

155 Topics in Current Chemistry

Small Ring Compounds in Organic Synthesis IV

Editor: A. de Meijere

With contributions by
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A. P. Molchanov, E. Nakamura

With 16 Tables



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Metal Homoenoates from Siloxycyclopropanes

Isao Kuwajima and Eiichi Nakamura

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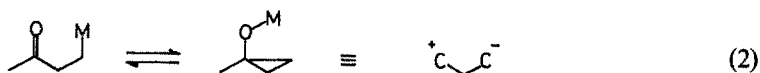
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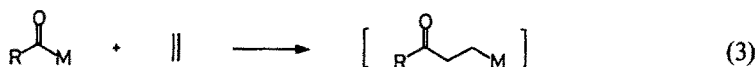
The potential of metal homoenoates as multifunctional reagents in organic synthesis has become recognized in the last decade. Ring opening of siloxycyclopropanes by Lewis acidic metals currently provides the best route to the metal homoenoates, which are either isolable as a stable complex or exist only as a transient organometallic species. This review summarizes, for the first time, the research activities of metal homoenoate chemistry. Other synthetically useful routes to metal homoenoates are also described.

1 Introduction

Although the chemistry of metal enolate/ α -metallo ketone tautomeric pairs Eq. (1) has attracted the interest of chemists for a long period, it still represents an important subject of organic chemistry. Recent vigorous activities in achieving stereocontrol in the aldol reaction, for instance, resulted in further refinement of enolate chemistry. Unlike enolates, the homo-enolate tautomeric pair Eq. (2) [1] in which the carbonyl group and the β -anionic center are homoconjugated, has eluded detailed investigation, in particular, that of synthetic applications [2].



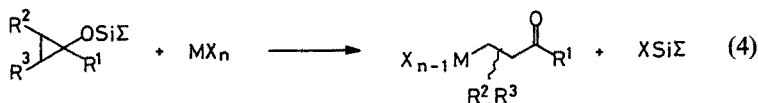
Like that of an enolate, the value of a homo-enolate stems from its amphoteric nature (Cf. Eqs. 1, 2). In addition, the homo-enolate serves as an archetypal synthon in the concept of Umpolung [3], acting as a nucleophilic, inverse-polarity Michael acceptor. Despite such conceptual importance, practical problems set great restrictions on the actual application of homo-enolate chemistry in organic synthesis. First, unlike the enolate anion, the homo-enolate anion cannot be stoichiometrically generated by deprotonation of a carbonyl compound, since the pK_a value of the β -hydrogen is only very slightly lowered [2]. An additional problem is created by an intrinsic property of reactive homo-enolates; namely sodium or lithium homo-enolates spontaneously cyclize to the cyclopropanolate tautomer [2]. This alkoxide tautomer has never reacted as a carbon-nucleophile toward standard electrophiles (except a proton). Therefore, in the subsequent paragraphs, the word homo-enolate refers specifically to the carbanionic form of the homo-enolate tautomeric pair Eq. (2). Transition metal homo-enolates have been postulated in the reactions of acyl transition metal complexes with olefins, which is a common process in reactions in a carbon monoxide atmosphere Eq. (3) [4]. However, without suitable precautions to stabilize the complex [5], these transition metal homo-enolates undergo further reactions.



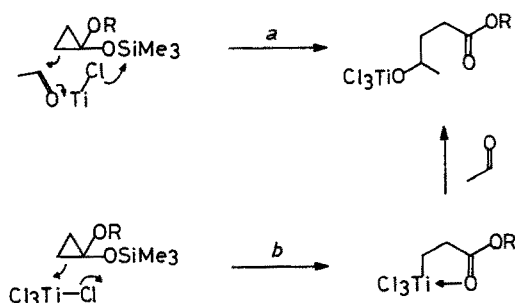
Nonetheless, "homo-enolates" have been much talked about as a species useful for carbon-carbon chain extension, and a number of "homo-enolate equivalents" have been prepared and used for organic synthesis. Reviews on these species have been published [6].

The last few years have seen the development of an entirely new methodology in which the metal homo-enolate is prepared by ring opening of siloxycyclopropanes with metal halides Eq. (4). In these reactions, a very subtle balance of

kinetic and thermodynamic factors allows certain metal halides to form reactive metal homoenolates which do not close back to the three-membered ring. Although the reaction in Eq. (4) tolerates a broad spectrum of structural variation with respect to the substituents, the nature of the substituent on the ring, particularly that at C-1, has a great influence on the chemistry following the ring cleavage. 1-Alkoxy substituents (R^1) exert particularly great effects, allowing the preparation of a variety of ester homoenolates. Cyclopropanes with $R^1 =$ alkyl or aryl thus far remain less viable as precursors to the corresponding homoenolates.



The chemistry of cyclopropanol [7] has long been studied in the context of electrophilic reactions, and these investigations have resulted in the preparation of some 3-mercurio ketones. As such mercury compounds are quite unreactive, they have failed to attract great interest in homoenolate chemistry. Only recent studies to exploit siloxycyclopropanes as precursors to homoenolates have led to the use of 3-mercurio ketones for the transition metal-catalyzed formation of new carbon-carbon bonds [8] (vide infra).



In 1977, an article from the authors' laboratories [9] reported an TiCl_4 -mediated coupling reaction of 1-alkoxy-1-siloxy-cyclopropane with aldehydes (Scheme 1), in which the intermediate formation of a titanium homoenolate (path b) was postulated instead of a then-more-likely Friedel-Crafts-like mechanism (path a). This finding some years later led to the isolation of the first stable metal homoenolate [10] that exhibits considerable nucleophilic reactivity toward (external) electrophiles. Although the metal-carbon bond in this titanium complex is essentially covalent, such titanium species underwent ready nucleophilic addition onto carbonyl compounds to give 4-hydroxy esters in good yield. Since then a number of characterizable metal homoenolates have been prepared from siloxycyclopropanes [11]. The repertoire of metal homoenolate reactions now covers most of the standard reaction types ranging from simple

elimination to substitution reactions. Homoenoates are now a reality in organic synthesis rather than a presumed intermediate of exotic reactivity. The purpose of this review is to summarize the current stage of development of the siloxycyclopropane route to metal homoenoates and convey information to chemists engaged in organic synthesis as well as organometallic chemistry. A few other recent routes to metal homoenoates are also reviewed briefly.

2 Preparation of Siloxycyclopropanes

In 1972 and 1973, four laboratories [12–15] reported the Simmons-Smith cyclopropanation of enol silyl ethers as a very flexible route to siloxycyclopropanes, Eq. (5). Reagents prepared either from a zinc/copper couple [13–15] or a zinc/silver couple [12] have been successfully used for the cyclopropanation of enol silyl ethers from ketones (Table 1). Regioselectivity is noted with polyolefinic substrates, the electron-rich enol silyl ether moiety being attacked preferentially. The reaction is stereospecific with retention of the double bond configuration in the starting material. Prolonged heating of the reaction mixture results in a Zn(II)-catalyzed rearrangement of siloxycyclopropanes to allylic ethers. Termination of the cyclopropanation by addition of pyridine, aqueous NH_4Cl [15], or gaseous ammonia [16] prevents side reactions which may otherwise occur during workup owing to the Zn(II) residues. Table I shows some representative types of compounds prepared by this carbenoid route.

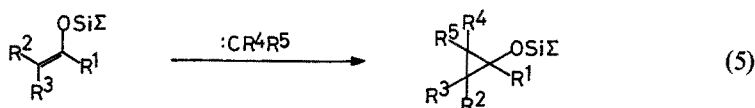
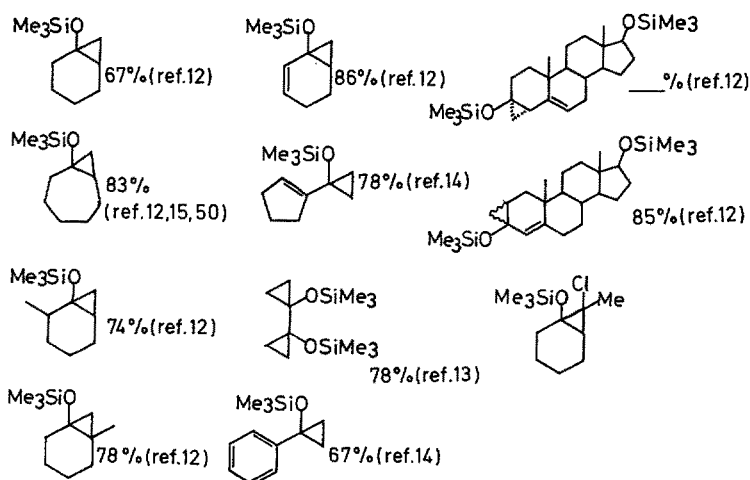
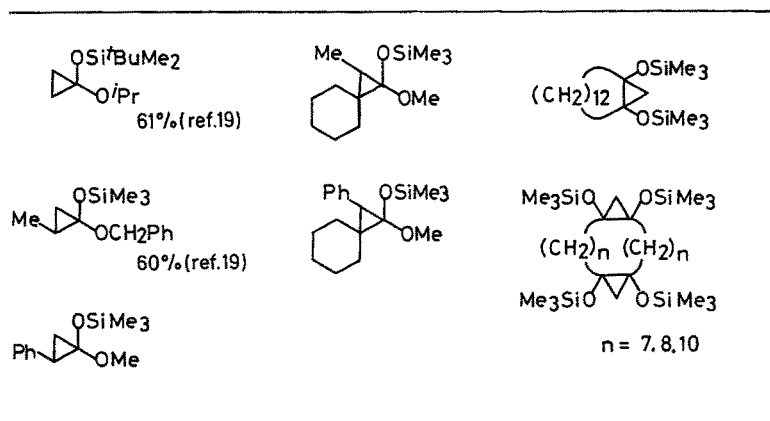


Table 1. Siloxycyclopropanes prepared by the Simmons-Smith reaction

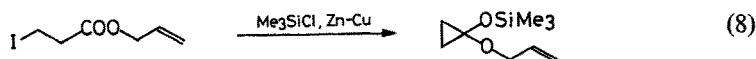
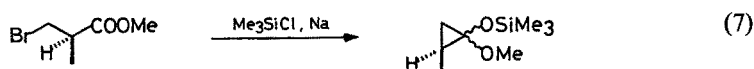
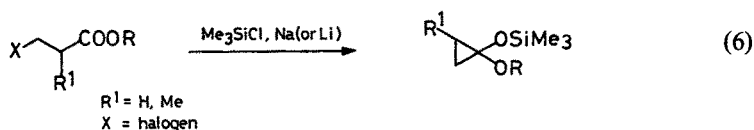


The carbenoid from $\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$ [17], particularly when generated in the presence of oxygen [18], is more reactive than the conventional Simmons-Smith reagents. The milder conditions required are suitable for the preparation of 1-[16, 19] or 2-alkoxy-1-siloxycyclopropanes [20], which are generally more sensitive than the parent alkyl substituted siloxycyclopropanes (Table 2). Cyclopropanation of silyl ketene acetals is not completely stereospecific, since isomerization of the double bond in the starting material competes with the cyclopropanation [19].

Table 2. Alkoxy siloxy cyclopropanes prepared by $\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$.



Acyloin-type reactions of esters provide the simplest route to 1-siloxy-1-alkoxycyclopropane [21, 22] Eq. (6). The reaction of commercial 3-halopropionate with sodium (or lithium) in refluxing ether in the presence of Me_3SiCl can easily be carried out on a one mole scale [21]. Cyclization of optically pure methyl 3-bromo-2-methylpropionate [23], available in both *R* and *S* form, gives a cyclopropane, which is enantiomerically pure at C-2, yet is a 1:1 diastereomeric mixture with respect to its relative configuration at C-1 Eq. (7). Reductive silylation of allyl 3-iodopropionate with zinc/copper couple provides a milder alternative to the alkali metal reduction [24] Eq. (8).



3 Preparation and Reactions of Isolable Metal Homoenoates

The recent surge of interests in metal homoenoate chemistry has been stimulated by the recognition that the siloxycyclopropane route can afford novel reactive homoenoate species that are stable enough for isolation, purification, and characterization. The stability of such homoenoates crucially depends on the subtle balance of nucleophilic and electrophilic reactivity of the two reactive sites in the molecule. Naturally, homoenoates with metal-carbon bonds that are too stable do not serve as nucleophiles in organic synthesis.

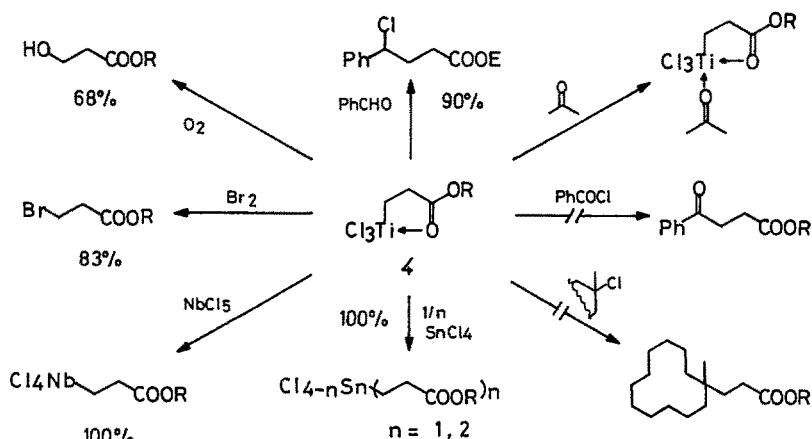
3.1 Preparation

3.1.1 Group 4 Metal Homoenoates

An exothermic reaction between cyclopropane **1** and TiCl_4 in methylene chloride produces a wine-red solution of a mixture of titanium homoenoate **2** and chlorotrimethylsilane [10, 19]. When the reaction is performed in hexane, the titanium species precipitates in the form of fine violet needles (approx 90% isolated yield, Eq. (9)).



This complex, while sensitive to oxygen and moisture, is stable for extended periods either neat or in solution. Its carbonyl stretching band (approx. 1610 cm^{-1}) in the IR spectrum in dilute solution clearly indicates a chelate structure, which endows the carbon-titanium bond of this complex with very high stability, as compared with that of simple alkyltrichlorotitaniums [25].



Scheme 2

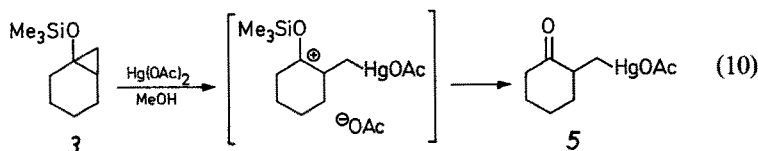
The chemical reactivities of such titanium homoenolates are similar to those of ordinary titanium alkyls (Scheme 2). Oxidation of the metal-carbon bond with bromine or oxygen occurs readily. Transmetalations with other metal halides such as SnCl_4 , SbCl_5 , TeCl_4 , and NbCl_5 proceed cleanly. Reaction with benzaldehyde gives a 4-chloroester as the result of carbon-carbon bond formation followed by chlorination [9]. Acetone forms an addition complex. No reaction takes place with acid chloride and *tert*-alkyl chlorides.

The reaction of the cyclopropane **1** with ZrCl_4 gave a complex mixture [11].

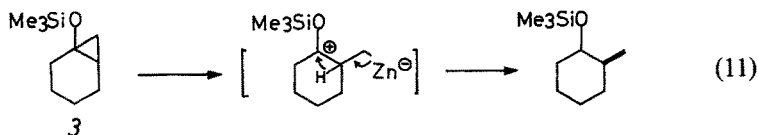
3.1.2 Group 12 Metal Homo-enolates

Cyclopropanols react with mercuric salts to give a variety of 3-mercurio ketones, and the chemistry of this ring cleavage has been thoroughly studied from the mechanistic viewpoint [7].

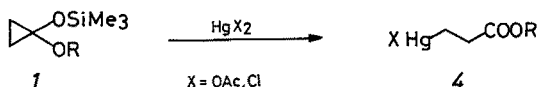
Similarly, siloxycyclopropanes (e.g., **3**) react smoothly with mercuric acetate in methanol at 20 °C to give 3-mercurio ketones (e.g., **4**) [8]. The attack of the metal occurs in such a way that the less alkyl-substituted bond is cleaved. Thus, starting from the enol silyl ether, the overall sequence represents α -mercurio-methylation of the parent ketone. The reaction is likely to proceed via an ionic intermediate Eq. (10).



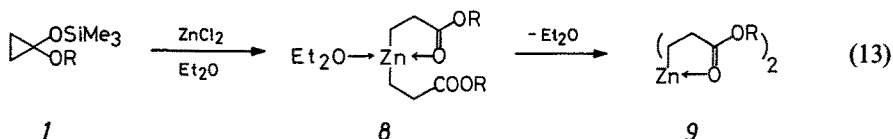
Isomerization of siloxycyclopropane **3** to the allylic silyl ether in the presence of ZnI_2 has close mechanistic similarity to the homo-enolate formation, Eq. (11) [26]. The initial zwitterionic intermediate after ring cleavage undergoes a hydride shift rather than elimination of the silyl group.



1-Alkoxy-1-siloxycyclopropanes **1** are also cleaved readily by HgCl_2 , $\text{Hg}(\text{OAc})_2$, or $\text{Hg}(\text{OCOCF}_3)_2$ to give monoalkylated mercuriaer **5** in high yield Eq. (12) [11]. Further alkylation of **5** was not observed. The methyl-substituted cyclopropane **6** produces 3-mercurio-2-methylpropionate as a single product, while the phenyl-substituted **7** gives a mixture of 2- and 3-phenylesters [27]. CdCl_2 reacts slowly in CDCl_3 under ultrasound irradiation at room temperature to give the cadmium homo-enolate [11].

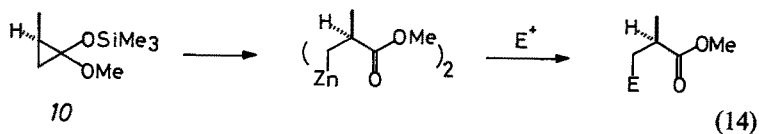


ZnCl₂ cleanly reacts with cyclopropane **1** in ether within a few hours at room temperature to give the zinc homoenoate etherate **8** in high yield Eq. (13) [11, 28]. Removal of the solvent gives the ether-free complex **9**, which can also be generated albeit, in lower yield, in a halomethane solvent. The zinc homoenoate, though sensitive to oxygen and water, is thermally very stable. The ring cleavage reaction is in fact an equilibrium, which in ether favors the homoenoate formation ($K = \text{approx } 30$) [29].



Methylcyclopropane **6** reacts selectively (>98%) with ZnCl₂ at the less hindered site to give the homoenoate of 2-methylpropionate, whereas phenyl substituted analogue **7** is cleaved selectively (>98%) at the more substituted site [27]. The latter homoenoate however suffers in situ protonation under the reaction conditions and could not be isolated.

The optically active cyclopropane **10** gave the chiral homoenoate of isobutyrate Eq. (14), an ethereal solution of which is both chemically and configurationally stable for a week at room temperature, and consequently can serve as a useful chiral building block [23].



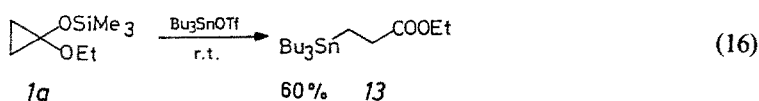
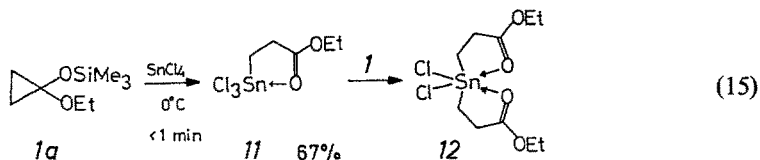
3.1.3 Group 13 Metal Homoenoates

The common Lewis acids in this group, AlCl₃ and BX₃, do not form metal homoenoates in their reaction with siloxycyclopropanes, only GaCl₃ reacts with 1-alkoxy-1-siloxycyclopropanes **1** to give propionate homoenoates [11].

3.1.4 Group 14 Metal Homoenoates

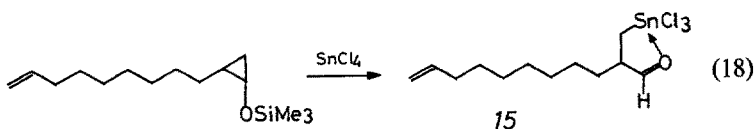
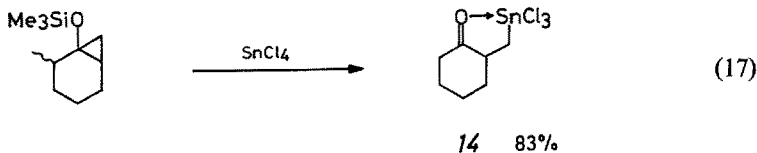
Upon addition of cyclopropane **1** to one equivalent of SnCl₄ in methylene chloride at 0 °C, an exothermic reaction occurs to give 3-stannyl propionate **11** in approx. 70% yield [9, 11]. Addition of a second equiv of the cyclopropane slowly converts **11** to the dialkylated tin compounds, **12** Eq. (15). No further alkylation was observed. Chelate structures of such homoenoates implied by their spectral properties are supported by single crystal X-ray analysis [30].

The cyclopropane is inert to tributyltin chloride, but reacts readily with more highly Lewis acidic tributyltin trifluoromethanesulfonate (triflate) [11]. The 3-stannyl ester **13** showed no sign of internal chelation Eq. (16).



The cyclopropane **1** was inert to GeCl_4 , SiCl_4 , Me_3SiCl , trimethylsilyl triflate, and PbCl_2 [11].

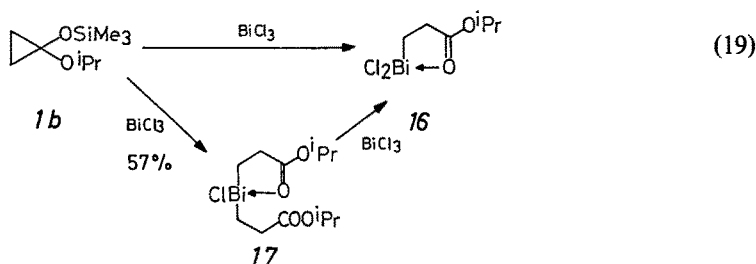
Siloxycyclopropanes corresponding to ketone homoenolates (e.g. **3**) also react smoothly with SnCl_4 at 15°C to give 3-stannyl ketones (e.g. **14**) Eq. (17) [31]. In the same manner, the 3-stannyl aldehyde **15** has been prepared in good yield. Eq. (18).



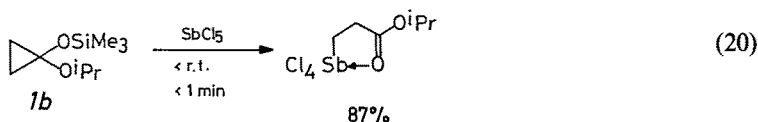
3.1.5 Group 15 Metal Homo-enolates

Treatment of cyclopropane **1** with one equivalent of dry BiCl_3 in methylene chloride results in an exothermic reaction producing monoalkylbismuth derivative **16** in 80% yield Eq. (19) [11]. Addition of another equivalent of the cyclopropane then affords the dialkylated bismuth species **17**, which in turn reacts with BiCl_3 to give the monoalkyl species. IR absorptions due to the carbonyl groups indicate the chelate structures shown. The two propionate moieties in the dialkylated compound **17** give rise to two distinctive carbonyl bands in the IR spectrum,

but are indistinguishable by ^1H NMR, indicating rapid internal ligand exchange at 35°C .

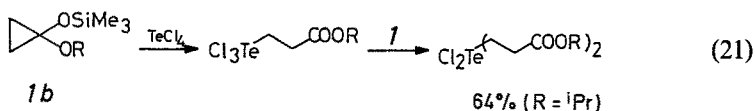


Strongly Lewis acidic SbCl_5 rapidly reacts with one equivalent of the cyclopropane **16** in chloroform to give monoalkylated antimony derivate **18** in 87% yield Eq. (20) [11]. The internal chelation is especially strong, as indicated by the carbonyl band in the IR spectrum at 1600 cm^{-1} . In contrast to the common monoalkyltetrachloroantimony, the chelated homoenoate **18** is stable at room temperature for many hours.



3.1.6 Group 16 Metal Homoenoates

Among the group 16 elements, mostly non-metallic ones like TeCl_4 were examined [11]. The reaction with TeCl_4 proceeds in a stepwise manner giving the monoalkyltellurium and the dialkyl compound in accordance with the stoichiometry of the reagents Eq. (21). As in the case of tin and bismuth, the second alkylation is much slower than the first and the dialkyl species could not be alkylated any further.

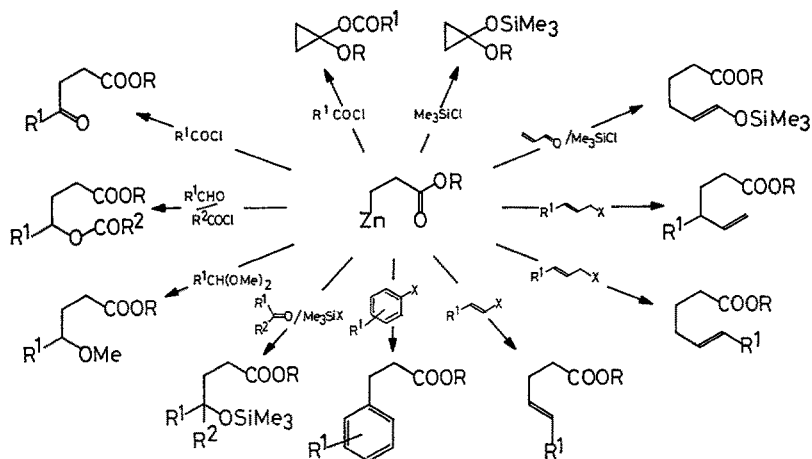


3.1.7 Metal Homoenoates of Other Groups [11]

The cyclopropane **1** reacts with none of the group 1 and 2 metal chlorides. Among early transition metal chlorides, NbCl_4 reacted with **1** in moderate yield to give the same homoenoate obtained by the reaction of equimolar amounts of titanium homoenoate **2** and NbCl_4 (Scheme 2). TaCl_5 , CrCl_3 , MoCl_5 , and WCl_5 did not give any characterizable products.

3.2 Carbon-carbon Bond Forming Reactions of Metal Homoenoates

Various types of carbon-carbon bond forming reactions of metal homoenoates have been reported, some of which are highly synthetically useful. Scheme 3 illustrates reaction types of zinc homoenoates (**8** or **9**). In this section the reactions of stable homoenoates are presented according to the reaction types. Examples, in which siloxycyclopropanes generate transient, unstable homoenoates, are described in Sect. 5.

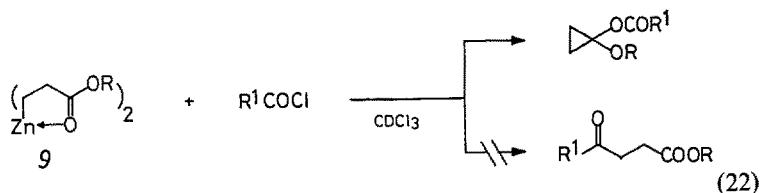


Scheme 3

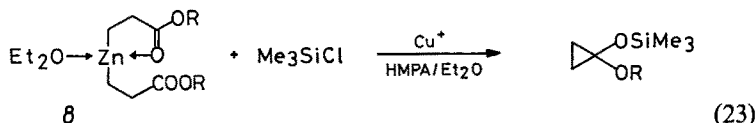
3.2.1 Cyclopropane Formation

Internal nucleophilic cyclization leading to alkoxy-cyclopropanes is the most typical reaction of reactive metal homoenoates [1, 2]. The nature of stable homoenoates, however, is such that the anionic carbon C-3 forms a covalent bond with the metal atom and does not show high nucleophilic reactivity.

Among isolable metal homoenoates only zinc homoenoates cyclize to cyclopropanes under suitable conditions. Whereas acylation of zinc alkyls makes a straightforward ketone synthesis [32], that of a zinc homoenoate is more complex. Treatment of a purified zinc homoenoate in CDCl_3 with acid chloride at room temperature gives O-acylation product, instead of the expected 4-keto ester, as the single product (Eq. (22) [33]). The reaction probably proceeds by initial electrophilic attack of acyl cation on the carbonyl oxygen. A C-acylation leading to a 4-keto ester can, however, be accomplished in a polar solvent Eq. (44).

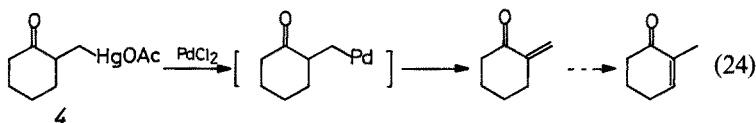


Treatment of zinc homoenoates with Me_3SiCl in a polar solvent also results in cyclopropane formation Eq. (23). This provides a very mild route to the siloxycyclopropanes [24].



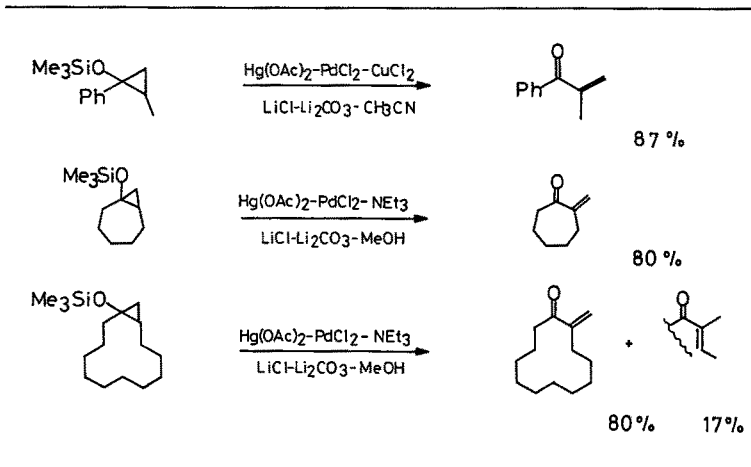
3.2.2 Elimination

Next to the cyclopropane formation, elimination represents the simplest type of a carbon-carbon bond formation in the homoenoates. Transition metal homoenoates readily eliminate a metal hydride unit to give α,β -unsaturated carbonyl compounds. Treatment of a mercurio ketone with palladium (II) chloride results in the formation of the enone presumably via a 3-palladio ketone (Eq. (24), Table 3) [8]. The reaction can be carried out with catalytic amounts of palladium (II) by using CuCl_2 as an oxidant. Isomerization of the initial exo-methylene derivative to the more stable *endo*-olefin can efficiently be retarded by addition of triethylamine to the reaction mixture.



Heating of the 3-trichlorostannyl ketone in DMSO also results in formation of 2-methylcyclohexanone (Eq. (25), Table 4) [31], which is formally the reverse reaction of a hydrostannylation of the enone with HSnCl_3 . This alternative route

Table 3. Synthesis α -methylene ketones via mercurio ketones (Ref. [8])



to α -methylene ketones has an obvious advantage over the above mentioned mercurial-palladium approach, but the overall reaction conditions of the latter are essentially neutral. The utility of the stannyl ketone route is illustrated by the preparation of an unstable α -methylene aldehyde, Eq. (26).

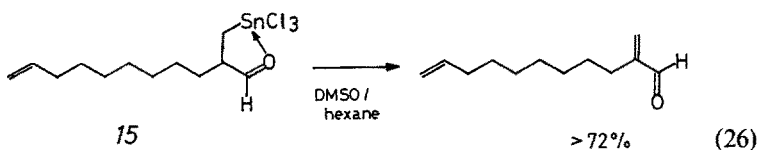
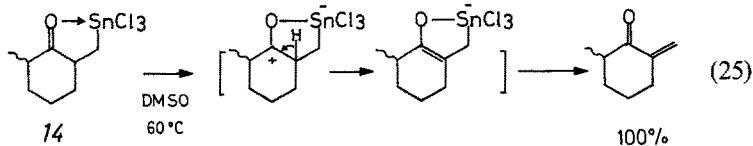
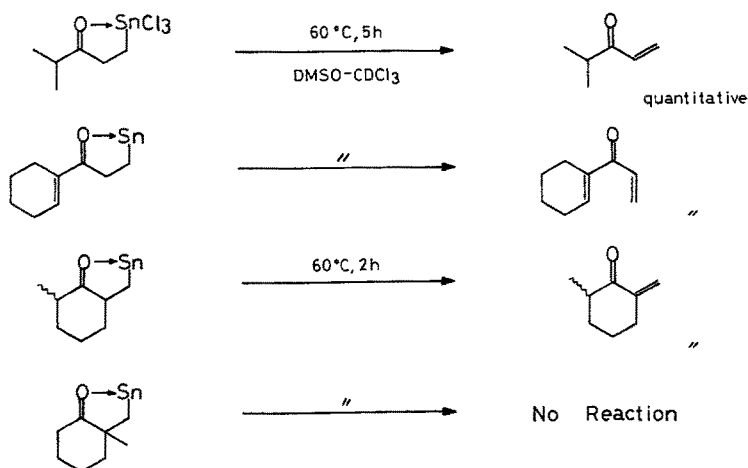
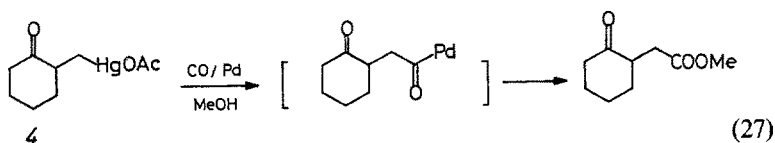


Table 4. Synthesis of α -methylene ketones from stannyl ketones (Rev. [3])

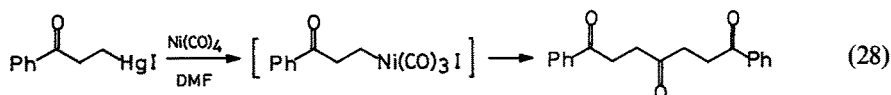


3.2.3 Carbonylation

The treatment of the mercurio ketone with palladium (II) in the presence of carbon monoxide and methanol, Eq. (27) results in the formation of a γ -keto ester with incorporation of one molecule of carbon monoxide [8]. The overall conversion of a siloxycyclopropane to the keto ester may be performed without isolation of the mercurio ketone.



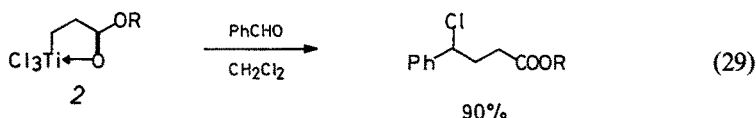
Treatment of the mercurio ketone with $\text{Ni}(\text{CO})_4$ results in a symmetrical coupling with incorporation of one molecule of carbon monoxide to give a triketone presumably via a 3-nickel substituted ketone Eq. (28) [34]. This symmetrical coupling reaction is general for alkyl mercury compounds.



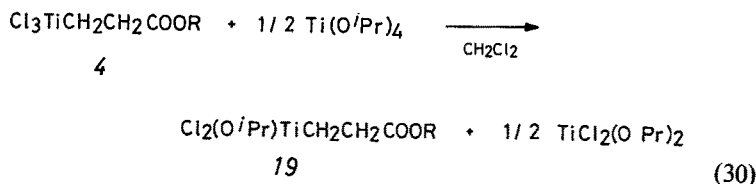
3.2.4 Carbonyl Addition

Addition of a homoenoate onto a carbonyl compound, which may be viewed as a "homo-aldol reaction", poses a significant conceptual problem. The nature of the homoenoate is such that the reaction with the internal carbonyl group is entropically greatly favored over that with the external target carbonyl group. Such a reaction can only compete with the internal electrophile, when it has a great enthalpic advantage. Up till now two types of homoenoates are known to undergo intermolecular addition onto carbonyl compounds, namely titanium [9, 10, 19] and zinc homoenoates of esters [33].

Trichlorotitanium homoenoate **2** smoothly adds to aldehydes at 0 °C [9, 10]. Due to the strongly acidic reaction conditions, however, addition products of aromatic aldehydes tend to undergo further transformations Eq. (29). The trichlorotitanium homoenoate does not react with ketones (Scheme 2).

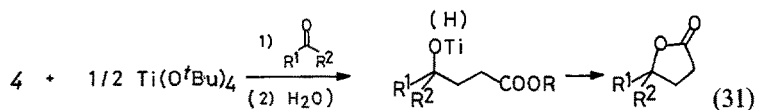


Ligand exchange provided a simple and effective solution to these problems. Addition of 0.5 eq. of $\text{Ti}(\text{O}^i\text{Pr})_4$ to the trichlorotitanium homoenoate produces an alkoxytitanium species **19** which is more reactive than the original homoenoate, Eq. (30). This allows the addition to proceed under nearly neutral conditions. Preparation of 4-hydroxy esters by this method is summarized in Table 5. The structure of **19** has been studied by ^1H NMR spectroscopy [19].



An even more reactive complex which is particularly useful for reactions with ketones is available by ligand exchange with $\text{Ti}(\text{O}^t\text{Bu})_4$, Eq. (31). The

initial adduct tends to cyclize in situ to a γ -lactone, unless the reaction is carried out at low temperatures. The results are summarized in Table 6.



These alkoxytitanium homoenolates show high propensity for equatorial attack in their ir reactions with substituted cyclohexanones (Table 6). The basic trend of their chemical behavior is similar to that of simple titanium alkyls [35]. Chemo-selectivity of the reagent **19** is also noteworthy. The alkoxytitanium homoenolate reacts preferentially with an aldehyde even in the presence of a ketone Eq. (32). A notable difference of rate between the reaction with cyclohexanone and that with 2-methylcyclohexanone was also observed, the latter being far less reactive toward the homoenolate.

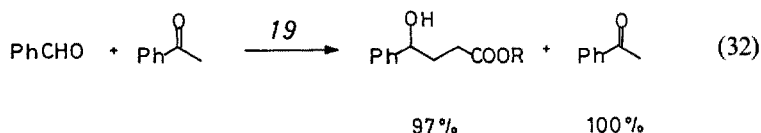
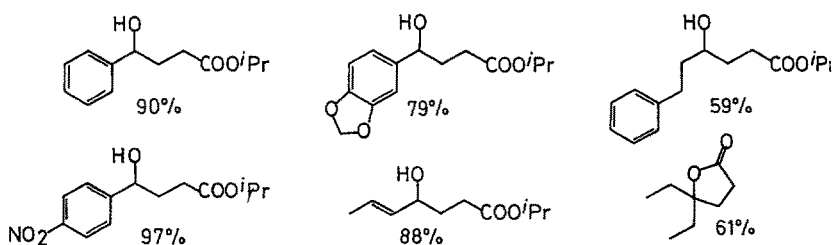
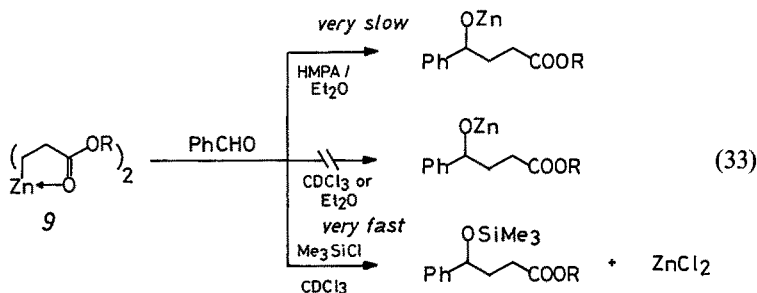
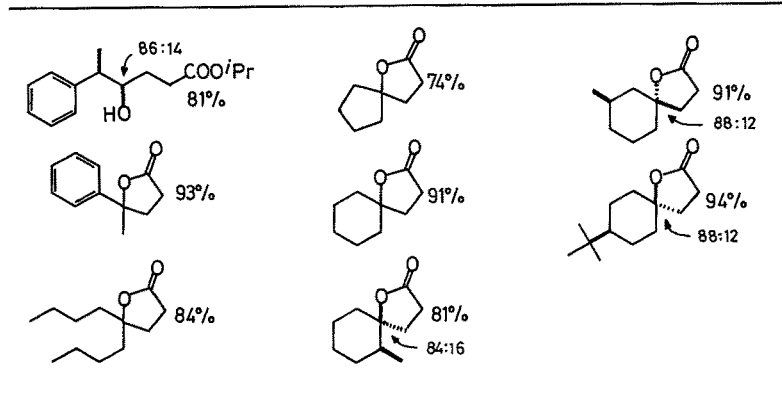


Table 5. 4-Hydroxyesters by Homo-Reformatsky addition of isopropoxytitanium homoenolate (Ref. [19])



In line with the chemistry of dialkylzinc [36], the zinc homoenolate is inert to carbonyl compounds in a variety of solvents, Eq. (33). Slow addition occurs only in an HMPA/THF mixture. When the reaction is conducted in halomethane in the presence of Me_3SiCl , however, a very rapid addition reaction occurs [33]. Control experiments indicate that the acceleration is due to the activation of the carbonyl group by Me_3SiCl . The activating effect of the chlorosilane disappears in ethereal solvents.

Table 6. Lactones by Homo-Reformatsky addition of *tert*-butoxytitanium homoenolate (Ref. [19])

ZnCl_2 is generated in the Me_3SiCl mediated reaction, Eq. (33). Taking advantage of this fact as well as the accelerating effect of the chlorosilane, the cyclopropanes (**1**, **6**, and **7**), and aldehydes have been coupled directly in the presence of ZnCl_2 . ZnI_2 , which in situ produces Me_3SiI , is an even more effective catalyst, only 1/1000 eq. of which suffices to obtain 4-siloxy esters in high yield Eq. (34) [33]. ZnI_2 , but not ZnCl_2 , promotes the addition reaction of 1-*tert*-butyldimethylsiloxy-1-isopropoxycyclopropane **20**. ZnI_2 also catalyzes the reaction of acetophenone or benzaldehyde dimethyl acetal, which fail to react under ZnCl_2 catalysis. Results of such of ZnX_2 catalyzed “homo-Reformatsky” reactions are summarized in Table 7.

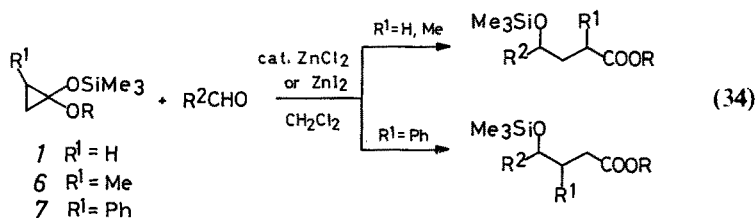
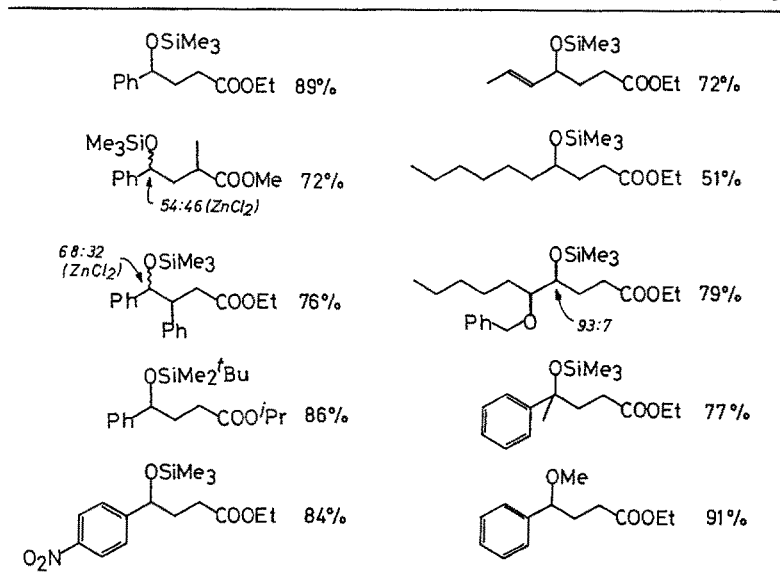
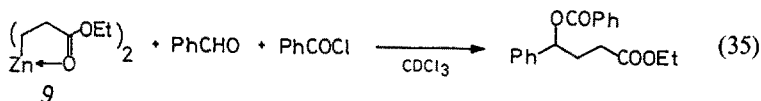


Table 7. 4-Siloxy esters by ZnX_2 -catalyzed Homo-Reformatsky reaction (Ref. [29, 33])

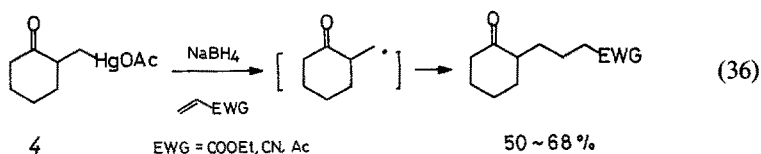
Interestingly, the carbonyl addition of the zinc homoenolate, in the presence of acid chloride, affords 4-acyloxyesters Eq. (35) [27].



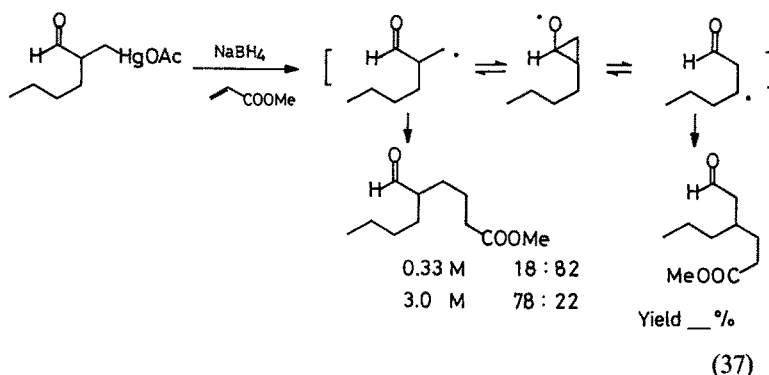
The fact that the above reactions allow isolation of 4-hydroxyesters, which are often unstable and lactonize quickly, is a merit of the homoenolate chemistry. Mesylation of the hydroxy group followed by appropriate operations provides stereocontrolled routes to γ -lactones and cyclopropane carboxylates [19]. Through application of such methodology steroid total synthesis has been achieved (Section 7).

3.2.5 Conjugate Additions

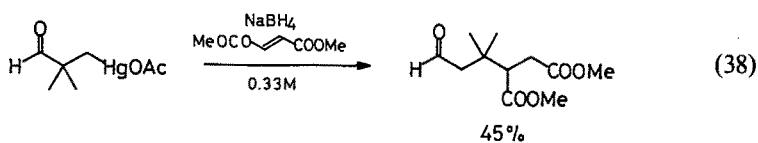
The mercurio ketone **4** upon reduction with NaBH_4 yields a radical which is trapped in situ by reactive acceptors such as vinyl ketones [37]. Treatment of a 1:3 mixture of mercurio ketone **4** and electron deficient terminal alkenes (or fumarate) in CH_2Cl_2 with a concentrated solution of NaBH_4 in water gives conjugate adducts, Eq. (36).



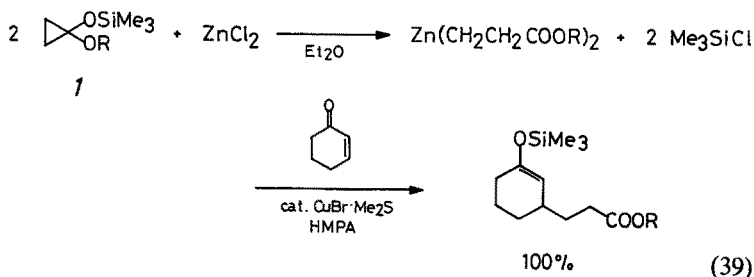
A highly intriguing isomerization of the "homoenolate radical" which probably proceeds via formation of a cyclopropyloxy radical, was noted in the reaction of a mercurio aldehyde [37]. The product ratio should reflect the ratio of internal/external trapping, and in fact the ratio of unrearranged and rearranged product depends on the concentration of the trapping reagent, Eq. (37).



When the stabilities of the two corresponding radicals are grossly different as in the case of gem-dimethyl homoenolate, one may obtain the product originating from the more stable homoenolate radical as the sole product, Eq. (38). A related isomerization reaction, albeit proceeding in the opposite direction, has often been recorded for anionic homoenoates.



A general method for the conjugate addition of ester homoenolate to an α,β -unsaturated ketone has been realized in a Cu(I)-catalyzed reaction of the zinc homoenolate [28]. Thus, successive addition of an enone, copper catalyst, and HMPA to the crude ethereal solution of the zinc homoenolate containing Me_3SiCl results in quantitative formation of the enol silyl ether (Eq. 39, Table 8). Me_3SiCl strongly accelerates the conjugate addition of intermediary organocopper species [38]. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ also enhances the rate, but may give different stereochemical results [39].



The reaction with an acetylenic ketone produced an allenic enol ether (Table 8), which upon hydrolysis gave the corresponding enones as an *E/Z* mixture. Dimethyl acetylenedicarboxylate gave the (*Z*)-olefinic adduct as a major product in accordance with the general behavior of organocopper conjugate addition. A high degree of chemoselectivity has been observed in this conjugate addition.

Table 8. Products of conjugate addition of zinc homoenolate in the presence of Cu(I) and Me₃SiCl (Ref. [28, 29])

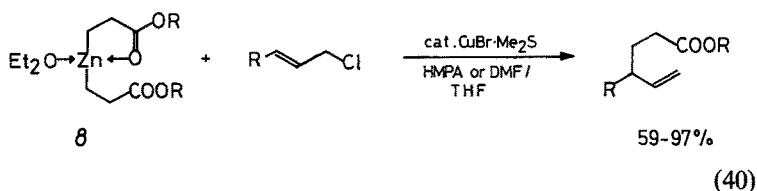
| | | | |
|--|-----|--|-----|
| | 92% | | 95% |
| | 78% | | 75% |
| | 91% | | 73% |
| | 75% | | 63% |

3.2.6 Substitution Reactions

Among the characterized metal homoenolates, only zinc homoenolate of alkyl propionate undergoes substitution reactions with electrophiles under suitable conditions. Two types of metal catalysts, copper(I) and metals of the nickel triad (e.g. Pd), have successfully been used to effect allylation, arylation, and vinylation reactions.

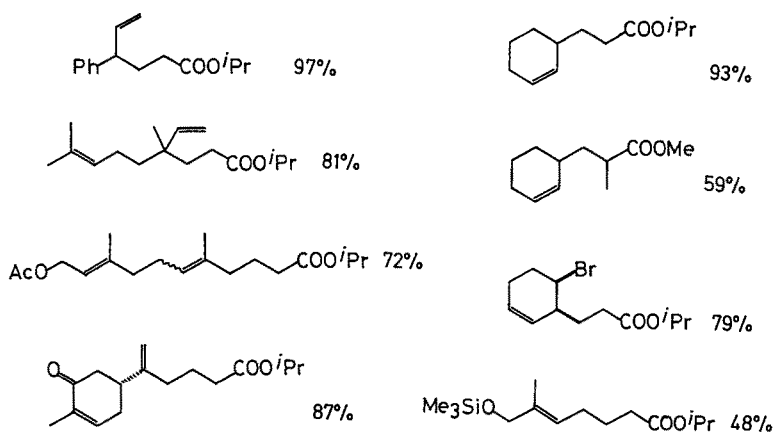
Zinc homoenolate reacts with allylic halides and diene monoepoxides under copper catalysis [29]. Treatment of the zinc homoenolate with a catalytic amount of Cu(II) in a polar solvent (e.g. hexamethylphosphoramide, HMPA, *N,N*-dimethylacetamide, DMA) generates a copper species which undergoes clean S_N2' allylation reactions Eq. (40). Polar solvents not only accelerate the reaction but greatly improve the S_N2' selectivity. A variety of allylating reagents can be employed in this reaction (Table 9). The S_N2'/S_N2 ratio is particularly high (close to 100%) when the alkylated carbon bears no substituents. The reaction of

trans-1,4-dibromo-2-cyclohexene gives a single stereoisomer which is presumably the *cis*-isomer arising from an *anti*-attack in the S_N2' reaction.

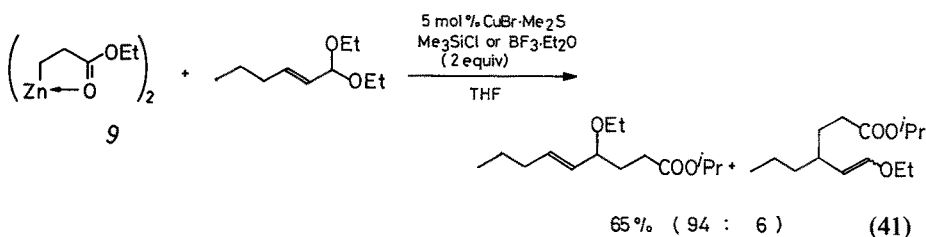


The allylation and the conjugate addition (vide supra) of zinc homoenoate proceed under essentially the same conditions except that the latter requires the presence of Me_3SiCl as well. Due to this subtle difference, selective allyl substitution is possible even with an enone function is present in the same molecule (Table 9).

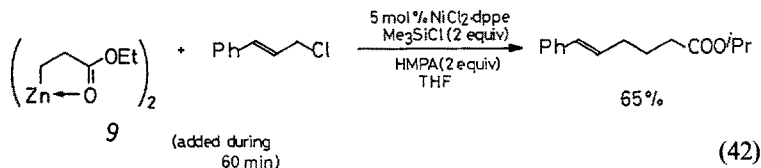
Table 9. Unsaturated esters by S_N2' -allylation of zinc homoenoate of esters (Ref. [29])



Copper catalyzed reaction of the homoenoate **9** with an acetal of an unsaturated aldehyde proceeds in an S_N2 manner, Eq. (41), the net reaction representing a 1,2-addition of the homoenoate. The presence of Me_3SiCl or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is mandatory in this reaction [29].



The nickel catalyzed reaction of **9** with an allyl chloride also proceeds in an S_N2 manner Eq. (42). Nickel dichloride complexed with a bidentate ligand (e.g. 1,2-bis(diphenylphosphino)ethane) effects a highly selective ($>99\%$) S_N2 reaction with cinnamyl chloride [29].



Substitution reactions involving aryl and vinyl halides have been achieved with the aid of palladium catalysts, among which $\text{PdCl}_2(o\text{-Tol}_3\text{P})_2$ with $o\text{-Tol}_3\text{P}$ ligands is the most efficient [40]. A variety of aryl bromides and iodides can serve as the electrophile in this reaction (Table 10). The coupling with vinyl halides occurs stereoselectively. Vinyl trifluoromethanesulfonates (vinyltriflates), readily available from ketones [41], react rapidly with the homoenolate. Mild reaction conditions keep ketone functions intact during the arylation reaction.

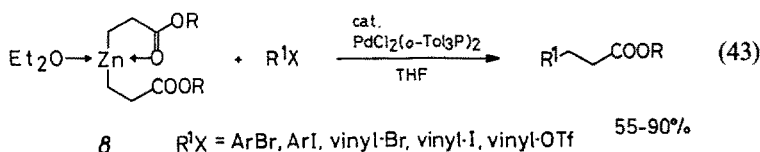
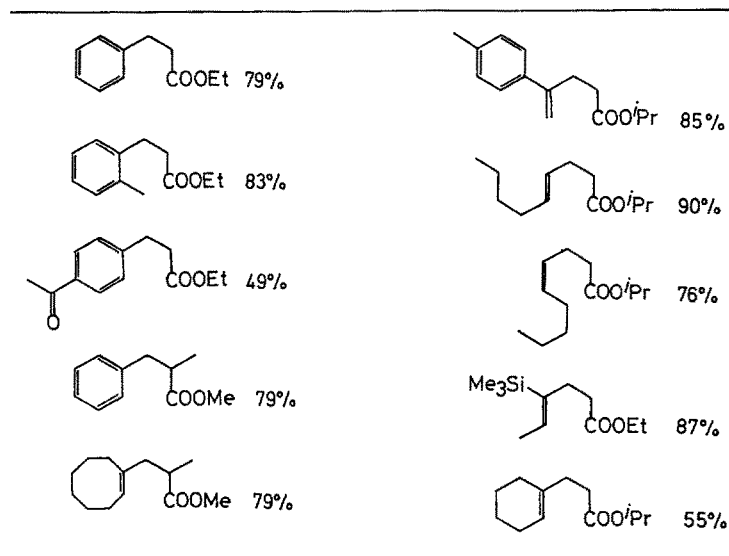
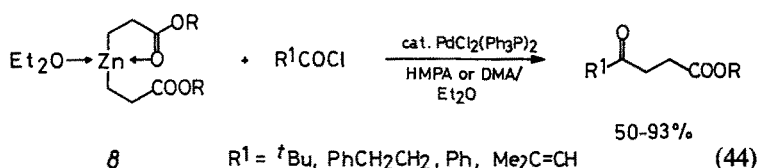


Table 10. Arylated and vinylyated propionates by palladium-catalyzed reaction of zinc homoenolate (Ref. [29, 40])



3.2.7 Acylation

The reaction of zinc homoenoate **9** with acid chlorides in ethereal solvents containing 2 equiv of HMPA rapidly produces 4-ketoesters in high yield Eq. (44) [33]. A palladium catalyst [40] (or less effectively a copper catalyst) [28] accelerates the reaction. This is in contrast to the cyclopropane formation in a nonpolar solvent see (Eq. 22 above).

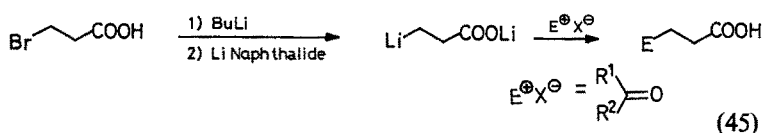


4 Other Routes to Reactive Metal Homoenoates

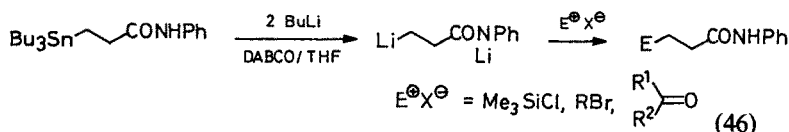
This section presents a summary of some recent reports on the chemistry of reactive metal homoenoates, which are generated by methods other than the siloxycyclopropane ring cleavage.

4.1 Anionically Protected Lithium Homoenoate

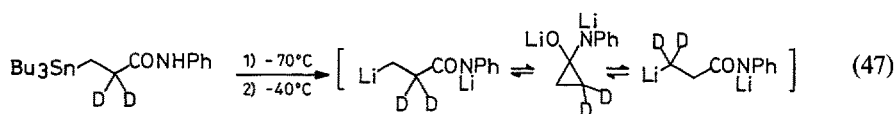
An early effort to generate a 3-lithiated propionic acid derivative and react it with (external) electrophiles was reported in 1978 [42]. Since simple 3-lithioesters failed to undergo the required reaction, the alkyl carboxylate portion was protected by preceding conversion to the carboxylate anion. Treatment of lithium 3-bromopropionate with lithium naphthalide generated the desired dilithiated propionic acid, which gave moderate yields of γ -hydroxy acid addition products with carbonyl compounds, Eq. (45).



Treatment of 3-stannylpropionamide with two equivalents of butyllithium at low temperature (-78°C) generates a similar dianionic homoenoate, which reacts with standard electrophiles Eq. (46) [43]. It is interesting to note that the propionate moiety rather than the butyl groups is selectively cleaved off the tin in the tin-lithium exchange.

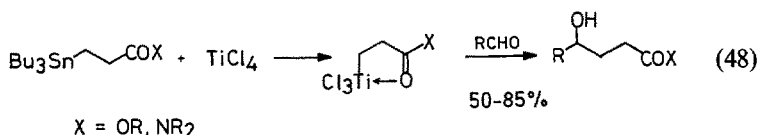


Dianions of the above types may not fall into the category of homoenolate in a strictly formal sense. Nevertheless the amide dianion does show a behavior typical of the homoenolate. Thus, the reaction of the isotopically labeled stannylpropionate results in scrambling of the label probably via a cyclopropane intermediate Eq. (47) [44]. As the result of such an equilibration, isomerization of α -methyl and α -phenyl substituted propionate homoenolates may occur to give the thermodynamically more favorable isomers, respectively.

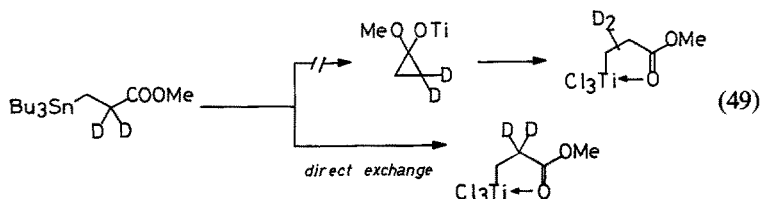


4.2 From 3-Stannyl- to 3-Titaniopropionate

Two groups independently reported the formation of titanium homoenolates by the transmetalation reaction of 3-stannyl-propionate esters with TiCl_4 , Eq. (48) [45, 46]. Amide homoenolates become available along this route [47]. The trichlorotitanium species thus obtained have been shown ($^1\text{H NMR}$) to be similar to that generated along the siloxycyclopropane route and indeed exhibit very similar reactivities. This method does provide a convenient alternative to the siloxycyclopropane route.



Isotopic labelling, Eq. (49), indicated that the transmetalation occurs via direct tin-carbon bond cleavage rather than via intermediate formation of an alkoxy-cyclopropane [45].



4.3 From 3-Stannyl- to 3-Palladioketoxime

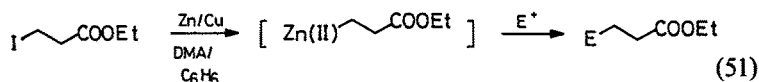
Selective transfer of the homoenolate moiety characterizes the transmetalation from tin to titanium described in the previous section. A very facile transmetalation of the same kind occurs for 3-stannylketoxime, Eq. (50) [48]. Reaction of the (*E*)-3-(tributyltin)ketoxime with dichlorobis(benzonitrile)palladium in CH_2Cl_2 at 0 °C for 30 min yields 78% of the transmetalation product. The

facility with which this reaction produced the stable palladium complex, and the high selectivity with which the oxime group carrying alkyl group is cleaved off, are remarkable. The reaction certainly proceeds with prior coordination of the metal to the oxime group, but the precise mechanism of the transmetalation remains unclear.



4.4 From 3-Iodoesters to Alkyl β -Zincpropionate

A very practical route to zinc homo-enolate involves reduction of 3-iodoesters with zinc/copper couple in the presence of a polar solvent, e.g. DMF, DMA [49] Eq. (51). The nature of the species obtained in this approach is not well-defined, but appears to be essentially the same as the one obtained along the siloxycyclopropane route. Acylation, arylation, and vinylation reactions have been reported.



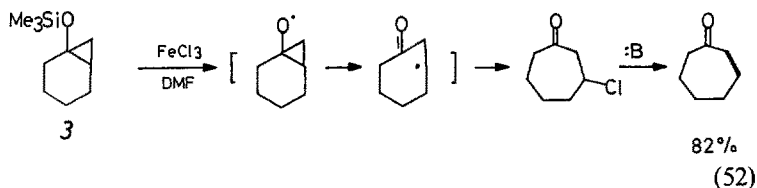
5 Reactions of Transient Homo-enolates Generated from Siloxycyclopropanes

There have been several reports on reactions of siloxycyclopropanes involving transient metal homo-enolates which eluded characterization owing to their instability.

5.1 Iron(III) Homo-enolates

Most ring cleavages of siloxycyclopropanes occur at the less substituted bond next to the siloxy group to give the more stable anionic species (Cf. Eq. 34). Chlorination with FeCl_3 in DMF provides a unique way to cleave the ring in the opposite direction, Eq. (52) [50]. Treatment of 1-siloxybicyclo[n.1.0]alkanes with FeCl_3 in DMF produces 3-chloro-ketones with cleavage of the internal bridging bond. Such regiochemistry has not been observed for ionic cleavages of siloxycyclopropanes, and must be due to the radical character of the intermediate formed in the reaction. It is not even clear whether a metal homo-enolate is involved in this reaction at all, and the reaction is believed to proceed with initial cyclopropoxy radical formation. The regiochemistry is consistent with the results obtained for reactions of discrete "homo-enolate radicals" (vide supra) for

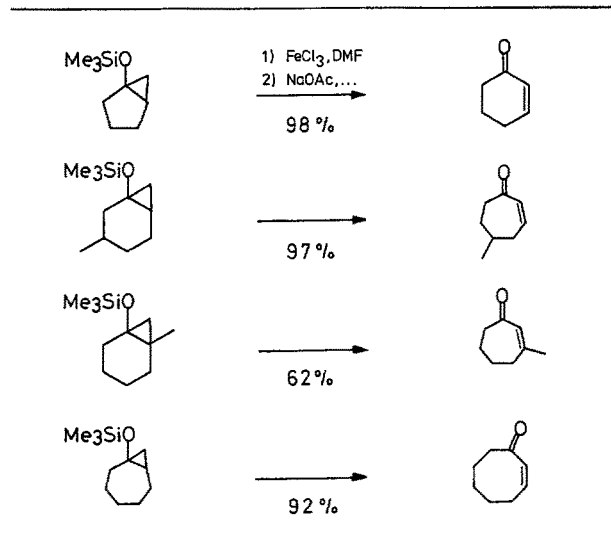
which thermodynamically more stable secondary radicals result by very rapid equilibration via cyclopropano radicals.



The overall sequence of cyclopropanation of a cyclic silyl enol ether, chlorination with FeCl_3 , and dehydrochlorination represents a very reliable one-carbon ring expansion method for cycloalkanone (Table 11).

Application of this ring enlargement and oxidation procedure to 2-alkoxy-1-siloxycyclopropanes incorporated in a large ring provides macrocyclic diketones which act as potent chelating agents for metal cations [50].

Table 11. Synthesis of 2-cycloalkanones by FeCl_3 -oxidation (Ref. [50])



5.2 Copper(II) Homo-enolates

Reaction between a siloxycyclopropane and $\text{Cu}(\text{BF}_3)_2$ in ether gives a product due to symmetrical coupling of two homo-enolate moieties (Eq. 53, Table 12) [51]. This is particularly noteworthy as a simple route to 1,6-ketones superior to classical approaches such as the Kolbe electrolysis [52]. Several lines of evidence suggest the intermediacy of $\text{Cu}(\text{II})$ homo-enolates. AgBF_3 and CuF_2 effect the same reaction albeit with lower yields. The reactions with cupric halides give

complex mixtures containing these homocoupled product and halogenated compounds [53].

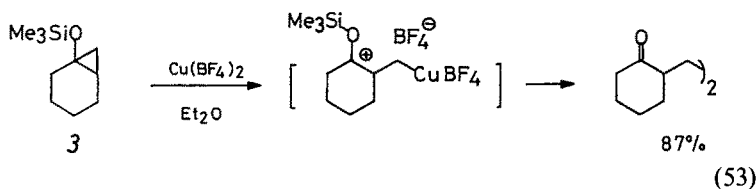
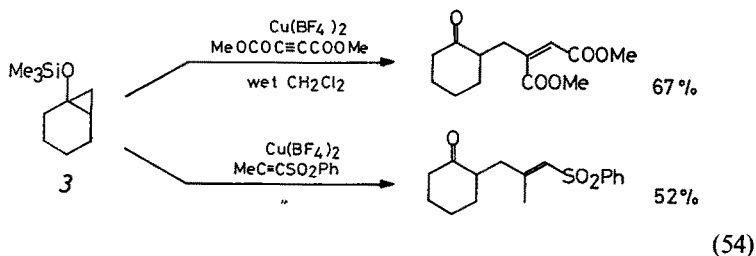


Table 12. 1,6-Diketones by homocoupling of siloxycyclopropanes in the presence of AgBF_4 or $\text{Cu}(\text{BF}_4)_2$ (Ref. [5])

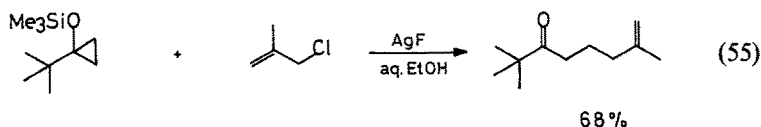
| | | | |
|--|-----|--|-----|
| | 78% | | 74% |
| | 81% | | 69% |
| | 68% | | 70% |
| | 87% | | 63% |

When the siloxycyclopropane and $\text{Cu}(\text{II})$ are allowed to react in the presence of dimethyl acetylenedicarboxylate or propynyl phenyl sulfone in wet CH_2Cl_2 , conjugate adducts are obtained in good yields Eq. (54) [54]. The same reaction conducted in CH_2Cl_2 containing D_2O gives the stereoselectively α -deuterated products, indicating the intermediacy of vinylcopper intermediates. Under strictly dry conditions homocoupling products are produced from these vinyl copper species.



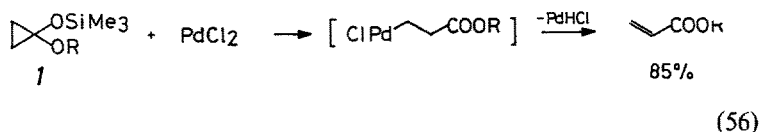
5.3 Silver Homo-enolates

A siloxycyclopropane reacts with an allylic chloride in the presence of AgF in aqueous ethanol to give an allylated product Eq. (55) [55]. In this case, the structure of the product does not reflect the regiochemistry of the nucleophilic attack on the starting allyl halide.

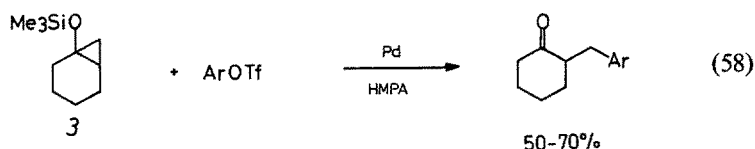
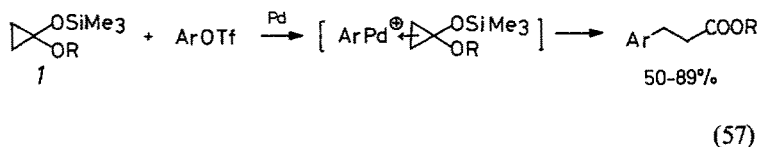


5.4 Palladium Homo-enolates

Palladium(II) chloride or its phosphine complex smoothly reacts with siloxycyclopropane **1** to produce acrylic ester and a palladium mirror. This reaction probably involves the formation of a chloropalladium homo-enolate followed by elimination of palladium hydride (Eq. (56) [56]).

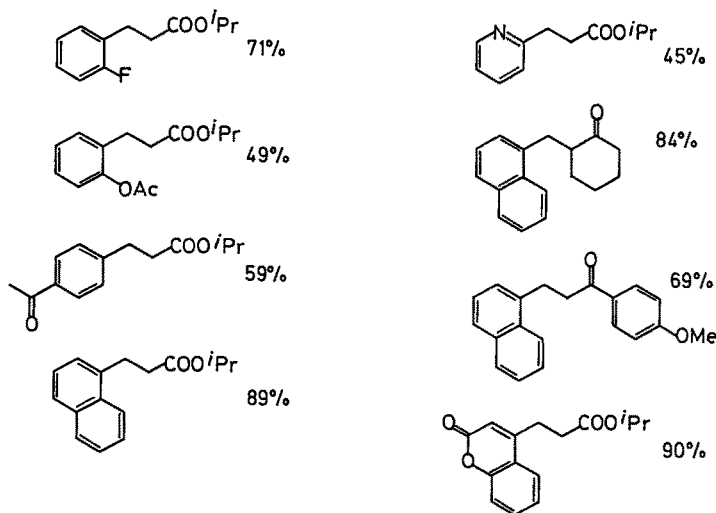


Nevertheless, the palladium homo-enolate can serve as a useful reaction intermediate. If certain requirements are met, such an organopalladium homo-enolate can be generated directly from the siloxycyclopropane, and then allowed to reductively eliminate to give an organylated homo-enolate. Heating a mixture of siloxycyclopropane **1** and an aryl triflate in benzene in the presence of a palladium catalyst effects such a transformation to give 3-arylpropionate Eq. (57) [57]. A siloxycyclopropane corresponding to a ketone homo-enolate (e.g. **3**) also undergoes reactions with aryl triflates, now in HMPA, to give arylated products Eq. (58) [57]. These results are summarized in Table 13.



The arylation reaction is not applicable to aryl bromides and iodides. Another line of experimental evidence also indicates that an arylpalladium *halide* complex, instead of an arylpalladium *triflate* complex, is not electrophilic (Lewis acidic) enough to cleave the cyclopropane ring.

Table 13. Arylated esters and ketones by direct arylation of siloxycyclopropanes (Ref. [57])



Reaction of siloxycyclopropane **1** with acid chlorides in the presence of a palladium catalyst also proceeds cleanly to give 4-ketoesters in high yields (Eq. 59, Table 14) [57]. Chloroform is a suitable solvent. Kinetic studies have revealed that the interaction between **1** and an acylpalladium chloride complex is the rate limiting step.

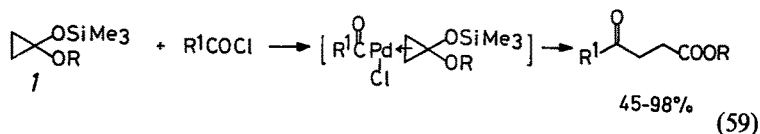
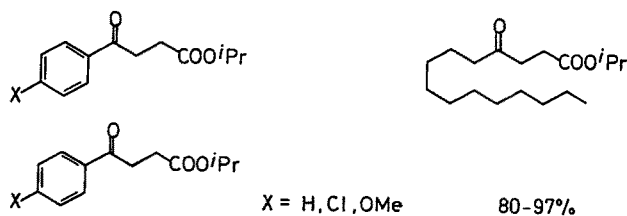
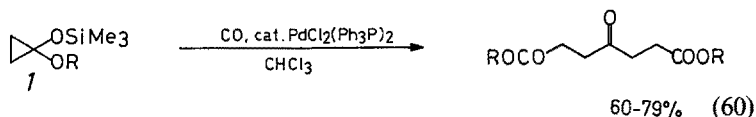


Table 14. Keto esters by direct palladium catalyzed acylation of siloxycyclopropanes (Ref. [56])



If the cyclopropane is heated in CHCl_3 in the presence of a catalytic amount of palladium-phosphine complex under CO atmosphere, a symmetrical coupling product incorporating one molecule of CO forms in high yield, Eq. (60) [57].



5.5 Zinc Homoenoates

In view of the remarkable stability of metal homoenoates of esters, the existence of homoenoate species containing a 3-halo substituent, i.e. zinc carbenoid moiety connected to an ester group, appeared to be possible. Indeed, when a silyl ketene acetal is treated with a carbenoid generated from CHBr_3 and Et_2Zn , two types of highly intriguing reactions ensue [58]. With a purely aliphatic substrate, Eq. (61), an alkyl cyclopropylcarboxylate due to intramolecular β -CH-insertion of the intermediate zinc carbenoid formed. When the substrate contained an olefinic double bond in the vicinity of the carbenoid function, Eq. (62), in particular an intermediate derived from an α,β -unsaturated ester, internal cyclopropanation occurred to give bicyclic or tricyclic product (Table 15).

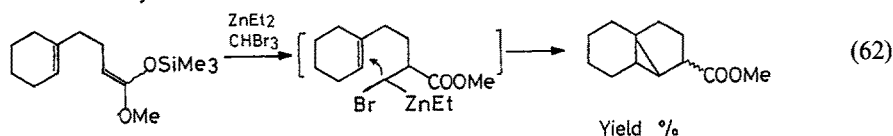
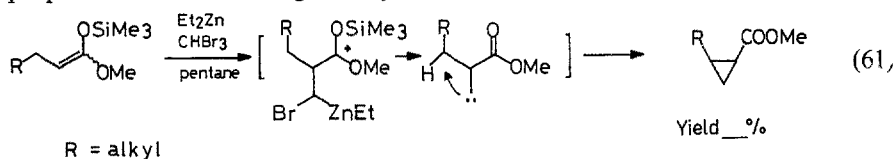
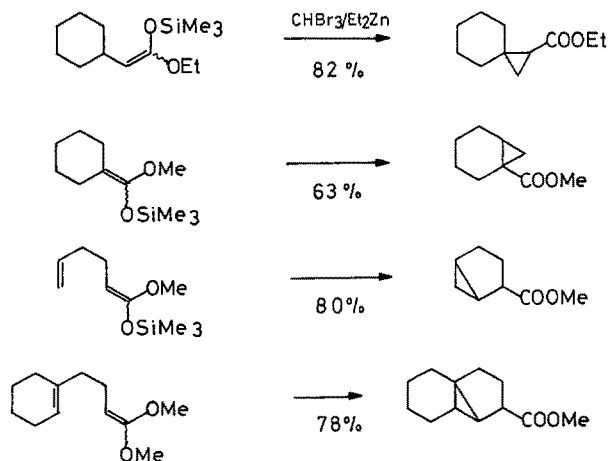
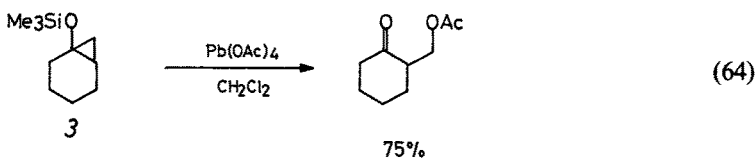


Table 15. Alkyl cyclopropanecarboxylates by carbene addition onto ketene acetals (Ref. [58])

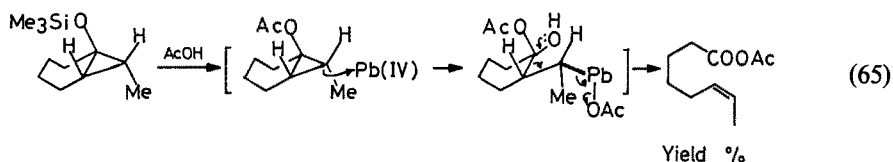


5.6 Lead(IV) Homoenoate

In contrast to the other examples in this review, the reaction of 1-siloxycyclo[n.1.0]alkenes with $\text{Pb}(\text{OAc})_4$ in acetic acid somewhat surprisingly leads to cleavage of two bonds to yield alkenoic acids, Eq. (63) [59]. The reaction involves the fission of both bonds connected to the carbon bearing the siloxy group. This reaction is considered to involve primary in situ conversion of the siloxycyclopropane to the corresponding cyclopropanol. Indeed, the siloxycyclopropane **3** reacts with $\text{Pb}(\text{OAc})_4$ in dichloromethane to give the β -acetoxyketone, Eq. (64), while the corresponding cyclopropanol undergoes the same fragmentation as with $\text{Pb}(\text{OAc})_4$ in acetic acid.



The observed stereoselectivity of this ring cleavage reaction [60] favors a mechanism, Eq. (65), in which formation of a lead(IV) homoenoate by cleavage of the external bond with inversion of configuration is followed by rapid cleavage of the second bond.

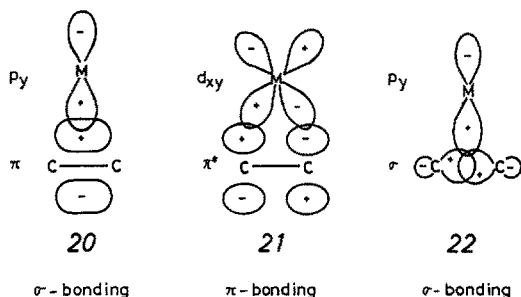


6 Mechanism of Cyclopropane Ring Cleavage

Except for some of the above reactions which proceed via radical intermediates, many of the ring cleavage reactions are likely to involve initial interaction of the metal and the cyclopropanering. The nature of this interaction between 1-siloxycyclopropane **1** with metals has been investigated by the authors in some detail, and the results are summarized below.

The Dewar-Chatt-Duncanson model of the binding of an olefin in a transition metal complex involves two types of interactions. Transfer of electron density from the relatively high-lying olefinic π -orbital to the metal (cf. 20) represents a Lewis acid Lewis base interaction (σ -bonding). A metal-olefin π -bond due to interaction

of a filled metal orbital with the π^* -orbital of the olefin (back donation) constitutes another mode of bonding (cf. 21).



Organometallic bonding to σ bonds possessing high p -character, in contrast, is due mainly to the electron donation from the carbon-carbon σ -bond into an empty metal orbital (cf. 22), because the antibonding σ^* -orbital is generally inaccessible for effective back donation from the metal [61]. It follows from such considerations that the donor character of the σ -bond of a cyclopropane derivative will be decisive. In addition, the Lewis acidity of the metal will be more important for the binding with cyclopropane. The summary chart of metals which cleave the alkoxyloxycyclopropane **1** (Table 16) [11] offers an idea for the kind of Lewis acidity needed.

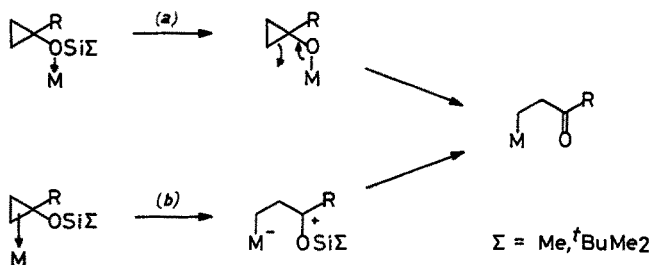
Table 16. List of metals, chlorides of **1** which react with cyclopropane **1** to form metal homo-enolate (Ref. [11])^a

| 1 | 2 | 3 | 5 | 12 | 13 | 14 | 15 | 16 |
|---|-----------------|------------------|-----------------|-----------------|-------------------|------------------|-------------------|-----------------|
| X | X | | | | B ⁺ | | | |
| X | Cu ^I | Ti ^{IV} | | Zn ^I | Al ^{III} | Sr ^{IV} | | |
| X | X | Zr ^{IV} | Nb ^V | Cd ^I | Ga ^{III} | Se ^V | | |
| X | X | | Ta ^V | Hg ^I | | Sn ^{IV} | Sr ^{IV} | Sb ^V |
| X | X | | | | | Pb ^{IV} | Bi ^{III} | Te ^V |

^a Signs X and / indicate no reaction and formation of no detectable homo-enolate, respectively

There are a few points to be addressed in order to understand the mechanism of homo-enolate formation. Several lines of experimental evidence for the reaction of 1-alkoxy-1-siloxycyclopropanes have provided insights into the nature of the metal interacting with the siloxycyclopropane.

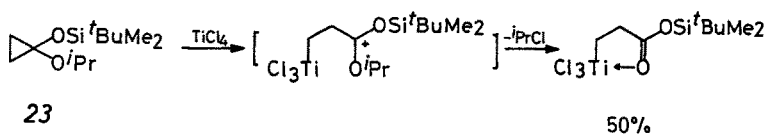
The initial interaction of the metal with the substrate (Scheme 4) may occur either on the siloxy oxygen to form a metal alkoxide (path (a)) or directly on the strained sigma bond to form an intermediate containing an oxygen-stabilized cationic center (path (b)). Molecular orbital considerations indicate that an orbital controlled interaction with a Lewis acid should occur preferentially at the ring carbons, which have the larger HOMO coefficient. Studies of the exchange of a Me₃Si group between Me₃SiOTf and silyl ethers eliminate the possibility of path (a) for a number of metal halides, including ZnCl₂ and SnCl₄ [11].



Scheme 4

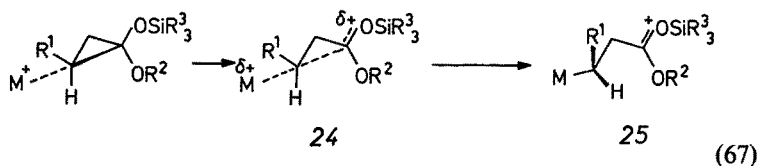
Some experimental data indicate the formation of a cationic species as postulated for path (b) and in turn show that the Si-O bond remains intact in the transition state. Evidence comes from the comparison of the reactivities of 1-trimethylsiloxy- (1) and 1-*tert*-butyldimethylsiloxycyclopropanes (23) in some reactions.

The reaction of 1-isopropoxy-1-trimethylsiloxycyclopropane (1, R = *i*-Pr) with TiCl_4 yields the titanium homoenoate of isopropyl propionate 2 (R = *i*-Pr) and Me_3SiCl (Eq. see 9). That of 23, in contrast, yields a considerable fraction of the homoenoate of silyl propionate as well, Eq. (66) [19]. Apparently, the loss of an isopropyl group from an oxygen-stabilized cationic intermediate competes with that of the silyl group with bulky substituents.

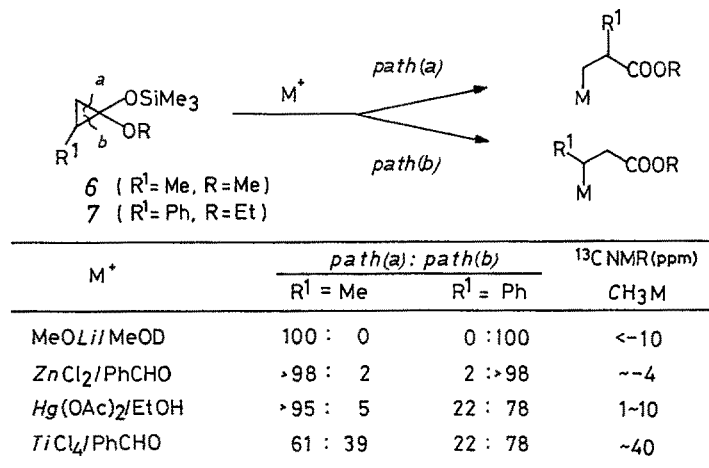


Kinetic analysis of the palladium catalyzed acylation reaction of 1 (R = *i*-Pr) and 23 indicates that the rate does not depend on the bulk of the trialkylsilyl substituent. Since the rate limiting step of this reaction is the interaction of a coordinatively unsaturated acylpalladium chloride with the cyclopropane (Cf. Eq. 59), the observed independence can reasonably be taken as an evidence that the Si-O bond remains intact in the transition state [56]. Semiquantitative data on the cleavage of 1 (R = *i*-Pr) and 23 with ZnCl_2 in ether, Eq. (13), led to the same conclusion [27].

The mechanisms of the ring cleavages which lead to Ti, Zn, and Pd homoenoates are similar to each other as described above in that the oxygen-stabilized cation is involved (path (b) in scheme 4). The fact that the regiochemistry of the ring cleavage strongly depends on the nature of the forming carbon-metal bond (Cf. Eq. 67), however, indicates that they are not identical.



Scheme 5 summarizes the regiochemistry of ring opening of methyl- (**6**) and phenyl-substituted alkoxy-siloxy-cyclopropane (**7**) by LiOMe, ZnCl₂, HgCl₂, and TiCl₄, as well as the ¹³C NMR chemical shifts of the respective metal methyls [27]. The NMR data correlate with the nature of the metal-carbon bond: The more polarized it is, the less positive the chemical shift of the methyl group.



Scheme 5

The regiochemistry with lithium methoxide and zinc chloride clearly reflects the stability of the incipient formal anionic charge on the carbon. Such a trend is less obvious for those metals which form covalent bonds to carbon. Electronic and steric factors compete with each other in the cleavage of the phenylsubstituted alkoxy-siloxy-cyclopropane **7**, in particular. In conclusion, the transition state (**24**) appears to anticipate the nature of the intermediate **25**, which on one hand reflects the property of R¹ and on the other that of the metal carbon bond (Eq. 67). More detailed information on the type of ring cleavage, namely, the choice between the side-on (i.e. **24**) or the end-on interaction (attack of the metal at the back-lobe of the opening C—C bond), is currently lacking: The mode of the mercury induced cleavage of cyclopropanols is sensitive to ring substituents [7].

7 Homo-enolates in Natural Product Synthesis

As demonstrated in the preceding chapters, metal homo-enolate chemistry centered around the ring cleavage of siloxycyclopropanes has realized a number of straightforward synthetic transformations only some of which have been possible with other existing methods.

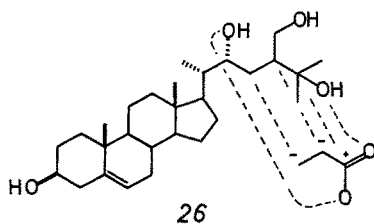
The current state of metal homo-enolate chemistry is still in its infancy, and very few examples of the actual applications have been reported. However, the diversity of reactivities of the homo-enolates shown in the preceding paragraphs will definitely lead future activities towards fruitful applications.

7.1 Steroidal Side Chains:

Depresosterol and 24-*epi*-Depresosterol [63]

Stereocontrolled functionalization of steroidal side chains in nature is closely related to the function of steroids in living organisms. The regio- and stereochemistry of functional groups exert strong influence on the biological activities of steroids. Due to their multi-functional nature, the homoenoates provide an effective tool for synthetic efforts in this field.

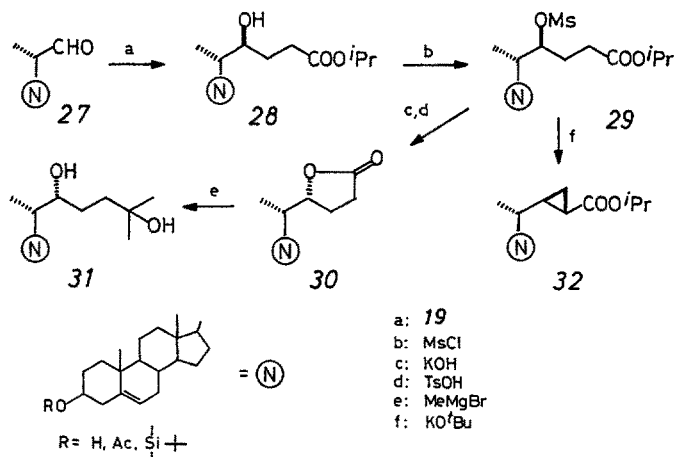
Depresosterol (**26**) is a marine natural product isolated from a soft coral in the Red Sea [64]. The structure of this sterol, in particular, the configuration at C²⁰ and C²², was assigned by comparative NMR studies, and that at C²⁴ was left unassigned. The latter configuration was of interest with respect to the biological significance of the sterol. The density of hydroxyl groups is higher than in any of the known sterols, the substitution pattern being reminiscent of the insect molting hormone, ecdysone. The synthesis of depresosterol **26** demonstrates the potential of the homoenoate as a multi-functional three carbon building block, which corresponds to the C₃ fragment C²³, C²⁴, C²⁵ in **26**. The stereochemical synthesis of both epimers at C²⁴ finalized the structure determination of this sterol [63].



The synthesis started with the “homo-Reformatsky” reaction between the alkoxytitanium homoenoate Eq. (30) and aldehyde **27**, which afforded the product **28** with Cram orientation with >6:1 selectivity. An inversion at the sterically hindered C²² position was readily achieved by mesylation, followed by KOH treatment in hot aqueous MeOH to give lactone **30** after acid-catalyzed lactonization.

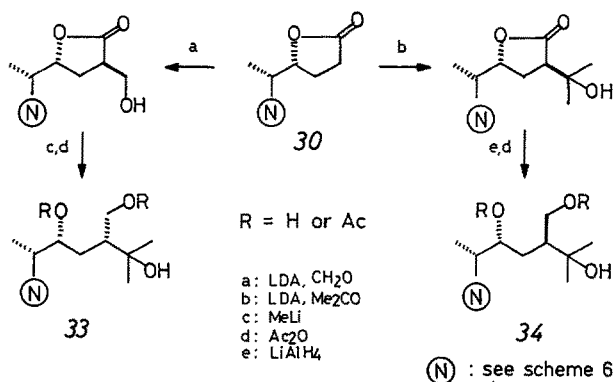
Synthesis of the 24*R* isomer was commenced by stereoselective hydroxymethylation of the enolate of lactone **30**. Introduction of methyl groups at C²⁵ and C²⁶ was achieved by addition of MeLi to give 24*R* depresosterol (**33**). Alternatively, trapping of the lactone enolate with acetone followed by LiAlH₄ reduction gave the 24*S* epimer (**34**). Spectral comparison indicated that the 24*R* sterol is identical with the natural product.

This approach not only enabled the preparation of a simpler structure such as that of ecdysone (cf. **31**), but also provides ways to introduce functional groups at C²³ and C²⁴ positions of the side chain. As an example, treatment of the mesylate **29** with non-nucleophilic *tert*-butoxide gives the cyclopropane **32** which



Scheme 6

can serve as a precursor to the structurally intriguing demethylgorgosterol [63].

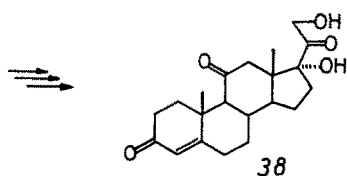
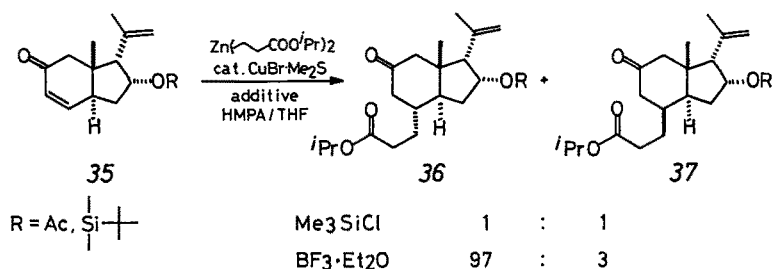


Schemes 6, 7

7.2 (\pm)-Cortisone [39]

Conjugate addition of catalytically generated zinc homoenolate (cf. Eq. 39) has been used for the stereoselective synthesis of a key intermediate to (\pm)-cortisone (**38**). Precedents of the cuprate addition onto a *trans*-fused hydrindane such as **35** was expected to give **36** but attack of the nucleophilic copper reagent from the desirable, less hindered α -side. Although treatment of the enone **35** with the zinc homoenolate under standard condition (Eq. 39, Me₃SiCl/HMPA/cat. CuBr · Me₂S) afforded the adduct in quantitative yield, the product was a 1 : 1 mixture of **36** and **37**. In contrast, use of BF₃ · Et₂O instead of Me₃SiCl gave the desired isomer **36** with better than 95% selectivity; with some additional steps

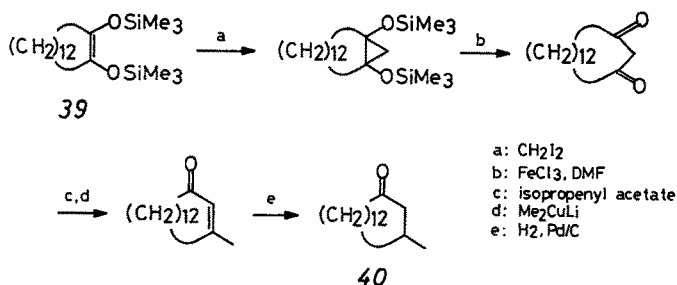
the total synthesis of **38** was completed. The precise reason for the change of the stereochemistry is currently unclear.



Scheme 8

7.3 (\pm)-Muscone [20]

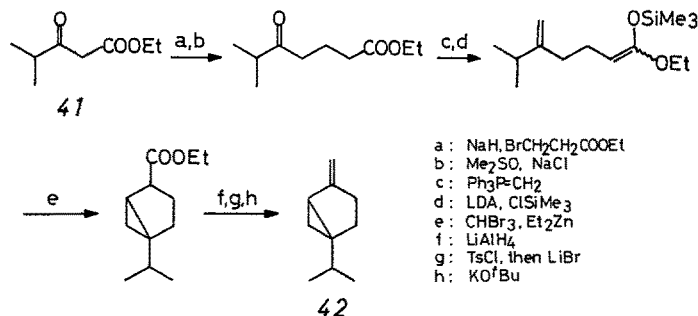
The acyloin condensation of α,ω -diesters in the presence of Me_3SiCl represents a highly efficient method for the synthesis of large rings. The application of the convenient sequence of cyclopropanation/oxidative ring cleavage for ring expansion cf. Eq. (52) to the appropriate macrocyclic enediol silyl ether **39** provided, a short, high-yield (23% overall) synthesis of muscone (**40**) [20].



Scheme 9

7.4 (\pm)-Sabinene [58]

The remarkably efficient cyclopropanation reaction with an in-situ-generated zinc carbenoid, Eq. (61) provided a straightforward synthesis of the monoterpene sabinene (**42**) starting from the β -keto ester **41** [58].



Scheme 10

8 References

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***Gem*-Dihalocyclopropanes in Organic Synthesis**

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Gem-Dihalocyclopropanes belong to the most readily available cyclopropane derivatives known today. They have been shown to be extremely valuable starting materials for the preparation of cyclopropanes and cyclopropenes, they may be converted to bicyclobutane derivatives and spiropentanes, can lead to allenes and the higher cumulenes, cyclopentenes and cyclopentadienes, and many other classes of compounds, both hydrocarbon systems and derivatives with valuable functional groups. The article summarizes the preparative developments in the area of *gem*-dihalocyclopropane chemistry during the last decade.

1 Introduction

Although the first *gem*-dihalocyclopropane — 1,1-dichlorocyclopropane — was described nearly a century ago [1], this class of organic halogen compounds played no role in preparative organic chemistry for many decades. In fact, even Doering and Hoffmann's 1954 paper [2] describing the generation of dichlorocarbene from chloroform under anhydrous conditions and its subsequent trapping by olefins to provide 1,1-dichlorocyclopropanes in an experimentally simple way for the first time was of no immediate consequence for synthetic organic chemistry. The process played a role for the preparation of bi- and polycyclic hydrocarbons, i.e. the two chlorine substituents were regarded as a necessary evil to get rid off as quickly as possible, rather than as functional groups in their own right to be used for further modifications in subsequent steps. This application of the *gem*-dihalocyclopropane group is still very popular [3], as will be shown by some examples discussed later. However, during the last two decades the great preparative potential of cyclopropanes of all types has become more and more apparent. In fact, these three-membered ring systems have been described as "pseudofunctional groups" [4].

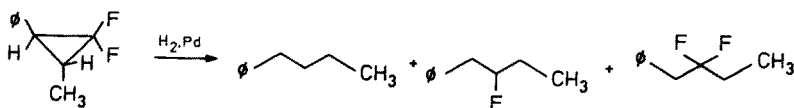
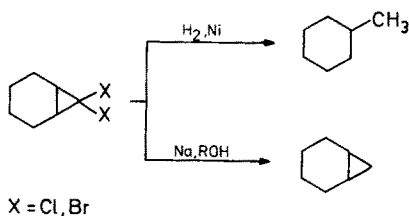
The published experimental material has thus accumulated rapidly, and a number of useful and comprehensive reviews have already appeared [5–10]. In particular, Weyerstahl has published an extensive review of articles published between 1967 and 1980 dealing with the preparation and the chemical behavior of dihalocyclopropanes [11]. The need for a further summary of this part of cyclopropane chemistry may thus not appear obvious. However, besides presenting work published since then, the present article strictly concentrates on the reactive behavior of the title compounds. Neither their preparation nor their spectroscopic, especially their NMR properties will be discussed here, since these questions are dealt with in depth in Weyerstahl's review [11]. For a summary of the work published prior to 1970, Wendisch's monumental contribution to the Houben-Weyl-Müller series remains unchallenged [10]. As far as cycloadditions of dichlorocarbene to olefins are concerned, the monograph by Zefirov, Kazimirchik and Lukin [12] is valuable (literature coverage up to 1984), although this book has not been translated into English. One of the most useful recent compilations listing the additions of all types of halocarbenes under phase transfer conditions to a very large collection of unsaturated systems — including numerous polyfunctional molecules — has been provided by Keller [13]. Although this monograph lists hundreds of dihalocyclopropanes, novel derivatives and routes to prepare them appear continuously [14–16].

When two *geminal* halogen substituents are introduced into a cyclopropane ring, a distinct and consistent change of geometry is observed. In 1,1-difluorocyclopropane the bond opposite the halogen bearing carbon, i.e. the C²—C³-bond is lengthened (155.3 pm) relative to cyclopropane itself (151.4 pm [17, 18]), whereas the adjacent bonds are shortened. This effect corresponds to a weakening of the former (by about 8 to 10 kcal/mol) and a strengthening of the latter bond type. More complex cyclopropane derivatives like 4,4,8,8-tetrafluoro-tricyclo-[5.1.0.0^{3,5}]octane show analogous effects [19]. Although the experimental results

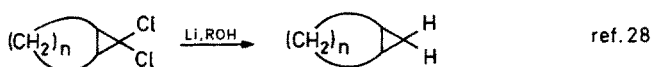
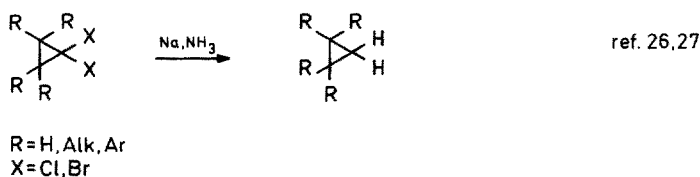
for 1,1-dichlorocyclopropane are contradictory [20–22], the above tendency is preserved. Extensive theoretical work on the influence of donor and acceptor substituents on the electronic and geometric properties of cyclopropanes has been published [23, 24]; it shows the same trends for 1,1-difluoro- and 1,1-dichlorocyclopropane, i.e. a bond length increase for the opposing and a decrease for the adjacent bonds. As expected, these changes in molecular geometry, and hence bond energies, exert a strong influence on the chemical behavior of the *gem*-dihalocyclopropanes: In those reactions in which ring-opening takes place, it is the C²—C³-bond that is broken preferentially, and in most cases this process occurs with a higher reaction rate than that observed for the corresponding unsubstituted cyclopropanes. It should be pointed out, though, that in many reactions of the *gem*-dihalocyclopropanes the integrity of the three-membered ring is preserved. Rather than subsuming the published experimental material under the two headings of reaction products with retained or destroyed cyclopropane moiety we prefer to discuss the reactions of the *gem*-dihalocyclopropanes according to reaction types.

2 The Reduction of *Gem*-Dihalocyclopropanes

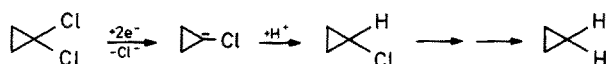
The catalytic hydrogenation of 7,7-dihalonorcaranes proceeds with opening of the three-membered ring and leads to methylcyclohexane, whereas the reduction with sodium in alcohols affords norcaradiene. Hydrogenolysis of 1,1-difluoro-2-methyl-3-phenylcyclopropane in the presence of a Ni—Re or Pd catalyst at atmospheric pressure provides a mixture of 1-phenyl-butane, 1-phenyl-2-fluorobutane, and 1-phenyl-2,2-difluorobutane, respectively [25].



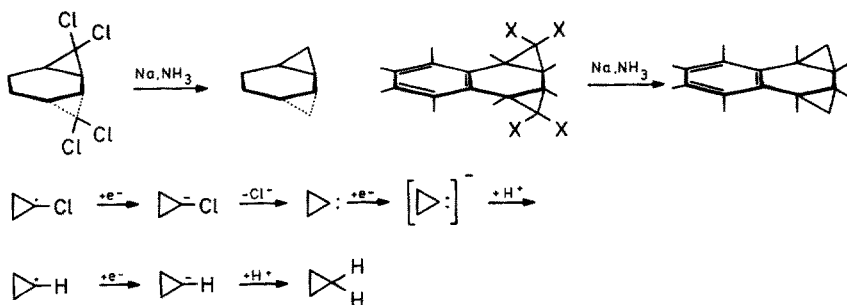
When the *gem*-dihalocyclopropanes are reduced by dissolving alkali metals in alcoholic solvents or in liquid ammonia the strained ring is retained.



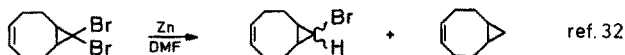
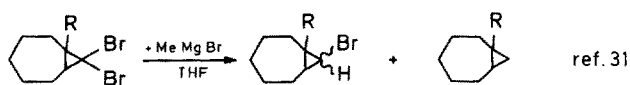
The former reduction is thought to occur by two single electron transfers (SET) from the metal surface to the cyclopropane derivative providing a halide and cyclopropyl anion initially. The latter is protonated by the solvent thus leading to the monohalogen derivative which can undergo the reduction process for a second time.



With sodium in liquid ammonia only the fully reduced compounds are obtained, even if the conversion is kept low. To explain the absence of the monohalide, it has been proposed that a cyclopropylidene radical anion is formed under these conditions, which is transformed to the dehalogenated product directly [29, 30].

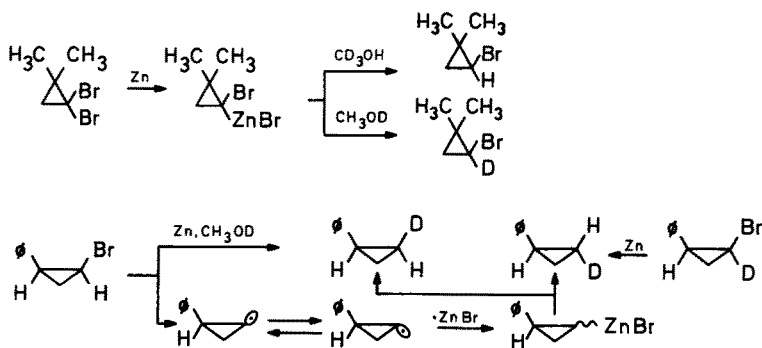


The reduction of 1-alkyl-8,8-dibromo-bicyclo[5.1.0]octanes by methyl magnesiumbromide in tetrahydrofuran provides mixtures of fully and partially reduced products [31]. A comparable result is obtained when zinc in dimethylformamide is employed; as a side reaction the formation of allenes is observed in this case (see below) [32].

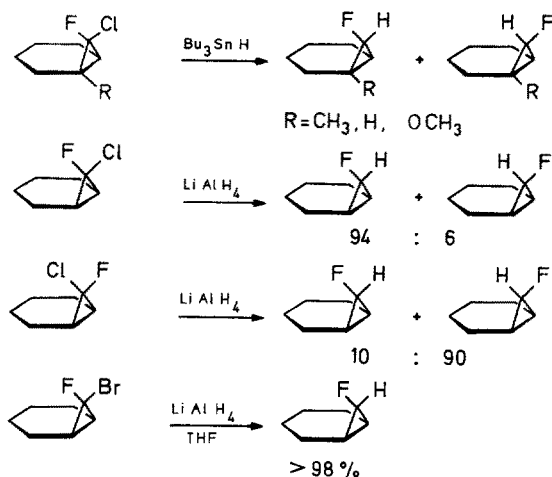


To increase the selectivity of the process and at the same time improve the yields of the partially reduced products many reduction systems have been studied: Zn/ROH [33], Mg/ROH—THF [34], Al/ROH—NaOH [35], LiAlH_4 [36], $(n\text{-C}_4\text{H}_9)_3\text{SnH}$ [37, 38], sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) [39], to name but a few. A simple and effective way to convert dibromocyclopropanes into their monosubstituted derivatives consists in the use of non-metallic reagents: diethyl phosphite in the presence of triethylamine [40], sodium dithionite in aqueous dimethylformamide [41], and a number of other reducing reagents like $\text{Na}_2\text{S}_2\text{O}_3$, Na_2SO_3 , Na_2S , Na_2HBO_2 [40]. Under these conditions the monobromides are obtained in up to 80% yield, with less than 10% of the fully reduced cyclopropanes. The stereoselectivity of the process is not very high, and depends both on the structure of the starting dibromide and the reduction conditions employed. Thus the ratio of the isomeric monobromides in the above scheme is 1:1 if zinc in ethanol is used [33], 1.7:1 (*cis*:*trans*) with aluminum in alcoholic alkali hydroxide [35], and only 0.11–0.35 when lithium aluminumhydride is employed. On the other hand, a *syn*-isomer is the main product with tri-*n*-butyltinhydride [38].

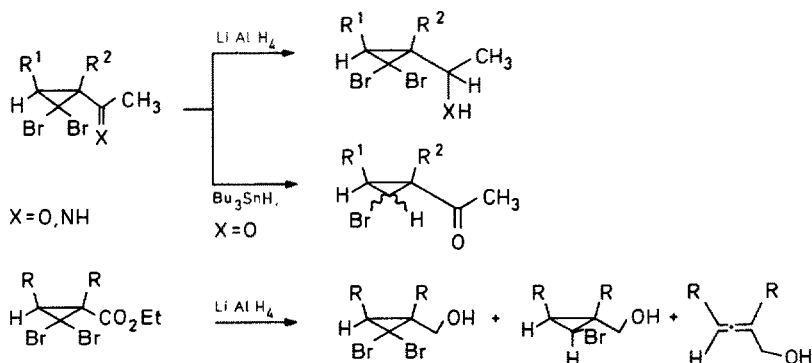
The reduction of the dibromo derivatives is thought to occur via zinc organic species [42], whereas radical intermediates are apparently involved in the reduction of the monohalogen compounds [43].



The selectivity of the reduction of dichlorocyclopropanes to the monohalogenated compounds is normally quite low; if, however, $\text{LiAlH}_4/(\text{C}_6\text{H}_5)_3\text{SnH}$ is employed the monochloro derivatives are obtained in good yields [44–47]. A stereoselective monoreduction of *gem*-dichlorocyclopropanes has recently been accomplished with potassium diphenylphosphide. For example, when 7,7-dichlorobicyclo[4.1.0]heptane is stirred with this reagent in dimethylsulfoxide *exo*-7-chlorobicyclo[4.1.0]heptane is formed in 85% yield, and only small amounts of its *endo*-isomer are produced as side-product [48a]. *gem*-Dibromocyclopropanes have been reduced stereoselectively by employing potassium dimethylphosphite [$\text{KP}(\text{O})(\text{OMe})_2$] [48b]. The reduction of fluorochlorocyclopropanes with tri-*n*-butyltinhydride proceeds chemoselectively leading to the corresponding fluorocyclopropanes [49, 50]. The stereoselectivity of the process appears to depend on the ability of the substituent to stabilize a radical center ($\text{CH}_3 > \text{H} > \text{OCH}_3$).

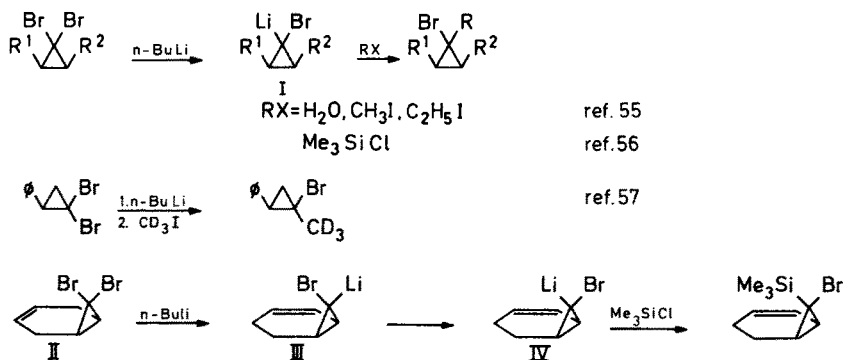


The reduction of bromofluorocyclopropanes with LiAlH_4 in tetrahydrofuran at 65°C proceeds stereoselectively with retention of configuration and formation of the monofluorocyclopropanes [50]. A similar result has been obtained for chlorofluorocyclopropanes (diglyme, 100°C) [44]. A configurationally stable carbanion has been invoked as the reaction intermediate in the latter case. When the dihalocyclopropane substrate contains another reducible reaction center, the chemoselectivity of the reduction process depends — as might have been expected — on the nature of the reducing agent employed. Thus, in dibromocyclopropanes containing an additional keto or imino function it is the latter group which is reduced by lithium aluminumhydride [51, 52]. On the other hand, the reduction by tri-*n*-butyltinhydride or zinc in ethanol yields the monobromocyclopropanes [53]. A complex reaction mixture is formed when dibromocyclopropanoic esters are subjected to LiAlH_4 -reduction, since both the ester function and the dibromomethylene group of the three-membered ring participate in the process. When excess lithium aluminumhydride is employed even allenic alcohols are produced in low yields, presumably via cyclopropylidene intermediates (cf. Sect. 3) [54].

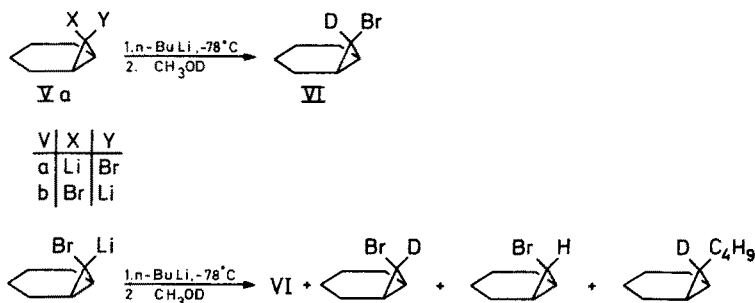


3 Reactions with Organolithium Compounds

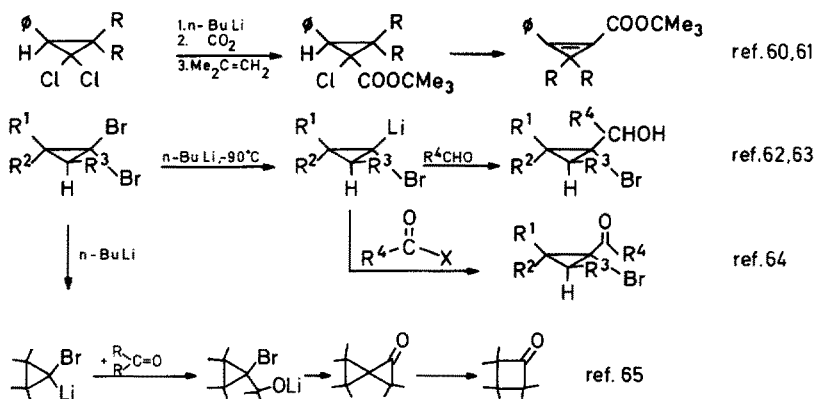
Lithium metal or alkyllithium derivatives react with dihalocyclopropanes to provide the corresponding lithiohalocyclopropanes I which are stable at temperatures around $-100\text{ }^{\circ}\text{C}$. These metalated species are easily trapped with electrophiles (R—X) like methyl or ethyl iodide, trimethylstannyl chloride, trimethylsilyl chloride etc. In the case of the unsaturated bicyclic substrate II a double bond migration is observed, which in the presence of excess starting bromide is accompanied by isomerization of the *exo*-lithio intermediate III to its *endo*-isomer IV [58].



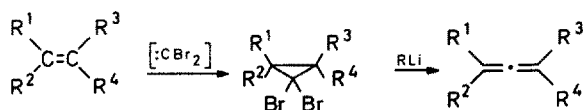
If 7,7-dibromonorcaradiene is metalated with *n*-butyllithium and the resulting intermediate trapped with CH_3OD the *endo*-lithio species Va furnishes only the *exo*-7-bromo-7-deuterionorcaradiene VI, whereas the epimeric organolithium compound Vb provides a mixture of both diastereomeric monobromides and an alkylation product [59].



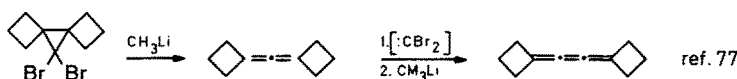
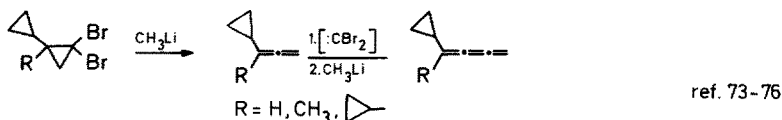
The trapping of lithiohalocyclopropanes by carbon dioxide, aldehydes and acid chlorides, respectively, constitutes a useful route to the corresponding cyclopropanecarboxylic acids, alcohols and ketones. In the case of ketones an intramolecular loss of lithium bromide may take place yielding spiroepoxides which in turn may be isomerized to cyclobutanones.

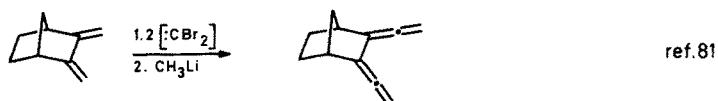
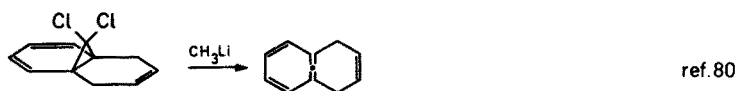


At temperatures above $-100\text{ }^{\circ}\text{C}$ the lithiohalocyclopropanes are converted to cyclopropylidenes by formal loss of one molecule of lithium halide. The main route of stabilization of these “carbenacyclopropanes” consists in the formation of allenes. The process which has been termed the Doering-Moore-Skattebøl allene synthesis (“DMS-synthesis”) [66–68], has been developed into the most general method for the preparation of these reactive compounds which especially during the last decade have been used in organic synthesis with growing success [69, 70].

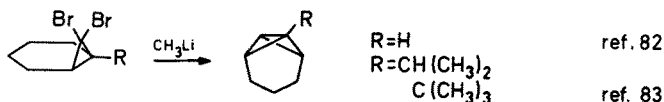


Formally, in the two steps of the DMS-process (dibromocyclopropanation and reaction with alkyl lithium) a carbon atom is inserted between the two centers of a double bond. The reaction may be extended to the preparation of still higher cumulated bond systems as well as to numerous other — including functionalized — allenic systems which cannot or only with much effort be prepared by other routes. The examples shown here serve illustrative purposes only, for more extensive coverage of the literature the reader is referred to the various reviews and monographs which have appeared recently [66, 69, 71, 72].

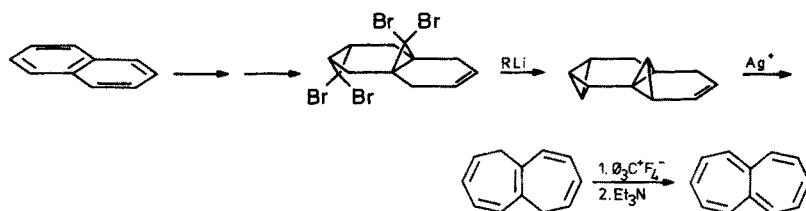




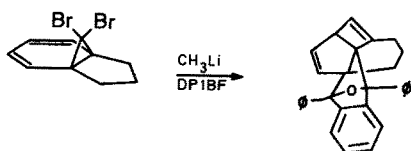
Occasionally the cyclopropylidene to allene isomerization cannot take place for structural reasons. If, for example, the expected allene would be very highly strained, as is the case for certain cyclic allenes, then the reaction is forced to follow an alternative path. A case in point is provided by 1-alkyl-7,7-dibromonorcaranes which undergo a carbene insertion reaction when treated with methyl lithium to provide bicyclobutanes rather than allene derivatives.



A more complex variant of this reaction has been used by Faquette in his short (six-step) synthesis of heptalene from naphthalene [84].

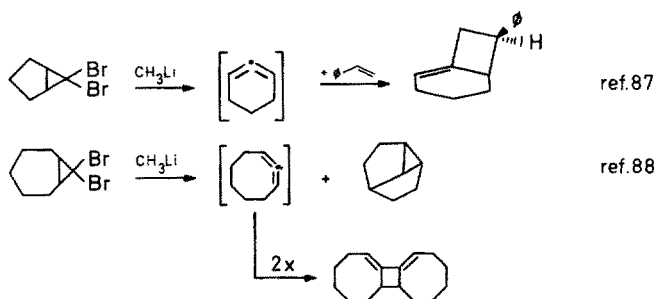


In another series of experiments involving tricyclic dibromocyclopropanes Warner and co-workers have studied the behavior of a propellane derivative towards methyl lithium either in the presence or absence of trapping agents. Whereas in the former case a dimer is produced, with diphenylisobenzofuran (DPIBF) two adducts are obtained in a 2:1 ratio in 24% yield [85].

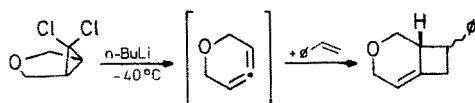


According to the authors an allene intermediate is not involved in this complex transformation [85]. If true, allenes are also unlikely to be produced in the dehalogenation reactions of some related dihalocyclopropanes [86].

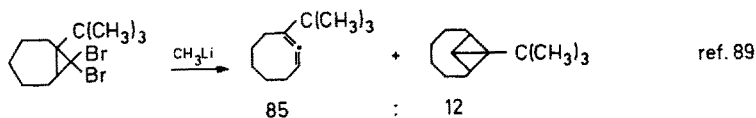
That the allene route should always be kept in mind, though, is demonstrated for example by 6,6-dibromobicyclo[3.1.0]octane and 8,8-dibromo-bicyclo[5.1.0]octane, respectively. When these bicyclic dibromides are reacted with methyl-lithium at room temperature they are evidently converted into the corresponding cyclic allenes since these intermediates may be either trapped by reagents like styrene or dimerize, [2+2]adducts being formed in both cases.



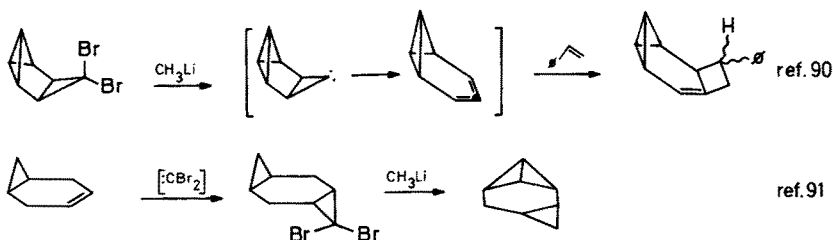
The successful application of the Doering-Moore-Skattebøl reaction to the preparation of relatively small-ring heteroorganic cycloallenes is of recent origin. A specific example is provided by 6,6-dichloro- and 6,6-dibromo-3-oxa-bicyclo[3.1.0]hexane, respectively, which yield 1-oxa-3,4-cyclohexadiene when treated with *n*-butyllithium at low temperatures. The formation of the allene was proven by various trapping experiments [89].



The trick of stabilizing reactive molecules by bulky substituents has often been exploited in organic chemistry. It has also been employed to make certain strained cycloallenes isolable compounds. In fact, the 1,2-cyclooctadiene shown is the first kinetically stable cycloallene of this type [88].

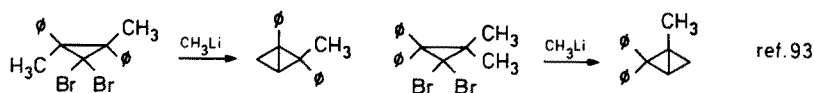


The allene generating reaction has also been applied to more complex bi- and polycyclic substrates. Two examples from the recent literature suffice to illustrate this point.

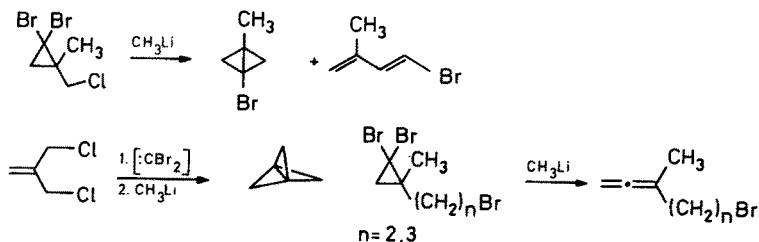


No other dibromocarbene adduct has probably been used in more subsequent reactions than that of benzvalene. Besides the allene producing reaction shown, Christl and his students have described dozens of transformations of this versatile *gem*-dibromocyclopropane, among them practically all reaction-types discussed in the different chapters of this review [92].

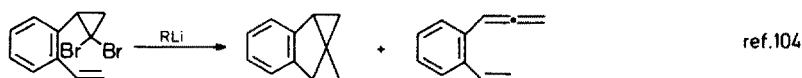
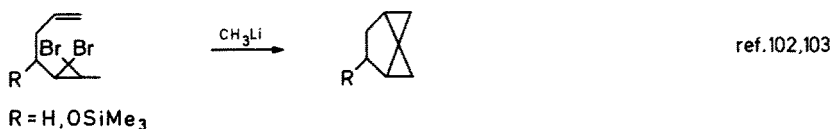
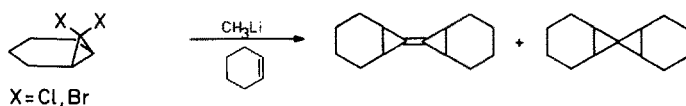
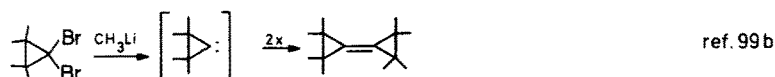
Furthermore, this approach has been applied to the synthesis of substituted bicyclobutanes. For example, tetra-substituted dibromocyclopropanes carrying one or more aromatic substituents provide the diphenyl-bicyclo[1.1.0]butanes shown when treated with methyllithium.



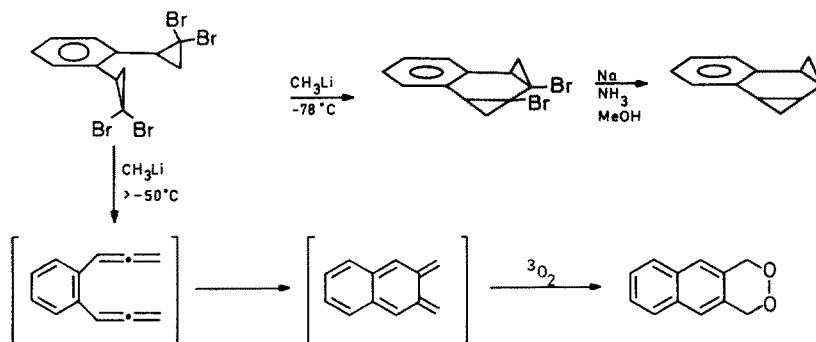
The cyclopropylidene intramolecular carbene insertion is not restricted to carbon hydrogen bonds; how carbon-halogen bonds may participate is illustrated by the following examples. Treatment of 1-chloromethyl-1-methyl-2,2-dibromocyclopropane with methyllithium leads preferentially to 1-methylbicyclobutane [94], and a particularly interesting and important carbon-halogen insertion takes place during the synthesis of [1.1.1]propellane from 2-chloromethyl-3-chloropropene [95–98]. Once the distance between the carbene center and the halogen atom becomes too large allene formation takes over again [94].



Substituted cyclopropylidenes have been shown to participate in both inter- and intramolecular addition reactions with olefins. The resulting products are spiro-pentane derivatives as well as carbene dimers which are formed as side-products [99, 100]. In the absence of olefinic reaction products the latter may even become the main products [99 b].



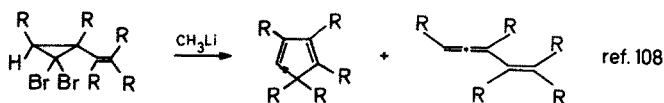
When the bis-dibromocarbene adduct of *o*-divinylbenzene is treated with methyl lithium a surprising influence of the reaction temperature on the product composition is noted.



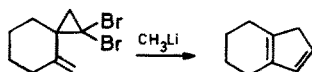
Whereas below $-50\text{ }^{\circ}\text{C}$ a ring closure reaction by 1,6-bromine elimination takes place to give — after reduction — the *trans*-bis-homobenzene derivative shown, at higher temperatures the typical allene forming process is observed. The resulting aromatic bisallene undergoes further cyclization providing an *ortho*-quinodimethane which may be trapped to an *endo*-peroxide by addition of oxygen [105].

If the double bond is connected directly to the three-membered ring, i.e. if the substrate is a dihalo-vinylcyclopropane derivative, a vinylcyclopropylidene to cyclopentadiene isomerization, the so-called Skattebøl rearrangement, takes place upon treatment with alkyllithium. Again, this ring-forming step competes with a ring-destruction process leading to allenic hydrocarbons (vinylallenes,

π -systems which possess both cumulated and conjugated diene subsystems and which are preparatively quite useful [106, 107]).

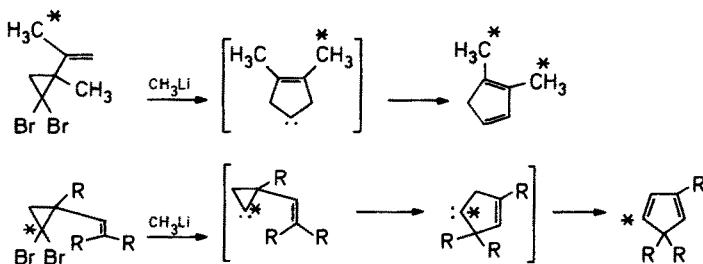


ref. 108

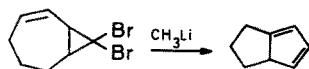
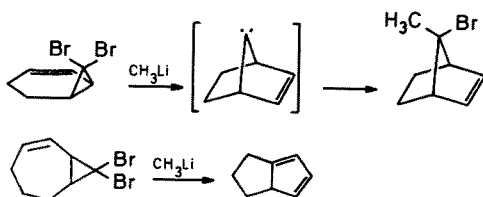


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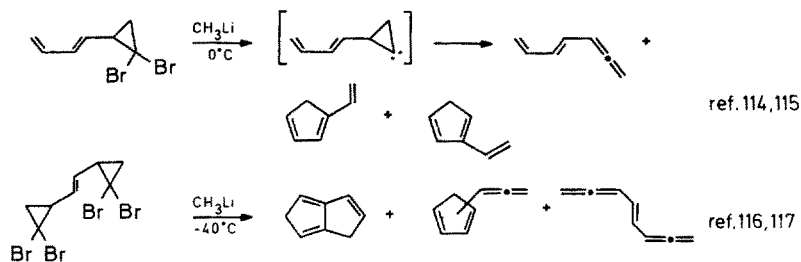
Mechanistically this process is interesting since it involves a carbene-carbene rearrangement as was shown by Skattebøl [110], Baird [111] and Brinker [112] using isotopically labeled substrates.



A vinylcyclopropylidene to cyclopentenylidene isomerization evidently also taken place when 7,7-dibromo-bicyclo[4.1.0]hept-2-ene and 8,8-dibromo-bicyclo[5.1.0]oct-2-ene are treated with methyl lithium. The former compound is converted to 7-bromo-7-methyl-norbornene by intermolecular insertion into the C—Br bond of methyl bromide, whereas tetrahydropentalene is obtained from the latter [113].

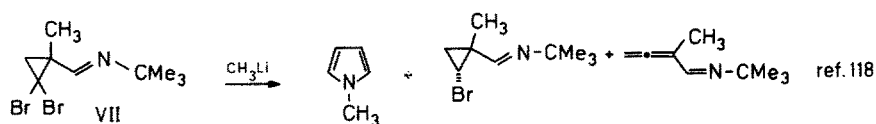


Skattebøl rearrangements in more complex dibromo-vinylcyclopropanes have also been reported. Thus, either a system consisting formally of two double bonds and one dibromocyclopropane unit or an educt containing two dibromocyclopropane moieties and one double bond undergo several carbene-carbene isomerizations upon treatment with methyl lithium. In both cases, complex product mixtures arise.



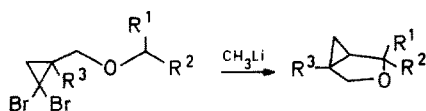
No systematic efforts have apparently been undertaken to replace the carbon atoms of the above molecules by isolated hetero atoms or hetero atom-containing fragments. That this may, in fact, be a worthwhile undertaking is demonstrated by the *tert*-butylimino derivative VII which is converted to a pyrrole (plus the other products shown in the scheme) by methyllithium.

Presumably, the vinylcyclopropylidene to cyclopentadiene isomerization is involved again.



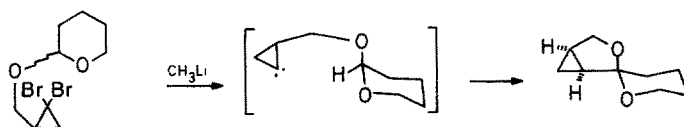
This process may also be employed for the preparation of specifically ring-substituted pyrroles [119].

Novel preparative possibilities arise when cyclopropylidene intermediates are generated from functionalized dihalocyclopropanes. Thus Baird has shown that bicyclic ethers may be formed in high yield by an intramolecular insertion from cyclopropyl alkyl ethers [120].



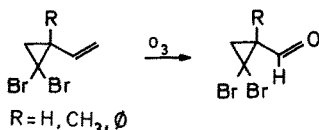
Similar processes have been reported for other ethers [121], alcohols [122], amines [123], sulfides [124], and acetals [125].

Concerning the latter class of compounds a carbene insertion has been employed to prepare the major constituent of the sex attractant of the olive fly (*Dacus oleae*).



Interestingly, no allenic products are formed during this reaction. The two oxygen atoms seem to prevent a competing cyclopropylidene to allene isomerization, at least at the reported reaction temperature of $-75\text{ }^{\circ}\text{C}$ [126].

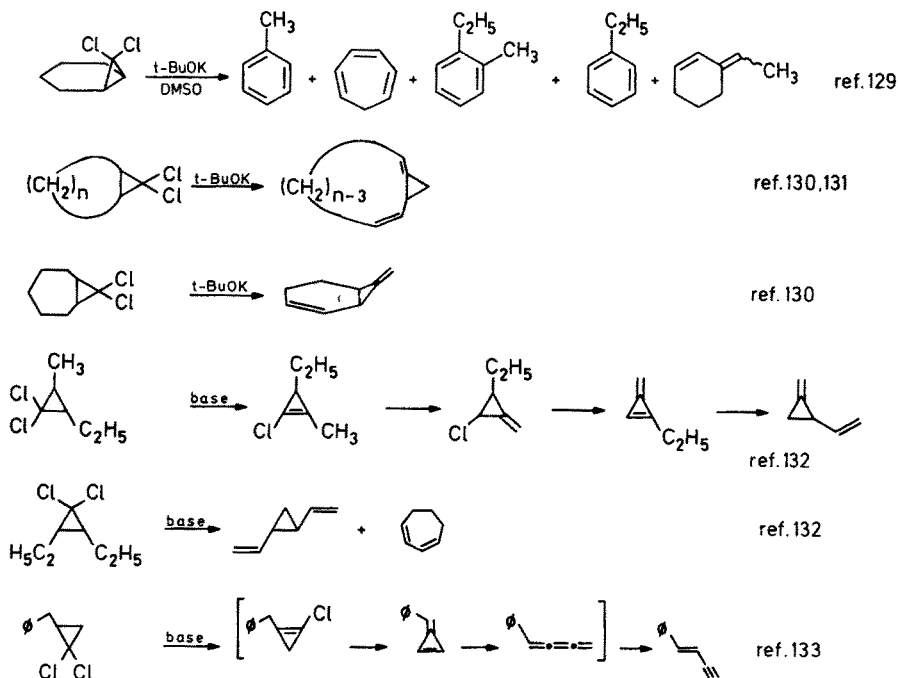
The preparative versatility of the dibromovinylcyclopropanes is further demonstrated by their oxidation to *gem*-dibromo-cyclopropylaldehydes, compounds which are difficult to obtain by other routes [127].



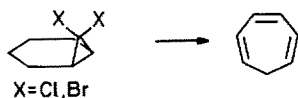
Over-all, this route allows the conversion of a conjugated diene into a highly reactive building block which may be subjected to further transformations [128]. The direct oxidation of the vinylcyclopropanes to the corresponding *gem*-dibromocyclopropanoic acids has also been reported [127, 128].

4 Dehydrohalogenation Reactions

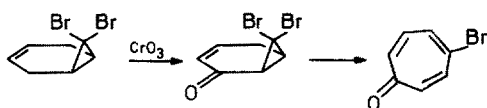
When subjected to strong bases, *gem*-dihalocyclopropanes undergo dehydrohalogenations, and cyclopropenes are formed. These are generally unstable under the reaction conditions and participate in further transformations. The most common of these processes is the isomerization of the newly formed double bond from the *endo*- to the *exo*-orientation, followed by a second dehydrohalogenation step. The methylenecyclopropenes thus generated are still not stable, and subsequently tend to rearrange to less strained systems.



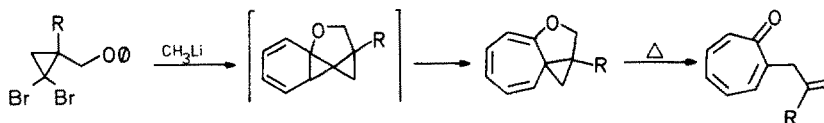
Whereas 7,7-dihalonorcaranes are converted to toluene at 500 °C, they provide cycloheptatriene in yields up to 66% when heated in quinoline or dimethylaniline [134, 135].



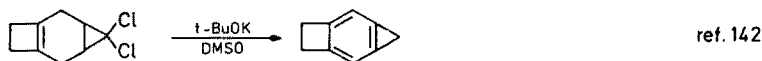
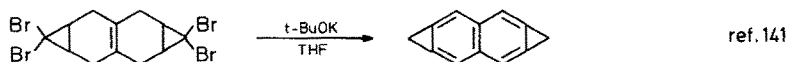
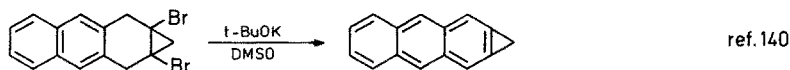
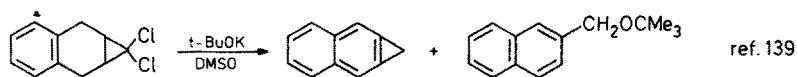
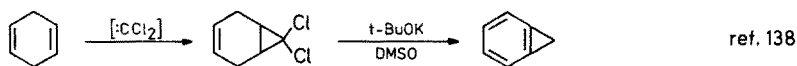
Tropones are obtained in good over-all yields when the dihalocarbene adducts of Δ^2 - and Δ^3 -norcaradienes are first allylically oxidized and the resulting ketones subsequently subjected to a dehydrohalogenation sequence [136].

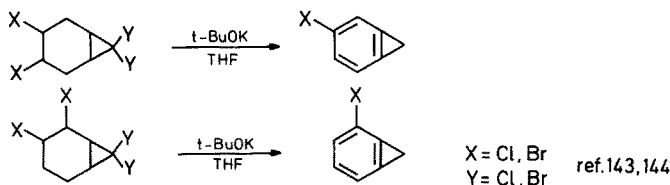


In yet another troponone synthesis Skattebøl has shown that dibromocyclopropanes carrying a phenylether function react to 11-oxa-tricyclo[5.5.0.0^{7,9}]undecatrienes when treated with methyl lithium. The strained polycyclic intermediate is converted into a 2-alkenyltroponone derivative when heated to about 200 °C [137].

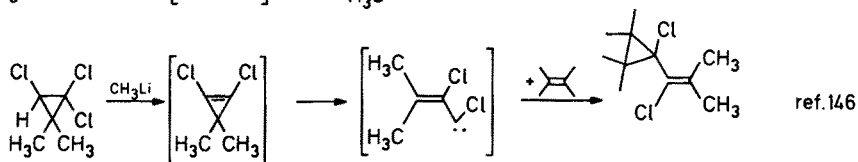
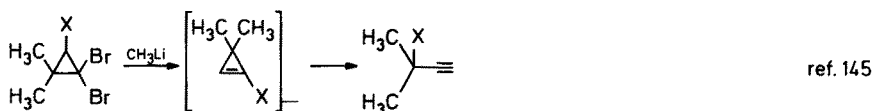


Stabilization of the cyclopropene formed during the dehydrohalogenation may also be achieved by letting its double bond become part of an aromatic system. By this approach several highly strained hydrocarbons like cyclopropabenzene, cyclopropanaphthalene etc. have been synthesized.

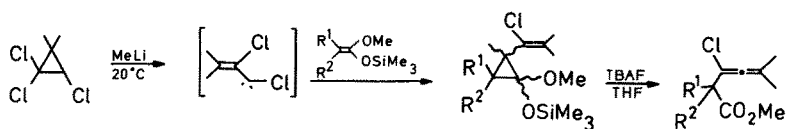




When cyclopropanes carrying three or more halogen substituents are treated with strong bases the initially formed halocyclopropenes may be isolated [147]. Quite generally, though, 1,1,2-trihalocyclopropanes form propargyl halides or enynes when treated with strong bases [147]. Vinylcarbenes may be intermediates in these transformations, as 1-halo-3,3-dimethylcyclopropenes and 1,2-dihalo-3,3-dimethylcyclopropenes easily undergo ring-opening to vinylcarbenes, which can be intercepted by olefins thus allowing the preparation of vinylcyclopropane derivatives [147, 148].

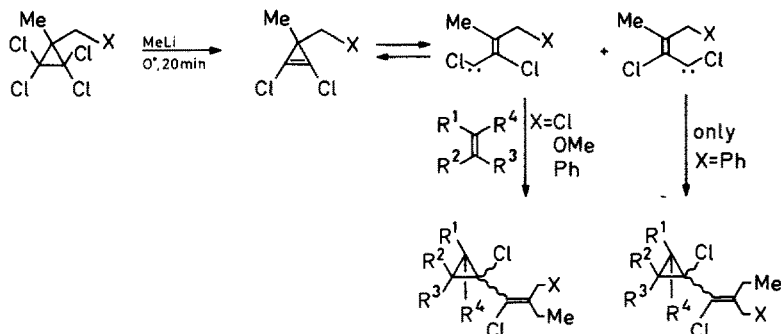


This method has successfully been applied for the addition of chloro(1-chloro-2,2-dimethylvinyl)carbene — formed from 1,1,2-trichloro-3,3-dimethylcyclopropane by dehydrochlorination and subsequent ring-opening — onto ketene methyl silyl acetals, the products of which are transformed to interesting allenic esters when treated with tetrabutylammonium fluoride [149].

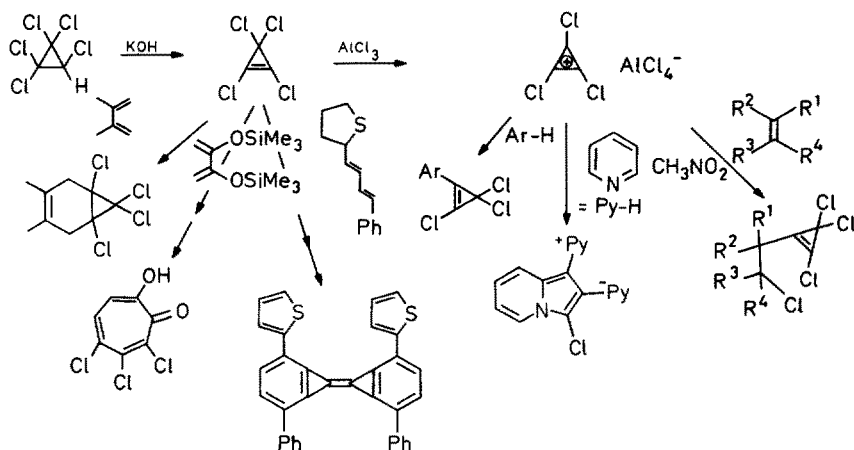


1,1,2-Tetrachloro-3,3-dimethylcyclopropanes with an additional substituent on one of the methyl groups have also been treated with methyl lithium to yield the corresponding 1,2-dichlorocyclopropenes which ring-open to the corresponding vinylcarbenes at 0 °C. The latter add intermolecularly to olefinic substrates giving highly substituted vinylcyclopropanes in high yields. These products in

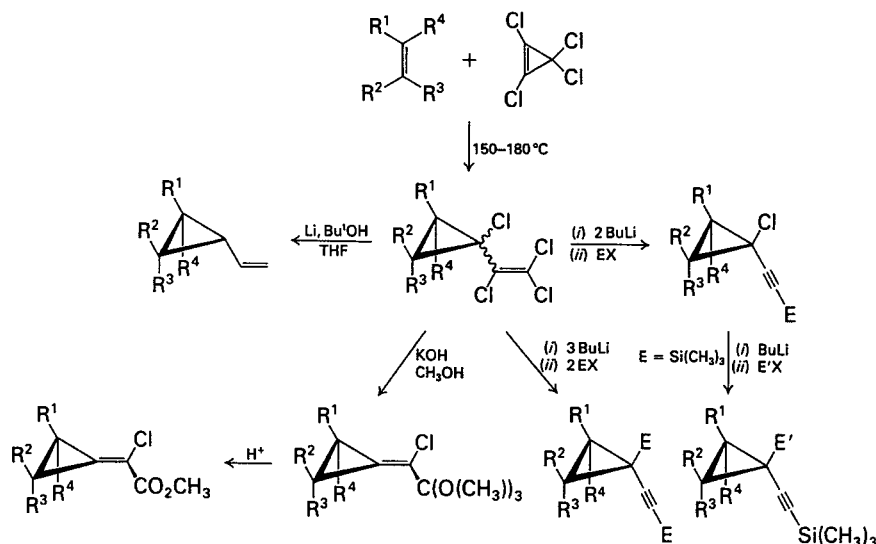
turn are quite useful for further transformations to building blocks for organic synthesis [148].



Dehydrochlorination of pentachlorocyclopropane, formed from trichloroethylene and sodium trichloroacetate as a source of dichlorocarbene, yields tetrachlorocyclopropene [150], a particularly versatile reagent for various applications. It is a reasonably reactive dienophile [151], a reagent applicable to heterocyclic synthesis [152], and an electrophile for aromatic substitutions [153] and additions to alkenes [154] in the presence of Lewis acids.

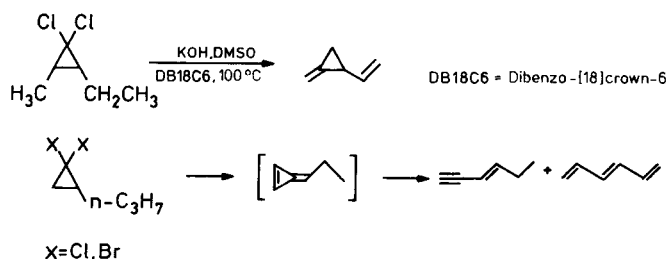


A. de Meijere and co-workers have extensively studied yet another application of tetrachlorocyclopropene [148]. When heated in the presence of olefins to temperatures between 150 and 180 °C, it ring-opens to tetrachlorovinylcarbene which very efficiently adds to the olefinic double bond providing high yields (60–90%) of the corresponding 1-chloro-1-(trichlorovinyl)cyclopropanes [148].

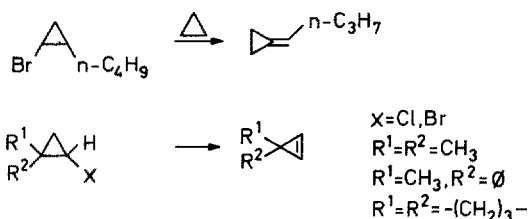


Quite a wide variety of alkenes have been subjected to this carbene addition [148]; the products are multifunctional small ring molecules which may not only be reduced to simple vinylcyclopropanes, but to various substituted cyclopropylacetylenes and cyclopropylideneacetates which are particularly useful and versatile building blocks for organic synthesis [155].

Phase transfer-catalyzed reactions have recently been employed to dehydrohalogenate *gem*-dihalocyclopropanes [156, 157]. Thus, 1-methylene-2-vinylcyclopropane has been prepared from 1,1-dichloro-2-ethyl-3-methylcyclopropane in 60% yield. Under the reaction conditions (solid KOH, DMSO in the presence of dibenzo-18-crown-6, 100–130 °C) further transformations may take place, however. For example, monoalkylated cyclopropanes have been converted to mixtures of acyclic enynes and conjugated trienes. And 7,7-dichloronorcaradiene is converted to toluene under these conditions.

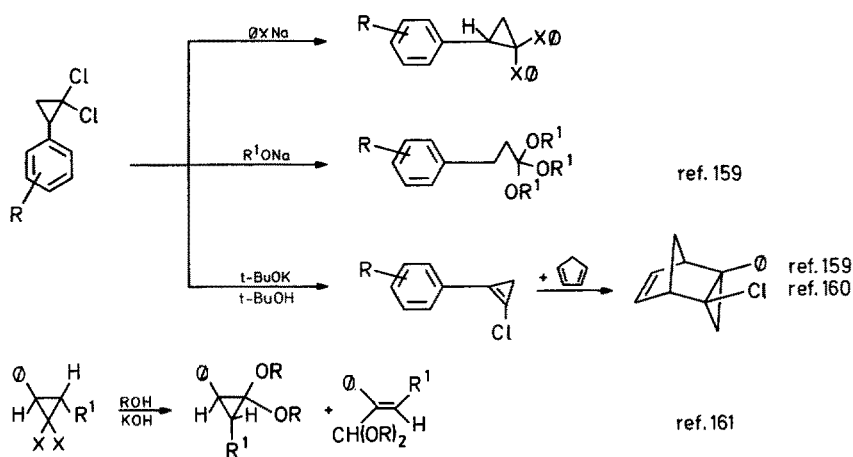


The dehydrohalogenation of monohalogenated cyclopropanes under phase transfer conditions has been of greater preparative importance: Monoalkylated bromocyclopropanes have been converted to alkylidene cyclopropanes, and 3,3-disubstituted cyclopropylhalides provide the corresponding cyclopropenes in good yield [158].

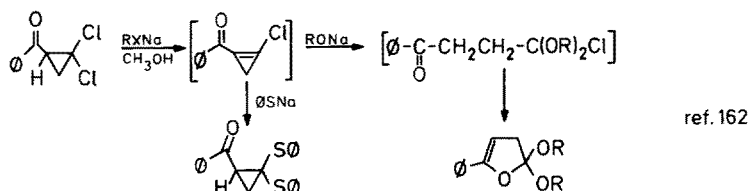


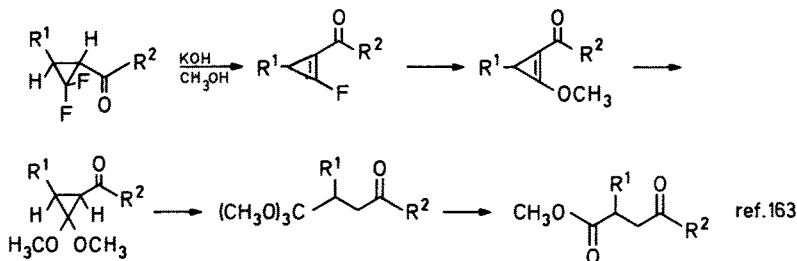
5 Halogen Nucleophilic Substitution (Solvolysis)

As already mentioned, treatment of dihalocyclopropanes with bases furnishes cyclopropenes. When nucleophilic reagents are present, these are added to the strained double bond, and the products thus formed correspond to the products of direct nucleophilic substitution of the substrate, i.e. the elimination/addition process is equivalent to an overall substitution. In fact, in some cases the unstable chlorocyclopropene intermediates could be trapped as Diels-Alder adducts with cyclopentadiene.

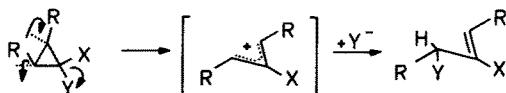


A similar mechanism is thought to be involved when functionalized dihalocyclopropanes are treated with sodium alkoxides as well as thiophenolates or subjected to the influence of potassium hydroxide in methanol.

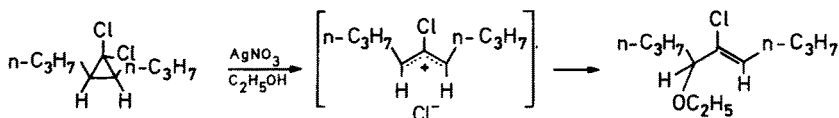




But even if strongly basic reagents are absent, a nucleophilic substitution can take place in *gem*-dihalocyclopropanes. In this case a cyclopropyl-allyl ring-opening occurs, which obeys — as has been known for several years now [164] — the Woodward-Hoffmann orbital symmetry conservation rules. During the ring-opening process the substituents oriented *trans* to the leaving group experience an outward, disrotatory movement. Or, to put it another way, the cyclopropane bond which is opened during the isomerization, attacks the carbon atom which carries the leaving group from the reverse side of the latter.

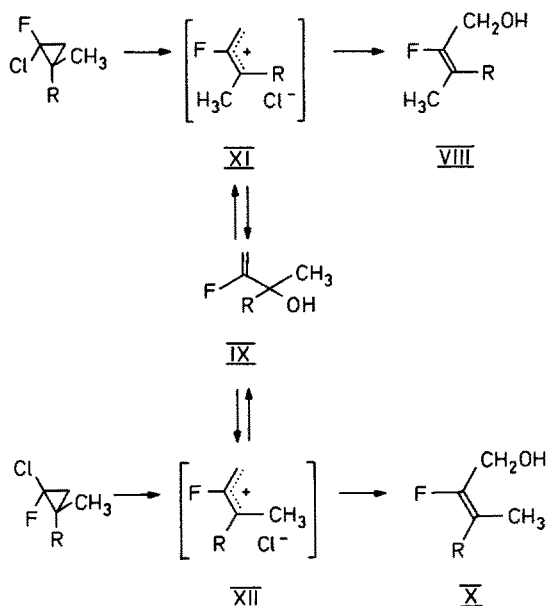


The allyl cation thus formed may stabilize itself either by readdition of the leaving group — leading to a 2,3-dihalopropene — or by the addition of a nucleophile. The influences of steric and electronic effects on the stereochemistry and on the solvolysis rates of various alkyl-substituted chlorocyclopropanes have been investigated by Parham and co-workers [165, 166], who could show for example that *cis*-2,3-dipropyl-1,1-dichlorocyclopropane solvolyzes 24 times faster than its *trans*-isomer, in accordance with predictions based on orbital symmetry arguments. When one propyl substituent of the *trans*-isomer is replaced by an ethoxy group the rate of solvolysis increases 200 fold.

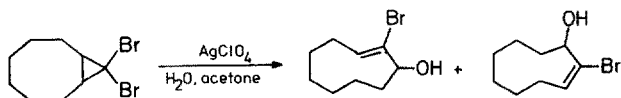


It is, however, not always possible to draw conclusions on the solvolysis mechanism from the configuration of the products, since the latter may not necessarily be the initially formed solvolysis products. Schlosser has shown for example, that the same product mixture, consisting out of the 2-fluoropropene derivatives VIII-X is obtained from the fluorochlorocyclopropanes shown, regardless whether the (*E*)- or the (*Z*)-isomer is solvolyzed. To rationalize this observation it has been proposed that the tertiary alcohol IX is formed first, and that this

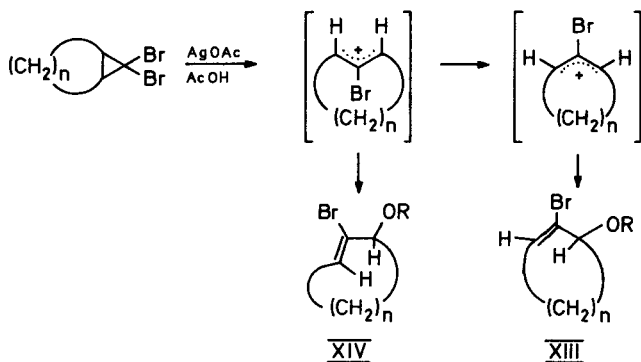
intermediate is converted via XI or XII to the more stable primary alcohols VIII and X, respectively [167, 168].



When dihalo-bicyclo[n.1.0]alkanes are solvolyzed, ring-enlargement products are formed. In fact, this reaction is often the method of choice for the preparation of medium-sized rings. As far as the stereochemical outcome of the reaction is concerned, there are conflicting reports in the literature. Thus a mixture of (*E*)- and (*Z*)-2-bromocycloheptenols has been obtained by solvolysis of 9,9-dibromobicyclo[6.1.0]nonane [169]; in earlier reports only the (*Z*)-diastereomer was mentioned [170], and the solvolysis in aqueous acetone in the presence of silver tosylate apparently provides only the (*E*)-isomer [171].

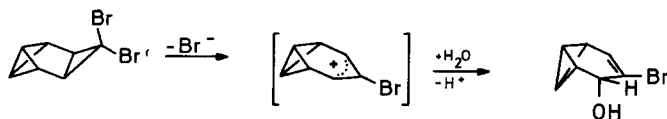


The solvolysis of 7,7-dibromo-bicyclo[4.1.0]heptane in methanol in the presence of silver perchlorate leads to (*E*)-2-bromo-3-methoxycycloheptene [172, 173]. A more detailed study of this reaction — having been performed by Ito in 1986 [174] — has revealed that the stereochemical result of the solvolysis depends on the length of the polymethylene chain in these bicyclic dihalides. For the lower homologs ($n = 2$ to 4) it is the (*E*)-isomer XIII that is produced, whereas for the more extended systems ($n = 5$ to 8) the *Z*-bromoethers XIV are produced.



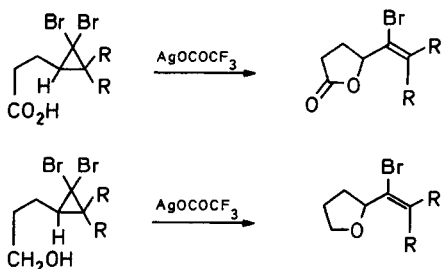
These results correlate with the thermodynamic stabilities of the cycloolefins: rings with $n > 10$ are more stable if their double bond is *trans*-configured. Their formation may be understood if free cations are postulated as reaction intermediates which can either isomerize from (*Z*) to (*E*) or react with a nucleophile. According to the authors the rate of interception of the various cations by acetate anion cannot compete with the isomerization rate.

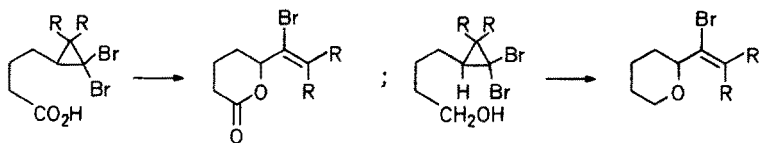
Analogous ionic ring-openings have been described for polycyclic *gem*-dibromocyclopanes. For example, when solvolyzed in 50% aqueous acetone in the presence of triethylamine, the already mentioned dibromocyclopropane adduct of benzvalene loses its *endo*-bromine substituent and opens in a disrotatory fashion to a tricycloheptenyl cation which may be intercepted by water to provide the bromoalcohol shown [175].



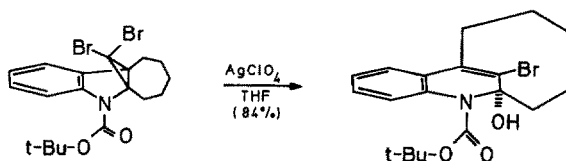
The carbocation intermediate, incidentally, is an isomer of the tropylium ion.

Ionic ring-opening reactions of cyclopanes under solvolytic conditions followed by ring-closure of the primarily produced cations have been employed for the synthesis of lactones, tetrahydrofuranes, and pyranes, respectively, as shown below [176].

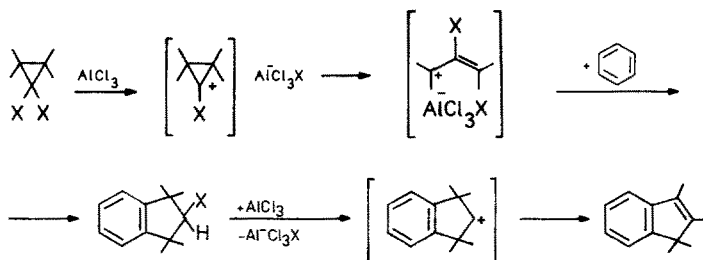




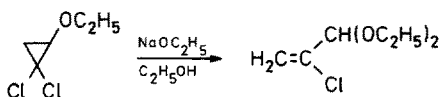
Products with a [5]metacyclophane skeleton are obtained when dihalocarbene adducts of certain cycloheptene derivatives are treated with silver(I) perchlorate in the presence of 2,4,6-collidine in tetrahydrofuran [177, 178].



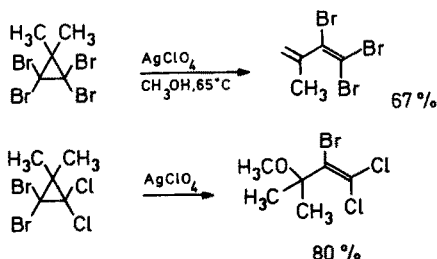
A number of *gem*-dibromocyclopropane derivatives has been reacted with aromatic compounds in the presence of aluminum chloride or ferric chloride providing indenenes in yields up to 80%. To rationalize this interesting anellation process it has been proposed that the cyclopropyl cation formed under the influence of the Lewis acid collapses to an allylic ion, which then functions as the alkylating agent [179].



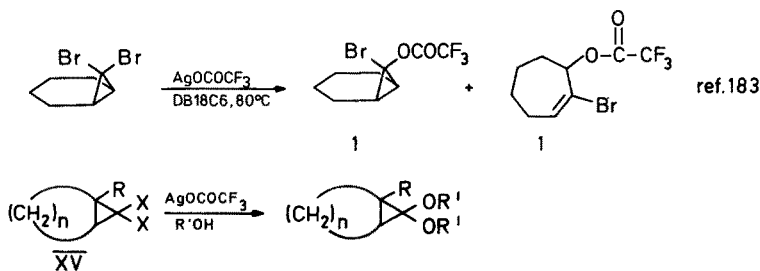
Allylic cations have also been discussed as intermediates in the conversion of *gem*-dichlorocyclopropylethers in alcoholic solvents in the presence of base resulting in the formation of acetals of the general structure $RR^1C=CClCH(OEt)OR^2$ in good yields [180, 181].



A silver-induced ring-opening reaction of various tri- and tetrahalocyclopropanes to produce polyhalogenated dienes or methyl polyhaloallyl ethers in good yields has recently been described [182]:

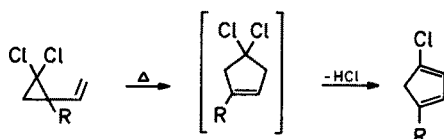


Some rare examples are known in which a cyclopropane ring is preserved during solvolysis, i.e. its halogen atoms are substituted by a nucleophilic group. When the substituted bicyclic substrates XV are solvolyzed, ring-enlarged products are formed exclusively for R=Cl, OCH₃, and CH₃. However, with R being trimethylsilyl the three-membered ring remains intact [184]:



6 Thermal Rearrangements

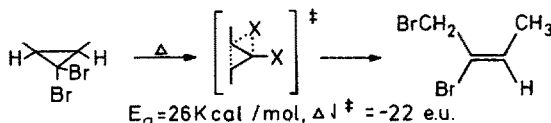
One of the classical papers in this area is Neureiter's discovery of the vinylcyclopropane to cyclopentene rearrangement [185]. This important process was first observed on a 1,1-dichloro-2-vinylcyclopropane derivative, which on heating yielded a chlorocyclopentadiene, presumably by the loss of hydrochloric acid from the initially formed 4,4-dichlorocyclopentene.



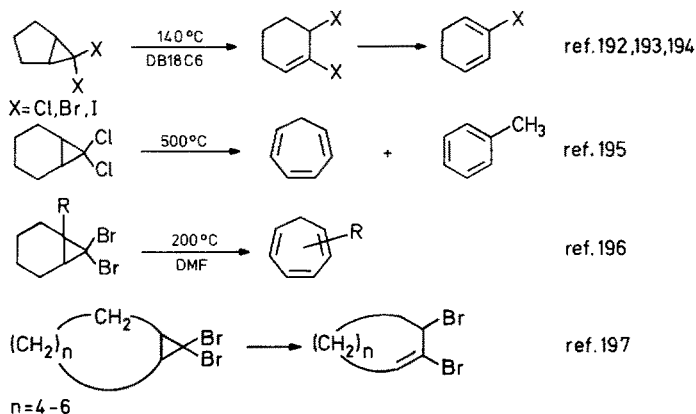
Since then numerous thermal rearrangements of dihalocyclopropanes have been observed and the isomerization has been reviewed several times [11, 186]. It therefore suffices to discuss some special features of these reactions here. The thermal isomerization of dihalocyclopropanes is often accompanied by a halogen migration and then leads to 2,3-dihalogenated propenes.

At first sight, one could suppose that this isomerization follows the Woodward-Hoffmann-allowed cyclopropyl-allyl pathway (see above). At least in some cases, however, the required heterolytic bond rupture is quite unlikely to take place under the reaction conditions (gas phase or apolar solvents). On the other

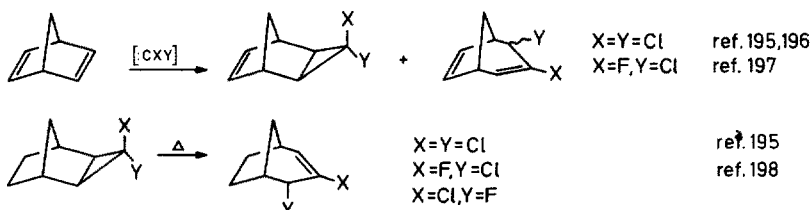
hand, the diradical mechanism which has been invoked to explain the thermal ring-opening of alkyl substituted cyclopropanes, fails to account for certain observations made with halocyclopropanes. For example, radical inhibitors do neither effect the rate of the thermal conversion of 1,1-dichlorocyclopropane to 2,3-dichloro-1-propene nor do they influence the nature of the reaction products [187]. From the activation parameters for the thermolysis of *cis*-1,1-dibromo-2,3-dimethylcyclopropane it has been concluded that halogen migration and ring-rupture occur in a concerted fashion via a cyclic transition state [188].



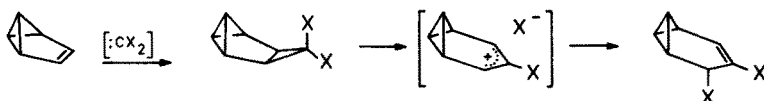
Other authors have postulated similar transition states for these isomerizations [189, 190]. According to extended-Hückel calculations the migration of an *endo*-halogen atom in certain bicyclic systems should be accompanied by a conrotatory ring-opening [191]. Thermal isomerizations of bi- and tricyclic substrates incorporating a halocyclopropane moiety have been studied in some detail. In these reactions the endocyclic bond of the three-membered ring (i.e. the zero bridge) is broken and cyclic dihaloolefins or consecutive products result. The ease, with which these reactions often occur, probably originates from the strain release which occurs when the polycyclic frameworks are destroyed.



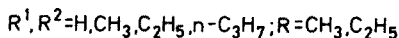
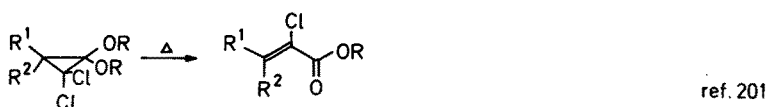
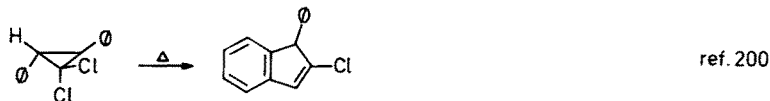
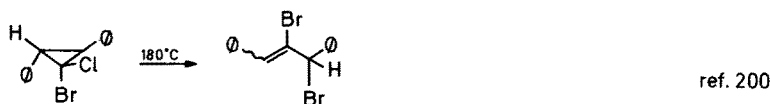
The *endo*-adducts of dihalocarbenes onto norbornadiene and norbornene are thermally so labile that they even isomerize under the conditions of their formation.



A detailed discussion of the thermal isomerization of *gem*-dihalocyclopropane — including polycyclic substrates — has been presented by Ioffe and Nefedov. It is proposed (and theoretically justified by MO calculations) that these concerted rearrangements of *gem*-dihalocyclopropanes to 2,3-dihaloolefins take place by synchronous migration of the halogen and rupture of the opposite bond of the cyclopropane ring [191]. The dibromocarbene adduct of benzvalene isomerizes in inert solvents like carbon tetrachloride to 4,5-dibromotricyclo[4.1.0.0^{2,7}]hept-3-ene when heated to 80 °C. Ring-opening presumably takes place by removal of the *endo*-bromine substituent and disrotatory opening of the C¹—C⁶-bond of the starting *gem*-dihalide [199].

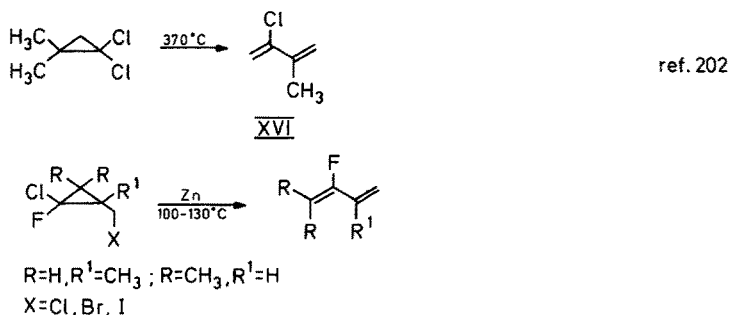


The thermal isomerization of dihalocyclopropanes is facilitated by the presence of aryl, alkyl and alkoxy substituents in the three-membered ring. Phenyl substituted systems may give rise to indenenes, and in the alkyl series the dehydrohalogenation of 2,3-dihalocyclopropane derivatives may lead to dienes.

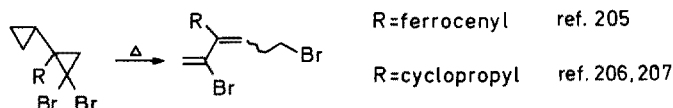


The yields of these thermal processes are low, however, especially if they are employed for the preparation of a specific target molecule. For example, the pyrolysis of 1,1-dichloro-2,2-dimethyl-cyclopropane furnishes a product mixture (total yield 63%) which contains the diene XVI in 24% yield only.

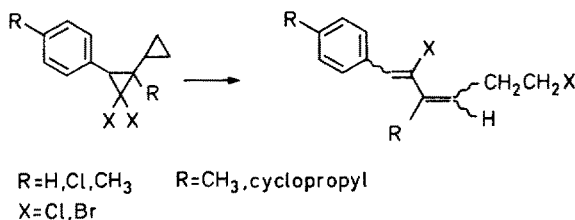
Schlosser and co-workers have developed a method for the preparation of fluoroisoprenes with yields ranging between 38 and 80%, consisting of the dehydrohalogenation of 2-chloro-2-fluoro-1-halomethylcyclopropanes at 100 °C in diglyme in the presence of zinc [203] or under the influence of potassium hydride [204].



When dihalocyclopropanes carrying a cyclopropyl substituent are thermolyzed both rings are opened and substituted 1,3-hexadienes are formed.

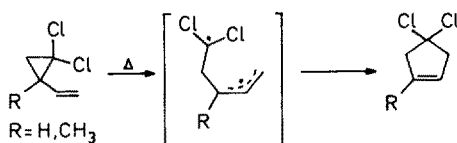


The thermal isomerization of 2-aryl-1,1-dicyclopropyl-3,3-dihalocyclopropanes has been interpreted as a $[\sigma_2 + \sigma_2 + \sigma_2]$ process in which three σ -bonds are broken in a concerted fashion [208].

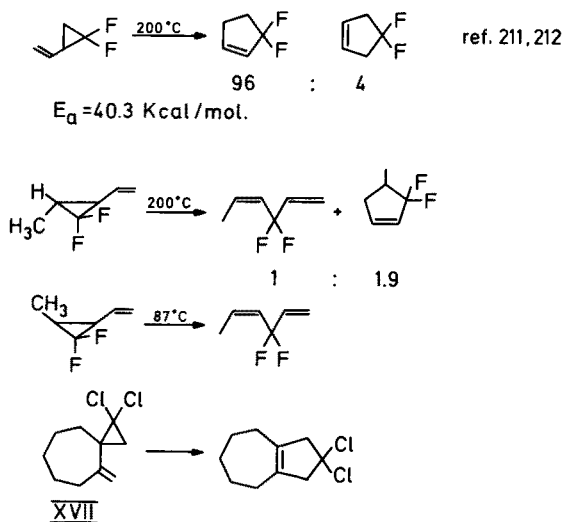


6.1 Vinylcyclopropane to Cyclopentene Isomerizations

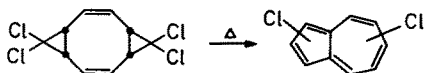
The thermal rearrangement of vinylcyclopropanes to cyclopentenes is one of the most thoroughly studied thermal processes known. It constitutes an important route to five-membered ring-systems, and has been applied widely in synthesis, even for the preparation of structurally complex products, i.e. numerous natural products [209]. This ring-enlargement has also been observed with dihalocyclopropanes, providing the expected dihalocyclopentenes. Like the parent system the halogen substituted vinylcyclopropanes isomerize via diradical intermediates [210]. The rearrangement rate for the latter is, however, much higher than that for the halogen-free substrates.



Whereas the parent difluoro-vinylcyclopropane isomerizes to difluorocyclopentene under pyrolysis conditions, the corresponding alkyl compounds also lead to acyclic dienes. The activation energy for the difluoro-vinylcyclopropane isomerization is practically identical with that observed for the unsubstituted hydrocarbon [211, 212]. If the alkyl group is oriented *cis* to the vinyl substituent, only dienes are isolated, and the process occurs at much lower temperatures. Presumably these stereoisomers rearrange by a different mechanism (a 1,5-homodieryl hydrogen shift [213]). When the dichlorocyclopropane XVII is subjected to flash vacuum pyrolysis it isomerizes to 9,9-dichloro-bicyclo[5.3.0]dec-1(7)-ene [214].



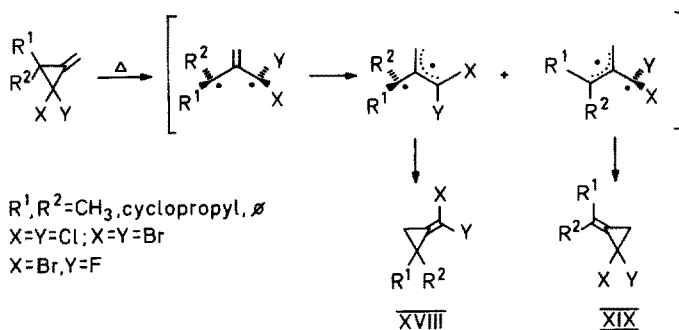
An interesting 1,2-divinylcyclopropane isomerization is observed when 5,5,10,10-tetrachlorotricyclo[7.1.0.0^{9,6}]deca-2,7-diene is subjected to flash vacuum pyrolysis: at 700 °C and 10⁻⁴ Torr a mixture of three isomeric dichloroazulenes is produced [215].



6.2 Thermal Rearrangements of Dichloromethylene-Cyclopropanes

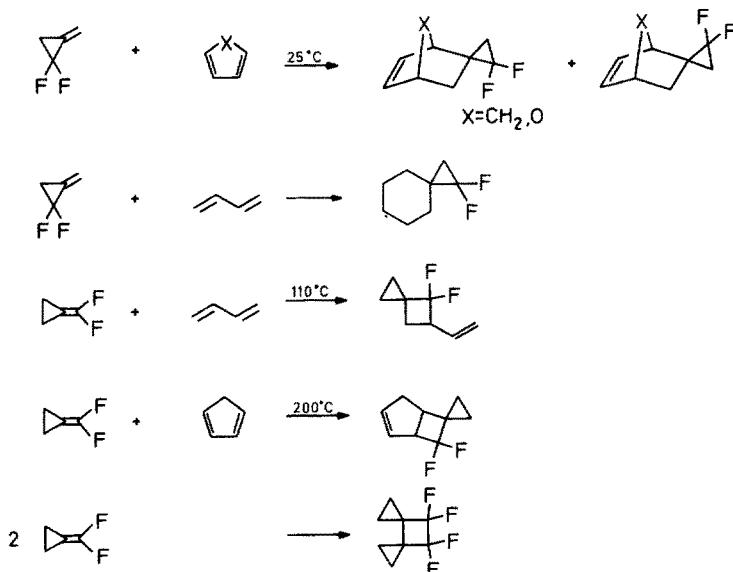
At elevated temperatures, methylenecyclopropane and its derivatives undergo a rearrangement which maintains the methylenecyclopropane skeleton. Obviously, for the parent system this process is degenerate [216, 217–222]. The 2,2-dihalo-methylene-cyclopropanes behave analogously, providing either mixtures of the

methylenecyclopropanes XVIII and XIX or only the dichloride XVIII, with the actual outcome of the reaction depending on the substituents again.



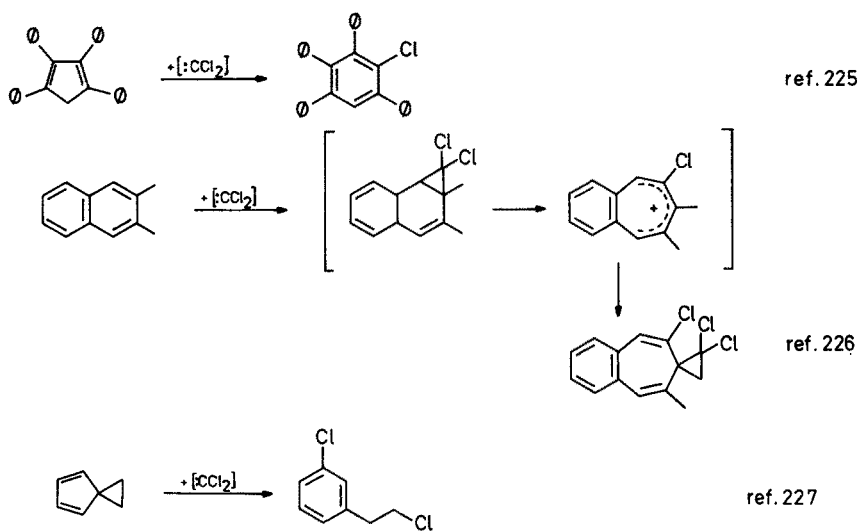
Chlorine and bromine as well as cyclopropyl and phenyl groups increase the rate of isomerization significantly by lowering the activation enthalpy. With an activation entropy approaching zero the process most likely occurs via diradicals [223].

Among the other reactions of the *gem*-dihalomethylene cyclopropanes the cycloadditions are of greatest importance, although they have so far been observed only for the fluorine containing compounds. It has been shown, that 2,2-difluoro-1-methylene-cyclopropane prefers the [4+2]cycloaddition mode, whereas the isomeric 1-(difluoromethylene)cyclopropane behaves like a typical fluoroolefin, i.e. it is a poor dienophile but active in [2+2]cycloadditions [224]:



6.3 Dihalocyclopropanes as Unstable Intermediates

Although the *gem*-dihalocyclopropanes are fairly stable compounds, they can participate — as has been shown in the above sections — in quite a number of chemical transformations. Several reactions between dihalocarbenes and alkenes have been described in which no dihalocyclopropane formation could be observed; that these intermediates might have been produced was only inferred from the type of products finally isolated. A typical process of this type is the *endo*-addition of dihalocarbenes to norbornene and norbornadiene as discussed above. Comparable rearrangements have been observed, when dichlorocarbene additions either lead to aromatic products or when they cycloadd to rather inert aromatic systems. In the latter case a ring-enlargement takes place. A reaction related to the concerted opening of two cyclopropane rings in a bicyclopropyl system as discussed above takes place when dichlorocarbene is added to spiro[2.4]hepta-4,6-diene [227].



When pyrroles, triazoles and other nitrogen containing heterocyclic compounds react with dichlorocarbene, no addition to their carbon-carbon double bonds has been observed. In some cases the formation of cyclopropane adducts has been suspected; however, alternate ways to explain the reaction products cannot be excluded [228].

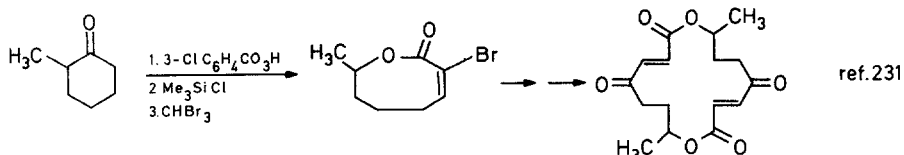
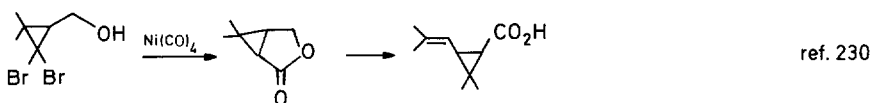
7 Conclusion and Outlook

To summarize, *gem*-dihalocyclopropanes may serve as starting materials for the preparation of cyclopropane and cyclopropene derivatives, they can lead to compounds with bicyclobutane and spirocyclopentane structures, provide allenes and

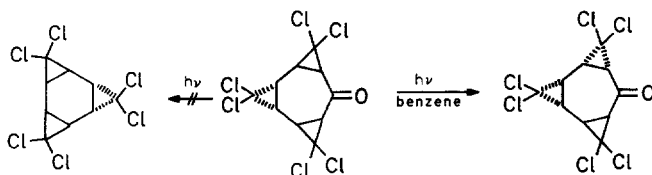
higher cumulenes, cyclopentenes and cyclopentadienes, and many other classes of compounds.

A few final examples may illustrate the quite general and steadily growing use of these versatile three-membered ring compounds.

Dihalocyclopropanes have been employed in the crucial steps of a synthesis of crepinine, chrysanthemic acid and (\pm)-pyrenoforin. Altogether the large variety of reaction types and ease of access to the dihalocyclopropanes makes them very useful in organic synthesis. Especially the possibility of introducing other functional groups as replacement for the halogen atoms makes them attractive substrates for the preparation of a large variety of practically important compounds like pheromones, prostaglandins and various insecticides [232].

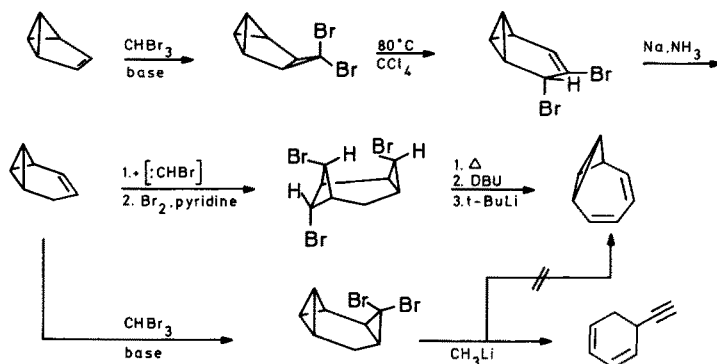


On the other hand there are certain groups of reactions that have been neglected so far, among them the photochemical behavior of the *gem*-dihalocyclopropanes. One of the few reported examples is by Weyerstahl who has attempted to generate hexachloro-tris- σ -homobenzene from the corresponding tris- σ -homocycloheptatrienone [233]. The latter, however, prefers to undergo *trans-cis* isomerization rather than decarbonylation.



It is not unreasonable to expect preparatively useful photoreactions of appropriately functionalized dihalocyclopropanes also. Although the present trend in *gem*-dihalocyclopropane chemistry clearly favors the use of more highly functionalized substrates, the traditional role — mentioned in the introduction — of employing these strained molecules in hydrocarbon synthesis, is by no means an approach of the past. This point is stressed by the recent synthesis of octavalene

by Christl and his students who used halocarbene adducts during several crucial transformations in their preparation of this interesting C_8H_8 -hydrocarbon [234 to 237].



Whereas the ring-enlargement of benzvalene to homobenzvalene and the second dibromocarbene addition posed no problems, the final insertion step provided 5-ethynyl-1,3-cyclohexadiene instead of the expected octavalene (tricyclo[5.1.0.0^{2,8}]-octa-3,5-diene). However, when homobenzvalene is first reacted with monobromocarbene and the resulting adduct with pyridinium perbromate, a tribromide is obtained, which after thermal ring-opening and dehydrobromination is finally converted to the target molecule by treatment with *tert*-butyllithium. In this sequence, two carbon atoms have eventually been inserted between the carbon atoms of the double bond which bridged the bicyclobutane moiety of the original molecule [238].

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Through-Bond Modulation of Reaction Centers by Remote Substituents

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A reaction center is under influence not only of substituent(s) which it bears, but also by those at a more distant location. The influence is reflected in its reactivities towards different reagents. This article examines the structural-reactivity relationships in terms of the number of intervening bonds and the nature of both the reaction center and the substituent(s). The polarity alternation rule is the basis for this reactivity assessment. Through-space interactions are not discussed.

1 Introduction

In organic chemistry it is well known that a substituent directly linked to a reaction center has a profound effect on the latter's reactivity. The influence of a remote substituent has also received much attention as more organic molecules are being scrutinized. Thus, neighboring group participations in solvolysis are generally observed. Certainly, the full attribution of a substituent must be the sum of electronic, steric, and stereoelectronic factors.

This article discusses many organic reactions as affected electronically by substituents situated more than one bond away. More specifically, the polarity alternation rule forms the basis for evaluation of organic reactivity [1]. The concept, with its simplicity and broad applicability, deserves to be the prime and initial focus for a student to learn about organic reactivity.

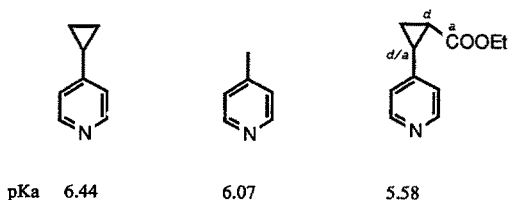
The polarity alternation rule (PAR) considers two kinds of substituents. The donors are those having unshared electronic pairs or π -electrons, and +I groups. These include OH, OR, OCOR, NH_2 , NRR' , $\text{N}(\text{R})\text{COR}'$, SH, SR, halogens and alkyl groups. The donor properties of the alkyl groups may reflect the existence of hyperconjugation. On the other hand, the acceptors are electron sinks, i.e. polarizable π -bonds, atoms with empty orbitals, and -I groups. Examples of acceptors are $\text{C}=\text{O}$ (aldehydes, ketones, carboxylic acid derivatives), CN, SO_2 , NO_2 , SiR_3 .

The coulombic forces determine linkage of a donor to an acceptor, and vice versa. In other words, direct covalent bonding of a donor or acceptor to another atom of its kind is unfavorable.

Since hydrocarbon subunits (methyl, methylene and methine groups) are not polarized to a great extent, their nature can be defined by a polar substituent. The high acidity of the α -hydrogen atoms of carbonyl compounds, nitriles, sulfones, and nitroalkanes follows from polarity alternation, the carbon atoms being a donor next to the acceptor substituent.

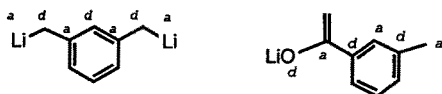
Theoretical appraisal of polar effects [2] has indicated a charge alternation associated with back-donation of lone pair electrons of donors. Coulombic interactions seem to be sufficient to stabilize certain acyclic systems and therefore it is not necessary to invoke resonance effects [3].

Long range electronic effects sometimes can be discerned. Thus, the striking difference in basicity [4] of 4-cyclopropylpyridine [pKa 6.44] and 4-(2-carbethoxy cyclopropyl)pyridine [pKa 5.58] is attributable to the field effect and through-bond interaction.

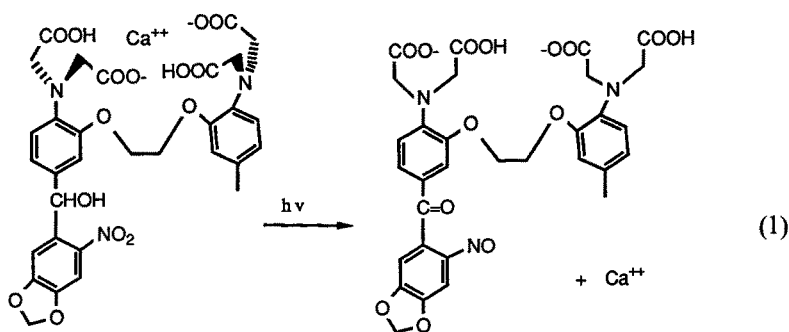


Lithiation study of xylenes indicates a much higher reactivity of the *meta* isomer (m - \gg o - $>$ p -). On the other hand, only the *meta* isomer of methylacetophenone

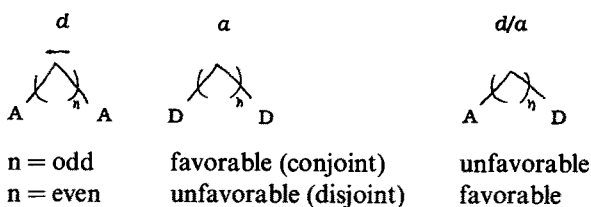
resists metalation at the sidechain. These observations are totally consistent with the polarity alternation rule which can be used to designate donor sites [5].



Another example concerns with the release of calcium ion from its chelate with phenylglycine analogs which contain an *o*-nitrobenzhydrol system as triggered by illumination [6]. The photochemical transformation of the latter moiety into a nitrosobenzophenone forces the amino nitrogen to adopt a different conformation in which its acetic acid chains can no longer bind the metal ion cooperatively. In the benzophenone the amino and the ketone groups are PA-related (conjugation).



Interesting situations develop when multiple (>2) substituents are placed in fairly close proximity. Depending on the donor or acceptor nature of the substituents and that of the carbon center in question, and the number of bonds separating them, there will be an activating or deactivating effect. Typical scenarios are summarized in the following diagrams.



In the favorable cases, polarity alternation prevails along the atomic chains within which the reaction centers reside. On the contrary, unfavorable interactions between the substituents and the reaction centers are due to disruption of the polarity alternation. As will be seen later, the favorableness/unfavorableness is in the thermodynamic context. Recent calculations [7] of energy changes for hydride transfer and chloride transfer to $^+\text{CH}_2\text{OH}$ from CH_3SH and ClCH_2SH , respectively, manifest a stabilizing interaction of the geminal Cl, OH relative to the Cl, SH pair.

It is possible, or even desirable, to activate a chemical species to undergo reactions by setting up an unfavorable situation. In short, *reaction activation can be achieved by either polarity alternation accentuation or polarity alternation disruption.*

The PAR is easy to apply, and the crucial need is only to identify correctly the donor or acceptor nature of a polar substituent. It should be mentioned that an interesting phenomenon called contrapolarization [8] can often be observed. This phenomenon pertains to a role change of an atomic center during a reaction step, it occurs ubiquitously in redox processes. Contrapolarization is unintentional and transitory umpolung.

2 Substitution Reactions

2.1 Aromatic Substitutions

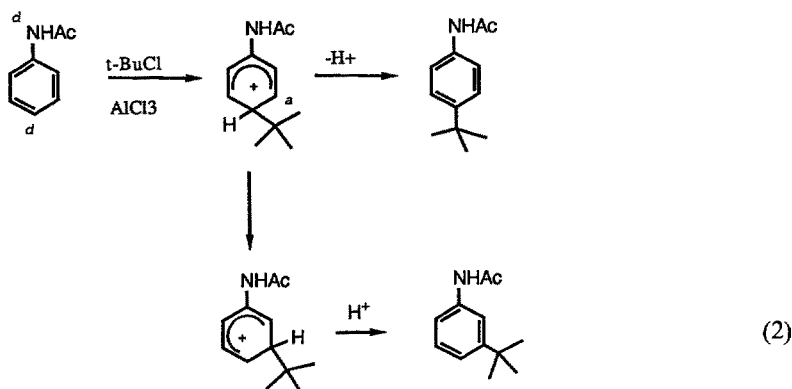
The most familiar set of organic reactions is perhaps the electrophilic aromatic substitutions. For monosubstituted benzenes the major products from the process are either *o*- or *p*-disubstituted benzenes or *m*-disubstituted analogs.

The *o*,*p*-directing groups are donors and the *m*-directing groups are acceptors. The cause-effect is readily revealed by the polarity alternating sequences shown in the following formulas.

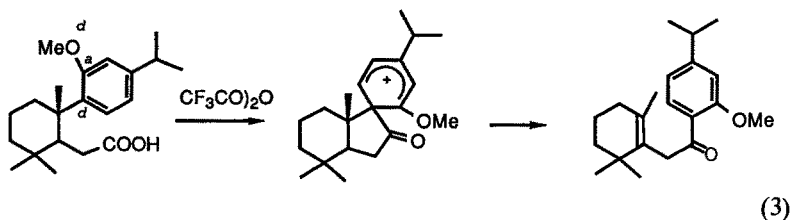


The “unusual” *meta*-bromination of phenols and their methyl ethers [9] under superacid conditions is quite expected because *O*-protonation inverts polarity of all the nuclear carbon atoms. This reaction is reminiscent of the better known electrophilic substitutions of aniline in acidic media.

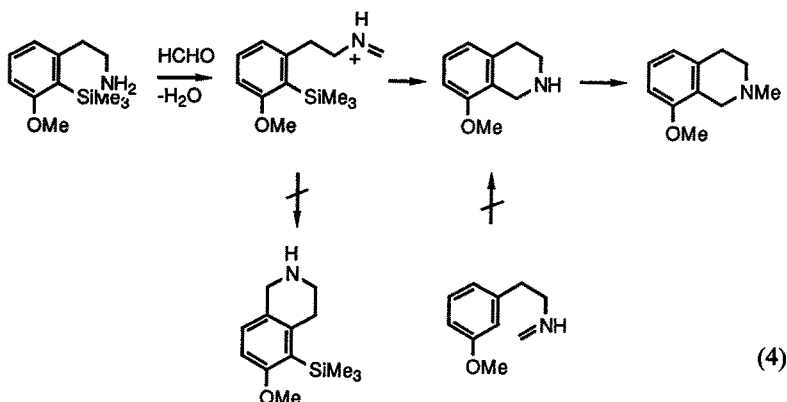
It has been shown that *t*-butylation of acetanilide [10] gives the 1,4-isomer as the kinetic product which is then converted into the 1,3-isomer. The isomerization is a 1,2-alkyl migration within the C-protonated intermediate which has a perfect set-up of donor and acceptor sites, and the two substituents of 3-(*t*-butyl)acetanilide are conjoint in polarity.



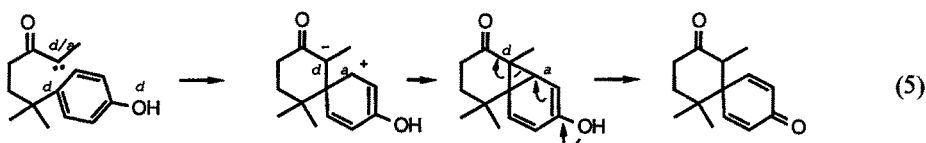
A significant Friedel-Crafts acylation-dealkylation sequence has been observed [11]. The powerful directing effect of an alkoxy group excludes the pathway leading to an intermediate with a condensed ring system.



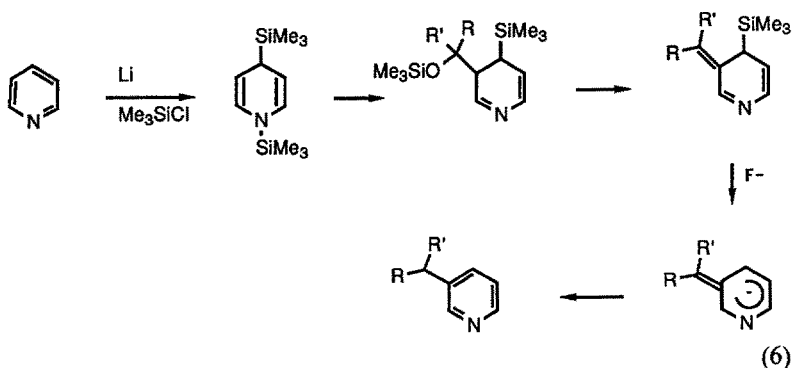
According to polarity alternation the acceptor substituted benzenes should also undergo *ipso* substitutions [12]. Indeed such reactions occur when $A = \text{SiMe}_3$, SnR_3 , HgR . A useful application of the silyl group as site determinant is found in a synthesis of 8-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline [13]. The donor character at the *ortho* position of the methoxy function is accentuated and steric disfavor is overcome.



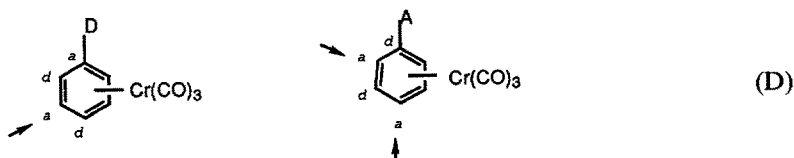
Intramolecular alkylation of phenol with diazoketone [14] can be analyzed as the following: The carbenoid center acts first as an acceptor and then a donor. Since the resulting cyclopropane derivative is vicinally substituted with an acceptor ($\text{C}=\text{O}$) and a donor (enol), fragmentation follows instantaneously (*vide infra*).



An indirect 3-alkylation of pyridine [15] is based on accentuation of the donor character of C-3 by reductive dearomatization.



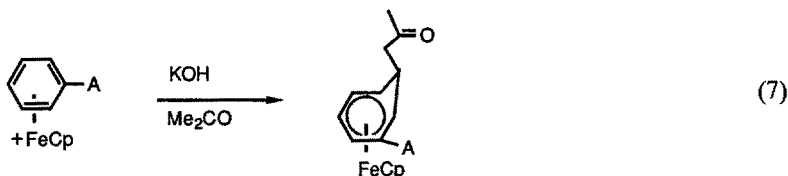
Nucleophilic substitutions of simple aromatic compounds which formally involve a hydride displacement are difficult to achieve because of the poor leaving group and the high electron density of the aromatic nucleus which repels approach of a nucleophile. However, π -electron deficient aromatic compounds such as metal carbonyl complexes are susceptible to attack by certain carbon nucleophiles. Studies of this chemistry have shown [16] an opposite regioselectivity to the corresponding electrophilic substitutions, in agreement with the polarity alternation rule.



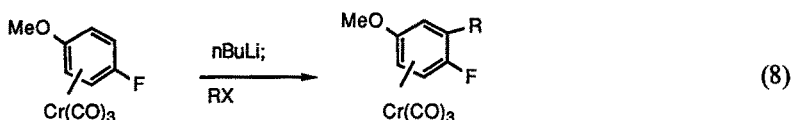
The possibility of readily introducing a *meta* sidechain to an anisole has enabled design an unusual synthesis of acorenone [17].

The σ -adducts from such reactions are generally subjected to oxidative decomplexation to generate the aromatic products. Protonation/deuteration of an adduct derived from a donor-substituted benzene could result in a net *meta* displacement of the donor [18]. *Ipsa* substitution has also been revealed when the σ -complex is warmed.

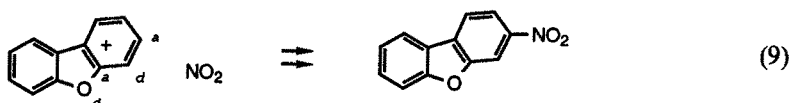
Reaction of η^6 -arene- η^5 -cyclopentadienyliron cations with ketone enolates results in regiospecific attack at the *ortho* position of the acceptor substituent [19].



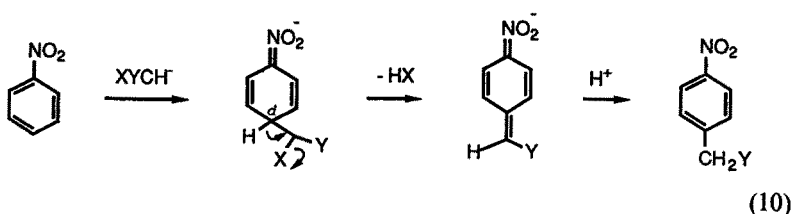
Relevant to the unveiling of the intrinsic electronic effects of various substituents is the selective lithiation of the fluoroanisole- $\text{Cr}(\text{CO})_3$ complexes [20]. The chelation control by the etheral oxygen atom which prevails in uncomplexed aromatic ethers becomes far less important.



Nitration of dibenzofuran at C-3 as opposed to other electrophilic substitutions such as acetylation at C-2 has been attributed to the intervention of a charge-transfer process [21]. The C-N bond formation step is mechanistically closer to the nucleophilic process, the aromatic moiety being the electron-deficient species. It is understandable that $\cdot\text{NO}_2$ attacks at a nuclear carbon which is *meta* to the oxygen donor.



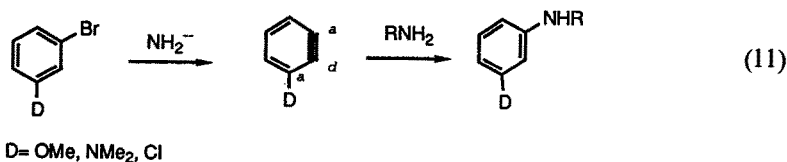
The vicarious substitutions of nitroarenes [22] involve nucleophiles which contain a leaving group X to enable elimination of HX from the σ -adducts. As expected, the substitution is *o*-/*p*-to the nitro acceptor.



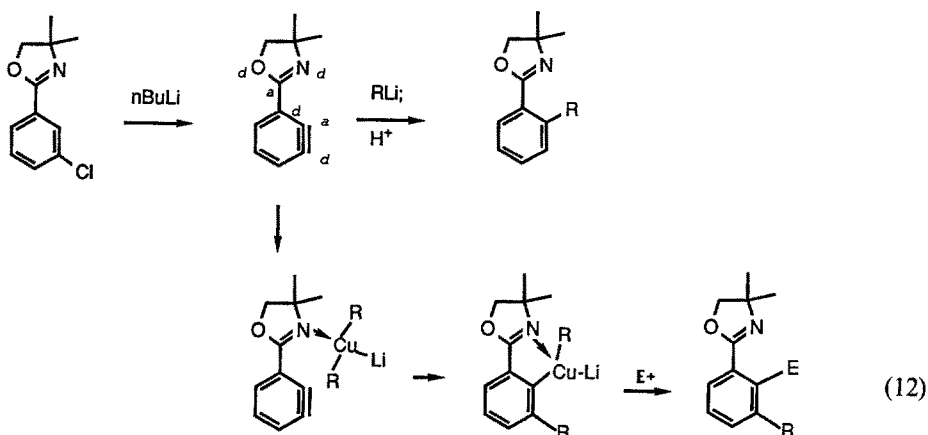
An interesting aspect of these substitutions is that the HX-elimination demands a contrapolarization at the nuclear carbon that acts as an acceptor during the addition.

As expected, *N*-pentafluorophenylpiperidine *N*-oxide undergoes substitution at positions *ortho* or *para* to the nitrogen atom [23]. Secondary amines give the *ortho* products because of their capability for hydrogen bonding in the transition state.

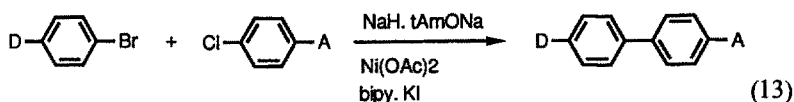
Remarkable regioselectivity is exhibited in aromatic substitutions via aryne intermediates. When there is a donor group at the *meta* position, apparent *ipso* substitution occurs [24]. The polarity alternation sequence indicates an electronic cause.



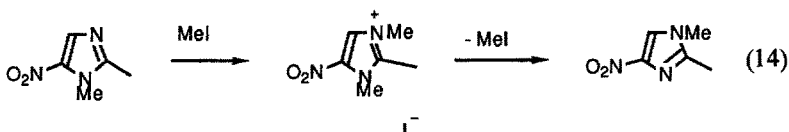
Interestingly, in the reaction of 2-(3-chlorophenyl)-4,4-dimethyloxazoline with an alkylolithium [25], the deprotonation is chelation-controlled, but the addition of R^- follows PAR. A reverse regioselectivity for alkylcuprate addition may well be explained by a complex-induced proximity effect which has been invoked to rationalize the alkylolithium additions. It is known that copper coordinates exceptionally well with amino and imino ligands.



Cross-coupling of aryl halides exhibits fair to excellent selectivities [26]. Each of the two aryl halides contains a donor or acceptor group at the *para* position, respectively. The coupling sites are activated and the 4,4'-biphenyl products are thermodynamically most stable in electronic terms.



1,2-Dimethyl-4-nitroimidazole contains a better conjoint circuit than the 5-nitro isomer. Consequently it is not surprising that the latter compound undergoes isomerization to the former on exposure to iodomethane [27].

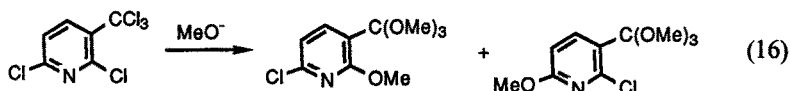
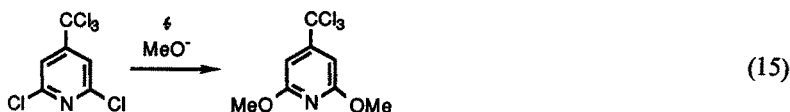


2.2 Aliphatic Substitutions

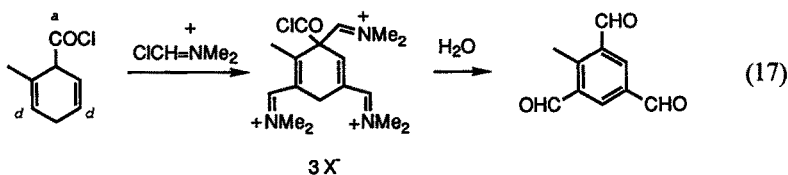
2,2,2-Trifluoromethyl iodide is a poor substrate for S_N2 reactions [28]. The increased “donativity” of the methylene carbon as rendered by the fluorine atoms is reflected in its reluctance to enter a bonding relationship with a nucleophile. Similar reactivity patterns are known for chloromethyl phenyl sulfone [28] and chloromethyltrimethylsilane. In these latter compounds the “reactive” center is directly linked to an acceptor group.

Benzylic halides and sulfonates show a wide range of reactivity towards nucleophiles. Activation and deactivation by *o*/*p*-donors (e.g. OR) and acceptors (e.g. NO_2), respectively, are consistent with PAR. In each case the benzylic carbon atom is identified as acceptor or donor. The trends are also reflected in the relative acidities of the corresponding toluene derivatives.

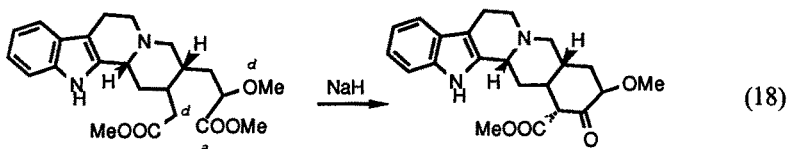
In pyridine derivatives, α - and γ -picolines readily lose a proton from the methyl group. It is easy to find parallel reactivity in the picolines and the nitrotoluenes $\{N=CHNO_2\}$. Further development of the reactivity patterns includes a methanolytic study of several trichloromethylpyridines [29].



Vilsmeier reaction of 1,4-dihydrobenzoyl chlorides leads to *ipso*- and *meta*-substitution products. Aromatic aldehydes are isolated as a result of aerial oxidation [30]. The allylic acceptor (COX) is responsible for the double bond activation as well as the observed regioselectivity.

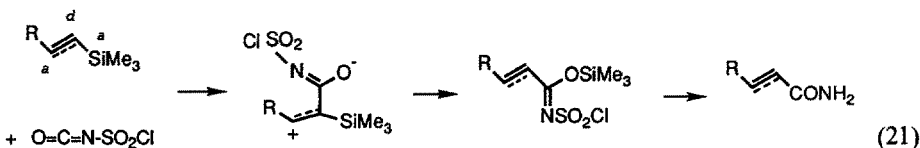
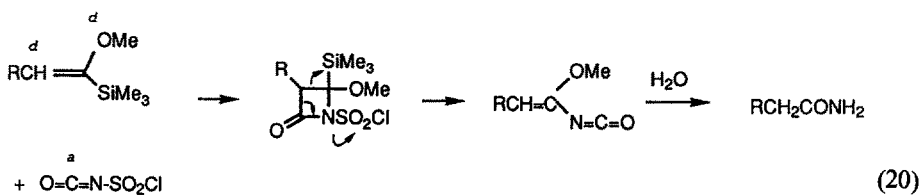
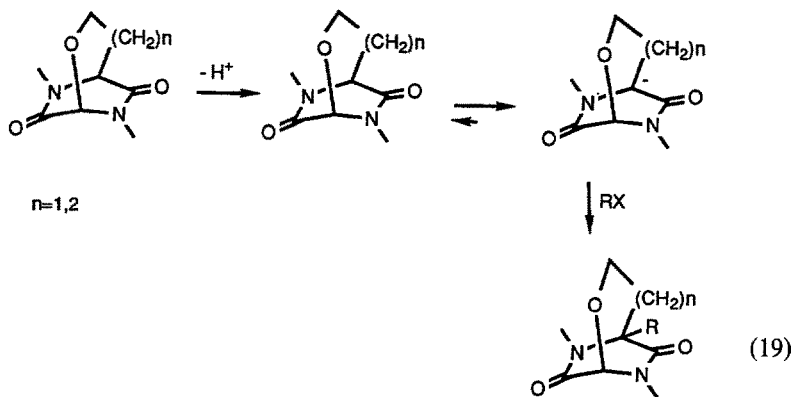


It may be of interest to point out that captodative [31] substituents on a carbon atom disfavor the removal of a proton attaching to it, reactions such as alkylation would occur preferentially at an alternative site by default. Thus a synthesis of yohimbine [32] via a Dieckmann cyclization for *E*-ring formation was facilitated by incorporating an extra methoxy group into one of the ester pendants.

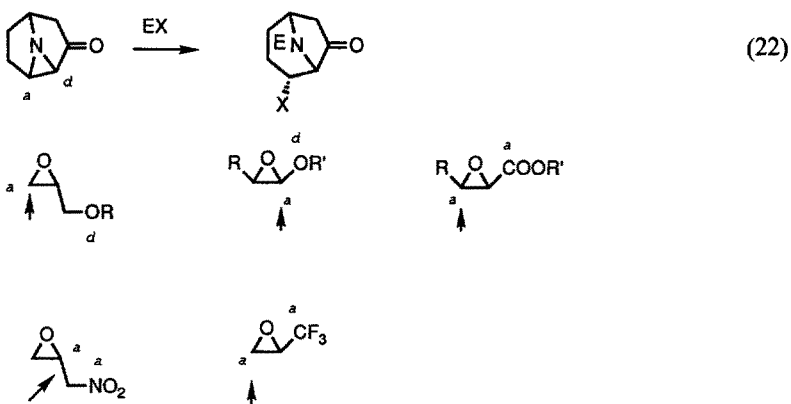


Another example of such effect is the increased regioselectivity for alkylation of certain bicyclic piperazinediones [33]. The stability difference of the two bridgehead carbanions is due to the third substituent (O vs. CH_2) {see Eq. 19}.

The dominance of an alkoxy group over a silyl group is manifested in the generation of amides from reaction of α -silyl enol ethers with chlorosulfonyl isocyanate, followed by hydrolysis. Simple vinylsilanes and alkynylsilanes undergo carbamidation [34].

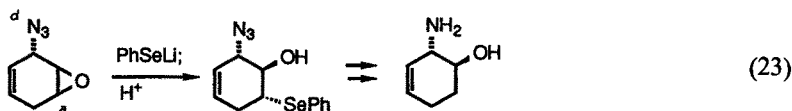


Substitutions at saturated carbon atoms that are subject to control by remote functionalities may be best illustrated by the ring opening of aziridines [35] and epoxides [36, 37].

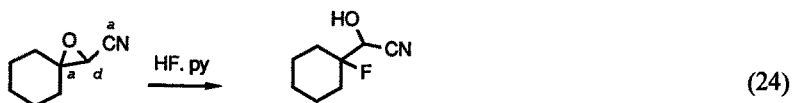


Notwithstanding the possible divergent reaction mechanisms for the two types of epoxides {direct displacement vs elimination-Michael addition sequence}, the polarity alternation rule reveals the correct regiochemistry. The same can be said for analysis of aromatic substitutions based on PAR or resonance considerations.

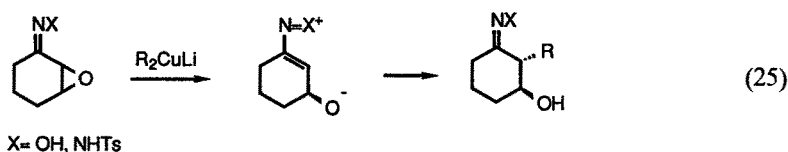
vic-Hydroxy azides and hence the corresponding hydroxy amines in which the hydroxy group is allylic may be prepared from epoxy azides [38].



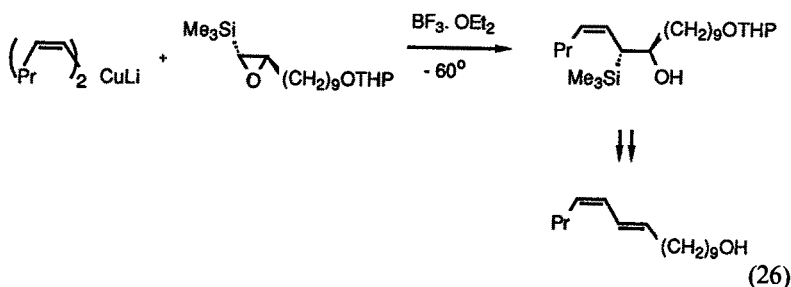
Another pertinent case is the formation of a tertiary fluoride from treatment of β,β -disubstituted α,β -epoxy nitriles [39].



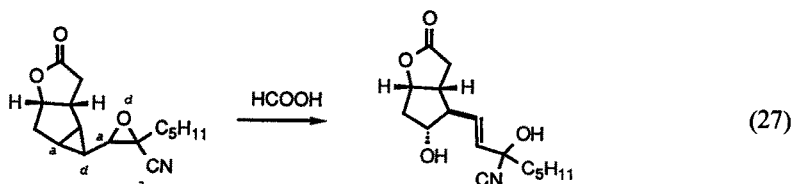
Regioselective alkylative opening of α,β -epoxy ketone oxime [40] and tosylhydrazones [41] with organocopper reagents is initiated by the generation of unsaturated azo compounds which undergo conjugate addition.



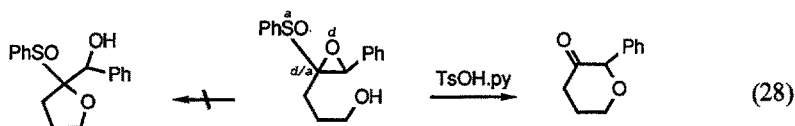
The reaction of epoxysilanes with organocuprate reagents has been employed in a synthesis of the silkworm pheromone bombykol [42]. The silyl group must be responsible for the interesting regioselectivity of the ring cleavage. The electrophilic center as shown is captodative (flanked by a donor oxygen and an acceptor silicon) and its destruction is thermodynamically driven.



In an approach to the prostaglandins [43], *seco*-solvolysis of an epoxycyclopropane serves to establish the oxy functionality in the cyclopentane subunit and an *E* double bond in the side-chain. Opening of the epoxide that triggers the sequence of events is directed by the cyclopropyl group (donor) and the cyano group (acceptor).

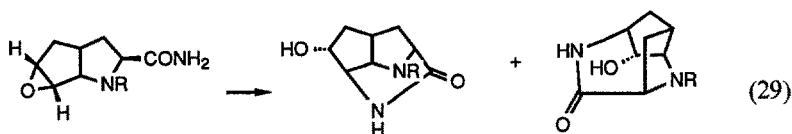


While the Baldwin rules [44] indicate both 5-*exo*-tri and 6-*endo*-tri modes of cyclization are favorable, only the latter is observed in the following reaction [45].

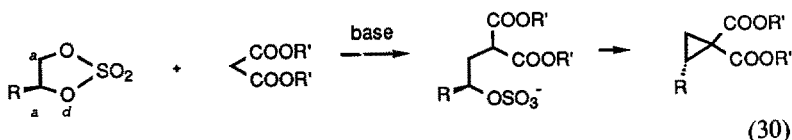


The cause for this regioselectivity may be the influence of the sulfoxide (acceptor) which renders its proximal carbon in the epoxide ring more donor like. Furthermore, ring opening at this site would not improve the unfavorable electronic status of the molecule, while attack on the distal carbon atom gives an intermediate in which the unfavorable captodative situation is dissolved on expulsion of phenylsulfenic acid, upon contropolarization at the sulfur atom.

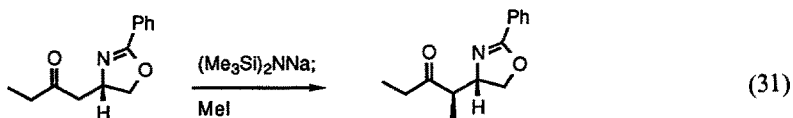
Intramolecular opening of 2-azabicyclo[3.3.0]oct-7-ene-3 *endo*-carboxamide epoxide displays a dependence on the substituent at the nuclear nitrogen [46]. The conformational preference for a proximal attack by the amide function is counterbalanced by an accentuated polarity alternating sequence which enforces the acceptor role of the distal carbon of the epoxide ring when the nuclear nitrogen is part of a carbamate group.



vic-Diol cyclic sulfates should prove more versatile than epoxides in synthesis as they contain two electrophilic centers [47]. The first reaction of a cyclic sulfate with a donor reagent is facile as the *a-a* arrangement is destroyed. It must be emphasized that these cyclic disulfates are more than synthetic equivalents of epoxides, the latter being unable to undergo cyclopropanation in one step.

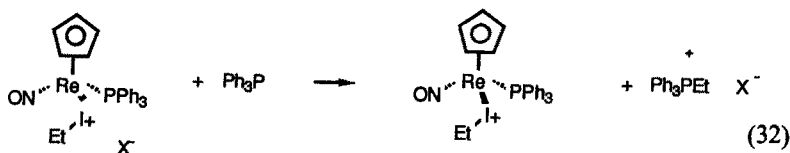


Regioselective enolization toward the nitrogen-bearing carbon in an oxazolinylmethyl ketone derived from aspartic acid has been observed [48]. The nitrogen atom of the heterocycle is conjoint with the carbonyl, therefore the creation of a conjugate system via enolization is favorable.

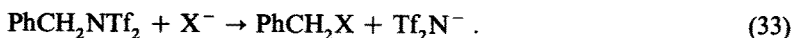


As implied in the above reaction, polarity alternation accentuation represents one strategy for activating organic molecules towards substitution. For example, there

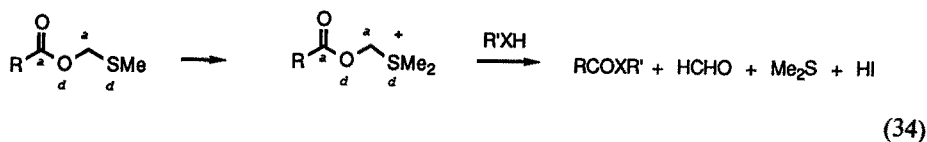
is a rate enhancement in the order of 10^5 in the ethylation of triphenylphosphine when ethyl iodide is first treated with a rhenium complex [49].



Bistriflyl amines constitute a rare class of amino derivatives which undergo S_N2 reactions at the α -carbon [50]. The presence of two strong acceptor groups in the β position of this carbon greatly facilitate the C-N bond cleavage.

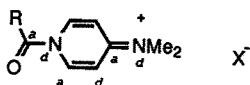


Ester hydrolysis, alcoholysis, and aminolysis may be regarded as substitution reactions (via addition-elimination pathways). The activation of (methylthio)methyl esters by *S*-methylation [51] is an example demonstrating the usefulness of polarity alternation accentuation.

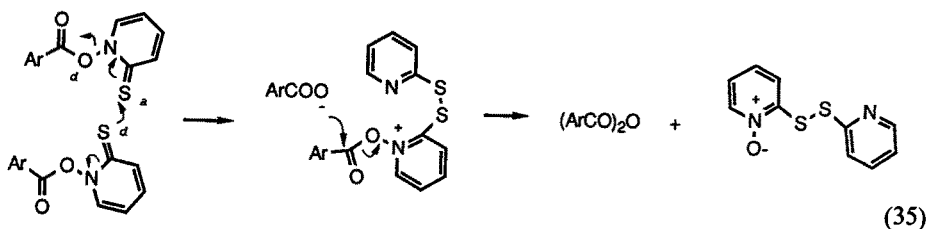


Acyl triflamides are excellent acylating agents for alcohols and amines [52].

Classical methods for carboxyl activation include formation of anhydrides, either homo- or mixed (e.g. phosphoryl, sulfonyl, etc.). Further activation is possible by adding 4-dimethylaminopyridine as catalyst [53]. The active acylating agents are thought to be

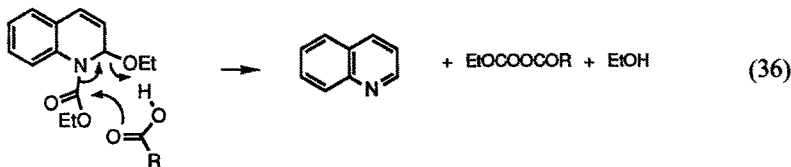


N-Acylloxypyridin-2-thiones derived from aromatic acids undergo thermal or photoinduced decomposition to give anhydrides [54]. Active pyridinium carboxylate intermediates are formed via a bimolecular reaction.

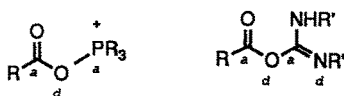


Extension of polarity alternating sequence in each case is apparent.

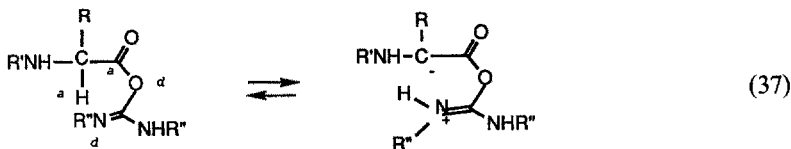
EEDQ is a valuable reagent for carboxyl activation in the coupling of amino acids [55]. Ideal *d-a* pairings of various reactive moieties facilitate the formation of the semicarboxylate intermediates. Of course, a major driving force for this transformation is the aromatization of the dihydroquinoline system.



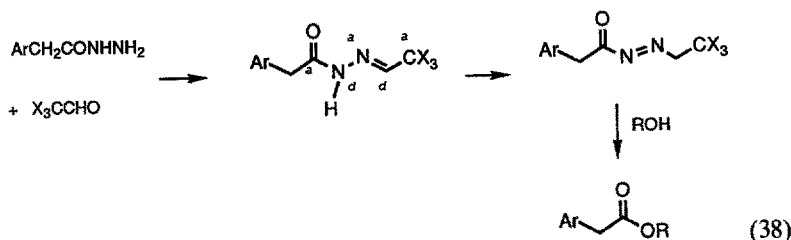
Other effective ways of carboxyl activation involves the use of carboxylphosphonium [56] and *O*-acylisourea intermediates [57].

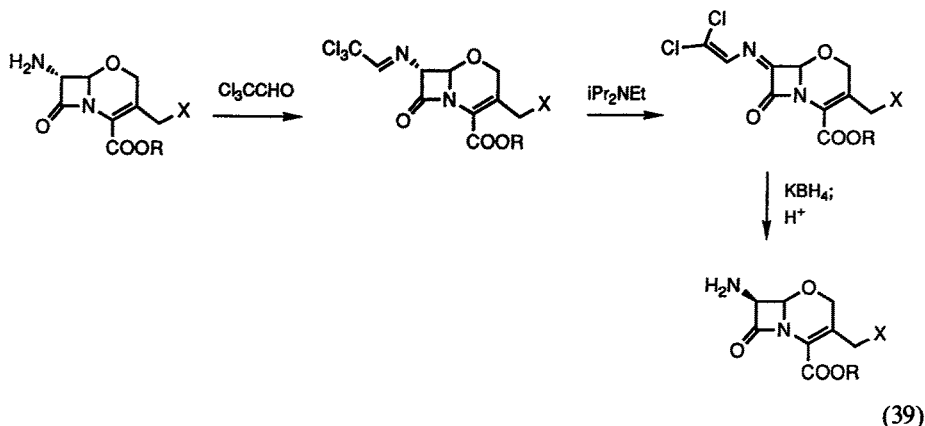


It seems proper to digress here to emphasize the importance of proximity effects which can outweigh electronic factors. Thus, racemization of an amino acid residue during peptide synthesis using carbodiimides is due to the ease of intramolecular C-to-N proton transfer within the *O*-acylisourea intermediate [58]. It should be noted that the proton transfer involves a six-centered transition state in which each atom is related to its neighbors in a polarity alternating sense, except the α -carbon of the amino acid residue. Apparently, the acquiescence of one individual atom to a larger system is energetically much less significant.

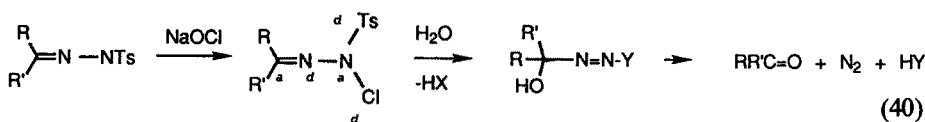


Alcoholysis of hydrazides [59] and epimerization of the 7α -epimers of cephalosporin analogues [60] can be effected with the aid of chloral. Because of the donor chlorine atoms the imines formed initially are conducive to conjugate dehydrochlorination or prototropic shift. It is likely that acylazo compounds are intermediates for the ester synthesis.

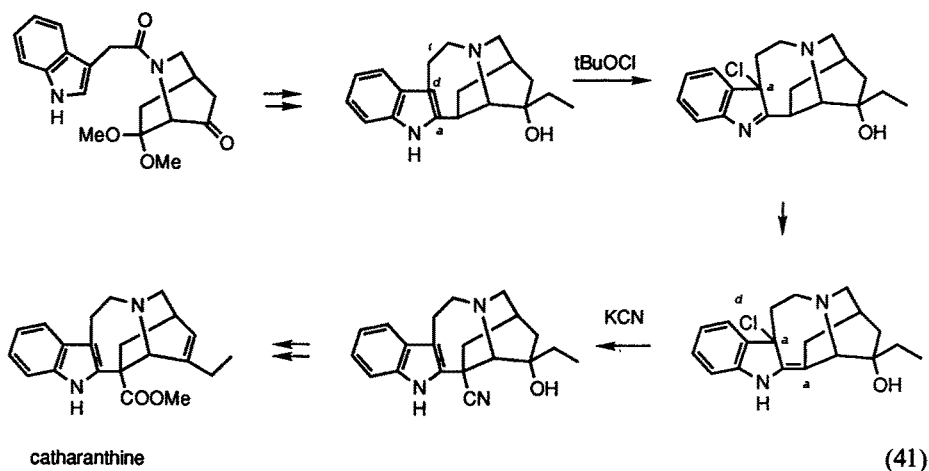




Hydrolysis of tosylhydrazones has been achieved by treatment with alkaline hypochlorite [61]. This allylic activation ensures the sp^2 hybridized carbon behave as an avid acceptor.

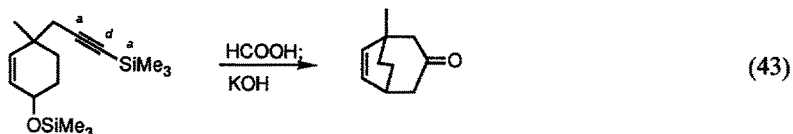
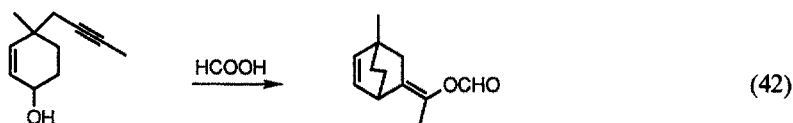


An S_N2' displacement constitutes the key operation in which the ester group at C-3 of catharanthine is introduced [62]. Thus, a contrapolarizing change of the β -position from d to a allows the desired reaction to be performed, using cyanide ion as the nucleophile.

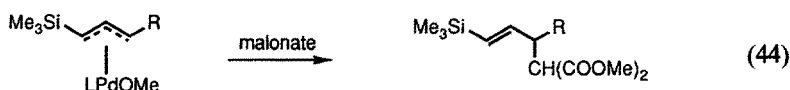


catharanthine

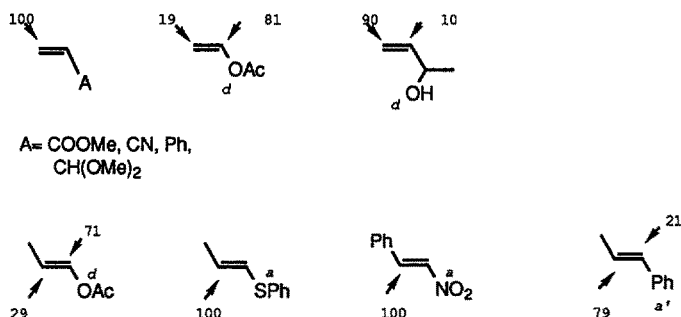
The following equations depict the intramolecular substitution of an allylic oxy group by a sp -hybridized carbon nucleophile [63]. A silyl group effectively directs its adjacent carbon to neutralize the allyl cation.



Palladium-mediated substitutions of silylated allylic compounds are not subject to steric hindrances. The silicon atom exerts control over the reaction site such that γ -substitution results [64]. While the electrophiles are unavoidably disjoint with respect to the acceptor silicon, one of the two limiting forms, i.e., the α -silylcarbenium ion, is much more unfavorable (a - a arrangement) and therefore its population is expectedly low.



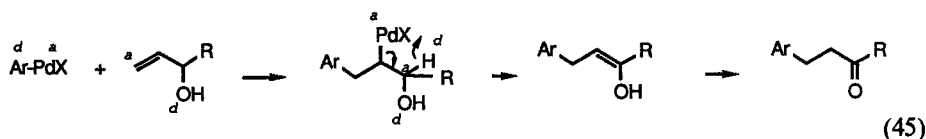
Arylation of alkenes catalyzed by palladium compounds is known as the Heck reaction [65]. While these reactions are very sensitive to steric effects, subtle electronic contributions to the regiochemical outcome may be assessed by comparing reactions of alkenes with similar substitution patterns. The arylating agents, being the nucleophilic arylpalladium species, tend to dictate the facility of their reaction with unsymmetrical, electron-deficient alkenes.



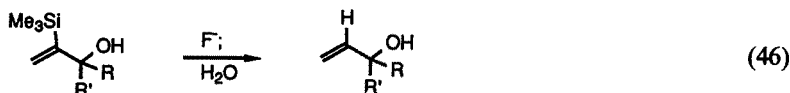
The ratios of attack represented in the formulas [66] reveal a pattern predictable by PAR. The differences between oxy and thio analogues are most intriguing because the sulfur substituent behaves as an acceptor. The dramatic dichotomy may not be purely attributable to a Pd..S coordination in one type of compounds.

Arylation of allylic alcohols leads to 1-aryl-3-alkanones. The orientation for this reaction is in compliance with the general trend indicated above. Furthermore, the accepted reaction mechanism points to a "Pd-H" elimination process in which H

departs as a hydride. The generation of enol intermediates is facilitated by the donor hydroxyl group.



It is interesting to note that the fluoride ion-promoted Si-C bond cleavage of vinyl silanes is greatly facilitated by the presence of a hydroxyl group at the tetrahedral β -carbon atom [67].



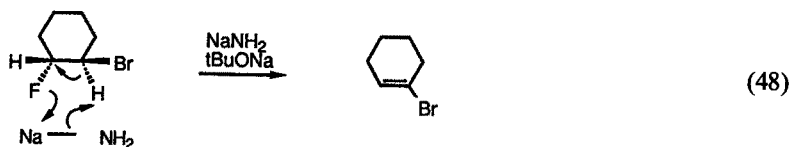
Many factors contribute to the success of the desilylation, including a six-centered transition state in which F^- associates with both Si and the proton of the hydroxyl group. Perhaps the electronic influence by the oxygen atom on the silylated sp^2 -carbon is such that a better donor for the latter atom results.

3 Eliminations and Fragmentations

Arynes are formed when haloarenes are treated with a strong base. Deprotonation at the ortho position of the halogen atom is favored because of polarity alternation, and the facility of benzyne formation from halobenzene ($PhF > PhCl > PhBr \gg PhI$) also corresponds with the relative strength of the donor.



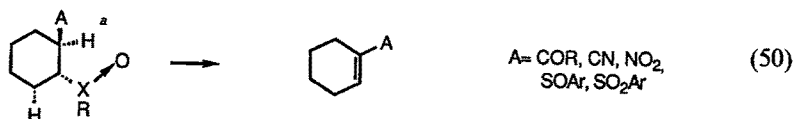
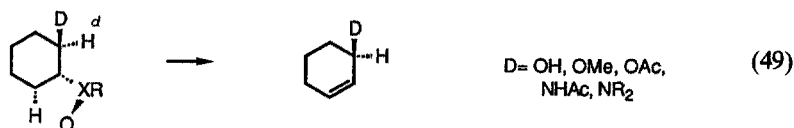
Reversal of the E2 leaving group ordering has also been observed in the alicyclic series, i.e. *syn* elimination of *trans*-1,2-dihalocycloalkanes [68]. This reactivity pattern is very well accounted for by considering the polarity influences. In general, the halogen atom with a highly acceptor character ($I > Br > Cl > F$) would loosen its geminal hydrogen toward a donor reagent, and contrarily, the highly donor congener (esp. F) renders its geminal hydrogen more difficult to be abstracted by bases (donors).



Dehydrohalogenation of 2,3-dihalo-2,3-dihydrobenzofurans gives 3-halobenzo-furans [69]. Rate measurements have indicated higher difficulties in deprotonation

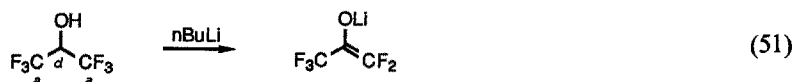
at the benzylic position when the benzylic halogen is highly donative (i.e. $F \gg Cl > Br$). The trend is evident for both *syn*-E2 and $E1_{\text{CBI}}$ mechanisms.

The thermal *syn*-elimination reactions of X-oxides have assumed great importance in synthesis because of their mildness and regioselectivity.

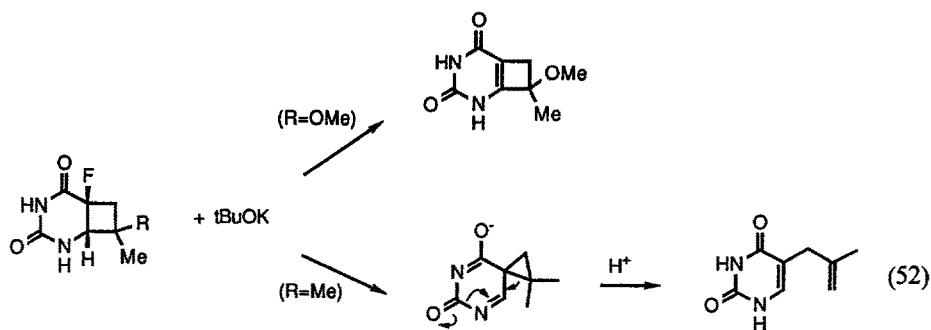


It is apparent that a *vicinal, trans* donor substituent favors the formation of an allylic product, whereas an acceptor group strongly biases the generation of a vinylic derivative. The regioselectivity is a result of the electronic transmission by the polar group in the same manner as discussed above [70].

The extraordinary dehydrofluorination of 1,1,1,3,3,3-hexafluoro-2-propanol [71] on exposure to *n*-butyllithium shows an overwhelming effect by the fluorine atoms on the carbinolic center. In other words, the influence of the single oxygen is largely suppressed.



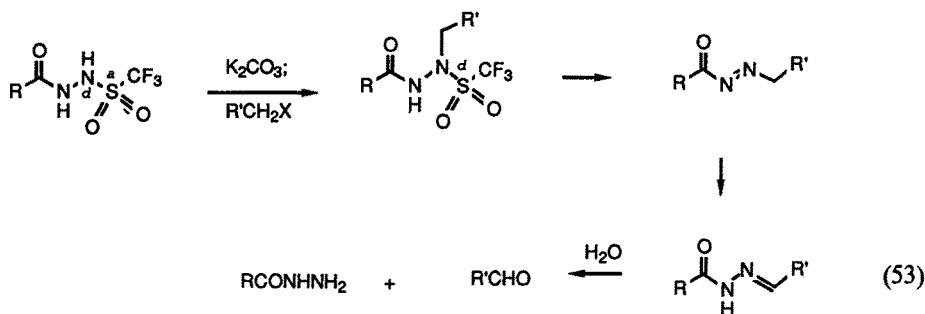
While no convincing reasons have been put forward to explain the different behavior of the two photocycloadducts derived from 5-fluorouracil, the elimination process is definitely favored by the presence of a methoxy group, and even more so with a *gem*-dimethoxy functions [72]. Such a methoxy donor would confer acceptor character to the angular hydrogen.



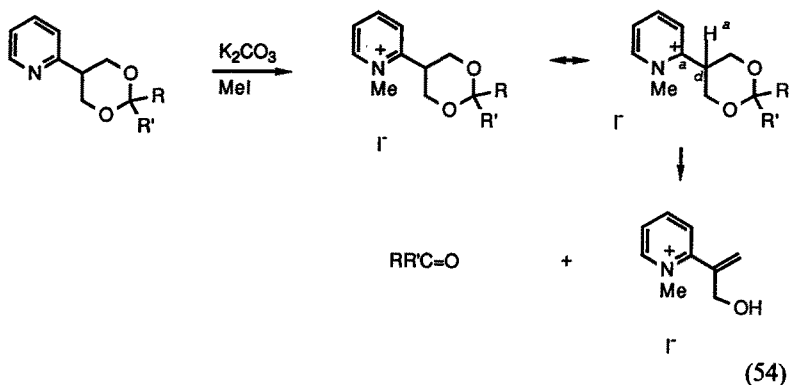
The solvolysis of 2-trimethylsilylcyclohexyl trifluoroacetates proceeds with enormous rate enhancements over the nonsilylated substrates, especially when the *vicinal*

heterosubstituents are trans [73]. This β -silicon effect is a special case of activation by polarity alternation.

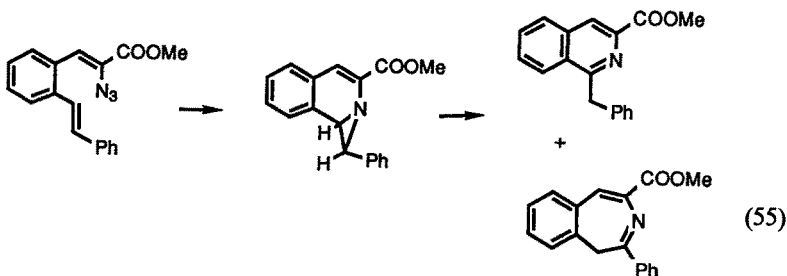
Oxidation of alkyl halides via reaction with *N'*-triflyl hydrazides exploits the facile elimination of triflinic acid [74]. Acidification of N-H and C-H by a β -donor is essential to the elimination and the prototropic shift.

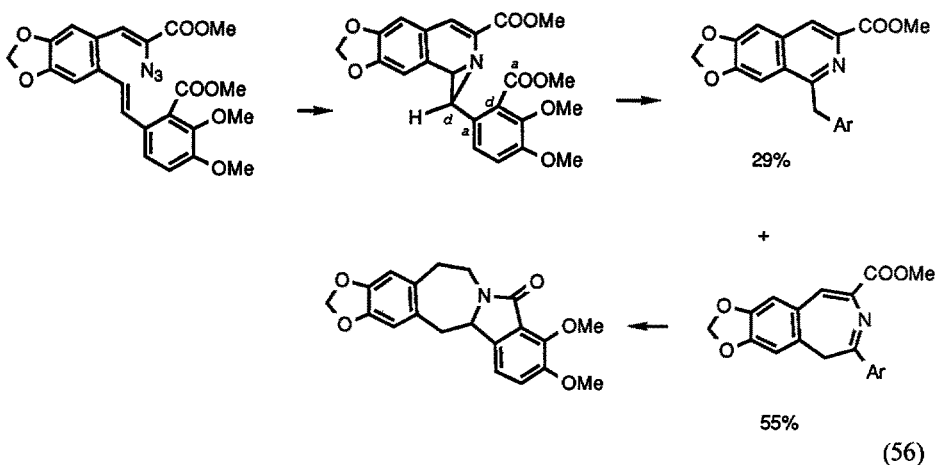


Regeneration of carbonyl compounds from 5-(2-pyridyl)-1,3-dioxanes [75] can be effected by *N*-methylation and treatment with a mild base. The picolyl carbon is a donor site, and the loss of a proton from that position is facile.

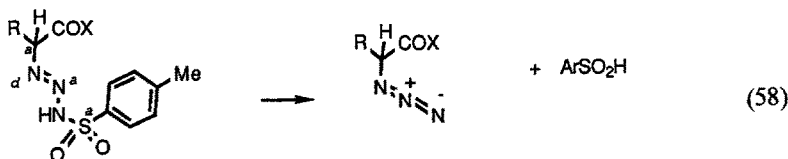
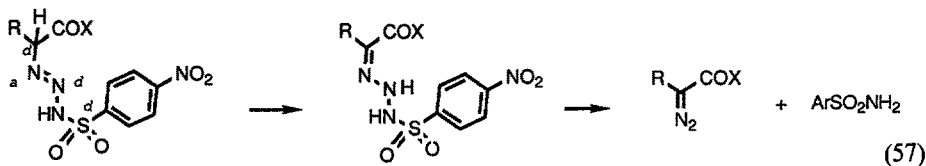


The following equations show the difference a strategically located ester group can make in the direction of aziridine opening [76]. The ester favors deprotonation at the conjoint benzylic position, leading to the benzazepine as the major product.





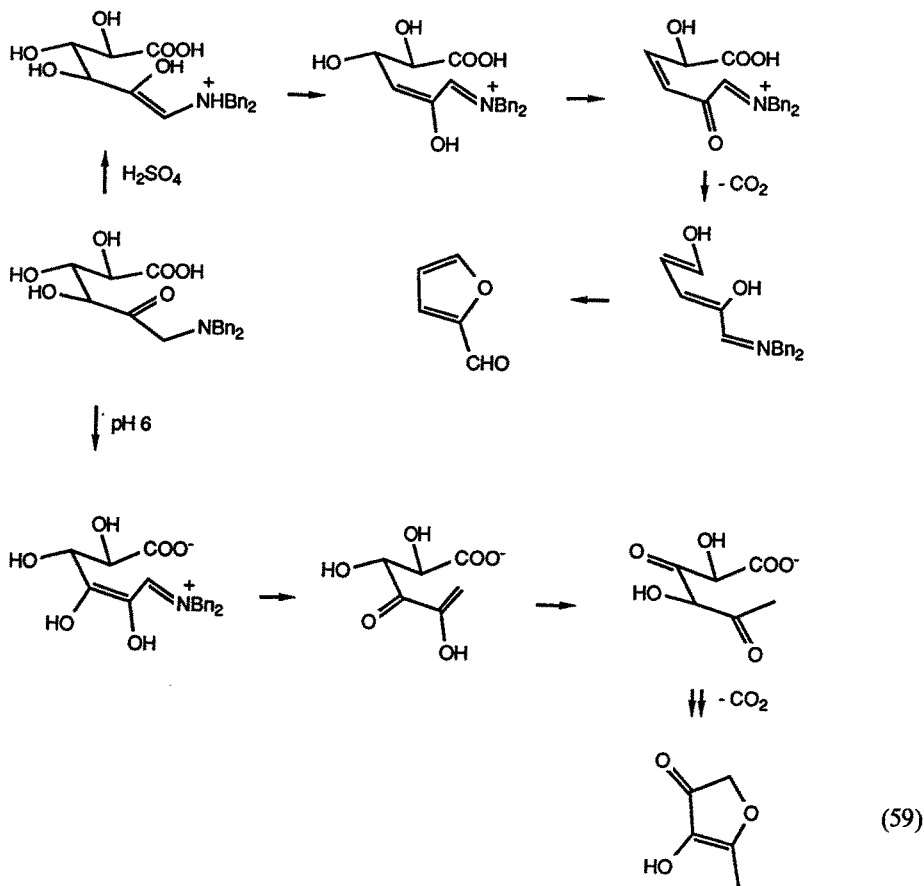
An intriguing reaction dichotomy arising from variation of the aryl group in *N*-arenesulfonyltriazenes [77] may be the consequences of polarity alternation. The subtle difference of the aromatic substituent can affect the acidity of the methine hydrogen. For example, the *p*-nitro group acidifies the methine very strongly, making a facile tautomerization of the diazo form to the hydrazo form. On the other hand, change of the aromatic moiety to a *p*-tolyl or trisyl group might be sufficient to impede the tautomerization such that elimination of the arenesulfonic acid can compete successfully. The end results are the preferential formation of diazo compounds and azido compounds, respectively, as indicated in the equations.



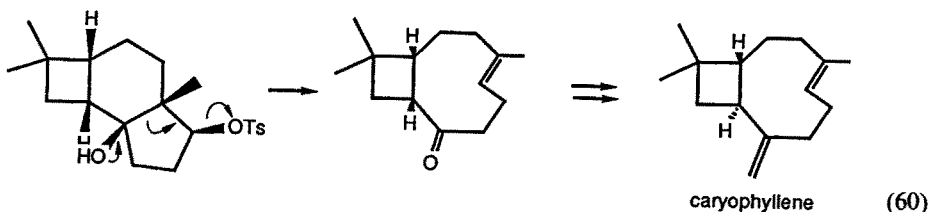
It should be noted that according to the distribution of the polar functionalities opposite results should have been obtained. However, a faster tautomerization than fragmentation in the nisyl system and a difference in mechanistic details for the two series might be responsible for the 'unexpected' observations. Perhaps a spirocyclic intermediate is involved in the fragmentation of the nisyl derivative.

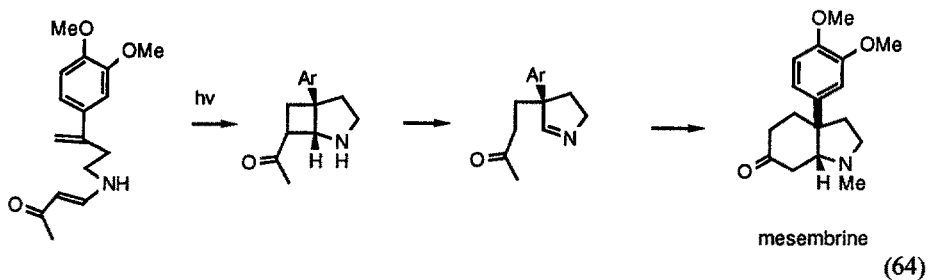
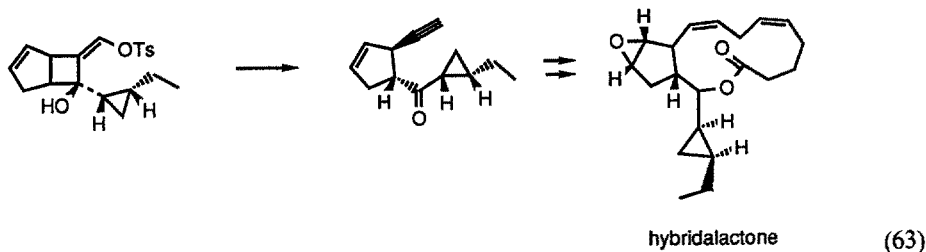
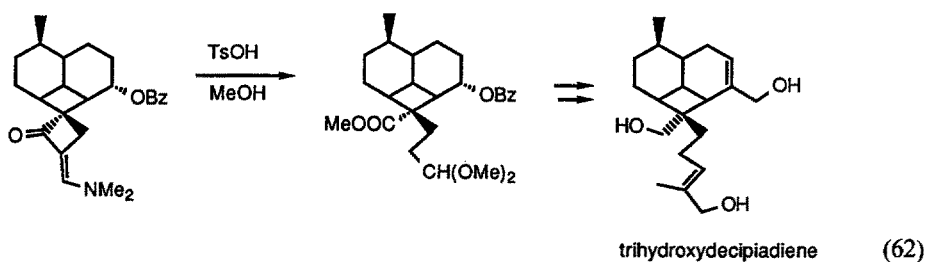
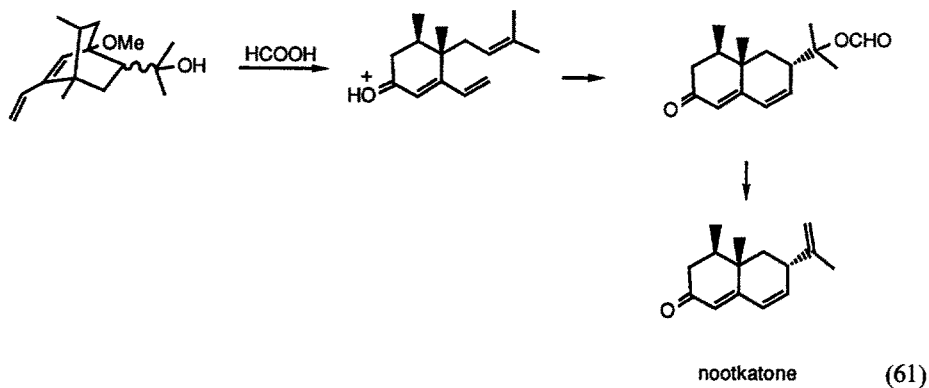
The major chloroform extractable product from the decomposition of 1-deoxy-1-dibenzylamino-D-fructuronic acid in pH 6.0 buffer is 4-hydroxy-5-methyl-3(2*H*)-furanone [78]. Treatment of the same Amadori compound in 2*N* sulfuric acid gives 2-furaldehyde [79].

The divergent pathways arise from selective enolization. Thus, in media of lower acidity enolization occurs toward C-3, whereas in a stronger acid complete *N*-protonation shifts the enolization toward C-1. The amino donor confers certain acceptor character C-1 (although this is a captodative situation), but upon protonation it is converted into an acceptor and its adjacent carbon atom, a donor.

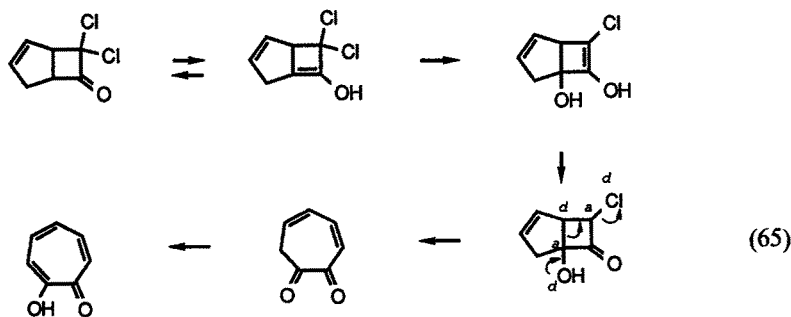


Compounds in which two donor atoms are linked by a three-carbon chain undergo C-C bond cleavage readily. Well-known reactions are the retro-aldolization, retro-Claisen, retro-Michael, and retro-Mannich reactions. Significant application of such processes to synthesis of complex natural products include approaches to caryophyllene [80], nootkatone [81], trihydroxydeciadiene [82], hybridalactone [83], and mesembrine [84].

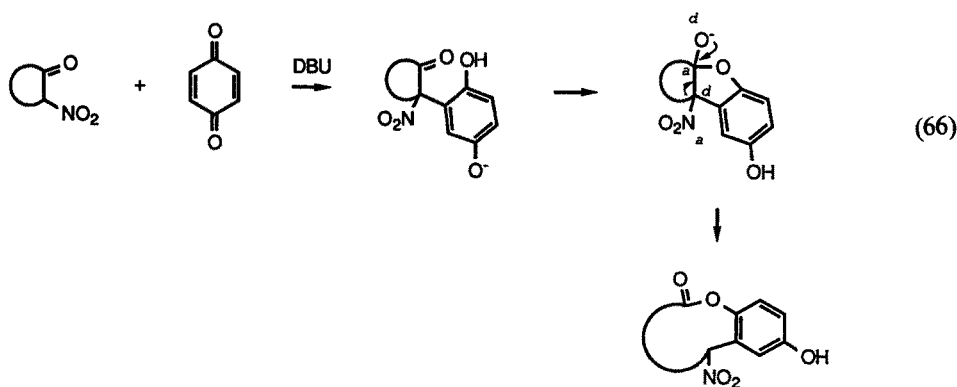




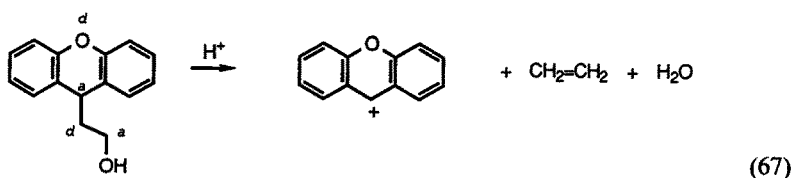
The base-catalyzed rearrangement of the cyclopentadiene-dichloroketene adduct gives tropolone. The reaction course passes through an S_N2' displacement of the enol, fragmentative dehydrochlorination, and enolization [85].

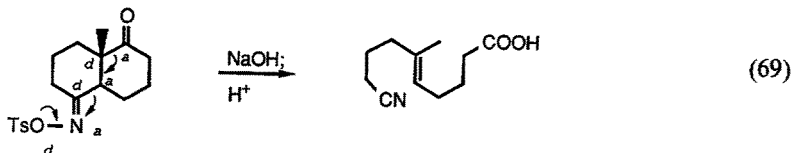
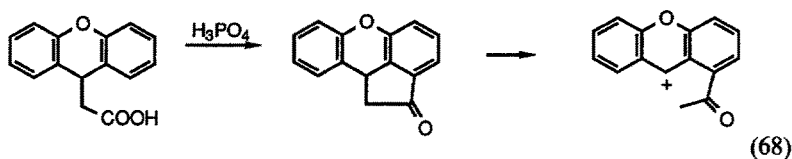


In α -nitrocycloalkanones the donor oxygens are also separated by three atoms. Consequently, these compounds can also undergo fragmentation. A synthetically useful method based on the enhanced donor activity of the α -carbon and the fragmentability is a macrolactone formation. Particularly interesting is the secoannulation onto a benzene ring by the ω -nitroacyl element via a Michael reaction with benzoquinone [86]. It is noteworthy that in the Michael adduct the ketol subunit is disjoint through switching (the proximal OH is not derived from the enone acceptor). Because benzoquinone contains two disjoint carbonyl functions, reactions of such molecules in the normal sense (i.e. without contrapolarization) always result in a pair of functional groups in disjoint arrangement.

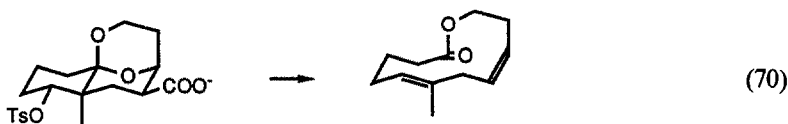


Generation of xanthyl cation from 2-(9-xanthyl)ethanol [87] is an extended Grob fragmentation. The intervening chain of separating the terminal donor groups may also incorporate heteroatoms, as shown in the deconvolution of a decalindione monoxime tosylate [88].

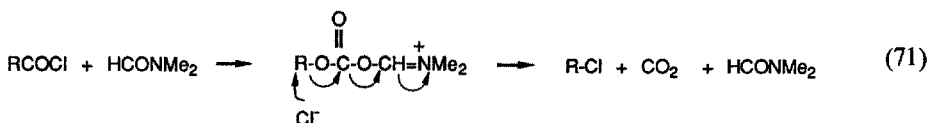




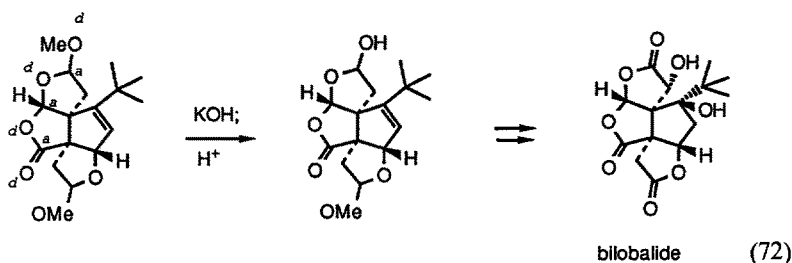
Noteworthy is a thermal cycloreversion of a tricyclic tosylate carboxylate that translates chirality of five carbon centers into three double bonds (2C=C and 1C=O) [89].



Decarboxylation of chloroformic esters is greatly catalyzed by dimethylformamide [90]. As indicated in the following equation, an iminium intermediate with contiguous *d-a* pairs is involved.

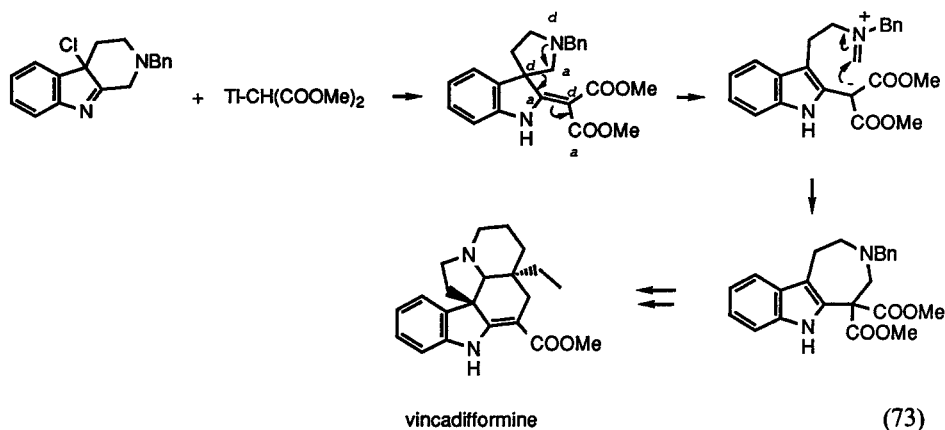


Acetals are acid sensitive but alkaline stable because their hydrolysis requires activation of the oxygen atom by protonation or coordination with a Lewis acid. An ingenious way of differentiating two 2-methoxytetrahydrofuran moieties during a synthesis of bilobalide [91] is to treat the tetracyclic intermediate with potassium hydroxide. Expulsion of a methoxide ion is triggered by attack of the γ -lactone ring five carbons away.

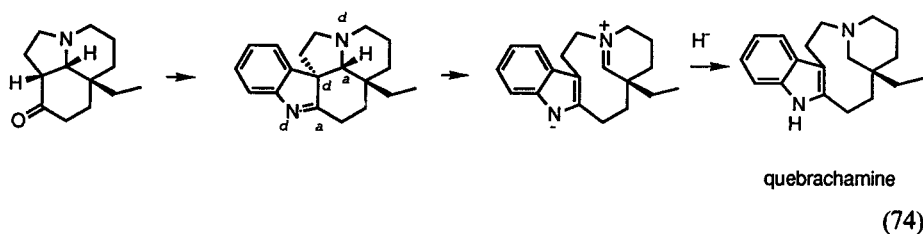


Assembly of the indolazepine intermediate for synthesis of vincadifformine [92] encompasses a 1,2-rearrangement-retro Mannich-Mannich reaction sequence. Need-

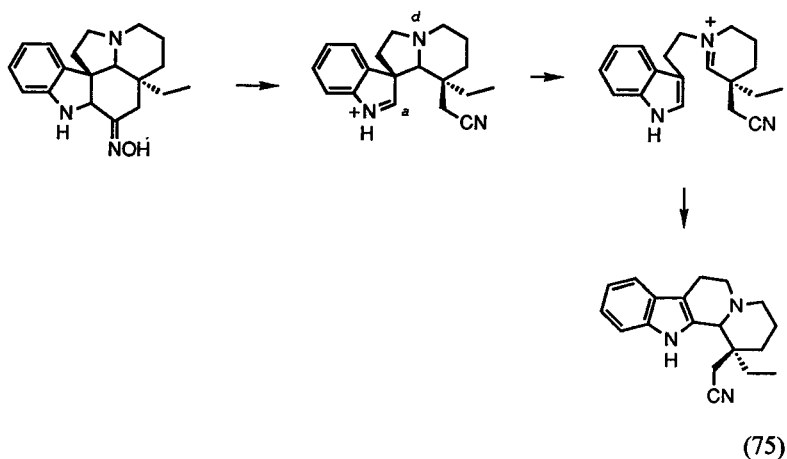
less to say, the smooth transformation is the result of a perfect polarity alternation set-up.



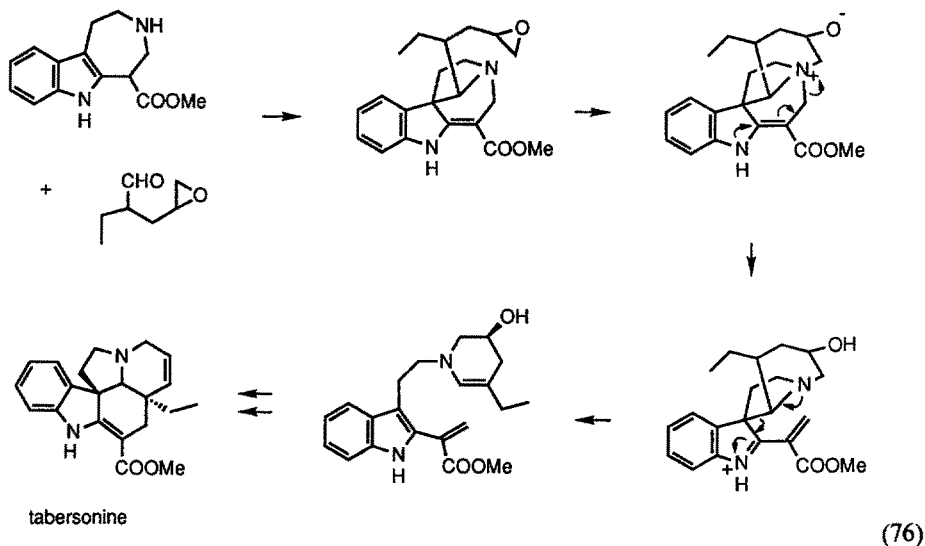
The 9-membered ring present in quebrachamine has also been established using the fragmentation strategy [93].



Aspidospermidine oxime undergoes double skeletal fragmentation to give a tricyclic iminium ion which cyclizes at the α -position of the indole nucleus [94].

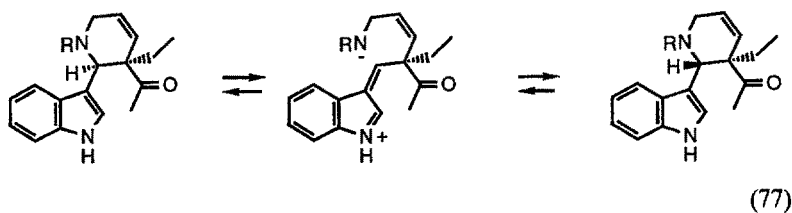


An even more complex series of bond formation and cleavage attends the construction of a secodine precursor for tabersonine [95]. The initial tetracyclic intermediate provides two 3-carbon links between the two nitrogen atoms and therefore reaction pathways for skeletal reorganization.



There is an intriguing observation concerning the equilibratability of certain indolytetrahydropyridine. The N_b -unsubstituted isomers undergo equilibration readily, yet the N_b -hydroxyethyl derivatives are stable [96].

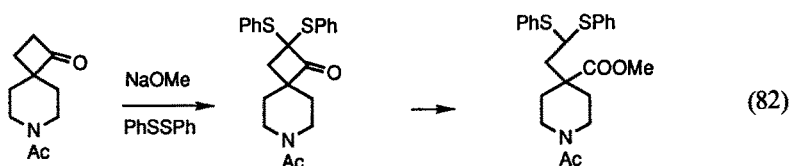
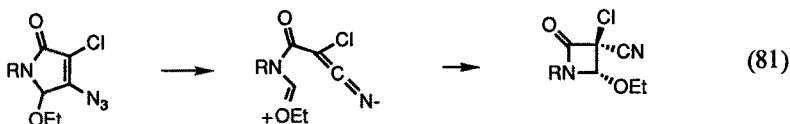
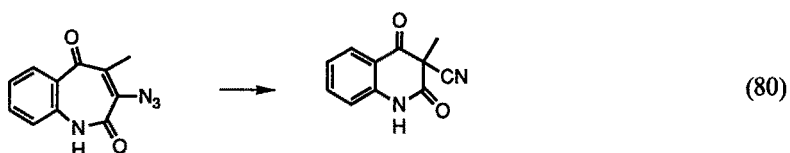
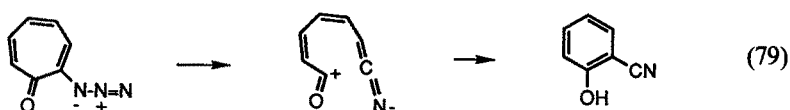
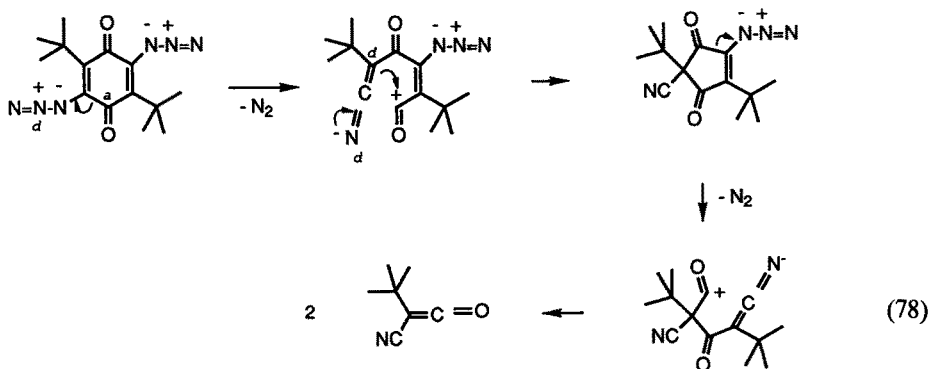
The simplest explanation seems to be that the hydroxyl group makes the nitrogen atom a poorer donor. Naturally other factors such as hydrogen bondings that render the molecules unfavorable to fragment must also be considered.



Thermolysis of certain vinylic azides gives rise to cyano compounds. Representatives of this interesting class of reactions (zwittazido cleavage) [97] are outlined in the following. The fragmentation is predicated by a β -atom which can assume an acceptor role readily.

In the zwittazido cleavage substituents of opposite polarity are present at each end of the C-C bond to be broken. This structural pattern also exists in the α -diketone monothioketals [98], and naturally, fragmentation occurs readily in those compounds.

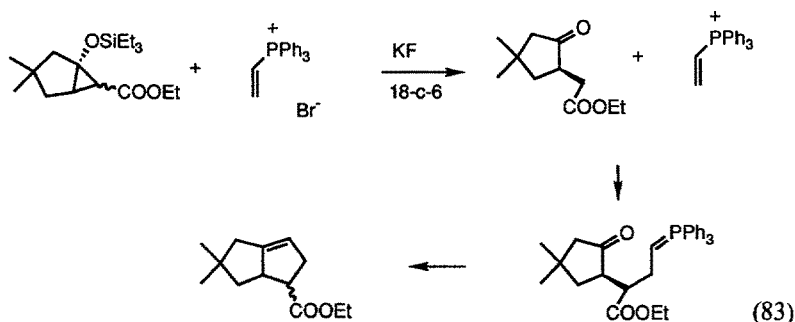
Through-Bond Modulation of Reaction Centers by Remote Substituents



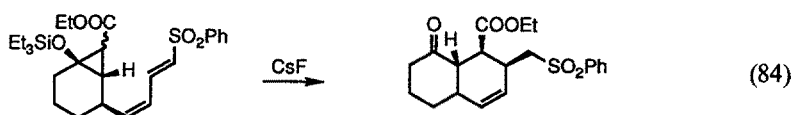
Another example is the indirect acetylation of a 1,2,3,4-tetrahydropyridine derivative at the β -position of the enamide system [99]. The reaction involves a double alkylation to furnish an acetylcyclopropane which undergoes fragmentation on acid treatment. It is noted that polarity alternation and ring strain relief allow the facile and regiospecific C-C bond cleavage to proceed, the intervention of a cyclopropane intermediate also leads to disjoint system. This is a fundamental strategy [100] which has been frequently employed to gain access to compounds with disjoint functionalities.

Such disjoint molecules may serve as synthetic intermediates. Thus a [3 + 2] annulation method exploits the facile ring opening of cyclopropanols and the transfer of the donor site to the β carbon of the resulting ketones, the nascent carbanions may

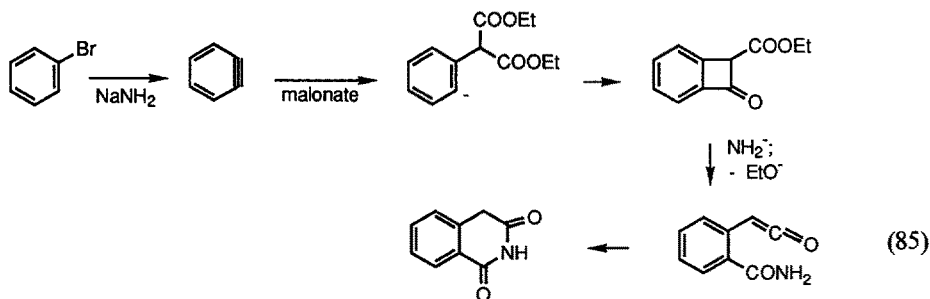
be intercepted by a vinylphosphonium species and an intramolecular Wittig reaction follows [101].



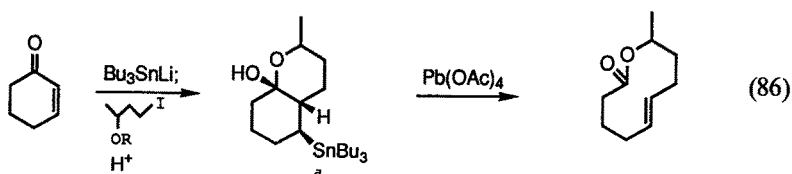
A variation at the final stage of the carbanion trapping to a Michael addition provides an entry to the octalone system. A synthon for dihydrocompactin is readily assembled [102].



A reaction of bromobenzene with ethyl malonate in the presence of sodamide affords homophthalimide [103]. This fascinating reaction involves sequential elimination, addition, intramolecular acylation, fragmentation, and addition. Excellent polarity alternation along the chains of atoms in various intermediates allows so many steps to proceed efficiently.



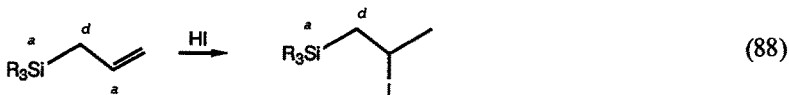
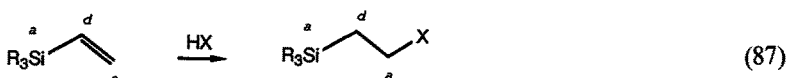
Fragmentation of a disjointly substituted carbon chain requires contrapolarizing operation such as oxidation. A method for synthesizing macrocyclic lactones is illustrated below [104]. Introduction of an oxyalkyl chain follows the conjugate addition of a stannyl anion to a cyclic enone results in a bicyclic lactol. Exposure of the lactol to lead tetraacetate initiates oxidation at the hydroxyl group and subsequent fragmentation. Thus, all four skeletal atoms constituting the original enone system undergo contrapolarization in this step.



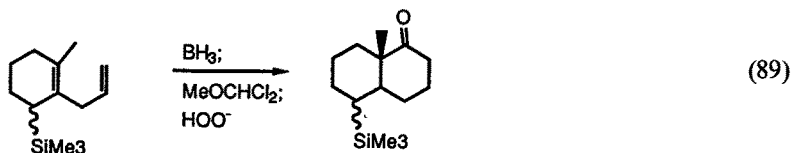
4 Additions and Cycloadditions

4.1 Additions to Multiple Bonds

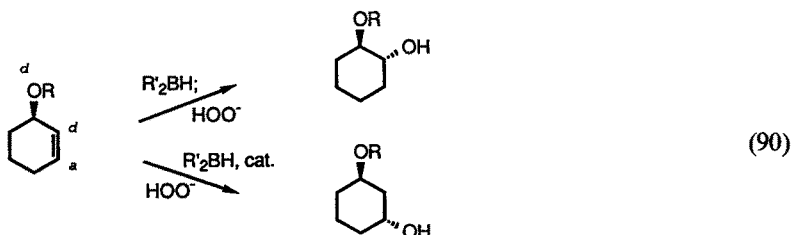
Additions to carbon-carbon multiple bonds initiated by electrophiles are generally governed by the Markovnikov rule. However, the rule must be modified to accommodate such substrates as vinylsilanes. The so-called anti-Markovnikov hydrohalogenation [105] is to be contrasted to the Markovnikov addition for allylsilanes. In fact, when one recognizes the acceptor role of the silicon atom and applying the polarity alternation rule, the puzzling results become self-consistent.



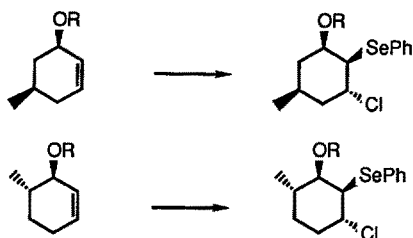
The directing effect of an allylic silicon atom is also manifested in hydroboration [106]. This exquisite control is extendable to tetrasubstituted olefins [107] making the access of *trans*- α -decalones quite readily.



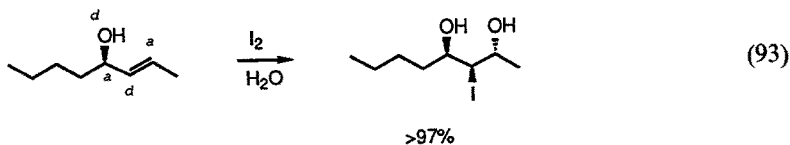
As expected, allylic alcohols and ethers afford *vic*-diol derivatives upon hydroboration. However, in the presence of Wilkinson's catalyst, a reverse regiochemistry for the hydroboration is observed [108]. There is the possibility that boron, rather than hydrogen, is transferred from the metal to the olefin. In other words, the boron acts as a donor.



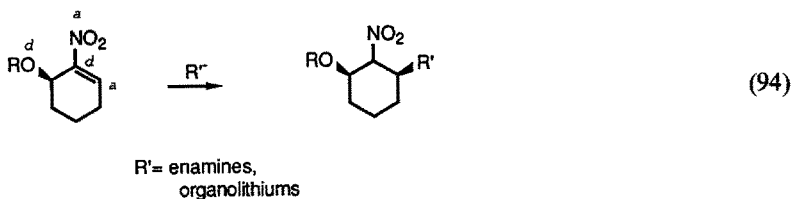
The regiochemistry of the addition of phenylselenenyl chloride to allylic alcohols and their esters [109] can simply be rationalized by using the polarity alternation rule except in those cases where steric factors become the controlling parameters.



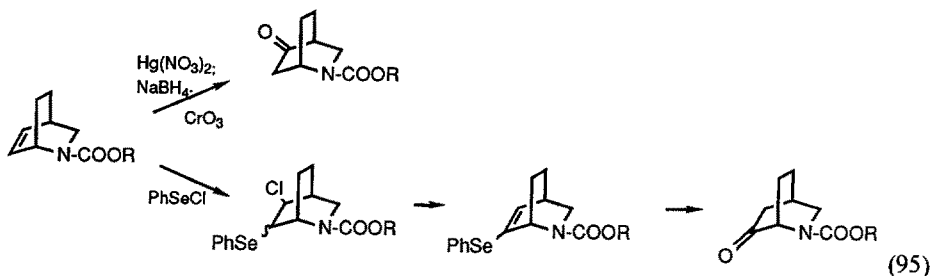
1,2-Disubstituted alkenes undergo iodohydroxylation regioselectively when the allylic position bears a hydroxyl group [110]. The attack on the distal carbon of the iodonium intermediates is favored on the polarity alternation basis.



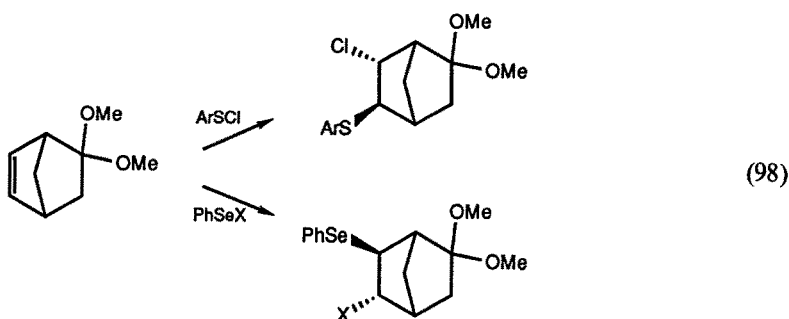
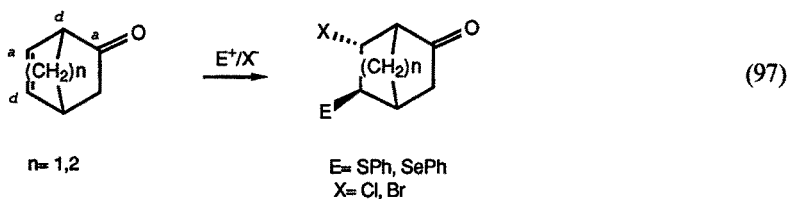
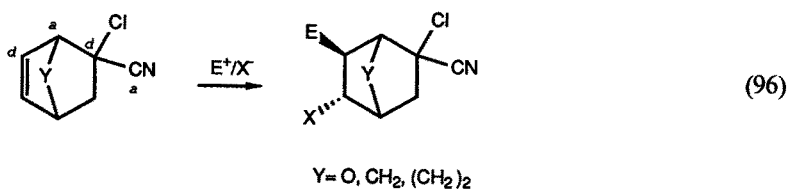
Nitrocyclohexene is rather unreactive toward many nucleophiles. Interestingly, an oxygen substituent at C-6 substantially enhances the reactivity, even if the substituent is non-leaving [111]. Evidently the donor exerts its effect through polarity alternation accentuation.



Functionalization of the double bond of 2-azabicyclo[2.2.2]oct-5-ene derivatives has been shown to be remarkably regioselective. Thus, oxymercuration [112] and selenohalogenation [113] lead to adducts which are convenient precursors of iso-quinuclidin-5-one and -6-one, respectively. This means an excellent control of the polarity at the double bond termini by the nitrogen atom (Note that simple allylic urethanes also undergo regioselective oxymercuration).

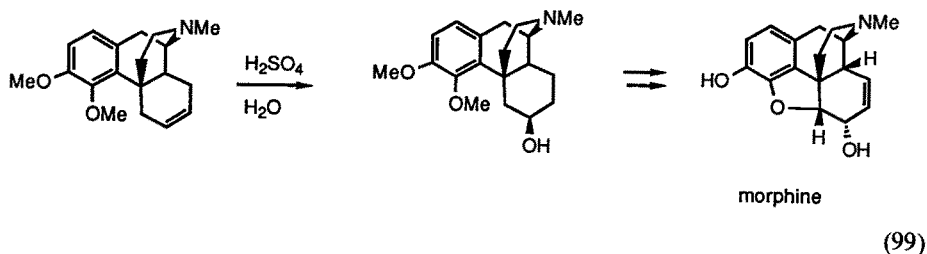


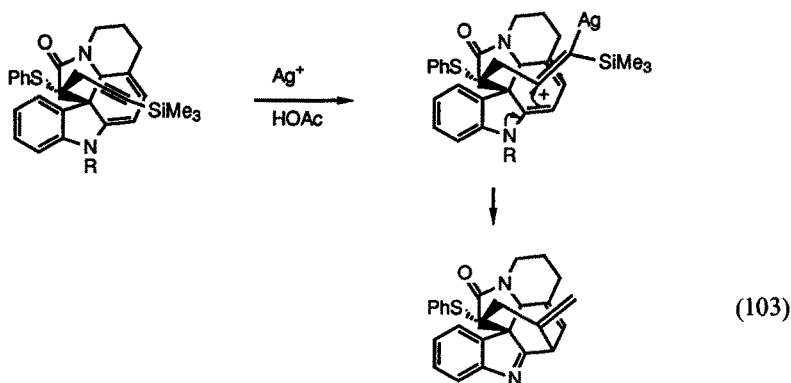
Remote function control of the regiochemistry for 1,2-addition in the bridged bicycloalkene systems [114] has been delineated. Again, the polarity alternation rule proves very useful for rationalizing these results.



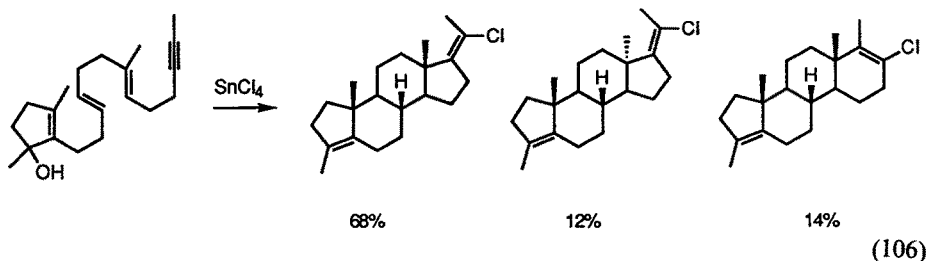
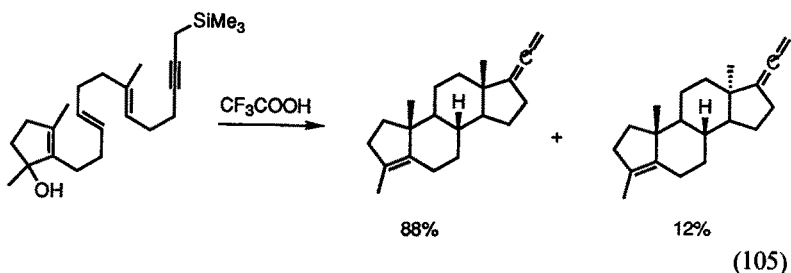
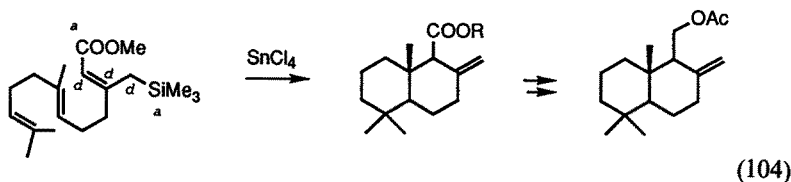
It should be noted that the last reaction is anomalous owing to the soft nature of the selenium such that the intermediate is an episelenonium species (i.e. less carbocationic) and the attack of the counterion is subject to steric effects such as the 2,6-*endo* interaction.

The first total synthesis of morphine [115] involves hydration of a tetracyclic intermediate. The attack of water from the more hindered face of the double bond could hardly have been predicted. However, the donor nitrogen atom of the molecule may have been responsible for the protonation at C-7 in favor of C-6 via a polarity alternation mechanism.

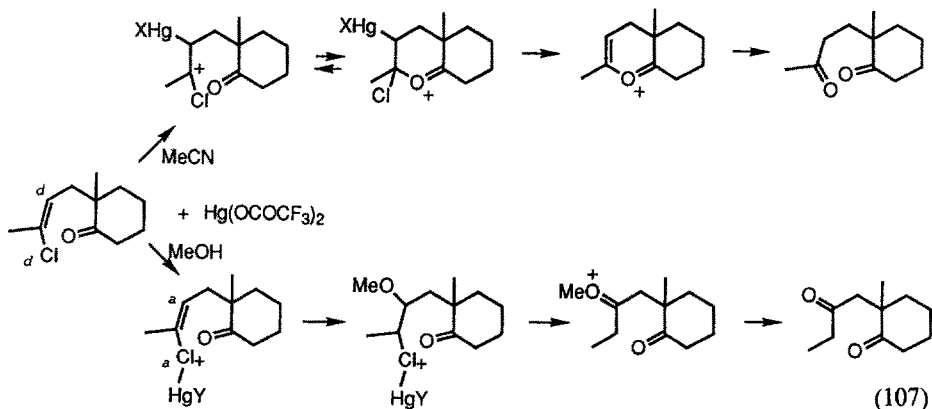




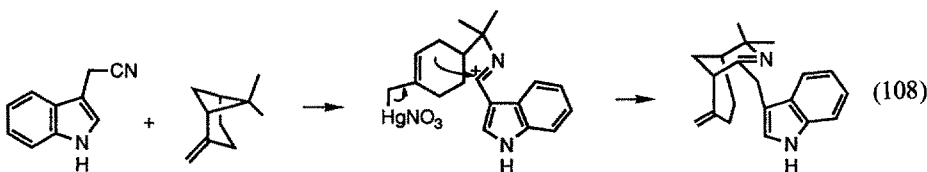
Polyene cyclization in terpene and steroid synthesis is critically dependent on the terminator in order to generate useful functionalities for further modification of the products. Allyl- and propargylsilanes have proven their value in facilitation of the cyclization and generation of an exocyclic methylene and allene, respectively. Thus, a concise approach to albicanyl acetate [126] and the rapid construction of a tetracyclic precursor of steroids [127] are sufficient to demonstrate the concept. Again, a comparison of the substrates with a silyl group with those having a simple alkyl moiety is very enlightening.



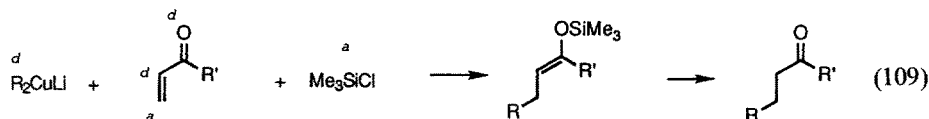
Anti-Markovnikov hydration of a vinyl chloride via oxymercuration with mercuric trifluoroacetate in methanol was surprising [128]. However, it might be speculated that solvent modified Hg(II) species show a higher affinity for the chlorine atom than the π -bond. The resulting chloronium ion is susceptible to attack by methanol in a manner analogous to Michael addition. Ejection of ClHgY is expected to be followed by a 1,2-hydride shift.



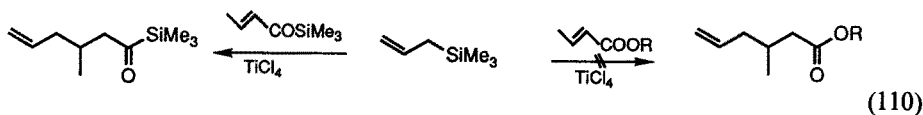
Mercury(II)-catalyzed insertion of a nitrile into the cyclobutane ring of β -pinene [129] is regio- and stereospecific. The strained C-C bond is ideally substituted such that complexation of the double bond with Hg^{2+} triggers its heterolysis to generate a relatively stable acceptor (C^+).



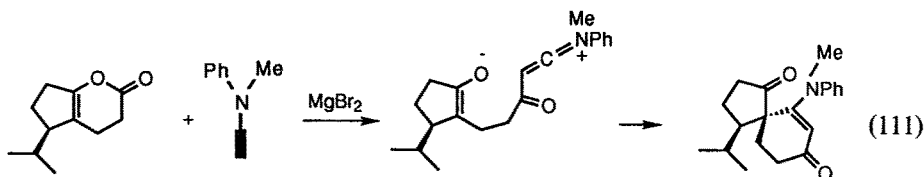
The Michael addition is a general name for conjugate addition to α,β -unsaturated carbonyl systems. The enol adducts are usually hydrolyzed to give saturated carbonyl compounds. The acceptor site is determined by the carbonyl group two bonds away, and the reaction is most efficient and selective (vs 1,2-addition) when a push-pull mechanism is operational. In other words, the reagent(s) should contain a hard acceptor and a soft donor component. Assistance of alkyl transfer from organocuprates by chlorotrimethylsilane [130] is an excellent example of such polarity alternation accentuation. Boron trifluoride etherate activation of the conjugate alkyl transfer with higher order organocuprate reagents [131] is based on the same principle.



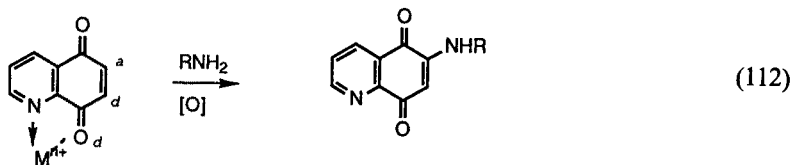
The very different reactivity toward allylation of α,β -unsaturated esters and acylsilanes [132] is due to stabilization of the allyl cation intermediates by the alkoxy group in the former class of substances, in contrast to those derived from acylsilanes which are expected to be less stable than 1-monooxyallyl cations. In the 1,1-dioxy substituted cations two donor atoms are bonded to the acceptor site, but in the 1-oxy-1-silyl congeners a *d,a*-antagonism (captodative) exists.



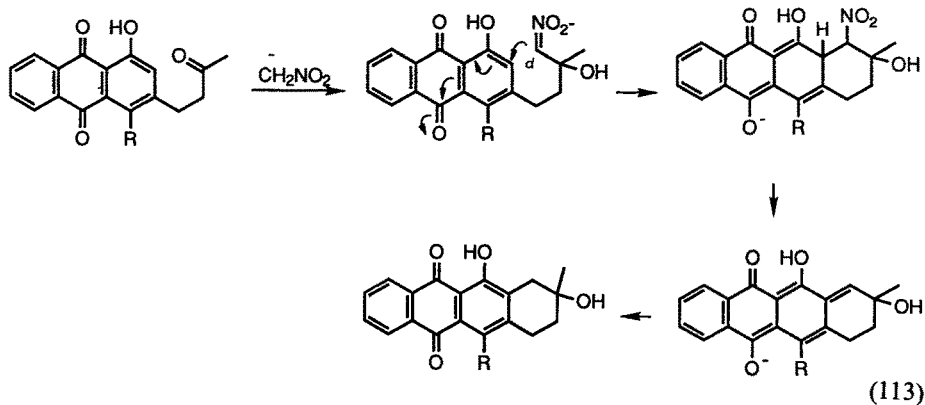
Accentuation of the β -acceptor of an enone by substitution with an iminium moiety greatly contributes to the facile intramolecular Michael addition involving an enolate. The reactive components are generated from an enollactone and an ynamine [133].



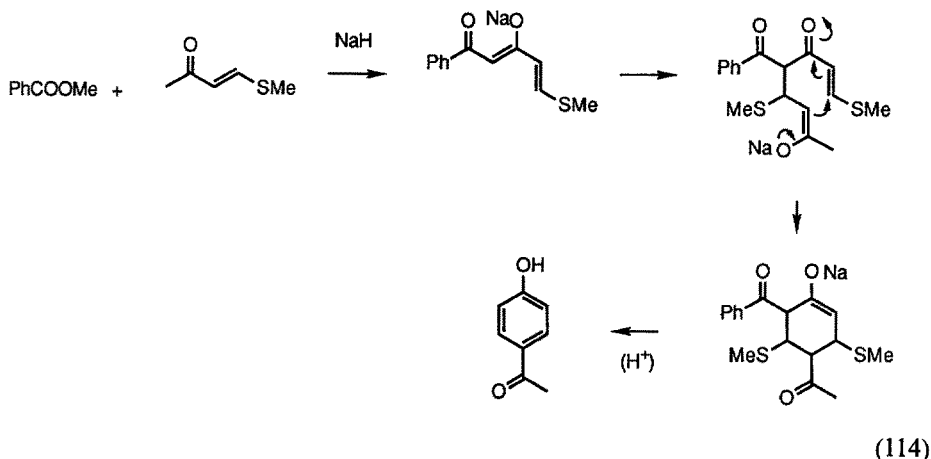
6-Amination of 5,8-quinolinedione [134] is the result of regioselective activation through chelation.



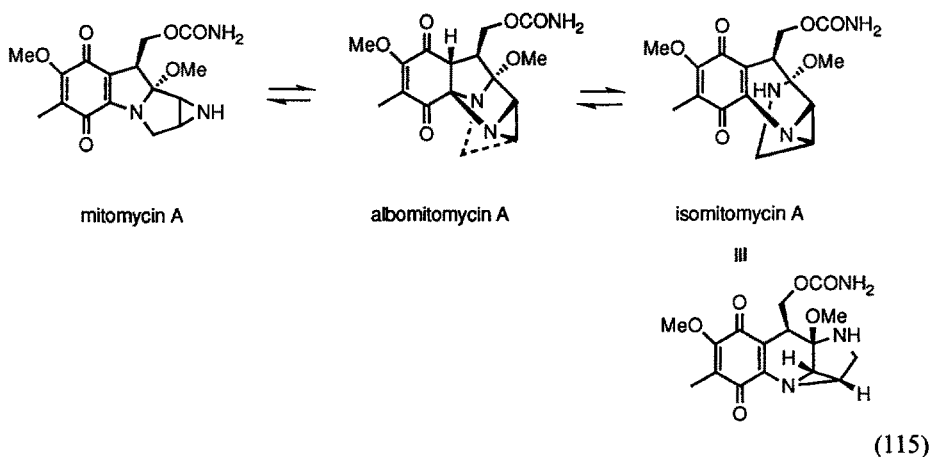
Closure of the nonaromatic ring of the anthracycline system has been effected by condensation of a 2-(3-oxobutyl)anthraquinone with nitromethane [135]. After the initial Henry reaction, a Michael-type reaction is induced by the quinone carbonyl in spite of the high electron density of the aromatic ring to be attacked, and the site of attack being a donor.



β -Alkylthio- α,β -enones undergo cyclodimerization in the presence of methyl benzoate [136]. A Claisen condensation activates the enone as Michael donor, and after cyclization by an intramolecular Michael process the benzoyl group is eliminated.

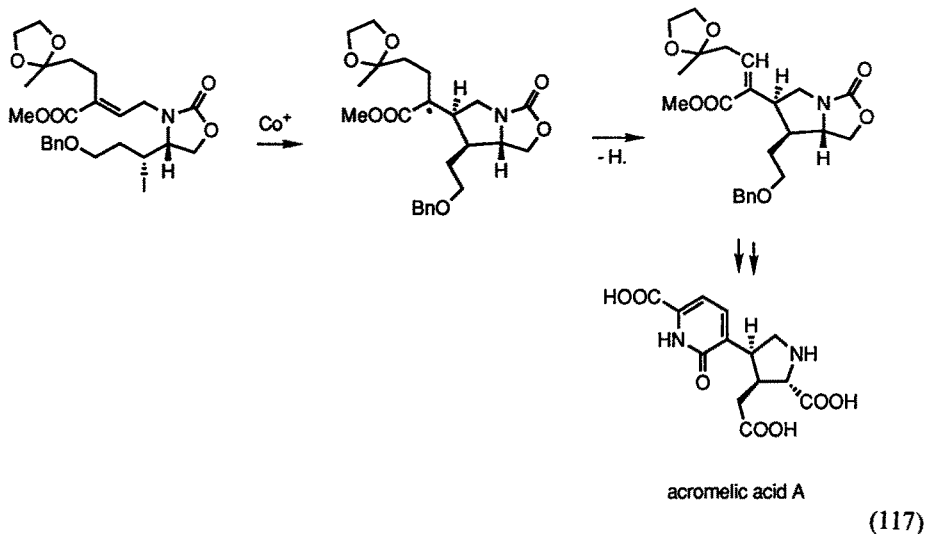
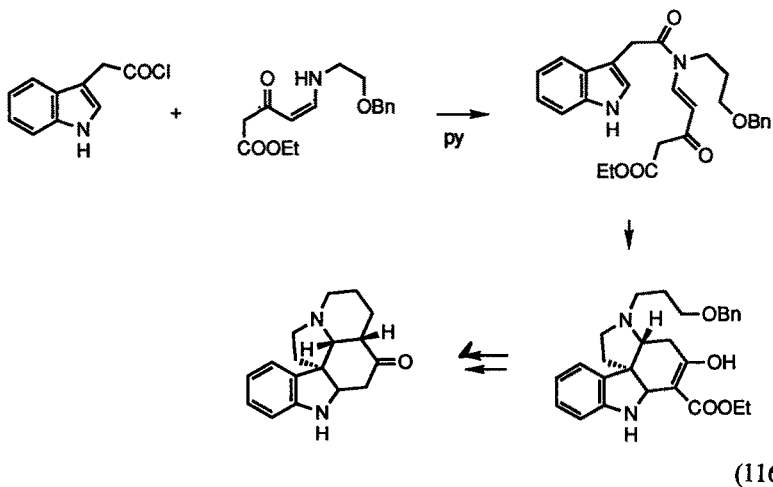


An intriguing tripartite interconversion of mitomycin A, albotomycin A, and isomitomycin A is the result of a Michael and a retro Michael reactions [137]. The transformation of mitomycin A to albotomycin A formally involves a *cis* addition, that from *isomitomycin A*, a *trans* addition.



The tandem Michael-Mannich reactions serve to assemble a tetracyclic intermediate with the aspidosperma alkaloid skeleton from 3-indoleacetyl chloride in one step [138].

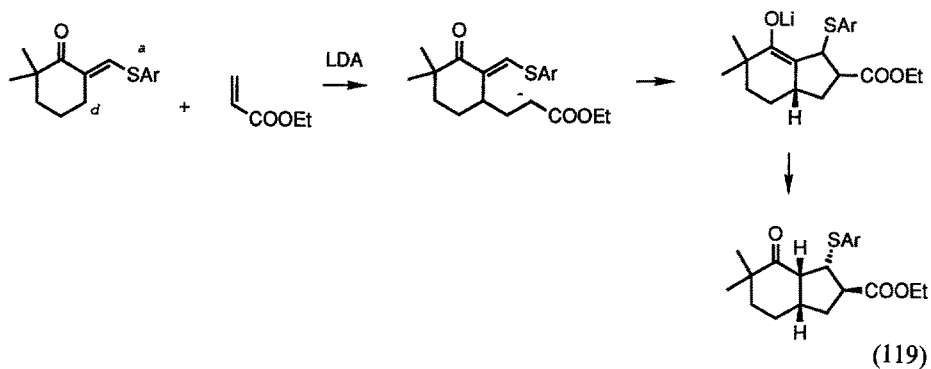
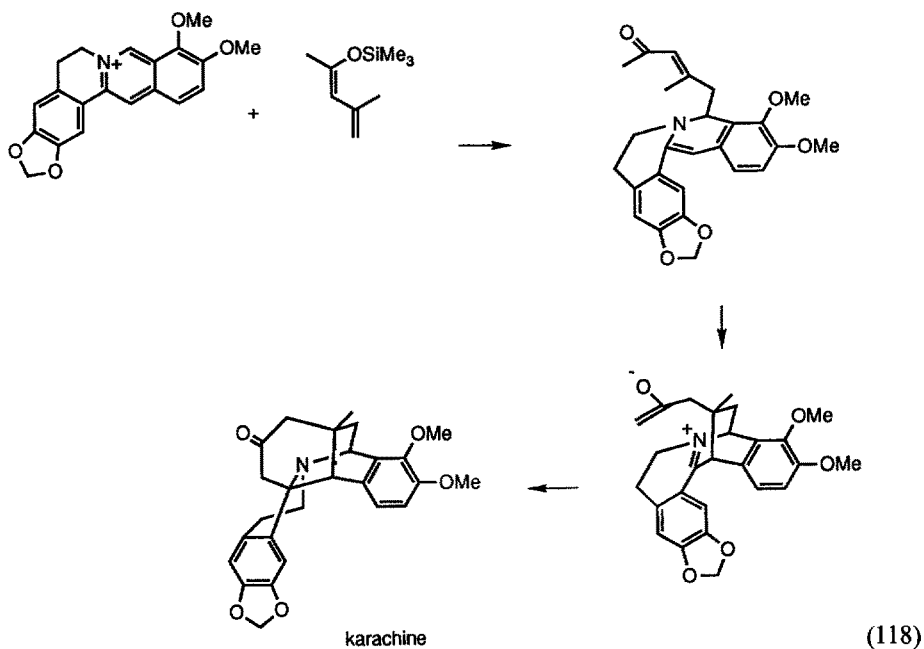
The Co(I) reduction of alkyl iodides which afford nucleophilic radicals has proven useful in a synthesis of acromelic acid A [139]. In a sense contrapolarization is involved and a Michael addition follows.



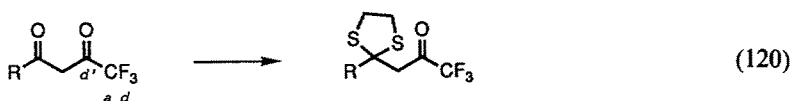
A Mannich-Michael combination is the process by which the intricate bridged skeleton of karachine [140] was constructed. One of the keys to the success is the reversibility of the Michael addition.

Very special amphiphilic properties of a divalent sulfur atom is witnessed in the reaction of α -thiomethylenecycloalkanones with acrylic esters under basic conditions [141]. The donor character of the allylic methylene group is enhanced by the sulfur (acting as an acceptor), yet the Michael cyclization that follows would be facilitated by a donor at that position.

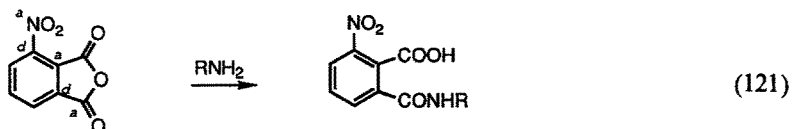
Dithioacetalization can be regarded as a combination of addition and elimination. A cogent example of electronic control by a remote substituent is the selective reaction of 1,1,1-trifluoroalkane-2,4-diones at the 4-oxo site [142]. Here, the three



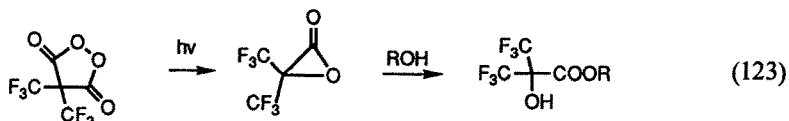
fluorine atoms imbue much donor character to the nearby carbonyl and hence a reduced reactivity toward thiols.



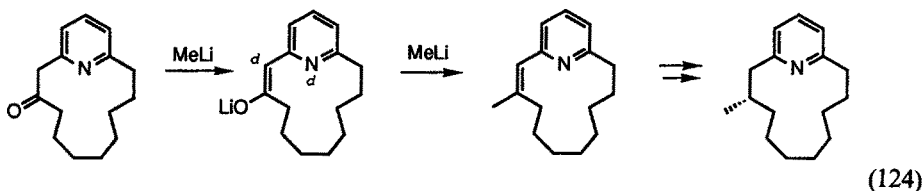
The high reactivity of 3-nitrophthalic anhydride (at C-1 carbonyl) towards amines [143] may be ascribed to the influence of the nitro group through polarity alternation.



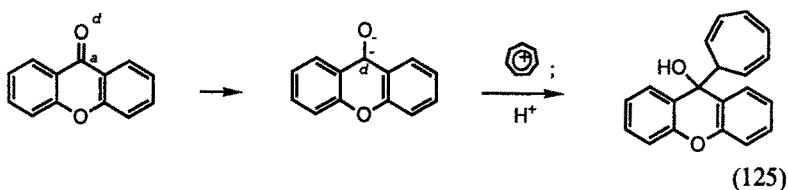
Addition to carbonyl group by a nucleophile is commonplace. However, α -lactones undergo alcoholysis with formation of α -alkoxy carboxylic acids [144]. The acceptor role of the carbonyl is restored in the bistrifluoromethyl- α -lactone [145]. It may also be considered that the α -carbon is reluctant to become an acceptor because of the fluorine atoms.



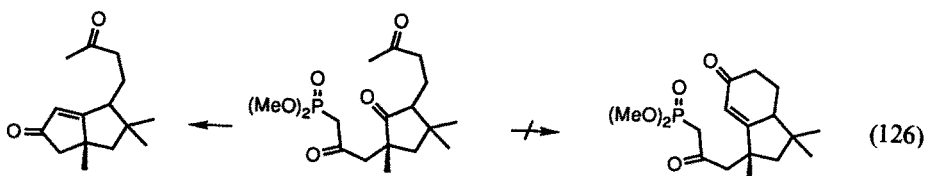
An unusual step in a synthesis of (+)-muscopyridine [146] is the methyl addition on an enolate. It appears that the oxygenated carbon still retains sufficient acceptor character by virtue of its relationship to the pyridine nitrogen (cf. reactivity of 2-vinylpyridine).



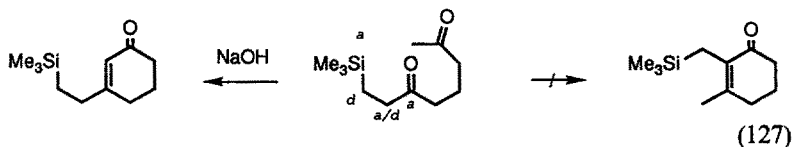
It is difficult to synthesize 9-[1-(2,4,6-cycloheptatrienyl)]-9-xanthinol [147] from xanthone by a simple addition, considering the potential nucleophile, cycloheptatrienide anion, is antiaromatic. An umpolung strategy works well in that reversed roles are given to the two reactants.



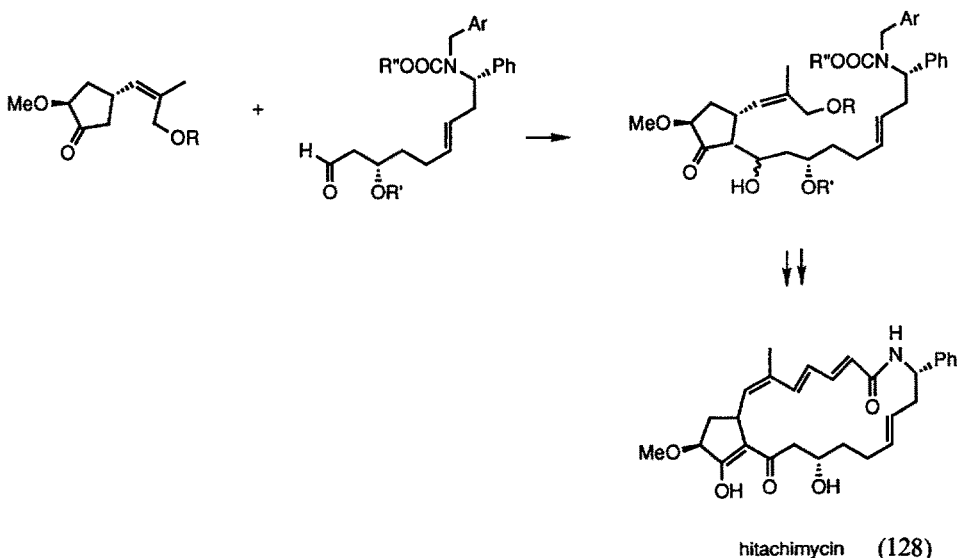
In an aldol condensation an enolate adds to a carbonyl group. Among the various methods which have been developed to achieve regioselectivity those involving polarity alternation accentuation are a time-honored technique. For example, the closure of a more strained diquinane nucleus rather than a hydrindane system is possible by installing a phosphoryl group in the α -position of the appropriate ketone [148].



Interestingly, suppression of enolization of a particular carbonyl of a diketone chain is witnessed during the cyclization of 8-trimethylsilyl-2,6-octanedione [149]. Thus, enolization of the internal ketone toward C-7 is discouraged by the acceptor silicon, the competing influences of the two functions tend to diminish the donor properties of C-7. It should be noted that enolization toward C-5 leads to a nonproductive enolate, as cyclization would result in a cyclobutanol, and a fast reversal to the acyclic tautomer is expected.

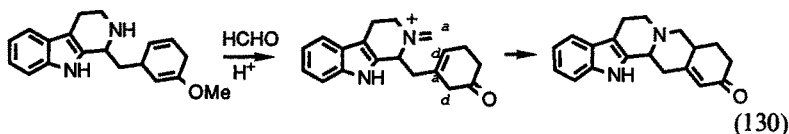
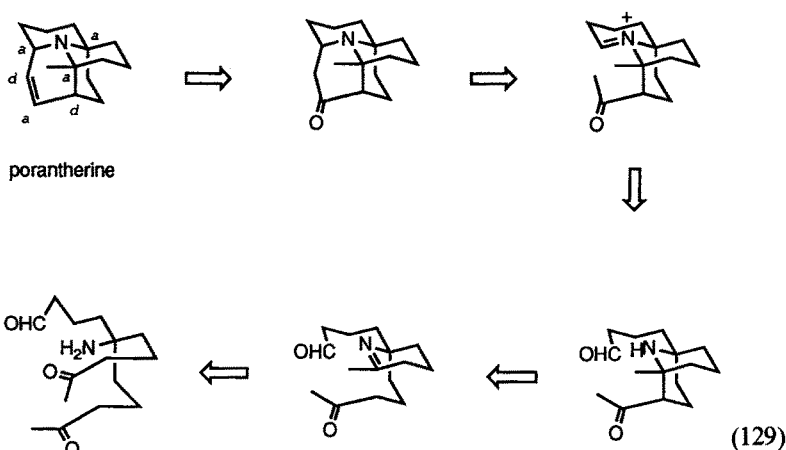


Captodative deterrence by an α -donor to guide the enolization of ketones has found an excellent application in an approach to hitachimycin [150]. Thus, aldolization of an α -methoxycyclopentanone serves to assemble the major segment of the skeletal elements.

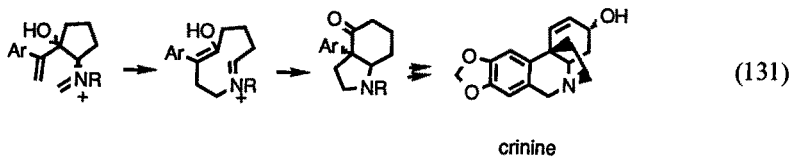


Systematic bond disconnection of porantherine [151] with recognition of the double bond-carbonyl equivalence for synthesis generated a synthetic pathway which is based on two intramolecular Mannich reactions. The symmetrical nature of the amino diketone precursor identified by the retrosynthetic analysis facilitates its preparation and subsequent transformations. Moreover, all the hetero atoms (donors) are separated by odd-numbered carbon chains and such arrangements are most amenable to normal modes of assembly.

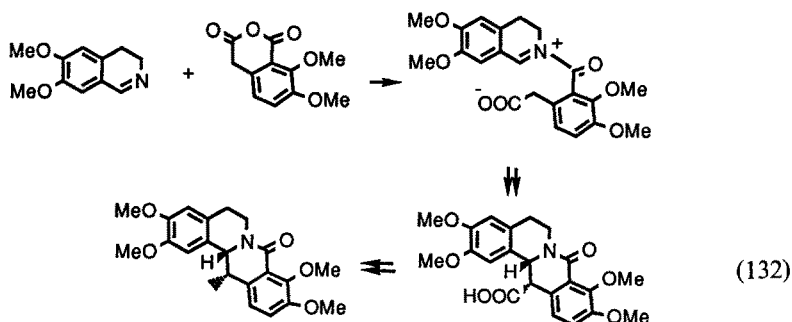
A preparation of yohimbenone [152] by closure of the D-ring with formaldehyde can be considered as a vinylogous Mannich reaction.

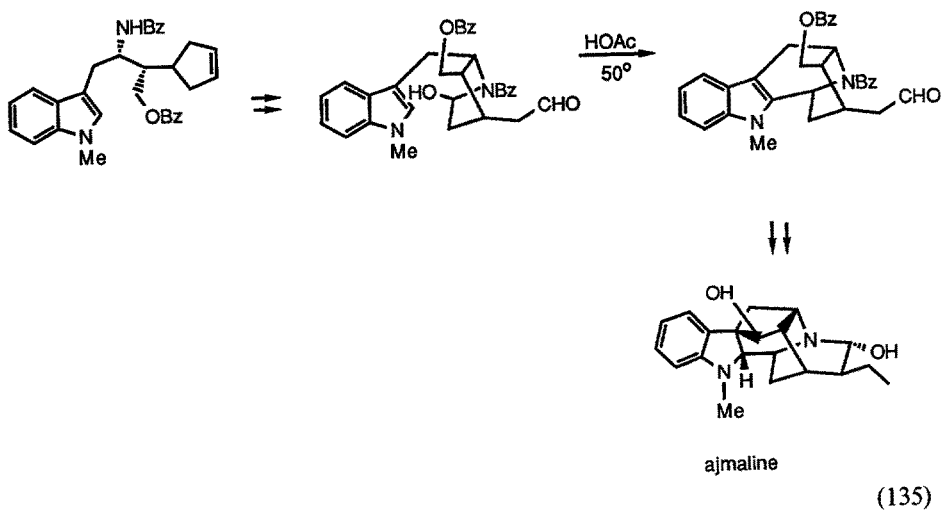
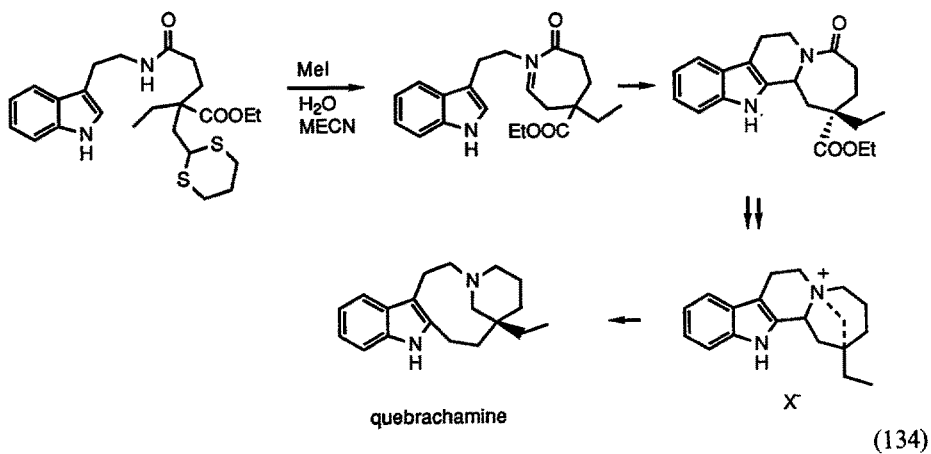
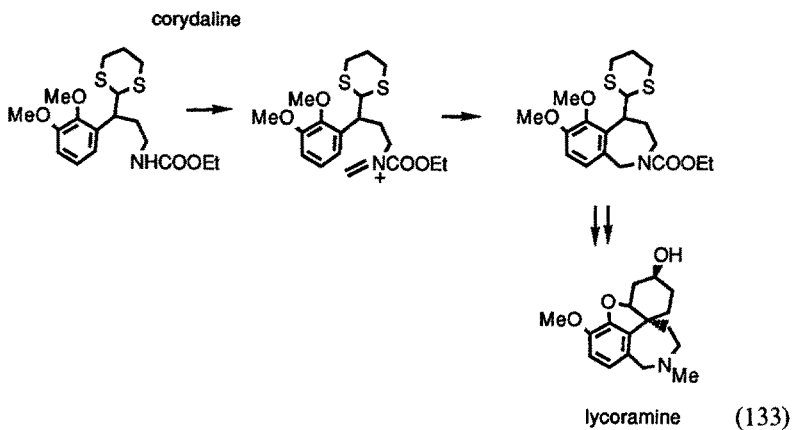


Transannular Mannich reaction of an iminium enol intermediate derived from an aza-Cope rearrangement allows access to an angular arylindolone derivative which is a synthetic precursor of crinine [153].

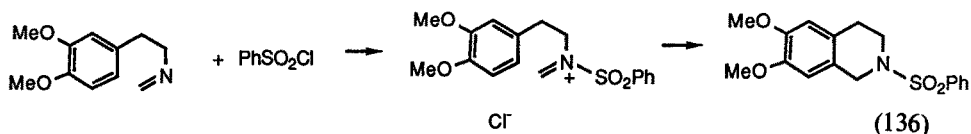


N-Acyliminium ions are versatile intermediates for synthesis of nitrogenous compounds, particularly alkaloids [154]. The conjugate system is very electrophilic such that it can be intercepted by various donors including carbonyl compounds and π -systems. In comparison with α,β -unsaturated ketones the replacement of the α -carbon with a nitrogen atom accentuates the reactivity of these species. Ingenious applications of the *N*-acyliminium ions include service to synthesis of corydaline [155], lycoramine [156], quebrachamine [157], and ajmaline [158], to name a very few.

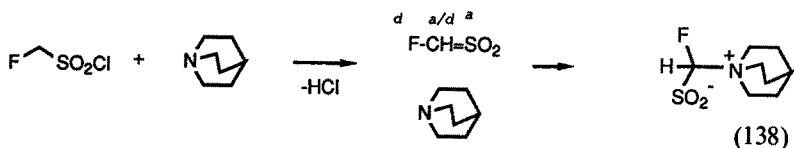
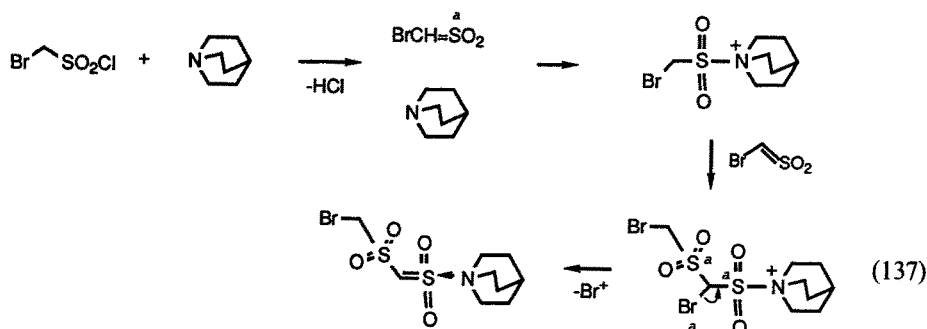




One can view *N*-acyliminium ions as activated Mannich intermediates. It is logical to expect other donors such as sulfonyl [159] can be used in lieu of the acyl moiety.



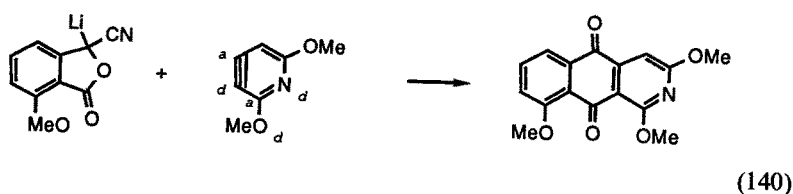
Sulfenes derived from α -halomethanesulfonyl chlorides undergo reactions with quinuclidine (used as dehydrochlorinating agent) in markedly different manners as the halogen changes from bromine to fluorine [160]. The ability of a bromine atom to assume an acceptor role which is coerced by the sulfur atom (*a-d-a* sequence) is responsible for the formation of a “dimer”. On the other hand, a fluorine atom imposes its neighbor the acceptor role.



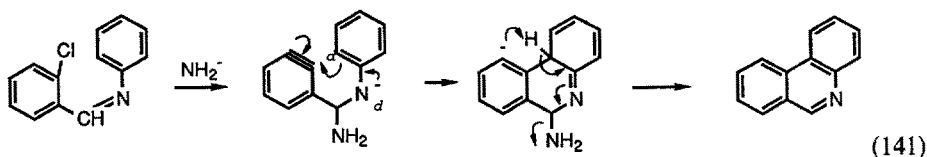
Dichlorosulfene can also behave in the unpoled fashion [161].



A method for synthesis of anthraquinones is by reaction of cyanophthalide carbanions with benzynes [162]. It is particularly useful for the access of 2-aza-1,3,8-trimethoxyanthraquinone because of the high regioselectivity imposed by the methoxy groups and the nitrogen atom of the pyridine.

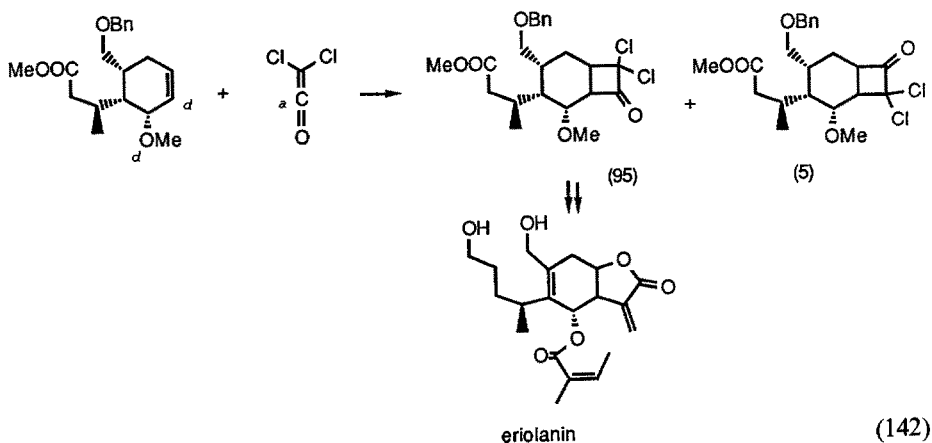


Intramolecular addition to benzyne generated from the Schiff base of aniline and *o*-chlorobenzaldehyde is thought to involve addition of an amide anion to the C=N bond [163]. This mechanism indicates donor accentuation of the *ortho* carbon.

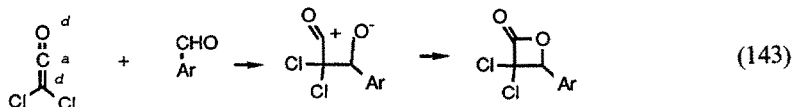


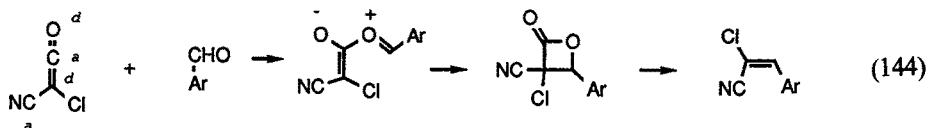
4.2 Cycloadditions

Cycloadditions give better efficiency and stereocontrol for ring formation. A high regioselectivity (95:5) for the cycloaddition of dichloroketene to a cyclohexene en route to synthetic eriolanin [164] has been observed. It appears that the allylic methoxy group play a dominant role. Note that the proximal *sp*²-carbon is a donor by virtue of its 1,3-relationship with the oxygen function.

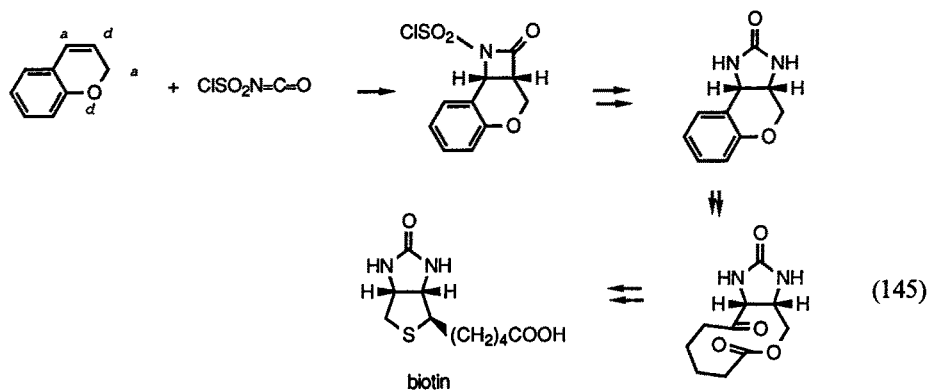


Dichloroketene acts as a donor toward aromatic aldehyde [165], but chlorocyanoketene behaves as an acceptor, as shown by the reactivity profile with a series of substituted benzaldehydes [97]. It must be remembered that chloro and cyano groups belong to different polarity categories, and although the fundamental donor/acceptor characters of the ketene unit do not change, the higher electrophilicity of the cyanoketene reflects the acceptor influence by the cyano function.

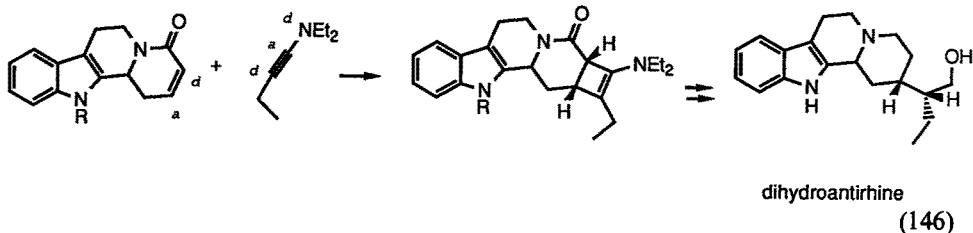




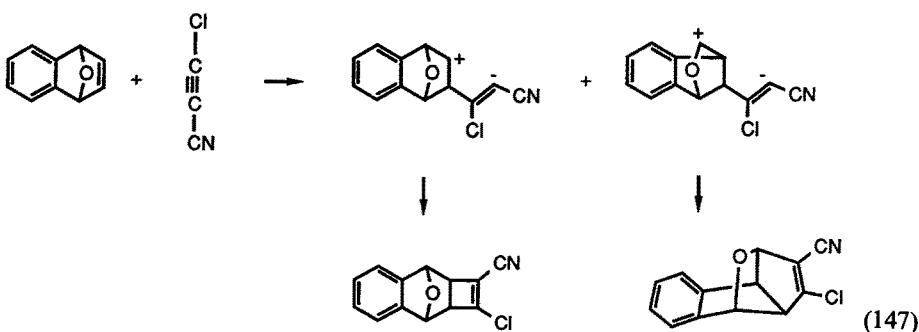
An approach to biotin [166] starts from a [2 + 2] cycloaddition of chlorosulfonyl isocyanate to chromene. The excellent regioselectivity of this reaction may be attributed, at least in part, to the ethereal oxygen.



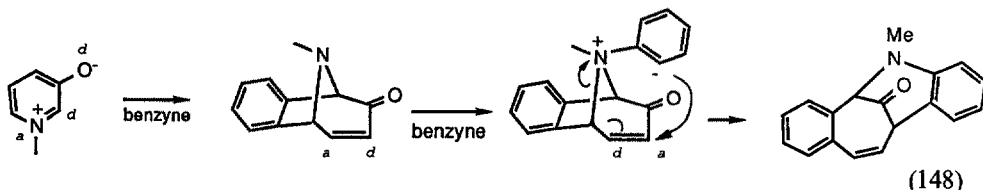
An application of the ynamine cycloaddition is found in a synthesis of dihydroantirrhine [167]. The transition state with matching polarized addends is adopted. The cycloadduct becomes fragmentable upon hydrolysis.



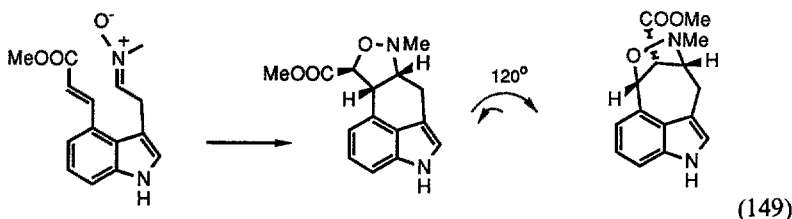
Cycloaddition of benzo-oxanorbonadiene with chlorocynoacetylene gives two adducts [168]. The disjointment in the cationic portion of the dipolar intermediate caused a 1,2-shift competitively with ring closure.



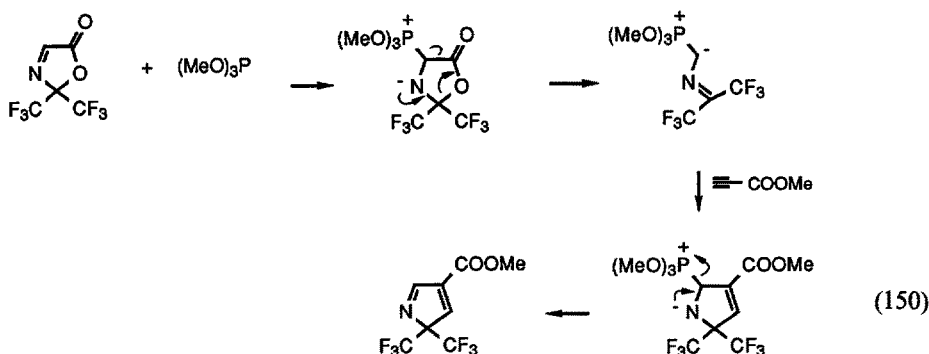
1-Methylpyridinium 3-oxide and benzyne form a 1:2 adduct [169]. Interestingly, in the second stage an S_N2' process is contrapolarizing with respect to the enone system.



In an approach to the clavine alkaloids [170] based on intramolecular nitrone-alkene cycloaddition, the condensed tetracyclic system is probably favored by steric factors. Equilibration at higher temperature leads to predominantly a bridged oxabicyclo-[3.2.1]nonane derivative in which a portion of the molecule contains polarity alternation sequence (O-C-C-C=O, N-C-C-C=O).



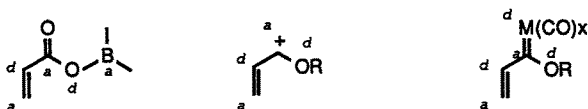
2,2-Bis(trifluoromethyl)-5(2*H*)-oxazolone undergoes decarboxylation on treatment with trimethyl phosphite. The resulting 1,3-dipole may be trapped by methyl propiolate [171]. The initial P-C bond formation is favored because the alternative mode of reaction would form a weak P-N bond. This counter-Michael addition also generates an *a-d-a-d* system which becomes fragmentable.



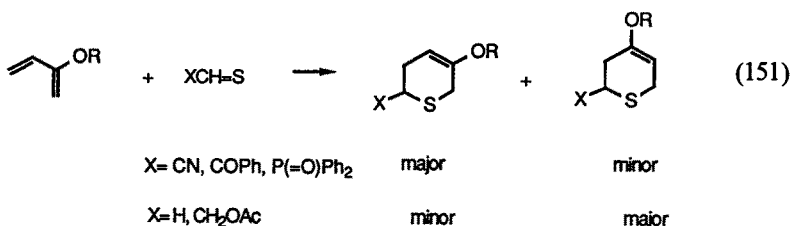
Despite the concerted nature of most Diels-Alder reactions, substituent effects are evident. Electronic compatibility of the reaction partners is of paramount importance, therefore while a normal Diels-Alder reaction is characterized by the union of an electron-rich diene and an electron-poor dienophile, the Diels-Alder reaction with inverse electron demand features an electron-poor diene and electron-rich dienophile.

Electron-rich/poor dienes do not generally condense with electron-rich/poor dienophiles.

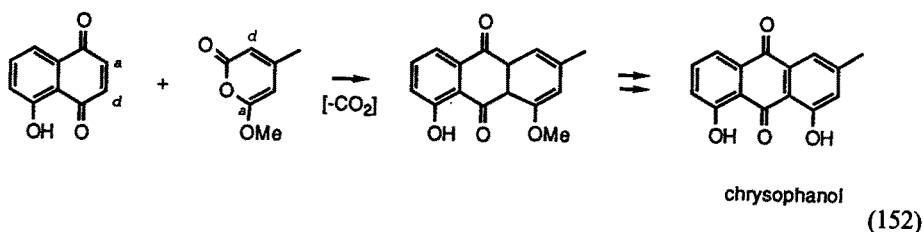
Given a typical diene, an increased reactivity is expected of the reaction with enhancing polarity alternation of the dienophile. This is easily appreciated in view of an ionic reaction being more exothermic. Thus, acryloxyboranes [172] undergo cycloaddition with cyclopentadiene even at $-78\text{ }^{\circ}\text{C}$. The same principle underlies dienophile activation by replacing an enone with an alkoxyallyl cation [173] or allylidene-metalcarbonyl [174].



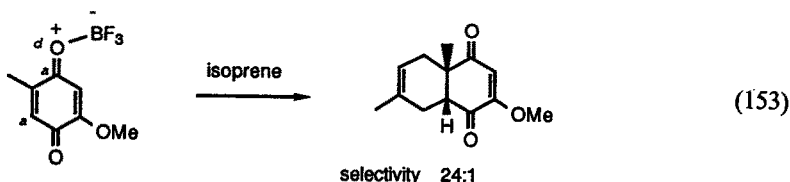
The regiochemistry of the Diels-Alder reaction of a thioaldehyde depends on the nature of the substituent directly linked to the sp^2 -carbon atom [175].

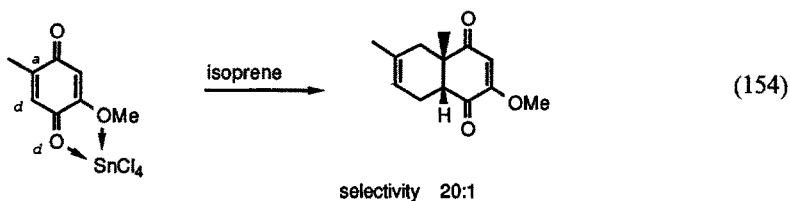


A *peri* hydrogen bonding enables juglone to partake in a Diels-Alder reaction in a regioselective fashion [176]. The H-bonded carbonyl group becomes more highly polarized which in turn causes its β -carbon more acceptor-like.

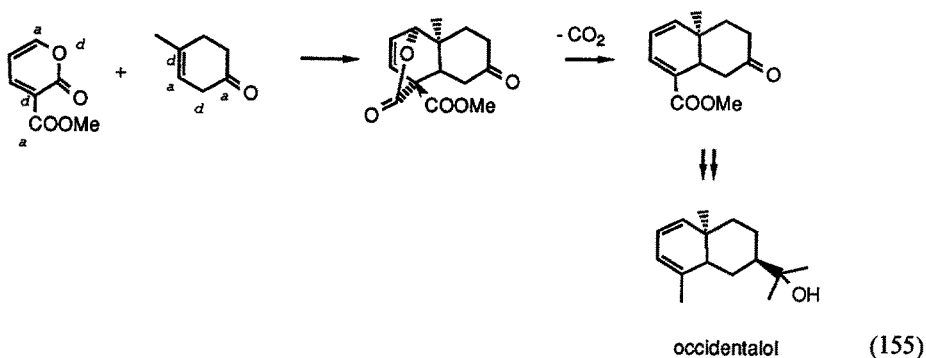


Lewis acids are frequently employed in catalyzing the Diels-Alder reaction. Particularly fascinating is the observation of the different regiochemistry arising from monodentate and bidentate chelation of 2-methoxy-5-methyl-1,4-benzoquinone with boron trifluoride and stannic chloride, respectively [177].

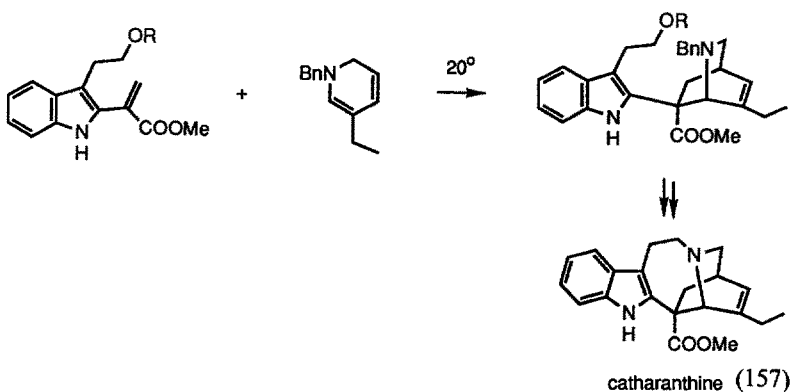
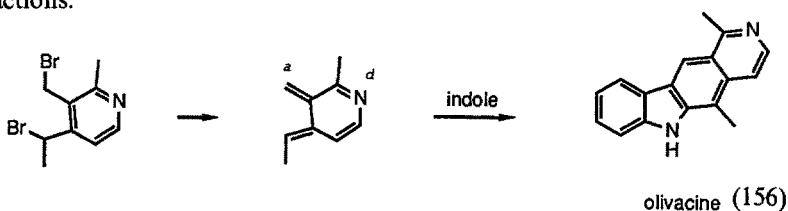




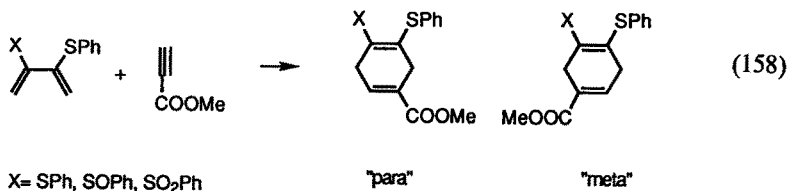
The regioselective formation of a *cis*-hexalone containing a homonuclear diene which is useful for elaboration into occidentalol [178] by the condensation of 4-methyl-3-cyclohexenone with methyl coumalate is rather surprising. It seems that C-3 of the cyclohexenone, under the influence of the ketone group (perhaps via the enol), prefers an acceptor role.



The most efficient and regioselective Diels-Alder reactions are those involving electronically compatible dienes and dienophiles. It might be instructive to mention the rapid syntheses of olivacine [179] and catharanthine [180] benefit from the well-designed reactions.

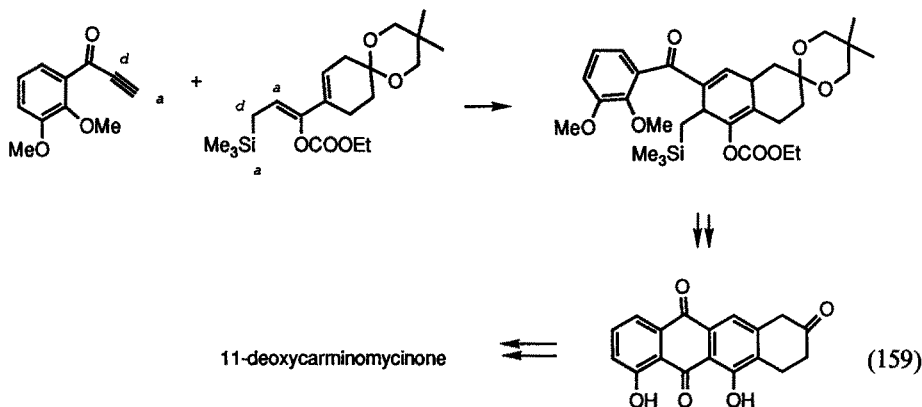


The study of the effects of competing functionalities often contributes to better understanding of a reaction. Thus, the regiocontrol, i.e. *p*-directing, a sulfur substituent at C-2 of 1,3-butadiene exerts has been shown to depend on its oxidation state [181], an observation in total agreement with the gradual transition from a donor to an acceptor.

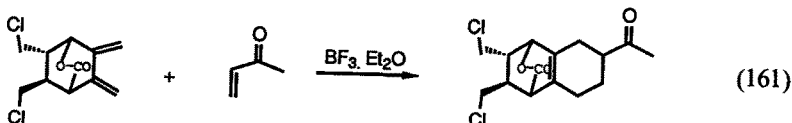
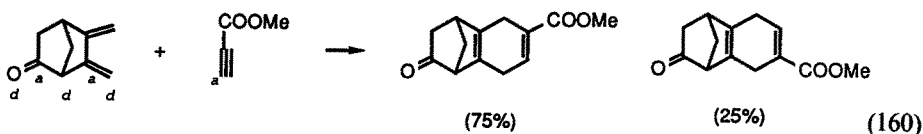


Complete redirection by the NHCOOR for 4-sulfurated (sulenyl, sulfinyl, and sulfonyl) *E*-1,3-butadiene-1-carbamates in their Diels-Alder reactions [182] is quite natural. The case at issue might be the sulfenylated compounds, but we must remember that divalent sulfur can act as an acceptor.

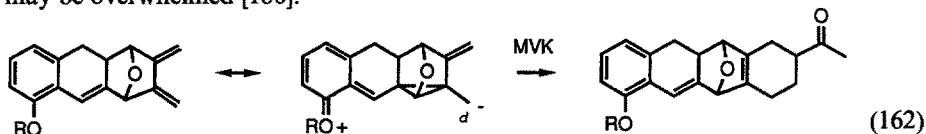
The strong directive effect of an allylic silicon in a diene on the regiochemistry of the Diels-Alder reaction proved to be a blessing in synthesis of 11-deoxycarminomycinone [183].



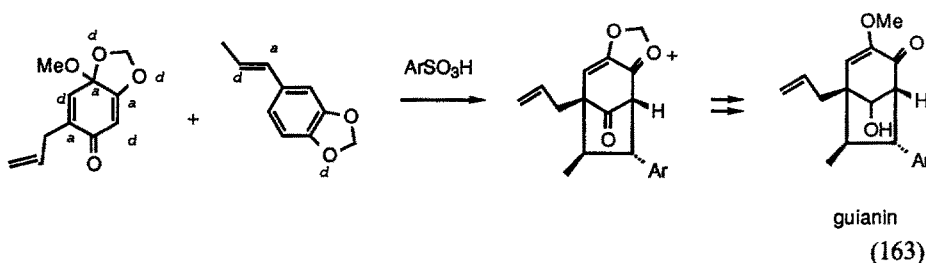
Simple polarity alternation arguments readily accommodate the regiochemical outcome of the Diels-Alder reactions of 5,6-bis(methylene)-2-bicyclo[2.2.1]heptan-2-one [184] and a lactone analogue [185].



However, in these ring systems through-space homoconjugative interactions are sterically very favorable, and the through-bond (polarity alternation) interactions may be overwhelmed [186].



Cationic [5 + 2]cycloaddition involving a styrene and *p*-benzoquinone ketals in the presence of a Lewis acid is the key reaction to a number of neolignans (e.g. guianin [187]). The oxygen atoms of the dioxolane function in the cycloaddend reinforce the *a* character of their neighboring carbons, and this character is transmitted to the termini which participate in the C-C bond formations.

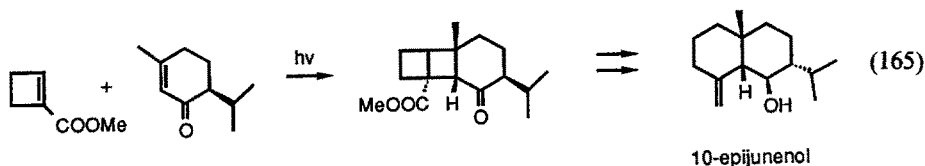
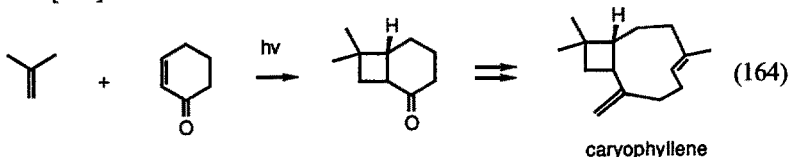


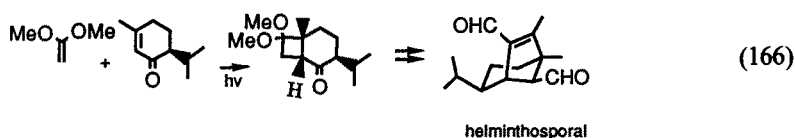
Photochemical [2 + 2]cycloadditions show very high regioselectivity. For example, dimerization of coumarin [188] gives head-to-head cycloadducts (singlet excited state → *syn*, triplet excited state → *syn* + *anti*).

More complex systems include α -lumicolchicine [189] which is an *anti*/head-to-head cycloadduct of the electrocycliczed β - and γ -lumicolchicine.

The cycloaddition of an enone with electron-rich alkenes also proceeds with remarkable regioselectivity. The rationalization is that in the excited state, polarization of the enone double bond is opposite in direction as compared with the ground state [190]. In other words, photochemical excitation induces contrapolarization. With this consideration the head-to-head dimerization generally observed is reasonable as it involves one molecule each in the ground and excited states.

Elegant applications of the contrapolarized orientation in such photocycloadditions include syntheses of caryophyllene/isocaryophyllene [80], 10-epijunol [191], and helminthosporal [192].

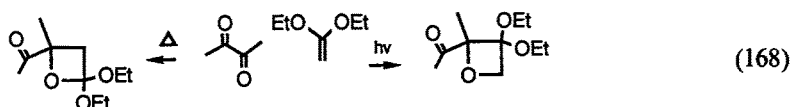




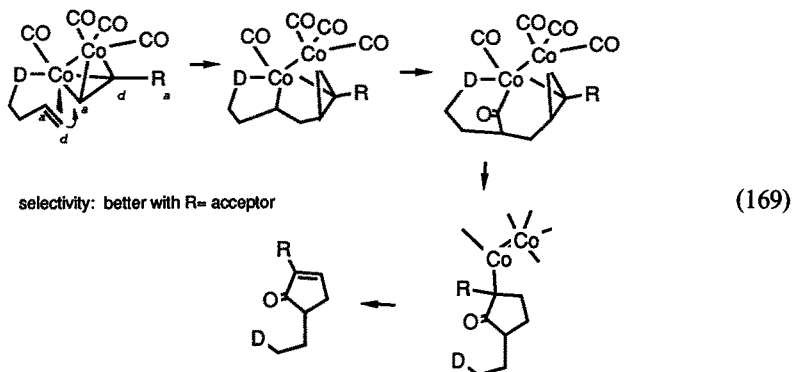
It is pertinent to mention the formation of γ -ketols by photochemical addition of alcohols to enones follows the same polarity pattern [193].



Thermally and photochemically induced cycloadditions of 2,3-butanedione with 1,1-diethoxyethylene show different regiochemistry [194]. This is expected on the basis of the above explanation. Perhaps electron transfer occurs between reactants before the bond formation starts.

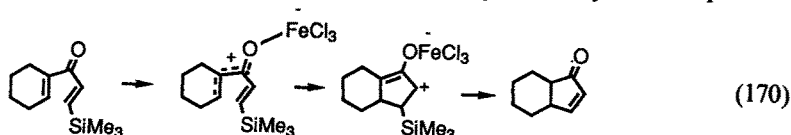


Concerning the regiocontrol of intermolecular Pauson cyclization in which a homoallylic donor group is present in the alkene subunit [195], there seems to be some electronic contributions.



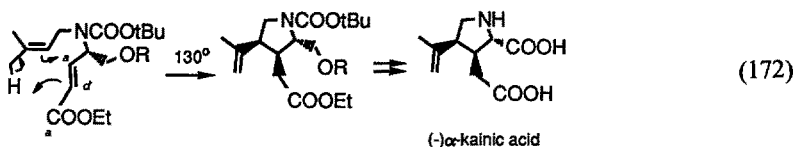
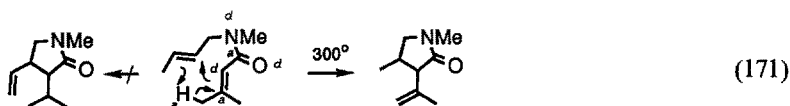
4.3 Electrocyclizations and Cycloreversions

The Nazarov reaction [196] is a conrotatory electrocyclic cyclization involving four electrons over a five-carbon span. Usually, a more highly substituted cyclopentenone is obtained. However, contrathermodynamic products may be generated by placing a silyl group at the β -position of a bare vinyl moiety in the cross-conjugated dienone [197]. The acceptor facilitates and controls the regiochemistry of the cyclization process.

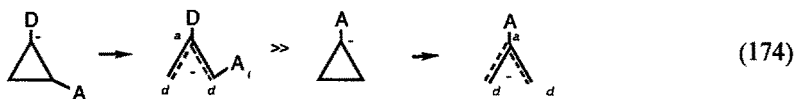
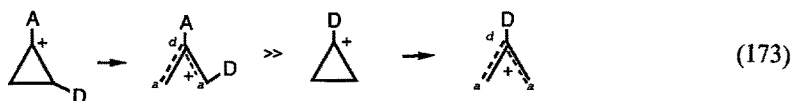


The rationalization for the regiocontrol is simple. Participation of the silylated double bond is disfavored on account of the substantial positive charge to be allotted to the carbon which is directly linked to the silicon atom, an *a-a* arrangement.

The intramolecular ene reaction [198] proceeds in good reioselectivity if either the ene or the enophile component is linked to polarizable groups. Based on the direction of polarization an excellent synthesis of (–)- α -kainic acid [199] has been designed.



The relative rates for electrocyclic ring openings of cyclopropyl ions [200] are shown in Eqs (173, 174). For the cations the faster rates are exhibited by compounds in which an acceptor is directly bonded to the electron deficient center (*a-a* arrangement), whereas precursors with a donor substituent at the center open most slowly.



The phenomena are explainable in terms of destabilization of the former series of cyclopropyl cations by the contiguous *a-a* array as well as stabilization of the resulting allyl cations by a beneficial polarity alternating sequence. The stabilization/destabilization situations are reversed in the least reactive compounds.

In the cases of cyclopropyl anions, destabilization by the *d-d* pairing and stabilization in the open forms for the most reactive substrates, and the opposite scenario for the least reactive substances are evident.

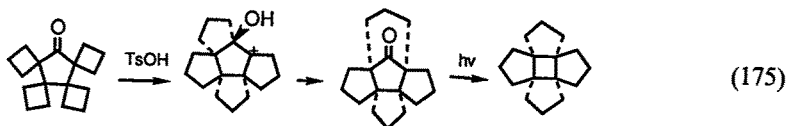
5 Rearrangements

5.1 1,2-Rearrangements

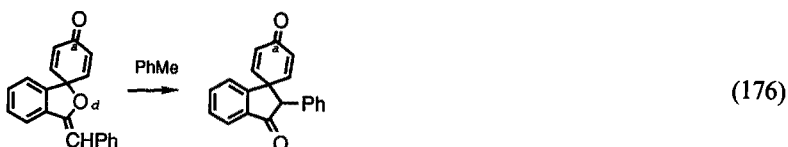
Most 1,2-rearrangements are provoked by the presence of a disjoint sequence of atoms. In other words, the molecule is not in the best electronic order. For example, epoxides, glycols and β -amino alcohols contain two *d-a* segments which are linked

head-to-head. Proper activation such as protonation or diazotization would induce a rearrangement to remove the unfavorable electronic interactions.

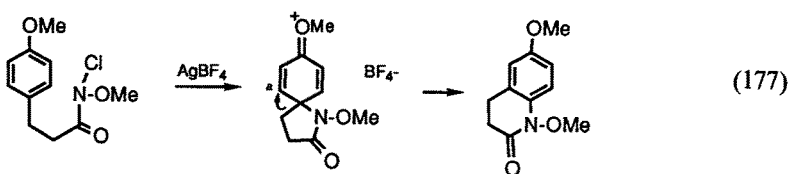
It must be pointed out that the 1,2-alkyl shift may be subverted by other factors such as steric strain. Thus the cascade rearrangement of a tetraspiroketoone on exposure to acid is most aesthetically appealing and synthetically useful for entry into [4.5]coronane [201].



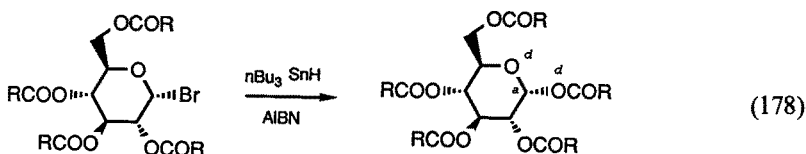
The thermal isomerization of a spirocyclic enol ether to the ketone [202] (Eq. 176) is probably a homolytic process. However, it is noted that part of the driving force for the reaction must be the bonding of the ethereal oxygen to a designated donor atom of the cross-conjugated cyclohexadienone moiety.



Intramolecular interception of an *N*-alkoxy-*N*-acylnitrenium ion by an aromatic ring results in a spirocyclic species [203]. There follows a C-migration (instead of N-migration) to restore aromaticity. This migration is assisted by the stabilization of the incipient carbocation by the resident donor nitrogen atom; N-migration would not profit from this favorable electronic interaction.

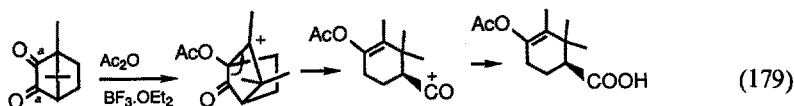


A convenient preparation of 2-deoxy sugars [204] from glycosyl halides is based on the rapid and irreversible migration of an acyloxy group from C-2 to the anomeric center upon generation of the glycosyl radicals. This is a thermodynamically controlled reaction because it restores a *d-a-d* arrangement.

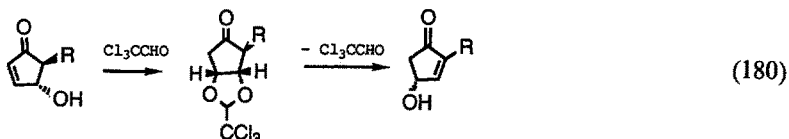


An intriguing C-C bond scission of camphorquinone is via rearrangement [205]. The rearrangement, which is induced by a destabilizing *a-a* disposition in addition

to ring strain, transfer an acceptor site to an adjacent atom and thereby creating a fragmentable situation.



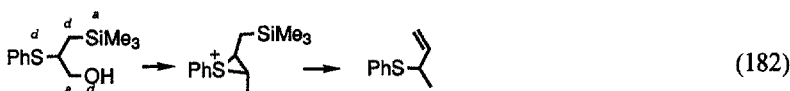
Disjoint functionalities also exist in chloral and this property has been exploited in the isomerization of 4-hydroxy-2-cyclopentenones [206].



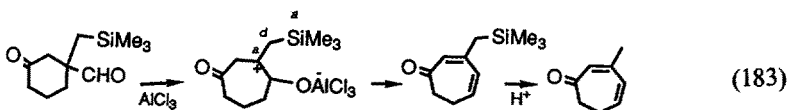
trans-2-(Trimethylsilyl)methylcyclohexyl *p*-nitrobenzoate is also disjoint. Fluoride ion promotes a ring contraction [207] which also removes the undesirable polar interactions.



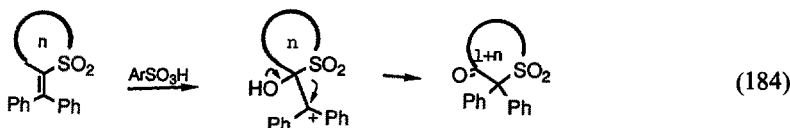
2-Phenylthio-3-trimethylsilylalkanols lose the element of trimethylsilanol on treatment with an acid [208]. Ionization of the hydroxyl group is participated by the sulfur atom and the episulfonium intermediates then undergo desilylation. The Si-C-C-S segment is conjoint and its fragmentation proceeds upon activation by episulfonium ion formation.



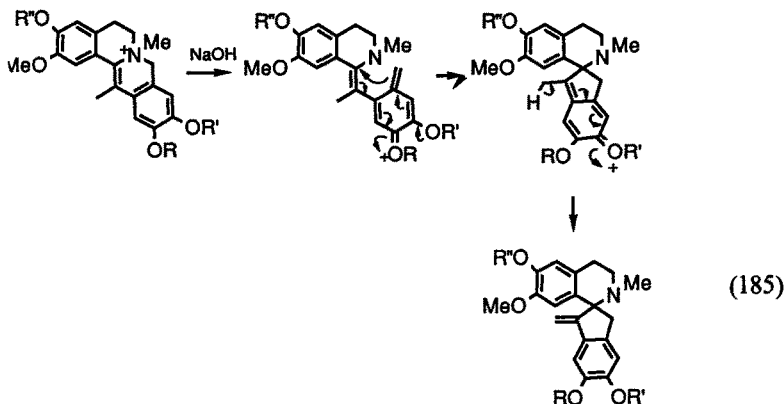
A silyl group directs ring expansion of a ketoaldehyde [209] via interaction with the incipient cation.



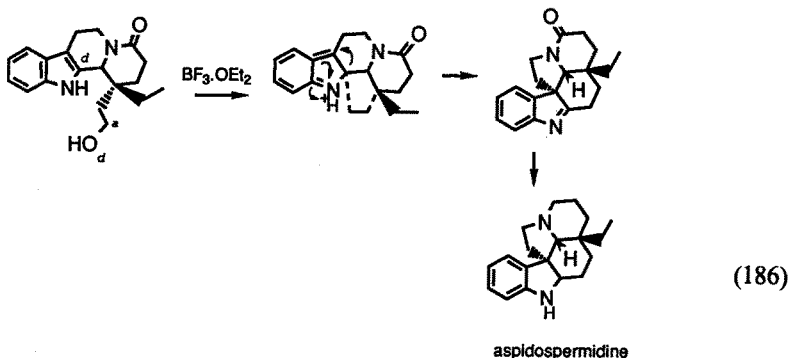
The attempted epoxidation of α -alkylidene cyclic sulfones led directly to enlarged sulfonyl cycloalkanones [210]. The rearrangement step is thermodynamically controlled in that products contain an *a-d-a* sequence.



A fascinating contrapolarization-driven reaction is the conversion of a protoberine skeleton to an ochotensine-type alkaloid [211]. The quinomethide carbon in the *seco* intermediate assumes a *d*-character which is made possible by electron supply from the oxy substituent at the meta position. Note the C-N bond cleavage step entrusts this carbon an acceptor role.

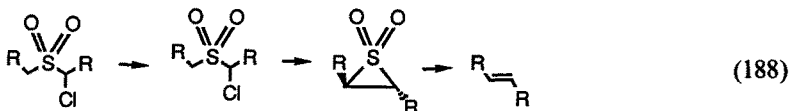
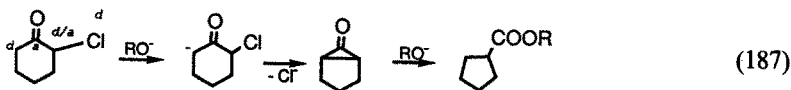


In a synthesis of aspidofermidine [212] an alkylative rearrangement was employed to gain entry into the pentacyclic skeleton.



Many other 1,2-rearrangements such as Hofmann, Curtius, Beckmann rearrangements and Baeyer-Villiger reaction can be rationalized in terms of response to unfavorable *a-a* situations.

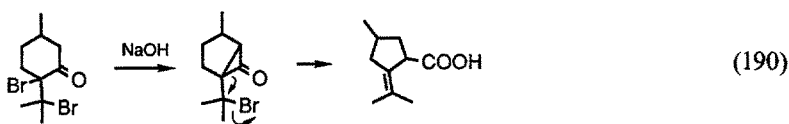
The Favorskii [213] and Ramberg-Bäcklund [214] rearrangements are mechanistically akin to the above. The first step is deprotonation (although in highly strained systems the Favorskii rearrangement proceeds by donor addition to the carbonyl group) which is followed by internal displacement of the α -halogen.



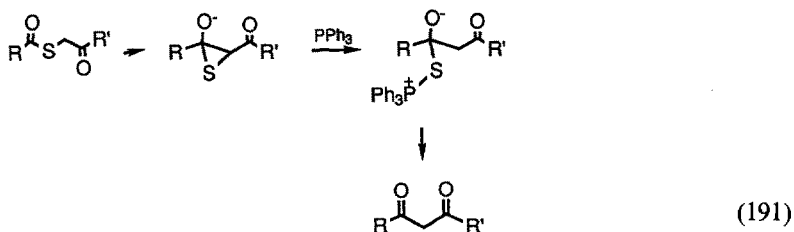
The apparent suppression of deprotonation at the α -carbon may be due its captodative nature. This carbon atom is bonded to both an acceptor ($C=O$) and a donor (Hal), the corresponding carbanion is destabilized by the donor substituent. In connection with this tendency is the selective silylation [215] of 1,3-oxathian-3,3-dioxide at C-4.



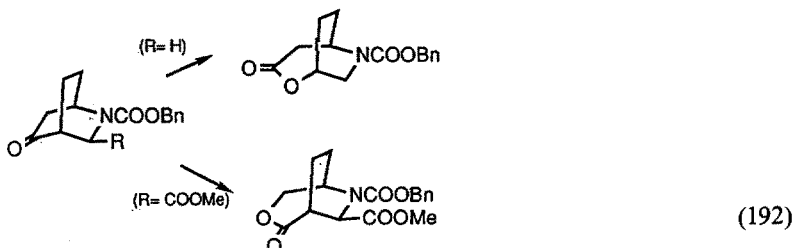
Treatment of pulegone dibromide with sodium hydroxide leads to a cyclopentane-carboxylic acid [216]. Unidirectional opening of the cyclopropanone intermediate is caused by the bromine atom at the β -position which acts as a donor.



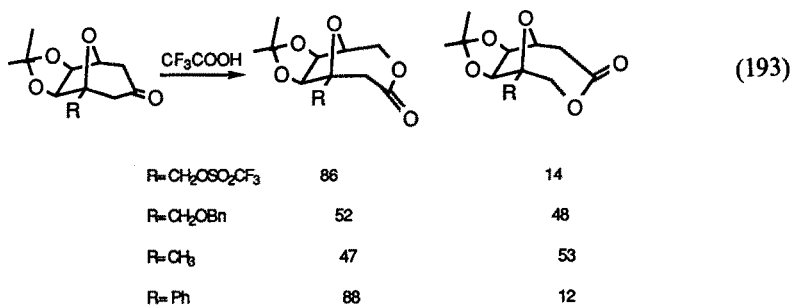
The desulfurative C-C bond formation process developed by Eschenmoser [217] is somewhat akin to the Ramberg-Bäcklund rearrangement. An episulfide intermediate is formed, which on being attacked by a phosphine, begets a carbon skeleton with polarity alternating sequence.



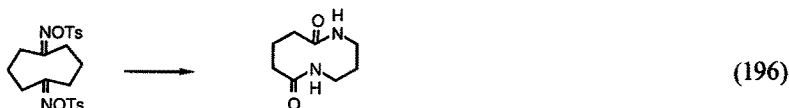
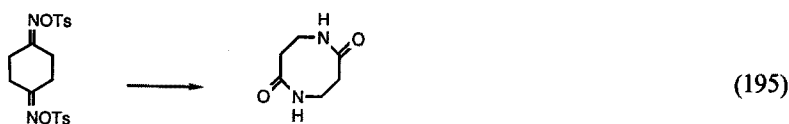
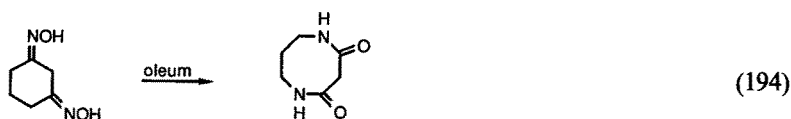
Bridgedhead migration during Baeyer-Villiger reaction of *N*-carbobenzoxy-2-azabicyclo-[2.2.2]octan-5-one [218] is expected, as its donor character is reinforced by the hetero atom. On the other hand, an ester group at C-3 completely suppresses the influence of the nitrogen atom [219].



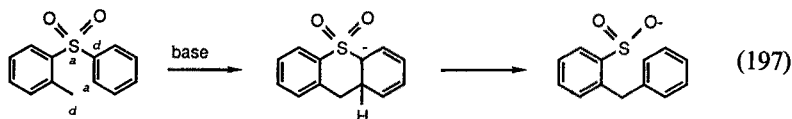
The subtle electronic effect of a γ -substituent is also evident in another bicyclic system [220]. In this case the substituent is located outside a bridgehead and free-rotating.



Beckmann rearrangement of certain cycloalkanedione dioximes [221] has revealed regioselectivity which indicates the presence of electronic interactions between the functionalities. No matter what the reason is, the products possess arrangement of amide groups which are related to one another in the polarity alternating sense (i.e. conjointment).



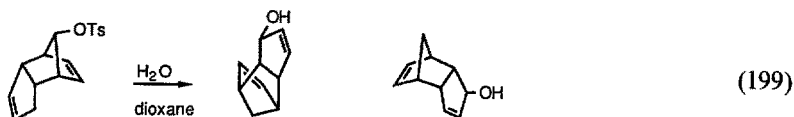
The Smiles-type rearrangement of phenyl *o*-tolyl sulfone [222] has been shown to proceed via an addition-elimination pathway by isolation of the tricyclic intermediate. Both sites of deprotonation and addition are controlled by the sulfonyl group with contrapolarization at the second stage.



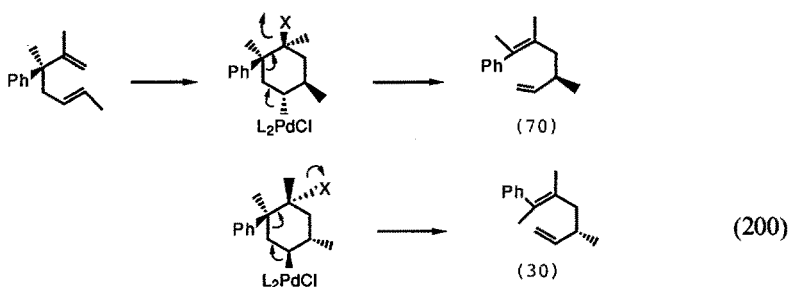
5.2 Sigmatropic Rearrangements

The Cope rearrangement is strongly accelerated when a polar group is placed at the allylic position of the 1,5-diene. Interestingly, both donors [223] and acceptors [224] are effective activators.

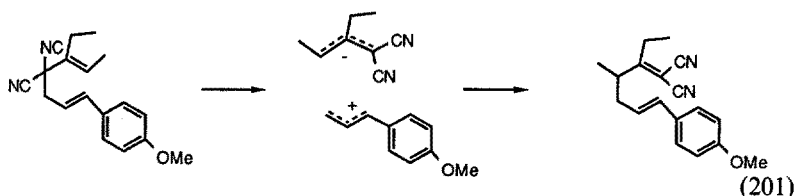




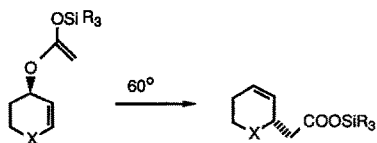
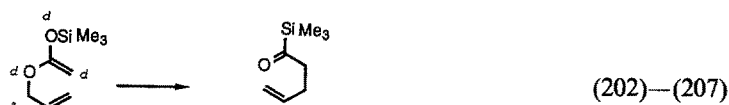
Pd(II)-catalyzed Cope rearrangement [225] occurs at room temperature, via chair-like transition states. A plausible mechanism is cyclization-induced rearrangement. Both the addition and fragmentation steps are assisted by the introduction and removal of, respectively, conjoint substituents. (Cf. Hg-salt catalyzed 1,3-transposition of allylic trichloroacetimidates [226]; for other transition metal-catalyzed Claisen rearrangement, see Ref. [227].



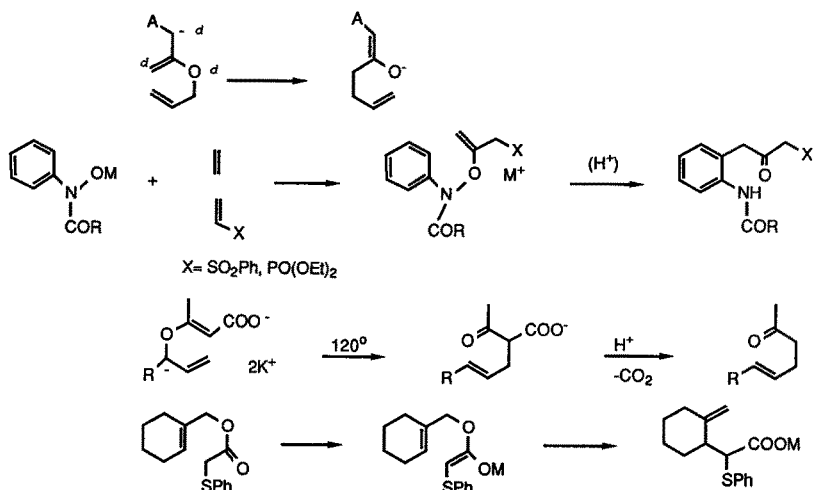
An extreme case of the Cope rearrangement proceeds via dissociation to an ion-pair [228]. Complementary donor and acceptor stabilization of the ionic species is the cause for this abnormal reaction.



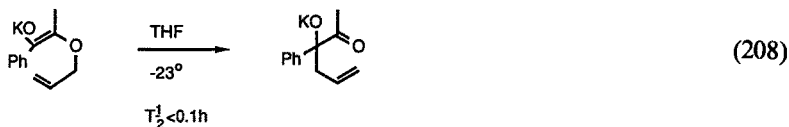
The Claisen rearrangement also benefits from a geminal donor to the framework oxygen atom [229]. This forms the basis of many synthetic applications. A newer version of the Claisen rearrangement is the carbanion-accelerated process [230]. It is noted that in all these cases the facilitation is always achieved by alternating polarity accentuation.



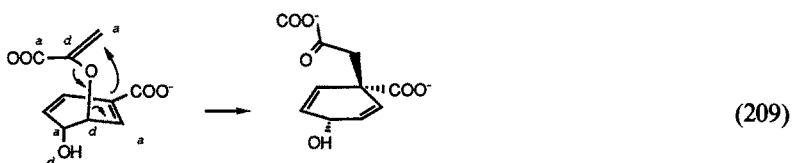
$$k[0] \approx 10\text{-}25 \times k[\text{CH}_2]$$



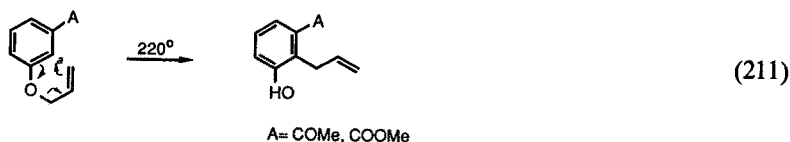
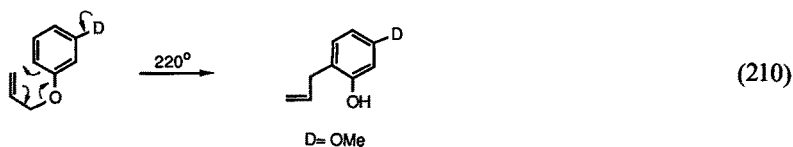
An apparent anomaly is the extremely efficient rearrangement of the enolates of α -allyloxy ketones [231]. It must be remembered that the disjoint enediolates suffer from an adverse electronic disposition and they would seek any relief.



A biochemically significant Claisen rearrangement is the transformation of chorismate into prephenate [232] via a chair transition state. Although it is impossible to settle the question of the direction of electron flow during the reorganization, that shown by the arrows in the formula should be preferred when the influence of the various substituents is considered.

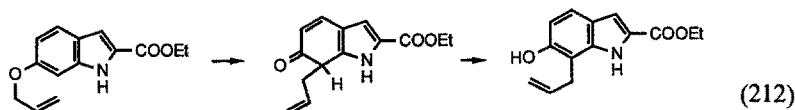


Concerning the aromatic Claisen rearrangement certain salient observations are summarized in the following equations [233].

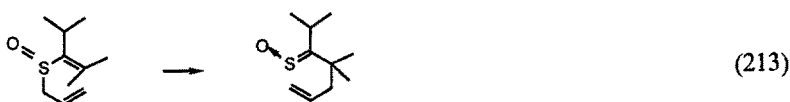


The *meta* substituent of the allyl aryl ether determines the major reaction terminus. Thus, a donor group favors the formation of 2,5-disubstituted phenol because in the transition state for the alternative sigmatropic rearrangement, allylic strain due to interference of the nuclear substituent and the CH₂ group develops. The rearrangement of the "electron-deficient" species might resemble nucleophilic aromatic substitution in terms of electron redistribution, and the sigma bonding occurs preferentially at the carbon closest to the acceptor group.

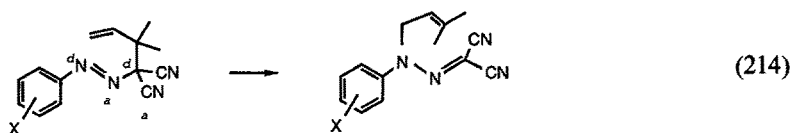
There are exceptions to this trend, as shown in the indole series [234]. The reason for this might be that the allyl migration to C-5 would forfeit all the aromatic stabilization.



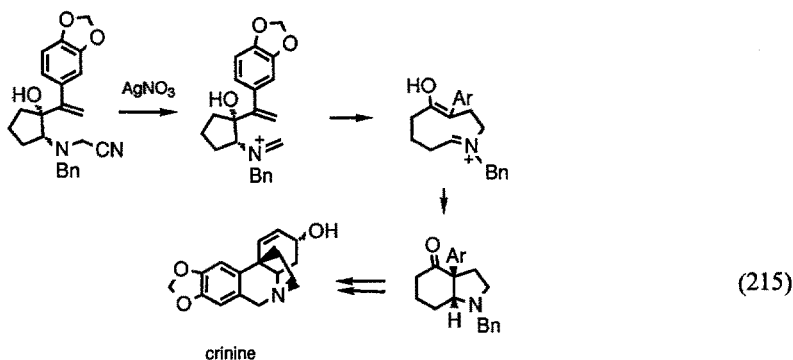
A 45-fold increase in the rearrangement rates of allyl vinyl sulfoxides relative to the corresponding sulfides has been observed [235]. The transition state for the former compounds is more polar.



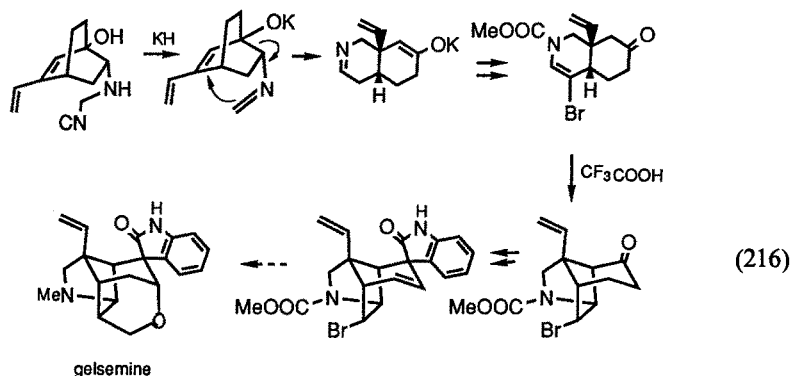
Cope rearrangement of arylazo-*t*-allylmalononitriles [236] shows rate acceleration by acceptor substituents in the phenyl ring. Again, a more polar transition state favors the reorganization.



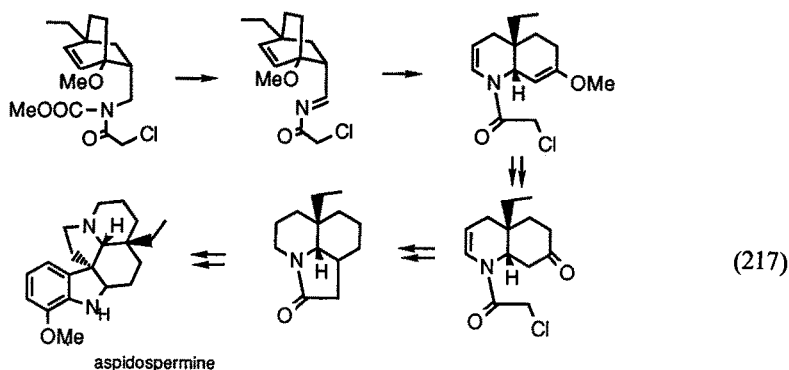
The enormous utility of a tandem aza/oxy-Cope rearrangement-Mannich cyclization is readily hinted by a neat synthesis of crinine [237]. The fragmentation as well as the C-C bond formation processes are orchestrated by the ideally situated hetero atoms.



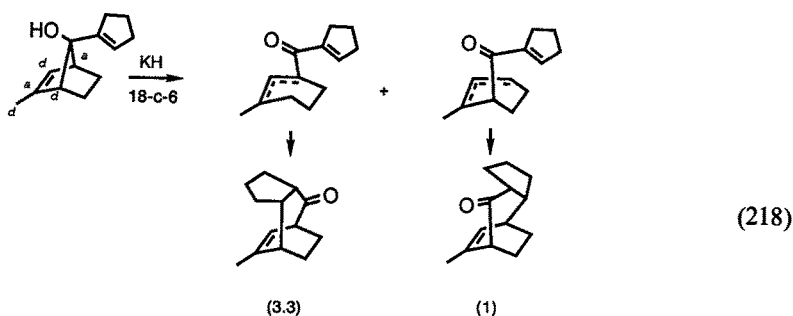
In an elegant approach to gelsemine [238] based on a similar strategy the cationic aza-Cope rearrangement was superseded by a simple Mannich reaction because the twistane skeleton is more highly strained. However, the desired transformation is achievable using the anionic version.



Another aza-Cope rearrangement which serves to elaborate a key intermediate of aspidospermine [239] may be mentioned. The distribution of functional groups facilitates the rearrangement as well as the subsequent cyclization.



The degree of regioselectivity in the rearrangement of 2-methyl-7-anti-cyclopentenyl-norborn-2-en-7-syn-ol [240] is perhaps unanticipated. The C-2 methyl group is responsible for the predominant generation of the allyl anion on which it has minimal electronic interaction.

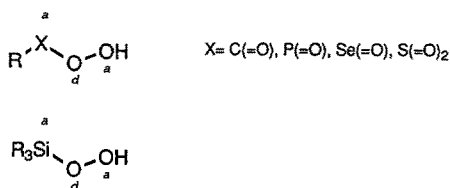


6 Redox Reactions

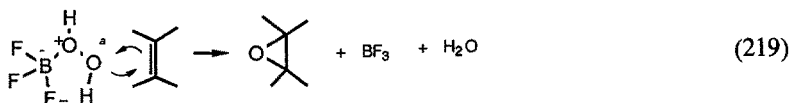
6.1 Oxidations

As a group the redox reactions are probably least well understood mechanistically. However, one common feature to all redox processes is the involvement of contrapolarization. Selected examples are discussed in this section concerning the effects of polar substituents on redox reactions.

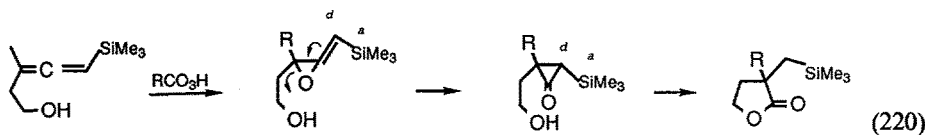
The ability of percarboxylic acids to transfer the terminal hydroxyl group as "HO⁺" to relatively weak donors such as alkenes is due to activation by the carbonyl via polarity alternation. As expected, other types of peracids with an acceptor heteroatom replacing the carbonyl behave similarly. Perhaps unanticipated by many chemists is the usefulness of Si as the C=O equivalent [241].



While hydrogen peroxide cannot be employed to epoxidize C,C double bonds, its combination with boron trifluoride is effective. Accentuation of polar character (in this case an acceptor) by an external agent through complex formation achieves the activation. Similar activation [242] of hydroperoxides by vanadium and titanium cations is now well known.



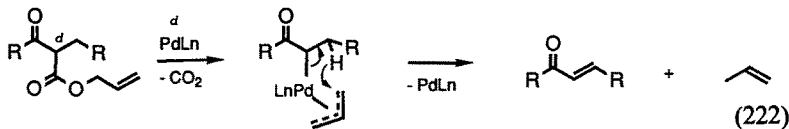
Epoxidation of silyllallenes [243] shown in the following equations is very interesting. In each case the unique direction of the cyclopropanone opening is governed by the silyl group which is conjoint with the carbonyl.



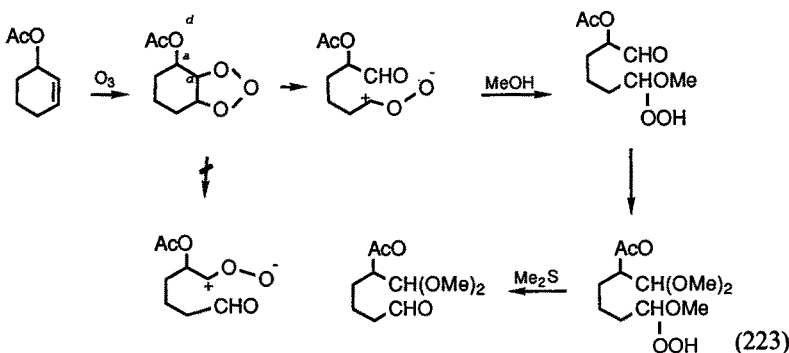
The difficult oxidation of α -oxy carbinols to α -oxy aldehydes has been experienced by many chemists [244]. One of the reasons might be the accentuation of the *a-a* inter-

action of the connecting carbon atoms. The situation worsens in the products.

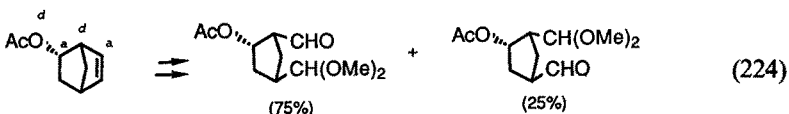
The synthesis of α,β -unsaturated carbonyl compounds and nitriles by Pd-catalyzed reaction [245] of allyl β -oxo esters and allyl α -cyano esters is an oxidative process. With the contra-polarizability of the metal ion, elimination of a hydride from the β -position is electronically favorable.



Ozonation of alkenes involves a cycloaddition-cycloreversion sequence. A synthetically significant differentiation of an alkene is shown below [246].



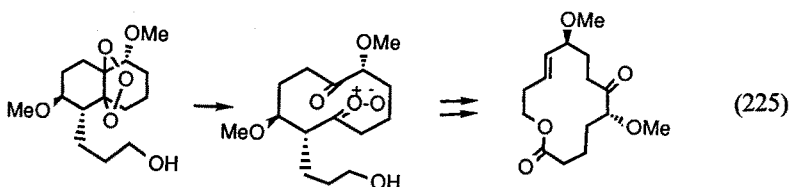
The electronic perturbation at the carbon of the primary ozonide by a proximal acetoxy group is that cycloreversion which gives rise to an intermediate with a more pronounced acceptor at the β position is disfavored. This effect is also manifested in 5-endo-acetoxynorborene, albeit in an attenuated fashion.



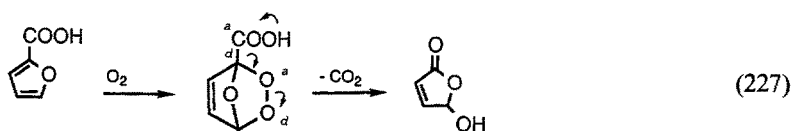
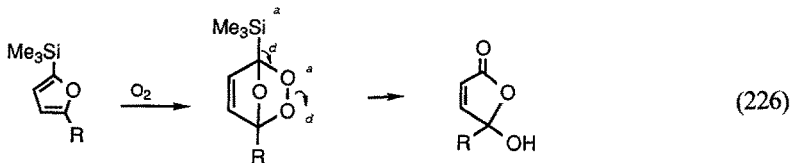
Note the donor group is now one carbon further apart and its influence on the nearest reaction center is in the opposite sense (polarity alternation). However, a through-space electronic interaction must be important also, as the *exo* isomer displays no selectivity.

The original investigators noted that the preferred mode of cleavage for 5-endo-acetoxynorborene is opposite to that predicted by the inductive effect consideration.

An application of the regiocontrol for ozonide decomposition by an allylic methoxy group (donor) is a macrolide synthesis [247].



Malaldehydic acid derivatives can be prepared regioselectively from 2-silylfurans by reaction with singlet oxygen [248]. Contrapolarization at the peroxy oxygen geminal to the silicon is involved, and ultimately the oxygen at the far end of the Si-C-O-O segment activates the Si-C bond cleavage. A carboxyl group serves the same purpose [249] as the silyl group.

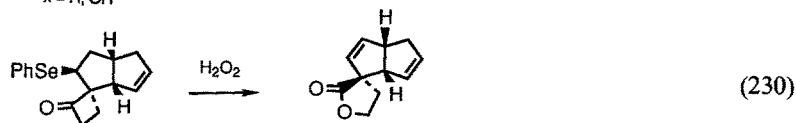
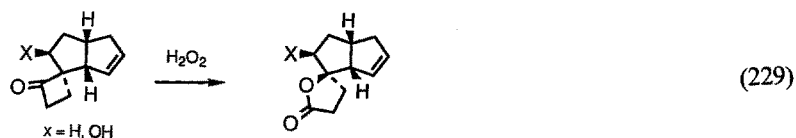


The Baeyer-Villiger oxidation of 3-trimethylsilylcyclohexanone [250] is regioselective as indicated. The reason for the selectivity is electronic which is revealed by an examination of the relationship between the polar groups of the ketone. Here we find a disjoint sequence, the α and β carbon atoms are both quasideficient as dictated by their respective neighbors. The observed rearrangement, but not the alternative mode, relieves the unfavorable electronic interactions.

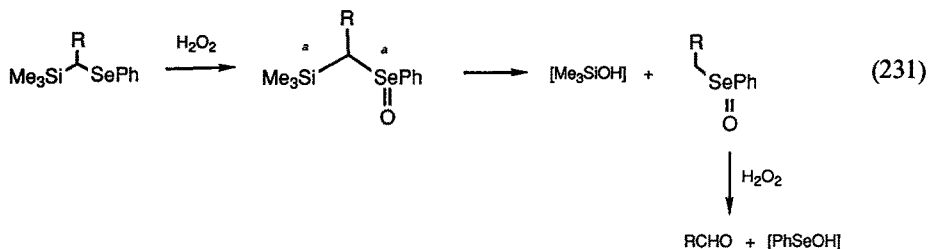


Many syntheses of natural products [251] have emerged taking advantage of this newly discovered electronic control.

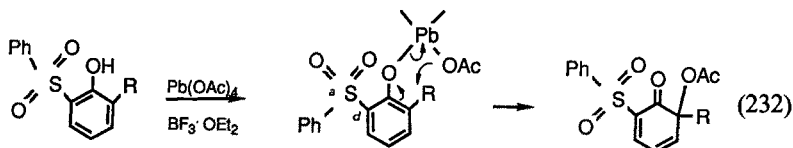
It is interesting to discern the different migratory aptitudes displayed by spirocyclic ketones on exposure to hydrogen peroxide [252] (Eq. 226, 227). Although participation of the selenium atom to direct the attack of the peroxide has been formulated, the results are also consistent with an electronic explanation. Thus, the rapid formation of selenoxide renders the spirocyclic center acceptor-like through polarity alternation, and the migration of the methylene group becomes more favorable.



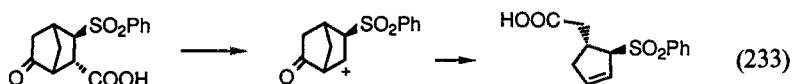
Oxidation of an α -silyl selenide with hydrogen peroxide leads to an aldehyde, silanol and selenol as the primary products [253]. Evidently, the fragmentation proceeds only after contrapolarization at Se, the intermediate now having an *a-d-a* array.



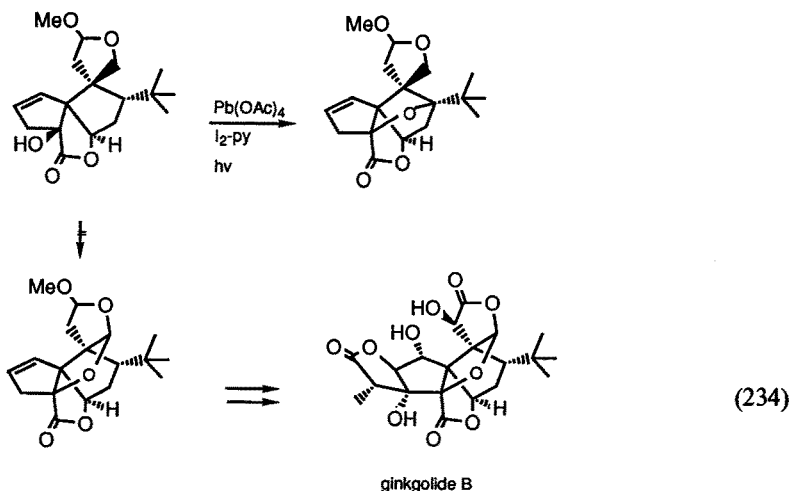
The Wessley acetoxylation of phenols is under regiocontrol when a sulfonyl group is present in one of the *ortho* positions [254]. The same *ortho* carbon, imbued with considerable donor character, is more reluctant to receive the nucleophile AcO^- .



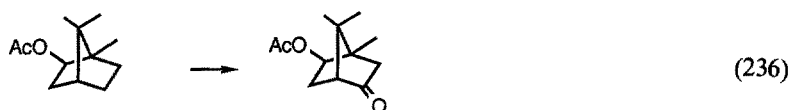
Anodic oxidation of a carboxylic acid generates a carbenium ion at the α -carbon. This contrapolarization enables a facile fragmentation of γ -keto acids [255].



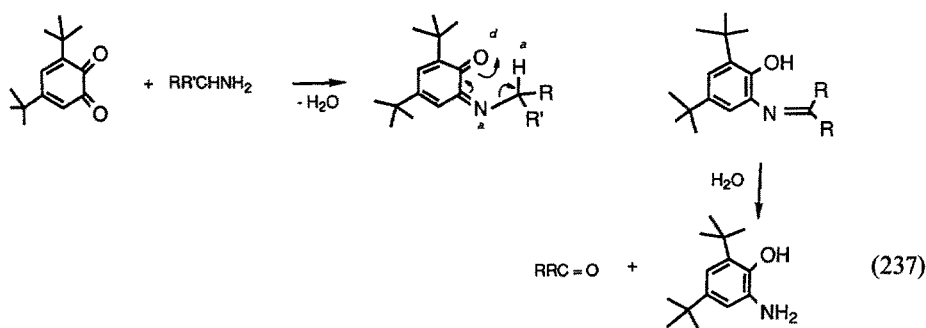
In a brilliant synthesis of ginkgolide B [91], it was planned to construct the tetrahydrofuran ring by a remote oxidation of a tertiary alcohol with a lead tetraacetate-iodine combination. However, an isomeric ring structure emerged. The non-occurrence of the desired reaction may be due to the resistant ethereal oxygen which discourages its α -carbon to assume a donor role. Although the reaction is essentially homopolar, it seems that a slight degree of polar characteristics has an enormous effect. In this case a negative influence on a proximal atom diverts the reaction site.



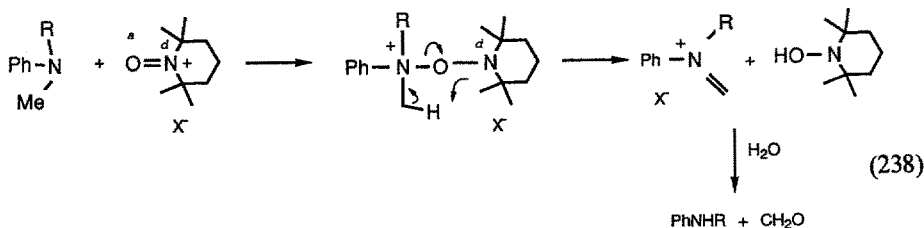
Despite the mechanistic obscurity of C-H bond oxidation by chromic acid, regioselectivity has been discerned in well defined systems [256]. For example, oxidation of *endo*-fenchyl acetate and the bornyl acetates (*exo* and *endo*) gives ketones in which the new carbonyl group is derived from a donor carbon.



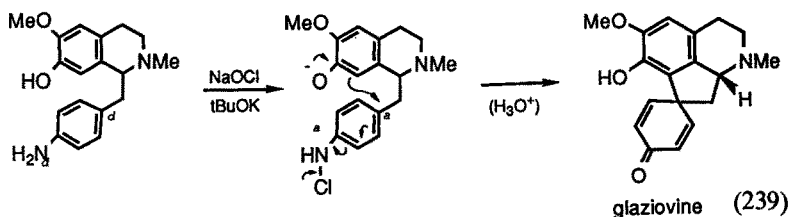
The oxidative deamination mediated by 3,5-di-*t*-butyl-*o*-quinone [257] could very well involve a C → O 1,5-sigmatropic hydrogen shift within the Schiff base network. This process in essence accomplishes oxidation of the amine and reduction of the quinone. The interesting point is the strong donor oxygen forces the nitrogen atom into an acceptor role during the reaction.



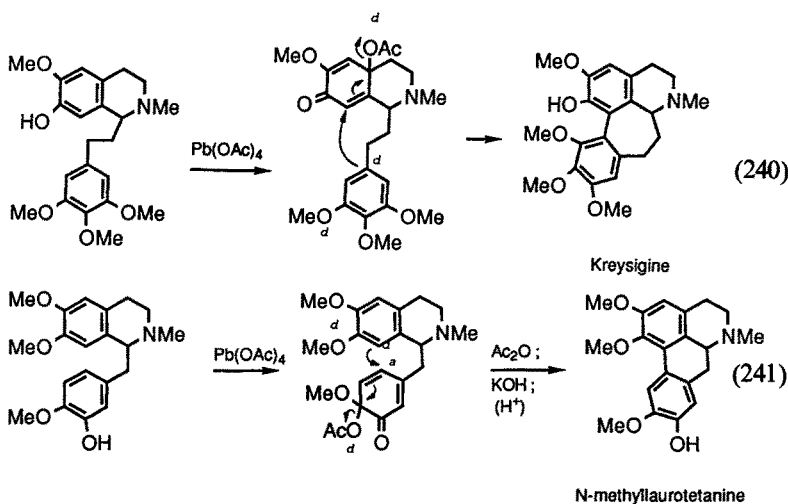
Oxidative demethylation of *N*-alkyl-*N*-methylanilines with nitron [258] proceeds via intermediates having a N-O-N subunit. A [2.3]sigmatropic rearrangement leads to the decomposition.



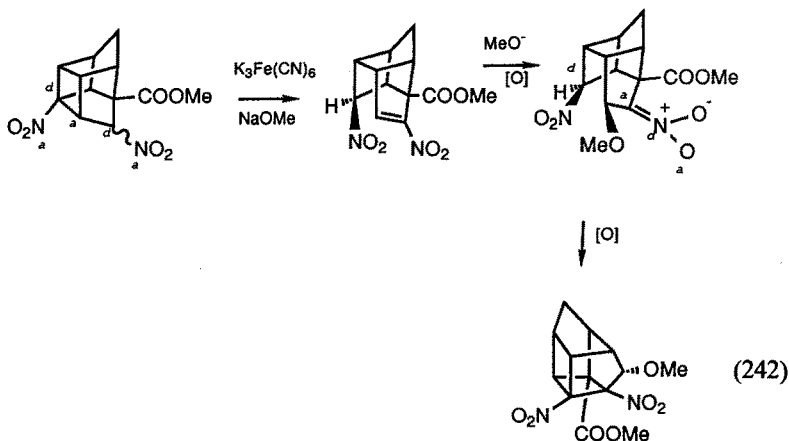
A synthesis of glaziovine [259] via oxidative phenol-aniline coupling involves contrapolarizing activation of the aromatic carbon para to the amino group.



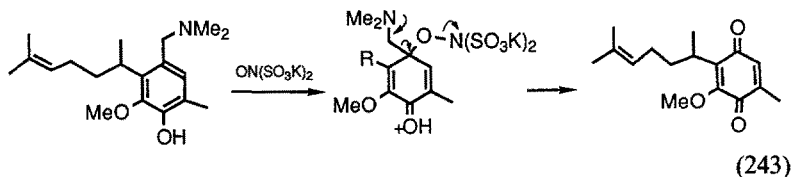
Other types of remote activation are illustrated in the syntheses of kreysigine [260] and *N*-methylaurotetanine [261].



An unexpected rearrangement of a 1,3-bishomocubyl ring system [262] accompanies an attempted nitration. The oxidative conditions are requisite for the transformation of a 1,3-dinitro substitution pattern to one with a disjoint polarity sequence (contrapolarization involved). The unusual contrathermodynamic reaction is allowed to occur because of the special steric confinement of the functionalized carbon atoms. The initial fragmentation and Michael addition are also set up by the proper disposition of the nitro groups.



Fremy's salt has been used to degrade a *p*-hydroxybenzylamine [263]. Aminoxylation at the *para* position of the phenol triggers fragmentation; the C-O bond formation gives rise to a conjoint 1,3-disubstituted system, despite contrapolarization at the intervening oxygen atom is required.

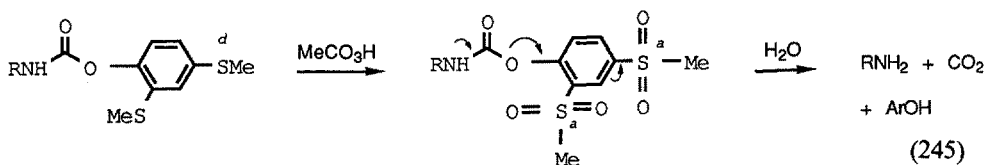


Succinic acids undergo bisdecarboxylation on exposure to lead tetraacetate [264]. Contra-polarization at one of the α -carbons through fragmentation of the lead(IV) carboxylate moiety enables a smooth decarboxylation of the remaining functionality.

In the presence of a juxtapositional double bond such succinic acids could form dilactones [265]. The ethereal oxygen of the lead(IV) carboxylate intermediate acts as an acceptor in this instance.



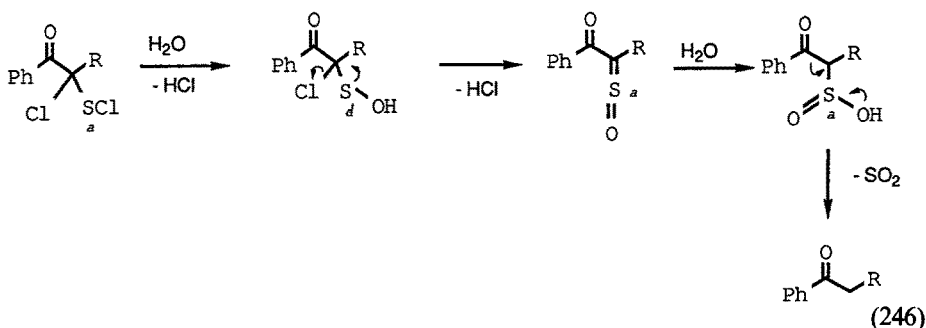
Protection of amino compounds by the 2,4-bis(methylthio)phenoxy carbonyl residue [266] converts them into acid stable entities. Removal of the protecting group can be achieved through oxidation at sulfur such that the resulting bisulfone provides conjoint pathways for ready fragmentation.



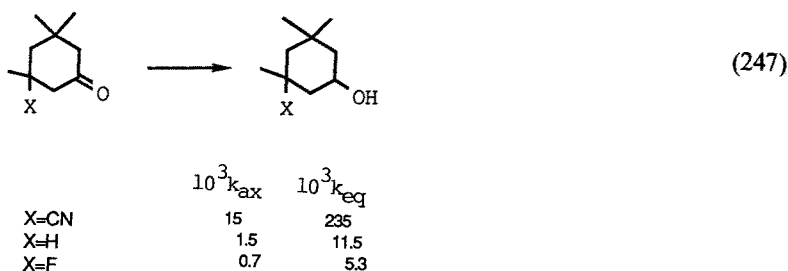
6.2 Reduction

The facilitation of the C-halogen bond reduction by a neighboring carbonyl group is due to the imposed donor character of the α -carbon, and by extension, the heightened acceptor character of the halogen atom.

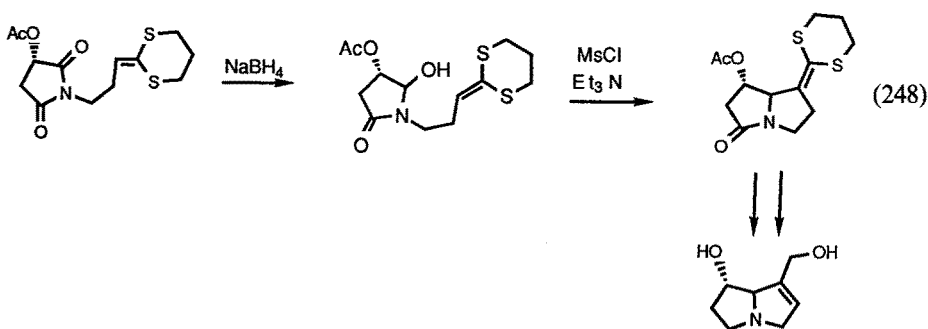
There is a net reduction of α -chlorosulfonyl- α -chloroketones under hydrolytic conditions [267]. The sulfur atom undergoes a series of contrapolarizing changes (*a-d-a*). The carbonyl group also plays a crucial accentuation role in the various steps of the reaction.



Hydride reduction of 3,3,5-trimethylcyclohexanone and its 5-substituted analogues exhibits a rate dependence on the substituent [268]. There is rate enhancement and rate retardation, respectively, with an acceptor and a donor. Enhancement is due to the existence of a stabilizing *d-d* bonding situation between the α - and β -carbon atoms, retardation might reflect a reluctance of the molecule to diminish a polarity alternating sequence.

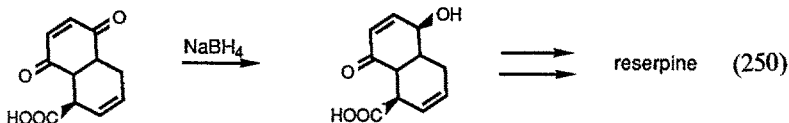
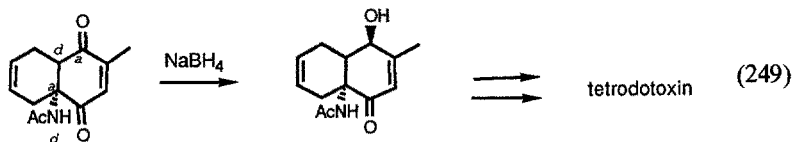


Regioselective reduction of a succinimide intermediate for a (+)-heliotridine synthesis [269] must be due to the influence of the acetoxy group. It is conjectured that the *a-a* array of the intervening carbon atoms activates the carbonyl. Steric effects should be minimal on the choice of the two sites.

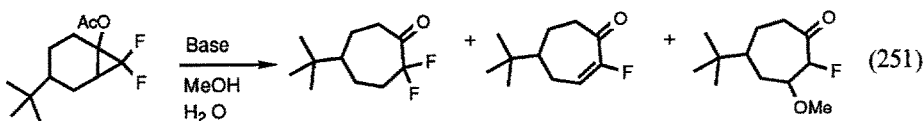


It is tempting to speculate the contribution of the remote polar substituent to the regioselective reduction of the endione intermediates employed for the syntheses of tetrodotoxin [270] and reserpine [271]. Without disregarding the steric hindrance of the substituent in each case to the proximal carbonyl, the disjoint relationship of which to

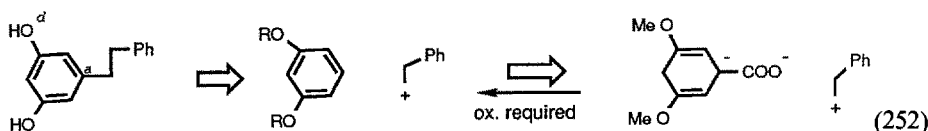
the substituent is noted. The increased donor character of this proximal carbonyl may also be translated into a lesser reactivity.



2,2-Difluorocyclopropyl esters behave quite differently from other halo analogs under solvolytic conditions [272]. The formation of 2,2-difluorocarbonyl compounds which emerges as an important pathway, may be considered as an internal redox process. The diminished significance of the concerted dehalogenative ring opening is due to the high strength of the C-F bond and the stabilization of the carbanion by the fluorine atoms via a polarity alternation mechanism.



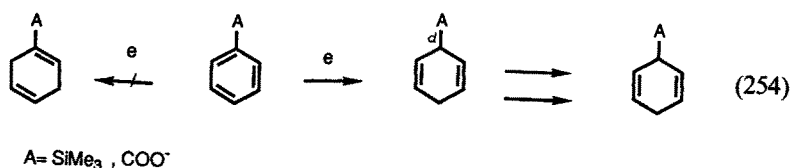
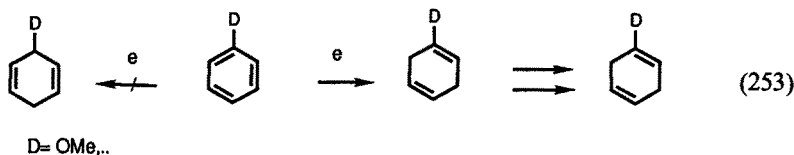
It may be difficult to imagine the alkylation of a 3,5-dialkoxyphenylcarbanion in which no ortho chelators are available to assist deprotonation at the desired position, not to mention the disjoint relationship of this donor carbon to the oxy substituents present. A solution to this problem is provided by redox manipulations and incorporation of a removable acceptor group to affirm the donor site. Thus, the Birch reduction product of 3,5-dimethoxybenzoic acid readily undergoes alkylation, and oxidative decarboxylation generates the aromatic compound [273].



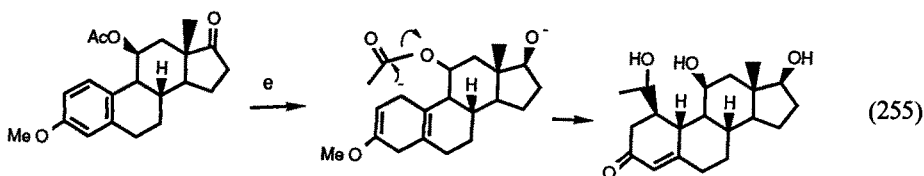
Two points are noteworthy. Birch reduction (and all other redox processes) always affords unpoled species; restoration of the original state must involve a reverse reaction (i.e. oxidation).

Perhaps it should be mentioned also the orientation of the Birch reduction which is strongly dependent on the nature of the aromatic substituents. Donor-substituted benzenes furnish predominantly 1-substituted 1,4-cyclohexadienes while acceptor-substituted analogues give 3-substituted 1,4-cyclohexadienes. The regioselectivities can be explained by the destabilizing *d-d* pairing in the intermediates from *d*-substituted cyclohexadienyl radical anions leading to the 3-substituted products, and the

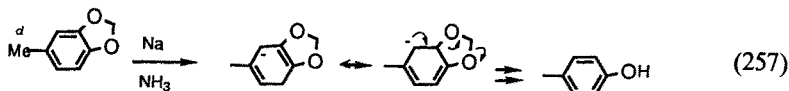
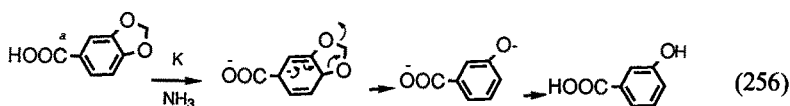
stabilizing effect of an *a-d* pairing in the *a*-substituted intermediates of the same pattern.



As a further illustration of the regiochemistry associated with the Birch reduction of anisole derivatives, 11 β -acetoxy-*O*-methylestrone [274] offers an interesting case.

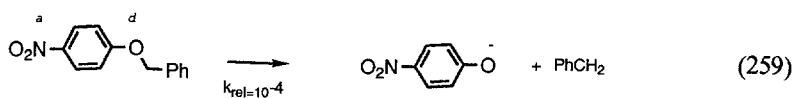
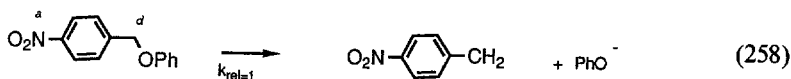


Cleavage of alkyl aryl ethers with sodium or potassium metal shows excellent regioselectivity [275]. Using limiting radical anion structures to analyze the results and noting the preference for such structures as dependent on the substituents, it is possible to formulate reaction pathways leading to the observed products.



It should be emphasized that, in piperonic acid, for example, the leaving oxygen is conjoint with the dominating acceptor (COO), and fragmentation as shown can only occur when contrapolarization intervenes.

Perhaps another set of reactions showing the pronounced effect of contrapolarization pertaining to redox processes should be discussed. In the following equations the relative rates for ether cleavage are indicated. Note the undesirable positioning of the ethereal oxygen in the two substrates. In *p*-nitrophenyl benzyl ether particularly, heterolysis is against natural polarity alternation, and only through contrapolarizing conditions is the alkyl C-O bond scission possible, albeit with great sluggishness.



7 Conclusions

In view of the extensive documentation outlined above, the usefulness of the polarity alternation concept as a primary guide for evaluation of substituent effects can hardly be denied. The influence of a substituent on the *ipso* site has not been discussed in this article but an even more direct and important effect is implicit. Among the innumerable examples one may cite the preferential formation of geminal dimetallic species [5] in hydrometalation and carbometalation of vinylmetals and acetylenes. On the other hand, chemical systems are usually very complex, inter- and intramolecular forces including steric and stereoelectronic factors may dominate over polarity alternation. Thus, chelation by a proximal donor often directs metalation and stabilizes certain organometallic entities. In these instances the stability gaining from polarity alternation is overwhelmed.

The sensible approach to employing the polarity alternation concept is to be flexible. When applied correctly to a reactivity problem the failure of PAR should elicit a deeper and more detailed analysis. New facets of an organic system may be revealed.

In a previous article [8] a brief review of bifunctional chains of atoms with respect to their reactivities and modes of formation was presented. Consequently, the polarity concept is of some value to systematization of organic reactions and it should be helpful to planning synthesis.

8 References

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