reaction of ArN = PPh_3 and aryl isocyanates forms the first step for the preparation of triarylguanidines.[41] Reactions of phosphoraniminato derivatives with alkyl isocyanates have been reported as well.[42] The aza-Wittig reaction of $[C_6H_3(CF_3)_2$-3,5]N = PPh_3 (39) and the pentanedione $CF_3C(O)CH_2C(O)CF_3$ has been reported to yield the electron-poor ligand (40). Copper(I) complexes (41) and (42), involving (40) as ligand, have been prepared and structurally investigated by IR and X-ray analysis.[43]

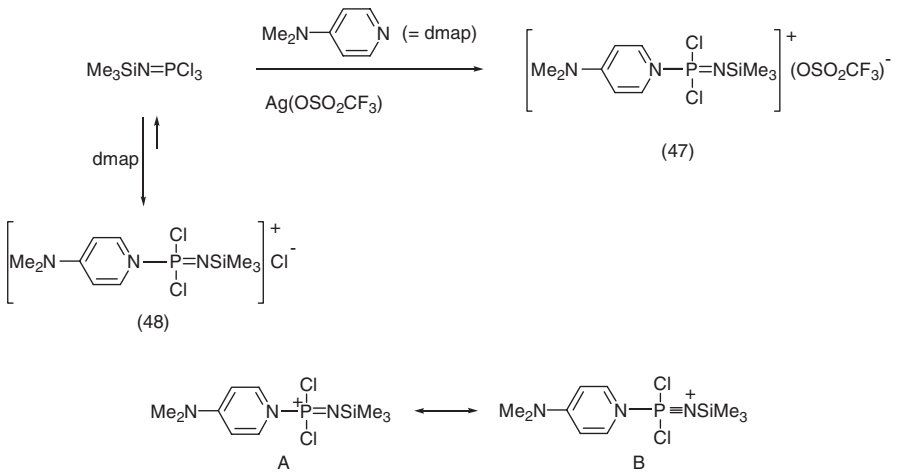


The reactions of the N = PPh_3 moiety with a wide variety of carbonyl compounds to form C = N bonds still underline the importance of the aza-Wittig protocol in synthetic chemistry.[44–48]

N-trimethylsilyl-*P*-bromophosphoranimimes $Me_3SiN = P(R)(X)Br$ (R = Pr^n, Pr^i, Bu^n; X = Br, OCH_2CF_3, OPh) have been prepared by oxidative bromination of the corresponding bis(trimethylsilyl)aminophosphines $(Me_3Si)_2NP(R)X$. Nucleophilic substitution reactions of $Me_3SiN = P(R)Br_2$ with two equivalents of $LiOCH_2CF_3$ or LiOPh afford the corresponding bis(trifluoroethoxy) and bis(phenoxy) derivatives.[49] Bromination of $(Me_3Si)_2NP(R)Pr^n$ (R = Me, Pr^n, Pr^i, Hex^n, OCH_2CF_3, OPh, Ph) followed by treatment with LiOPh yields the phosphoranimines $Me_3SiN = P(R)(Pr^n)OPh$.[50] An analogous procedure has been used to prepare the sterically hindered phosphoranimines $Bu^tR_2SiN = P(R')(Me)R''$ (R = Me, Ph; R′ = Me, Ph; R″ = OCH_2CF_3, OPh) and $Et_3SiN = P(R)(Me)R'$ (R = Me, Ph; R′ = OCH_2CF_3, OPh) from the phosphine precursors $(Bu^tR_2Si)(Me_3Si)NP(R')(Me)$ (R = Me, Ph; R′ = Me, Ph) and $(Et_3Si)_2NP(R)(Me)$ (R = Me, Ph), respectively.[51] The *N*-borylphosphoranimine (44) has been synthesized by a bond cleavage reaction of $Me_3SiN = P(Me_2)OCH_2CF_3$ (43) with $(Me_2N)PhBCl$. A similar reaction with $(Me_2N)_2BCl$ does not result in a phosphoranimine derivative, instead cyclophosphazenes $(NPMe_2)_n$ were formed. The formation of cyclic products appeared to be independent of the amount of chloroborane used. For the borane $Ph(OCH_2CF_3)BCl$ a similar result was obtained, suggesting that the boranes $(Me_2N)_2BCl$ and $Ph(OCH_2CF_3)BCl$ can act as novel catalysts in the formation of cyclic products or even polymers from suitable silylphosphoranimines.[52] Linear Si-N = P-N-B compounds have been prepared by deprotonation of $Me_3SiN = P(R)MeN(R')H$ (45) by Bu^nLi followed by a reaction with $(Me_2N)_2BCl$ yielding $Me_3SiN = P(R)MeN(R')B(NMe_2)_2$ (46). No cleavage of the SiN bond was observed.[52]



A novel *N*-trimethylsilylphosphoranimine cationic salt (47) has been obtained from the reaction of $Me_3SiN = PCl_3$ with $Ag(OSO_2CF_3)$ in the presence of the strong base 4-(dimethylamino)pyridine (dmap). The $NP(Cl_2)$ bond [149.0(3) pm] in the cation of (47) approaches that of a triple NP bond. This is in line with the two resonance structures A and B.[53] The reaction of $Me_3SiN = PCl_3$ with dmap in the absence of a halide abstractor also gives a cation (48) with Cl^- as counter ion. This chloride slowly decomposes in the solid state into its starting materials. This process appears to be reversible, as (48) is regenerated when dissolved in CH_2Cl_2.[53]



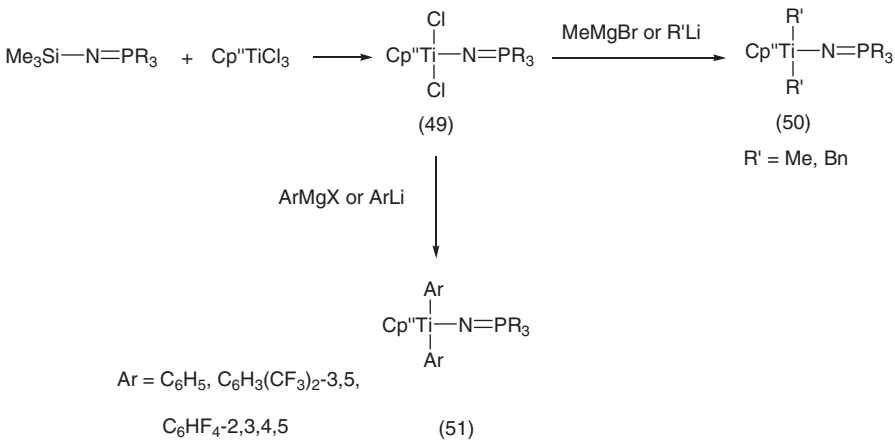
Metathetical reactions of $(C_6H_4F\text{-}2)N = PCl_3$ and imines have been described.[54]

Metal complexes involving linear phosphazenes still continue to attract attention, in particular because of their possible application as catalysts in

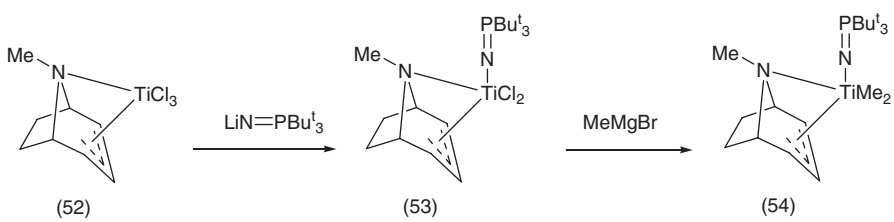
polymerization processes. Three review papers describe recent advances in the field of metal complexes having M = N-E bridges among which are phosphoraniminato complexes (E=P).[55–57] A general overview has appeared on phosphoraniminato and iminophosphoraniminato complexes of group 4 transition metals.[58]

The effect of metal coordination on the NP bond length in $Me_3SiN(H)PPh_2$ and $Me_3SiN{=}PPh_3$ compared to their respective complexes $[(Me_3Si)_2NZn(Ph_2PNSiMe_3)]_2$ and $[Li(o\text{-}C_6H_4)PPh_2{=}NSiMe_3]_2.Et_2O$ has been studied by FT Raman and infrared spectroscopy in combination with density functional theory calculations. The close agreement between calculated and experimental data validates a more general application of this approach.[59]

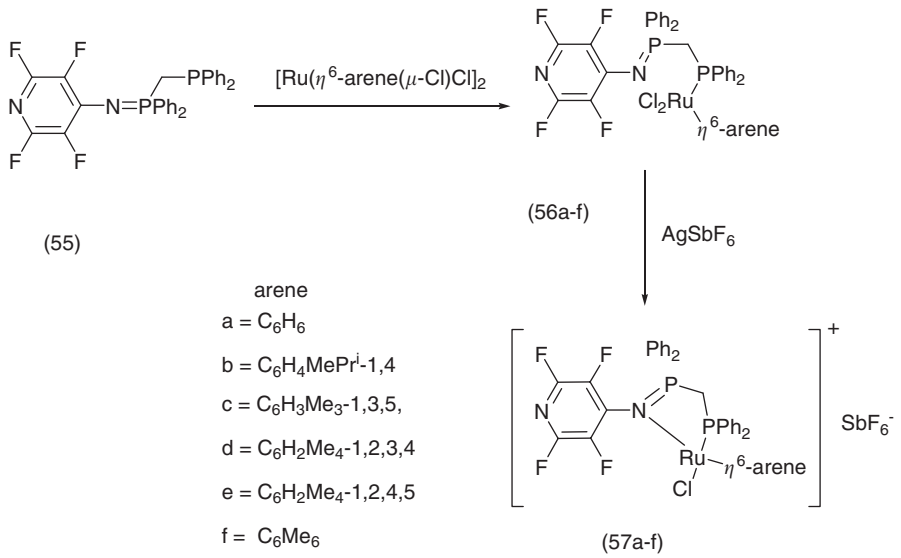
The synthesis of titanium complexes (49), (50) and (51) with bulky phosphoraniminato and cyclopentadienyl ligands Cp′, whether substituted or not, has been reported, including the X-ray structural data of some of these compounds. It turns out that the phosphoraniminato ligand exhibits some steric resemblance to the cyclopentadienyl ligand with respect to the metal environment. Ethylene polymerization experiments reveal the titanium phosphoraniminato complexes to be effective catalyst precursors.[60]



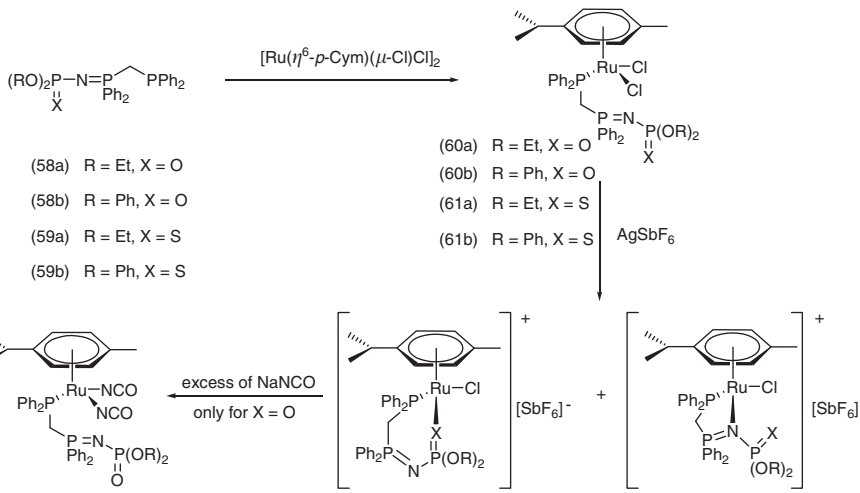
In a related paper, the catalytic activity of the titanium complex (54), prepared from (52) via (53), has been investigated in a high-temperature solution polymerization of ethylene. A lower activity was observed in comparison to that of Cp_2ZrMe_2.[61]



Reactions of the phosphoranimine-phosphine ligand (55) with the ruthenium(II) complexes $\{Ru(\eta^6\text{-arene})(\mu\text{-Cl})Cl_2\}$ afford the neutral complexes (56a–f) with metalligand coordination at the phosphine phosphorus. These complexes can be transformed in the cationic complexes (57a–f) by treatment with $AgSbF_6$. Both the neutral and cationic complexes have been used as catalysts in the transfer hydrogenation of cyclohexanone by 2-propanol. All complexes appear to be efficient catalysts, the most active being (57f).[62]



Reactions of the Ru(II) complex $[Ru(\eta^6\text{-}p\text{-cym})(\mu\text{-Cl})Cl]_2$ (*p*-cym = *p*-cymene, $C_6H_4MePr^i$-1,4) with the phosphoranimine-phosphine ligands (58a–b) and (59a–b) result in the complexes (60a-b) and (61a-b), respectively. Treatment of these complexes with one equivalent of $AgSbF_6$ leads to cationic complexes (62a–b) and (63a–b) with additional coordination at double-bonded X (X = O, S); only complex (60a) yields a mixture of (62a) and the imino-N complex (64). Phosphoranimine-phosphine ligands (58a–b) and (59a–b) react in a similar way with the Ru(IV) complex $[Ru(\eta^3\text{: }\eta^3\text{-}C_{10}H_{16})(\mu\text{-Cl})Cl]_2$, *viz*. formation of complexes (66a–b) and (67a–b). On treatment with one equivalent of $AgSbF_6$, they can be converted in the complexes (68a–b) and (69a–b). By using two equivalents of $AgSbF_6$, the compounds (60a–b), (61a–b), (66a–b) and (67a–b) react to give dicationic complexes. It has been shown that these additional coordination modes in the complexes (62a–b) and (64) can be disrupted by a reaction with an excess of NaX (X = Cl, Br, I, N_3, NCO), but leaving the coordination to phosphine-P intact. This is exemplified by the reaction of (62a–b) with NaNCO, affording (65a-b).[63,64]



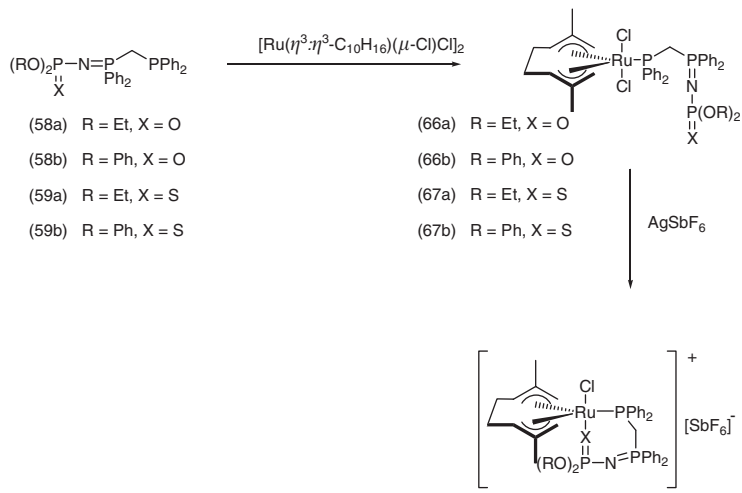
(58a) R = Et, X = O
(58b) R = Ph, X = O
(59a) R = Et, X = S
(59b) R = Ph, X = S

(60a) R = Et, X = O
(60b) R = Ph, X = O
(61a) R = Et, X = S
(61b) R = Ph, X = S

(65a-b)

(62a) R = Et, X = O
(62b) R = Ph, X = O
(63a) R = Et, X = S
(63b) R = Ph, X = S

(64) R = Et, X = O



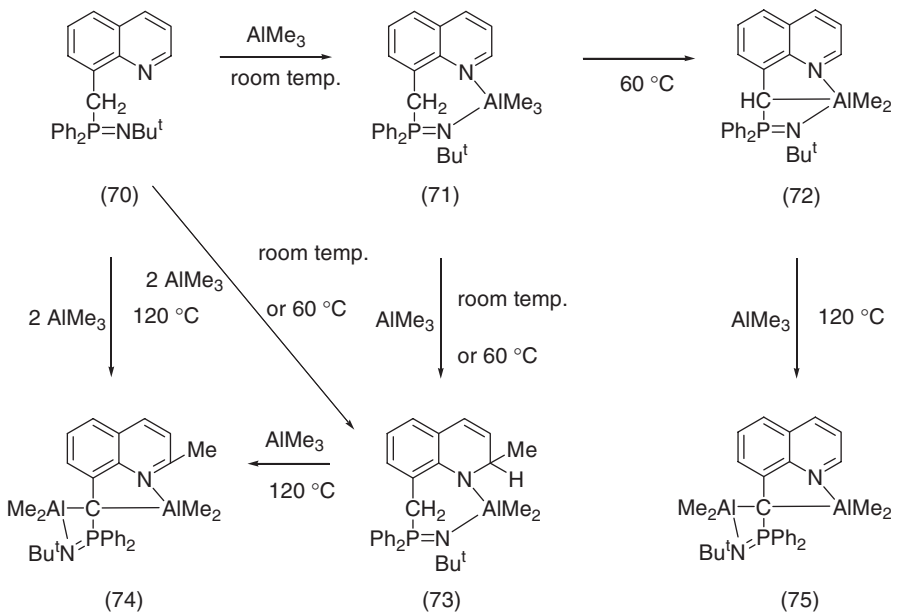
(58a) R = Et, X = O
(58b) R = Ph, X = O
(59a) R = Et, X = S
(59b) R = Ph, X = S

(66a) R = Et, X = O
(66b) R = Ph, X = O
(67a) R = Et, X = S
(67b) R = Ph, X = S

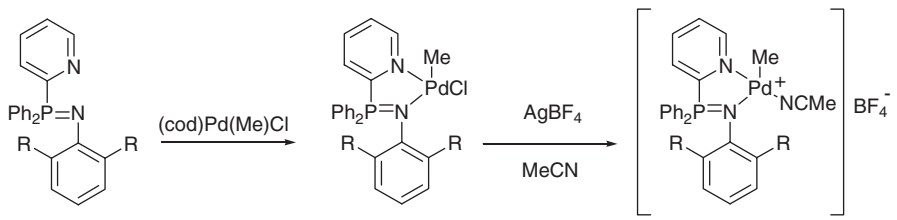
(68a) R = Et, X = O
(68b) R = Ph, X = O
(69a) R = Et, X = S
(69b) R = Ph, X = S

Efforts to cleave the S-Ru bond by an excess of NaX failed, demonstrating a greater stability of this bond when compared with the O-Ru, which is in accordance with the soft character of the metal atom. Investigations of the catalytic activity of these complexes in the transfer hydrogenation of cyclohexanone by 2-propanol reveal all complexes to be active and efficient catalysts with a higher activity for the Ru(IV) compounds compared to the corresponding Ru(II) compounds.[63,64]

The quinoline derivative (70) reacts with $AlMe_3$ to give complexes [(71)–(75)] in which the aluminum centers are coordinated to both the aromatic and imino nitrogen. Reaction temperature and molar ratio govern the product formation which includes methylation of the quinoline ring.[65]



Palladium(II) complexes (77a-c) have been prepared from (cod)Pd(Me)Cl (cod = cyclooctadiene-1,5) and pyridinylphosphoranimines (76a–c). Treatment with $AgBF_4$ in MeCN solution affords the corresponding cationic complexes (78a–c), of which (78b) shows the highest catalytic activity in copolymerizations of norbornene with CO or ethylene.[66]

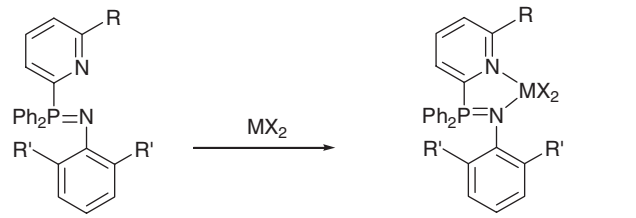


(76a) R = H
(76b) R = Me
(76c) R = Pr^i

(77a) R = H
(77b) R = Me
(77c) R = Pr^i

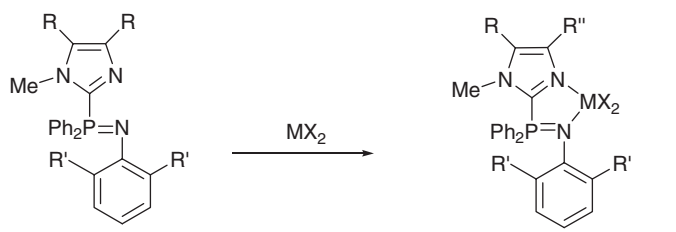
(78a) R = H
(78b) R = Me
(78c) R = Pr^i

In addition to (76), pyridinylphosphoranimine ligands (79) have been prepared together with their Fe(II) (80a) and Ni(II) (80b) complexes. In all cases metal complexation results in a five-membered MN_2CP chelate ring as observed for complexes (77).[67] Also the imidazolylphosphoranimine ligands (81) form five-membered MN_2CP rings with Fe(II) and Ni(II), (82a) and (82b), respectively.[67] Ligand (83), however, forms chelate rings in which the phosphorus atom does not participate in complexation leading to the complexes (84a–c).[67]



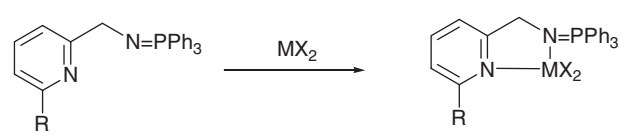
(79)

(80a) $MX_2 = FeCl_2$
(80b) $MX_2 = NiBr_2$



(81)

(82a) $MX_2 = FeCl_2$
(82b) $MX_2 = NiBr_2$

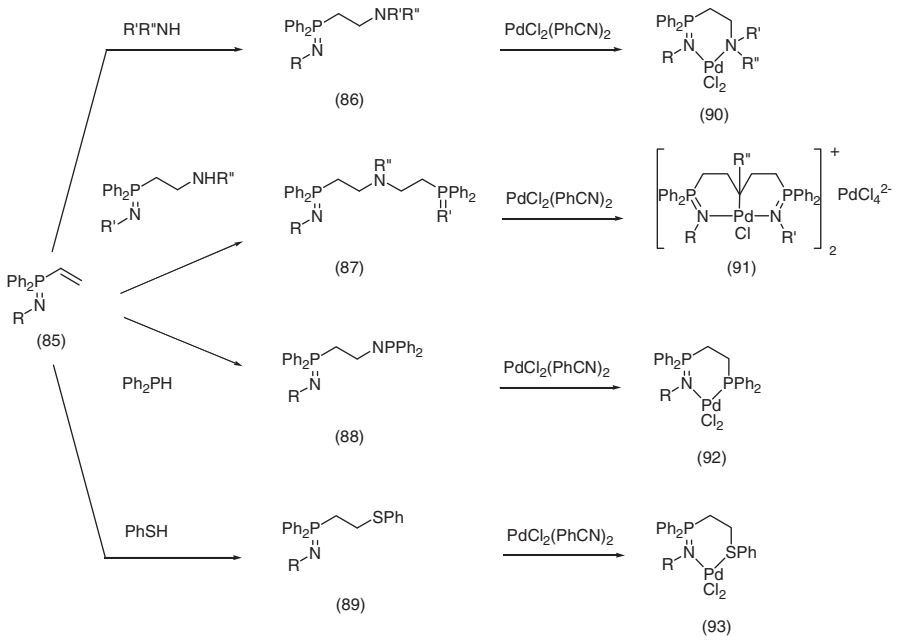


(83)

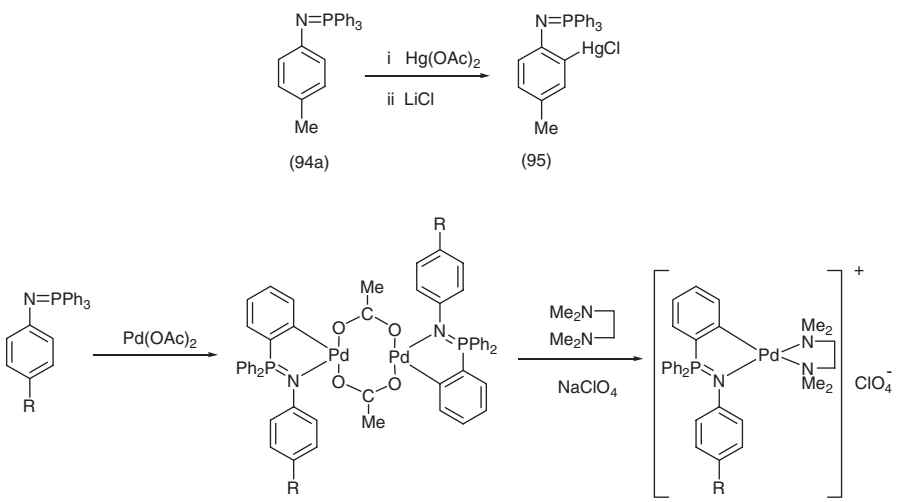
(84a) $MX_2 = FeCl_2$
(84b) $MX_2 = CoCl_2$
(84c) $MX_2 = NiBr_2$

A modest catalytic activity in ethylene oligomerization has been observed for the complexes (80a) and (80b) with R = Ph, R′ = Pr^i, (82a) with R = H, R′ = Pr^i, R″ = Bu^t, and (82b) with R = R″ = C_4H_4, R′ = Pr^i in the presence of $Et_2AlCl(ClC_6H_5)$. In general the Ni(II) complexes are more active than Fe(II) complexes.[67]

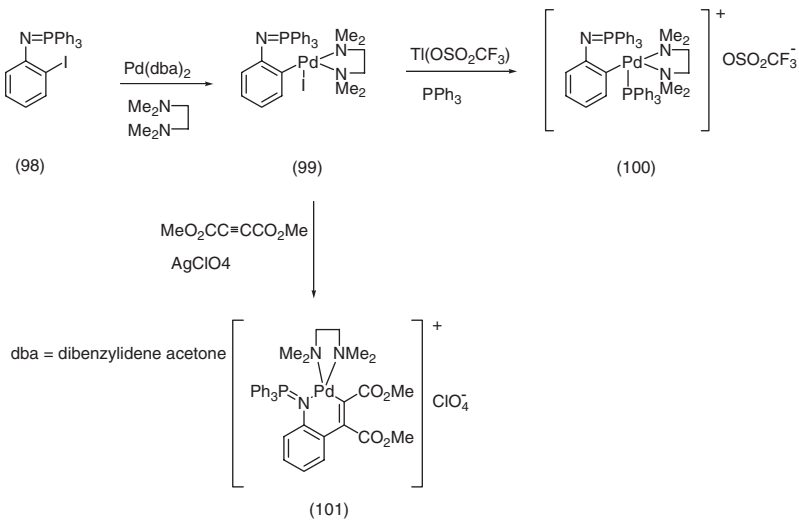
Ligands (86–89) have been prepared by reaction of $RN = P(Ph_2)CH = CH_2$ (85) with amines, diphenylphosphine and thiophenol. Reaction of these ligands with $PdCl_2(PhCN)_2$ generates the cyclic palladium complexes (90–93).[68]



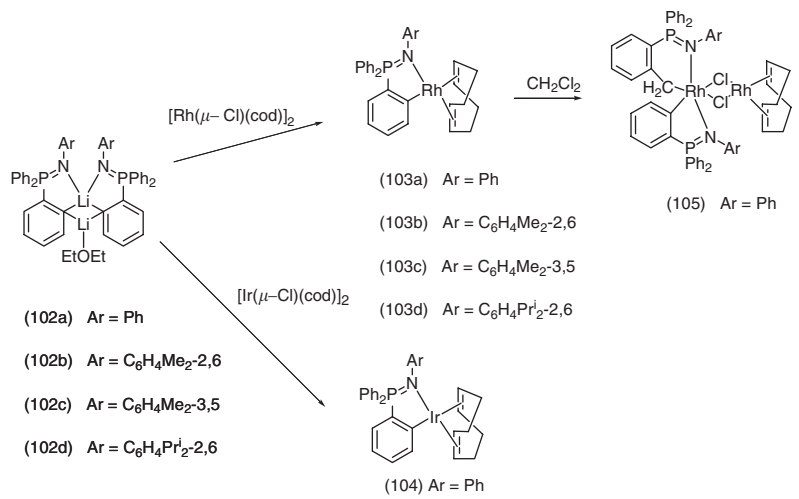
Metalation of (94a) by $Hg(OAc)_2$ in the presence of LiCl affords complex (95) in which the mercury atom is connected to *o*-carbon atom of the *N*-bonded phenyl group. The reaction of $Pd(OAc)_2$ with (94a-b) gives metalation at one of the P-bonded phenyl groups together with coordination at nitrogen, resulting in five-membered PdCN rings with a dimeric structure (96a–b). The dimer reacts with tetramethylethylenediamine (tmeda) to form a monomeric cationic complex (97a–b).[69]

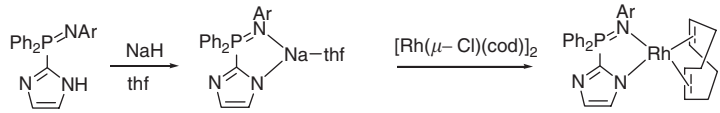


Ortho-palladation at the P-bonded phenyl group can also be achieved by treatment of the *o*-iodo derivative (98) with a mixture of $Pd(dba)_2$ (dba = dibenzylidene acetone) and tmeda. The resulting neutral complex (99) reacts with $Tl(OSO_2CF_3)$ and Ph_3P to yield a cationic complex (100). An insertion reaction of (99) with $MeO_2CC{\equiv}CCO_2Me$ results in a six-membered PdC_4N chelate ring (101).[69]



Complexes (103a–d) can be readily obtained from $[Rh(\mu\text{-Cl})cod]_2$ and the *o*-metalated Li complexes (102a–d). Complex (102a) reacts with $[Ir(\mu\text{-Cl})cod]_2$ to produce (104). By oxidative addition of CH_2Cl_2, (103a) can be converted to (105), the structure of which has been confirmed by X-ray analysis.[70] The Staudinger reaction of imidazolyldiphenylphosphine with appropriate arylazides results in imidazolylphosphoranimines (106a–b), which react with NaH to yield the corresponding Na derivatives (107a–b). The rhodium complexes (108a–b) have been synthesized by treatment of these Na derivatives with $[Rh(\mu\text{-Cl})cod]_2$. The reactivity of the rhodium complexes towards oxidative addition by CH_2Cl_2 has been discussed in terms of steric and electronic effects.[70]



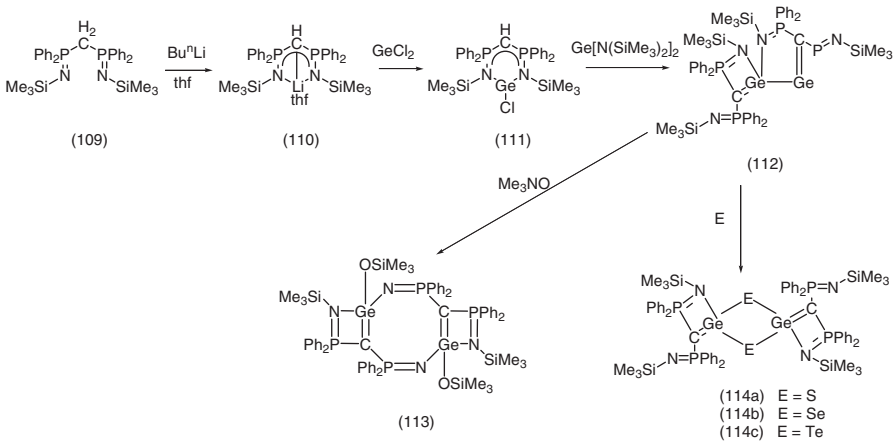


(106a) Ar = Ph (107a) Ar = Ph (108a) Ar = Ph

(106b) Ar = $C_6H_3Me_2$-2,6 (107b) Ar = $C_6H_3Me_2$-2,6 (108b) Ar = $C_6H_3Me_2$-2,6

Synthesis and X-ray structures of complexes formed by the reaction of the anionic ligand $[Me_3SiN = P(Me)_2C(PPh) = CPhR]^-$ (R = H, $SiMe_2Bu^t$) with metal chlorides MCl_4 (M = Zr, Hf) have been reported.[71]

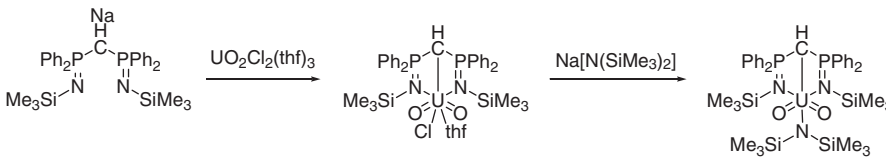
The versatile chelating agent bis(diphenylphosphoraniminato)methane derivative (109) has been used to synthesize the germanium complex (111) *via* the ligand transfer agent (110) and subsequent treatment with one equivalent of $GeCl_2$.[72] The reaction of (111) with $Ge[N(SiMe_3)_2]_2$ affords complex (112), which can also be obtained from the reaction of (110) with 0.5 equivalent of $GeCl_2$.[73] The structure of (110) reveals a four-coordinated Li atom with a Li-C carbon distance of 262.2(9) pm. Both in (110) and in (111) the bond lengths in the NPCPN chain suggest a considerable delocalization of the double bonds. Oxidation of (112) by Me_3NO gives complex (113), probably *via* a dimeric intermediate. The reaction of (112) with stoichiometric amounts of elemental chalcogens (S, Se, Te) affords the chalcogen-bridged germaketene analogues (114a–c).[72]



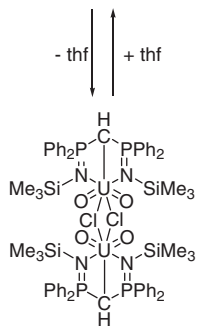
(114a) E = S
(114b) E = Se
(114c) E = Te

The reaction of (109) with anhydrous $NiCl_2$ has been reported to yield $NiCl_2CH_2[P(Ph_2) = NSiMe_3]_2$ in which the nickel is surrounded tetrahedrally by two nitrogens and two chlorines. A similar reaction with anhydrous NiI_2 also gives a tetrahedral Ni(II) complex, however, accompanied by exchange of

a $SiMe_3$ group by hydrogen.[74] The reaction of the sodium salt (115) with $UO_2Cl_2(thf)_3$ generates a uranyl (VI) complex (116) with uranium in the center of a distorted pentagonal bipyramid with the oxygens in apical position. A slightly distorted tetragonally bipyramidal environment of uranium by nitrogen and oxygen has been found for amido complex (117), which results from the reaction of (116) with $Na[N(SiMe_3)_2]$. A restricted rotation of the amido group around the U-N axis has been observed in this compound.[75] When recrystallized from dichloromethane, complex (116) forms a red-coloured chloro-bridged dimer (118). The dimerization appears to be a reversible process as, by addition of thf, the monomer is regenerated. The uranium- carbon distance (about 270 pm) in the complexes (116), (117) and (118) points to a considerable U(VI)-C interaction.[75,76]

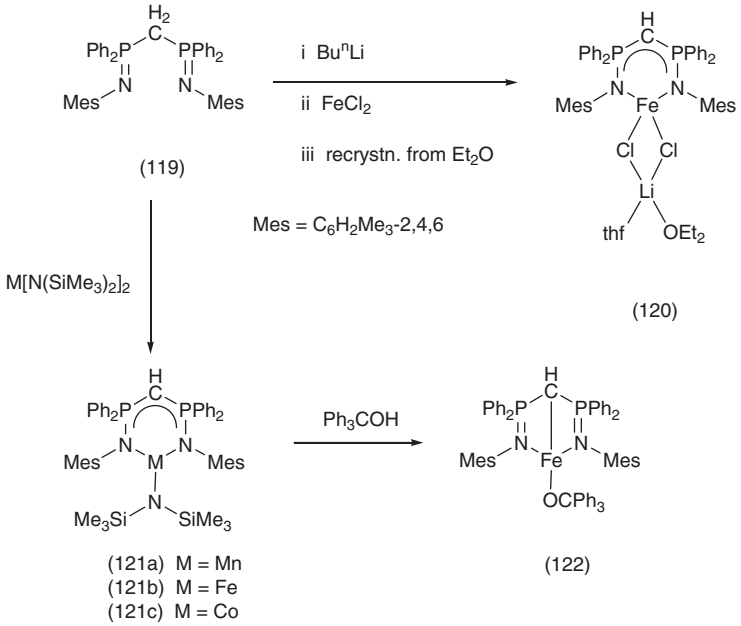


(115) (116) (117)

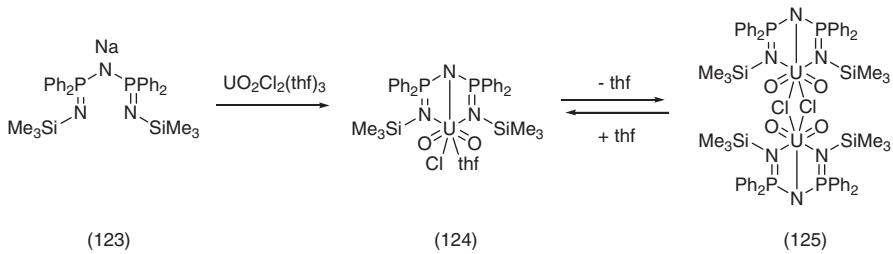


(118)

In addition to (109) the *N*-mesityl (mesityl = $C_6H_2Me_3$-2,4,6) derivative (119) has been applied as a coordination agent. Complexes (120) and (121a-c) have been shown to possess bidentate coordination of the metal atom. The reaction of (121b) with triphenylmethanol shows an exchange of the $N(SiMe_3)_2$ by the $OCPh_3$ group, affording (122) in a high yield. The structure of (122) is characterized by a distinct boat conformation of the six-membered chelate ring, which results in a close Fe-C(H) contact of 237.5 pm.[77]



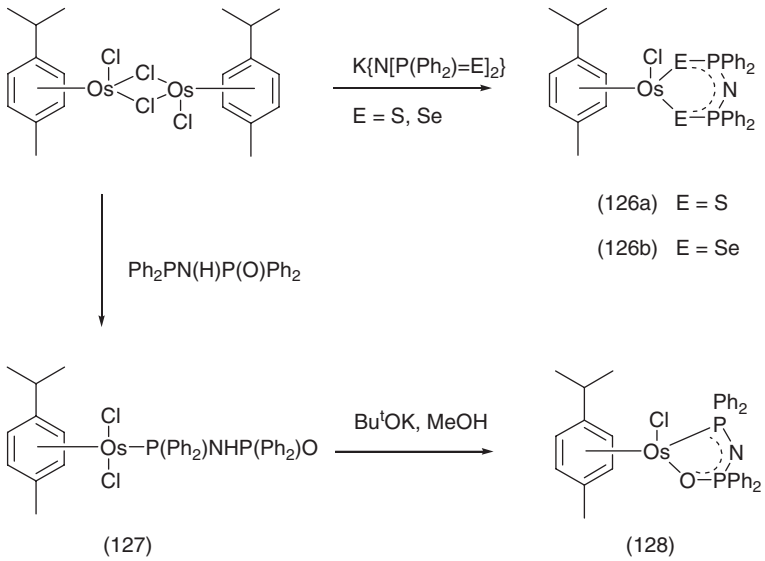
The nitrogen analogue of (115), (123) has been used as a ligand as illustrated by the synthesis of the uranium (VI) complexes (124) and (125). These complexes are fully comparable to their carbon counterparts (116) and (118), even with respect to their equilibrium behavior towards thf.[75]



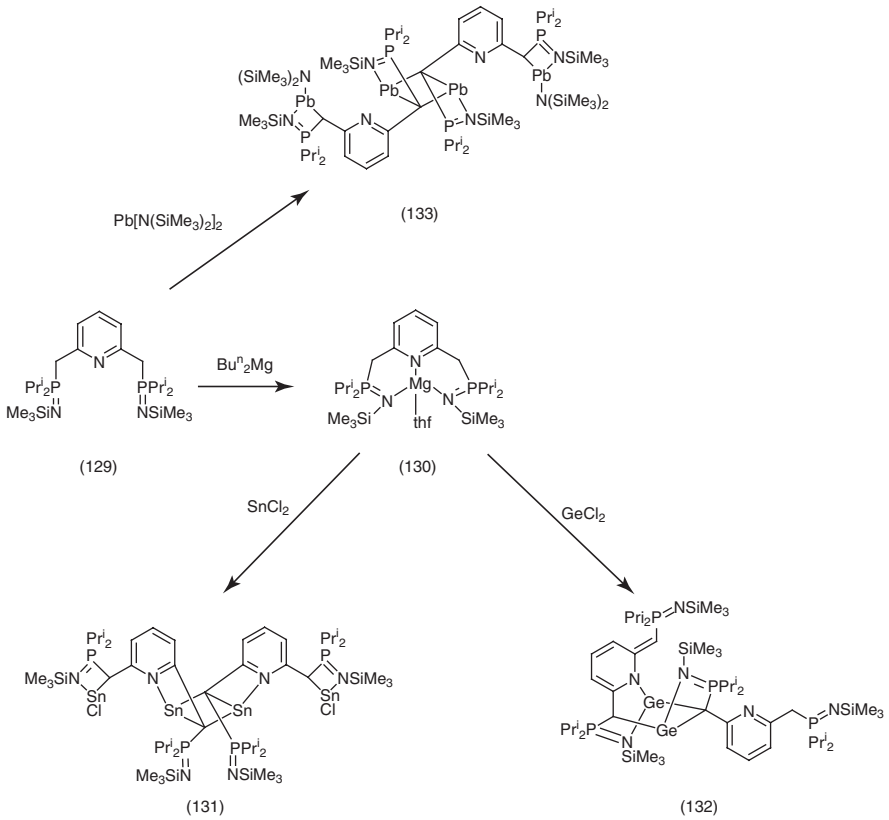
Oxo-vanadium(IV) complexes and oxo-vanadium(V) complexes have been prepared from $HN[(P(Ph_2) = NR]_2$ (R = Ph, $SiMe_3$) and $VO(acac)_2$ (acac = acetylacetonato) or $VOCl_3$.[78] The preparation of spirocyclic arsenic(III)[79] and antimony(III)[80] complexes with general formula $N[(P(Ph_2) = NR]_2MOR'O$ (R = Ph, $SiMe_3$; R′ = ethylene or propylene (whether or not alkyl-substituted) has been reported. Spectroscopic methods have been used for the characterization of these products.

This year the number of papers dealing with metal complexes of the anion $N[P(R_2) = E]_2^-$ (E = O, S, Se, Te) has notably decreased. The dimeric osmium

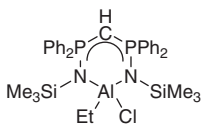
complex $[Os(\eta^6\text{-}p\text{-cym})Cl_2]_2$ has been shown to react with $KN[P(Ph_2) = E]_2$ (E = S, Se) to give the new osmium(II) complexes (126a-b) with an *E,E* osmium-phosphazene coordination mode. The reaction of $[Os(\eta^6\text{-}p\text{-cym})Cl_2]_2$ with $Ph_2PN(H)P(O)Ph_2$ affords the donor-acceptor complex (127), which can be converted to complex (128) upon treatment with Bu^tOK and MeOH. The unequal NP bond lengths in (128) indicate a less pronounced delocalization than in (126a–b), where the NP bonds are equal within their standard deviations.[81]



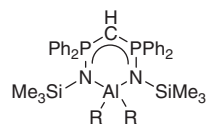
X-ray structure determinations have shown a bridging *S,O*-chelation mode in the dimeric complexes $\{PhHg[Ph_2P(S)NP(O)Me_2]\}_2$ and $\{PhHg[Ph_2P(S)NP(O)Ph_2]\}_2$, forming 12-membered rings with mercury atoms connected to a sulfur and an oxygen atom from different PNP units.[82] Metalation of the novel ligand 2,6-bis(trimethylsilylphosphoraniminato)lutidine (129) by $Bu^n{}_2Mg$ has been reported to give the magnesium complex (130) in a high yield. Further reaction of (130) with $SnCl_2$ affords the 1,3-distannabutane (131). It has been argued that in this reaction (130) not only acts as a ligand transfer reagent, but also as a strong base for dehydrochlorination.[83] The reaction with $GeCl_2$ does not yield a dimetallacyclobutane, but instead an asymmetric digermanium ring (132) is formed with different germanium environments. The Ge-pyridinyl-N coordination causes a redistribution of electron density, implying a non-aromatic character of the pyridine ring concerned and a short exocyclic C–C bond of 135.9(6) pm to the $Ph_2PNSiMe_3$ group. 1, 3-Diplumbabutane (133) has been isolated from the reaction of (129) and $Pb[(N(SiMe_3)_2]_2$.[83]



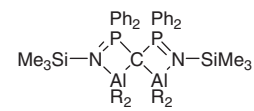
Ethylene polymerization experiments have been carried out with a number of aluminum complexes (134–136) as catalyst precursors. It turned out that the dialuminum complexes (136a) and (136b) are much more effective than their monometal counterparts.[84] The catalytic activity of nickel complexes (137), (138), (139a) and (140a) immobilized in 1-*n*- butyl-3-methylimidazolium organochloroaluminate has been evaluated for the biphasic oligomerization of ethylene.[85] Preparation and catalytic activity in ethylene oligomerization of the nickel complexes (139b) and (140b–e) have been patented.[86] The copolymerization of ethylidenenorbornene with a mixture of ethylene and propylene in the presence of $(C_6H_2Cl_3\text{-}2,4,6)N = V(Cl_2)N = PPh_3$ has been described.[87]



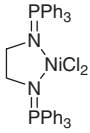
(134)



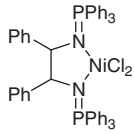
(135a) R = Me
(135b) R = Bu^i



(136a) R = Me
(136b) R = Bu^i



(137)



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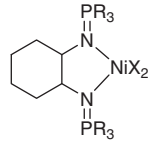
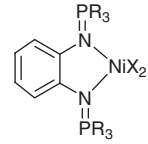


(139a) R = Ph, X = Cl
(139b) R = cyclopentyl, X = Br



(140a) R = Ph, X = Cl
(140b) R = cyclopentyl, X = Br
(140c) R = cyclohexyl, X = Br
(140d) R = *o*-tolyl, X = Br
(140e) R = 2,4,6-trimethylphenyl, X = Br

N-phosphorylphosphoranimines $Cl_2(O)PN{=}P(Me)(R)X$ (R=Me, X=OCH_2CF_3; R=Ph, X=OCH_2CF_3; R=Me, X=OPh) have been prepared from $Me_3SiN{=}P(Me)(R)X$ by Si-N bond cleavage induced by $POCl_3$. Analogous reactions with $R'P(O)Cl_2$ (R′=Me, Ph) afford compounds $Cl(O)P(R')N{=}P(Me)(R)OCH_2CF_3$ (R=R′=Me; R=Ph, R′=Me; R=Me, R′=Ph; R=Ph, R′=Ph) and Cl(O)P(Me)N = P(Me)(Me)OPh. Substitution of chlorine by dimethylamino groups can be readily achieved by the silylamine Me_2NSiMe_3.[88] Arylation of $Cl_3P{=}NPOCl_2$ by aryl Grignard reagents (Ar=Ph, *o*- and *p*-tolyl, *p*-chlorophenyl and 2-mesityl) and 2-thienyllithium has been shown to yield the fully aryl-substituted compounds $Ar_3P = NPOAr_2$ and $(C_4H_3S)_3P{=}NO(C_4H_3S)_2$, respectively.[89] Alkylation of $Cl_3P = NPOCl_2$ by the Grignard reagents RMgBr (R = Bn, $PhCH_2CH_2$, Me_3SiCH_2, Bu^n) to obtain penta-substituted products, does not appear to be successful. Only the pentacyclohexyl derivative could be isolated, albeit in a very low yield.[90] In addition the preparation and characterization of some pentaalkoxy and pentaaryloxy derivatives $(RO)_3P = NPO(OR)_2$ (R = alkyl, aryl) have been described.[91,92] The antimicrobial and biological activity of $R_3P = NPOR_2$ (R = Ph, *o*-tolyl) on bacterial and yeast cells have been studied.[93]

The basicity of a number of phosphazene bases in the gas phase has been calculated.[94] In this study the theoretical model used is claimed to be a reliable and accurate method for predicting pK_a values. It turns out that Bu^t-P4 [$\{(Me_2N)_3P = N\}_3P = NBu^t$] is by far the strongest phosphazene base, even stronger than Verkade's superbase.[94] New phosphazene bases with one to four phosphorus atoms (P1–P4) have been synthesized and their relative basicities determined by a UV-vis spectrophotometric titration method.[95] Solutions of Bu^t-P4 have been used as titrant for UV-vis spectrophotometric titrations of acids.[96] The deprotonating capacity of phosphazene bases have also been used in various synthetic procedures. The base Et-P2 ($(Me_2N)_3P = N\text{-}P(NMe_2)_2$ = NEt) has been applied to the asymmetric synthesis of disubstituted *N*-tosyl aziridines.[97] The facile reaction of *O*-acyl hydroxamic acid derivatives with Bu^t-P2 have been shown to yield 2,3-dihydro-4-isoxazole carboxylic ester derivatives.[98] α- Amino acids can be solubilized in MeCN by treatment with Bu^t-P1, Et-P2 or BEMP [$\overline{N(Me)(CH_2)_3N(Me)}P(NEt_2){=}NBu^t$], , thus allowing a facile entry to the synthesis of peptides.[99] Dehydrochlorination has been observed when treating decachlorotetrahydroazulene with BTPP ($Bu^tN = P(Pyr)_3$, Pyr = pyrrolidino).[100] Rearrangement of allylic ammonium ylides by BBr_3 has been

optimized by addition of Bu^t-P4.[101] The phosphazene base Bu^t-P4 has also been successfully applied to the preparation of 1,2-disubstituted alkenes in the Julia–Kociensky olefination[102] and in the cyclization of silyl-protected iodohydrins.[103] Anionic ring-opening polymerization of cyclosiloxanes has been initiated by Bu^t-P4.[104,105]

Kinetic studies have been performed on the condensation and disproportionation of oligosiloxanols in the presence of hexapyrrolidinodiphosphazenium hydroxide $[pyr_3P = N = Ppyr_3]OH$.[106]

The immobilized phosphazenium chloride $\equiv O_3Si\text{-}[(CH_2)_3\text{-}N(Bu^n)\ P(NMe_2)_3]^+\ Cl^-$ appears to be a reusable catalyst in the chlorination of organic acids by thionyl chloride. It also exhibits high activity and selectivity.[107] The application of $[(R_2N)_3PN = P(NR_2)_3]SF_5$ (R = Me, Et) as fluorinating agents has been described.[108] 1,1,1,3,3,3-Hexaaminophosphazenium salts have been used to inhibit or to regulate the enzyme-catalyzed hydrolysis of urea[109] and as phase transfer catalysts for chlorine-fluorine exchange reactions.[110] It is reported that ring opening of epoxides or epoxide resins can be catalyzed by $[(Me_2N)_3P = N]_4P^+$ [111] or $[(Me_2N)_3P = N]_3PO$.[112]

X-ray structure determinations of some miscellaneous linear compounds containing a N = P entity are summarized in Section 5.[113–128,153]

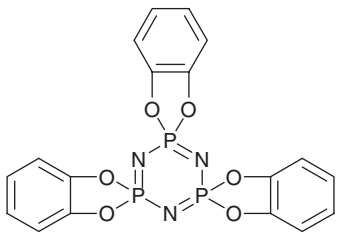
3 Cyclophosphazenes

An extended review has appeared on advances in the chemistry of chlorocyclophosphazenes.[129] Another review describes the role of cyclophosphazenes as polymer modifiers with emphasis on 2-oxazoline and epoxy derivatives.[130] A short review has been published on the physical properties of the host-guest adducts involving tris(*o*-phenylenedioxy)cyclotriphosphazene (TPP) (141) as host.[131]

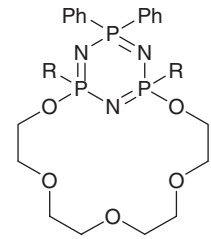
Ab initio RHF (restricted Hartree-Fock level of theory) and DFT (density functional theory) calculations have been presented for compounds $(NPF_2)_n$ and $(NPX_2)_3$ (X = H, Cl, Br).[132] The ring planarity found for all these compounds is not in line with the experimental data. Full geometry optimization at the *ab initio* HF level of theory for the series of compounds $(NPX_2)_n$ (X = H, F, Cl, Br; n = 2–6) has resulted in planar and non-planar systems, the molecular symmetry for $n \geq 4$ being dependent on the size and electronegativity of the substituent X. Phosphorus d basis functions appear to play only a role as polarization functions and are not explicitly involved in bonding.[133] *Ab initio* MP2 calculations revealed that the most stable configuration for $(NPX_2)_4$ (X=H, F, Cl) corresponds to a non-planar ring with D_{2d} symmetry.[134] The structures of $(NPX_2)_3$ (X=H, F, Cl, NH_2) and the vanadium(V) complex $(NPCl_2)_3.VOCl_3$ have been studied by the *ab initio* HF method.[135]

Crystal structures of compounds with general formula $N_3P_3(NHR)_6$ (R = Bu^t, Cy, Pr^i, Bn, $CH_2CH_2C_6H_5$, Bu^i, Ph, C_6H_4Me-4, Pr^n, $CH_2CH = CH_2$, $CH_2C{\equiv}CH$, Me) possess a large variety of supramolecular architectures due to

NH ... N bridges. Only for R = Bu^t are hydrogen bridges absent, which results in the presence of monomers in the unit cell.[136] Packing of (TPP) molecules (141) leads to the well-known host channel matrix. These channels have been used for the alignment of 1,3,5-trithia-2,4,6-triazapentalenyl radicals[137] and for the inclusion of 4,4′-dipentoxy-2,2′-dithiophene molecules in order to investigate their photoexcited triplet state.[138] Mobilities of the linear alkane $C_{36}H_{74}$ and the polymers poly(ethylene-d_4) and poly(ethylene oxide-d_4) in the channel matrix of TPP have been studied at different temperatures.[139] Inclusion phenomena have also been observed for the tetramer octakis (4-methylpyridin-2yloxy)cyclotetraphosphazene [$N_4P_4(OC_5NH_3Me\text{-}4)_8$]. As determined by Xray structure analysis, compounds $N_4P_4(OC_5NH_3Me\text{-}4)_8.2CH_2Cl_2$ and $N_4P_4(OC_5NH_3Me\text{-}4)_8.H_2O$ crystallize with channels of about 7.5 and 5.5 Å in diameter, respectively, entrapping solvent molecules CH_2Cl_2 and H_2O. The strong interaction of the water hydrogens with the pyridinyl nitrogens has been put forward as an explanation for the difference in channel diameter between the two crystalline forms. No channel formation has been observed for $N_4P_4(OC_5NH_4)_8$.[140] The influence of the substituent R in compounds (142a–f) on the endocyclic NP bond lengths and angles has been discussed.[141]

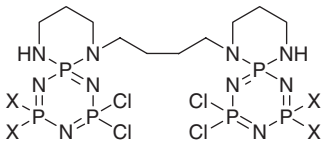


(141)

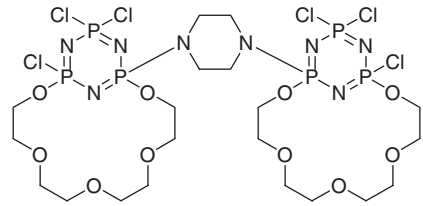


(142a) R = Cl (142d) R = OMe
(142b) R = OCH_2CF_3 (142e) R = NHPh
(142c) R = OPh (142f) R = $NHBu^t$

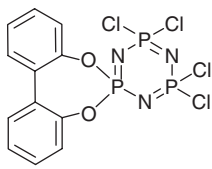
For a number of symmetrically organo-substituted cyclotriphosphazenes a study has been carried out with respect to the influence of the $^{31}P - {}^{31}P$ coupling constants on the ^1H and ^{13}C NMR spectra of the organic substituents.[142] An interesting paper deals with unusual NMR phenomena that occurs upon addition of a chiral shift reagent or a chiral solvating agent to the meso forms of single-bridged cyclotriphosphazenes (143a-c) and (144). In these cases the ^{31}P NMR spectrum shows an unexpected doubling of the signals, which can be expected only for the racemic form. The doubling of the resonance lines has been explained by an equilibrium complexation of a chiral ligand with the meso compounds, assuming an independent complexation with each of the two phosphazene rings.[143]



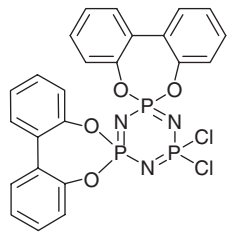
(143a) X - Ph
(143b) X = $NHBu^t$
(143c) $X_2 = O(CH_2)_3O$



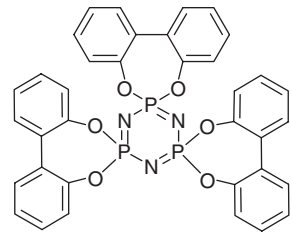
(144)



(145)



(146)

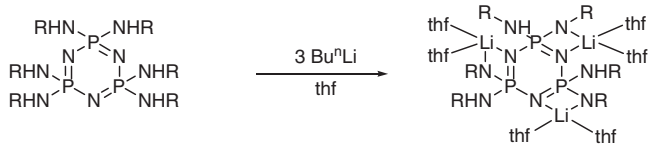


(147)

The stereochemistry of the compounds (145), (146) and (147) has been investigated by NMR methods in combination with molecular dynamics simulations.[144] Absorption and fluorescence spectra of $N_3P_3(OC_6H_4NH_2\text{-}4)_6$ have been reported.[145] Studies of the fragmentation patterns of protonated and cationized $N_nP_n(OPh)_{2n}$ and $N_nP_n(NHPh)_{2n}$ (n = 3, 4) have been carried out by means of liquid secondary ion mass spectrometry.[146] The phenolysis of $(NPCl_2)_3$ in a triphase reaction medium consisting of phenol in an aqueous NaOH solution, CH_2Cl_2 and polymer-immobilized-$CH_2NBu^n{}_3{}^+Cl^-$ has been studied.[147]

It has been shown that cyclophosphazenes (148a-f)) with general formula $N_3P_3[N(H)R]_6$ react with three equivalents of Bu^nLi in thf to form the lithium complexes (149). Structure analyses reveal that in these complexes the lithium ions are in *cis* position with respect to the mean plane of the ring and coordinated by two nitrogen (endo- and exo-cyclic) and two oxygen atoms (thf).[148–150] The reaction of (149d) with one equivalent of Me_3Al results in the formation of the first mixed-metal phosphazenate complex (150). NMR spectra of this compound in thf solution show a fluxional behavior of the lithium atoms with respect to their chelation by the nitrogen atoms.[149] An interesting compound (151) has been obtained by treatment of (149e) with three equivalents of $Et_3N.HCl$. The structure determination of this compound reveals the presence

of two Li-N bonds together with Li-Cl and Li-O interactions.[150] An analogous bonding pattern has been found for the (lithium salt)-doped polyphosphazenes $\{^{15}NP[(OCH_2CH_2)_2OMe]_2\}_n$-$LiSO_3CF_3$ with lithium directly bonded to the nitrogen of the polymer backbone.[249] The cyclophosphazene-LiCl adduct (151) can also be prepared by treatment of (148e) with anhydrous HCl, followed by a reaction with two equivalents of Bu^nLi. Similar to the synthesis of (152e), compound (152f) can be obtained from (148f).[150]



(148a) R = C_6H_4F-2 (148e) = $(CH_2)_3OMe$

(148b) R = C_6H_4Cl-2 (148f) = Pr^i

(148c) R = C_6H_4Br-2

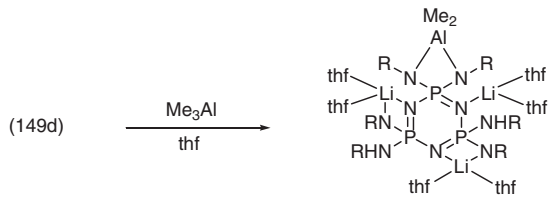
(148d) R = Ph

(149a) R = C_6H_4F-2 (149e) = $(CH_2)_3OMe$

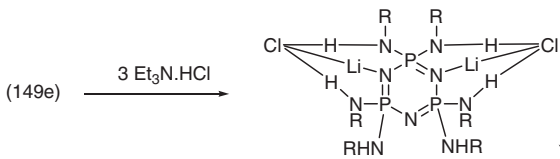
(149b) R = C_6H_4Cl-2 (149f) = Pr^i

(149c) R = C_6H_4Br-2

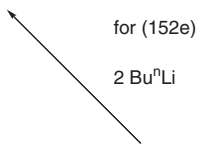
(149d) R = Ph

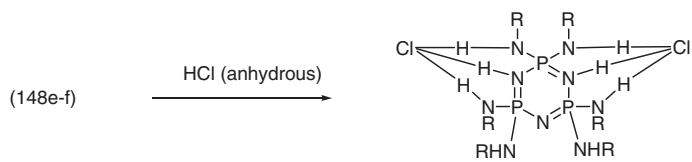


(150) R = Ph



(151) R = $(CH_2)_3OMe$

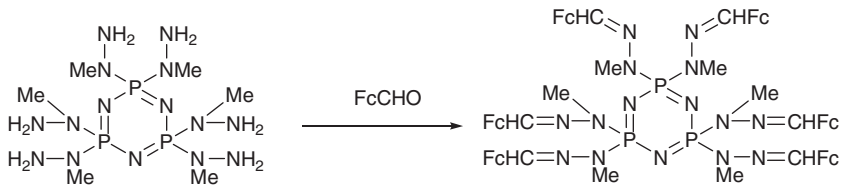




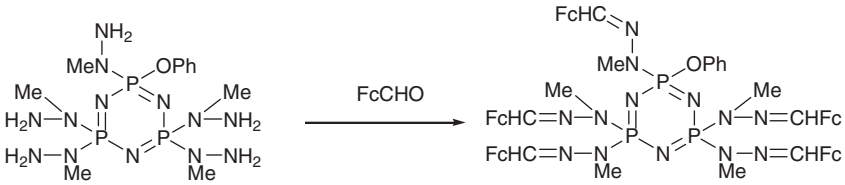
(152e-f)

Metal bonding to the endocyclic nitrogen has also been observed for complexes $N_3P_3[N(H)R]_6$ (R = Pr^n, Cy, Bn, Pyr) with $AgNO_3$ or $AgClO_4$, resulting in coupling of the phosphazene rings by N-Ag-N bridges. In this way supramolecular coordination compounds arise, the topology of which depends on the donor ability of the anion and the steric demand of the group R.[151] Other examples of supramolecular patterns have been found in crystals of (153) and (165), where N–H ... N and C–H ... N bridges [in (153)] or only N–H ... N bridges [in (165)] are responsible for network formation.[152]

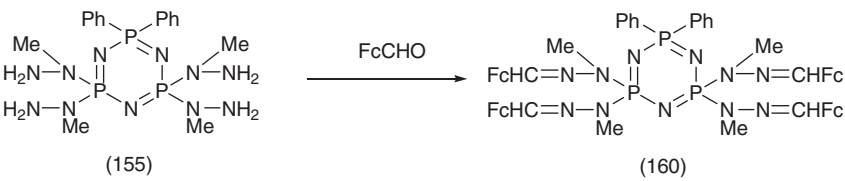
The NH_2 groups in the *N*-methylhydrazine derivatives (153–157) have been reacted with ferrocene-2-carboxaldehyde (FcCHO, Fc=ferrocenyl) to yield the corresponding hydrazones (158–162). Electrochemical studies of these compounds reveal only a single reversible oxidation pattern, pointing to an electrochemical equivalence of the ferrocenyl groups.[153]



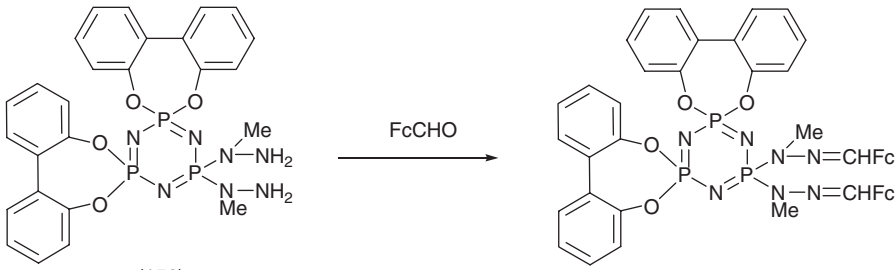
(153) (158)



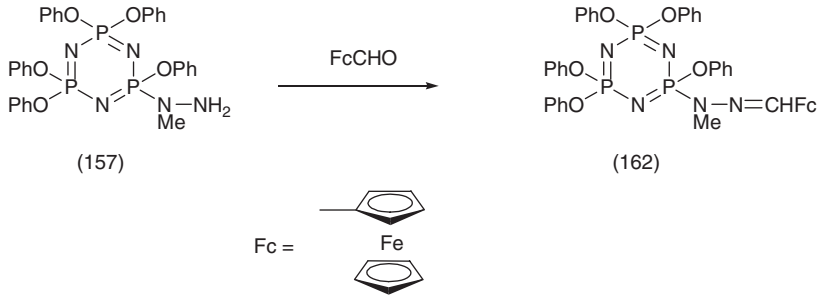
(154) (159)



(155) (160)

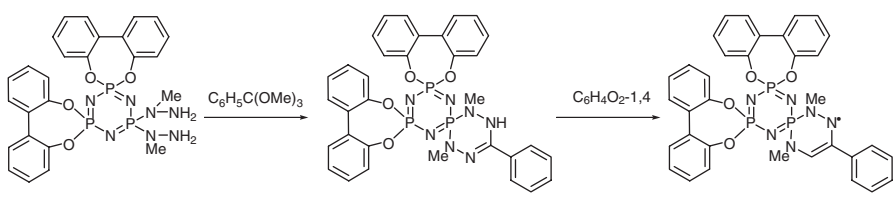


(156) (161)



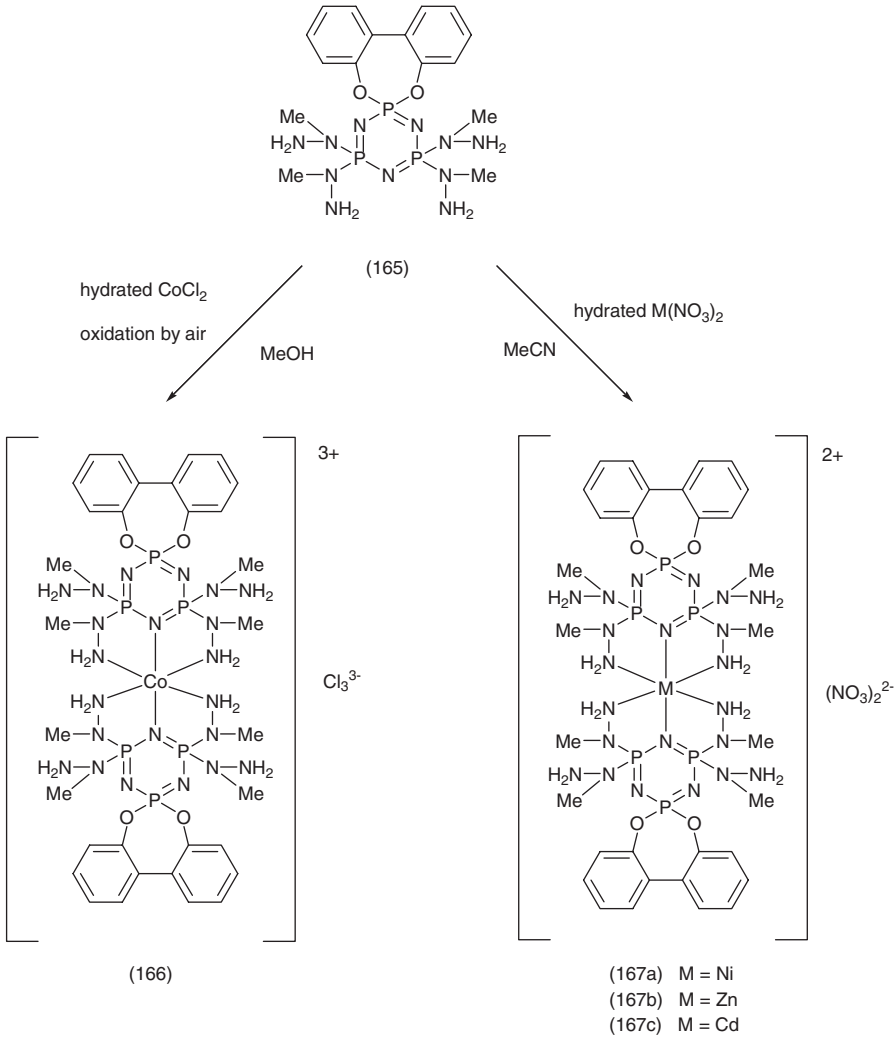
(157) (162)

The difunctionality of NH_2 moiety in the methylhydrazine derivatives has also been underlined by the reaction of (156) with trimethylorthobenzoate to afford the 1-phospha-2,3,5,6-tetrazine derivative (163), which on oxidation with benzoquinone can be transformed to the radical species (164). EPR and ENDOR spectroscopic experiments clearly point to a spin polarization through the spirocyclic phosphorus atom to the other phosphorus and nitrogen nuclei in the phosphazene ring of (164).[154]



(156) (163) (164)

The *N*-methyl hydrazine derivative (165) has proven to be a multidentate ligand towards 3d-transition metals as shown by the formation of the complexes (166) and (167a–c). Two NH_2 groups are involved in the ligation of the central metal atom.[155]

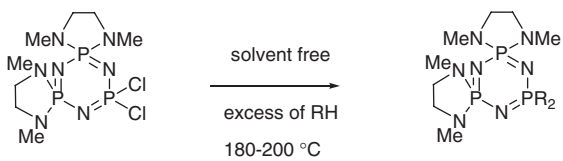


(165)

(166)

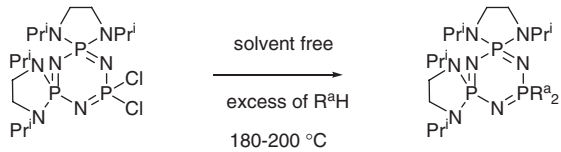
(167a) M = Ni
(167b) M = Zn
(167c) M = Cd

The spirocyclic compounds (170–172) also form metal complexes in which endocyclic and exocyclic nitrogens coordinate to the metal centers. It is worthy to note that the compounds (170–172) can only be prepared from the dichloro precursors (168, 169 and 146) under forcing reaction conditions.[156]

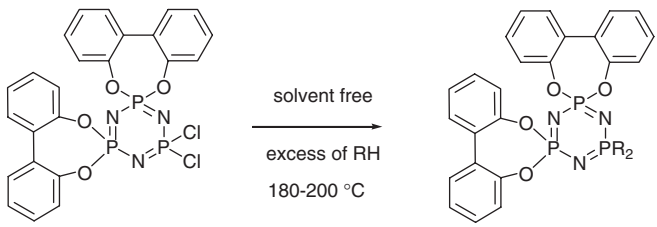


(168)

(170a) R = R^a
(170b) R = R^c
(170c) R = R^f



(169) (171)

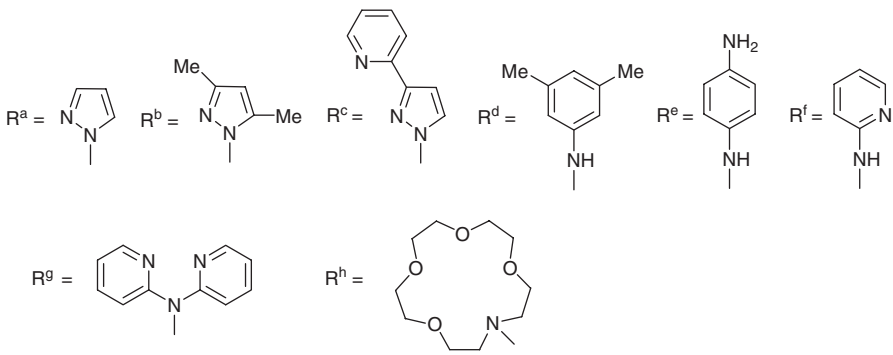


(146)

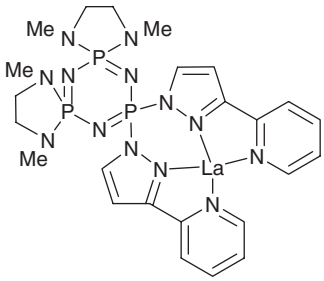
(172a) R = R^a (172d) R = R^e

(172b) R = R^b (172e) R = R^g

(172c) R = R^d (172f) R = R^h

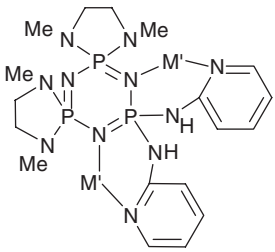


The mononuclear metal complex {[$La(NO_3)_3$][170b]} (173) and dinuclear complexes {[$ReCl(CO)_3]_2$[170c]} (174a), {[$FeI_2]_2$[170c]} (174b) and {[$PdCl_2]_2$ [170c]} (174c) have been prepared and characterized including their X-ray structures.[156]



nitrate groups omitted for clarity

(173)

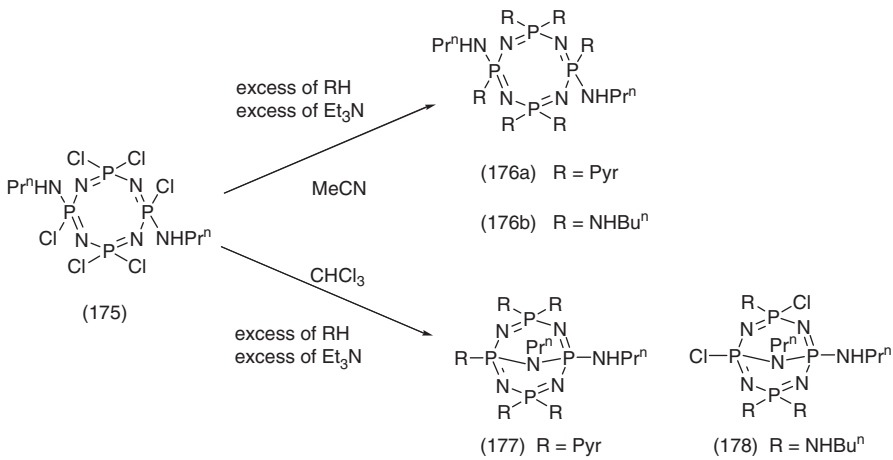


(174a) M' = $ReCl(CO)_3$

(174b) M' = FeI_2

(174c) M' = $PdCl_2$

Aminolysis studies of the cyclic system N_4P_4 were restricted to reactions of 2,-*trans*-6-$N_4P_4Cl_6(NHPr^n)_2$ (175) with pyrrolidine and *t*-butylamine. Compounds (176a) and (176b) were obtained, when the aminolysis was carried out with an excess of amine in MeCN in the presence of an excess of Et_3N. Applying analogous conditions with $CHCl_3$ as a solvent, compounds (177) and (178) could be isolated, the latter however in a very low yield.[157]



(175)

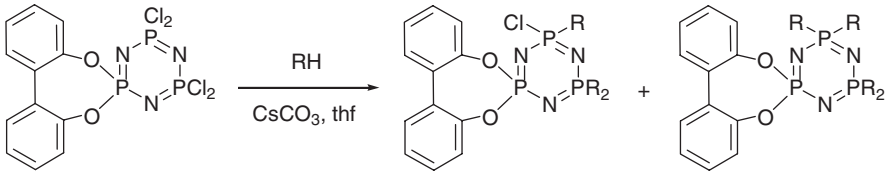
(176a) R = Pyr

(176b) R = $NHBu^n$

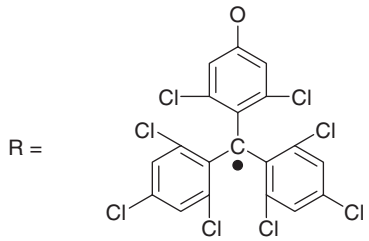
(177) R = Pyr

(178) R = $NHBu^n$

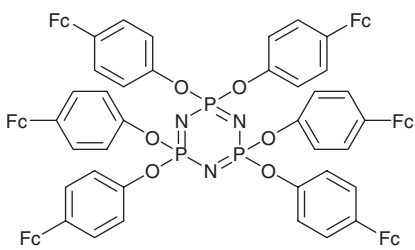
Cyclophosphazenes with three radical centers (179) and four radical centers (180) have prepared by the reaction of (145) with the (4-hydroxy-2,6-dichlorophenyl)bis(2,4,6-trichlorophenyl)methyl radical in thf in the presence of Cs_2CO_3. In contrast with (164) where a distinct spin leakage into the phosphazene ring is present, EPR measurements on the compounds (179) and (180) show only weak electron-electron dipolar interactions.[158] X-ray structural data for (145) is given in Section 5.[159]



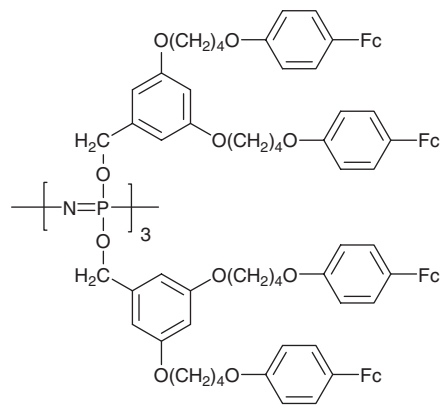
(145) (179) (180)



The ferrocene derivatives (181)[160] and (182)[161] have been prepared from $N_3P_3Cl_6$ by alcoholysis with the appropriate sodium alcoholates. In both compounds the ferrocenyl units appear to be electrochemically equivalent, as was found for compounds (158–162).[153]

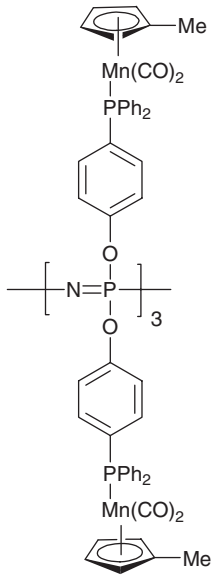


(181)

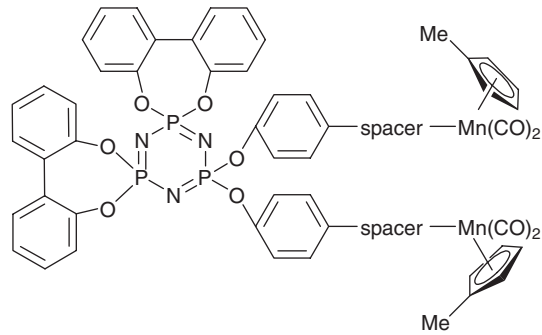


(182)

The trimer $(NPCl_2)_3$ and its bis(dioxybiphenyl) derivative (146) react with the diphenylphosphinophenol complex $\{Mn(CO)_2(\eta^5\text{-}C_5H_4Me)[PPh_2(C_6H_4OH\text{-}4)]\}$ in the presence of Cs_2CO_3 and thf as a solvent to afford high yields of the cyclophosphazene-phosphine complexes (183) and (184a), respectively.[162] An analogous complex (184b) with a benzylcyanide spacer has been prepared by the reaction of $N_3P_3(O_2C_{12}H_8)_2[OC_6H_4(CH_2CN\text{-}4)]_2$ with $Mn(CO)_2(\eta^5\text{-}C_5H_4Me)$thf.[163]



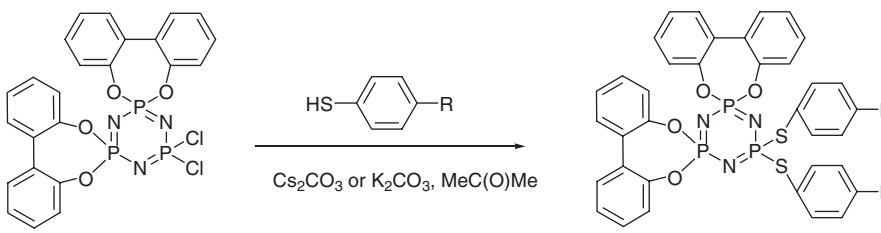
(183)



(184a) spacer = - $P(Ph_2)$ -

(184b) spacer = - CH_2CN -

The dioxybiphenyl derivative (146) has also been used as starting material for the preparation of thiophenolate-substituted analogues. Formation of the compounds (185a–d) from (146) and RC_6H_4-SH appears to be a two-step process, the second step being much faster than the first. This is in contrast with reactions with substituted phenols RC_6H_4-OH, where the first substitution step is faster than the second one and consequently mono-substitution products can be isolated under appropriate conditions.[164]



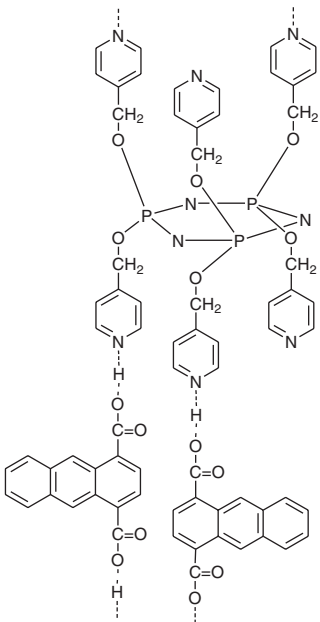
(146)

(185a) R = H
(185b) R = Br
(185c) R = OMe
(185d) R = NO_2

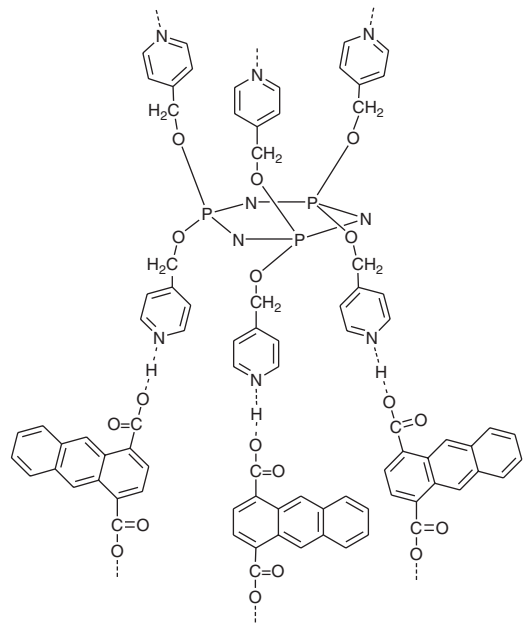
The synthesis and spectral characterization of the high-melting (>300°C) fully substituted reaction product of $(NPCl_2)_3$ and 2-[2-(2-hydroxyphenyl)quinoxalin-3-yl]phenol has been reported.[165] New hexakis(*p*-phenylazo-*o*-allylphenoxy)cyclotriphosphazenes with mono- or disubstituted phenyl groups

have been prepared by the reaction of $(NPCl_2)_3$ and the appropriate sodium phenoxides.[166]

Hydrogen bonding between pyridinyl groups of the (pyridinyl-4-yl)methoxy derivative $N_3P_3(OCH_2C_5H_4N\text{-}4)_6$ and the carboxyl groups of 1,4-anthracenedicarboxylic acid leads to the formation of macromolecules, the composition depending on the solvent used. From dimethyl sulfoxide a crystalline compound (186) has been isolated with an acid/phosphazene ratio equal to 2, whereas crystals (187) isolated from dimethylformamide had a ratio of 3. An Xray structure determination of (186) shows strong hydrogen bonding [mean N(H) ... O = 2.62 Å] at both sides of the phosphazene ring, leaving two pyridinyl groups without hydrogen bonds.[167]

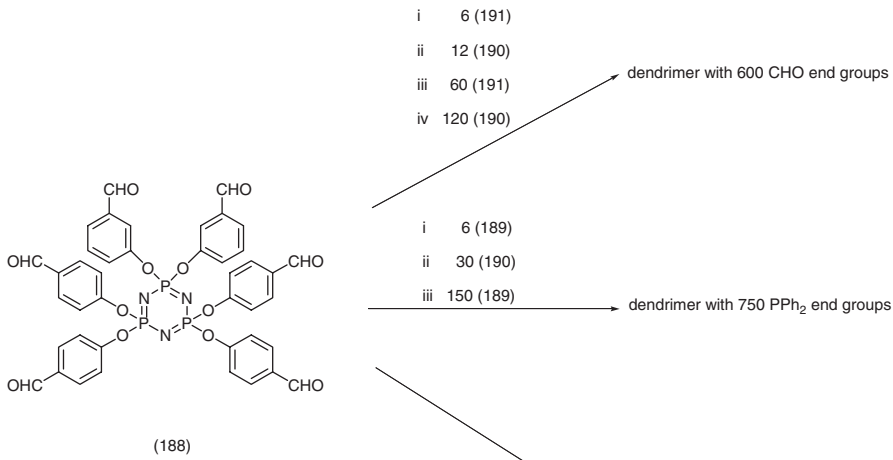


(186)

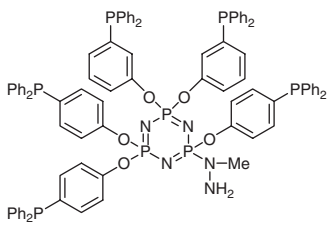


(187)

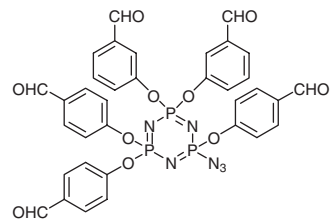
As already described in Section 2, the use of branched reagents for the preparation of dendrimers can reduce the number of reaction steps significantly, while still attaining a large number of end groups. Three examples of this "divergent dendrimer synthesis" approach have been given using $N_3P_3(OC_6H_4CHO\text{-}4)_6$ (188) as starting material, applying condensation reactions between phosphorohydrazides and aldehydes and Staudinger reactions between phosphines and azides.[168]



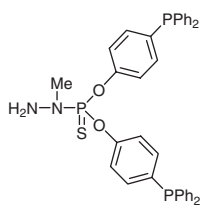
(188)



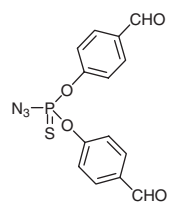
(189)



(190)

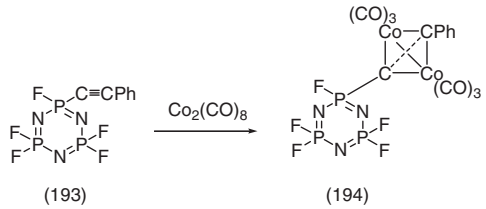


(191)

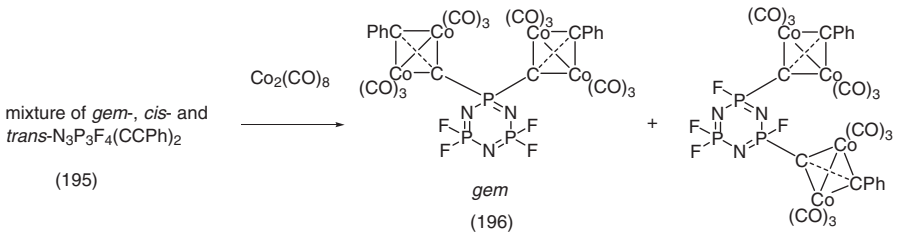


(192)

Phenylethynylfluorocyclotriphosphazenes (193) and (195) react readily with $Co_2(CO)_8$ to form the corresponding cobalt complexes. In contrast to the inseparable isomer mixture of (195), the isomers *gem*-(196), *cis*-(197) and *trans*-(197) could be separated by chromatography. Electrochemical experiments showed that reduction of compound (194) occurs via a reversible one-electron transition, whereas for gem-(196) there were two independent one-electron reductions. ESR spectra of the radical anions point to localization of the unpaired electron on the organometallic moiety.[169]

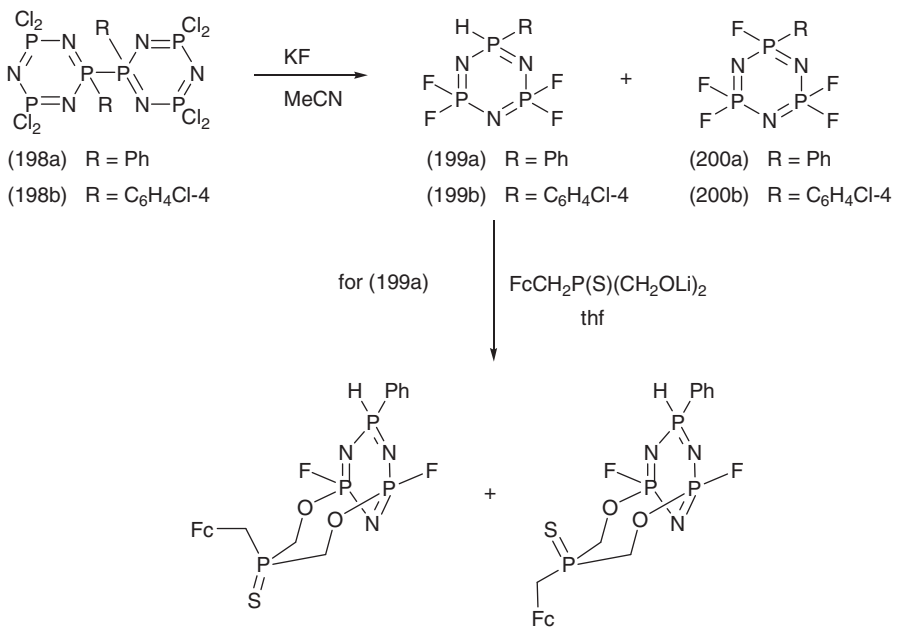


(193) (194)



(195) (196) (197)

Treatment of the bicyclophosphazenes (198a–b) with KF in acetonitrile induced cleavage of the P–P bond and the formation of two six-membered fluorocyclotriphosphazenes (199a–b) with small amounts of (200a–b). It is assumed that acetonitrile acts as proton donor for the formation of (199a–b). The hydridofluoro phosphazene (199a) and $FcCH_2P(S)(CH_2OLi)_2$) react to give the endo- and exo-ansa-substituted derivatives (201).[170]



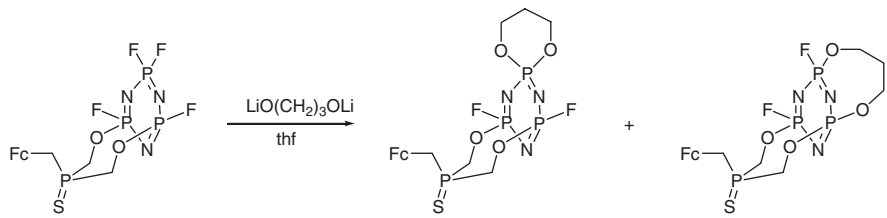
(198a) R = Ph
(198b) R = C_6H_4Cl-4

(199a) R = Ph
(199b) R = C_6H_4Cl-4

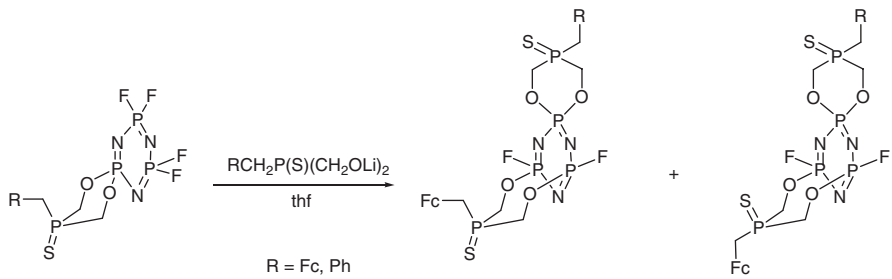
(200a) R = Ph
(200b) R = C_6H_4Cl-4

endo-ansa-(201) exo-ansa-(201)

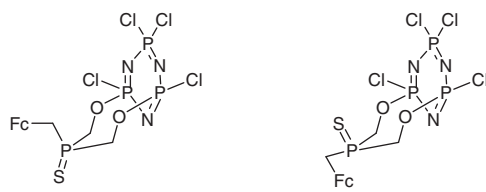
From substitution reactions of ansa- and spiro-substituted tetrafluorocyclotriphosphazenes with dinucleophiles it has been concluded that formation of ansa-spiro isomers is preferred, as shown by the reaction of the ansa-compound (202) with $LiO(CH_2)_3OLi$ and by the reaction of spiro-(205) with $RCH_2P(S)(CH_2OLi)_2$. When treated with CsF the ansa-spiro derivatives (203) and (206) can be transformed into the corresponding spiro-spiro compounds. This indicates a higher thermodynamic stability for the spiro isomers with respect to the ansa isomers.[171] Also the endo-ansa fluorinated fluorocyclotriphosphazenes (202) and the corresponding exo-ansa isomer can be easily transformed into the spiro-substituted compound (205) in the presence of CsF. Non-fluorinated bases Cs_2CO_3, K_2CO_3, $KOBu^t$ and Et_3N produce the same isomerization. This behavior of fluorinated cyclophosphazenes is in sharp contrast to that of the chloro analogues (207), which cannot be isomerized into the spiro form.[172]



endo-ansa-(202) endo-ansa-spiro-(203) endo-ansa--ansa-(204)

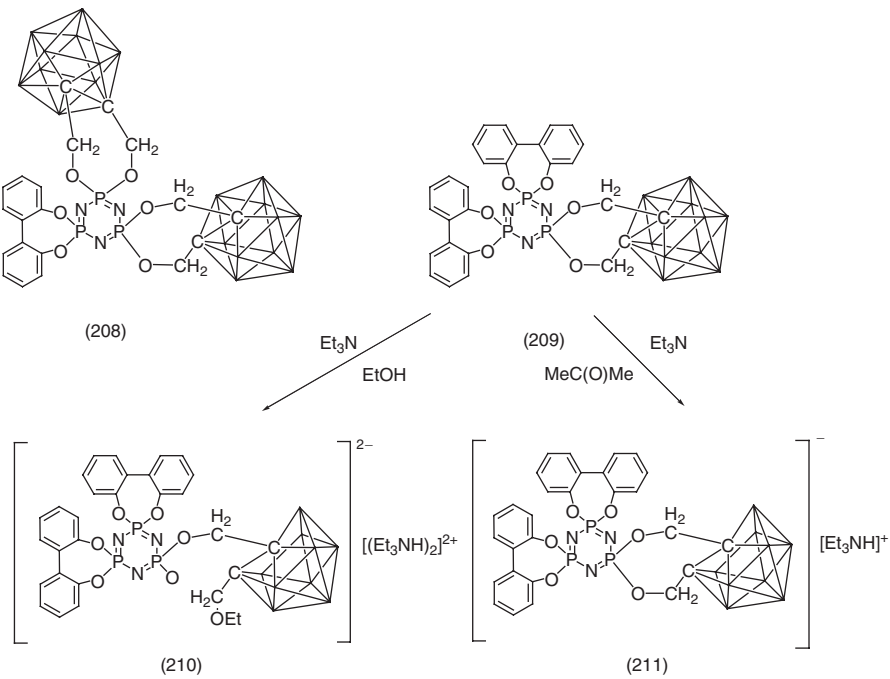


spiro-(205) endo-ansa-spiro-(206) exo-ansa-spiro-(206)



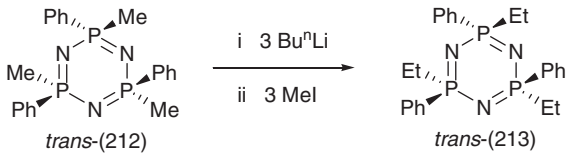
endo-ansa-(207) *exo-ansa*-(207)

Reactions of $(NPCl_2)_3$ with the 1,2-*closo*-carborane derivative $C_2B_{10}H_{10}(CH_2OH)_2$ in acetone in the presence of K_2CO_3 have been reported to yield a mixture of mono-, bis- and tris-spiro derivatives as well as a mono ansa derivative. By using (*o*-phenylenedioxy)cyclotriphosphazenes (145) and (146) as starting material, the bis(carboranyl) (208) and the mono(carboranyl) (209) derivatives are formed as the only reaction products. Treatment of (209) with an excess of Et_3N in ethanol affords (210), involving the formation of a *nido*-derivative together with nucleophilic attack by an ethoxide anion. By changing the solvent to acetone the reaction could be restricted to the formation of *nido*-carboranyl derivative (211) without side-reactions.[173]

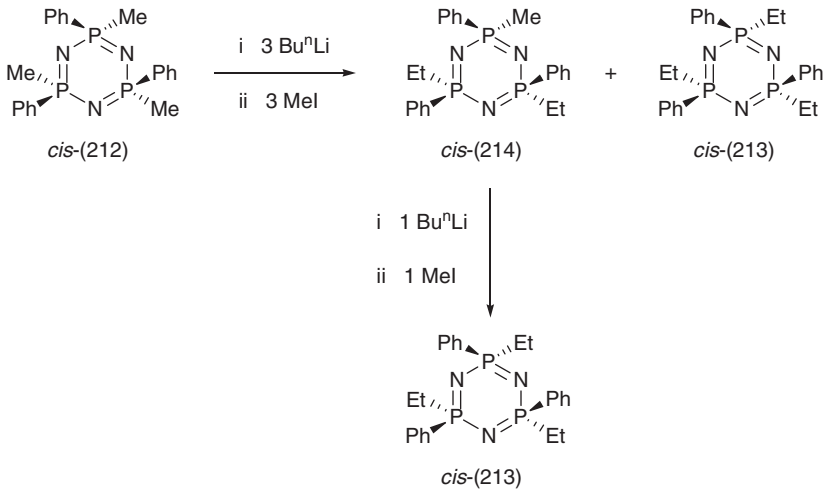


The deprotonation-substitution reactions of methylphenyl substituted cyclotriphosphazenes can be considered to be an important synthetic tool for the expansion of the area of organo-substituted cyclophosphazenes possessing a direct P-C bond. The reaction of *trans*-$(NPMePh)_3$ (212) with 3 moles of Bu^nLi followed by treatment with 3 moles of MeLi affords *trans*-$(NPEtPh)_3$ (213) in high yield. The same reaction with *cis*-$(NPMePh)_3$ (212) gives a mixture of bis(ethyl) [*cis*-(214)] and tris(ethyl) [*cis*-(213)] derivatives.

Cis-(214) can be easily converted to *cis*-(213) by treatment with 1 mole of Bu^nLi and 1 mole of MeLi.[174]



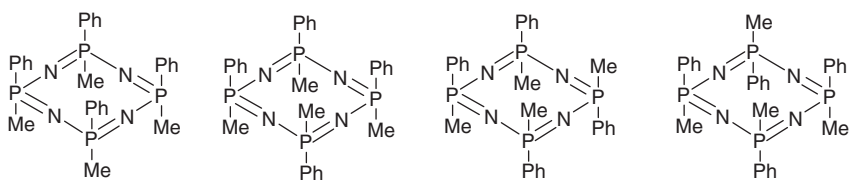
trans-(212) *trans*-(213)



cis-(212) *cis*-(214) *cis*-(213)

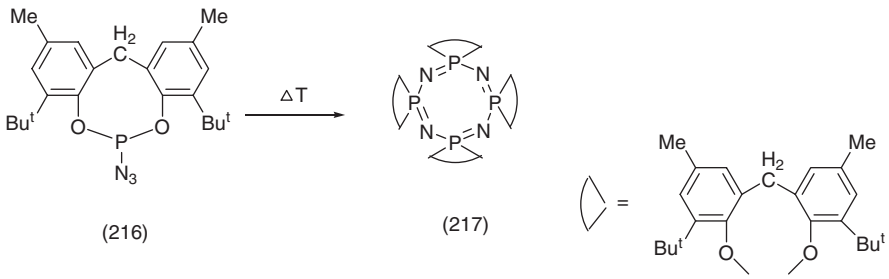
cis-(213)

The isomers *cis*- and *trans*-$(NPMePh)_3$ (212) have also been used for the preparation of organo-substituted tetramers. When heated at 200–250°C ring opening occurs, leading to two additional processes, viz. *cis*-*trans* isomerization and tetramer formation. Higher temperatures and longer reaction times favour the formation of tetramers, in which all four possible isomers $(NPMePh)_4$ (215) are formed. Isomerization is more prevalent than ring expansion at lower temperatures and shorter reaction times.[175] Thermolysis of the azide (216) has been reported to yield the fully *spiro*-substituted tetramer (217).[176]



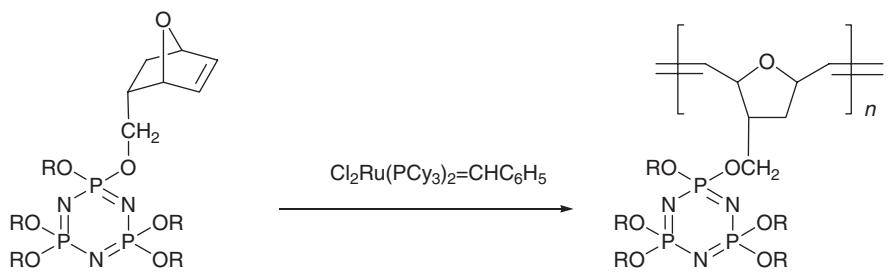
2, *cis*-4, *cis*-6, *cis*-8 2, *cis*-4, *cis*-6, *trans*-8 2, *cis*-4, *trans*-6, *trans*-8 2, *trans*-4, *cis*-6, *trans*-8

(215)



(216) (217)

New polymers have been prepared in which cyclophosphazene or cyclocarbaphosphazene rings function as pendant groups. Analogous to the preparation of phosphazene-substituted polynorbornenes, ring opening polymerization of 7-oxanorbornene derivatives (218a–c), in the presence of the initiator $Cl_2(PCy_3)_2Ru{=}CHPh$, gives the polymers (219a-c) in high yields. Ionic conductivities of the $LiN(SO_2CF_3)_2$-salt complexes of (219a–c) increase with increasing length of the oligoethyleneoxy group. For $LiN(SO_2CF_3)_2$-complexes of (219a) and (219b) the conductivities also increase with increasing amounts of salt. The effect of higher salt concentrations for salt complexes of (219c) manifests itself only at higher temperatures, probably caused by a gradual disappearance of ionic crosslinks present in the long ethyleneoxy chains.[177]



(218a) R = CH_2CH_2OMe

(218b) R = $(CH_2CH_2O)_2Me$

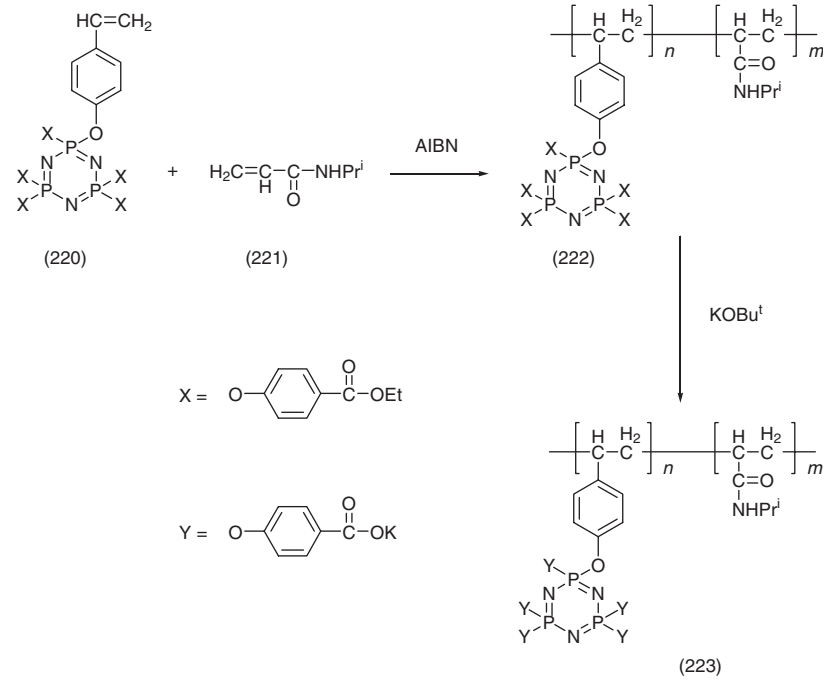
(218c) R = $(CH_2CH_2O)_3Me$

(219a) R = CH_2CH_2OMe

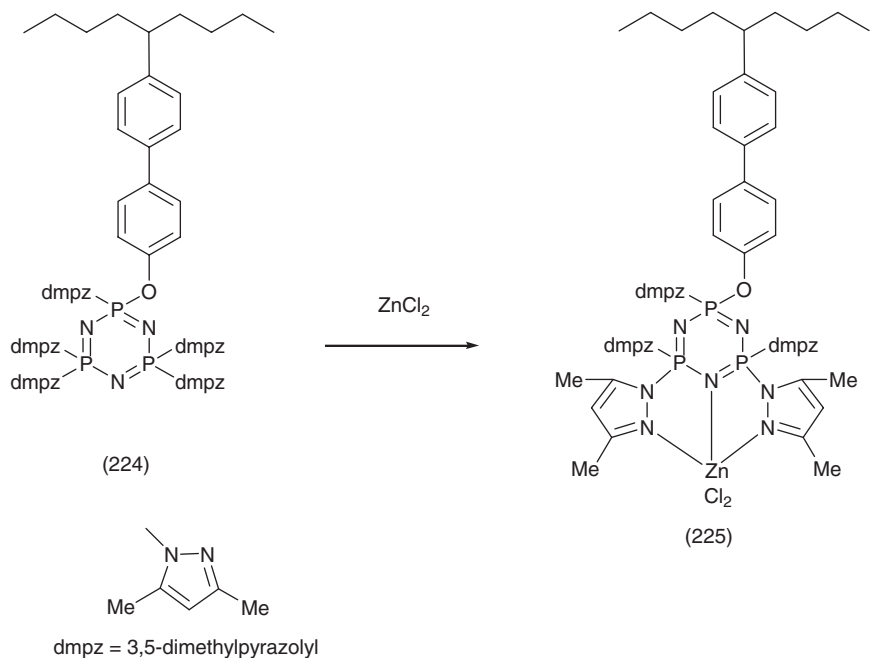
(219b) R = $(CH_2CH_2O)_2Me$

(219c) R = $(CH_2CH_2O)_3Me$

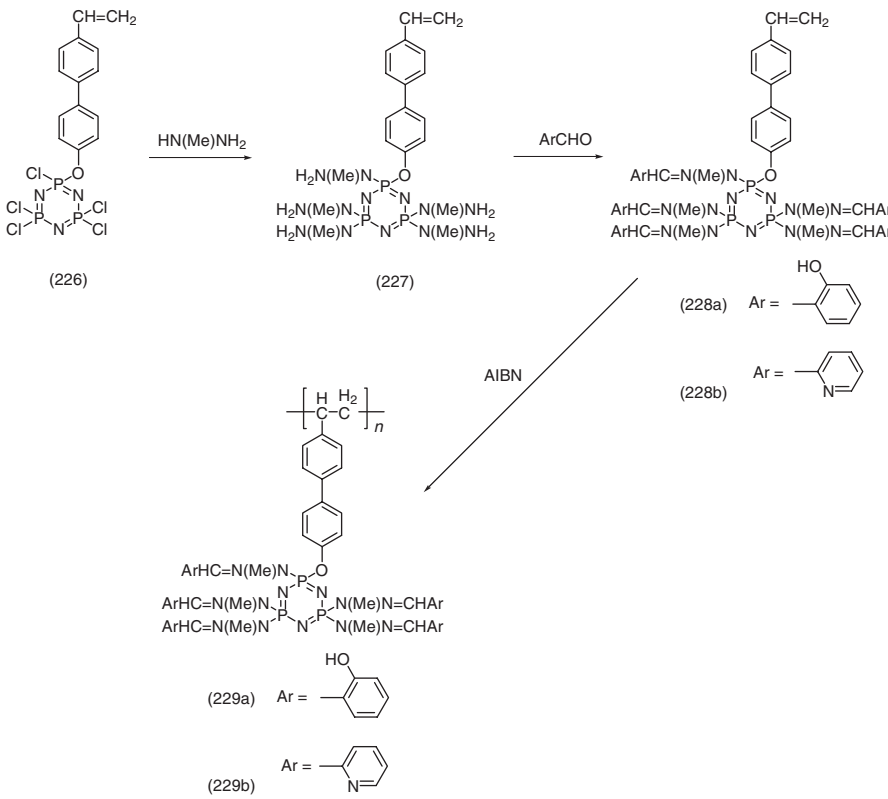
Copolymers (222) have been prepared by radical copolymerization of the monomers (220) and (221). Further reaction with Bu^tOK yields a water-soluble copolymer (223) that can be used as host for Eu^{3+}-ions. The Eu^{3+} guest-host complex shows a strong fluorescence due to an interaction with carboxylatophenoxy groups.[178]



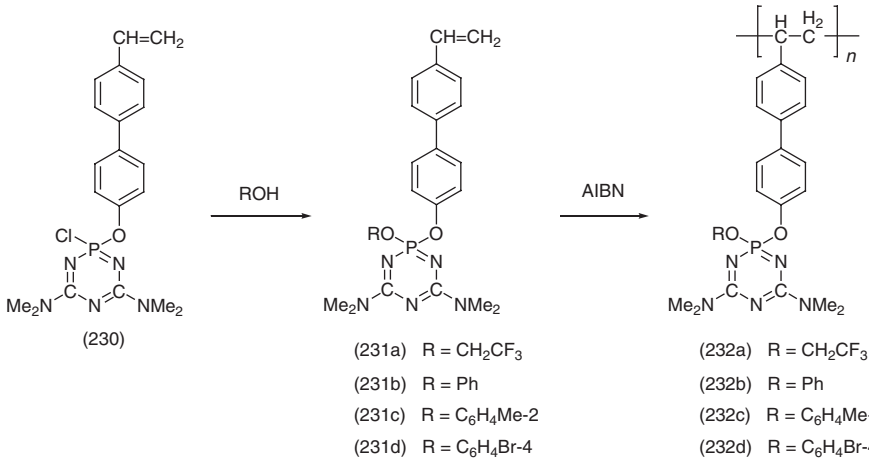
The zinc-containing polymer (225) prepared from (224) and $ZnCl_2$ has proven to be an effective heterogeneous catalyst for phosphate ester hydrolysis and cleavage of supercoiled plasmid DNA.[179]

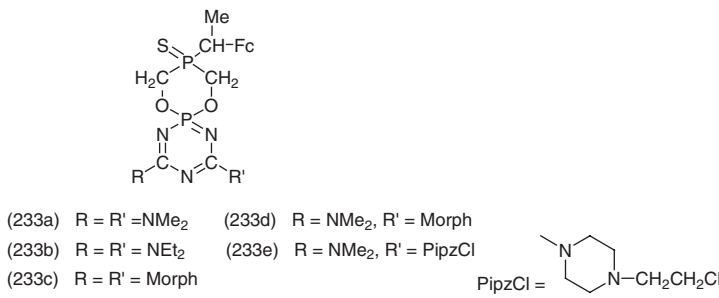


The reaction of $(NPCl_2)_2NPCl(OC_6H_4C_6H_4CH{=}CH_2\text{-}4)$ (226) and $HN(Me)NH_2$ yields the *N*-methylhydrazine derivative (227), which can converted into the corresponding hydrazones (228a) and (228b), respectively, by *o*-hydroxybenzaldehyde or pyridine-2-carboxaldehyde. Subsequent radical polymerization results in the formation of homopolymers (229a) and (229b).[180]

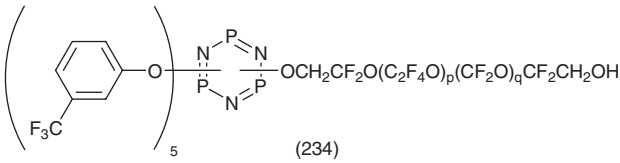


Polymers with pendant cyclodicarbaphosphazene groups (232a–d) have been readily obtained by radical polymerization of the monomers (231a–d). In their turn these precursors can be obtained by nucleophilic substitution of the chlorine atom in (230). The polymers, which have moderate molecular weights and Tg values ranging from 116–126°C, are stable up to about 370°C. Compound (230) and the polymer precursors (231) have been fully characterized by X-ray structure determinations.[181] In addition to the carbaphosphazenes mentioned above, the preparation and characterization of ferrocenyl derivatives (233a–e) have been reported.[182]

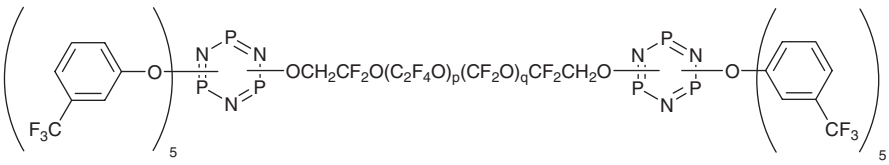




The application of the cyclophosphazene $N_3P_3(OC_6H_4F\text{-}4)_n(OC_6H_4CF_3\text{-}3)_{6-n}$ ($n \approx 2$; code name X-1P) as a lubricant is well known. Comparative studies of the tribological properties of X-1P and ionic liquids of alkylimidazolium tetrafluoroborates have shown a preference for the tetrafluoroborates as lubricants.[183–185] The interaction of X-1P with a carbon-coated head at the head-disk interface of hard disk magnetic storage systems in the presence of a perfluoropolyether (PFPE) lubricant, has been discussed.[186,187] Attention has been paid to the application of a novel lubricant (A2OH) which consists of (234) as the major component and small quantities of (235).[188] The new lubricant displays a lower mobility on carbon surfaces than hydroxyl-terminated PFPE and consequently a reduced sensitivity to film thinning.[189] It has been argued that in monolayers on carbon-coated surfaces both the phosphazene and the OH groups interact with the surface.[190] The influence of the molecular weight on the tribological properties of A2OH has been discussed.[191]



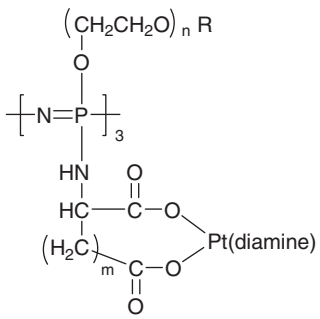
(234)



(235)

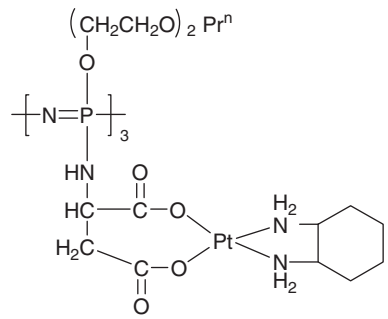
Trimeric compounds $N_3P_3(PFPE)_6$ with molecular weights of the PFPE entities ranging from about 500 to 700 have been developed for use as lubricant additives.[192] In addition compounds have been patented in which two PFPE-substituted trimers are connected to each other by a PFPE bridge, a configuration similar to that in (235).[192]

Three dendrimers based on the cyclotriphosphazene core and having 48, 96 and 192 $N(CH_2)_2NHEt_2^+$ surface groups have been evaluated as drugs in the treatment of diseases related to abnormal aggregation of proteins.[193] The same class of polycationic dendrimers has been the subject of an *in vitro* study with respect to their cytotoxicity and ability to deliver oligopeptides and plasmids in human cell cultures.[194] The preparation and cytostatic activity of a number of thermosensitive platimum(II)-cyclotriphosphazenes chelates (236) have been discussed. All compounds reveal an *in vitro* and *in vivo* cytostatic activity against the murine leukemia cell line L1210. The highest antitumor activity, which is comparable with that of cisplatin, was found for (237). The critical solution temperature (LCST) of 15°C of (237) opens the possibility for local administration at the tumor site.[195]



R = Me, Et, Pr^n, Bu^n

(236)

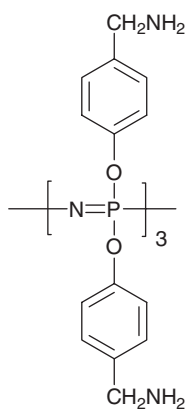


(237)

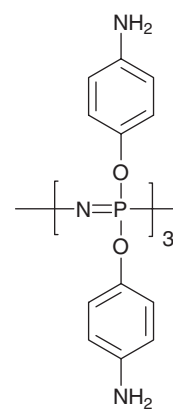
The application of compounds $N_3P_3F_n[O(CH_2)_2OC(O)C(Me) = CH_2]_{n-6}$ (n = 1–5)[196,197] and $N_4P_4F_n[O(CH_2)_2OC(O)C(Me)=CH_2]_{n-8}$ (n = 1–7)[197] as components of dental bonding compositions has been described. In a small

molecule approach the tyrosine derivatives $N_3P_3\{OC_6H_4[CH_2CH(NH_2)CO_2Et\text{-}4]\}_6$ and $N_3P_3\{OC_6H_4[CH_2CH(NH_2)CO_2H\text{-}4]\}_6$ have been synthesized in order to gain knowledge about reaction conditions at a macromolecular level.[267]

Hexakis(allylamino)cyclotriphosphazene $N_3P_3[N(H)CH_2CH{=}CH_2]_6$ has been applied as a coupling agent for blending isotactic polypropylene and poly (ethylene-*co*-propylene-*co*-methylenenorbornene) in the presence of a peroxide initiator.[198] Flame-retardant resins have been obtained by curing mixtures of $N_3P_3[N(H)CH_2CH{=}CH_2]_6$ and unsaturated polyesters in the presence of benzoyl peroxide.[199] Poly(2-hydroxyethyl methacrylate) networks have been prepared by radical polymerization of $HO(CH_2)_2OC(O)C(Me){=}CH_2$ with $N_3P_3Morph_4[N(H)CH_2CH{=}CH_2]_2$ (Morph=morpholino) or $N_3P_3[N(H)CH_2CH{=}CH_2]_6$ as crosslinking reagents.[200] Condensation polymerization of a cyclophosphazene with approximate composition $N_3P_3(OPh)_{4.5}(OC_6H_4CH_2CH{=}CH_2\text{-}4)_{0.5}[OC_6H_3(OH)_2\text{-}3,5]$ and hexamethylene-1,6-diisocyanate yields a polyurethane with pendant cyclophosphazene groups, of which the allyl functions can be used to synthesize polyurethane-polyethylene grafted polymers.[201] Ring opening polymerization of ε-caprolactone in the presence of $N_3P_3[OC_6H_4(CH_2OH\text{-}4)]_6$ as initiator and catalytic amounts of stannous octanoate yields star-shaped poly(ε-caprolactone) with a phosphazene ring core.[202] The hydroxyl end-capped poly(ε-caprolactone) can be used as an initiator for the ring opening polymerization of L-lactide, thus forming block copolymers of ε-caprolactone and L-lactide.[203] Polymerization of *N*-carboxy-γ-benzyl-L-glutamic acid anhydride with $N_3P_3[OC_6H_4(CH_2NH_2\text{-}4)]_6$ (238) results in a star-shaped poly(γ-benzyl-L-glutamate) with the polymer chains situated on both sides of the phosphazene ring. A helical secondary structure for the polymer chains has been proposed.[204] Compound $N_3P_3[OC_6H_4NH_2\text{-}4]_6$ (239) appears to be less reactive than (238) in the reaction with glutamic acid anhydride.[204]



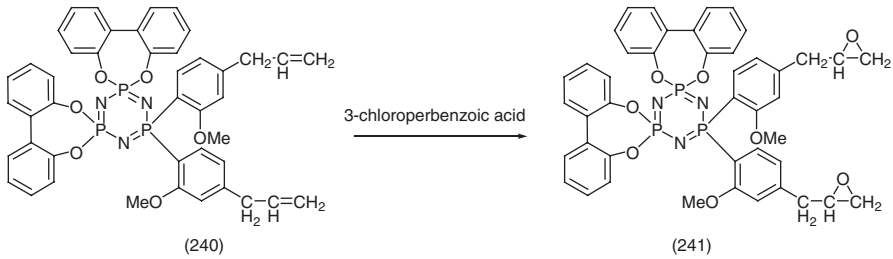
(238)



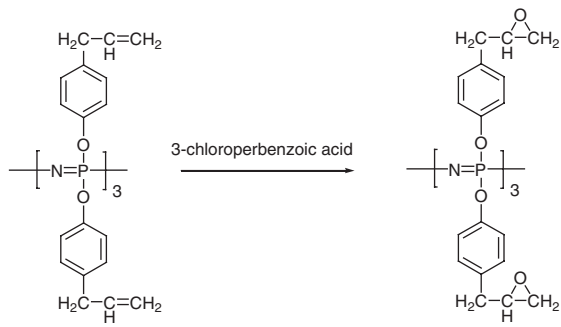
(239)

Deprotonation of α-ketal-ω-hydroxy and α-pyridinyl-ω-hydroxy poly(ethylene oxide) by Ph_2CHK, followed by quenching with $(NPCl_2)_3$ results in the formation of the corresponding poly(ethylene oxide) stars based on the

cyclophosphazene ring.[205] Compounds (241) and (243) have been prepared from their corresponding eugenol derivatives (240) and (242) by treatment with 3-chloroperbenzoic acid. It has been demonstrated that the viscoelastic and rheological properties of Nylon-6 can be changed when treating the polyamide at 240°C with quite small quantities of the cyclophosphazene derivatives (241) or (243).[206]



(240) (241)



(242) (243)

New hybrid materials have been synthesized from a mixture of $N_3P_3(O\text{-}C_6H_4OH\text{-}4)_6$ and a SiO sol-gel matrix prepared by acid hydrolysis of $Si(OEt)_4$. It has been argued that the interaction between phosphazene and SiO network arises from -C_6H_4-O-Si- bonds.[207] The compounds $N_3P_3(OPh)_n(OC_6H_4NH_2\text{-}4)_{6-n}$ (n = 3–5) and $N_3P_3\{OC_6H_4[OP(O)(OEt)_2]\text{-}4)\}_{2.94}(OC_6H_4OH\text{-}4)_{3.06}$ have been used for the preparation of cyclolinear polymers with polyimides[208] and polyurethanes[209], respectively.

A large number of patents (mostly Japanese) has covered the use of $[NP(OPh)_2]_3$ whether or not crosslinked as flame retardant component in various formulations. In addition phenoxytolyloxycyclotriphosphazenes and tetraphosphazenes[210], hexakis(*p*-cumylphenyloxy)cyclotriphosphazene[211], hexakis(*o*-cresoxy)cyclotriphosphazene[212] and hexakis(4-hydroxy-3-methylphenoxy)cyclotriphosphazene[213] have been used as flame retardants. The methylhydroxyphenoxy derivative has also been used in flame retardant formulations in combination with $N_3P_3(OPh)_{5.95}\{OC_6H_4[S(O_2)C_6H_5\text{-}4]\}_{0.05}$.[214] The synthesis of cyclotriphosphazenes containing benzoxazine or naphthoxazine groups in combination with phenoxy groups has been reported.[215] The synthesis of fluorine-containing cyclophosphazenes $N_3P_3F_{6-n}(OAlk)_n$ and

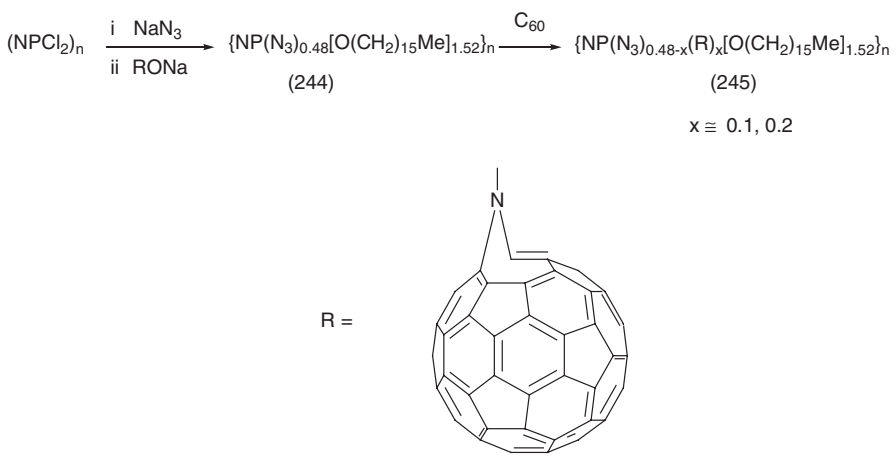
$N_3P_3F_{6-n}(OAr)_n$ and their application as stabilizing agents in $LiPF_6$-containing batteries has been patented.[216] The compound $[NP(OMe)_2]_3$ has also been used as stabilizer in lithium-ion batteries.[217] Cyclotriphosphazenes having phenoxy and UV-absorbing groups have been patented.[218] Immobilization of dendrimers based on a cyclotriphosphazene core has been covered.[219]

4 Polyphosphazenes

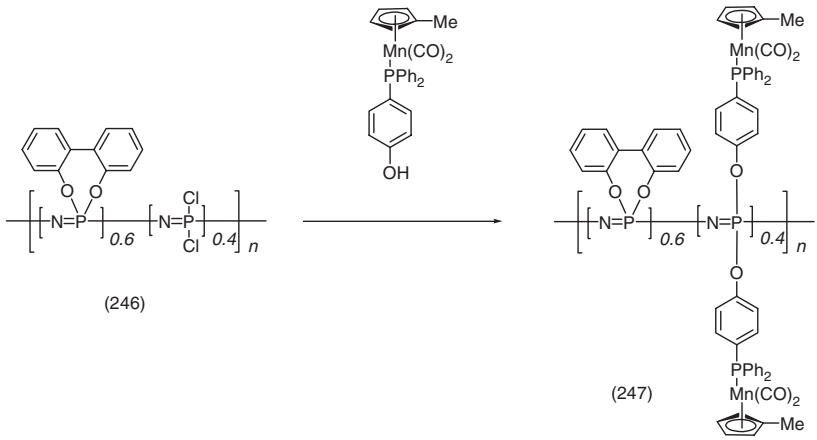
A number of reviews have appeared focused on biomedical applications of polyphosphazenes.[220–225] Other reviews cover membrane separations with polyphosphazenes[226] and fluorine-containing polyphosphazenes.[227]

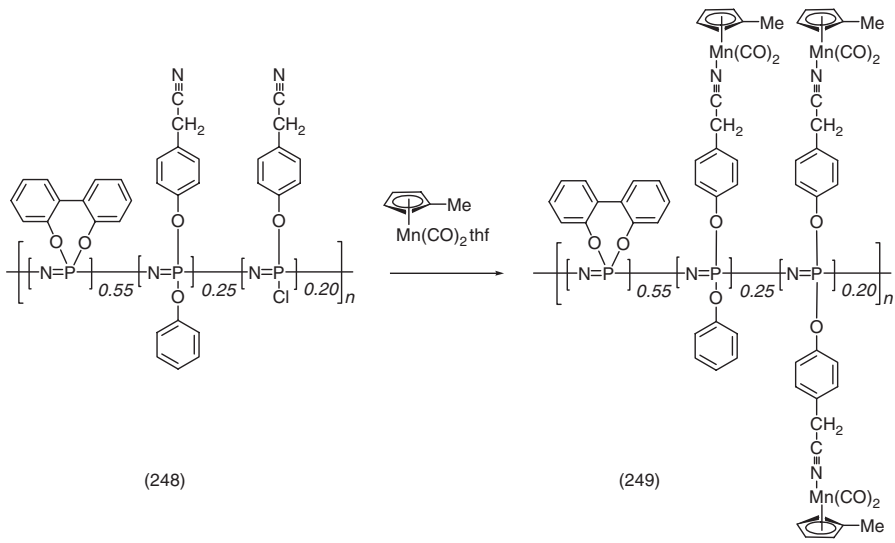
Typical physico-chemical studies describe the relaxation of poled guest-host polyphosphazenes with 4-[(4′-nitrophenyl)azo]phenoxy side groups[228], charge cycling and impedance of a polyphosphazene-based Mn(IV) oxide cathode[229], rheology and relaxation behavior of polydianilinylphosphazene-polyethylene blends[230] and optical properties of carbazolyl-containing polyphosphazenes.[231]

High-molecular weight $(NPCl_2)_n$ has been synthesized on a small-scale from equimolar mixture of PCl_5 and NH_4Cl in refluxing 1,2,4-trichlorobenzene in the presence of sulfamic acid and calcium sulfate dihydrate.[232] Reaction conditions to obtain well-defined samples of $(NPCl_2)_n$ by ring opening polymerization of $(NPCl_2)_3$ have been put forward. Long term stabilization of $(NPCl_2)_n$ solutions has been achieved by using diethylene glycol dimethyl ether as solvent. In this way crosslinking phenomena appear to be fully suppressed.[233] The azido-substituted polymer $\{NP(N_3)_{0.48}[O(CH_2)_{15}Me]_{1.52}\}_n$ (244) has been prepared from $(NPCl_2)_n$ by nucleophilic chlorine-substitution involving NaN_3 and $Me(CH_2)_{15}ONa$. Subsequent reaction of (244) with C_{60} in refluxing chlorobenzene affords the first example of a bucky ball containing polyphosphazene (245). The structure of (245) has been assigned from spectroscopic evidence.[234]



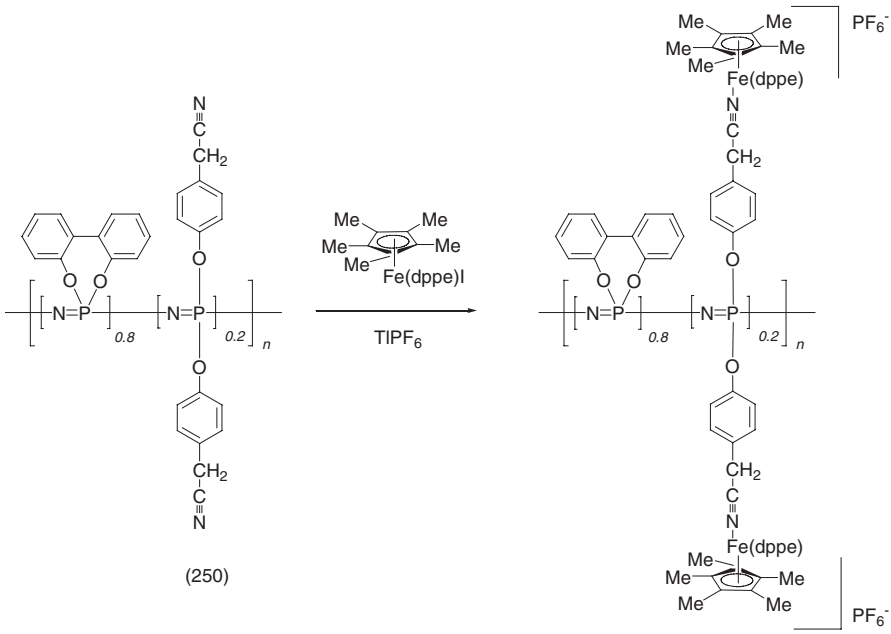
Along with the trimeric phosphine complex (184a), its polymeric counterpart (247) has been synthesized from the 2,2′-dioxybiphenyl polymeric derivative (246) and diphenylphosphine complex {$Mn(CO)_2(\eta^5\text{-}C_5H_4Me)[PPh_2(C_6H_4OH\text{-}4)]$}.[162] The polymeric analogue of (184b), (294), has been reported as well, prepared from (248) and {$Mn(CO)_2(\eta^5\text{-}C_5H_4Me)$thf.[163]





Copolymer (250) and {$Fe(dppe)(\eta^5\text{-}C_5Me_5)I$ [dppe=1,2-bis(diphenylphosphino)ethane] react in the presence of $TlPF_6$ to give an iron-containing

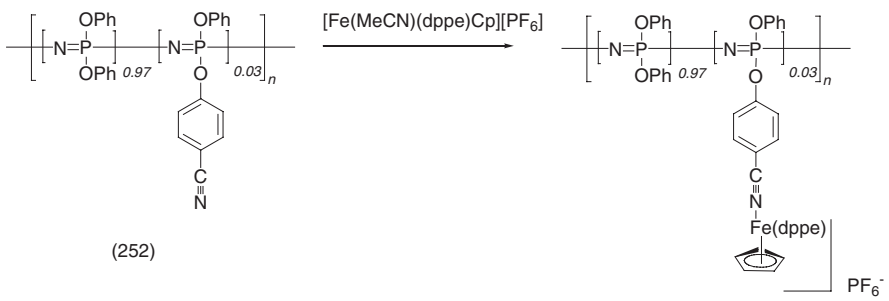
copolymer (251), its structure being comparable to that of (249). The coordination of the iron fragment to the cyanide group has been established by spectroscopic data.[235] Another approach to introduce a cyclopentadienyliron moiety to a polyphosphazene has been given by the reaction of (252) with [Fe(MeCN)(dppe)Cp][PF_6], affording copolymer (253).[236]



(250)

dppe = $Ph_2P-C_2H_2-C_2H_2-PPh_2$

(251)

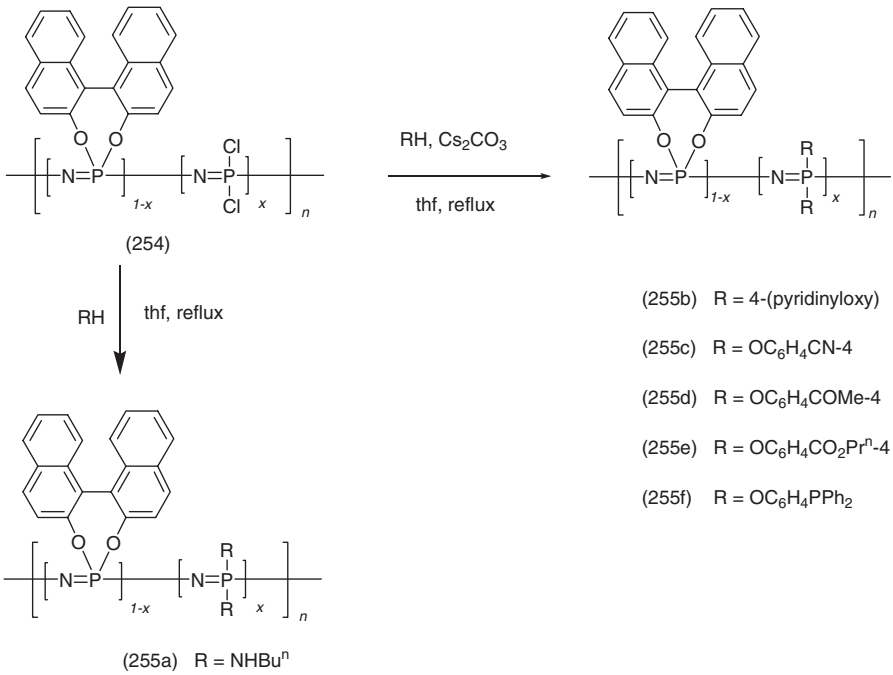


(252)

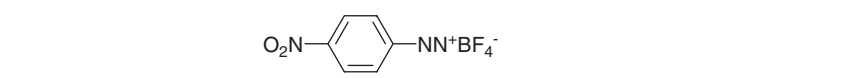
(253)

Copolymers (255a-f) have been obtained by the reaction of $\{(NPCl_2)_x[NP(O_2C_{20}H_{19})]_{1-xn}$ [(254), $O_2C_{20}H_{19}$=1,1′-binaphthyl-2,2′-dioxy] and the appropriate nucleophiles in the presence of Cs_2CO_3 in refluxing thf. High T_g values are observed pointing to rigid polymeric structures. The

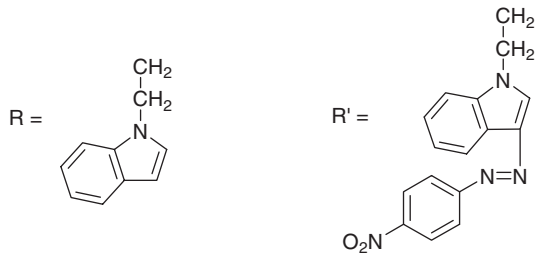
4-diphenylphosphinophenyl derivative is sensitive to oxidation, which leads to copolymers with $OC_6H_4P(O)Ph_2$ in combination with $OC_6H_4PPh_2$ groups.[237]



The indole-substituted polyphosphazene (256), obtained from $(NPCl_2)_n$ by alcoholysis with the sodium salts of (*N*-hydroxyethyl)indole and ethanol, has been reported to react with 4-nitrobenzenediazonium fluoroborate (post azo coupling reaction) in *N*-methylpyrrolidinone yielding copolymer (257). The ratio of side groups has been estimated from spectroscopic evidence. The indole-based chromophores in (257) are responsible for photoconductivity as well as for NLO activity.[238] Similar properties have been found for the copolymer (258), in which the nitrobenzenediazo group is attached to an anilinyl group. The synthesis of (258) proceeds along the route outlined for the preparation of (257), *viz*. nucleophilic substitution reactions to introduce carbazolylhexyloxy, anilinylhexoxy and ethoxy groups to the polymer backbone followed by azo coupling with 4-nitrobenzenediazonium fluoroborate.[239]

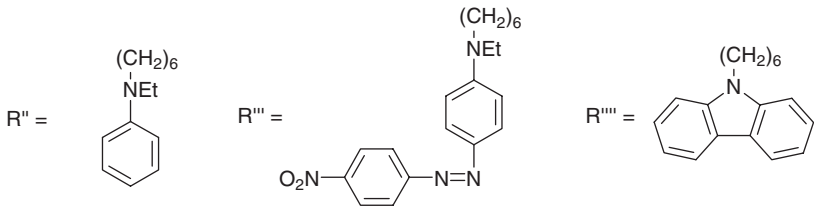


(256) (257)



$[NP(OR'')_{0.11}(OR''')_{0.07}(OR'''')_{0.58}(OEt)_{0.24}]_n$

(258)



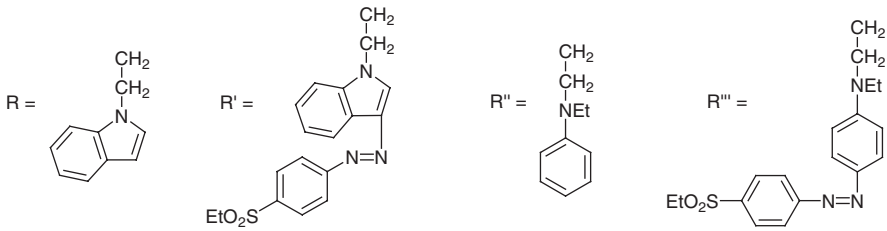
In addition to nitro derivatives, polyphosphazenes with sulfonyl-based chromophores (259) and (260) have been prepared according to a post-azo coupling approach with 4-ethylsulfonylbenzenediazonium fluoroborate. Absorptions of these polymers are blue-shifted compared to the absorptions of the nitro analogues. NLO activities of poled films of (259) and (260) have been determined by second harmonic generation measurements.[240]

$[NP(OR)_{1.14}(OR')_{0.42}(OEt)_{0.44}]_n$

(259)

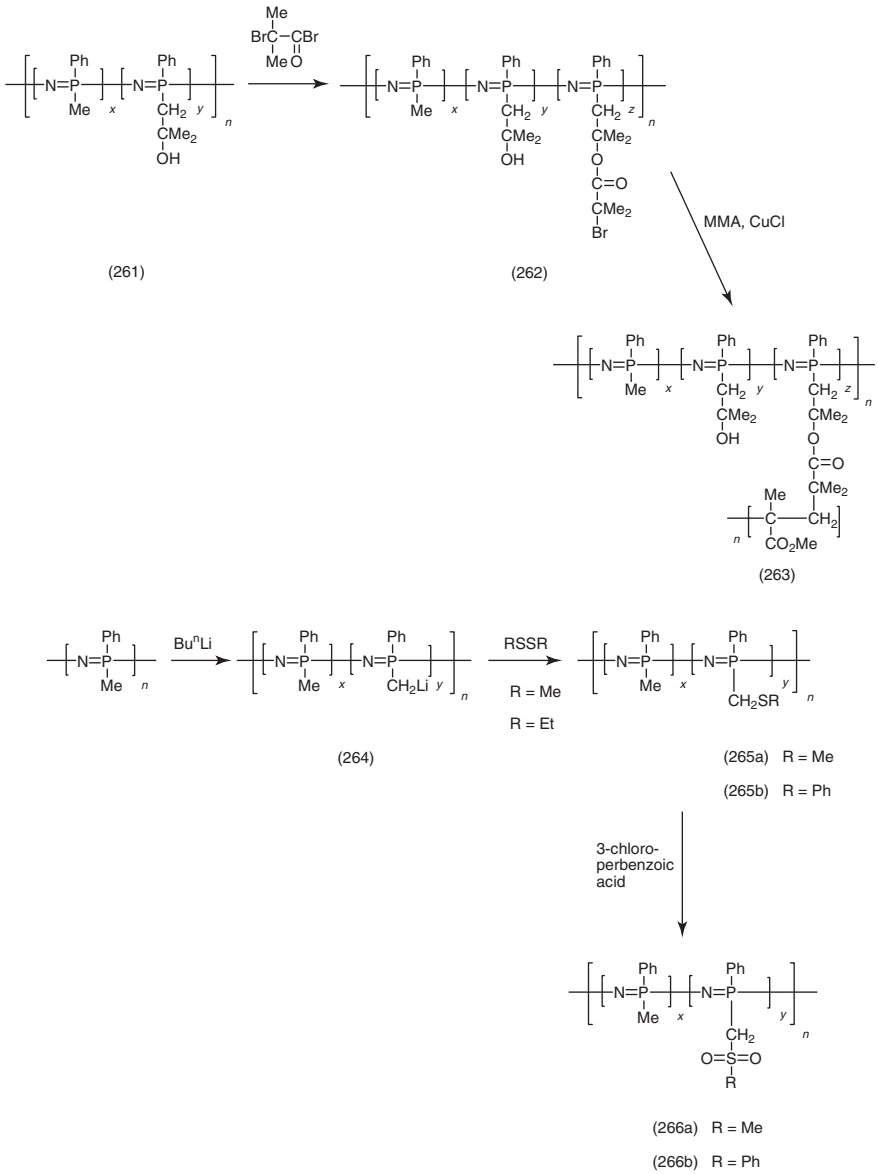
$[NP(OR'')_{1.12}(OR''')_{0.52}(OEt)_{0.36}]_n$

(260)



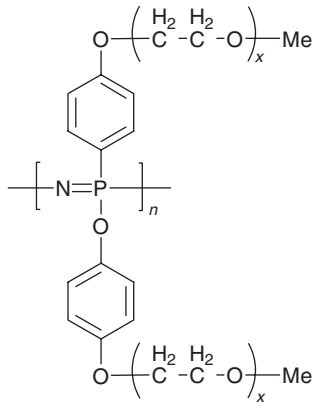
Polymethylethylphosphazene $(NPMePh)_n$ has been used as a starting material for the preparation of new polyorganophosphazenes with a direct P-C coupling. The polymer (261), prepared from $(NPMePh)_n$ by a nucleophilic addition reaction involving acetone, can be converted into polymer (262) by treatment with 2-bromo-2-methylpropionyl bromide. In its turn polymer (262) has been used as starting material for the preparation of graft copolymers (263) by application of Atom Transfer Radical Polymerization (ATRP) with CuCl and methyl methacrylate (MMA).[241] Treatment of $(NPMePh)_n$ with Bu^nLi,

followed by quenching of (264) with Me_2S_2 or Ph_2S_2 yields copolymers (265a–b) with a sulfide side group. These polymers can be transformed to sulfon-substituted polymers (266a–b) upon oxidation with 2-chloroperbenzoic acid.[242]

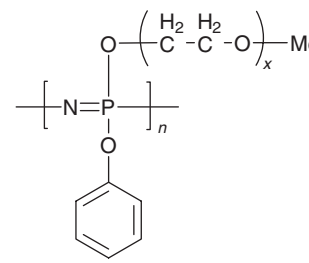


A number of chlorinated and fluorinated alkoxy- and aryloxy-substituted polyphosphazenes has been prepared in order to investigate the influence of the side-group on refractive index and birefringence.[243] New polymers with (4-ethyleneoxy)phenoxy side groups (267) as well as polymers with a combination of phenoxy and ethyleneoxy groups (268) have been prepared aiming at

new solid polymer electrolytes. The presence of phenoxy nuclei increases the glass transition temperatures compared to the values found for ethyleneoxy-substituted polymers without phenoxy groups. This effect renders the polymers more suitable for the construction of solid electrodes. however, the improved mechanical performance has a negative effect on the ionic conductivity.[244]



(267)



x = 2, 3, 7.3

(268)

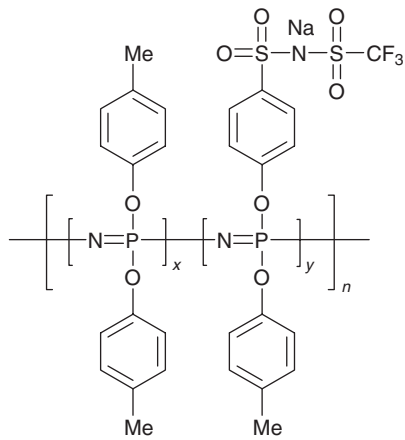
Another method to improve the mechanical stability of the $\{NP[(OCH_2CH_2)_2OMe]_2\}_n$ (MEEP) matrix has been found in the formation of an intercalated MEEP-MoS_2 nanocomposite. The structure of MEEP-MoS_2 can be described as a layer of the polyphosphazene embedded in layers of MoS_2. It is worthy to note that conductivity measurements of MEEP-MoS_2 at room temperature show an enhancement of the conductivity by a factor of 10 compared to that of pristine MoS_2.[245] Addition of α-Al_2O_3 has shown to increase the conductivity of the $LiClO_4$-doped MEEP system. It has been proposed that the Li^+-ion transport occurs not only along the polymer chain, but also *via* interchain migration with the surface of the Al_2O_3 particles as hopping sites.[246] The formulation of the MEEP/$LiClO_4$/α-Al_2O_3 polymer electrolyte has been patented.[247] Conductivity measurements of blends of MEEP and poly(ethylene oxide) doped with lithium salts and Al_2O_3 or TiO_2 have been reported.[248]

^{15}N labeled polyphosphazenes ^{15}N-MEEP and ^{15}N-poly$\{NP[(OC_6H_4Allyl\text{-}2)_{0.12}(OC_6H_4OMe\text{-}4)_{1.02}[(OCH_2CH_2)_2OMe)_{0.86}]\}$ have been synthesized and fully characterized by spectroscopic methods. Spectroscopic studies of the $LiSO_3CF_3$ doped ^{15}N labelled polyphosphazenes clearly show an association of the Li^+-ion with the nitrogen of the polymer backbone. A so-called "pocket" around lithium is created together with chelation by the P-attached oxygens belonging to the MEE ligands. Molecular dynamics simulations of the movement of Li^+-ion in MEEP matrix confirm this picture.[249]

Cyclomatrix phosphazene polymers have been synthesized by curing blends of bis(4-maleimidophenyl) methane with $\{NP[(OC_6H_4CH_2CH{=}CH_2\text{-}2)(OPh)]\}_3$ or blends of bis(4-maleimidophenyl) methane with a combination of

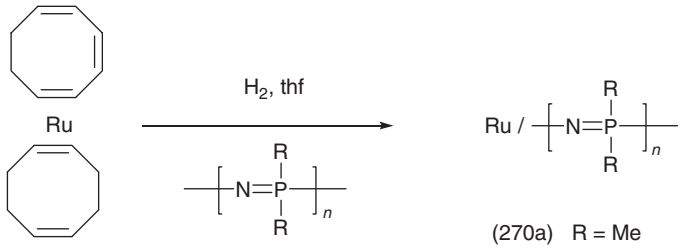
$\{NP[(OC_6H_4CH_2CH{=}CH_2\text{-}2)(OPh)]\}_3$ and tris(2-allylphenoxy)-1,3,5-triazine, affording two-[250] and three-component[251] resins, respectively. A rheological analysis has been carried out on the curing of the three-component blend.[252]

Examination of the properties of the sulfonimide-substituted polyphosphazene (269) has continued. The sulfonimide content appears to govern properties as ion-exchange capacity and water uptake to a large extent.[253] Crosslinked (269) has been applied to the construction of membranes in proton exchange H_2/O_2 fuel cells. Results are fully comparable to those obtained with the commercially available Nafion membranes.[254]



(269)

The performance of sulfonated and phosphonated poly(aryloxy)phosphazenes membranes in methanol fuel cells has proven to exceed that of Nafion membranes, showing a lower methanol permeability.[255] The introduction of $OC_6H_4SO_3H$ substituents at the NP polymer backbone has been achieved by a new, so-called non-covalent protection method, using the sodium salt of 4-hydroxybenzenesulfonic acid with dimethyldipalmitylammonium counter ions for the reaction with $(NPCl_2)_n$.[256,257] The application of the resulting polymers as membranes in fuel cells has been covered.[257] Polymers with $OC_6H_4OC(O)N(H)(CH_2)_3Si(OEt)_3$ side groups have proven to be suitable sol-gel precursors to form phosphazene-SiO networks by acid hydrolysis.[258] Ruthenium nanoparticles supported on organo-substituted polyphosphazenes have been prepared by the reduction of the complex $Ru(\eta^6\text{-cot})(\eta^4\text{-cod})$ by hydrogen in the presence of a polyphosphazene (cot = cycloocta-1,3,5-triene, cod = cycloocta-1,5-diene). The $Ru\text{-}(NPMe_2)_n$ assembly (270a) appears to be a suitable catalyst both in homogeneous and heterogeneous reaction media for the hydrogenation of a wide range of unsaturated organic compounds. The stability of the catalyst has been demonstrated by electron microscopy. The catalytic activity of the Ru-polybis(aryloxy)phosphazenes (270b–e) depends on the structure of the aryloxy substituent, but is in all cases lower than that of $Ru\text{-}(NPMe_2)_n$.[259]



(270a) R = Me

(270b) R = OC_6H_5

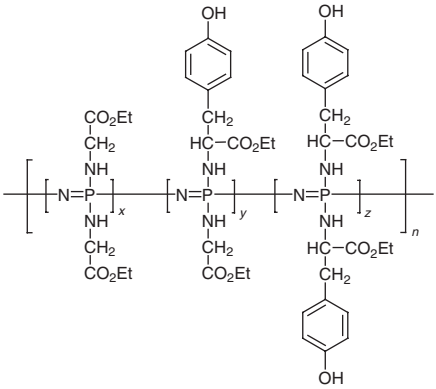
(270c) R = OC_6H_4OMe-4

(270d) R = OC_6H_4OMe-3

(270e) R = $OC_6H_4[C(O)C_6H_5$-4]

Membranes of ruthenium-doped polydimethylphosphazene before and after hydrogenation have been studied by a combination of physical and spectroscopic methods. The results obtained point to conformation changes of the polymer caused by the dopant.[260]

As already reflected by the number of review papers, the interest in biomedical applications of polyphosphazenes continues to grow. The biodegradable polymer $\{NP(NHC_6H_4CO_2H\text{-}4)_{1.8}(NHC_6H_4CO_2H\text{-}4)_{0.2}\}_n$ has been prepared and fully characterized. The carboxylato groups can react with Ca^{2+}-ions to form crosslinks and to convert the water-soluble polymer to a hydrogel.[261] Controlled drug release experiments have been carried out for chitosan entrapped in coatings of this Ca^{2+}-polyphosphazene hydrogel.[262] Polymer $\{NP(NHCH_2CO_2Et)_{0.6}[N(CH_2CH_2Cl)_2]_{1.4}\}_n$ did not possess anti-tumour activity.[263] Synthesis, *in vitro* degradation and cytotoxicity of $\{NP[NH(CH_2)_3CO_2Et]_2\}_n$ have been reported.[264] The biodegradable polyphosphazenes $\{NP[NHCH_2)_2NMe_2]_2\}_n$ and $\{NP[OCH_2)_2NMe_2]_2\}_n$ have been shown to be suitable as carriers for gene delivery.[265] Blends of $[NP(NHCH_2CO_2Et)_x(OC_6H_4Me\text{-}4)_{2-x}]_n$ and poly(lactide-*co*-glycolide) have been used to produce a biodegradable auricular prosthetic device.[266] Two groups of L-tyrosine-functionalized polyphosphazenes have been prepared, one in which the tyrosine is linked to the polymer chain by the amino nitrogen (271), the other where linkage occurs *via* the phenoxy group (272a–c). Unlike the latter polymers (272a–c), the *N*-linked tyrosine polymer (271) is sensitive to hydrolysis. The rate depends on the ratio of the substituents, polymers with the highest glycine ester content being the most affected. Both (272a) and (272b) form hydrogels upon addition of Ca^{2+}-ions. Polymers (272b) with a tyrosine content larger than 55 % show a pH-dependent solubility in water, *viz*. soluble in water at pH 2–3 and at pH 5–12, but are insoluble at pH 3–4.This indicates the presence of a zwitterionic form. Polymers (272a) are soluble in the pH range 2–12, whereas polymers (272c) are insoluble.[267]



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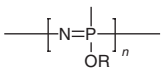
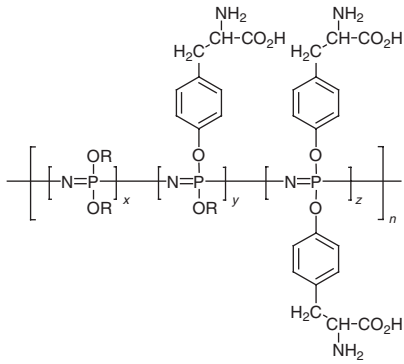


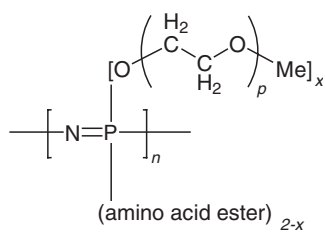


(272a) R = $(CH_2CH_2O)_2Me$

(272b) R = Pr^n

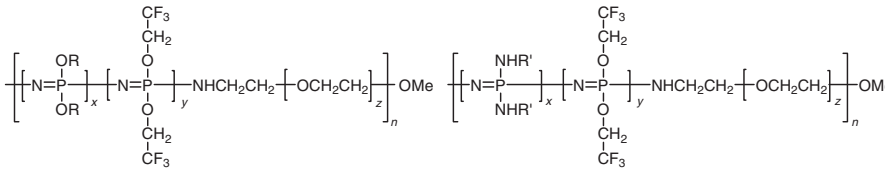
(272c) R = CH_2CF_3

The fluorine-containing polyphosphazene $[NP(OCH_2CF_3)_2]_n$ acting as matrix material for pharmacological agents, has been applied to the fabrication of implants.[268] It has been suggested that the selective adsorption of albumin might be responsible for the suppression of platelet adhesion on $[NP(OCH_2CF_3)_2]_n$ surfaces in blood plasma.[269] Blends of acrylic acid or 2-hydroxymethyl methacrylate with $\{NP(NHCH_2CO_2Et)_x[(NP(OCH_2CH_2O-C(O)C(Me) = CH_2]_{2-x}\}_n$ have been polymerized with AIBN as radical initiator. The resultant crosslinked polymers exhibit improved mechanical properties. The methacrylate-crosslinked polymer is more stable towards hydrolysis than the acrylic acid analogue.[270] It has been shown that the lower critical solution temperature (LCST) of aqueous solutions of polymers with methoxy poly(ethylene glycol) and amino acid ester substituents (273) decreases by the addition of aqueous saccharide solutions with an exception for saccharide acids. The reduction has been discussed in terms of the ability of the saccharide to form intramolecular hydrogen bonds and is almost independent of the polymer substituents.[271]



(273)

Poly(ethylene oxide)-*block*-poly(organophosphazene) copolymers (274a–c) and (275a–b) have been prepared by controlled cationic polymerization of phosphoranimines. The self-aggregation process of (274a) in aqueous solution as a function of the temperature has been studied.[272]



(274a) R =$(CH_2CH_2O)_2Me$

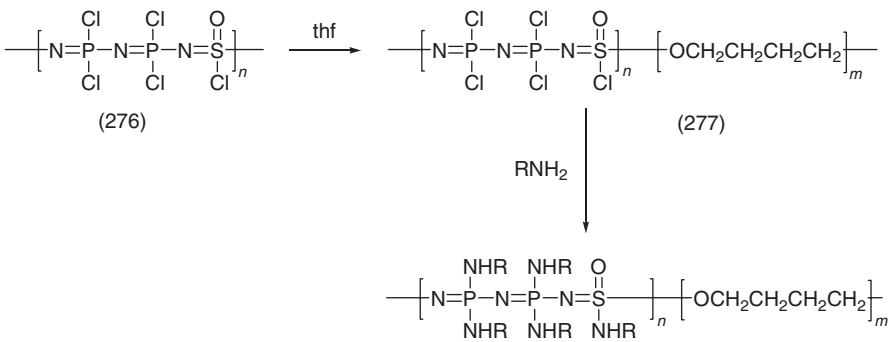
(274b) R = CH_2CF_3

(274c) R = Ph

(275a) R' = CH_2CO_2Et

(275b) R' = $CH(Ph)CO_2Et$

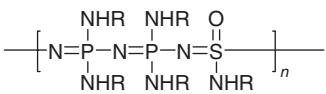
Poly(thionyldiphosphazene-*block*-tetrahydrofuran) polymers (277) have been prepared by dissolving polythionyldiphosphazene (276) in thf at low temperature. The length of the organic chain can be qualitatively controlled by the exposure time of (276) to thf. Subsequent reaction with methylamine or *n*-butylamine yields the block copolymers (278a–b). Phosphorescent oxygen sensor coatings have been prepared by spray coating solvent mixtures of (278b) with phosphorescent dye agents.[273] The oxygen quenching process for a number of phosphorescent dyes embedded in the polymer matrix of (279) has been investigated.[274]



(276) (277)

(278a) R = Me

(278b) R = Bu^n



R = Bu^n

(279)

Flame retardant resins have been prepared using the condensation product of $[NP(OPh)_x(OC_6H_4OH\text{-}4)_{2-x}]_n$ and formaldehyde as starting material.[275] The

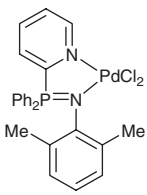
fluorine-containing polymer $\{(NP(OCH_2CF_3)_x[OCH_2(CF_2)_nCF_2H]_{2-x}\}_n$ has been applied in a flame retardant formulation.[276] The fire behavior and flammability of a number of polyphosphazenes with phenoxy or 4-substituted phenoxy side groups have been investigated and compared to properties of an aircraft polyurethane foam. A striking difference is the much lower peak heat release of the polyphosphazenes.[277] Nanofibers of polydiphenoxyphosphazene have been prepared by electrospinning.[278] Their possible applications, when doped with rare-earth nitrates, have been described.[279]

5 Crystal Structures of Phosphazenes and Related Compounds

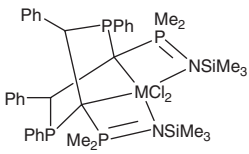
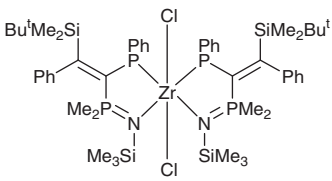
The following compounds have been examined by diffraction methods. Distances are given in picometers and angles in degrees. Standard deviations are given in parentheses. Endo (exo) means endo (exo) cyclic.

Compound	Comments	Ref.
20	NP 157.3(1), 158.1(2) ∠PNP 134.7(1)	25
21 (cation)	NP 153.7(2), 159.5(2) ∠PNP 137.7(1)	25
$Bu^tPh_2SiN{=}P(Me_2)OPh$	NP 151.2(6)	51
RNP(Ph)N(R)P(Ph)=NR	NP (endo) 168.9(7) – 176.5(6)	51
$R = Bu^tPh_2Si$	NP (exo) 151.4(7) ∠NPN (endo) 84.0(3), 87.0(3) ∠PNP (endo) 94.0(3), 95.0(3)	
47	$NP(cl_2)$ 149.0(3)	53
$Cp'TiCl_2(NPR_3)$ $Cp' = Cp$, R = Cy (cyclohexyl)	NP 160.6(2)	60
$Cp'TiCl_2(NPR_3)$ $Cp' = Cp$, $R = Pr^i$	two independent mols. in unit cell mean NP 161.1(3)	60
$Cp'TiCl_2(NPR_3)$ $Cp' = Cp$, $R = Bu^t$	NP 159(1)	60
$Cp'TiCl_2(NPR_3)$ $Cp' = C_5Me_5$, $R = Pr^i$	NP 160.8(4)	60
$Cp'TiCl_2(NPR_3)$ $Cp' = C_5Me_5$, $R = Bu^t$	NP 159.5(3)	60
$Cp'TiCl_2(NPR_3)$ Cp′ = indenyl, $R = Pr^i$	mean NP 160.6(6)	60
$Cp'TiCl_2(NPR_3)$ $Cp' = C_5H_4Bu^t$, $R = Bu^t$	NP 161.2(2)	60
$Cp'TiCl_2(NPR_3)$ $Cp' = C_5H_4Bu^n$, $R = Bu^t$	NP 160.3(2)	60

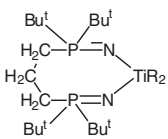
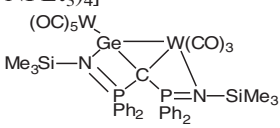
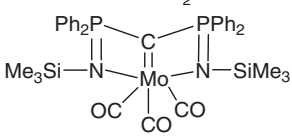
(*continued*)

Compound	Comments	Ref.
$Cp'TiPh_2(NPR_3)$ $Cp' = Cp$, $R = Bu^t$	NP 160.2(4)	60
$Cp'Ti(CH_2SiMe_3)_2(NPR_3)$ $Cp' = Cp$, $R = Ph$	NP 158.1(2)	60
$Cp'TiCl(OC_6H_3Pr^i_2\text{-}2,6)(NPR_3)$ $Cp' = Cp$, $R = Bu^t$	mean NP 158.3(7)	60
53	NP 159.6(3)	61
60b	mean NP 157.4(5) ∠PNP 133.7(3)	63
62b	mean NP 155.1(4) ∠PNP 147.7(3)	63
65b.CH_2Cl_2	mean NP 158.4(5) ∠PNP 128.6(3)	63
73	NP 161.4(2)	65
74	NP 161.1(3)	65
75	NP 162.0(3)	65
77b	NP 159.5(6)	66
77c	NP 159.2(3)	66
78a	NP 159.7(3)	66
	NP 159.0(3)	66
2-($Me_3SiN{=}PPh_2$)C_5NH_4.$PdCl_2$	two independent mols. in unit cell mean NP 158.0(2)	67
80a R = benzyl (Bn), R′ = Me	NP 160.8(6)	67
80a $R = SiMe_3$, R′ = Me	NP 160.0(2)	67
80a R = Ph, $R' = Pr^i$	NP 160.2(3)	67
80b R = Bn, $R' = Pr^i$	NP 161.3(7)	67
80b.Ch_2Cl_2 $R = SiMe_3$, R′ = Me	NP 158.6(9)	67
82a.$2CH_2Cl_2$ R = R″ = Ph, $R' = Pr^i$	NP 160.0(3)	67
82a R = H, $R'' = Bu^t$, $R' = Pr^i$	NP 159.8(2)	67
84b R = H	NP 160.1(2)	67
84c R = H	NP 161.5(5)	67
84c R = Me	NP 160.9(3)	67
84c.H_2O R = Ph	two independent mols. in unit cell mean NP 159(1)	67
90.$0.5CH_2Cl_2$, $R = C_6H_4OMe\text{-}4$, R′ = R″ = Et	NP 161.0(4)	68
91.$10CH_2Cl_2$, R = R′ = $C_6H_4OMe\text{-}4$, $R'' = Pr^n$	NP 159.6(5) – 162.3(4)	68
92.$2CH_2Cl_2$, $R = Ch_2CN$	NP 160.8(3)	68

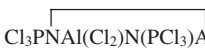
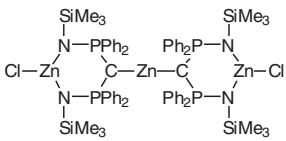
(*continued*)

Compound	Comments	Ref.
95	NP 157.6(4)	69
96a.CH_2Cl_2	mean NP 160.8(3)	69
97a	NP 160.7(3)	69
100	NP 157.0(7)	69
101	NP 163.2(2)	69
$(C_6H_3Me_2\text{-}2,6)N{=}PPh_3$	NP 155.3(2)	70
103a	NP 161.0(2)	70
103b	NP 161.3(2)	70
103c.thf	NP 161.6(3)	70
103d	NP 160.5(2)	70
104	NP 162.8(5)	70
105	NP 160.3(5), 161.7(5)	70
107b	NP 157.5(2)	70
108b	NP 161.9(2)	70
 M = Zr M = Hf	M = Zr	NP 157.6(8) – 161.6(8) 71
	M = Hf	NP 160.7(3)
	NP 161.9(4), 163.2(4)	71
110	mean NP 157.4(2)	72
111	mean NP 163.9(3)	72
113	NP 157.4(5), 164.2(4)	72
114a	NP 155.2(5), 164.5(4)	72
114b	NP 153.1(2), 165.5(2)	72
114c	NP 156.0(3), 166.4(3)	72
$NiCl_2\{CH_2[P(Ph_2){=}NSiMe_3\text{-}N]_2\}$	NP 159.1(2)	74
$NiI_2\{CH_2[P(Ph_2){=}NSiMe_3\text{-}N][P(Ph_2){=}NH\text{-}N]\}$	N(Si)P 160(1), N(H)P 160.3(9)	74
$\{Ni\{CH_2[P(Ph)_2{=}NH\text{-}N,P]_2\}_2\}^{2+}$	mean NP 159.9(1)	74
$[MeP(Ph_2){=}N{=}P(Ph_2)NH_2]^+$	mean NP 157.4(2), $N(H_2)P$ 163.3(2) ∠ $N(H_2)PN$ 121.4(1) ∠ PNP 142.9(1)	74
116.thf	mean NP 159.9(3)	75
117.0.5toluene	mean NP 160.0(3)	75
118.2.5CH_2Cl_2	mean NP 159(3)	76
120	mean NP 163.4(2)	77
121a	NP 160.9(2), 161.8(2)	77

(*continued*)

Compound	Comments	Ref.
121b	NP 162.0(3), 163.2(3)	77
121c	mean NP 161.7(2)	77
122	NP 160.3(2), 161.4(2)	77
124	NP 158.4(3), 159.8(3)	75
125.0.5CH_2Cl_2	NP 157(1), 160(1)	75
126a	two independent mols. in unit cell mean NP 159.9(2) ∠PNP 126.5(3), 127.7(3)	81
126b.$CHCl_3$	mean NP 159.9(4) ∠PNP 131.6(3)	81
128	NP(O) 158.6(5), NP 163.7(6) ∠PNP 114.1(3)	81
{PhHg[$Ph_2P(S)NP(O)Me_2$]}$_2$	NP 158.7(4), 161.0(4) ∠PNP 131.1(3)	82
{PhHg[$Ph_2P(S)NP(O)Ph_2$]}$_2$	NP 157.4(5), 160.2(6) ∠PNP 134.7(4)	82
130	NP 162(2), 163.0(2)	83
131	NP 156.2(7), 160.6(7)	83
132	NP 153.7(4), 162.0(4)	83
133	mean NP 161.3(7)	83
$Cl_2P(O)N{=}P(Me)(Ph)OCH_2CF_3$	NP(O) 155(1), NP(Me) 160(1) ∠PNP 137(1)	88
	R = Me: NP 156.9(2), 158.9(3) R = Bn: mean NP 158.6(2)	113
{$Cl_3(\mu$-Cl)Ta[$N{=}P(Cl_2)N(SiMe_3)_2$]}$_2$	NP 157.8(4), 160.0(4)	114
[$(IN{=}PEt_3)$]$^+$	NP 162(2)	115
[$BrMn_4(CH{=}Cme_2)_3(\mu_3$-$NPEt_3)_4$]	mean NP 158.3(2)	116
	NP 160.3(4), 162.6(4)	117
	NP 157.9(2), 158.2(2)	117
 $Cl_2BN(L)B(Cl_2)NL$	NP 153.5(3) – 157.7(3)	118
L = $PCl_2N{=}PCl_3$	∠NPN 111.5(1), ∠PNP 138.7(2)	
$(Br_2BN{=}PCl_3)_2$	NP 155.1 (5)	118

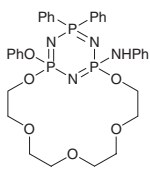
(*continued*)

Compound	Comments	Ref.
$Li[CHMeP(Ph_2)=NCO_2Me]_2.(thf)_2$	NP 163.4(2)	119
$Ph(Morph)(Cy_2N)P=N\text{-}S_3N_3$	mean NP 164.2(2)	120
$Ph_2(C_6H_{12}N)P=N\text{-}S_3N_3.C_7H_8$ C_7H_8 = norbornadiene	N(S)P 158.6(3), N(C_2)P 164.9(3)	121
$[Ph_3P=N=PPh_3]^+$	two independent PNP units mean NP 158.4(3) ∠PNP 138.0(2), 140.3(2)	122
$[Ph_3P=N=PPh_3]^+$	NP 151.9(3), 158.4(3) ∠PNP 136.3(2)	123
$[Ph_3P=N=PPh_3]^+$	NP 157.4(2), 158.4(2) ∠PNP 139.2(1)	124
$[Ph_3P=N=PPh_3]^+$	X-ray diffraction. mean NP 157.3(5) ∠PNP 145.1(4) neutron diffraction NP 156.1(9), 160.5(9) ∠PNP 140.0(5)	125
	NP 153.1(3)	126
$Me_3SiN=PCl_3.AlCl_3$	NP 160.6(6)	127
	mean NP 162.3(2)	128
$OP(Ph_2)N(Me)N=CHFc$	NP 168.0(3)	153
$N_3P_3(NHBu^t)_6$	two independent mols. in unit cell NP(endo) 156.3(4) – 158.5(4) NP(exo) 162.5(4) – 166.4(4) ∠NPN (endo) 115.1(2) – 116.4(2) mean ∠NPN (exo) 101.7(1) ∠PNP 120.2(2) – 123.4(2)	136
$N_3P_3(NHCy)_6$	NP(endo) 159.3(4) – 160.9(4) NP(exo) 164.0(5) – 166.2(5) mean ∠NPN (endo) 116.3(1) ∠NPN (exo) 99.6(2) – 102.0(3) mean ∠PNP 123.6(2)	136
$N_3P_3(NHPr^i)_6$	NP(endo) 159.2(2) – 160.1(2) NP(exo) 162.9(3) – 167.0(3) ∠NPN (endo) 115.3(1) – 116.4(1) ∠NPN (exo) 98.2(1) – 105.7(2) ∠PNP 121.9(2) – 124.0(2)	136

(*continued*)

Compound	Comments	Ref.
$N_3P_3(NHCH_2CH_2C_6H_5)_6$.thf	NP(endo) 159.3(2) – 160.8(1) NP(exo) 163.9(2) – 166.9(2) ∠NPN (endo) 115.0(1) – 116.8(1) ∠NPN (exo) 98.0(1) – 104.8(1) ∠PNP 118.4(1) – 125.0(1)	136
$N_3P_3(NHC_6H_5)_6$	NP(endo) 158.2(3) – 160.2(2) mean NP(exo) 165.6(2) ∠NPN (endo) 114.7(2), 116.6(2) ∠NPN (exo) 95.1(3), 101.5(2) ∠PNP 122.4(3), 124.8(2)	136
$N_3P_3(NHC_6H_4Me\text{-}4)_6$	mean NP(endo) 159.9(3) NP(exo) 162.7(6) – 167.6(6) ∠NPN (endo) 114.0(3) – 116.8(3) ∠NPN (exo) 95.6(3) – 103.9(3) ∠PNP 121.9(4) – 125.5(4)	136
$N_3P_3(NHPr^n)_6$	two independent mols. in unit cell NP(endo) 158.6(4) – 161.2(3) NP(exo) 162.2(4) – 165.6(4) ∠NPN (endo) 115.0(2) – 117.1(2) ∠NPN (exo) 99.5(2) – 104.7(2) ∠PNP 121.1(2) – 124.2(2)	136
$N_3P_3(NCH_2C{\equiv}CH)_6$	mean NP(endo) 159.9(1) NP(exo) 163.5(2) – 165.5(2) ∠NPN (endo) 114.4(1) – 115.5(1) ∠NPN (exo) 98.4(1) – 101.7(1) ∠PNP 122.2(1) – 125.4(1)	136
$N_4P_4(OC_5NH_3Me\text{-}4)_8.2CH_2Cl_2$	NP 154.2(1) – 156.6(1) ∠NPN 123.3(1), 124.7(1) ∠PNP 134.1(1), 146.0(1)	140
$N_4P_4(OC_5NH_3Me\text{-}4)_8.H_2O$	NP 155.2(2) – 156.5(2) ∠NPN 122.6(1) – 123.8(1) ∠PNP 141.1(1) – 143.8(1)	140
$N_4P_4(OC_5NH_4)_8$	NP 155.4(1) – 156.2(1) ∠NPN 123.5(1), 125.4(1) ∠PNP 138.7(1), 141.1(1)	140
142a	NP 157.0(2) – 161.1(2) ∠NPN 115.4(1) – 119.9(1) ∠PNP 119.9(1) – 122.1(1)	141

(*continued*)

Compound	Comments	Ref.
142b	NP 156.5(2) – 160.5(2) mean ∠NPN 117.4(1) ∠PNP 121.8(1) – 122.8(1)	141
142c	two independent mols. in unit cell NP 156.9(3) – 160.6(3) ∠NPN 116.8(2) – 118.5(2) ∠PNP 120.4 (2) – 122.9(2)	141
142d	NP(endo) 157.4(2) – 160.3(2) ∠NPN 116.8(1) – 117.3(1) ∠PNP 120.9(1) – 123.0(1)	141
142e.H_2O	NP(endo) 159.2(2) – 160.2(2) mean NP(exo) 164.3(2) ∠NPN 116.2(1) – 117.3(1) ∠PNP 119.8(1) – 121.0(1)	141
142f	NP(endo) 158.9(2) – 159.9(2) NP(exo) 163.4(2), 164.7(2) mean ∠NPN 117.1(6) ∠PNP 121.2(1) – 123.6(1)	141
	NP(endo) 158.0(2) – 161.2(2) NP(exo) 164.7(2) ∠NPN 116.6(1) – 118.3(1) ∠PNP 121.7(1) – 122.5(1)	143
143b (meso)	NP(endo) 155.8(3) – 163.4(4) NP(exo) 163.2(4) – 166.6(4) ∠NPN(endo) 113.8(2) – 122.1(2) mean ∠N(C)PN(C) 105.1(1) ∠PNP 119.2(2) – 124.4(2)	143
143b (racemate)	NP(endo) 153.8(4) – 163.4(4) NP(exo) 163.2(4) – 175.4(6) ∠NPN(endo) 112.6(2) – 122.4(3) mean ∠N(C)PN(C) 105.1(3) ∠PNP 118.1(2) – 123.1(3)	143
143c (meso)	NP(endo) 154.6(4) – 162.5(4) NP(exo) 162.6(4), 165.9(4) ∠NPN(endo) 114.5(2) – 120.3(2) ∠N(C)PN(C) 105.6(2) ∠PNP 119.9(2) – 123.4(2)	143
148a	NP(endo) 155.2(5) – 161.2(5) NP(exo) 162.5(5) – 169.2(4) ∠NPN(endo) 115.8(3) – 117.9(3) ∠N(H)PN(H) 100.0(3) – 103.0(3) mean ∠PNP 120.4(2)	148

(*continued*)

Compound	Comments	Ref.
148b	NP(endo) 158.6(2) – 159.8(2) NP(exo) 163.9(3) – 165.6(3) ∠NPN(endo) 115.5(1) – 117.2(1) ∠N(H)PN(H) 101.5(1) – 102.7(1) ∠PNP 119.4(1) – 121.3(1)	148
148c	NP(endo) 158.8(5) – 160.5(5) NP(exo) 164.8(6) – 166.8(5) ∠NPN(endo) 116.2(2) – 117.7(2) mean ∠N(H)PN(H) 101.8(2) ∠PNP 119.2(3) – 121.3(3)	148
149a.0.5C_6H_{14}	NP(endo) 160.1(6) – 163.6(5) NP(exo) 159.0.(6) – 161.4(5) N(H)P (exo) 169.7(6) – 171.7(6) ∠NPN(endo) 115.0(3) – 116.1(3) ∠N(H)PN(C) 111.1(3) – 112.3(3) ∠PNP 117.9(3) – 119.7(3)	148
149b.0.5C_6H_{14}.2thf	mean NP(endo) 161.5(3) mean NP(exo) 159.9.(4) mean N(H)P (exo) 169.8(4) mean ∠NPN(endo) 115.2(3) mean ∠N(H)PN(C) 111.8(2) mean ∠PNP 119.1(4)	148
149c.4thf	NP(endo) 160.8(3) – 162.2(3) mean NP(exo) 159.9.(2) mean N(H)P (exo) 170.5(2) mean ∠NPN(endo) 115.2(1) ∠N(H)PN(C) 110.7(2) – 112.8(2) ∠PNP 118.7(2) – 121.3(2)	148
150.2thf	NP(endo) 160.5(3) – 162.2(3) mean N(Al)P 166.3(3) mean NP(Ph) 159.4(2) mean N(H, Ph)P (exo) 170.7(4) ∠NPN(endo) 113.3(2) – 114.2(2) ∠N(Al)PN(Al) 89.8(2) ∠N(H)PN(C) 111.0(2), 111.8(2) ∠PNP(endo) 118.5(2) – 125.6(2)	149

(*continued*)

Compound	Comments	Ref.
151	NP(endo) 159.4(2) – 161.7(2) NP(exo) 163.5(3) – 165.7(3) ∠NPN(endo) 113.9(1) – 115.4(1) ∠N(R)PN(R)(exo) 99.9(1) – 104.9(1) ∠PNP(endo) 124.0(1) – 124.8(1)	150
152f	mean NP(endo) 156.0(2) N(H)P(endo) 162.7(3) – 166.2(3) NP(exo) 158.9(3) – 162.4(3) ∠NPN(endo) 104.9(2) – 110.4(2) ∠N(R)PN(R)(exo) 105.9(2) – 107.8(2) ∠PNP(endo) 129.1(2) – 130.1(2)	150
$[N_3P_3(NHR)_6]_2(AgClO_4)_3$, R = Pr^n	NP(endo) 160.9(3) – 163.6(3) NP(exo) 161.2(3) – 164.0(4) ∠NPN(endo) 109.6(2) – 112.7(2) ∠N(H)PN(H)(exo) 102.4(2) – 109.0(2) ∠PNP 122.6(2) – 128.3(2)	151
$[N_3P_3(NHR)_6](AgNO_4)_2$, R = Pr^n	two independent mols. in unit cell NP(endo) 160(1) – 163.3(9) NP(exo) 157(1) – 168(1) mean ∠NPN(endo) 110.1(2) ∠N(H)PN(H)(exo) 100.7(6) – 105.0(6) mean ∠PNP 127.6(3)	151
$[N_3P_3(NHR)_6]$ $(AgClO_4)$, R = Cy	NP(endo) 157.9(7) – 166.3(7) NP(exo) 161.0(7) – 165.4(7) mean ∠NPN(endo) 112.4(2) ∠N(H)PN(H)(exo) 101.5(3) – 106.0(4) ∠PNP 124.3(4) – 128.6(4)	151
$[N_3P_3(NHR)_6](AgClO_4)_2$, R = Bn	NP(endo) 161.1(3) – 162.4(3) NP(exo) 161.0(4) – 163.2(4) ∠NPN(endo) 109.9(2) – 112.1(2)	151

(*continued*)

Compound	Comments	Ref.
	∠N(H)PN(H)(exo) 100.5(2) – 104.4(2) mean ∠PNP 125.0(2)	
$[N_3P_3(NHR)_6](AgNO_3)_2$, R = Bn	mean NP(endo) 161.6(1) NP(exo) 160.6(4) – 163.4(3) ∠NPN(endo) 110.7(2) – 111.4(2) ∠N(H)PN(H)(exo) 101.1(2) – 105.5(2) ∠PNP 123.9(2) – 125.3(2)	151
$[N_3P_3(NHR)_6](AgNO_3)(AgClO_4)$, R = Bn	NP(endo) 161.6(2) – 162.6(2) NP(exo) 161.6(2) – 164.4(3) ∠NPN(endo) 109.9(1) – 111.8(1) ∠N(H)PN(H)(exo) 100.5(1) – 105.1(1) ∠PNP 123.4(1) – 125.1(1)	151
$[N_3P_3(NHR)_6](AgClO_4)$, R = Pyr	NP(endo) 158.3(3) – 163.1(2) NP(exo) 162.0(3) – 164.5(3) ∠NPN(endo) 111.5(2) – 113.2(2) ∠N(H)PN(H)(exo) 104.1(1) – 105.6(1) ∠PNP 122.3(2) – 123.9(2)	151
153	NP(endo) 160.0(1) – 160.9(1) NP(exo) 166.2(1) – 168.8(1) mean ∠NPN(endo) 117.3(3) ∠N(Me)PN(Me)(exo) 100.5(6) – 106.3(6) mean ∠PNP 121.8(4)	152
158	mean NP(endo) 158.1(6) mean NP(exo) 166.8(4) mean ∠NPN(endo) 118.3(6) ∠N(Me)PN(Me)(exo) 105.2(3), 108.3(3) ∠PNP 119.7(7), 122.1(5)	153
160	NP(endo) 156.4(6) – 161.2(6) NP(exo) 167.1(5) – 180.8(5) ∠NP(N,N)N(endo) 117.1(3), 119.1(4) ∠NP(C,C)N(endo) 116.6(3) ∠N(Me)PN(Me)(exo) 102.9(3), 105.2(3) ∠PNP 116.6(4) – 119.1(3)	153

(*continued*)

Compound	Comments	Ref.
161	NP(endo) 155.7(5) – 159.2(5) mean NP(exo) 167.1(5) ∠NP(N,N)N(endo) 115.5(3) mean ∠NP(O,O)N(endo) 118.8(3) ∠N(Me)PN(Me)(exo) 106.4(3) ∠PNP 120.2(3) – 122.2(3)	153
162	NP(endo) 157.5(2) – 159.3(2) NP(exo) 166.2(2) ∠NPN(endo) 117.4(1) – 118.7(1) ∠PNP 121.2(1) – 121.8(1)	153
163	NP(endo) 156.1(4) – 159.7(4) NP(exo) 164.8(5), 167.9(4) ∠NP(N,N)N(endo) 115.9(2) mean ∠NP(O,O)N(endo) 118.8(1) ∠N(Me)PN(Me)(exo) 99.9(2) ∠PNP 120.1(3) – 123.0(3)	154
165	two independent mols. in unit cell NP(endo) 154.5(6) – 159.3(5) NP(exo) 162.4(6) – 167.7(5) ∠NP(N,N)N(endo) 115.0(3) – 116.7(3) ∠NP(O,O)N(endo) 119.2(3), 120.5(3) ∠N(Me)PN(Me)(exo) 100.4(3) – 106.7(3) ∠PNP 121.0(3) – 123.7(3)	152
166.2MeOH	NP(endo) 156(1) – 167(1) NP(exo) 163(1) – 167(1) mean ∠NP(N,N)N(endo) 116.1(3) mean ∠NP(O,O)N(endo) 117.5(5) mean ∠N(Me)PN(Me)(exo) 102.9(3) ∠PNP 120.0(8) – 125.7(9)	155
167a.2$CHCl_3$.2.5H_2O	NP(endo) 156.2(4) – 162.4(4) NP(exo) 164.7(4) – 167.3(1) ∠NP(N,N)N(endo) 115.7(2), 116.4(2) ∠NP(O,O)N(endo) 118.2(2) mean ∠N(Me)PN(Me)(exo) 101.7(2) ∠PNP 122.1(2) – 124.0(2)	155

(*continued*)

Compound	Comments	Ref.
167b.2MeCN.2H_2O	NP(endo) 157.2(2) – 161.8(2) NP(exo) 165.1(2) – 166.1(2) ∠NP(N,N)N(endo) 115.3(1), 116.0(1) ∠NP(O,O)N(endo) 119.0(1) mean ∠N(Me)PN(Me)(exo) 101.2(1) ∠PNP 122.2(1) – 123.5(1)	155
167c	NP(endo) 157.1(4) – 162.1(3) NP(exo) 164.6(4) – 166.6(3) ∠NP(N,N)N(endo) 116.5(2), 117.4(2) ∠NP(O,O)N(endo) 118.2(2) mean ∠N(Me)PN(Me)(exo) 105.6(2) ∠PNP 121.1(2) – 122.1(2)	155
172f	NP(endo) 156.9(3) – 161.1(3) mean N(C)P(exo) 165.6(2) ∠NPN(endo) 116.2(2) – 119.2(2) ∠N(C)PN(C) 106.2(2) ∠PNP 120.8(2) – 122.1(2)	156
174a.4$CHCl_3$	NP(endo) 155.7(8) – 166.0(7) NP(exo) 163.4(8) – 168.6(7) ∠NPN(endo) 109.4(4) – 120.4(4) mean ∠N(C)PN(C) (exo) 95.1(3) ∠N(H)PN(H)(exo) 106.0(4) ∠PNP 120.5(4) – 135.0(5)	156
174b.0.75thf	NP(endo) 158.3(5) – 165.4(5) NP(exo) 162.4(5) – 167.9(5) ∠NPN(endo) 109.8(2) – 118.6(2) mean ∠N(C)PN(C) (exo) 94.8(2) ∠N(H)PN(H)(exo) 104.3(2) ∠PNP 122.4(3) – 133.6(3)	156
174c.2dmf (dmf = dimethylformamide)	NP(endo) 157.5(6) – 165.5(6) NP(exo) 163.3(7) – 166.0(6) ∠NPN(endo) 108.9(3) – 113.3(3) mean ∠N(C)PN(C)(exo) 95.3(2) ∠N(H)PN(H)(exo) 102.0(3) ∠PNP 124.8(3) – 133.2(4)	156

(*continued*)

Compound	Comments	Ref.
176b	NP(endo) 154.8(6) – 159.3(5) NP(exo) 161.7(7) – 169(1) ∠NPN(endo) 118.9(3) – 120.7(3) ∠N(H)PN(H)(exo) 105.2(4) – 108.4(3) ∠PNP 125.6(3) – 133.4(4)	157
145	NP 154.4(4) – 160.4(4) ∠NPN 116.5(2) – 119.9(2) ∠PNP 119.4(2) – 122.9(2)	159
186	NP 156.4(4) – 158.1(4) ∠NPN 117.2(2) – 118.2(2) ∠PNP 120.7(3) – 122.2(3)	167
exo-ansa-**201**	NP 155.0(9) – 161(1) ∠NPN 117.5(5) – 120.7(5) ∠PNP 117.1(6) – 121.5(6)	170
endo-ansa-spiro-(**203**)	NP 155.7(6) – 158.2(6) ∠NPN 116.6(3) – 118.8(3) ∠PNP 119.8(4) – 122.1(3)	171
endo-ansa-spiro-(**206**) R = Fc	NP 156.2(5) – 158.0(5) mean ∠NPN 118.5(2) ∠PNP 115.7(3) – 120.2(3)	171
endo-ansa-(**207**)	NP 155.7(8) – 158.4(6) ∠NPN 117.9(4) – 119.1(4) ∠PNP 116.2(4) – 120.0(5)	172
exo-ansa-(**207**)	NP 157.3(2) – 158.6(2) ∠NPN 118.1(1) – 118.9(1) ∠PNP 118.9(1) – 121.5(1)	172
210.2CH_2Cl_2	NP 155.0(5) – 161.1(5) ∠NPN 112.8(3) – 119.7(3) ∠PNP 119.2(3) – 124.4(3)	173
211	NP 156.3(2) – 159.9(2) ∠NPN 116.0(1) – 118.7(1) ∠PNP 120.3(1) – 121.4(1)	173
cis-**213**	NP 159.8(2) – 160.8(2) ∠NPN 116.4(1) – 117.3(1) ∠PNP 120.4(1) – 121.8(1)	174
trans-**213**	NP 158.9(4) – 162.1(4) ∠NPN 116.9(2) – 117.6(2) mean ∠PNP 122.0(1)	174
cis-**214**	NP 159.2(2) – 160.3(2) ∠NPN 116.9(1) – 117.5(1) ∠PNP 121.1(1) – 122.3(1)	174
2, *cis*-4, *cis*-6, *cis*-8-**215**	NP 158.9(2) – 160.4(2) ∠NPN 119.3(1), 120.1(1) ∠PNP 128.0(1), 133.9(1)	175

(*continued*)

Compound	Comments	Ref.
2, *cis*-4, *cis*-6, *trans*-8-**215**	NP 159.1(2) – 159.9(2) ∠NPN 119.2(1) – 120.4(1) ∠PNP 129.6(1) – 131.6(1)	175
2, *cis*-4, *trans*-6, *trans*-8-**215**	NP 158.2(2) – 159.3(2) ∠NPN 117.9(1), 121.2(1) ∠PNP 132.6(1), 133.6(1)	175
2, *trans*-4, *cis*-6, *trans*-8-**215**	NP 157.4(2) – 159.6(2) ∠NPN 119.6(1) – 121.7(1) ∠PNP 127.5(1) – 137.0(2)	175
217.4$CHCl_3$.2C_6H_5Me	mean NP 156.4(6) ∠NPN 119.4(3) ∠PNP 139.7(3)	176
230	mean NP 157.0(2) ∠NPN 115.0(2)	181
231a	two independent mols. in unit cell mean NP 158.0(1) ∠NPN 114.8(1), 115.3(1)	181
231b	mean NP 157.9(1) ∠NPN 114.3(1)	181
231c	NP 158.0(2), 158.8(2) ∠NPN 114.3(1)	181
231d	mean NP 159.0(1) ∠NPN 114.4(1)	181

References

1. H.R. Allcock, *Chemistry and Applications of Polyphosphazenes*, John Wiley & Sons Inc., Hoboken, N. J., 2003.
2. M. Gleria and R. De Jaeger (eds.), *Phosphazenes, A Worldwide Insight*, Nova Science Publishers, Inc., New York, 2004.
3. I. Yavari, M. Adib and L. Hojabri, *Tetrahedron*, 2002, **58**, 7213.
4. (*a*) S.K. Rastogi, G.K. Srivastava, S.K. Singh, R.K. Grover, R. Roy and B. Kundu, *Tetrahedron Lett*., 2002, **43**, 8327; (*b*) B.J. Neubert and B.B. Snider, *Org. Lett*., 2003, **5**, 765; (*c*) J. Chen and C. J. Forsyth, *Org. Lett*., 2003, **5**, 1281; (*d*) S. Woo, C. Leung, V. Santhakumar and M. Tomaszewski, *PCT Int. Appl*., WO 2003051274; (*e*) D. Skropeta, R. Schwörer and R.R. Schmidt, *Bioorg. Med. Chem. Lett*., 2003, **13**, 3351; (*f*) D.R. Williams, K. Shamim, J.P. Reddy, G.S. Amato and S.M. Shaw, *Org. Lett*., 2003, **5**, 3361; (*g*) I.A. O'Neil, S. Thompson, S.B. Kalindjian and T.C. Jenkins, *Tetrahedron Lett*., 2003, **44**, 7809; (*h*) M.E. Bunnage, A.J. Burke, S.G. Davies, N.L. Millican, R.L. Nicholson, P.M. Roberts and A.D. Smith, *Org. Biomol. Chem*., 2003, **1**, 3708; (*i*) P. Langer, I. Freifeld and H. Shojaei, *J. Chem. Soc. Chem. Commun*., 2003, 3044; (*j*) M. Köhn, R. Wacker, C. Peters, H. Schröder, L. Soulère, R. Breinbauer, C.M. Niemeyer and H. Waldmann, *Angew. Chem. Int. Ed*., 2003, **42**, 5830; (*k*) H. Fuwa, Y. Okamura, Y. Morohashi, T. Tomita, T. Iwatsubo, T. Kan, T. Fukuyama and H. Natsugari, *Tetrahedron*

Lett., 2004, **45**, 2323; (*l*) G. Durand, A. Polidori, J.-P. Salles and B. Pucci, *Bioorg. Med. Chem. Lett*., 2003, **13**, 859; (*m*) Y. Sun and M. W. Ding, *Huaxue Shiji*, 2003, **25**, 285; (*n*) Y. Sun and M.W. Ding, *Chem. Abstr*., 2004, **140**, 163774; (*o*) K. Hemming, C. Loukou, S. Elkatip and R.K. Smalley, *Synlett*, 2004, 101; (*p*) W. Kurosawa, T. Kan and T. Fukuyama, *J. Am. Chem. Soc*., 2003, **125**, 8112; (*q*) M.-X. Zhao, M.-X. Wang, C.-Y. Yu, Z.-T. Huang and G.W.J. Fleet, *J. Org. Chem*., 2004, **69**, 997; (*r*) A. Csámpai, G. Túrós, V. Kudar, K. Simon, H. Oeynhausen, H. Wamhoff and P. Sohár, *Eur. J. Org. Chem*., 2004, 717; (*s*) A. Grieder and A.W. Thomas, *Synthesis*, 2003, 1707; (*t*) J. S. Yadav and C. Srinivas, *Tetrahedron*, 2003, **59**, 10325; (*u*) C. Bonini, M. Funicello, R. Scialpi and P. Spagnolo, *Tetrahedron*, 2003, **59**, 7515; (*v*) F. Palacios, A. M. Ochoa de Retana, E. Martínez de Marigorta, M. Rodríguez and J. Pagalday, *Tetrahedron*, 2003, **59**, 2617; (*w*) E.M.E. Viseux, P.J. Parsons, J.B.J. Pavey, C.M. Carter and I. Pinto, *Synlett*, 2003, 1856; (*x*) F. Palacios, C. Alonso, J. Pagalday, A. M. Ochoa de Retana and G. Rubiales, *Org. Biomol. Chem*., 2003, **1**, 1113; (*y*) B. Alcaide, P. Almendros and J.M. Alonso, *J. Org. Chem*., 2004, **69**, 993; (*z*) A.R. Modarresi-Alam and F. Khamooshi, *Synth. Commun*., 2004, **34**, 129.

5. S. Obika, J. Andoh, M. Onoda, O. Nakagawa, A. Hiroto, T. Sugimoto and T. Imanishi, *Tetrahedron Lett*., 2003, **44**, 5267.
6. J.L. Wolfe, T. Kawate, A. Belenky and V. Stanton, Jr., *Nucleic Acids Res*., 2002, **30**, 3739.
7. N.E. Poopeiko, M. Juhl, B. Vester, M.D. Sørensen and J. Wengel, *Bioorg. Med. Chem. Lett*., 2003, **13**, 2285.
8. (*a*) L. Kovács, E. Ösz and Z. Györgydeák, *Carbohydr. Res*., 2002, **337**, 1171; (*b*) M.I. García-Moreno, P. Diaz-Pérez, J.M. Benito, C. Ortiz Mellet, J. Defaye and J.M. García Fernández, *Carbohydr. Res*., 2002, **337**, 2329; (*c*) J. Xie, *Carbohydr. Res*., 2003, **338**, 399; (*d*) R.M. van Well, M.E.A. Meijer, H.S. Overkleeft, J.H. van Boom, G.A. van der Marel and M. Overhand, *Tetrahedron*, 2003, **59**, 2423; (*e*) D.H. Ryu, C.-H. Tan and R.R. Rando, *Bioorg. Med. Chem. Lett*., 2003, **13**, 901; (*f*) A. Bianchi and A. Bernardi, *Tetrahedron Lett*., 2004, **45**, 2231.
9. J. Xue, J. Wu and Z. Guo, *Org. Lett*., 2004, **6**, 1365.
10. M. Basato, G. Facchin, R.A. Michelin, M. Mozzon, S. Pugliese, P. Sgarbossa and A. Tassan, *Inorg. Chim. Acta*, 2003, **356**, 349.
11. M. Basato, F. Benetollo, G. Facchin, R.A. Michelin, M. Mozzon, S. Pugliese, P. Sgarbossa, S.M. Sbovata and A. Tassan, *J. Organomet. Chem*., 2004, **689**, 454.
12. A. Tárraga, P. Molina and D. Curiel, *ARKIVOC (Gainesville)*, 2002, 85.
13. J.E. Klare, G.S. Tulevski, K. Sugo, A. de Picciotto, K.A. White and C. Nuckolls, *J. Am. Chem. Soc*., 2003, **125**, 6030.
14. E. Saxon, S.J. Luchansky, H.C. Hang, C. Yu, S.C. Lee and C.R. Bertozzi, *J. Am. Chem. Soc*., 2002, **124**, 14893.
15. J.A. Restituyo, L.R. Comstock, S.G. Petersen, T. Stringfellow and S.R. Rajski, *Org. Lett*., 2003, **5**, 4357.
16. D.J. Vocadlo, H.C. Hang, E.-J. Kim, J.A. Hanover and C.R. Bertozzi, *Proc. Natl. Acad. Sci. U.S.A*., 2003, **100**, 9116.
17. H.C. Hang, C. Yu, D.L. Kato and C.R. Bertozzi, *Proc. Natl. Acad. Sci. U.S.A*., 2003, **100**, 14846.
18. C.C.-Y. Wang, T.S. Seo, Z. Li, H. Ruparel and J. Ju, *Bioconjugate Chem*., 2003, **14**, 697.
19. H.C. Hang, C. Yu, M.R. Pratt and C.R. Bertozzi, *J. Am. Chem. Soc*., 2004, **126**, 6.

20. G.A. Lemieux, C.L. de Graffenried and C.R. Bertozzi, *J. Am. Chem. Soc.*, 2003, **125**, 4708.
21. B.L. Nilsson, R.J. Hondal, M.B. Soellner and R.T. Raines, *J. Am. Chem. Soc.*, 2003, **125**, 5268.
22. M.B. Soellner, K.A. Dickson, B.L. Nilsson and R.T. Raines, *J. Am. Chem. Soc.*, 2003, **125**, 11790.
23. O. David, W.J.N. Meester, H. Bieräugel, H.E. Schoemaker, H. Hiemstra and J.H. van Maarseveen, *Angew. Chem. Int. Ed.*, 2003, **42**, 4373.
24. L.L. Kiessling, B.L. Nilsson, Y. He, R.T. Raines, R.J. Hinklin and M.B. Soellner, *PCT Int. Appl.*, WO 2003104243.
25. G. Magro, B. Donnadieu, A.-M. Caminade and J.-P. Majoral, *Chem. Eur. J.*, 2003, **9**, 2151.
26. V. Maraval, J. Pyzowski, A.-M. Caminade and J.-P. Majoral, *J. Org. Chem.*, 2003, **68**, 6043.
27. C.-O. Turrin, V. Maraval, J. Leclaire, E. Dantras, C. Lacabanne, A.-M. Caminade and J.-P. Majoral, *Tetrahedron*, 2003, **59**, 3965.
28. E. Dantras, J. Dandurand, C. Lacabanne, A.-M. Caminade and J.-P. Majoral, *Macromolecules*, 2004, **37**, 2812.
29. M. Alajarin, C. López-Leonardo and P. Llamas-Lorente, *Synlett.*, 2003, 801.
30. P.M. Fresneda and P. Molina, *Synlett*, 2004, 1.
31. W.C. Lu, R.Q. Zhang, Q.J. Zang and N.B. Wong, *J. Phys. Chem. B*, 2003, **107**, 2061.
32. Y. Xue and C.K. Kim, *J. Phys. Chem. A*, 2003, **107**, 7945.
33. W.C. Lu and C.C. Sun, *J. Mol. Struct. (THEOCHEM)*, 2002, **593**, 1.
34. (*a*) M.-W. Ding, Y. Sun, X.-P. Liu and Z.-J. Liu, *Chin. J. Chem.*, 2003, **21**, 577; (*b*) M. -W. Ding, Y. Sun, S.-J. Yang, X.-P. Liu and Z.-J. Liu, *Synth. Commun.*, 2003, **33**, 1651; (*c*) M.-W. Ding, G.-P. Zeng and Z.-J. Liu, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1315; (*d*) M.-W. Ding, J. Zhu, S.-F. Shi and X.-P. Liu, *Chin. Chem. Lett.*, 2002, **13**, 942; (*e*) M.-W. Ding, S.-J. Yang, Y. Sun, Z.-J. Liu and X.-P. Liu, *Heterocyclic Commun.*, 2002, **8**, 493; (*f*) Z.F. Xu and M.W. Ding, *Yingyong Huaxue*, 2003, **20**, 198; (*g*) Z. F. Xu and M. W. Ding, *Chem. Abstr.*, 2003, **139**, 101228; (*h*) M.-W. Ding, Y. Sun, X.-P. Liu and Z.-J. Liu, *Heterocyclic Commun.*, 2003, **9**, 135.
35. Y. Sun and M.-W. Ding, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 2137.
36. (*a*) Y. Liang, M.-W. Ding, Z.-J. Liu and X.-P. Liu, *Synth. Commun.*, 2003, **33**, 2843; (*b*) S. Yang and M. Ding, *Huaxue Shiji*, 2003, **25**, 132; (*c*) S. Yang and M. Ding, *Chem. Abstr.*, 2003, **139**, 364896.
37. V. Kumar, A. Sharma and M.P. Mahajan, *Synth. Commun.*, 2004, **34**, 49.
38. X. Lu, J.L. Petersen and K.K. Wang, *J. Org. Chem.*, 2002, **67**, 7797.
39. M.-W. Ding, S.J. Yang and J. Zhu, *Synthesis*, 2004, 75.
40. D.V. Vilarelle, C.P. Veira and J.M. Quintela López, *Tetrahedron*, 2004, **60**, 275.
41. P. Molina, E. Aller and A. Lorenzo, *Synlett.*, 2003, 714.
42. (*a*) C.E. Hoesl, A. Nefzi and R.A. Houghten, *J. Comb. Chem.*, 2003, **5**, 155; (*b*) C.E. Hoesl, A. Nefzi and R.A. Houghten, *J. Comb. Chem.*, 2004, **6**, 220.
43. D.S. Laitar, C.J.N. Mathison, W.M. Davis and J.P. Sadighi, *Inorg. Chem.*, 2003, **42**, 7354.
44. A.R. Katritzky, S.K. Nair and A. Silina, *J. Org. Chem.*, 2002, **67**, 7530.
45. C.H. Lee and K.J. Lee, *J. Heterocycl. Chem.*, 2002, **39**, 845.
46. C.H. Lee, B.G. Kim and K.J. Lee, *J. Heterocycl. Chem.*, 2002, **39**, 1329.
47. K.T. Kim, C.H. Lee and K.J. Lee, *J. Heterocycl. Chem.*, 2003, **40**, 187.

48. F. Palacios, E. Herrán and G. Rubiales, *Heterocycles*, 2002, **58**, 89.
49. J.R. Klaehn and R.H. Neilson, *Inorg. Chem.*, 2002, **41**, 5859.
50. J.R. Klaehn, T.A. Luther, M.K. Harrup and F.F. Stewart, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1587.
51. R.C. Samuel, R.P. Kashyap, M. Krawiec, W.H. Watson and R.H. Neilson, *Inorg. Chem.*, 2002, **41**, 7113.
52. K. Azimi and R.H. Neilson, *J. Cluster Sci.*, 2002, **13**, 553.
53. E. Rivard, K. Huynh, A.J. Lough and I. Manners, *J. Am. Chem. Soc.*, 2004, **126**, 2286.
54. M.C. Burland and T.Y. Meyer, *Inorg. Chem.*, 2003, **42**, 3438.
55. K. Dehnicke and A. Greiner, *Angew., Chem. Int. Ed.*, 2003, **42**, 1340.
56. K. Dehnicke, *Z. Anorg. Allg. Chem.*, 2003, **629**, 729.
57. K. Weber, K. Korn, A. Schorm, J. Kipke, M. Lemke, A. Khvorost, K. Harms and J. Sundermeyer, *Z. Anorg. Allg. Chem.*, 2003, **629**, 744.
58. M. Raab, J. Tirreé, M. Nieger and E. Niecke, *Z. Anorg. Allg. Chem.*, 2003, **629**, 769.
59. M. Bolboaca, T. Stey, A. Murso, D. Stalke and W. Kiefer, *Appl. Spectrosc.*, 2003, **57**, 970.
60. D.W. Stephan, J.C. Stewart, F. Guérin, S. Courtenay, J. Kickham, E. Hollink, C. Beddie, A. Hoskin, T. Graham, P. Wei, R.E.v.H. Spence, W. Xu, L. Koch, X. Gao and D.G. Harrison, *Organometallics*, 2003, **22**, 1937.
61. S.J. Brown, X. Gao, M.G. Kowalchuk, R.E.v.H. Spence, D.W. Stephan and J. Swabey, *Can. J. Chem.*, 2002, **80**, 1618.
62. V. Cadierno, P. Crochet, J. García-Álvarez, S.E. García-Garrido and J. Gimeno, *J. Organomet. Chem.*, 2002, **663**, 32.
63. V. Cadierno, P. Crochet, J. Díez, J. García-Álvarez, S.E. García-Garrido, J. Gimeno, S. García-Granda and M.A. Rodríguez, *Inorg. Chem.*, 2003, **42**, 3293.
64. V. Cadierno, P. Crochet, J. Díez, J. García-Álvarez, S.E. García-Garrido, S. García-Granda, J. Gimeno and M.A. Rodríguez, *J. Chem. Soc., Dalton Trans.*, 2003, 3240.
65. Z.-X. Wang and Y.-X. Li, *Organometallics*, 2003, **22**, 4900.
66. H.-R. Wu, Y.-H. Liu, S.-M. Peng and S.-T. Liu, *Eur. J. Inorg. Chem.*, 2003, 152.
67. L.P. Spencer, R. Altwer, P. Wei, L. Gelmini, J. Gauld and D.W. Stephan, *Organometallics*, 2003, **22**, 3841.
68. M. Alajarin, C. López-Leonardo, P. Llamas-Lorente, D. Bautista and P.G. Jones, *J. Chem. Soc., Dalton Trans.*, 2003, 426.
69. J. Vicente, J.-A. Abad, R. Clemente, J. López-Serrano, M.C. Ramírez de Arellano, P.G. Jones and D. Bautista, *Organometallics*, 2003, **22**, 4248.
70. K.T.K. Chan, L.P. Spencer, J.D. Masuda, J.S.J. McCahill, P. Wei and D.W. Stephan, *Organometallics*, 2004, **23**, 381.
71. Z.-X. Wang and Y.X. Li, *Inorg. Chem.*, 2002, **41**, 5934.
72. W.-P. Leung, C.-W. So, Z.-X. Wang, J.-Z. Wang and T.C.W. Mak, *Organometallics*, 2003, **22**, 4305.
73. W.-P. Leung, Z.-X. Wang, H.-W. Li and T.C.W. Mak, *Angew. Chem. Int. Ed.*, 2001, **40**, 2501.
74. M. Ganesan, P.E. Fanwick and R.A. Walton, *Inorg. Chim. Acta*, 2003, **346**, 181.
75. M.J. Sarsfield, H. Steele, M. Helliwell and S.J. Teat, *J. Chem. Soc., Dalton Trans.*, 2003, 3443.
76. M. J. Sarsfield, H. Steele and M. Helliwell, *J. Chem. Soc., Chem. Commun.*, 2002, 2264.
77. D.J. Evans, M.S. Hill and P.B. Hitchcock, *J. Chem. Soc., Dalton Trans.*, 2003, 570.

78. Y. Paul and S.K. Pandey, *Synth. React. Inorg. Met. -Org. Chem.*, 2003, **33**, 1515.
79. Y. Paul and S.K. Pandey, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 159.
80. Y. Paul and S.K. Pandey, *Pol. J. Chem.*, 2003, **77**, 1113.
81. J. Parr, M.B. Smith and M.R.J. Elsegood, *J. Organomet. Chem.*, 2002, **664**, 85.
82. O. Bumbu, A. Silvestru, C. Silvestru, J.E. Drake, M.B. Hursthouse and M.E. Light, *J. Organomet. Chem.*, 2003, **686**, 118.
83. W.-P. Leung, Q.W.-Y. Ip, S.-Y. Wong and T.C.W. Mak, *Organometallics*, 2003, **22**, 4604.
84. R.G. Cavell, K. Aparna, R.P. Kamalesh Babu and Q. Wang, *J. Mol. Catal. A: Chem.*, 2002, **189**, 137.
85. K. Bernardo-Gusmão, L.F. Trevisan Queiroz, R.F. de Souza, F. Leca, C. Loup and R. Réau, *J. Catal.*, 2003, **219**, 59.
86. L. Beaufort, D. Jan, F. Benvenuti and A. Noels, *Eur. Pat. Appl.*, EP 1402949.
87. M. Arndt-Rosenau, M. Hoch, J. Sundermeyer, J. Kipke and M. Lemke, *Eur. Pat. Appl.*, EP 1284270.
88. J.J. Longlet, S.G. Bodige, W.H. Watson and R.H. Neilson, *Inorg. Chem.*, 2002, **41**, 6507.
89. M. Arslan, F. Aslan and A.I. Öztürk, *Heteroatom Chemistry*, 2003, **14**, 138.
90. F. Aslan, A.I. Öztürk and M. Arslan, *Heteroatom Chemistry*, 2003, **14**, 413.
91. A.I. Öztürk, F. Aslan, E. Çil, M. Arslan and A. Kiliç, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 2097.
92. E. Çil, M. Arslan, F. Aslan and A.I. Öztürk, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1037.
93. Ö. Yilmaz, F. Aslan, A.I. Öztürk, N.S. Vanli, S. Kirbağ and M. Arslan, *Bioorg. Chem.*, 2002, **30**, 303.
94. B. Kovaćević, D. Barić and Z.B. Maksić, *New J. Chem.*, 2004, **28**, 284.
95. I. Kaljurand, T. Rodima, A. Pihl, V. Mäemets, I. Leito, I.A. Koppel and M. Mishima, *J. Org. Chem.*, 2003, **68**, 9988.
96. E.I. Rõõom, I. Kaljurand, I. Leito, T. Rodima, I.A. Koppel and V.M. Vlasov, *J. Org. Chem.*, 2003, **68**, 7795.
97. A. Solladié-Cavallo, M. Roje, R. Welter and V. Šunjić, *J. Org. Chem.*, 2004, **69**, 1409.
98. A.J. Clark, D. Patel and M.J. Broadhurst, *Tetrahedron Lett.*, 2003, **44**, 7763.
99. C. Palomo, A.L. Palomo, F. Palomo and A. Mielgo, *Org. Lett.*, 2002, **4**, 4005.
100. Y. Lou, J. Chang, J. Jorgensen and D.M. Lemal, *J. Am. Chem. Soc.*, 2002, **124**, 15302.
101. J. Blid and P. Somfai, *Tetrahedron Lett.*, 2003, **44**, 3159.
102. D.A. Alonso, C. Nájera and M. Varea, *Tetrahedron Lett.*, 2004, **45**, 573.
103. C.-J. Koch, G. Höfner, K. Polborn and K.T. Wanner, *Eur. J. Org. Chem.*, 2003, 2233.
104. C.J. Teng and W.P. Weber, *Macromolecules*, 2003, **36**, 5126.
105. (*a*) S. Okawa, *Jpn. Kokai Tokkyo Koho*, JP 2003073476; (*b*) S. Okawa, *Chem. Abstr.*, 2003, **138**, 222300.
106. A. Grzelka, J. Chojnowski, M. Cypryk, W. Fortuniak, P.C. Hupfield and R.G. Taylor, *J. Organomet. Chem.*, 2002, **660**, 14.
107. K.-S. Kim, J.-H. Kim and G. Seo, *J. Chem. Soc., Chem. Commun.*, 2003, 372.
108. P. Kirsch, G. Röschenthaler, D. Sevenard and A. Kolomeitsev, *Ger. Offen.*, DE 10321114.
109. H.-J. Michel, H.-J. Niclas, M. Fuchs, A. Hucke, C. Schuster and H. Wozniak, *Ger. Offen.*, DE 10216751.

110. D. Decker, T. Wessel, H. Huenig and R. Schwesinger, *PCT Int. Appl.*, WO 2003101926.
111. (*a*) H. Kawanabe, S. Yamazaki and K. Takeda, *Jpn. Kokai Tokkyo Koho*, JP 2003082057; (*b*) H. Kawanabe, S. Yamazaki and K. Takeda, *Chem. Abstr.*, 2003, **138**, 222836; (*c*) T. Kawabata, T. Urakami, S. Maeda, T. Nobori and K. Suzuki, *PCT Int. Appl.*, WO 2003029322; (*d*) T. Urakami, K. Suzuki and S. Maeda, *Jpn. Kokai Tokkyo Koho*, JP 2003286330; (*e*) T. Urakami, K. Suzuki and S. Maeda, *Chem. Abstr.*, 2003, **139**, 293074; (*f*) H. Kinoshita, T. Maeda, M. Morita and K. Nishihara, *Jpn. Kokai Tokkyo Koho*, JP 2004018720; (*g*) H. Kinoshita, T. Maeda, M. Morita and K. Nishihara, *Chem. Abstr.*, 2004, **140**, 112459.
112. (*a*) T. Kawabata, S. Maeda, T. Urakami and K. Suzuki, *Jpn. Kokai Tokkyo Koho*, JP 2003261649; (*b*) T. Kawabata, S. Maeda, T. Urakami and K. Suzuki, *Chem. Abstr.*, 2003, **139**, 246535; (*c*) T. Urakami, K. Suzuki and S. Maeda, *Jpn. Kokai Tokkyo Koho*, JP 2003286330; (*d*) T. Urakami, K. Suzuki and S. Maeda, *Chem. Abstr.*, 2003, **139**, 293074; (*e*) H. Kinoshita, S. Maeda, M. Morita and K. Nishihara, *Jpn. Kokai Tokkyo Koho*, JP 2004018718; (*f*) H. Kinoshita, S. Maeda, M. Morita and K. Nishihara, *Chem. Abstr.*, 2004, **140**, 112501.
113. U. Siemeling, L. Kölling, A. Stammler and H.-G. Stammler, *J. Chem. Soc., Dalton Trans.*, 2002, **3277**.
114. E. Rivard, A.J. Lough and I. Manners, *Acta Crystallogr., Sect. E: Struct. Reports*, 2003, **E59**, m239.
115. J. Grebe-Metz, F. Weller and K. Dehnicke, *Z. Anorg. Allg. Chem.*, 2003, **629**, 1110.
116. U. Rölle, K. Harms and K. Dehnicke, *Z. Anorg. Allg. Chem.*, 2003, **629**, 936.
117. W.-P. Leung, C.-W. So, J.-Z. Wang and T.C.W. Mak, *J. Chem. Soc., Chem. Commun.*, 2003, **1**, 248.
118. B. Jäschke and M. Jansen, *Z. Anorg. Allg. Chem.*, 2002, **628**, 2000.
119. I. Fernández, J.M. Álvarez Gutiérrez, N. Kocher, D. Leusser, D. Stalke, J. González and F.L. Ortiz, *J. Am. Chem. Soc.*, 2002, **124**, 15184.
120. S. Janaswamy, G.S. Murthy, T. Mohan and M.N.S. Rao, *Crystallogr. Reports*, 2003, **48**, 68.
121. J. Srinivas, M.V. Rao, G.S. Murthy, C.J. Thomas and M.N.S. Rao, *J. Chem. Crystallogr.*, 2004, **34**, 19.
122. B. Tinant, J.P. Declercq, H. Wullens and M. Devillers, *Z. Kristallogr. NCS*, 2002, **217**, 385.
123. R.-Y. Liau, H. Ehlich, A. Schier and H. Schmidbaur, *Z. Naturforsch.*, 2002, **57b**, 1085.
124. P. G. Jones and M. M. Álvarez-Falcón, *Acta Crystallogr. Sect. E Struct. Reports.*, 2003, **E59**, m192.
125. S. Detti, V.T. Forsyth, R. Roulet, R. Ros, A. Tassan and K.J. Schenk, *Z. Kristallogr.*, 2004, **219**, 47.
126. B. Jäsche and M. Jansen, *Z. Naturforsch.*, 2002, **57b**, 1237.
127. B. Jäsche and M. Jansen, *Z. Kristallogr., NCS*, 2003, **218**, 381.
128. T. Bollwein, M. Westerhausen and A. Pfitzner, *Z. Naturforsch.*, 2003, **58b**, 493.
129. V. Chandrasekhar and V. Krishnan, *Adv. Inorg. Chem.*, 2002, **53**, 159.
130. M. Gleria, R. Po, G. Giannotta, L. Fiocca, R. Bertani, L. Fambri, F.P. La Mantia and R. Scaffaro, *Macromol. Symp.*, 2003, **196**, 249.
131. P. Sozzani, A. Comotti, R. Simonutti, S. Bracco and A. Simonelli, in *'Strength from Weakness Structural Consequences of Weak Interactions in Molecules Supermolecules and Crystals'*, NATO Science Series II, Mathematics, Physics and

Chemistry, Vol. 68, ed. A. Domenicano and I. Hargittai, Kluwer Academic Publishers, The Netherlands, 2002, 319.
132. H. Sabzyan and Z. Kalantar, *J. Mol. Struct. (THEOCHEM)*, 2003, **663**, 149.
133. M. Enlow, *Polyhedron*, 2003, **22**, 473.
134. M. Breza, *Polyhedron*, 2003, **22**, 3243.
135. F. Kandemirli, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 2331.
136. J.F. Bickley, R. Bonar-Law, G.T. Lawson, P.I. Richards, F. Rivals, A. Steiner and S. Zacchini, *J. Chem. Soc., Dalton Trans.*, 2003, **1235**.
137. H.I. Süss, T. Wuest, A. Sieber, R. Althaus, F. Budde, H.-P. Lüthi, G.D. McManus, J. Rawson and J. Hulliger, *Cryst. Eng. Comm.*, 2002, **4**, 432.
138. A. Barbon, M. Bortolus, M. Brustolon, A. Comotti, A.L. Maniero, U. Segre and P. Sozzani, *J. Phys. Chem. B.*, 2003, **107**, 3325.
139. R. Simonutti, M. Mauri, S. Bracco, A. Comotti and P. Sozzani, *Polym. Prepr. (Am. Chem. Soc. Div. Polym. Chem.)*, 2003, **44**(1), 361.
140. E.W. Ainscough, A.M. Brodie and A. Derwahl, *Polyhedron*, 2003, **22**, 189.
141. S. Beşli, S.J. Coles, D.B. Davies, M.B. Hursthouse, A. Kiliç, T.A. Mayer and R.A. Shaw, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2002, **B58**, 1067.
142. V. Vicente, A. Fruchier and H.-J. Cristau, *Magn. Reson. Chem.*, 2003, **41**, 183.
143. S. Beşli, S.J. Coles, D.B. Davies, R.J. Eaton, M.B. Hursthouse, A. Kiliş, R.A. Shaw, G.Y. Çiftçi and S. Yeçilot, *J. Am. Chem. Soc.*, 2003, **125**, 4943.
144. M.E. Amato, G.A. Carriedo, F.J. Garcia Alonso, J.L. García-Alvarez, G.M. Lombardo and G.C. Pappalardo, *J. Chem. Soc., Dalton Trans.*, 2002, 3047.
145. (*a*) X.W. Wu, C.S. Fang, X.F. Cheng, D.X. Cao, Z.Q. Liu, M. Wang and Z. Wang, *J. Mater. Sci. Lett.*, 2002, **21**, 1767; (*b*) X.W. Wu, D.X. Cao, Z.Q. Liu, X.F. Cheng, C.S. Fang, M. Wang and Z. Wang, *Chin. Chem. Lett.*, 2003, **14**, 535.
146. R. Franski, N. Lyapchenko, G. Schroeder and A.E. Shumejko, *J. Mass Spectrom.*, 2003, **38**, 582.
147. (*a*) H.-S. Wu and C.-L. Lee, *Chem. Eng. J.*, 2002, **90**, 241; (*b*) H.-S. Wu and C.-S. Wang, *chem. eng. sci.*, 2003, **58**, 3523.
148. F. Rivals and A. Steiner, *Z. Anorg. Allg. Chem.*, 2003, **629**, 139.
149. F. Rivals and A. Steiner, *Eur. J. Inorg. Chem.*, 2003, 3309.
150. P.I. Richards, M.A. Benson and A. Steiner, *J. Chem. Soc., Chem. Commun.*, 2003, 1392.
151. P.I. Richards and A. Steiner, *Inorg. Chem.*, 2004, **43**, 2810.
152. V. Chandreasekhar, V. Krishnan, G. Thangavelu, S. Andavan, A. Steiner and S. Zacchini, *Cryst. Eng. Comm.*, 2003, **5**, 245.
153. V. Chandrasekhar, G.T.S. Andavan, S. Nagendran, V. Krishnan, R. Azhakar and R.J. Butcher, *Organometallics*, 2003, **22**, 976.
154. T.M. Barclay, R.G. Hicks, A.S. Ichimura and G.W. Patenaude, *Can. J. Chem.*, 2002, **80**, 1501.
155. V. Chandrasekhar, V. Krishnan, A. Steiner and J.F. Bickley, *Inorg. Chem.*, 2004, **43**, 166.
156. M. Harmjanz, I.M. Piglosiewicz, B.L. Scott and C.J. Burns, *Inorg. Chem.*, 2004, **43**, 642.
157. M. Işiklan, Z. Kilic, N. Akduran and T. Hökelek, *J. Mol. Struct.*, 2003, **660**, 167.
158. G.A. Carriedo, F.J. García Alonso, P.G. Elipe, E. Brillas, A. Labarta and L. Juliá, *J. Org. Chem.*, 2004, **69**, 99.
159. G.A. Carriedo, F.J. Garcia-Alonso, J.L. García-Alvarez, G.C. Pappalardo, F. Punzo and P. Rossi, *Eur. J. Inorg. Chem.*, 2003, 2413.
160. S. Sengupta, *Polyhedron*, 2003, **22**, 1237.

161. S. Sengupta, *Tetrahedron Lett*., 2003, **44**, 7281.
162. G.A. Carriedo, F.J. García Alonso, P.A. González, C. Díaz Valenzuela and N. Yutronic Sáez, *Polyhedron*, 2002, **21**, 2579.
163. C. Díaz, P. Castillo, G.A. Carriedo, P. Gómez-Elipe and F.J. García Alonso, *Macromol. Chem. Phys*., 2002, **203**, 1912.
164. G.A. Carriedo, F.J. García Alonso, S. López Vizcaíno, C. Díaz Valenzuela and N. Yutronic Sáez, *Phosphorus, Sulfur Silicon Relat. Elem*., 2003, **178**, 1549.
165. A. Tarassoli and M.R. Shushizadeh, *Phosphorus, Sulfur Silicon Relat. Elem*., 2003, **178**, 803.
166. M. Odabasoglu, G. Turgut and H. Icbudak, *J. Mol. Struct*., 2004, **691**, 249.
167. T. Itaya, N. Azuma and K. Inoue, *Bull. Chem. Soc. Jpn*., 2002, **75**, 2275.
168. V. Maraval, A.-M. Caminade, J.-P. Majoral and J.-C. Blais, *Angew. Chem., Int. Ed*., 2003, **42**, 1822.
169. M. Bahadur, C.W. Allen, W.E. Geiger and A. Bridges, *Can. J. Chem*., 2002, **80**, 1393.
170. A.J. Elias and K. Muralidharan, *Inorg. J. Chem. Soc., Chem. Commun*., 2003, **6**, 584.
171. K. Muralidharan and A. J. Elias, *Inorg. Chem*., 2003, **42**, 7535.
172. K. Muralidharan, P. Venugopalan and A.J. Elias, *Inorg. Chem*., 2003, **42**, 3176.
173. D. Abizanda, O. Crespo, M. Concepcion Gimeno, J. Jiménez and A. Laguna, *Chem. Eur. J*., 2003, **9**, 3310.
174. J.-H. Jung, H. Zhang and P. Wisian-Neilson, *Inorg. Chem*., 2002, **41**, 6720.
175. J.-H. Jung, J.C. Pomeroy, H. Zhang and P. Wisian-Neilson, *J. Am. Chem. Soc*., 2003, **125**, 15537.
176. P. Kommana, S. Kumaraswamy and K.C.K. Swamy, *Inorg. Chem. Commun*., 2003, **6**, 394.
177. H.R. Allcock, J.D. Bender, R.V. Morford and E.B. Berda, *Macromolecules*, 2003, **36**, 3563.
178. T. Itaya, T. Honda, N. Kusumoto, A. Matsumoto and K. Inoue, *Polymer*, 2003, **44**, 2927.
179. V. Chandrasekhar, P. Deria, V. Krishnan, A. Athimoolam, S. Singh, C. Madhavaiah, S.G. Srivatsan and S. Verma, *Bioorg. Med. Chem. Lett*., 2004, **14**, 1559.
180. V. Chandrasekhar, V. Krishnan, A. Athimoolam and G.T.S. Andavan, *Can. J. Chem*., 2002, **80**, 1415.
181. V. Chandrasekhar, A. Athimoolam, N.D. Reddy, S. Nagendran, A. Steiner, S. Zacchini and R. Butcher, *Inorg. Chem*., 2003, **42**, 51.
182. T.V.V. Ramakrishna and A.J. Elias, *Phosphorus, Sulfur Silicon Relat. Elem*., 2002, **177**, 2513.
183. W. Liu, C. Ye, Q. Gong, H. Wang and P. Wang, *Tribol. Lett*., 2002, **13**, 81.
184. W. Liu, C. Ye, Y. Chen, Z. Ou and D.C. Sun, *Tribol. Int*., 2002, **35**, 503.
185. C. Ye, W. Liu, Y. Chen and Z. Ou, *Wear*, 2002, **253**, 579.
186. D.J. Perettie, *Tribol. Int*., 2003, **36**, 489.
187. D.J. Perettie, J. Chao, S. Chen, B. Shin and B.M. DeKoven, *Tribol. Lett*., 2003, **14**, 77.
188. (*a*) K. Tani, H. Matsumoto, Y. Ogawa, Y. Matsuda, M. Osaki, T. Kanbe, M. Shoda, K. Sakamoto, Y. Yaku and K. Sonoda, *Jpn., Kokai Tokkyo Koho*, JP 2003006837; (*b*) K. Tani, H. Matsumoto, Y. Ogawa, Y. Matsuda, M. Osaki, T. Kanbe, M. Shoda, K. Sakamoto, Y. Yaku and K. Sonoda, *Chem. Abstr*., 2003, **138**, 82324; (*c*) M. Osaki, H. Matsumoto, K. Tani, M. Shoda and K. Sonoda, *Jpn. Kokai Tokkyo Koho*, JP 2003132520; (*d*) M. Osaki, H. Matsumoto, K. Tani, M. Shoda and K. Sonoda, *Chem. Abstr*., 2003, **138**, 347763; (*e*) K. Hara and K. Shimokawa, *U.S. Pat. Appl*., US 2004072034.

189. N. Tagawa, T. Tateyama, A. Mori, N. Kobayashi, Y. Fujii and M. Ikegami, *IEEE Trans. Magn.*, 2003, **39**, 2441.
190. R.J. Waltman, D.J. Pocker, H. Deng, N. Kobayashi, Y. Fujii, T. Akada, K. Hirasawa and G.W. Tyndall, *Chem. Mater.*, 2003, **15**, 2362.
191. R.J. Waltman, N. Kobayashi, K. Shirai, A. Khurshudov and H. Deng, *Tribol. Lett.*, 2004, **16**, 151.
192. A. Russo, P. Maccone, and C. Tonelli, *Eur. Pat. Appl.*, EP 1336614.
193. A.-M. Caminade, J.-P. Majoral, J. Leclaire, S. Lehmann, C. Loup, B. Meunier and J. Solassol, *Fr. Demande*, FR 2834988.
194. M. Maszewska, J. Leclaire, M. Cieslak, B. Nawrot, A. Okruszek, A.-M. Caminade and J.-P. Majoral, *Oligonucleotides*, 2003, **13**, 193.
195. S.-C. Song, S.B. Lee, B.H. Lee, H.-W. Ha, K.-T. Lee and Y.S. Sohn, *J. Controlled Release*, 2003, **90**, 303.
196. M. Anzai, Y. Ishikawa, K. Yoshihashi, H. Hirose and M. Nishiyama, *J. Oral Sci.*, 2002, **44**, 147.
197. (*a*) S. Fujiwara, *Eur. Pat. Appl.*, EP 1346717; (*b*) N. Hattori, *U.S. Pat. Appl.*, US 2004054028.
198. K.N. Ludwig and R.B. Moore, *J. Elastomers Plast.*, 2002, **34**, 171.
199. J.-F. Kuan and K.-F. Lin, *J. Appl. Polym. Sci.*, 2003, **91**, 697.
200. D. Christova, S.D. Ivanova, R.S. Velichkova, P. Tzvetkova, P. Mihailova, I. Uzunov, L. Lakov and O. Peshev, *Designed Monomers Polym.*, 2003, **6**, 11.
201. I. Dez and R. De Jaeger, *J. Appl. Polym. Sci.*, 2003, **89**, 1925.
202. Y. Cui, X. Ma, X. Tang and Y. Luo, *Eur. Polym. J.*, 2003, **40**, 299.
203. Y. Cui, X. Tang, X. Huang and Y. Chen, *Biomacromolecules*, 2003, **4**, 1491.
204. K. Inoue, S. Horibe, M. Fukae, T. Muraki, E. Ihara and H. Kayama, *Macromol. Biosci.*, 2003, **3**, 26.
205. S. Hou, D. Taton, M. Saule, J. Logan, E.L. Chaikof and Y. Gnanou, *Polymer*, 2003, **44**, 5067.
206. R. Bertani, A. Boscolo-Boscoletto, N. Dintcheva, E. Ghedini, M. Gleria, F. La Mantia, G. Pace, P. Pannocchia, A. Sassi, R. Scaffaro and A. Venzo, *Design. Monom. Polym.*, 2003, **6**, 245.
207. S. Dirè, G. Facchin, R. Ceccato, L. Guarino, A. Sassi and M. Gleria, *J. Inorg. Organomet. Polym.*, 2002, **12**, 59.
208. Y.W. Chen-Yang, S.F. Chen, C.Y. Yuan, H.F. Lee, J.L. Li, C.Y. Li and Y.S. Chiu, *J. Appl. Polym. Sci.*, 2003, **90**, 810.
209. Y.W. Chen-Yang, C.Y. Yuan, C.H. Li and H.C. Yang, *J. Appl. Polym. Sci.*, 2003, **90**, 1357.
210. (*a*) H. Harashina and S. Yamada, *Jpn. Kokai Tokkyo Koho*, JP 2003342482; (*b*) H. Harashina and S. Yamada, *Chem. Abstr.*, 2004, **140**, 17333.
211. (*a*) N. Fukuoka, H. Yasuda, M. Nishimatsu, J. Inada and Y. Omae, *Jpn. Kokai Tokkyo Koho*, JP 2004018475; (*b*) N. Fukuoka, H. Yasuda, M. Nishimatsu, J. Inada and Y. Omae, *Chem. Abstr.*, 2004, **140**, 112217.
212. (*a*) F. Murakami and J. Nakahashi, *Jpn. Kokai Tokkyo Koho*, JP 2004107374; (*b*) F. Murakami and J. Nakahashi, *Chem. Abstr.*, 2004, **140**, 304706.
213. (*a*) H. Takenaka, M. Osada, K. Tomiyoshi and T. Shiobara, *Jpn Kokai Tokkyo Koho*, JP 2003138101; (*b*) H. Takenaka, M. Osada, K. Tomiyoshi and T. Shiobara, *Chem. Abstr.*, 2003, **138**, 386464; (*c*) M. Osada, H. Takenaka, K. Tomiyoshi and T. Shiobara, *Jpn. Kokai Tokkyo Koho*, JP 2003138102; (*d*) M. Osada, H. Takenaka, K. Tomiyoshi and T. Shiobara, *Chem. Abstr.*, 2003, **138**, 386467; (*e*) M. Osada, H. Takenaka, T. Shimoda and T. Shiobara, *Jpn. Kokai Tokkyo Koho*, JP 2003138103;

(*f*) M. Osada, H. Takenaka, T. Shimoda and T. Shiobara, *Chem. Abstr.*, 2003, **138**, 369981; (*g*) M. Osada, T. Shimoda, H. Takenaka and T. Shiobara, *Jpn. Kokai Tokkyo Koho*, JP 2003138104; (*h*) M. Osada, T. Shimoda, H. Takenaka and T. Shiobara, *Chem. Abstr.*, 2003, **138**, 369982.
214. (*a*) M. Osada, S. Ando, H. Takenaka, K. Tomiyoshi and T. Shiobara, *Jpn. Kokai Tokkyo Koho*, JP 2003226796; (*b*) M. Osada, S. Ando, H. Takenaka, K. Tomiyoshi and T. Shiobara, *Chem. Abstr.*, 2003, **139**, 150841.
215. (*a*) Y. Tada, Y. Nishioka and H. Takase, *Jpn. Kokai Tokkyo Koho*, JP 2004043339; (*b*) Y. Tada, Y. Nishioka and H. Takase, *Chem. Abstr.*, 2004, **140**, 164743.
216. S. Endo, T. Ogino and Y. Horikawa, *PCT Int. Appl.*, WO 2003005479.
217. K. M. Abraham, R. Gitzendanner, B. Lucht and B. Ravdel, *U.S*, US 2004091772.
218. (*a*) H. Takase, T. Kameshima, Y. Tada and S. Nakano, *Jpn. Kokai Tokkyo Koho*, JP 2003012805; (*b*) H. Takase, T. Kameshima, Y. Tada and S. Nakano, *Chem. Abstr.*, 2003, **138**, 91014.
219. A.-M. Caminade, J.-P. Majoral, J. Francois, J. Leclaire, B. Meunier, G. Pratviel, and E. Trevisiol, *Fr. Demande*, FR 2838737.
220. H. R. Allcock and A. Ambrosio, in 'Polymer Gels, Fundamentals and Applications', ed. H. B. Bohidar, P. Dubin and Y. Osade, ACS Symposium Series no. 833, Oxford University Press USA, 2003, 82.
221. S. Lakshmi, D.S. Katti and C.T. Laurencin, *Adv. Drug Deliv. Rev.*, 2003, **55**, 467.
222. D.S. Katti and C.T. Laurencin, in *'Advanced Polymeric Materials Structure Property Relationships'*, ed. G. O. Shonaike and S. G. Advani, CRC Press LLC, Boca Raton Fla, 2003, 479.
223. M.V. Chaubal, A.S. Gupta, S.T. Lopina and D.F. Bruley, *Crit. Rev. Therap. Drug Carrier Systems*, 2003, **20**, 295.
224. C.T. Laurencin and A.M.A. Ambrosio, in PBM Series Vol. 2, *'Biodegradable Polymers'*, ed. R. Arshady, Citrus Books, London, 2003, 153.
225. K. Zhu and L. Qiu, in Biopolymers, Vol. 9, *'Other Polymers and Biodegradation of Synthetic Polymers'*, ed. S. Matsumura and A. Steinbüchel, Wiley-VCH Verlag, GmbH Weinheim, Germany, 2003, 491.
226. F.F. Stewart and M.K. Harrup, *Polymer News*, 2001, **26**, 78.
227. M. Gleria, R. Bertani, R. De Jaeger and S. Lora, *J. Fluorine Chem.*, 2004, **125**, 329.
228. G. Martin, G. Rojo and F. Agulló-López, *J. Appl. Phys.*, 2004, **95**, 3477.
229. L. Gao, D.D. MacDonald, M. Urquidi-Macdonald, D.L. Olmeijer and H.R. Allcock, *Electrochim. Acta*, 2002, **47**, 3863.
230. D.-H. Chen, L. Hong, X.-W. Nie, X.-L. Wang and X.-Z. Tang, *Eur. Polym. J.*, 2003, **39**, 871.
231. V.M. Yashchuk, D. Bogdal, J. Pielichowski, Y.T. Kononenko, K.M. Kushnir, V.Y. Kudrya and A. Hanusek, *J. Mol.*, 2003, **105**, 185.
232. G.A. Carriedo, F.J. García Alonso, P. Gómez-Elipe, J.I. Fidalgo, J.L. García Álvarez and A. Presa-Soto, *Chem. Eur. J.*, 2003, **9**, 3833.
233. A.K. Andrianov, J. Chen and M.P. LeGolvan, *Macromolecules*, 2004, **37**, 414.
234. Z. Li and J. Qin, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 194.
235. C. Diaz and P. Castillo, *Polym. Bull.*, 2003, **50**, 123.
236. G.A. Carriedo, F.J. García Alonso, P. Gomez-Elipe, C. Díaz Valenzuela and N. Yutronic Sáez, *J. Chil. Chem. Soc.*, 2003, **48**, 25.
237. G.A. Carriedo, F.J. García Alonso and A. Presa-soto, *Eur. J. Inorg. Chem.*, 2003, 4341.
238. Z. Li, J. Qin, S. Li, C. Ye, J. Luo and Y. Cao, *Macromolecules*, 2002, **35**, 9232.
239. Z. Li, J.-G. Qin, S.-J. Li and C. Ye, *Chin. J. Chem.*, 2003, **21**, 1395.

240. Z. Li, C. Huang, J. Hua, J. Qin, Z. Yang and C. Ye, *Macromolecules*, 2004, **37**, 371.
241. J.N. Cambre and P. Wisian-Neilson, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 2003, **44**(1), 919.
242. T. Kmecko and P. Wisian-Neilson, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 2003, **44**(1), 921.
243. J.D. Bender, Y. Chang, M. McKenzie and H.R. Allcock, *Polym. Mater. Sci. Eng.*, 2003, **89**, 460.
244. H.R. Allcock and E.C. Kellam III, *Solid State Ionics*, 2003, **156**, 401.
245. R. Bissessur, D. Gallant and R. Brüning, *Solid State Ionics*, 2003, **158**, 205.
246. Y.W. Chen-Yang, H.C. Chen, F.J. Lin, C.W. Liao and T.L. Chen, *Solid State Ionics*, 2003, **156**, 383.
247. H.C. Chen, F.L. Lin and Y.W. Chen-Yang, *U.S.*, US 2002185627.
248. G. Saibaba, D. Srikanth and R. Reddy, *Bull. Mater. Sci.*, 2004, **27**, 51.
249. (*a*) T.A. Luther, F.F. Stewart, J.L. Budzien, R.A. LaViolette, W.F. Bauer, M.K. Harrup, C.W. Allen and A. Elayan, *J. Phys. Chem. B*, 2003, **107**, 3168; (*b*) T.A. Luther, M.K. Harrup and F.F. Stewart, in *'NMR Spectroscopy of Polymers in Solution and in the Solid State'*, ed. H.N. Cheng and A.D. English, ACS Symposium Series no. 834,Oxford University Press, USA, 2003, 409.
250. C.P.R. Nair, M. Sunitha and K.N. Ninan, *Polym. Polym. Comp.*, 2002, **10**, 457.
251. C.P.R. Nair and K.N. Ninan, *Polym. Polym. Comp.*, 2004, **12**, 55.
252. C.P.R. Nair and K.N. Ninan, *J. Appl. Polym. Sci.*, 2003, **88**, 908.
253. C.M. Ambler, A.E. Maher, R.M. Wood, H.R. Allcock, E. Chalkova and S.N. Lvov, *Polym. Mater. Sci. Eng.*, 2003, **89**, 595.
254. E. Chalkova, X. Zhou, C. Ambler, M.A. Hofmann, J.A. Weston, H.R. Allcock and S.N. Lvov, *Electrochemical and Solid-State Letters*, 2002, **5**, A221.
255. X. Zhou, J. Weston, E. Chalkova, M.A. Hofmann, C.M. Ambler, H.R. Allcock and S.N. Lvov, *Electrochim. Acta*, 2003, **48**, 2173.
256. A.K. Andrianov, A. Marin, J.R. Sargent and J. Chen, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 2003, **44**(1), 724.
257. J.R. Sargent, J. Chen, A Andrianov and A. Marin, *PCT Int. Appl.*, WO 2003102050.
258. Y. Chang and H.R. Allcock, *Adv. Mater.*, 2003, **15**, 537.
259. A. Spitaleri, P. Pertici, N. Scalera, G. Vitulli, M. Hoang, T.W. Turney and M. Gleria, *Inorg. Chim. Acta*, 2003, **352**, 61.
260. A.J. Hill, T.J. Bastow, P. Meakin, T.W. Turney, M. Hoang, N. Scalera, P. Pertici and G. Vitulli, *Desalination*, 2002, **144**, 61.
261. L. Qiu, *J. Appl. Polym. Sci.*, 2003, **87**, 986.
262. L. Qiu, *J. Appl. Polym. Sci.*, 2004, **92**, 1993.
263. A. Lacherai and R. Dejaeger, *Phys. Chem. News*, 2003, **9**, 125.
264. M. Gümüşderelioğlu and A. Gür, *React. Funct. Polym.*, 2002, **52**, 71.
265. J. Luten, J.H. van Steenis, R. van Someren, J. Kemmink, N.M.E. Schuurmans-Nieuwenbroek, G.A. Koning, D.J.A. Crommelin, C.F. van Nostrum and W.E. Hennink, *J. Control. Release*, 2003, **89**, 483.
266. R. D'Eredita', *PCT Int. Appl.*, WO 2003059406.
267. (*a*) H.R. Allcock, A. Singh, A.M.A. Ambrosio and W.R. Laredo, *Biomacromolecules*, 2003, **4**, 1646; (*b*) H.R. Allcock, W.R. Laredo, J.D. Bender and A.M.A. Ambrosio, *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)*, 2002, **43**(2), 654.
268. R. Denk, *PCT Int. Appl.*, WO 2004004795.
269. S. Kanezaki, H. Kawakami, S. Nagaoka and S. Kubota, *J. Biomater. Sci. Polym. Edn.*, 2003, **14**, 469.

270. Y. Cui, X. Zhao, X. Tang and Y. Luo, *Biomaterials*, 2003, **25**, 451.
271. S.B. Lee, Y.S. Sohn and S.-C. Song, *Bull. Korean Chem. Soc.*, 2003, **24**, 901.
272. (*a*) Y. Chang, E.S. Powell, H.R. Allcock, S.M. Park and C. Kim, *Macromolecules*, 2003, **36**, 2568; (*b*) Y. Chang, E. Powell, H.R. Allcock, S.M. Park and C. Kim, *Polym. Prepr. (Am. Chem. Soc. Div. Polym. Chem.)*, 2003, **44**(2), 922.
273. M.A. Winnik, I. Manners, Z. Pang, X. Gu and Y. Ni, *U.S.*, US 6565992.
274. X. Lu, B.-H. Han and M.A. Winnik, *J. Phys. Chem. B*, 2003, **107**, 13349.
275. (*a*) Y. Nishioka, Y. Tada and H. Takase, *Jpn. Kokai Tokkyo Koho*, JP 2003342339; (*b*) Y. Nishioka, Y. Tada and H. Takase, *Chem. Abstr.*, 2004, **140**, 5941; (*c*) Y. Nishioka, Y. Tada and T. Kameshima, *Jpn. Kokai Tokkyo Koho*, JP 2004083823; (*d*) Y. Nishioka, Y. Tada and T. Kameshima, *Chem. Abstr.*, 2004, **140**, 254403.
276. (*a*) K. Sawai and T. Hosoi, *Jpn. Kokai Tokkyo Koho*, JP 2003306595; (*b*) K. Sawai and T. Hosoi, *Chem. Abstr.*, 2003, **139**, 324477.
277. R.E. Lyon, L. Speitel, R.N. Walters and S. Crowley, *Fire Mater.*, 2003, **27**, 195.
278. (*a*) W. Kataphinan, R. Teye-Mensah, E.A. Evans, R.D. Ramsier, D.H. Reneker and D.J. Smith, *J. Vac. Sci. Technol.*, 2003, **21**, 1574; (*b*) W. Kataphinan, R. Teye-Mensah, E.A. Evans, R.D. Ramsier, D.J. Smith and D.H. Reneker, *Polym. Mater. Sci. Eng.* 2003, **88**, 282.
279. D.H. Reneker, R.D. Ramsier, G.G. Chase, E.A. Evans and D.J. Smith, *PCT Int. Appl.*, WO 2004019115.