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Metalation of Azoles and Related Five-Membered Ring Heterocycles

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29
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Metalation of Azoles and Related Five-Membered Ring Heterocycles

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Aims and Scope

The series *Topics in Heterocyclic Chemistry* presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community. The series consists of topic related volumes edited by renowned editors with contributions of experts in the field.

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Example:
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Dedicated to Professor Lloyd J. Dolby for sharing his love of organic chemistry, for his faithful commitment to his students, and for introducing me to the captivating field of indole chemistry.

Preface

This volume consists of 11 chapters covering the metalation of azoles and related five-membered ring aromatic heterocycles. Given that metalation reactions are currently an extremely important synthetic method in all of organic chemistry, the present volume is very timely. Notably absent is a chapter dealing with the "Metalation of Indole," which was covered in "Topics in Heterocyclic Chemistry" (2010), Vol. 26, *Heterocyclic Scaffolds II: Reactions and Applications of Indoles.*

In Chap. 1, Kishbaugh presents the "Metalation of Pyrrole" with applications to natural products and important materials and dyes.

In Chap. 2, "Furans and Benzofurans," Yeung discusses the metalation chemistry of these oxygen heterocycles and related furo-heterocycles.

In Chap. 3, "Lithiation- and Magnesation-Based Strategies for the Functionalization of Imidazole: 2001-2010," Alford summarizes the metalation chemistry of this important heterocycle.

In Chap. 4, Fu discusses the "Metalation of Oxazoles and Benzoxazoles" coverage that also includes the synthesis of these heterocycles involving metalation strategies.

In Chap. 5, Roy, Roy, and Gribble review the "Metalation of Pyrazoles and Indazoles," including the application to the synthesis of pharmaceutical agents.

In Chap. 6, Badenock reviews the "Metalation Reactions of Isoxazoles and Benzisoxazoles," including coverage of direct metalation, halogen-metal exchange, and Grignard formation.

In Chap. 7, "Thiazoles and Benzothiazoles," Wu highlights the metalation of these ring systems and illustrates the power of metalation in total synthesis.

In Chap. 8, Nutaitis presents the metalation chemistry of "Isothiazoles and Benzisothiazoles," including both benz[*c*]isothiazoles and benz[*d*]isothiazoles.

In Chap. 9, Biehl reviews the "Recent Advances in the Synthesis of Thiophenes and Benzothiophenes" mainly in the context of metalation chemistry.

In Chap. 10, Lopchuk details the metalation of "Mesoionics," which are fascinating aromatic heterocycles that include sydnones, münchnones, and isomünchnones.

In Chap. 11, Lopchuk concludes this volume with the metalation of "Azoles with 3–4 Heteroatoms," which include triazoles, tetrazoles, and oxadiazoles.

I am indebted to my authors for their truly outstanding contributions to what I believe is a timely and important addition to the chemistry of azoles. I particularly

thank my former students (Badenock, Kishbaugh, Alford, Fu, Roy, Roy, and Nutaitis) and one current student (Lopchuk) for their willingness to participate in this endeavor, and my heterocyclic colleagues and friends (Wu, Yeung, and Biehl) for their equally hard work. I especially thank my series editor Bert Maes for the opportunity to be the editor of this volume.

Hanover, New Hampshire Gordon W. Gribble
2012

Contents

Metalation of Pyrrole 1
Tara L.S. Kishbaugh

Furans and Benzofurans 47
Kap-Sun Yeung

Lithiation-Based and Magnesation-Based Strategies for the Functionalization of Imidazole: 2001–2010 77
Philip E. Alford

Metalation of Oxazoles and Benzoxazoles 103
Liangfeng Fu

Metalation of Pyrazoles and Indazoles 155
Sudipta Roy, Sujata Roy, and Gordon W. Gribble

Metalation Reactions of Isoxazoles and Benzisoxazoles 261
Jeanese C. Badenock

Thiazoles and Benzothiazoles 307
Yong-Jin Wu

Isothiazoles and Benzisothiazoles 329
Charles F. Nutaitis

Recent Advances in the Synthesis of Thiophenes and Benzothiophenes 347
Edward R. Biehl

Mesoionics 381
Justin M. Lopchuk

Azoles with 3-4 Heteroatoms 415
Justin M. Lopchuk

Index 441

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Metalation of Pyrrole

Tara L.S. Kishbaugh

Abstract Metalation reactions of pyrrole and indolizine are reviewed. While the use of pyrrole-based materials in the Suzuki reaction is increasingly popular, several examples of other palladium-catalyzed reactions, such as Negishi, Stille, Sonogashira, and Heck couplings, are included. In addition to these palladium-catalyzed cross-coupling reactions, direct proton abstraction, directed metalation, and halogen–metal exchange are discussed. Applications of these reactions to synthesis of pyrrole natural products and other interesting materials such as BODIPY dyes are summarized.

Keywords Directed metalation · Halogen–metal exchange · Heck · Lithiation · Negishi · Palladium · Pyrrole · Sonogashira · Stille · Suzuki

Contents

1 Introduction 2
2 Direct Metalation at the Nitrogen 2
2.1 Base Removal of H 2
2.2 Catalyzed *N*-Arylation 3
3 Direct Metalation at C-2 7
3.1 Pyrrolyl Grignards 7
3.2 Cadmium 9
3.3 Zinc 9
3.4 Lithium 11

T.L.S. Kishbaugh (✉)
Eastern Mennonite University, 1200 Park Road, Harrisonburg, VA 22802, USA
e-mail: tara.kishbaugh@emu.edu

4 Metal–Halogen Exchange 16
4.1 Lithium or Magnesium at C-2 or C-5 16
4.2 Lithium or Magnesium at C-3 or C-4 17
5 Palladium Cross-Coupling Reactions of Pyrroles 18
5.1 Stille 18
5.2 Sonogashira 21
5.3 Negishi 22
5.4 Heck 23
5.5 Suzuki with Halopyrroles 26
5.6 Suzuki with Pyrrolyl Triflates 34
5.7 Suzuki with Pyrrole Boronic Acids/Esters 35
5.8 Suzuki Reaction of Indolizines 41
5.9 Other Palladium-Catalyzed Reactions 42
References 43

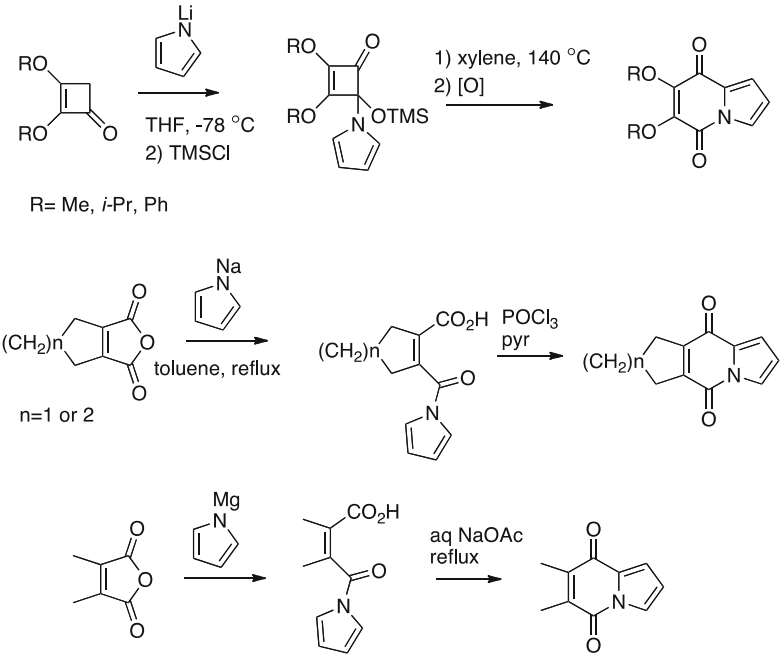
1 Introduction

Metalation reactions are increasingly popular and powerful tools for the organic chemist during the past decades. Metalation of pyrrole has been widely studied as means of preparing complex natural products or other interesting materials, such as probes for calcium or fluoride [1–3]. The use of palladium-catalyzed reactions of pyrrole has also been reviewed several times [4–9]. While numerous examples of direct C–H activation on pyrroles exist, these reactions are beyond the scope of this review [10–12].

2 Direct Metalation at the Nitrogen

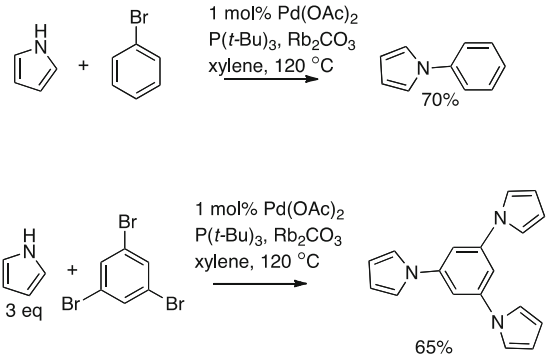
2.1 Base Removal of H

The well-known *N*-lithio, magnesio, or sodium pyrrole salts were employed in two different routes to produce indolizine-5,8-diones in order to study their herbicidal activity [13]. In the first method, 6,7-dialkoxy-substituted indolizine-5,8-diones were formed; in the second, indolizine-5,8-diones with a ring fused at 6,7 were accessed.



2.2 *Catalyzed* N-*Arylation*

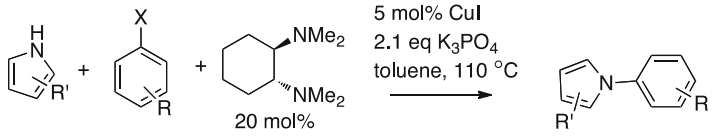
Increasing interest has been shown in the Ullmann coupling of *N*-heterocycles to form *N*-aryl azoles, for their possible application in organic light emitting diodes or as biologically active compounds. Palladium-catalyzed *N*-arylation has been successful on pyrrole when Rb_2CO_3 is used as the base. A triple arylation reaction is also possible if 3 equivalents of pyrrole are used with 1,3,5-tribromobenzene [14].

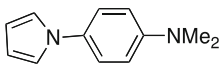
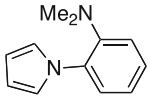
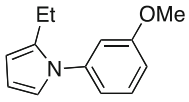
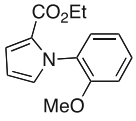
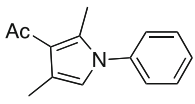


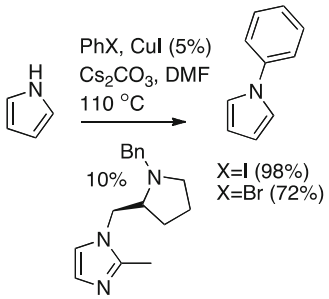
The copper-catalyzed *N*-arylation reaction works well on a number of aryl bromides or halides with the diamine ligand shown in Table 1 [15, 16]. Less expensive ligands resulted in lower yields. The substitution pattern on the aryl halide appears to be unimportant (entries 1 and 2 or 3 and 4), as does the electron withdrawing or donating nature of substituents on both the pyrrole and the aryl halide (entries 1–4). While some steric constraints are tolerated, a 2,6-disubstituted aryl iodide was too hindered to react with pyrrole. However, a trisubstituted pyrrole (entry 5) will undergo *N*-arylation albeit more slowly and only with a large excess of the aryl halide (neat aryl halide, no solvent).

Another ligand, a pyrrolidinylmethylimidazole, provided catalytic copper(I) iodide *N*-arylation of nitrogen heterocycles under similar conditions [17].

Table 1 Copper-catalyzed *N*-arylation of pyrrole with a diamine ligand

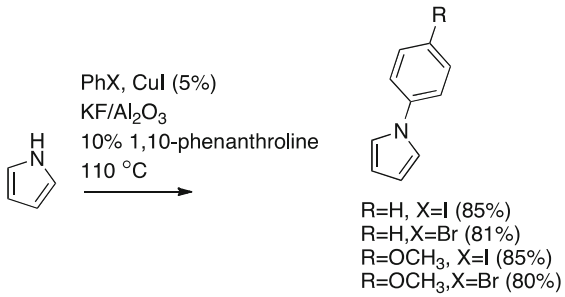


Entry	X	Product	%Yield
1	Br		94
2	Br		83
3	I		84
4	I		96
5	I		92



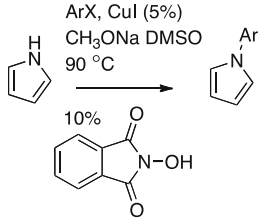
N-Hydroxyimides are also efficient ligands for catalytic copper(I) iodide-catalyzed *N*-arylation of nitrogen heterocycles [18]. This method is tolerant of a range of functional groups on the aryl halides, such as nitrile, nitro, and free amines. Bromides and chlorides reacted more slowly than the iodides (Table 2).

Copper-catalyzed arylation of nitrogen heterocycles using potassium fluoride on alumina as the base works with both aryl iodides and bromides [19].

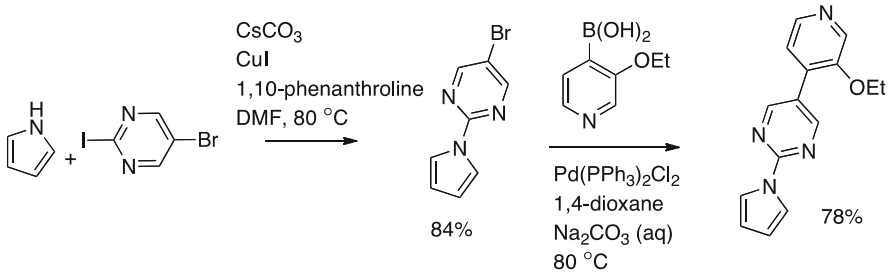


Sequential copper-catalyzed arylation and Suzuki coupling provide a quick route to a number of tris(hetero)aryl systems [20]. The two reactions can even be carried out in one pot.

Table 2 Copper-catalyzed *N*-arylation of pyrrole with a hydroxyimide ligand

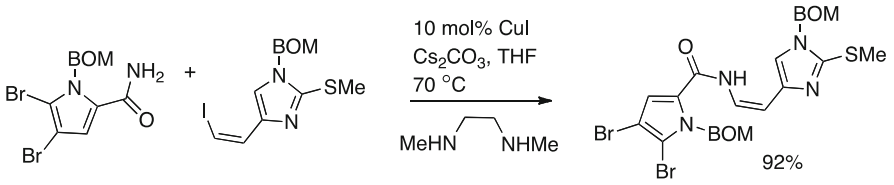


Entry	Aryl halide	%Yield
1	Iodobenzene	97
2	4-Iodoanisole	93
3	*p*-Chloronitrobenzene	45
4	*p*-Chlorotrifluoromethylbenzene	45



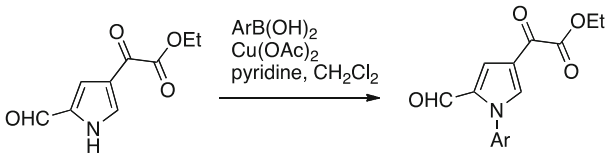
In the development of an antiangiogenic drug (Table 3, entry 5), an easy approach to *N*-arylpyrroles was needed [21]. Electron-deficient pyrroles coupled with arylboronic acids in the presence of stoichiometric amounts of copper(II) acetate. Electron-releasing groups such as methoxy (entry 1) on the arylboronic acid decreased reaction time (from 8 days to 2). Sterics appears to limit the reaction progress (entry 2). For unclear reasons, heteroaryl boronic acids (entry 4) did not couple well.

Weinreb and Meketa also employed this strategy to coupling the amide of a side chain on pyrrole to a vinyl iodide as part of a biogenetically modeled approach to Ageladine A [22, 23].



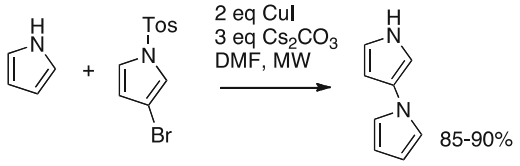
Finally, a copper-catalyzed *N*-arylation approach was also employed as part of the total synthesis of (±)marinopyrrole A [24]. Amination of the model system, 3-bromo-*N*-tosylpyrrole, by pyrrole was optimized with the use of microwave irradiation and an excess of copper iodide. However, when these conditions were used

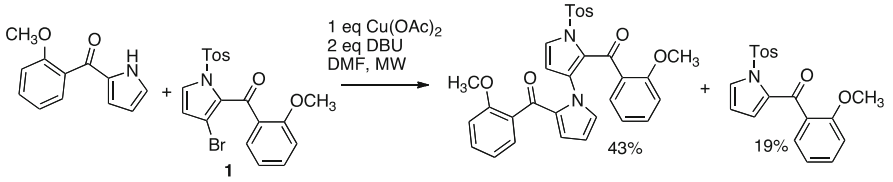
Table 3 Copper-catalyzed *N*-arylation of a pyrrole with arylboronic acids



Entry	$ArB(OH)_2$	Time (days)	%Yield
1	4-Methoxyphenylboronic acid	2	95
2	2-Methoxyphenylboronic acid	2	14
3	4-Acetylphenylboronic acid	8	91
4	3-Thienylboronic acid	4	44
5	4-(4′-Cyanophenyl)phenylboronic acid	3	93

on the ketopyrrole **1** only 20% of the product was formed with a large amount of unreacted starting material. Increasing reaction time did not improve the yield. Eventually, changing the copper source and base provided the desired product in moderate yield (43%) with some dehalogenation (19%).

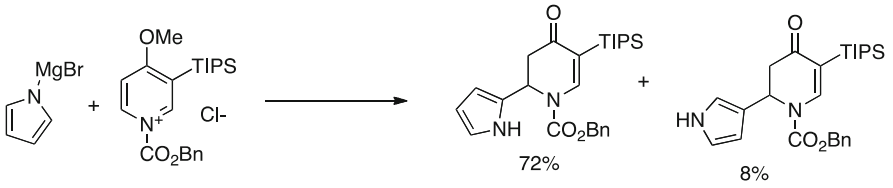




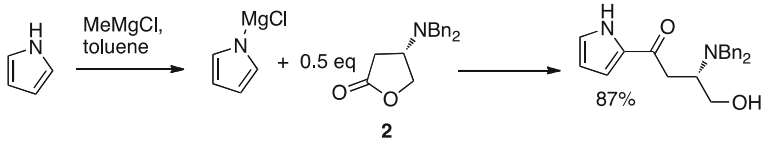
3 Direct Metalation at C-2

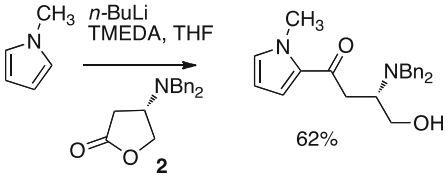
3.1 Pyrrolyl Grignards

The Grignard reagent formed from pyrrole is known to react at both C-2 and C-3 [25]. The addition of a pyrrolyl Grignard reagent to acylpyridinium salts proceeds smoothly as long as the Grignard reagent is preformed [26]. The resulting mixture was easily separated.



A chiral approach to dopaminergic tetrahydroindoles employed the addition of either magnesiopyrrole or lithiopyrrole to the dibenzylamino-substituted lactone **2** [27].





Because the *N*-sulfonylpyrroles are easier to handle than the unprotected version, Dinsmore examined their magnesiation with *i*-propylmagnesium chloride and catalytic amounts of diisopropylamine [28]. Without the presence of the amine, no product (in this case, the 2-iodopyrrole) was detected; an alternate Grignard reagent (PhMgCl) or amine (diethylamine) was not effective. The magnesiopyrrole reacted with a variety of electrophiles, including TMS-OTf but not the chloride. Formation of the boronic acid with either trimethyl or triisopropylborate was also not successful (5% product isolated) (Table 4).

Additionally, the magnesiopyrrole was found to undergo Kumada coupling with iodobenzene to form the biaryl in good yield (73%); however, attempts to couple the magnesiopyrrole with heteroaryl halides (2-chloropyridine, 2-bromopyridine, and 2-iodopyridine) were not successful unless a submolar equivalent of zinc chloride was added [28]. With the additional zinc, the magnesiopyrrole coupled to 2-chloropyridine (24%, 54% with recovered starting material) and 2-chloroquinoline (32%, 44% with recovered starting material).

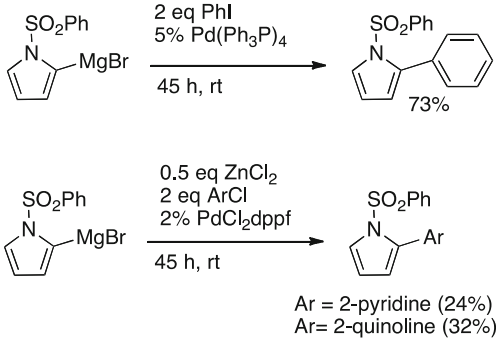
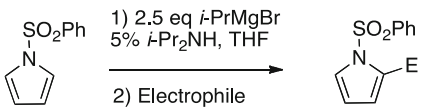


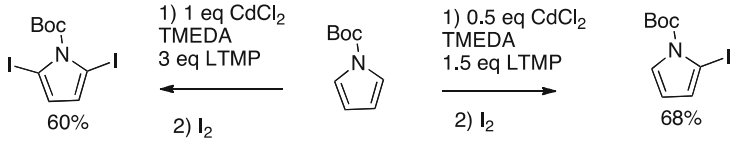
Table 4 Reaction of pyrrolyl Grignard reagent with different electrophiles



Electrophile	E	%Yield
TMS-OTf	TMS	57
Allyl bromide	$CH_2CH{=}CH_2$	52
γ-Butyrolactone	$CO(CH_2)_3OH$	52
Acetone	$C(CH_3)_2OH$	45
Benzaldehyde	CHOHPh	57

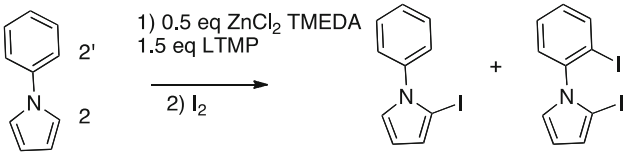
3.2 Cadmium

While organocadmium reagents are often prepared by transmetalation or halogen–metal exchange, *N*-Boc pyrrole, as well as other aromatics, can be deprotonated by a mixture of cadmium chloride and LTMP [29]. The formation of the iodopyrrole was as efficient as the procedure using $ZnCl_2$TMEDA and LTMP. The pyrrole could also be dimetalated in moderate yields.



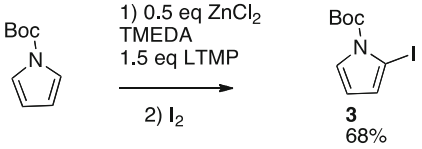
3.3 Zinc

N-Phenylpyrrole can be metalated at the 2 and 2′ sites. Kinetic conditions with TMEDA activated butyllithium provide the dimetalated pyrrole; whereas thermodynamic conditions provide the 2-monolithiated pyrrole [30]. The lithium-mediated metalation of *N*-phenylpyrrole with zinc has been optimized by examining the effect of solvent, equivalents of base, reaction time, and temperature on the conversion and selectivity. When *N*-phenylpyrrole is treated with $ZnCl_2$·TMEDA (0.5 equivalent) and LTMP (1.5 equivalents) in THF at room temperature, incomplete metalation (56%) and lack of selectivity (86: 14, 2-iodo and 2,2′-diiodo after quenching) was observed. Other solvents, such as diethyl ether, toluene, and hexane, also gave poor conversion (17–38%) but selectivity increased. By increasing the amount of TMEDA (0–5 equivalents) the conversion in hexanes could be increased (23–92%), but this effect was not seen in other solvents. Two days were necessary to obtain the most complete and selective metalation of *N*-phenylpyrrole in hexane; moreover, the zincated pyrrole was stable for days at room temperature. Dimetalation in hexane was found to occur at temperatures higher than 40°C. A synergistic effect between both THF or DME and TMEDA was not observed; in fact in both situations a low conversion was found (18% and 4%).



This method of deprotonation works for other nitrogen-protecting groups. Normally, *t*-butyllithium is not appropriate for deprotonation of *N*-Bocpyrrole;

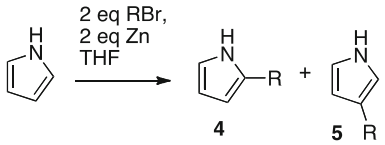
LTMP will selectively deprotonate the pyrrole and provide the iodide **3** in 68% yield without degradation [31].

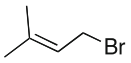
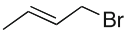
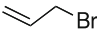
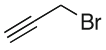


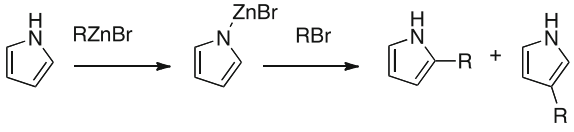
N-Methyl pyrrole can also be zincated at C-2 using TMEDA Na(*t*-Bu)(TMP)Zn (*t*-Bu) avoiding lithium reagents [32].

Pyrrole reacted with a number of alkyl zinc halides to yield the 2- and 3-alkyl pyrroles (Table 5) [33]. The protected pyrroles (methyl, benzyl, or Boc) did not react under these conditions leading Yadav to speculate that the reaction proceeds through the formation of a pyrrolyl zinc bromide as shown in Scheme 1.

Table 5 Alkylation of pyrrolyl-zinc bromide

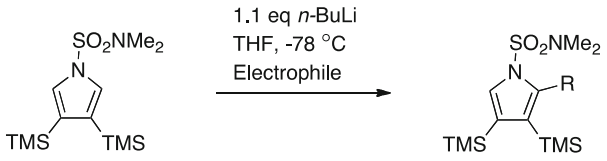


RBr	%Yield **4**	%Yield **5**
	10	70
	15	68
	12	65
	10	60



Scheme 1 Formation of pyrrolyl zinc bromide

Table 6 Reaction 2-lithio-3,4-bistrimethylsilylpyrroles with different electrophiles

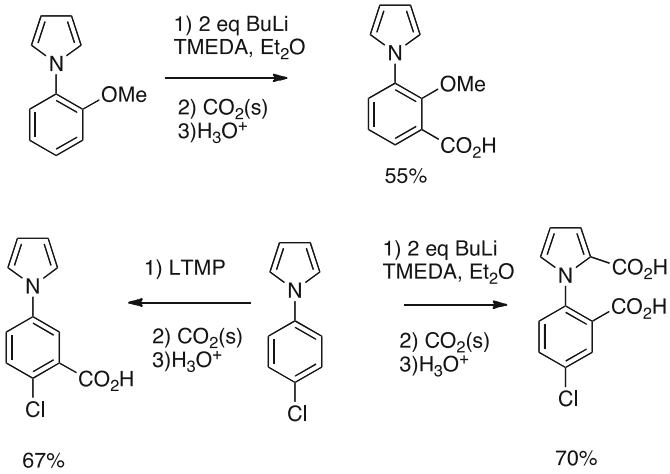


Electrophile	E	%Yield
$ClCO_2Me$	CO_2Me	58
$ClCO_2Et$	CO_2Et	40
PhCHO	CH(OH)Ph	52
MeCHO	CH(OH)Me	47

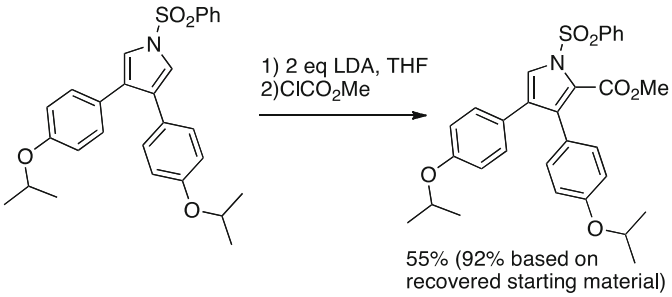
3.4 Lithium

The lithiation of *N*-protected pyrroles by *n*-butyllithium has been well known for many years and is typically directed to C-2 [34]. α-Lithiation of 3,4-bistrimethylsilylpyrroles was found to work best with a sulfonamide-protecting group [35]. *n*-Butyllithium reacted with a Boc or *p*-toluenesulfonyl-protecting group (Table 6). Subsequent quenching with electrophiles provided the 2-substituted 3,4-bistrimethylsilylpyrroles in good yields (40–80%).

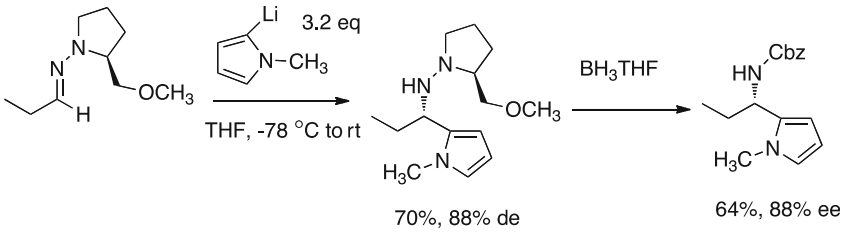
Monolithiation and dilithiation of 1-(chlorophenyl) and 1-(methoxyphenyl) pyrroles are controlled by temperature, solvent, and metalating agent [36]. For example, selective monolithiation of 1-(2-methoxyphenyl)pyrrole occurs with 2 equivalents of BuLi-TMEDA in ether. If 1-(4-chlorophenyl)pyrrole is treated with LTMP in THF, the product is from monolithiation; with 2 equivalents of BuLi-TMEDA in ether the dilithiation predominates.



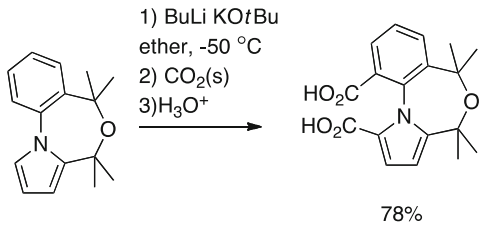
The lamellarins O, P, Q, and R were synthesized using a common starting material prepared by Suzuki coupling of a dibromopyrrole, followed by phenylsulfonyl-directed lithiation at C-2 for installation of the ester [37]. While other conditions were attempted to maximize the yield, no improvements were seen.



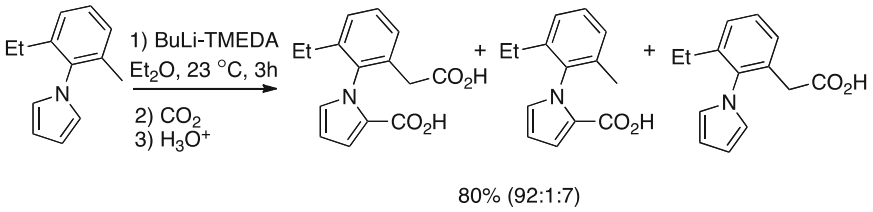
There are a few examples of either asymmetric addition of lithiopyrroles or the use of lithiated pyrroles to produce chiral pyrroles. 1,2-Addition of 2-lithio pyrroles, as well as other lithiated heterocycles, to aldehyde-SAMP-hydrazones provided an enantioselective approach to α-(heteroaryl)alkylamines after the N–N bond was cleaved using BH_3-THF [38].



A new structurally rigid atropisomeric *N*-arylpyrrole was prepared using Schlosser's superbase (1:1 potassium *t*-butoxide and butyllithium) to dimetalate the pyrrolo[1,2-*a*][4,1]benzoxazepine [39]. Dicarboxylation with dry ice provided the desired product in 78% yield.

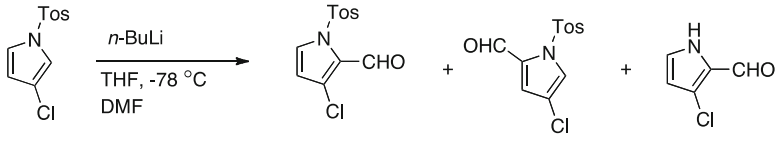


Lithiation at C-2 of pyrrole has been employed to prepare another optically active atropisomeric *N*-aryl pyrrole [40]. The yields were dependent on the temperature of the lithiation as well as the duration of the lithiation, but the desired product was easily isolated from the mixture.



3.4.1 Direction by Other Groups on the Ring

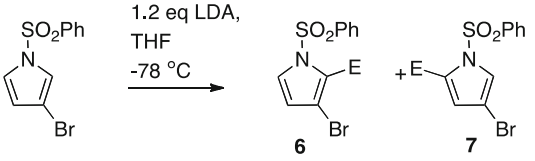
The directed lithiation of 3-chloro-1-tosylpyrrole was explored as part of an approach to the pyrrolo-furan substructure of roseophilin [41]. Deprotonation with *n*-butyllithium proceeds smoothly and regioselectively at C-2, demonstrating the *ortho*-directing effects of the chlorine. The difficulty came in separating the C-2 and C-5 formylated products from each other. Thus, 2.5 equivalents of *n*-butyllithium affected a detosylation, and the resulting mixture was easily separated.



The electrophile can control the regioselectivity apparently through a dynamic equilibrium between C-2 and C-5 lithiated intermediates [42]. Lithiation at C-2 was first maximized using either LDA or LICA (lithium isopropylcyclohexamide) in THF (91% yield, 97:3, C2:C5 selectivity or 95% yield, 94:6, respectively). Reaction at C-5 was preferentially seen when LTMP was used (95%, 32:68) or when the solvent was switched to ethyl ether or toluene. Lithiation by lithium hexamethyldisiliazide was found to be ineffective. Quenching the 2-lithio intermediate provided the expected product most of the time (see Table 7); however, formylation with DMF formed the 5-substituted pyrrole while treatment with ethyl formate provided the expected 2-formylated pyrrole (entries 4 and 5). This electrophile controlled regioselectivity was seen in the silylation of the 2-lithiopyrrole with TIPSCl or TIPS-OTf (entries 6 and 7). Further study of the lithiated pyrroles indicates that the two are in dynamic equilibrium in the presence of diisopropylamine. While the C-2 lithiated pyrrole appears to be more stable, it is also less reactive due to steric and/or electron withdrawing effects of the adjacent bromine.

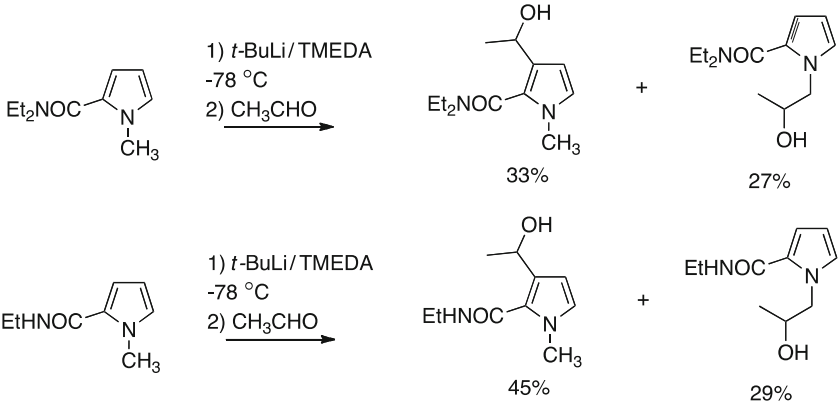
Pujol et al. examined directed metalation by carboxyl groups on pyrrole, furan, thiophene, and indole in order to access the 2,3-disubstituted heterocyclic systems [43].

Table 7 Electrophile controlled regioselectivity

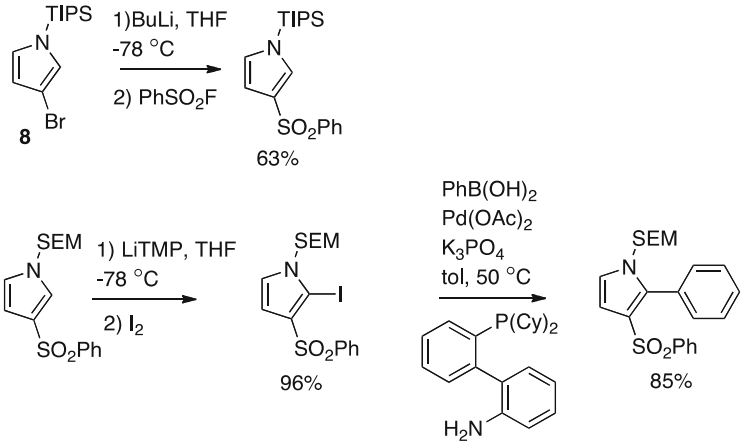


Entry	Electrophile	E	%Yield	Ratio (**6**:**7**)
1	$ClCO_2CH_3$	CO_2CH_3	86	>99:1
2	$BrCF_2CF_2Br$	Br	90	>99:1
3	*p*-$MeOC_6H_4CHO$	$CH(OH)C_6H_4$ *p*-MeO	86	>99:1
4	$HCON(CH_3)_2$	CHO	76	35:65
5	HCO_2Et	CHO	71	>99:1
6	TIPSCl	TIPS	45	>1:99
7	TIPS-OTf	TIPS	82	95:5

For *N*-methylpyrrole the carboxylic acids can be lithiated but the dianions are unstable, and so the carboxamides are better alternatives. In both cases, the combination of TMEDA and *t*-butyllithium was necessary to produce the alkylated products; LDA did not provide sufficient basicity.



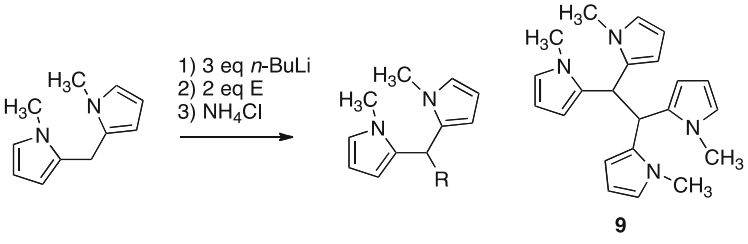
The directed metalation of 3-phenylsulfonylpyrroles was optimized by Demont et al. in order to functionalize the C-2 position [44]. The 3-phenylsulfonylpyrroles were themselves prepared by a metal–halogen exchange on the commercially available 3-bromopyrrole **8**. Of the protecting groups (Boc, SEM, and SO_2Ph) examined, SEM provided the highest regioselectivity and overall yield when the pyrrole was treated with LTMP followed by d-methanol. The SEM protected pyrrole could also be iodinated, and the resulting product will undergo Suzuki coupling.



3.4.2 Remote Lithiation: Off a Side Chain

Dipyrromethanes are of interest in the preparation of synthetic porphyrins and related compounds; the synthesis of *meso*-substituted dipyrromethanes from the condensation of aldehydes and pyrroles can be difficult due to unreactive starting materials or competitive side reactions [45]. The unsubstituted dipyrromethanes were found to undergo regioselective lithiation in the presence of 3 equivalents of *n*-butyllithium; the resulting anion can be quenched with a number of electrophiles and forms the dimer **9** in about 20% in all cases. If the protecting group is benzyl, the reactions only provided benzylic substitution (Table 8).

Table 8 Alkylation of dipyrromethanes



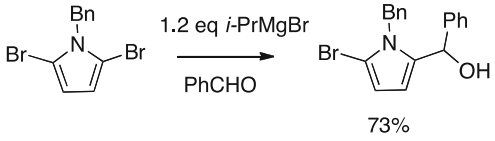
Electrophile	R	%Yield
EtBr	Et	61
BnCl	Bn	51
Acetone	$C(OH)(CH_3)_2$	54
4-Cl-C_6H_4CHO	$CH(OH)C_6H_4$-4-Cl	30

4 Metal–Halogen Exchange

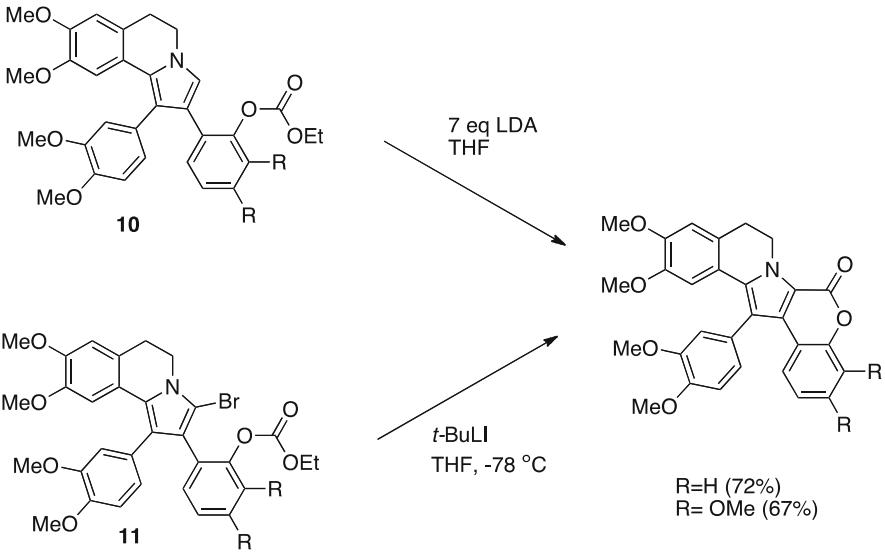
The metal–halogen exchange reaction on pyrrole has been well known for years as a means to access complicated biologically active materials, such as the metabolite of the sponge *Oscarella lobularis I* as well as the antibiotic verrucarin E [46, 47].

4.1 Lithium or Magnesium at C-2 or C-5

N-Benzyl-3,4-dibromopyrrole undergoes monobromine magnesium exchange to yield the magnesiopyrrole which can be selectively alkylated in high yields. This procedure is fairly general for other heterocycles with electron withdrawing groups on the ring [48].

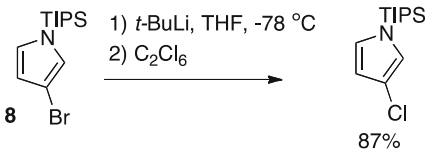


Metal–halogen exchange on 2-bromopyrrole carbonates provides a route to the lamellarin alkaloids [49]. A directed remote metalation on **10** with 7 equivalents of LDA was only mildly successful (R = OMe, 35% yield) in producing the intramolecular lactonization needed to form the lamellarin scaffold. However, the lithium halogen exchange on **11** using *t*-butyllithium provided good yields of the desired product (67–72%).

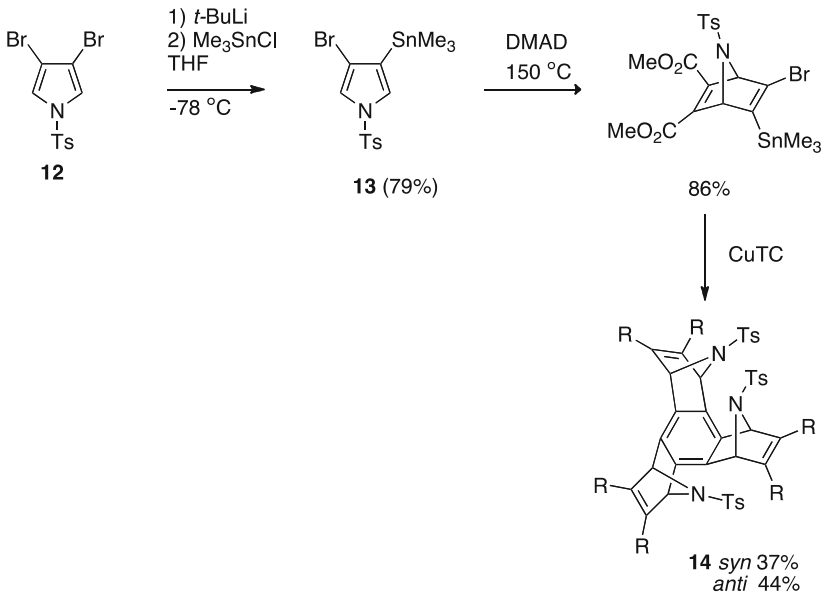


4.2 Lithium or Magnesium at C-3 or C-4

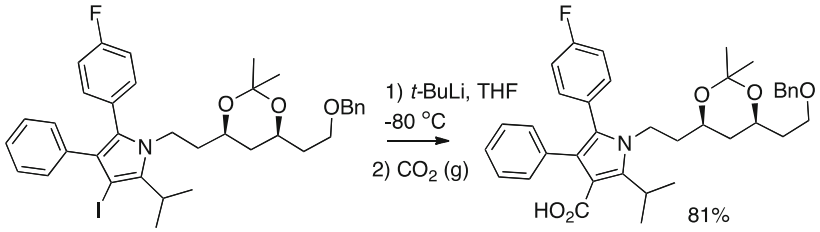
A metal–halogen exchange on 3-bromopyrrole **8** can be used to regioselectively prepare a 3-chloropyrrole, which is difficult to form under other conditions [50].



Zonta et al. used a vicinal halogen–metal vinyl system in pyrroles to synthesize via cyclotrimerization cup-shaped molecules with a protected aza bridge that allows for additional functionalization [51]. The 3,4-dibromopyrrole **12** undergoes mono metal–halogen exchange followed by treatment with trimethyltin chloride to form the stannane **13**. Diels-Alder cycloaddition of the stannane followed by cyclotrimerization with copper thiophenecarboxylate (CuTC) provides the cup-shaped compound **14** in good yields.



Maier et al. used a metal–halogen exchange on iodopyrrole **15** to install a carboxy group as part of his synthesis of the atorvastatin (61% over the next four steps) [52]. This pathway serves as a way to access amide derivatives of atorvastatin.

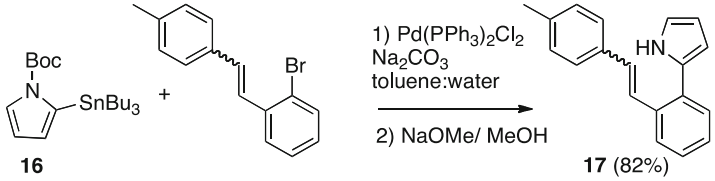


15

5 Palladium Cross-Coupling Reactions of Pyrroles

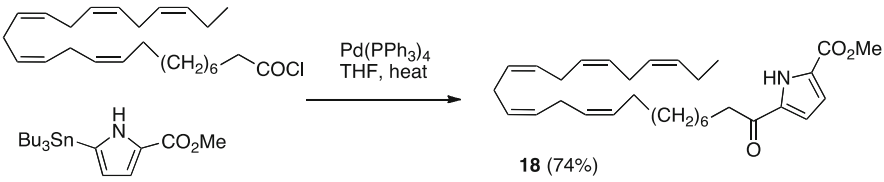
5.1 *Stille*

Stannyl pyrroles can be prepared by lithiation followed by reaction with a chlorostannane and have been used to form a number of interesting pyrrole-based materials. A Stille coupling of the stannyl pyrrole **16** forms the stilbenzylpyrrole **17** which then will undergo photochemical ring closure to produce indole and isoindole derivatives [53].



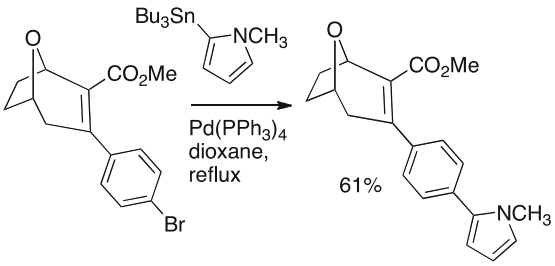
16 **17** (82%)

Mycalazal 2 (**18**) can be prepared in good yield using a Stille coupling of a stannyl pyrrole with an acid chloride [54].

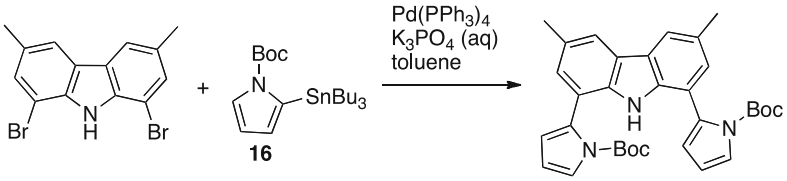


18 (74%)

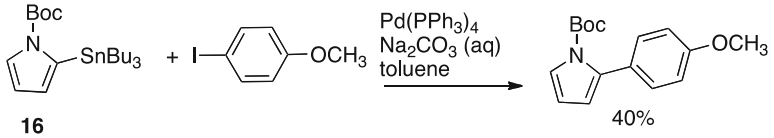
A Stille procedure was used to form a pyrrole example in a series of serotonin selective uptake inhibitors based on the 8-oxabicyclooctane ring [55]. Two possible approaches using a 2-stannyl pyrrole were investigated to form the 3-(4-heteroaryl-phenyl)-8-oxabicyclo[3.2.1.]octane-2-carboxylic acid methyl esters.

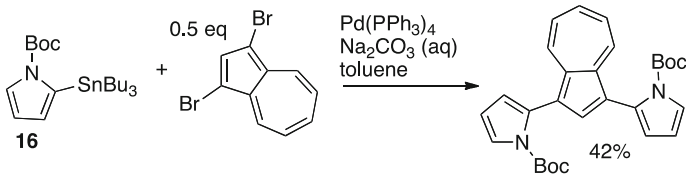


The 2-stannylpyrrole **16** can also be employed as part of an approach to expanded calixpyrroles [56]. It couples to the known carbazole under standard conditions; the product can be deprotected and condensed with acetone to form the calix[4]pyrrole[2]carbazole in overall 40% yield.

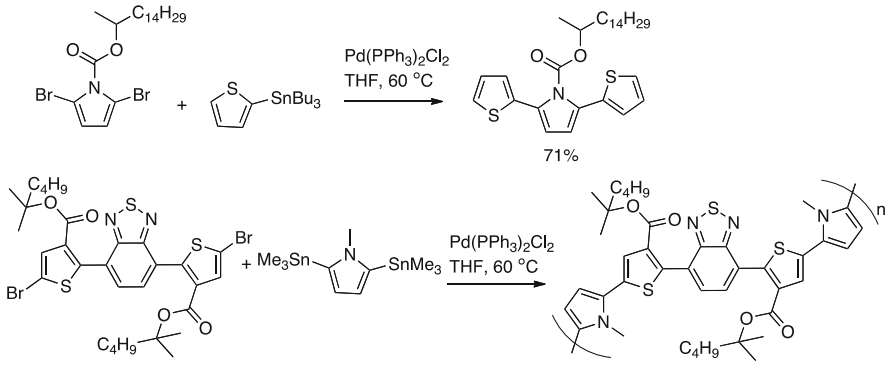


Additionally, 2-stannylpyrrole **16** couples with iodoanisole to form a BODIPY fluorescent indicator with low affinity for calcium [1]. The maximum yield was 40% when aqueous sodium carbonate was included to suppress the Pd-catalyzed cleavage of the tin-carbon bond. In a similar manner 2-stannylpyrrole **16** reacted with 1,3-dibromoazulene to ultimately form a fluorescent probe for fluoride ion [2].



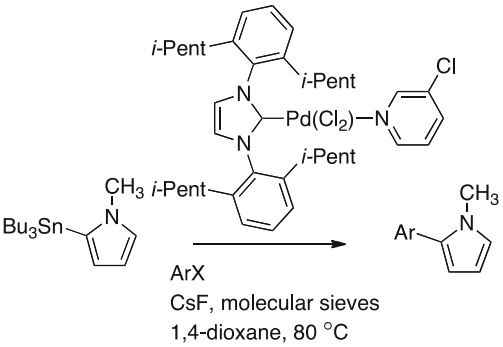


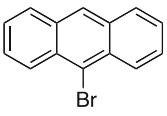
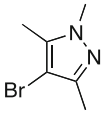
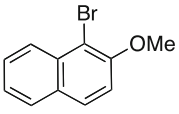
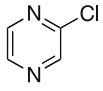
Pyrrole-based and benzothiadiazole-based polymers were formed in good yields using Stille couplings where the pyrrole either functions as the aryl halide or as the stannane [57]. In both cases, an excess of the stannylated monomers insured longer polymer chains.



A low-temperature Stille coupling can be effected for stannyl pyrroles using Pd-PEPPSI-IPent (pyridine, enhanced, precatalyst, preparation, stabilization, and initiation, diisopentylphenylimidazolium derivative) [58]. The reactions proceeded in good yields even with hindered aryl bromides and without poisoning of the palladium catalyst (Table 9).

Table 9 Stille coupling with Pd-PEPPSI-IPent

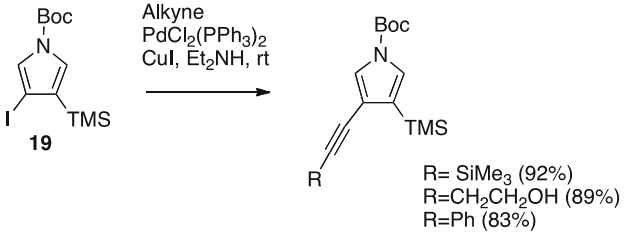


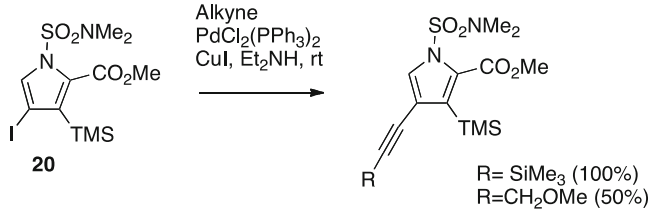
ArX	%Yield	ArX	%Yield
	78		98
	90		89

5.2 *Sonogashira*

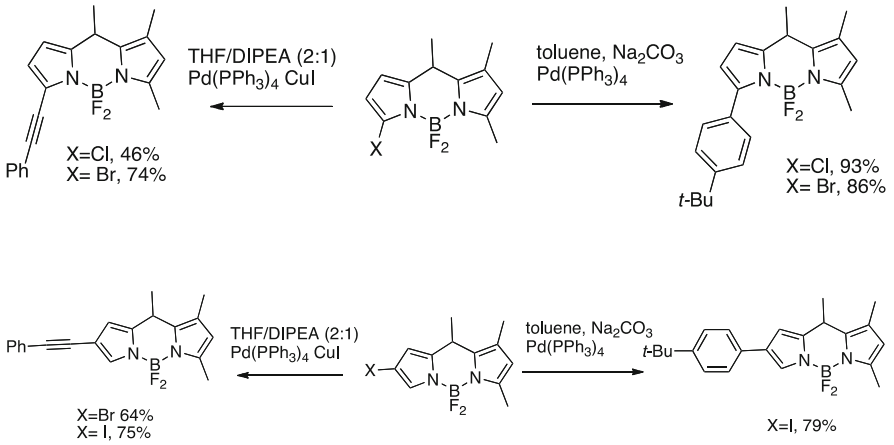
An alkynyl-substituted calix[4]pyrrole has been prepared to react with a number of aryl iodides in a Sonogashira coupling yielding arylalkynyl-calix[4]pyrroles (67–87%) which are of interest for their application in fluorescent anion sensing [59].

The Sonogashira reaction has been useful in the sequential preparation of either 3,4-disubstituted or 2,3,4-trisubstituted pyrroles [35, 60]. The ability of the trimethylsilyl group to direct adjacent iodination provides the starting material for the first palladium-catalyzed reaction. Moreover, the trimethylsilyl group can be transformed into another iodine allowing for additional palladium-catalyzed coupling reactions. Sonogashira coupling of the iodopyrroles **19** and **20** provided the alkynylpyrroles in good yields.



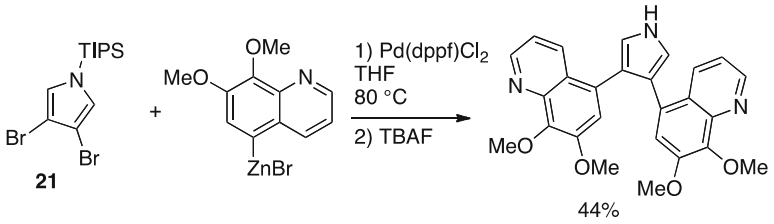


The coupling reactions of BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dyes have been explored for their potential as ion or pH sensors or in optoelectronic devices. The 3,5-dichloro-BODIPY dyes undergo palladium cross-coupled reactions [1, 61, 62]. The drawback is the need for disubstitution to avoid a vacant reactive position. The monohalogenated BODIPY dyes were studied for their reactivity toward Sonogashira and Suzuki coupling conditions [63]. The 3-halogenated compounds all reacted successfully under Sonogashira conditions. While the 2-chloro resulted in very low yields, the 2-bromo and 2-iodo compounds underwent palladium-catalyzed coupling with higher yields and under milder reaction conditions. The reactivity of the halogenated dyes toward Suzuki conditions also increased Cl to Br to I.



5.3 *Negishi*

Negishi coupling of the 3,4-dibromopyrrole **21** provides access to the halitulin core [64].



An approach to the lamellarins using solid phase synthesis employed a Negishi reaction to connect the pyrrole to the resin [65]. The best yields were obtained with a large excess (10 equivalents) of the pyrrolozinc reagent.

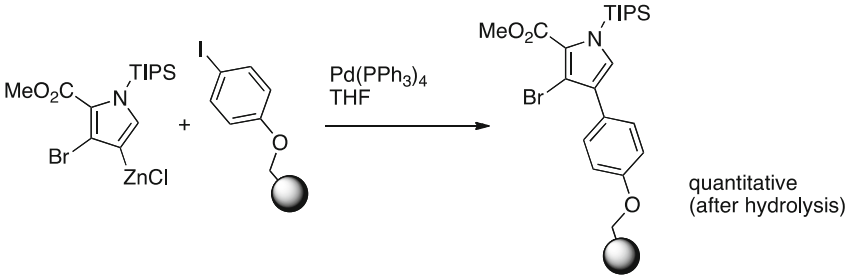
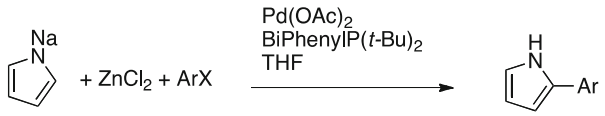


Table 10 Negishi reaction of pyrrolyl zinc chlorides

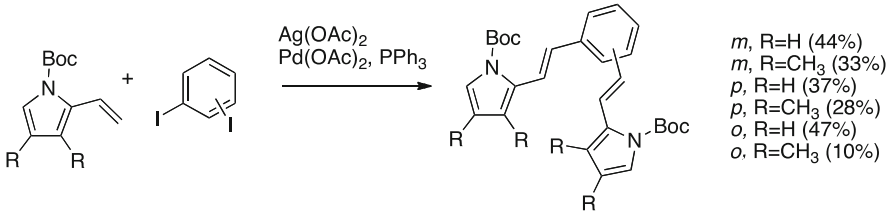


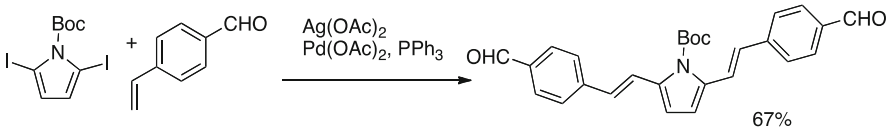
Entry	ArX	Temperature (°C)	%Yield
1	1-Bromo-2,4,6-triisopropylbenzene	100	70
2	1-Bromo-3,5-ditrifluoromethylbenzene	80	90
3	1-Chloro-4-*n*-butylbenzene	60	71
4	1-Chloro-2-methoxybenzene	60	93
5	1-Chloro-3,5-dimethoxybenzene	60	91

Pyrrolyl zinc chlorides can be prepared from pyrrolyl sodium and zinc chloride [66]. The pyrrolyl zinc chlorides are arylated at C-2 using palladium catalysis in the presence of dialkylphosphinobiphenyl ligands. Steric hindrance is tolerated (Table 10, entry 1). Pyrrolyl zinc chloride will react with aryl bromides and chlorides as well as both electron rich and electron poor aryl halides.

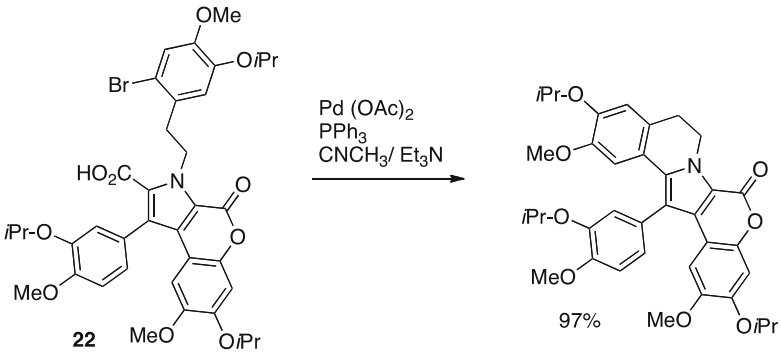
5.4 Heck

Linear pyrrole oligomers were prepared using Heck coupling reactions of either iodopyrroles or vinylpyrroles [67, 68]. While initially the reaction produced a mixture of constitutional isomers, the addition of silver acetate as a base provided the linear product [67]. Both symmetrical and unsymmetrical oligomers could be prepared, and a sequential twofold Heck provided a pentacyclic oligomer in 45% yield [68].

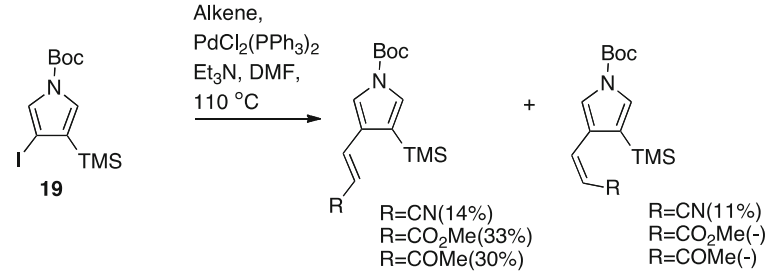




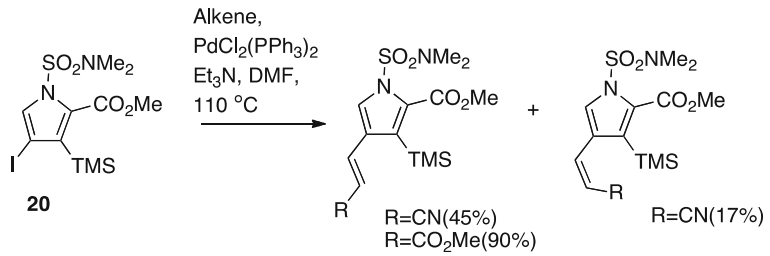
Lamellarin L triisopropyl ether was formed by Heck coupling of **22** in high yields [69, 70]. The reaction proceeded with decarboxylation, which is rare under Heck conditions.



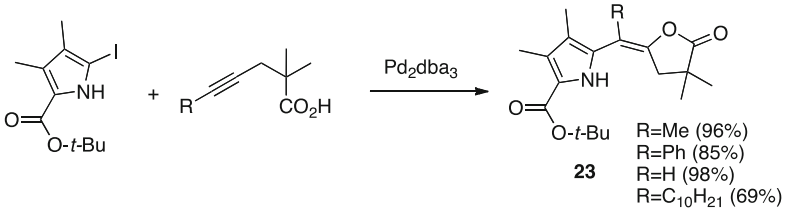
3,4-Disubstituted pyrroles have been prepared using the directing properties of the trimethylsilyl group to introduce an iodine; the resulting compound, **19**, will react under a number of palladium-catalyzed conditions [60]. Further transformation of the trimethylsilyl group into an iodine allows for a second palladium-catalyzed alkylation or arylation. The Heck reaction under standard conditions proved to be difficult, providing only a viscous oil. The use of $PdCl_2(PPh_3)_2$ did result in modest yields; with acrylonitrile a mixture of *cis* and *trans* isomers was formed. Heck reaction of **19** with styrene showed less regioselectivity, with only 28% of the product resulting from attack at the less substituted end of the alkene and 13% at the more substituted end.



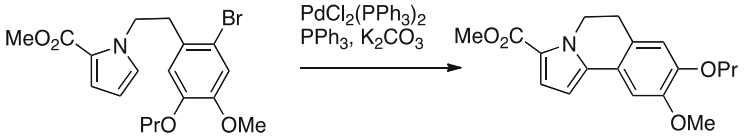
Heck coupling of the iodopyrrole **20** provided a mixture of *cis* and *trans* isomers that could be separated by column chromatography [35]. Moreover, the remaining trimethylsilyl group can be transformed into an iodine allowed for additional palladium-catalyzed coupling reaction to prepare 2,3,4-trisubstituted pyrroles.



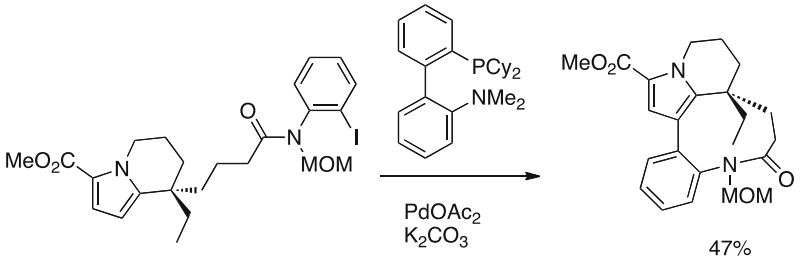
In the synthesis of dihydrodipyrrins, Jacobi et al. coupled an iodopyrrole to a number of alkynoic acids to provide the enelactones **23** in good yields [71]. While the most common side reaction was dehalogenation of the iodopyrrole, use of Pd_2dba_3, or a large excess of K_2CO_3 in DMF minimized this problem.



An intramolecular Heck reaction functions as the first step in the synthesis of a series of lamellarins [72, 73]. In this case, the pyrrole ring functions as the π system rather than the aryl halide.

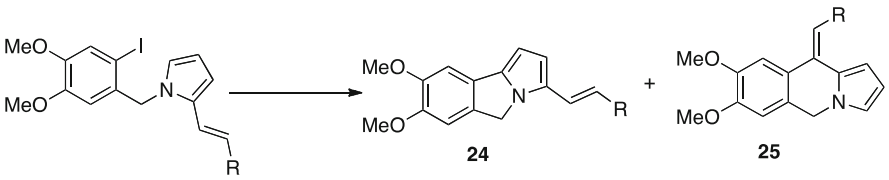


In another Heck example of the pyrrole functioning as the π system, the core of rhaziniliam was synthesized in moderate yield by an intramolecular coupling after a number of unsuccessful ligands and metal sources were studied [74].



Lete compared the competition between the Heck reaction and direct arylation in the synthesis of pyrroloisoquinolines and isoindoles [75]. By changing the catalytic system, in particular varying the ligand on the palladium (acetate vs. iodide),

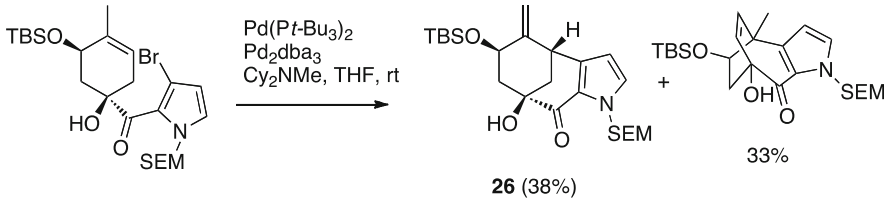
Table 11 Comparison of Heck and direct arylation



R	Reaction conditions	**24** (%)	**25** (%)
CO_2Bn	$Pd(OAc)_2$ PPh_3 Bu_4NCl, DMSO, 60°C	73	8
CO_2Bn	$Pd(OAc)_2$ PPh_3 Bu_4NOAc, DMSO, 60°C	92	–
$CONEt_2$		84	–
Ph		92	–
CO_2Bn	$Pd(PPh_3)_4$, Bu_4NCl, $NaHCO_3$ CH_3CN, 60°C	–	42
$CONEt_2$		–	94
Ph		–	76

the intramolecular reaction could be switched from the alkene to the pyrrole nucleus (Table 11).

One approach to dragmacidin F involved an intramolecular Heck reaction to form the [3.3.1] bicycle **26**. Many standard conditions were unsuccessful in this coupling; ultimately, the yield could not be increased beyond 38% [76, 77].



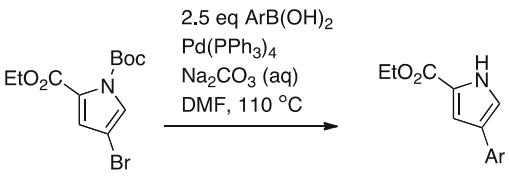
5.5 *Suzuki with Halopyrroles*

5.5.1 Mono-Arylation of Pyrrole

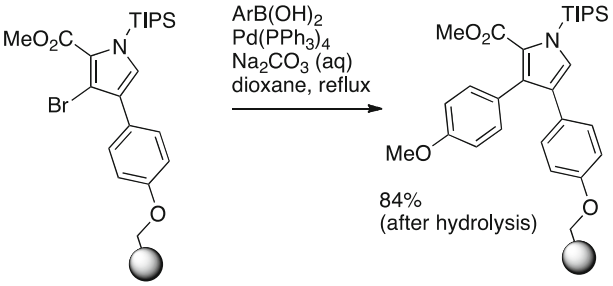
Handy found that both Stille and Suzuki conditions were likely to dehalogenate 4-bromopyrrole-2-carboxylates in significant amounts (28–65%) [78]. By protecting the pyrrole, dehalogenation could be suppressed, and good yields of the Suzuki products were isolated (Table 12).

Lamerallins Q and O were synthesized by solid phase Suzuki coupling in good yields, whereas initial attempts to employ a Negishi reaction resulted in a crude mixture that was difficult to use [65].

Table 12 Suzuki reaction of 4-bromopyrrole-2-carboxylates

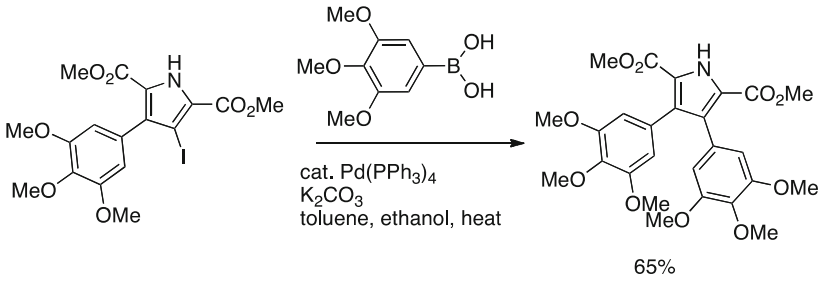


Entry	Ar	%Yield
1	3,4-Dimethoxyphenyl	80
2	4-Fluorophenyl	68
3	3-Isopropoxy-4-methoxyphenyl	82
4	2,3,4-Trimethoxyphenyl	84



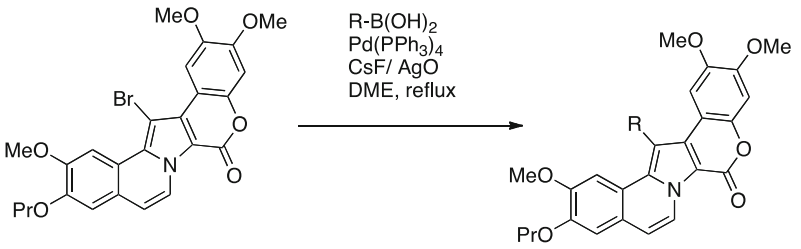
In another approach to the lamellarins, Iwao employed a Suzuki coupling in the presence of a cesium fluoride–silver oxide promoter, perhaps necessary to overcome the steric hindrance at C-1 (Table 13), to create a series of lamellarin D analogues [79].

Gupton's group used a Suzuki coupling in a relay synthesis of permethylstorniamide A; in this case they coupled an iodopyrrole to 3,4,5-trimethoxybenzeneboronic acid to form the Boger intermediate in 65% yield [80].



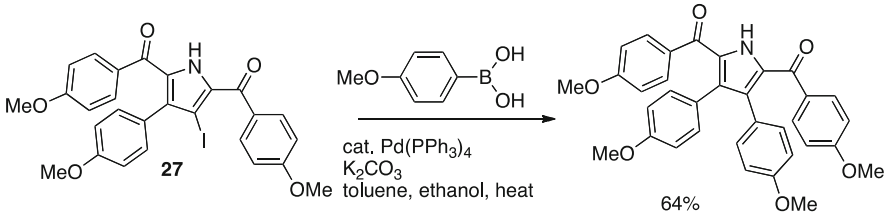
In an analogous synthesis, Gupton studied the palladium-catalyzed coupling of both an iodo and bromo pyrrole with 4-methoxyphenylboronic acid to form the

Table 13 Suzuki couplings to form lamellarin D analogues

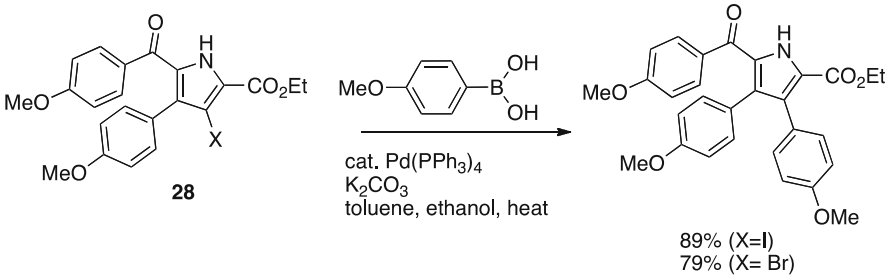


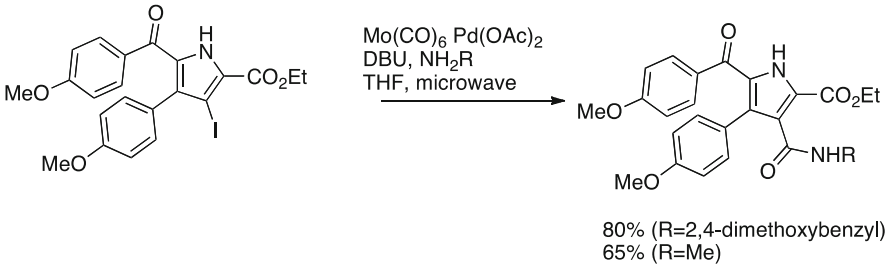
R	%Yield
Methyl	82
Phenyl	81
3,4-Dimethoxyphenyl	87
3-Methoxy-4-isopropoxyphenyl	69

Steglich synthon in an approach to polycitone A and B [81]. In this study, the bromopyrrole failed to react even in the presence of microwave activation.



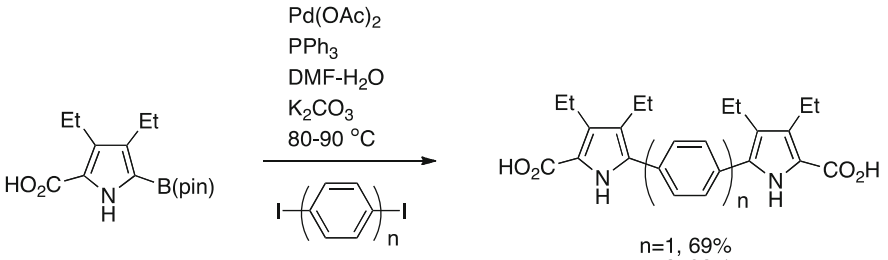
With an ethyl ester at C-2 (**28**) instead of the ketone (**27**), the reactivity toward the Suzuki reaction is much higher. With either a bromo or iodo, the reaction proceeds with conventional heating and without the need for microwave acceleration. This product can then be transformed into the Steglich synthon. This iodopyrrole can also be aminocarbonylated in the presence of $Mo(CO)_6$ and $Pd(OAc)_2$ as a means of accessing Rigidin and Rigidin E [82].



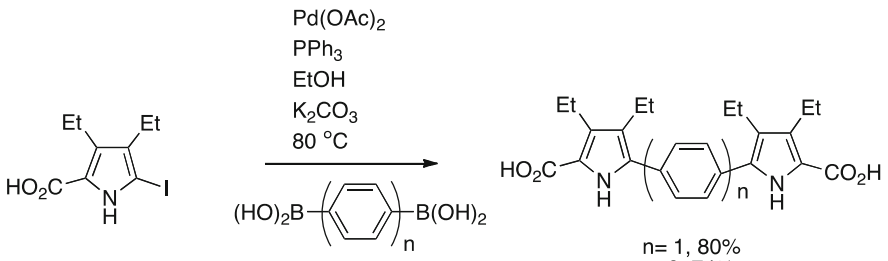


80% (R=2,4-dimethoxybenzyl)
65% (R=Me)

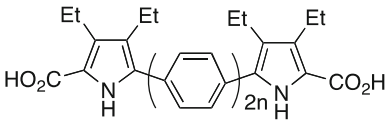
Bis(pyrrol-2-yl)arenes which demonstrate strong fluorescence and are seen as useful monomers for polymeric materials as well as for expanded porphyrins can be prepared by the Suzuki–Miyaura coupling of 2-borylpyrrole [83]. The coupling reaction of 2-iodopyrrole with 1,4-phenylenebisboronic acids resulted in oxidative self-coupling and 4,4′-bis(pyrrol-2-yl)biphenyl (5–19%) as a side product.



n=1, 69%
n=2, 92%



n= 1, 80%
n=2, 74%



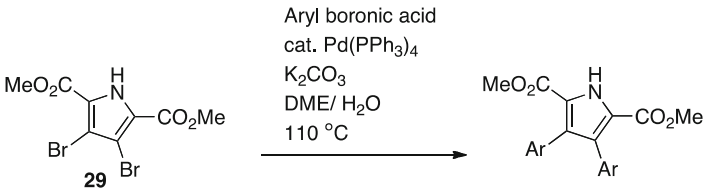
n= 1, 5%
n=2, 19%

5.5.2 Diarylation of Pyrrole with the Same Arylboronic Acid

If a symmetric diaryl pyrrole is desired, a double Suzuki reaction is easily accomplished with an excess of the aryl boronic acid. Furstner coupled the readily available 3,4-dibromopyrrole **29** to a number of benzene boronic acids in good yields [64]. Storniamide was formed by alkylation of the product in entry 2. Other 3,4-diarylated pyrroles of interest, such as the lycogalic acid dimethyl ester which exhibits some anti-HIV I activity, were formed using this approach (see Table 14, entry 4).

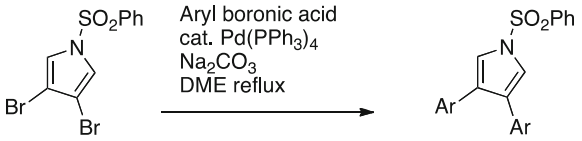
3,4-Diarylpyrroles are also available in very high yields from *N*-phenylsulfonyl-3,4-dibromopyrrole [37]. While incomplete conversion was observed with THF as the solvent, DME provided complete conversion regardless if the group on the arylboronic acid was electron donating (Table 15, entry 1), electron withdrawing (entry 2), or sterically challenging (entry 5). The phenylsulfonyl group was far

Table 14 Double Suzuki couplings of a 3,4-dibromopyrrole



Entry	Aryl boronic acid	%Yield
1	Phenylboronic acid	60
2	3,4,5-Trimethoxybenzeneboronic acid	88
3	4-Methoxyphenylboronic acid	99
4	*N*-TBS-indole-3-boronic acid	81

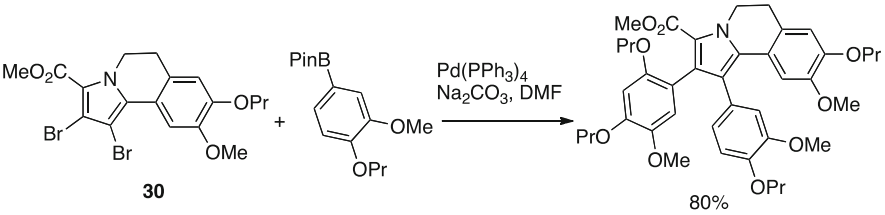
Table 15 Double arylation by Suzuki reaction of a 3,4-dibromopyrrole



Entry	Aryl boronic acid	%Yield
1	4-Methoxyphenylboronic acid	93
2	4-Fluorophenylboronic acid	96
3	4-Isopropoxyphenylboronic acid	94
4	3,4,5-Trimethoxybenzeneboronic acid	91
5	2,6-Dimethoxybenzeneboronic acid	93

superior to TIPS under these conditions; only 5–6% of the arylated product was observed with TIPS. Moreover, entry 3 was used to provide access to the lamellarins O, P, Q, and R.

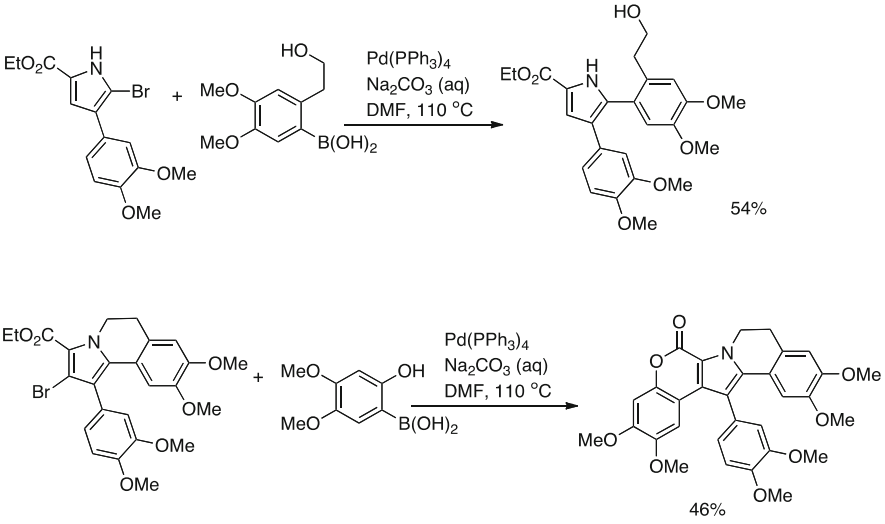
One approach to lamellarin D starts with the dibromide **30** to form the diaryl compounds in good yields [72].



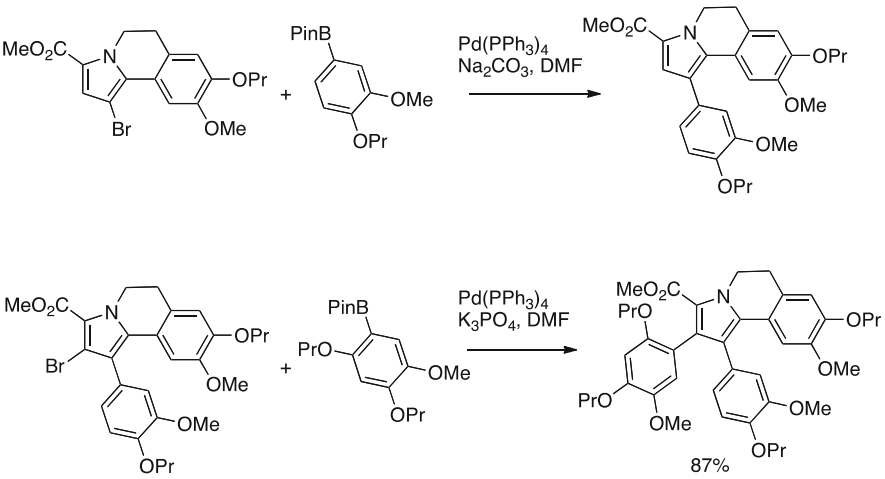
5.5.3 Sequential Diarylation and Regioselectivity in Diarylation

To introduce different aryl groups, a series of palladium-catalyzed transformations can be employed or with care, regioselectivity in the reactivity of di or tri halogenated pyrroles can also lead to more complex products.

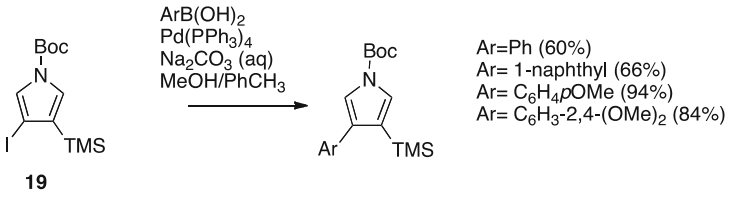
For the synthesis of lamellarin G trimethyl ether, a sequential transformation was undertaken [84]. The first coupling proceeded smoothly as long as an excess (3 equivalents) of the boronic acid was employed. However, the second step suffered from what appears to be the thermal instability of the boronic acid. When an excess (8 equivalents) of the boronic acid was added slowly over the course of the reaction the yield improved from 8% to 46%.

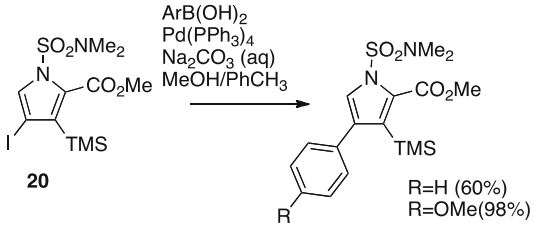


In a similar fashion, a sequential bromination and Suzuki coupling provided a route to lamellarin D [73]. The second coupling step was also problematic, presumably due to steric hindrance. Slow addition of an excess of the boronic acid provided the best yield in this example.



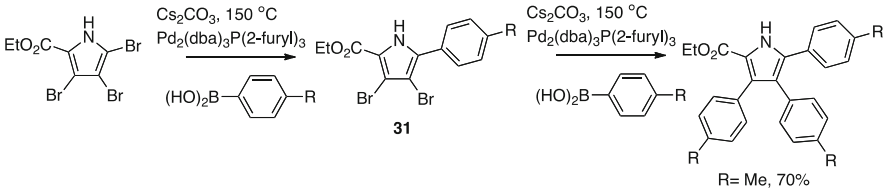
Suzuki reaction of the iodopyrroles **19** and **20** gave arylpyrroles in good yields [35, 60]. Moreover, the trimethylsilyl group can be transformed into an iodine allowing for additional palladium-catalyzed coupling reaction to prepare either 3,4-disubstituted or 2,3,4-trisubstituted pyrroles. This approach provides access to lamellarin *O*-dimethyl ether and Lukianol A.





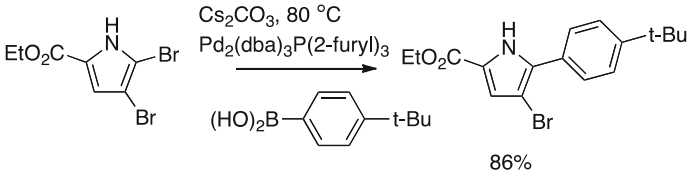
Di- and tri-brominated pyrroles can undergo the Suzuki cross-coupling reaction with a variety of *para*-substituted phenylboronic acids in a regioselective manner

at C-2 [85]. During optimization studies, cesium carbonate was found to be the best base as neither sodium nor potassium carbonate resulted in any reaction. High temperatures (reflux in mesitylene) and the catalyst $Pd(PPh_3)_4$ or $Pd_2dba_3P(2\text{-furyl})_3$ were key to a successful reaction; further substitution reactions were possible if additional equivalents (4–5) of the boronic acids were used (Table 16).



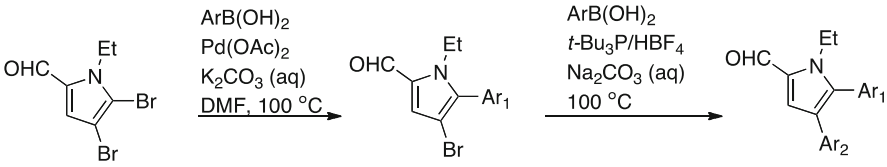
Another approach to regioselective sequential dicouplings involved using a ligand-free palladium catalyst for the first step [86]. When a phosphine ligand is added with a different boronic acid, the second coupling step proceeds (Table 17).

Table 16 Sequential Suzuki arylation of a tri-brominated pyrrole



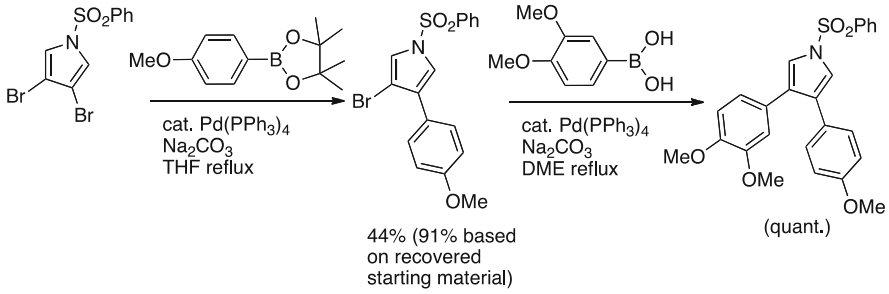
Entry	R	%Yield (**31**)
1	H	51
2	Cl	33%
3	Me	52%
4	OMe	46%

Table 17 Sequential Suzuki reactions of dibromopyrroles

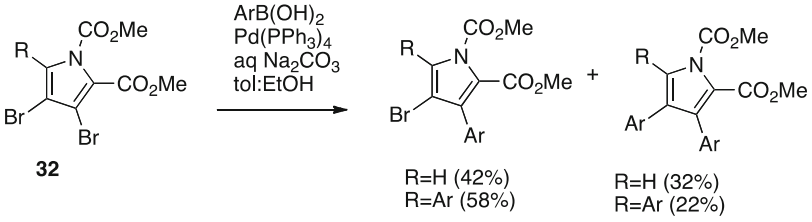


Ar_1	Ar_2	%Yield
4-Methoxyphenyl	4-Fluorophenyl	58
4-Fluorophenyl	4-Methoxyphenyl	51
4-Methoxyphenyl	Styrenyl	56

Selective monoarylation and sequential diarylation are also possible if a lower temperature solvent (THF) is used for the first step [37].



In selectively coupling dibromopyrrole **32**, the electron poor site is favored with some influence by sterics; however, the conversion rate is rather low [87]. In fact, there is a strong a connection between the (larger) chemical shift related to electron deficiency and the reactivity of this site toward coupling reactions, such as Suzuki, Stille, Negishi, and Sonogashira reactions, with heterocycles [88].

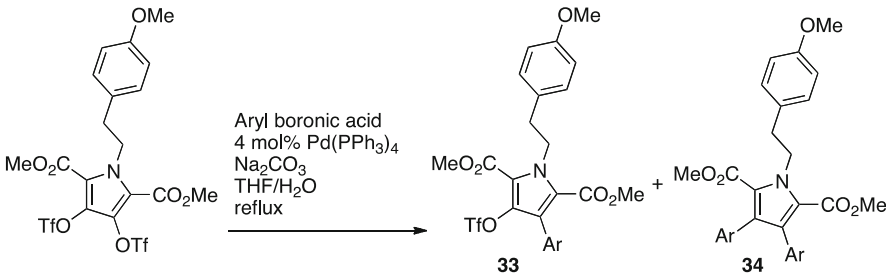


5.6 *Suzuki with Pyrrolyl Triflates*

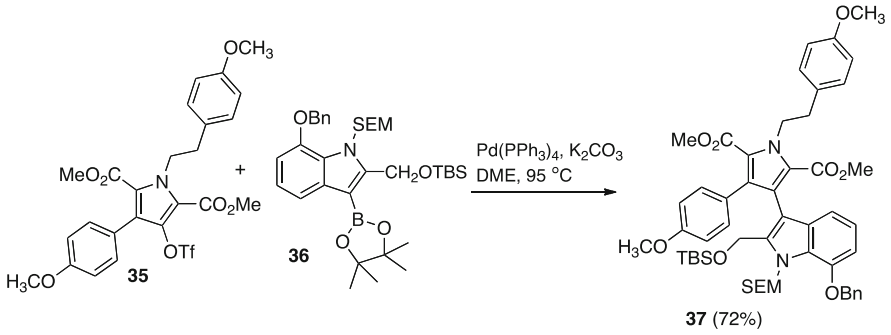
Iwao et al. demonstrated the utility of Suzuki coupling of pyrrole triflates to provide a formal synthesis of storniamide A (entry 3), ningalin B, and lamellarin G trimethyl ether as well as lamellarin D, L, and N [89, 90]. In order to maximize production of the diaryl pyrroles **34**, a longer time (20 h) and an excess of the aryl boronic acids (3 equivalents) were employed. When only 1 equivalent of the boronic acid was used mono-arylated pyrroles were formed in good yields (entry 4). This selectivity was used to sequentially arylate the pyrrole forming ningalin B and lamellarin G trimethyl ether from entry 5 (Table 18).

The telomerase inhibitory marine alkaloid dicytodendrin B was synthesized using a series of palladium cross-coupling reactions [91]. One of these involved the reaction between pyrrolotriflate **35** and indole-3-borate **36** to provide **37** in high yield.

Table 18 Selectivity in Suzuki reactions of pyrrole triflates



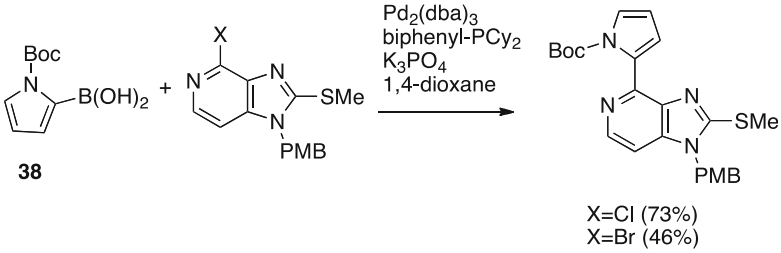
Entry	Arylboronic acid	Equivalents	**33** (%)	**34** (%)
1	4-Methoxyphenylboronic acid	2.2	1	99
2	2-Methoxyphenylboronic acid	3	1	99
3	3,4,5-Trimethoxyphenylboronic acid	3	0	100
4	4-Methoxyphenylboronic acid	1	77	9
5	3,4-Dimethoxyphenylboronic acid	1	78	11

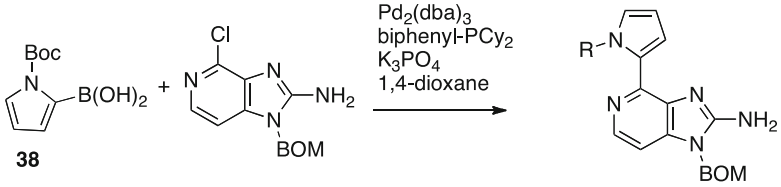


5.7 *Suzuki with Pyrrole Boronic Acids/Esters*

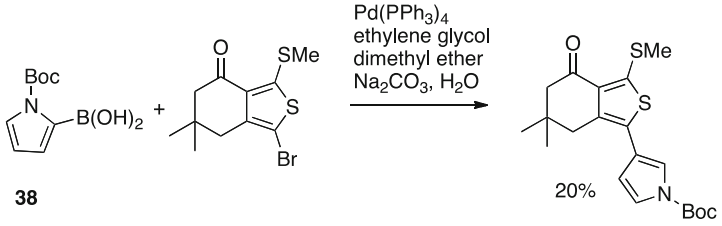
N-Boc pyrrole-2-boronic acid (**38**), which can be formed by the boronation of the 2-lithio pyrrole, has been used in a number of Suzuki–Miyaura coupling reactions. For example, Weinreb and Meketa coupled **38** with a chlorimidazopyridine to form ageladine A as well as a number of analogues [23, 92, 93]. In their initial approaches, they tried coupling halopyridines with *N*-Boc pyrrole-2-boronic acid or the 2-tributylstannylpyrrole; however, the starting halopyridines were recovered. Negishi coupling of the *N*-phenylsulfonyl pyrrole-2-zinc also failed to provide the desired product. While the Suzuki–Miyaura did form the desired product, this pathway ultimately did not lead to ageladine A until the protecting group was

changed and the thiomethyl group was converted to the amine. While the coupling was difficult to achieve using Stille coupling of the stannane or standard Suzuki–Miyaura conditions, when Buchwald's 2-biphenyldicyclohexylphospine ligand was employed, the coupling went smoothly.

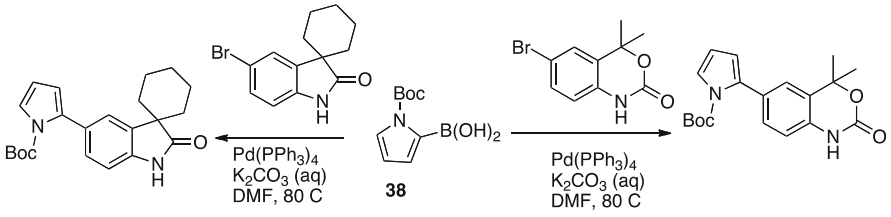




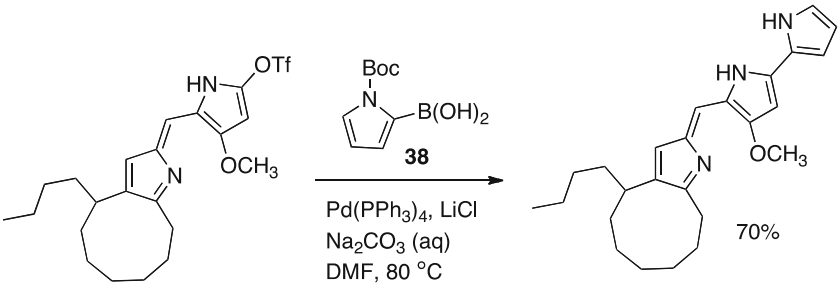
The pyrrol-2-yl-boronic acid **38** was also coupled with a 6,7-dihydro-2-benzothiophen-4(*5H*)-one as one of the series of possible $GABA_A$ receptor ligands [94].



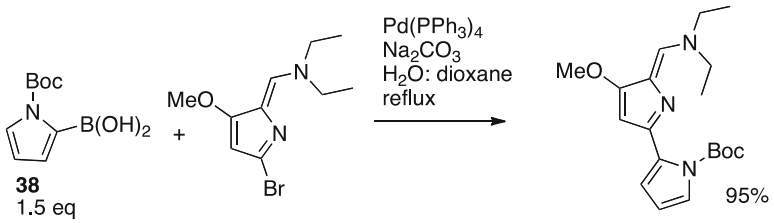
Suzuki coupling of **38** formed two series of progesterone receptor modulators in good yields (60–80%). These were synthesized to explore how the substituent pattern as well as the substituent itself changed the activity (agonist vs. antagonist) [95].



The last step in the synthesis of cycloheptylprodigison, one of a series of compounds with immunosuppressive without cytotoxic activity, involved the palladium coupling of **38** to a pyrrolotriflate [96].

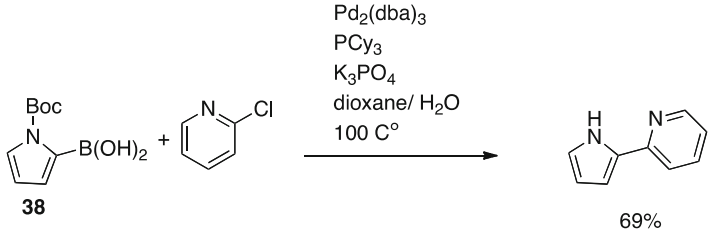


The key intermediate in the biosynthesis of a number of polypyrrole natural products is 4-methyoxy-2,2′-bipyrrole-5-carboxyaldehde; this compound can be formed in high yield (95%) from a Suzuki cross-coupling reaction with **38** [97].



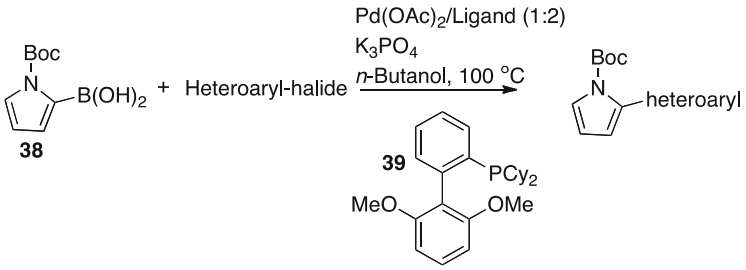
The ligand appears to be quite important to reaction success, as Buchwald also reports facile coupling of **38** with a number of heteroaryl halides using ligand **39** as long as water is excluded [98]. Under these conditions, homocoupling and protodeboronation were not seen (Table 19).

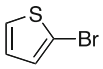
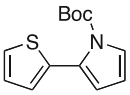
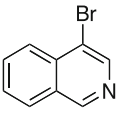
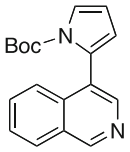
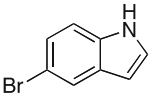
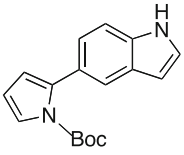
While there are numerous examples of successful Suzuki couplings, the catalytic system often has to be tweaked to provide high yields. Fu et al. found that PCy_3 not only is inexpensive but also provides high yields for the palladium-catalyzed reaction of a number of nitrogen heterocycles when it is employed with K_3PO_4 in dioxane, but not with KF in THF [99].



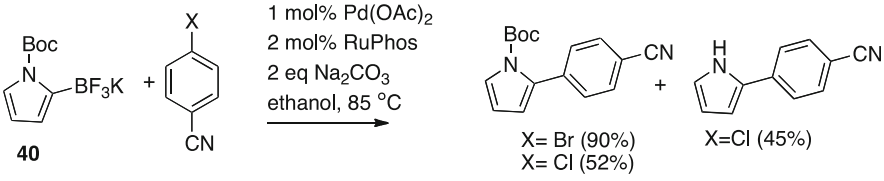
The Suzuki coupling of the potassium pyrrolo-trifluoroborate **40** has also been studied [100]. These organotrifluoroborates are air and moisture stable as well as

Table 19 Suzuki reactions of the pyrrole-2-boronic acid with heteroaryl halides



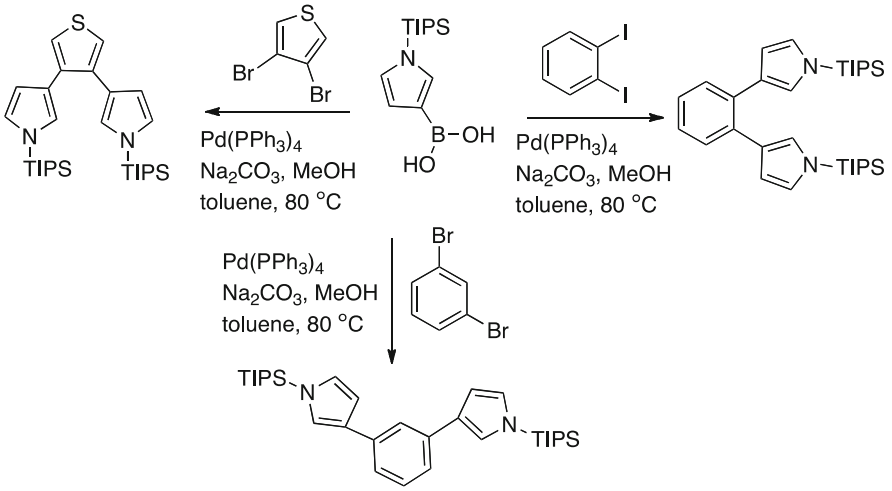
Aryl halide	Product	%Yield
		84
		95
		79

less prone to protodeboronation. The pyrrolotrifluoroborate **40** coupled with both 4-bromobenzonitrile and 4-chlorobenzonitrile in good yields; however, in the case of the chlorobenzonitrile 45% of the product deprotected.

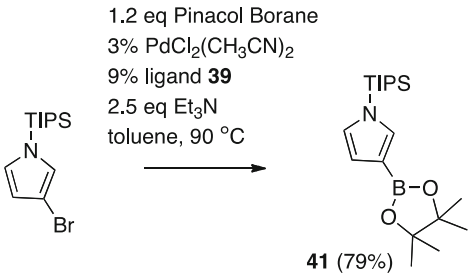


The pyrrol-3-yl-boronic acid has been employed in the formation of β-linked pyrrole monomers as potential stable, conductive electrochromic polymers [101]. While other palladium coupling methods (Stille and Kumada) were explored,

the yields were poor and not reproducible when scaled up. The Suzuki coupling with 1,2-diiodobenzene, 3,4-dibromothiophene, and 1,3-dibromobenzene provides the monomers in modest yield (40–60%).



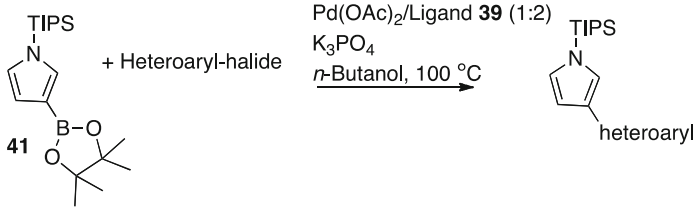
Buchwald et al. discovered that the boronate ester **41** was easy to purify and more stable than the pyrrol-3-yl boronic acid is reported to be [98, 102]. While initial studies of the coupling of the boronate ester were unsuccessful due to reduction of the aryl halide, when water was added to the reaction, it proceeded efficiently with low catalyst loadings. The optimal ratio was found to be 2.5 *n*-butanol:1 water. The protecting group (TIPS, Boc, or Benzyl) appears to have little impact on the yield of the coupling reaction. However, when there is no protecting group, only trace product is seen (Table 20).

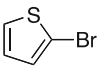
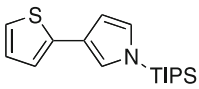
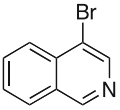
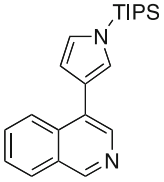
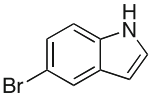
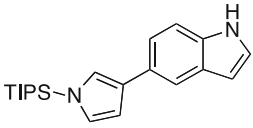


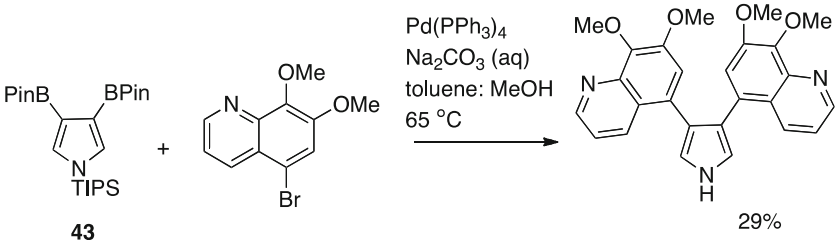
Pyrrole pinacolboranate ester **42** also undergoes couplings with bromoanilines and bromonitrobenzenes in good yields (Table 21). The product in entry 4 can be deprotected with TBAF to form the antibiotic antifungal pyrrolnitrin [50].

An approach to the cytotoxic halitulin also involved Suzuki coupling of pyrrole pinacolboranate ester **43** with a bromoquinoline [103]. While the diarylated product was desired, the starting pinacolboranate ester was contaminated with the mono-borolated material which explains the low yield.

Table 20 Suzuki couplings of pyrrol-3-yl boronic ester **41** with heteroaryl halides

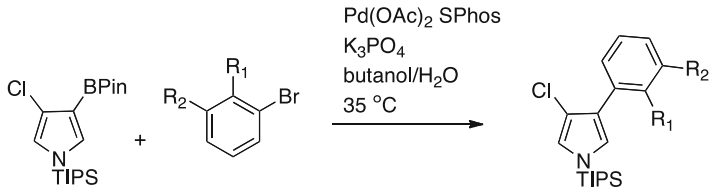


Aryl halide	Product	%Yield
		99
		93
		97



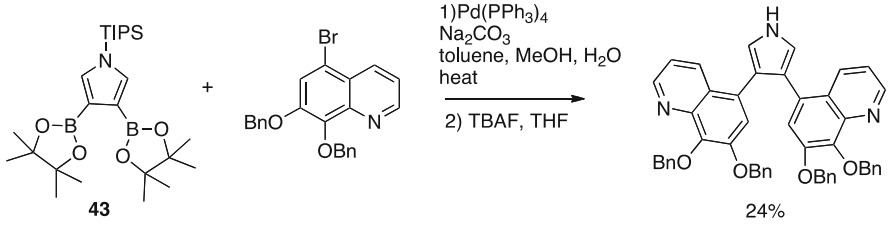
The halitulin core can be formed via a double Suzuki coupling of the pyrrole-3,4-diboronate **43** [104].

Table 21 Suzuki couplings of pyrrole pinacolboranate ester **42**



42

Entry	R1	R2	%Yield
1	NH_2	H	81
2	NO_2	H	86
3	NH_2	Cl	82
4	NO_2	Cl	89



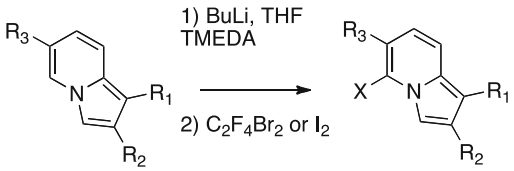
43

24%

5.8 Suzuki Reaction of Indolizines

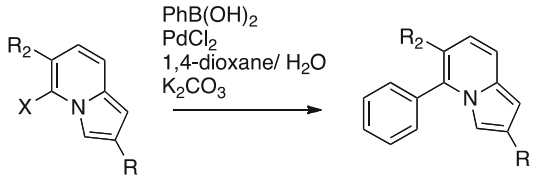
The difficult to access 5-halo-indolizines were formed in good yields by treatment with *n*-BuLi-TMEDA followed by quenching with either 1,2-dibromotetrafluoroethane or iodine (Table 22) [105]. The resulting halo-indolizines will undergo Suzuki coupling with a number of arylboronic acids. The 5-halo-2-*tert*-butyl indolizines were generally more reactive than the 2-phenyl ones. A methyl near the halogen decreased the reactivity and the halogen (bromine or iodine) appears to have little impact on the yields when sterics is not an issue (Tables 22 and 23).

Table 22 Formation of the haloindolizines



R1	R2	R3	X = Br yield (%)	X = I yield (%)
H	Ph	H	80	76
H	*t*-Bu	H	97	95
H	*t*-Bu	Me	92	87
Me	*t*-Bu	H	98	–

Table 23 Suzuki reaction of 5-haloindolizines

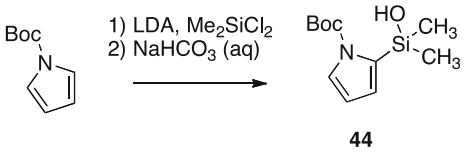


Entry	X	R	R2	%Yield
1	I	*t*-Bu	H	80
2	Br	*t*-Bu	H	73
3	I	Ph	H	78
4	Br	Ph	H	41
5	Br	*t*-Bu	Me	44
6	I	*t*-Bu	Me	78

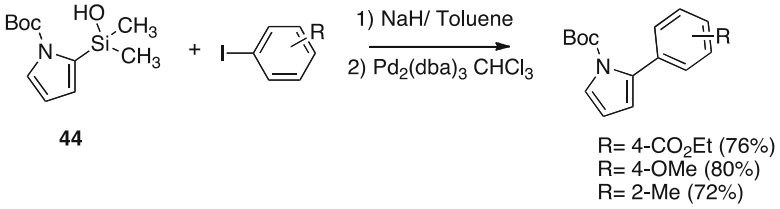
5.9 Other Palladium-Catalyzed Reactions

5.9.1 Coupling of Organosilanols

The palladium coupling of the organosilanols of heteroaromatics has also been reported [106]. The advantages of the silanol over the borane or stannane are the inherent low toxicity and ease of manipulation. The pyrrolylsilanol **44** was prepared by lithiation. The silanol **44** can be deprotonated with NaH and then treated under palladium cross-coupling reactions to form the 2-arylpyrroles in good yield. While coupling proceeded smoothly with aryl iodides, the reaction with aryl bromides failed.



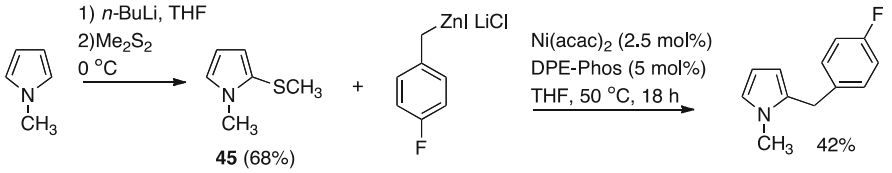
44



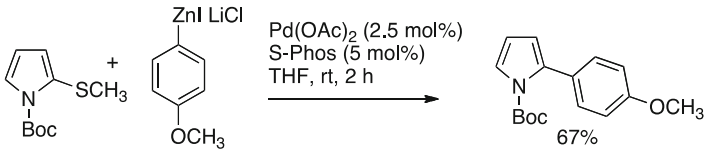
44

5.9.2 Coupling of Thioethers

C-2 lithiation of *N*-methylpyrrole and quenching of dimethyl disulfide formed the 2-methylthiopyrrole **45** in good yield (68%) [107]. This thio ether, as well as other heteroaryl versions, will undergo Pd- or Ni-catalyzed cross-coupling reactions with organozinc reagents.



45 (68%)



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Furans and Benzofurans

Kap-Sun Yeung

Abstract This chapter reviews the significant developments in the metalation of furans and benzofurans and applications of the resulting metalated species in the past decade. New and interesting metalated furan and benzofuran derivatives and their novel reactions are featured. Topics encompass lithiation, magnesation and zincation, the use of boronated and other metalated furans and benzofurans in cross-coupling reactions, as well as the use of metalated furans and benzofurans in addition reactions. Examples of regioselective metalation are highlighted, and metalation of related furo heterocycles is also summarized.

Keywords Addition reactions · Benzofurans · Cross-coupling · Furans · Metalation

Contents

1 Introduction 48
2 Lithiation of Furans and Benzofurans 50
3 Magnesation of Furans and Benzofurans, and Their Applications 52
4 Zincation of Furans and Benzofurans, and Their Applications 56
5 Boronated Furans and Benzofurans in Cross-Coupling Reactions 59
6 Other Metalated Furans and Benzofurans in Cross-Coupling Reactions 62
7 Regioselective Functionalization of Poly-halogenated Furans and Benzofurans 65
8 Metalated Furans and Benzofurans in Addition Reactions 67
9 Lithiation of Related Furo Heterocycles 70
References 71

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1 Introduction

Furan and benzofuran are common structural elements present in numerous bioactive natural products as well as pharmaceuticals, molecular electronic and functional polymers [1]. Recent noteworthy examples from natural sources, as shown in Fig. 1, include the cytotoxic diterpenoid salvileucalin B [2] and the selective phosphoinositide-3-kinase α inhibitor liphagal [3]. The total syntheses of both of these unusual molecular structures have recently been accomplished [3, 4]. Due to their electron-rich character, furans also function as versatile precursors to a variety of functional moieties as well as carbocycles and heterocycles through the transformation of the furan nucleus, for example, by oxidation and cycloaddition reactions [5–7].

A broadly employed approach for the incorporation of furan and benzofuran rings is by utilizing their metalated species that participate primarily in metal-catalyzed cross-coupling reactions and as nucleophiles in addition reactions. Conventionally, direct deprotonation of furan and benzofuran takes place at the most acidic C2 position (or the C5 position in 2-substituted furans) by using alkyl lithiums with or without TMDEA, or using lithium amide bases. For example, as shown in Scheme 1, lithiation using *n*-BuLi presumably generated a 2,5-dianion,

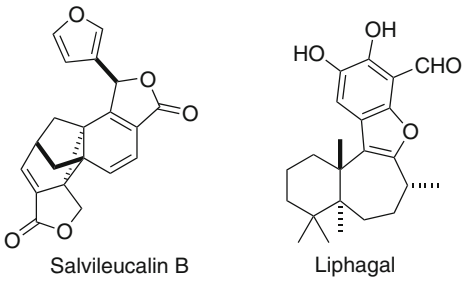
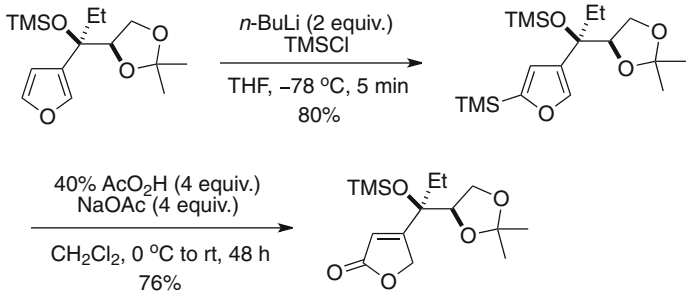


Fig. 1 Furan- and benzofuran-containing natural products



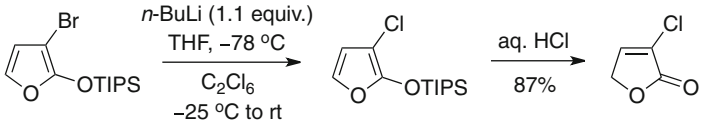
Scheme 1 Direct metalation of furan at C2 (C5) position

which was regioselectively silylated at the less hindered C5 position [8]. The incorporation of the TMS group directed the subsequent regioselective oxidation to the γ-butenolide.

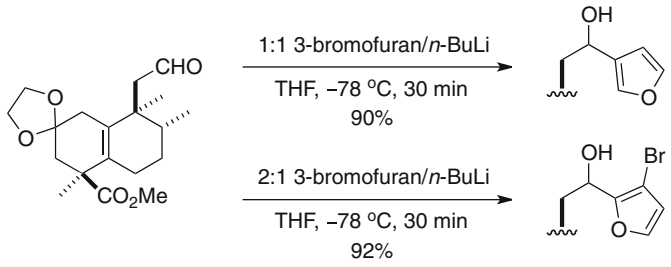
Metalation at the C3 position of furan generally requires lithium–halogen exchange using alkyl lithium bases. As exemplified in Scheme 2, Li–Br exchange of 3-bromo-2-triisopropylsilyloxyfuran occurred smoothly under standard conditions. The anion formed can be quenched with C, S, Se, Si, and halogen electrophiles to generate α-substituted γ-butenolides after acidic hydrolysis [9].

However, metalation outcomes were influenced by the stoichiometries of 3-bromofuran and *n*-BuLi used. For example, as demonstrated in a key addition reaction of furyllithium to an aldehyde during a synthesis of chettaphanin shown in Scheme 3 [10], mixing equimolar amounts of the two reactants generated 3-furyllithium as expected, while metalation occurred at the C2 position when half an equivalent of *n*-BuLi was used.

Lithiation followed by transmetalation of lithiofurans is commonly used to generate various metalated furan derivatives. Earlier developments in the metalation of furans and benzofurans and their applications have been reviewed extensively [6, 11, 12]. This chapter serves to capture the significant advances in these areas in the past decade, highlighting new and interesting metalated furan and benzofuran species and their novel transformations. Examples of regioselective metalation are described, and metalation of related furo heterocycles is also summarized.



Scheme 2 Lithium–bromide exchange of furan at C3 position



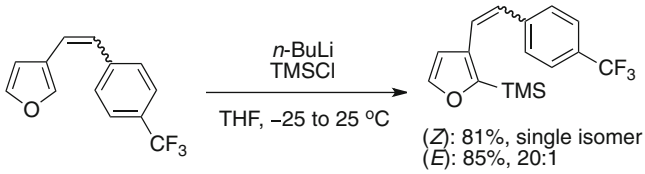
Scheme 3 Metalation of 3-bromofuran using different equivalent of *n*-BuLi

2 Lithiation of Furans and Benzofurans

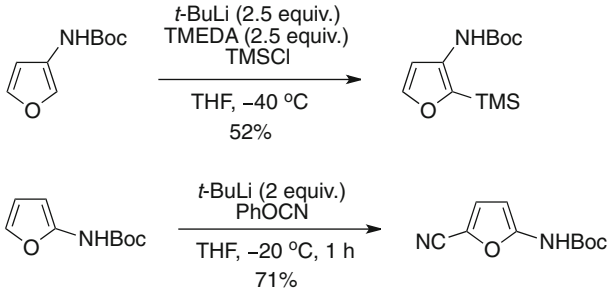
An interesting counter-steric regioselectivity was unexpectedly obtained in the lithiation of 3-phenyl as well as (*E*)- and (*Z*)-3-styrylfurans under conventional conditions using *n*-BuLi. The lithiation preferentially occurred at the more hindered C2-position, as illustrated in Scheme 4 [13]. The regioselectivity was increased by a phenyl ring bearing an electron-withdrawing group, attributed to the stabilization of the furyl anion in a late transition state.

The lithiation of 3-(*N*-*tert*-butoxycarbonyl)furan by using *t*-BuLi occurred regioselectively at the C2 position as assisted by the apparent *ortho*-directing effect of *N*-*tert*-butoxycarbonyl group to provide 2-substituted 3-(*N*-*tert*-butoxycarbonyl) furans after quenching with a range of electrophiles [14], as exemplified in Scheme 5. This is in contrast to an example of lithiation/cyanation of 2-(*N*-*tert*-butoxycarbonyl)furan, which took place at the C5 position [15].

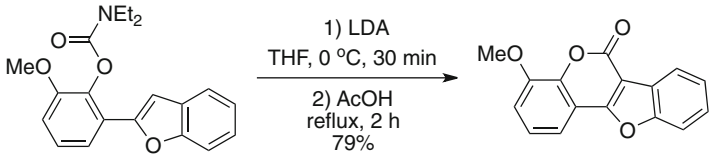
Directed *ortho* metalation could occur remotely at the C3 position of benzofuran as illustrated in a synthesis of a coumestan depicted in Scheme 6 [16].



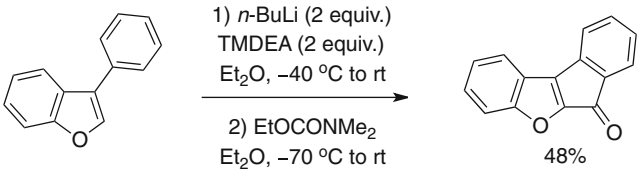
Scheme 4 Regioselective lithiation of (*E*)- and (*Z*)-3-styrylfurans



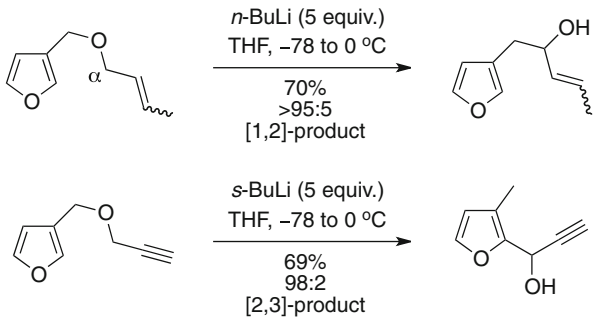
Scheme 5 Regioselective lithiation of 3- and 2-(*N*-*tert*-butoxycarbonyl)furans



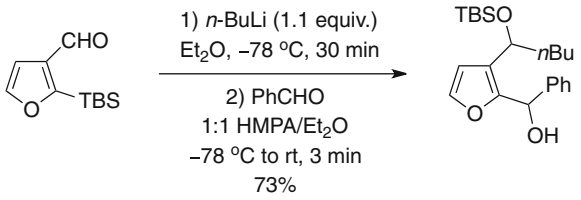
Scheme 6 Directed *ortho* remote metalation of benzofuran



Scheme 7 Dilithiation of 3-phenylbenzofuran



Scheme 8 Deprotonation at the ethereal α position of 3-furylmethyl ethers

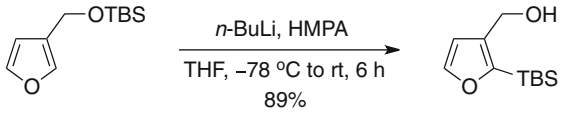


Scheme 9 Addition of organolithium reagent to 2-TBS-3-formylfuran

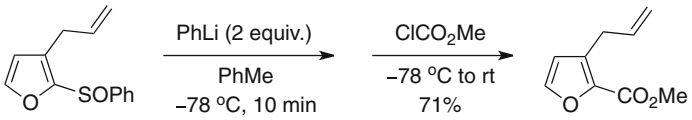
Dilithiation of 3-phenylbenzofuran also followed an *ortho* remote manner. As demonstrated in Scheme 7, this method was used for the synthesis of hetarenoindanones, which were reduced to provide hetarenoindenes [17].

Deprotonation at the ethereal α position of 3-furylmethyl ethers by alkyl lithiums (*n*-, *s*-, or *t*-BuLi) or LDA occurred more readily than deprotonation at the furan C2 position. As illustrated in Scheme 8, products arising from a formal [1,2]- and [2,3]-Wittig rearrangements were selectively obtained by using different bases [18].

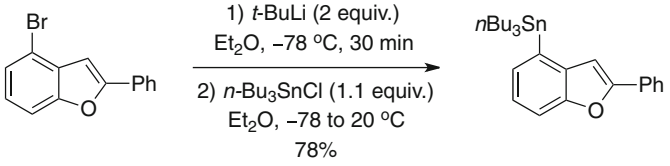
A furan C2 anion was regioselectively generated via the addition of organolithium reagents to 2-TBS-3-formylfuran and subsequent 1,4-Brook silyl migration of the intermediate lithium alkoxide [19]. Quenching the anion with aldehydes and ketones provided 2,3-disubstituted furans as exemplified in Scheme 9.



Scheme 10 retro-Brook rearrangement of a 2-lithiofuran



Scheme 11 Regioselective lithiation of furan via sulfoxide–lithium exchange



Scheme 12 Lithium–bromide exchange of 4-bromo-2-phenylbenzofuran using *t*-BuLi

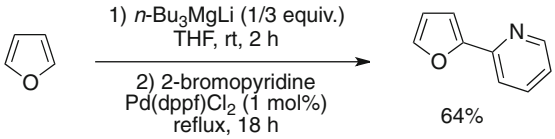
Interestingly, lithiation of the 3-furylmethyl TBS ether shown in Scheme 10 initiated a retro-Brook rearrangement of the corresponding 2-lithiofuran that conveniently installed a silyl blocking group regioselectively at the furan C2 position [20].

Another example of regioselective lithiation of furan resulted from a lithium–sulfoxide exchange that was carried out by using phenyllithium as a base [21], as shown in Scheme 11.

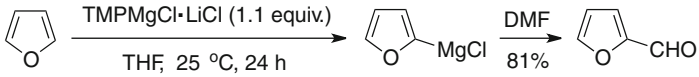
As depicted in Scheme 12, lithium–bromide exchange of 4-bromobenzofuran required the use of the strong base *t*-BuLi to generate 4-benzofuranyllithium, which was converted to the tin derivative [22].

3 Magnesation of Furans and Benzofurans, and Their Applications

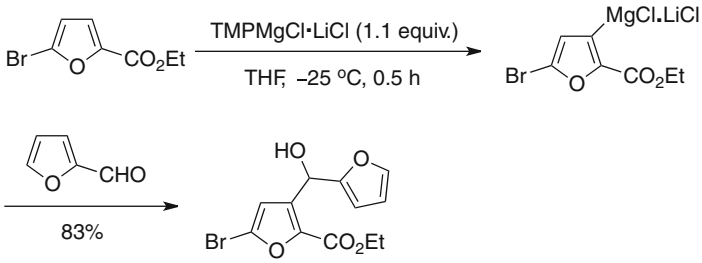
Metalation of furans and benzofurans can be performed at or near ambient temperature under new conditions that seek to avoid undesirable side reactions resulted from high reactivity and nucleophilicity of lithium bases. Deprotonation at the C2 position of unsubstituted furan and benzofuran at room temperature was achieved by using lithium magnesates Bu_3MgLi and Bu_4MgLi_2 [23], and the resulting lithium 2-furylmagnesate was stable and reactive toward Kumada-type cross-coupling, as exemplified in Scheme 13.



Scheme 13 Magnesation of furan using Bu_3MgLi and the subsequent cross-coupling



Scheme 14 Magnesation of furan using TMPMgCl·LiCl



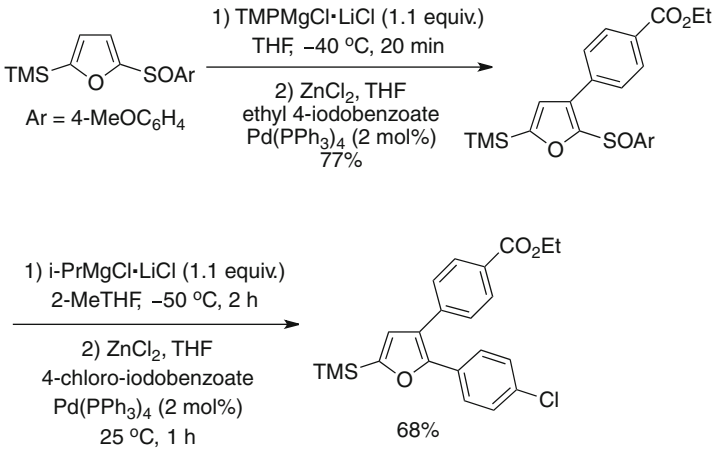
Scheme 15 Regioselective magnesation of ethyl 5-bromofuran-2-carboxylate

As represented in Scheme 14, direct magnesation of unsubstituted furan by using a mixed Mg/Li amide TMPMgCl·LiCl (TMP = 2,2,6,6,-tetramethylpiperidine) also occurred at room temperature to generate 2-furylmagnesium chloride in situ, which was quenched with an electrophile [24].

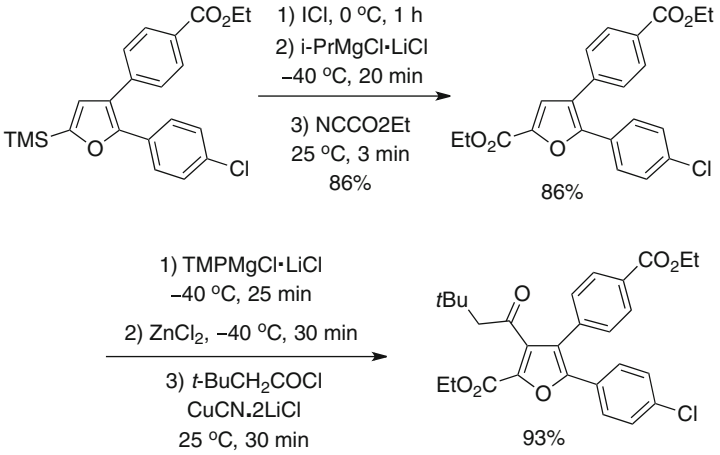
Interestingly, regioselective direct magnesation at the C3 position of ethyl 5-bromofuran-2-carboxylate, presumably activated by the carboxylate group, has been demonstrated by employing TMPMgCl·LiCl at lower temperature as depicted in Scheme 15 [24].

2-(4-Methoxyphenyl)sulfinyl-substituted benzofuran and 5-trimethylsilylfuran were also magnesated at the C3-position by using TMPMgCl·LiCl and then transmetalated to the corresponding zinc reagents for Negishi coupling [25, 26]. Subsequent sulfoxide–magnesium exchange was performed by using *i*-PrMgCl·LiCl for the formation of 2,3-disubstituted derivatives as illustrated in Scheme 16.

As represented in Scheme 17, further manipulation of the C4 and C5 positions of 2,3-disubsituted-5-trimethylsilylfurans again by consecutive application of these two different magnesium bases, i.e. iodide–magnesium exchange with *i*-PrMgCl·LiCl followed by magnesation using TMPMgCl·LiCl, led to tetrasubstituted furans.



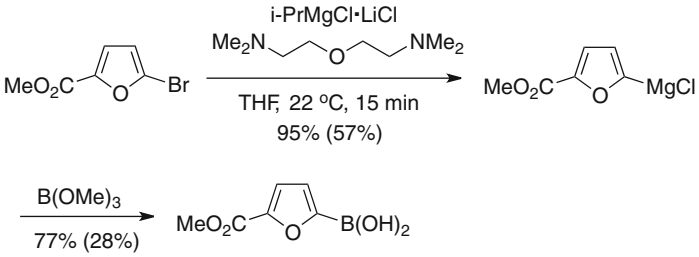
Scheme 16 Magnesation of 2-(4-methoxyphenyl)sulfinyl-5-trimethylsilylfuran



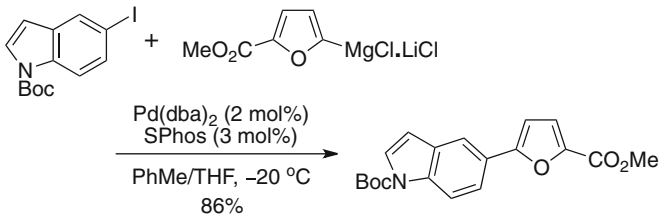
Scheme 17 Consecutive application of magnesium bases, *i*-PrMgCl·LiCl and TMPMgCl·LiCl, on a 2,3-disubstituted-5-trimethylsilylfuran

Efficient magnesium–bromide exchange of methyl 5-bromofuran-2-carboxylate could be performed at 22°C by using *i*-PrMgBr in the presence of bis[2-(*N*, *N*-dimethylamino)ethyl] ether [27]. The resulting Grignard reagent was presumably stabilized by the formation of a tridentate complex with the diamine, leading to a 95% conversion as shown in Scheme 18. Addition of the complex to trimethylborate provided the corresponding boronic acid in high yield compared to the reaction without using the diamine.

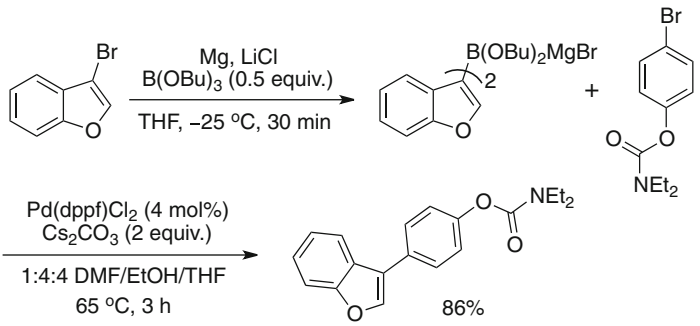
As shown in Scheme 19, a palladium-catalyzed Kumada coupling of the above Grignard reagent, generated via the usual Knochel's Mg/I exchange protocol, with an aryl iodide proceeded at lower temperature than is commonly used in the presence of SPhos as a ligand [28].



Scheme 18 Magnesation of methyl 5-bromofuran-2-carboxylate in the presence of bis[2-(*N*, *N*-dimethylamino)ethyl] ether. The numbers in brackets correspond to the yields of the reactions in the absence of the diamine.



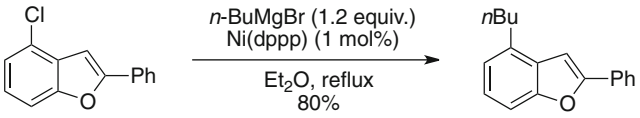
Scheme 19 Kumada coupling of (5-(methoxycarbonyl)2-furyl)magnesium chloride at low temperature



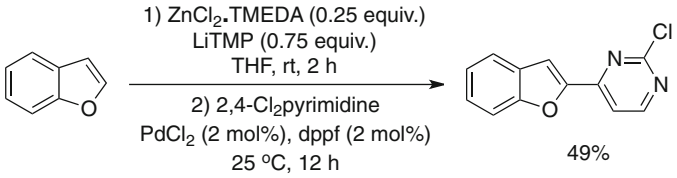
Scheme 20 Suzuki–Miyaura coupling of magnesium dibenzofuranylboronate

The interesting magnesium dibenzofuranylboronate depicted in Scheme 20 was prepared from 3-bromobenzofuran under Grignard-type conditions in the presence of 0.5 equivalents of $B(OBu)_3$. This type of boronate was reactive toward Suzuki–Miyaura coupling, as illustrated [29].

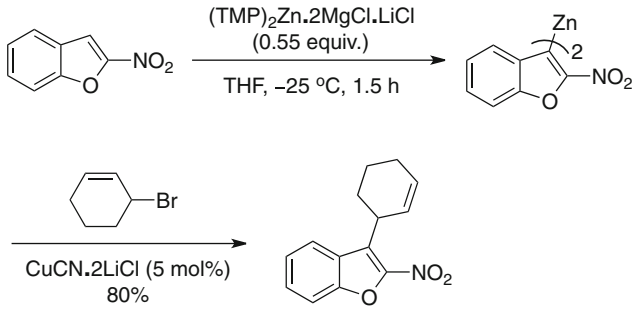
4-Chlorobenzofuran was sufficiently reactive toward a nickel-catalyzed sp^3–sp^2 Kumada coupling with an alkylmagnesium bromide, as depicted in Scheme 21 [22].



Scheme 21 Nickel-catalyzed Kumada coupling of 4-chloro-2-phenylbenzofuran



Scheme 22 Zincation of benzofuran using $ZnCl_2$·TMEDA/LiTMP and subsequent cross-coupling with aryl chloride

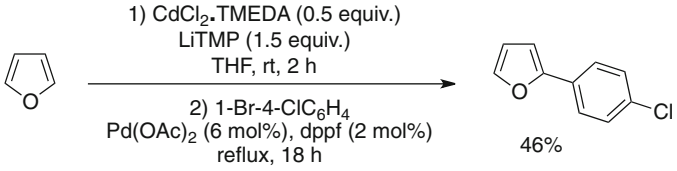


Scheme 23 Zincation of 2-nitrobenzofuran and subsequent Negishi coupling

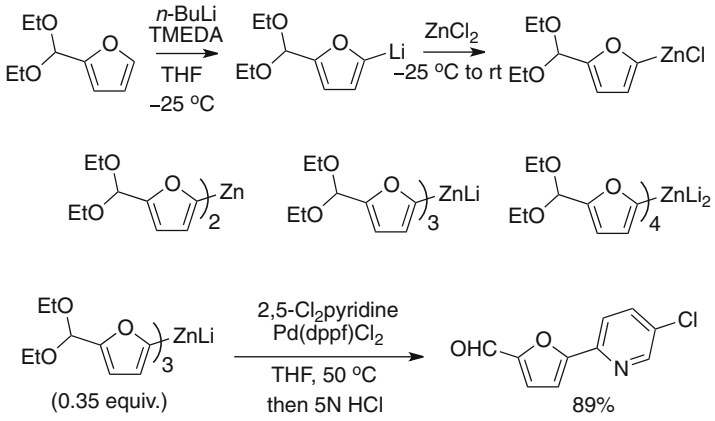
4 Zincation of Furans and Benzofurans, and Their Applications

Zincates at the C2 position of unsubstituted furan and benzofuran were prepared at room temperature by using a mixed base generated in situ from a 1:3 mixture of $ZnCl_2$·TMEDA/LiTMP [30, 31], and used for the addition to aldehydes or a palladium-catalyzed coupling with aryl and heteroaryl chlorides and bromides, as illustrated in Scheme 22.

Addition of 0.5 equivalent of $ZnCl_2$ to TMPMgCl·LiCl generated a complex mixed base $(TMP)_2Zn$·2MgCl·2LiCl [32]. This was used for zincation of arenes and heteroarenes bearing sensitive functional groups, e.g., aldehyde and nitro groups that are not compatible with lithium or magnesium bases, at or near ambient temperature. For example, as shown in Scheme 23, the zincate of 2-nitrobenzofuran



Scheme 24 Cross-coupling of 2-furyl cadmate with arylbromide



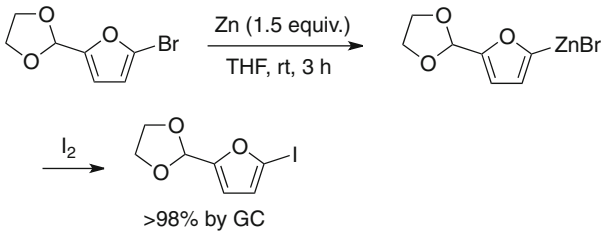
Scheme 25 Palladium-catalyzed cross-coupling of 2-furyl zincate

was formed smoothly at the C3 position using this base and then subjected to a copper-catalyzed Negishi coupling with 3-cyclohexenylbromide.

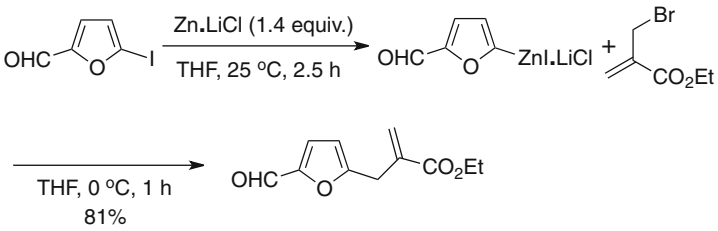
Similar to zincation, unsubstituted furan and benzofuran were also metalated at room temperature by using a cadmium–lithium mixed base generated in situ by mixing 0.5 equivalent of $CdCl_2$·TMDEA with LiTMP [33]. The resulting 2-furyl cadmate directly participated in reaction with acid chlorides to form ketones and palladium-catalyzed cross-coupling with arylbromides, as demonstrated in Scheme 24. However, competing homocoupling and the toxicity associated with cadmium species may limit the application of this metalation method.

As shown in Scheme 25, a 2-furylzinc chloride as well as the corresponding di-, tri-, and higher order zincates were prepared from the 2-lithiofuran by transmetalation using the appropriate stoichiometries of $ZnCl_2$ [34]. These zincates were found to transfer all of the furyl groups during a palladium-catalyzed cross-coupling reaction, as exemplified in Scheme 25.

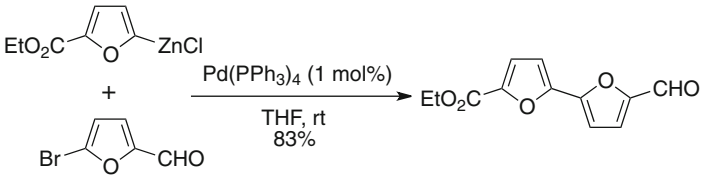
The related 5-(1,3-dioxolan-2-yl)-2-furylzinc was prepared by the direct insertion of Rieke's active zinc to the corresponding bromide at room temperature as shown in Scheme 26 [35]. However, furylzinc reagents could also be generated from unprotected 5-iodo-2-furaldehyde and ethyl 5-bromofuran-2-carboxylate by a LiCl-mediated direct insertion of zinc powder at room temperature, as demonstrated in Scheme 27 [36].



Scheme 26 Formation of 2-furylzinc by the direct insertion of active zinc to 2-bromofuran



Scheme 27 Formation of 5-formyl-2-furylzinc by LiCl-mediated direct insertion of zinc to 5-iodo-2-furaldehyde



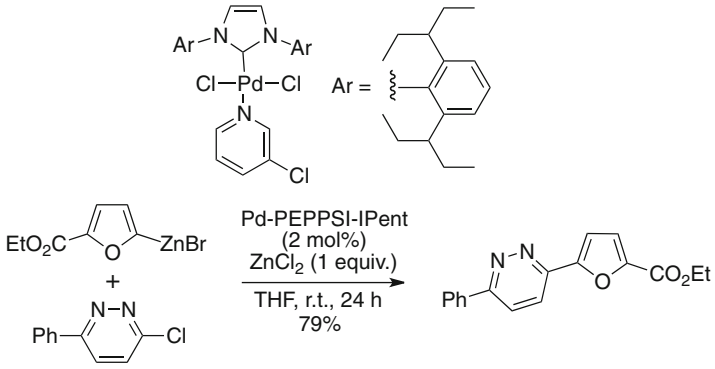
Scheme 28 Palladium-catalyzed cross-coupling of 5-bromo-2-furaldehyde

5-Aryl- and 5-heteroaryl-2-furaldehydes were also prepared from the cross-coupling of 5-bromo-2-furaldehyde with zinc reagents by employing 1 mol% of $(Ph_3Ph)_4Pd$ as catalyst [36, 37], as shown by the interesting example summarized in Scheme 28.

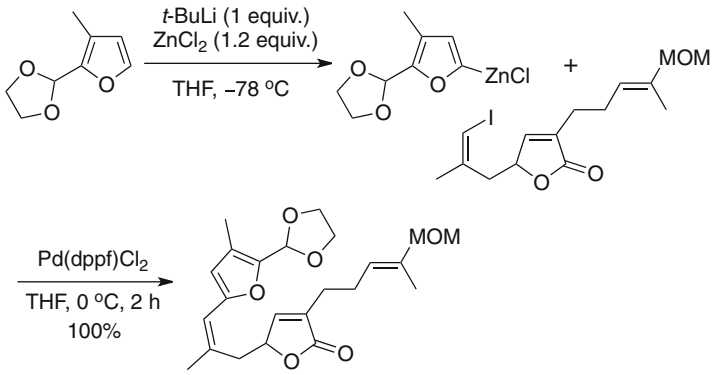
A new palladium-N-heterocyclic carbene (Pd-PEPPSI-IPent) complex was efficient for the Negishi coupling of a 2-furylzinc, enabling the reaction to proceed at room temperature, as depicted in Scheme 29 [38]. This catalyst was also useful for the Suzuki–Miyaura coupling of 3-furylboronic acid and 2-benzofuranylboronic acid [39]. A one-pot zincation of ethyl 5-bromofuran-2-carboxylate using Zn/LiCl followed by a Negishi coupling employing an *i*-Pr analog of Pd-PEPPSI-IPent as a catalyst was also reported [40].

The utility of zinc reagents of 2-furaldehyde derivatives as described above in Negishi coupling was further exemplified by a key step in a total synthesis of the marine natural product bipinnatin J, as shown in Scheme 30 [41].

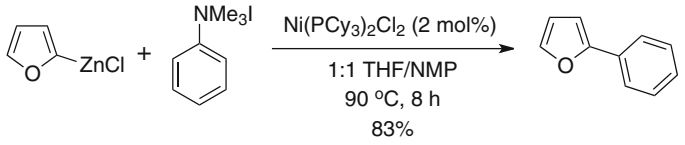
A Negishi coupling of 2-furylzinc with aryltrimethylammonium iodides was promoted by a nickel catalyst, as represented in Scheme 31 [42].



Scheme 29 Negishi coupling of 2-furylzinc using Pd-PEPPSI-IPent catalyst



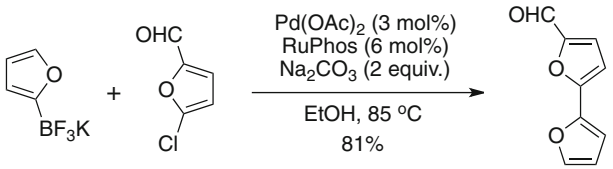
Scheme 30 A key Negishi coupling in a total synthesis of bipinnatin J



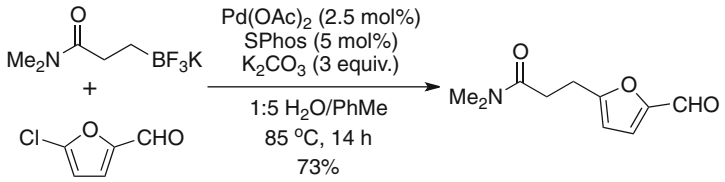
Scheme 31 Nickel-catalyzed cross-coupling of furylzinc with phenyltrimethylammonium iodide

5 Boronated Furans and Benzofurans in Cross-Coupling Reactions

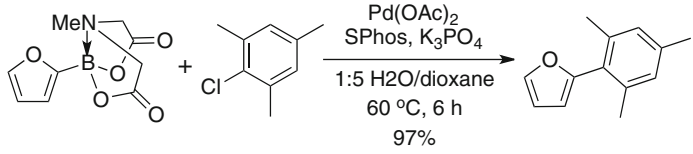
Potassium 2-furyl, 3-furyl, and 2-benzofuranyl trifluoroborates served as efficient nucleophilic coupling partners in equimolar amount in Suzuki–Miyaura cross-coupling reaction. By employing RuPhos as a ligand, the reaction proceeded even with less reactive aryl and heteroaryl chlorides [43]. An interesting example is depicted in Scheme 32. Potassium 2-furyl trifluoroborate, which was prepared by



Scheme 32 Suzuki–Miyaura cross-coupling of potassium 2-furyl trifluoroborate with 5-chloro-2-furaldehyde



Scheme 33 Suzuki–Miyaura cross-coupling of 5-chloro-2-furaldehyde with potassium β-trifluoroborato amide

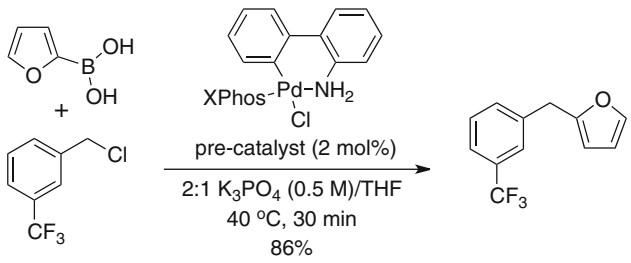


Scheme 34 Suzuki–Miyaura cross-coupling of 2-furyl MIDA boronate

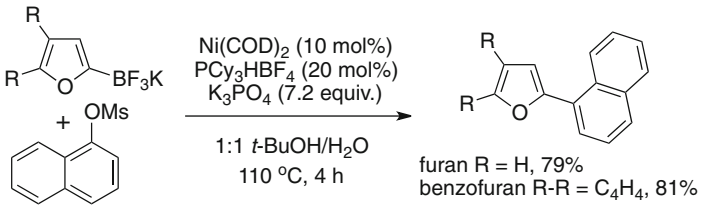
the addition of KHF_2 to 2-furylboronic acid, exhibited stability at ambient temperature for 3 months without sign of proto-deboronation.

Interestingly, 5-chloro-2-furaldehyde reacted with primary alkyl [44] and aminomethyl tetrafluoroborate [45] potassium salts, as well as potassium β-trifluoroborato amide [46], as shown in Scheme 33. Note that the reaction using SPhos as a ligand was sufficiently efficient to prevent undesirable β-hydride elimination.

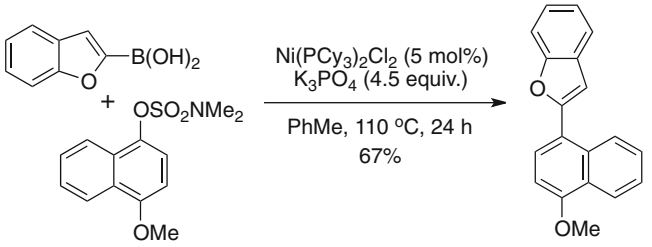
Cross-coupling methods were developed to circumvent the problem of instability of certain aryl and heteroaryl boronic acids, including 2-furyl and 2-benzofuranyl boronic acids, particularly during the reaction with unactivated substrates, e.g., aryl chlorides. 2-Furyl and 2-benzofuranyl *N*-methyliminoacetic acid (MIDA) boronates demonstrated bench-top stability compared to the corresponding boronic acids. Slow release of the boronic acid via in situ hydrolysis of the boronate using K_3PO_4 increased the reaction efficiency of Suzuki–Miyaura cross-coupling, as exemplified by the reaction with the hindered aryl chloride shown in Scheme 34 [47]. Another method employed a XPhosPd precatalyst [48], as illustrated by the benzylic sp^3–sp^2 coupling depicted in Scheme 35, to ensure a rapid formation of the catalytically active XPhosPd(0) species for the transmetalation of the boronic acids.



Scheme 35 Suzuki–Miyaura cross-coupling of 2-furyl boronic acid using a XPhosPd precatalyst



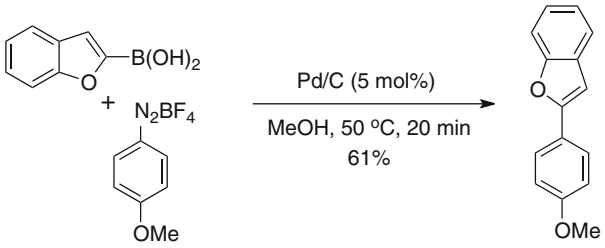
Scheme 36 Nickel-catalyzed cross-coupling of potassium 2-furyl and 2-benzofuranyl trifluoroborates with naphthalen-1-yl mesylate



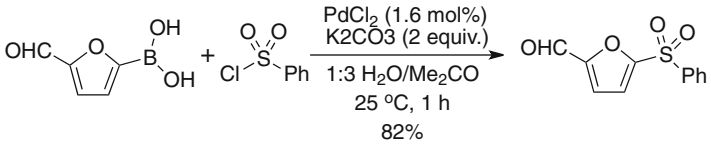
Scheme 37 Nickel-catalyzed cross-coupling of 2-benzofuranyl boronic acid with naphthalen-1-yl dimethylsulfamates

Cross-couplings of boronated furans and benzofurans were expanded to those with halide equivalents as electrophilic partners. For example, potassium 2-furyl, 3-furyl, and 2-benzofuranyl trifluoroborates reacted with various aryl and heteroaryl mesylates in a nickel-catalyzed reaction, providing cross-coupling products in good yields [49], as represented by the examples shown in Scheme 36.

Cross-coupling of 2-benzofuranyl boronic acid and 3-furyl boronic acid with naphthalen-1-yl dimethylsulfamates was accomplished by using $NiCl_2(PCy_3)_2$ as a catalyst [50], as represented in Scheme 37. An example of $(BINAP)PdCl_2$-catalyzed coupling of 3-furyl boronic acid with naphthalen-1-yl imidazolylsulfonate was also reported [51].



Scheme 38 Pd/C-catalyzed cross-coupling of 2-benzofuranyl boronic acid with arenediazonium salt



Scheme 39 Reaction of 2-furyl boronic acid with phenylsulfonyl chloride

2-Benzofuranyl boronic acid also underwent a fast cross-coupling reaction with an arenediazonium salt under ligand-free Pd/C-catalyzed conditions in methanol, as shown in Scheme 38 [52].

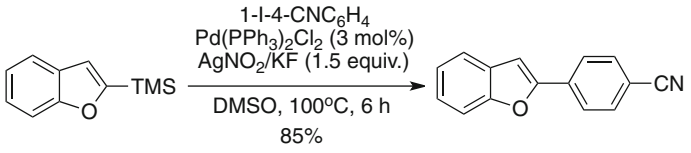
As shown in Scheme 39, a 2-furyl boronic acid also reacted with an arylsulfonyl chloride under palladium catalysis to give unsymmetrical diaryl sulfones at ambient temperature [53].

6 Other Metalated Furans and Benzofurans in Cross-Coupling Reactions

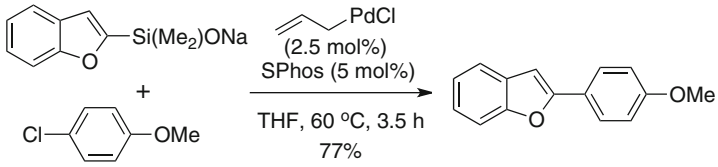
2-Trimethylsilylbenzofuran underwent a palladium-catalyzed Hiyama-type coupling with aryl iodides in the presence of $AgNO_2$/KF as an activator [54], as depicted in Scheme 40. Homocoupling to form 2,2′-bibenzofuran also occurred under these conditions.

Sodium dimethyl(2-furyl)silanolate [55], and sodium dimethyl(2-benzofuryl) silanolate [56] participated in palladium-catalyzed cross-couplings with aryl iodides and bromides through a palladium silanolate complex, which underwent transmetalation at the furan (benzofuran) C2 position. Cross-coupling of the 2-benzofurylsilanolate with aryl chlorides was also made possible by using allylpalladium chloride as a palladium source and SPhos as a ligand, as represented in Scheme 41.

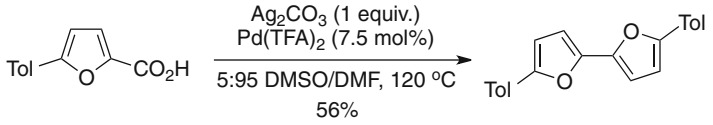
Various metalated furan species were postulated as intermediates in the decarboxylative coupling of furan-2-carboxylic acid. Decarboxylation of



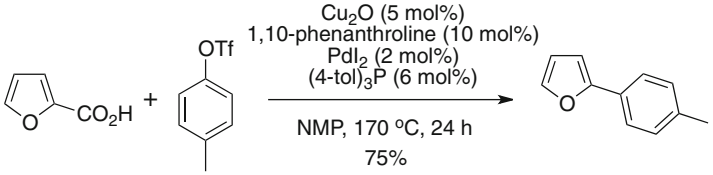
Scheme 40 Hiyama-type cross-coupling of 2-trimethylsilylbenzofuran



Scheme 41 Palladium-catalyzed cross-couplings of sodium dimethyl(2-benzofuryl)silanolate with aryl chloride



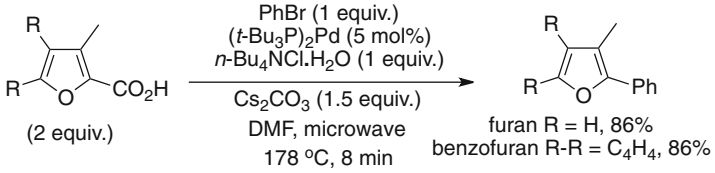
Scheme 42 Decarboxylative homocoupling of 5-tolylfuran-2-carboxylic acid



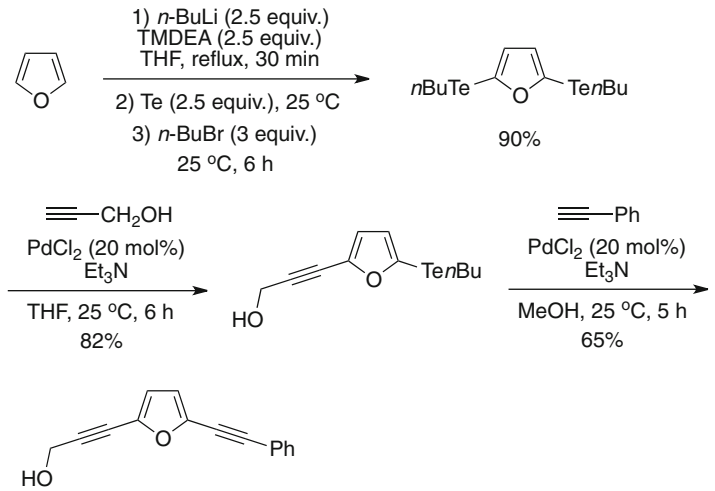
Scheme 43 Decarboxylative hetero-coupling of furan-2-carboxylic acid

5-tolylfuran-2-carboxylic acid or 3-methylbenzofuran-2-carboxylic acid derivatives by silver carbonate generated a (benzo)furan-2-yl silver species that underwent a subsequent palladium-catalyzed homocoupling to give 2,2′-bi(benzo)furan products, as illustrated in Scheme 42 [57]. In the presence of $AsPPh_3$, cross-coupling of 3-methylbenzofuran-2-carboxylic acid with 4-iodoanisole could be achieved [58]. However, the generality of this type of decarboxylative coupling of furan and benzofuran substrates has not been demonstrated.

Another example of decarboxylative hetero-coupling of furan-2-carboxylic acid with 4-tolyl triflate, as depicted in Scheme 43, involved a 2-furyl copper species in the catalytic cycle that underwent transmetalation with palladium [59, 60].



Scheme 44 Palladium-catalyzed decarboxylative coupling of furan- and benzofuran-2-carboxylic acids



Scheme 45 Palladium-catalyzed cross-coupling of 2,5-bis(butyltelluro)furan with acetylenes

A related palladium-catalyzed decarboxylative coupling only proceeded with furan- and benzofuran-2-carboxylic acids, but not with the corresponding 3-carboxylic acid, as represented in Scheme 44 [61]. A mechanism that involved an electrophilic palladation at the furan C3 position followed by C3–C2 palladium migration and decarboxylation was postulated.

2-Furyl zinc chloride reacted with vinyl tellurides in a Pd-catalyzed cross-coupling in the presence of CuI [62]. As demonstrated in Scheme 45, 2-(butyltelluro)furan [63] and 2,5-bis(butyltelluro)furan [64] were prepared via lithiofuran. Successive palladium-catalyzed coupling of 2,5-bis(butyltelluro)furan with different acetylenes was feasible, forming unsymmetrical 2,5-bis-alkynyl furans [64], as represented. 2-(Butyltelluro)furan is also reactive toward $(Ph_3P)_4Pd$-catalyzed Ag_2O-promoted cross-coupling with potassium phenyl tetrafluoroborate [65].

7 Regioselective Functionalization of Poly-halogenated Furans and Benzofurans

Earlier chemistry focused on the regioselective functionalization of 2,3-dibromofurans and 2,4-dibromofuran, as depicted in Fig. 2, through Suzuki–Miyaura, Stille and Sonogashira cross-couplings with reaction occurring initially at the C2 position has been demonstrated and recently reviewed [66].

A recent example in this area is the preparation of a template for the synthesis of a skeletally diverse small molecule library [67] through an sp^3–sp^2 Suzuki–Miyaura coupling between a solid support-bound alkyl borane and 4,5-dibromo-2-furaldehyde, as shown in Scheme 46. Competitive β-hydride elimination was minimized by the use of $Pd(dppf)Cl_2$ as a catalyst.

Interestingly, the Suzuki–Miyaura coupling of (*Z*)-2-(2-bromo-2-nitroethenyl)-5-bromofuran with one equivalent of a boronic acid also occurred regioselectively at the C2 position rather than at the exocyclic carbon–bromine bond, as illustrated in Scheme 47 [68].

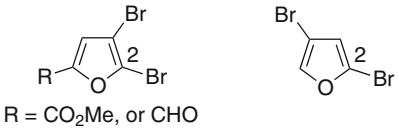
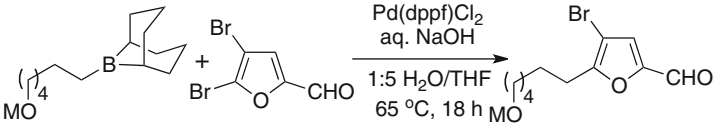
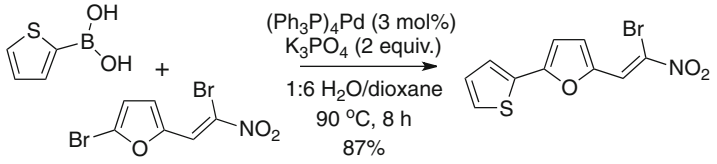


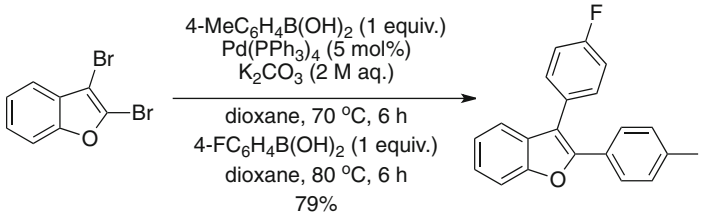
Fig. 2 2,3-Dibromofurans and 2,4-dibromofuran



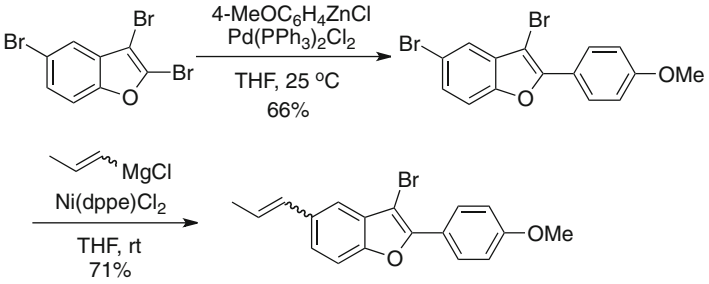
Scheme 46 Regioselective sp^3–sp^2 Suzuki–Miyaura coupling of 4,5-dibromo-2-furaldehyde (M = macrobead)



Scheme 47 Suzuki–Miyaura coupling of (*Z*)-2-(2-bromo-2-nitroethenyl)-5-bromofuran with boronic acid



Scheme 48 Regioselective Suzuki–Miyaura coupling of 2,3-dibromobenzofuran



Scheme 49 Regioselective cross-coupling of 2,3,5-tribromobenzofuran

Regioselective cross-coupling of polybromobenzofuran is also feasible. The selectivity is based on the electronic nature of the substituted carbon atom, with the initial reaction occurs at the less electron-rich carbon atom. As illustrated in Scheme 48, 2,3-dibromobenzofuran could be sequentially functionalized at the C2 position and then the C3 position in a one-pot fashion in a $(Ph_3Ph)_4Pd$-catalyzed Suzuki–Miyaura coupling reaction using two different aryl boronic acids [69]. Benzofuran-3-yl triflates, prepared from benzofuran-3-ones, participated in palladium-catalyzed Stille, Heck, Suzuki–Miyaura and Sonogashira couplings [70]. A Stille coupling of 2-bromobenzofuran-3-yl triflate was observed to occur at the C3 position in a modest ~2:1 selectivity [71]. A related Stille coupling of 2,5-dibromo-7-methoxybenzofuran, however, took place predominantly at the C2 position [72].

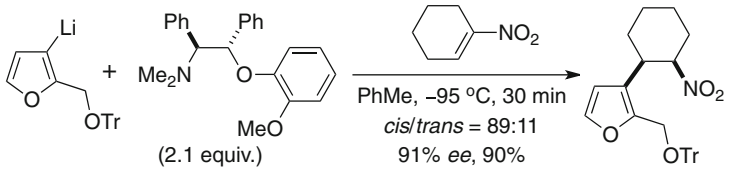
Negishi and Sonogashira couplings also occurred at the C2 position of 2,3,5-tribromobenzofuran first [73]. However, it was more challenging to differentiate the C3 and C5 positions by a palladium-catalyzed coupling. This was solved by a lithium–bromide exchange with *t*-BuLi that occurred selectively at the C3 position or by a nickel-catalyzed C5-selective Kumada coupling as shown in Scheme 49 [74]. The approach was applied to the synthesis of eupomatenoids [75].

8 Metalated Furans and Benzofurans in Addition Reactions

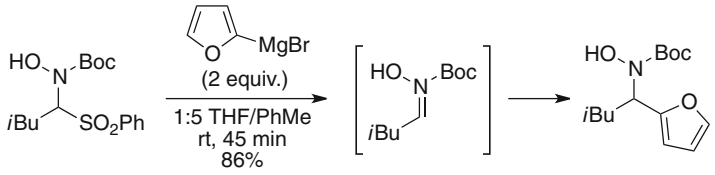
Metalated furans have been increasingly used in diastereoselective and enantioselective addition reactions. For example, reaction of 2-furyllithium with a chiral *tert*-butanesulfinyl imine provided the adduct with >12:1 diastereomeric ratio [76]. Addition of 2-furyllithium or 2-benzofuryllithium to chiral SMAP-hydrazone furnished the adduct in >95% diastereomeric excess [77]. A diastereoselective and enantioselective addition of a sterically bulky 3-(2-trityloxymethyl) furyllithium, prepared in situ from the corresponding 3-bromofuran and *n*-BuLi, to nitroalkene was realized by the use of a chiral amino ether ligand, as shown in Scheme 50 [78]. This method provided an access to interesting furo-fused piperidine ring.

2-Furylmagnesium bromide acted as a base and then a nucleophile in the reaction with a *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamate to form the furyl-substituted hydroxylamine product through a *N*-Boc nitrone intermediate, as depicted in Scheme 51 [79].

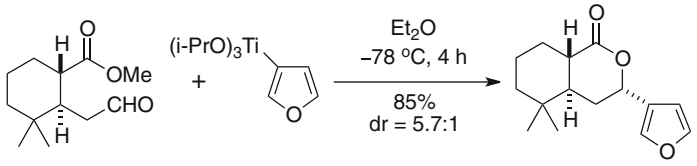
3-Furyltitanium, [(3-furyl)Ti(O*i*-Pr)$_3$]$_2$, was prepared from the reaction of 3-furyllithium with Ti(O*i*-Pr)$_3$Cl in THF at −78°C. Addition of this reagent to a range of acetophenone derivatives at 0°C in the presence of (*S*)-BINOL furnished tertiary 3-furanylcarbinols with *ee* up to 97% [80]. Similarly, the use of 2-furylaluminum (2-furyl)AlEt$_2$(THF) provided 2-furanylcarbinols with *ee* up to 93% [81]. 3-Furyltitanium also appeared to be more effective in addition to aliphatic aldehydes compared to the corresponding lithium, magnesium, and zinc reagents. As exemplified in a total synthesis of (+)-ricciocarpins A shown in Scheme 52, the



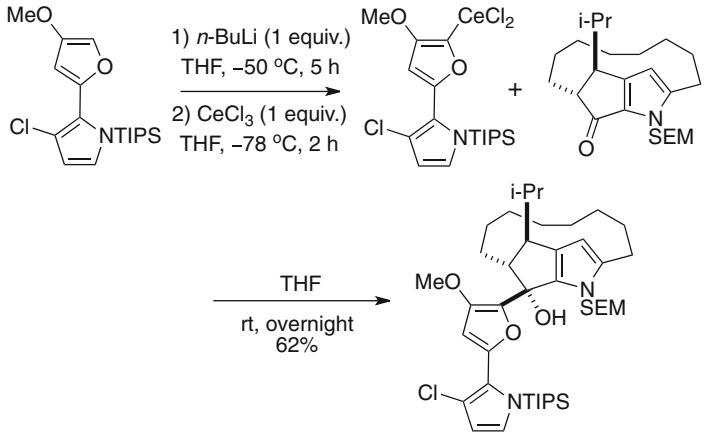
Scheme 50 Asymmetric addition of 3-(2-trityloxymethyl)furyllithium to nitroalkene



Scheme 51 Reaction of 2-furylmagnesium bromide with *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamate



Scheme 52 Addition of 3-furyltitanium to an aliphatic aldehyde



Scheme 53 Addition of 2-furylcerium to a ketone

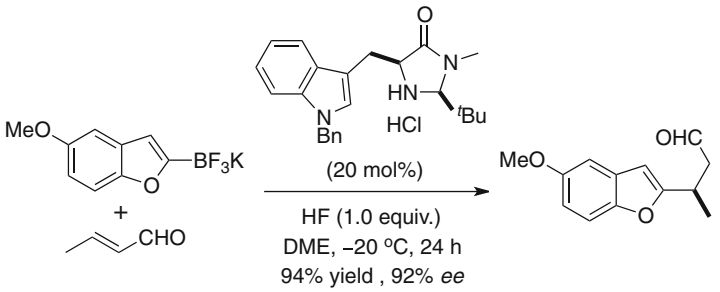
use of the titanium reagent provided the highest yield and diastereoselectivity in the reaction with the penultimate aldehyde bearing an acidic α-proton [82].

2-Furylcerium derivatives are less commonly used; however, they also appear to show high nucleophilicity to allow reactions with ketones and sterically demanding substrates. A remarkable example is the key penultimate reaction in a total synthesis of roseophilin, as shown in Scheme 53 [83]. Note that the furan C2 position was exclusively lithiated and transmetalated primarily due to the steric hindrance around the pyrrole C2 position that was imparted by the bulky TIPS group.

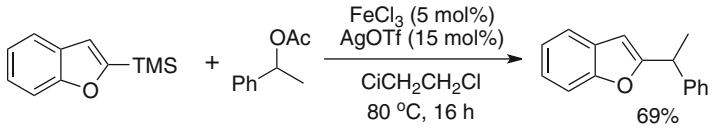
2-Benzofuranyl boronic acid and its potassium trifluoroborate salt reacted as nucleophiles in an enantioselective organocatalytic Friedel–Crafts alkylation with crotonaldehyde, as shown in Scheme 54. An example using potassium 2-furyl trifluoroborate was also reported [84]. This method was employed in a total synthesis of (+)-frondosin B [85].

A similar type of reaction involves the addition of 2-trimethylsilylbenzofuran to benzylic acetates in the presence of a catalytic amount of $FeCl_3$/AgOTf to form 2-benzyl substituted benzofurans as shown in Scheme 55 [86].

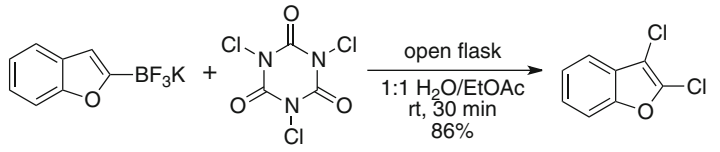
Potassium 2-benzofuranyl trifluoroborate reacted with trichloroisocyanuric acid to furnish 2,3-dichlorobenzofuran, as depicted in Scheme 56 [87]. Although it was shown that the dichloro product was not derived from an initial chlorodeboronation, the mechanism of this reaction remains uncertain.



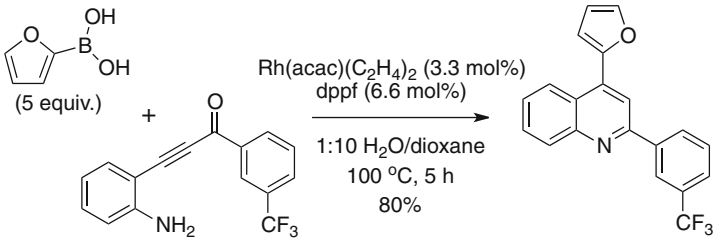
Scheme 54 Nucleophilic addition of potassium 2-benzofuranyl trifluoroborate to crotonaldehyde



Scheme 55 Iron-catalyzed addition of 2-trimethylsilylbenzofuran to benzylic acetate

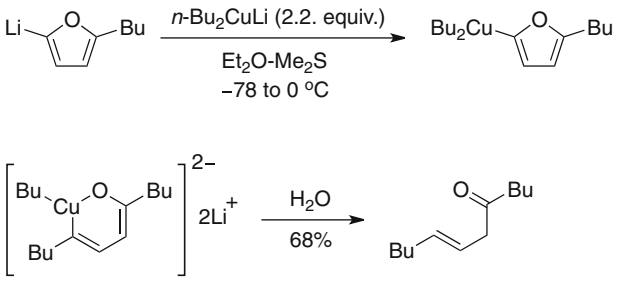


Scheme 56 Reaction of potassium 2-benzofuranyl trifluoroborate with trichloroisocyanuric acid

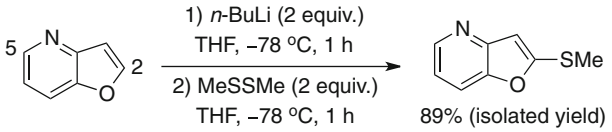


Scheme 57 Rhodium-catalyzed hydroarylation of a β-aminophenyl alkynone with 2-furyl-2-boronic acid

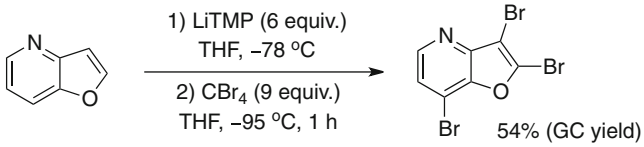
Hydroarylation of a β-aminophenyl alkynone with 2-furylboronic acid to provide a quinolone derivative was achieved by using a rhodium catalyst, as illustrated in Scheme 57 [88].



Scheme 58 1,2-Metalate rearrangement of 2-furylcuprate



Scheme 59 Lithiation of 4-azabenzofuran (furo[3,2-*b*]pyridine) using *n*-BuLi



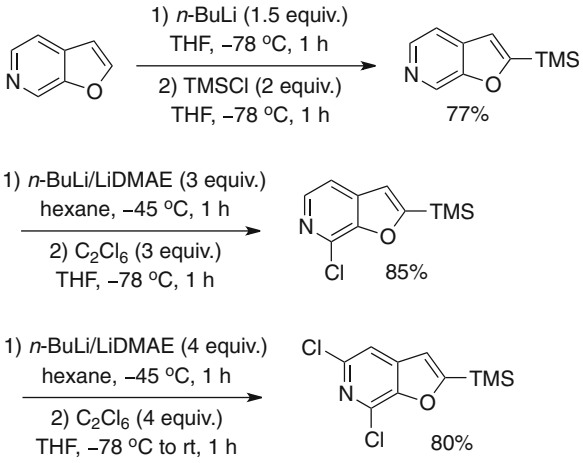
Scheme 60 Lithiation of 4-azabenzofuran (furo[3,2-*b*]pyridine) using LiTMP

The 2-furylcuprate shown in Scheme 58 underwent a 1,2-metalate rearrangement to provide the ring-opened product [89].

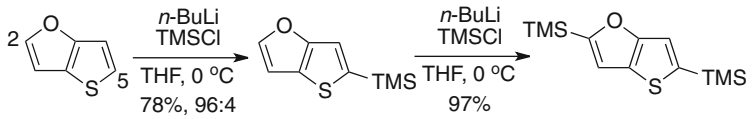
9 Lithiation of Related Furo Heterocycles

Lithiation of 4-azabenzofuran (furo[3,2-*b*]pyridine) using *n*-BuLi in THF occurred predominantly at the C2 position, which was quenched with various electrophiles (e.g., Br, Si, Sn, S, and B), as exemplified in Scheme 59 [90]. The use of an increased excess amount of LiTMP resulted in the di- and tri-lithiation at the C2, C3, and C7 positions as indicated by the 2,3-dibromo and 2,3,7-tribromo derivatives that were detected (Scheme 60). It was observed that the corresponding C3 mono-lithiated species was unstable and the lithiation at the C5 position had not occurred under these conditions.

The corresponding lithiation of 6-azabenzofuran (furo[2,3-*c*]pyridine) using *n*-BuLi in THF also occurred exclusively at the C2-position [91]. If the C2 position



Scheme 61 Sequential lithiation of 6-azabenzofuran (furo[2,3-*c*]pyridine)



Scheme 62 Lithiation of thieno[3,2-*b*]furan

was blocked by a TMS group, deprotonation occurred at the C7 position followed by at the C5 position using an *n*-BuLi/lithium dimethylaminoethoxide (LiDMAE) mixed base, as illustrated in Scheme 61.

However, deprotonation of thieno[3,2-*b*]furan, first isolated in 2009, using *n*-BuLi occurred predominantly at the C5 position [92]. Deprotonation at both the C2 and C5 was feasible by using two equivalents of the base, as shown in Scheme 62.

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Lithiation-Based and Magnesation-Based Strategies for the Functionalization of Imidazole: 2001–2010

Philip E. Alford

Abstract A review of lithiation-based and magnesation-based strategies for the functionalization of imidazole reported from 2001 to 2010.

Keywords Imidazole · Lithiation · Magnesation · Metalation

Contents

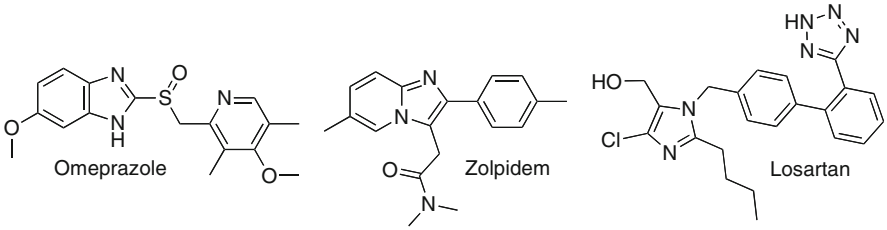
1 Introduction 77
2 Background 78
3 Direct Lithiation 81
3.1 Lithiation at N–1 81
3.2 Lithiation at C–2 82
3.3 Lithiation at C–4 87
3.4 Lithiation at C–5 89
3.5 Lateral Lithiation 90
4 Metal-Halogen Exchange 92
4.1 Lithium- and Magnesium-Halogen Exchange 92
4.2 Dilithio and Dimagnesioimidazoles 94
4.3 Sequential Metalation 96
5 Applications in Total Synthesis 97
References 100

1 Introduction

Imidazole is a common structural element in biology and medicinal chemistry. As the defining functionality in the amino acid histidine, imidazole is a component of the fundamental building blocks of life. Imidazole moieties provide a molecular

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framework capable of interacting with a diverse range of biological receptors. For this reason, imidazoles form the core architecture of many biologically active natural products as well as several blockbuster drugs (Scheme 1). The functionalization of imidazoles is an important process in drug discovery and total synthesis, particularly when functionalization involves the formation of new carbon–carbon bonds.

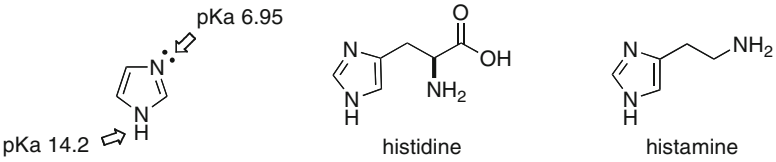


Scheme 1

One of the most important methods for the C–C functionalization of imidazole is via organometallic intermediates. The accessibility and versatility of imidazolyllithium salts in particular are simply unrivaled. Generated from either direct lithiation or via lithium-halogen exchange, these reactive intermediates allow transmetalation, reduction, and reaction with the complete range of electrophilic reagents. This review will discuss some of the metalation-based strategies used and advancements made for the functionalization of imidazole, particularly those that involve the formation or use of imidazolyl lithium and imidazolyl magnesium salts.

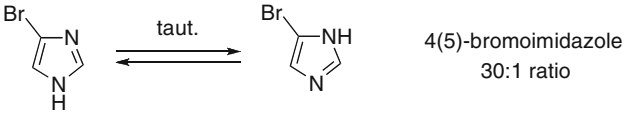
2 Background

The amphoteric heterocyclic structure of imidazole offers contradictory reactivities. Due to the unsubstituted nitrogen at the 3-position, imidazole is a mild Lewis base (p*K*a 6.95) with a propensity to form metal chelates and other Lewis base adducts. At the same time, imidazole contains a mildly acidic N–H that is easily deprotonated (p*K*a 14.2) with only moderately strong bases. It is due to this dual nature that imidazole, as histidine, plays a frequent role at the active sites of enzymes and other biological systems (Scheme 2). For example, at the iron-heme center of hemoglobin, histidine covalently binds iron tightly linking the porphyrin to the globulin protein and inducing conformational changes in response to oxygenation. Produced via decarboxylation of histidine, histamine triggers the inflammatory response in the immune system as well as modulating neurotransmitter release in the central nervous system.



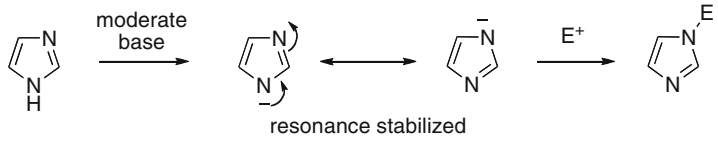
Scheme 2

Imidazole readily tautomerizes in protic solvent or simply via proton exchange with itself [1]. In the case of nonsymmetrical imidazoles, the presence of these tautomers results in a mixture of isomers. Nomenclature can be used to specifically articulate the presence of these tautomers as shown in Scheme 3 [2].



Scheme 3

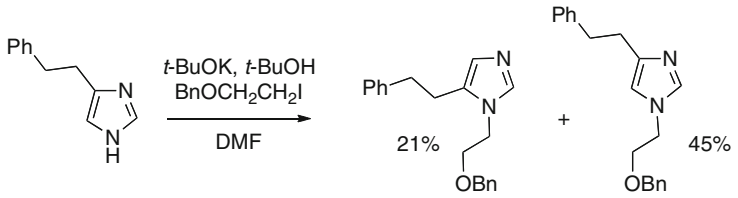
In synthetic and organometallic chemistry, the Lewis basicity of imidazole has allowed the molecule to find use as a Brönsted base, ligand, and directing-chelating moiety [3]. The acidity of N–1 allows facile formation of N–1 metalated imidazoles. Deprotonation generates the symmetrical resonance stabilized imidazolyl anion as shown in Scheme 4.



Scheme 4

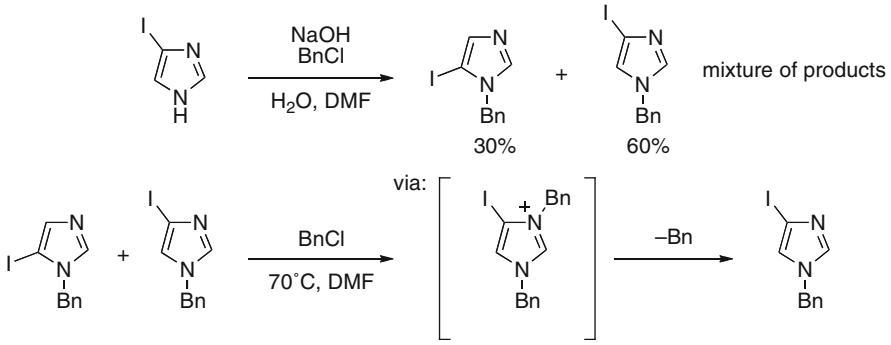
Addition of an electrophile conveniently furnishes N–1 substituted imidazoles. However, in some substituted imidazoles, due to the resonance stabilized imidazolyl anion, addition of electrophiles can produce a mixture of products depending on which nitrogen initiates nucleophilic attack and the relative reactivities of each [4, 5]. A recent example from Vasella in Scheme 5 illustrates this phenomenon [6].

However, two different groups have reported that in several exemplary cases, the mixture resulting from electrophilic substitution at N–1 can be converged to the less sterically hindered 1,4-substituted imidazole by treatment with an additional equivalent of the electrophilic species used to originally substitute the N–1 position [7, 8]. Addition of a reactive electrophile such as benzyl chloride results in attack by the nucleophilic nitrogen at the N–3 position to produce a disubstituted imidizolium



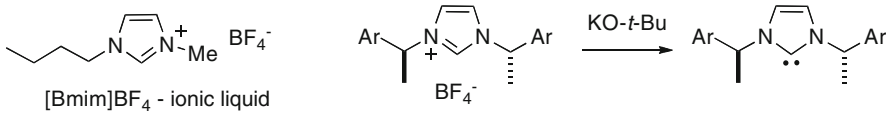
Scheme 5

ion which subsequently eliminates one equivalent of the more N-substituent. Scheme 6 exemplifies use of this method to resolve a mixture of products resulting from unselective electrophilic substitution at N–1.



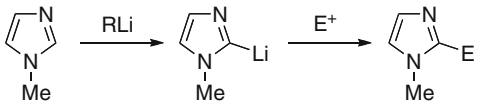
Scheme 6

Imidazolium salts produced from substitution at both nitrogens are commonly used as ionic liquids, which have been the subject of several recent reviews [9–11]. These compounds are also precursors to useful imidazolylidene carbenes (Scheme 7) used in organocatalytic reactions and stabilized carbenes for ligands in organometallic chemistry [12, 13]. Both chiral ionic liquids [9] and chiral imidazolylidene carbenes [14, 15] have been employed in recent years.



Scheme 7

For the functionalization of imidazole at the C–2, C–4, and C–5 positions, lithiation provides direct access to highly versatile organometallic species. The 2-position is the most easily lithiated carbon center of imidazole assuming that the N-position has been protected with a suitable protecting or blocking group (Scheme 8).



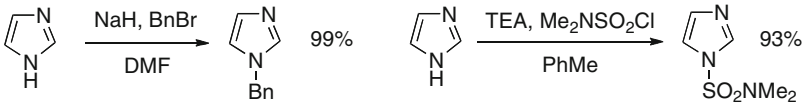
Scheme 8

The 2-position of *N*-methylimidazole has a p*K*a of 33.7, allowing facile deprotonation with a variety of common organolithium bases [16]. However, because some imidazoles, benzimidazoles, and their substituents can be vulnerable to nucleophilic attack and ring-opening reactions, a bulky organolithium reagent such as LDA is sometimes preferred over *n*-butyllithium [17]. For lithiation at other positions, the order of carbon acidity is as follows: C–2 > C–5 > C–4.

3 Direct Lithiation

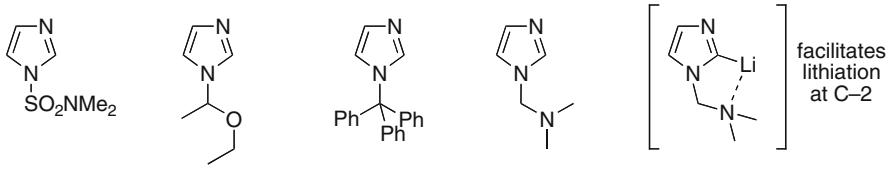
3.1 Lithiation at N–1

As described above, N–1 deprotonated imidazolyl anions are convenient precursors to 1-substituted imidazoles and can be prepared using moderate bases (Scheme 9). This approach is commonly used to prepare N-protected imidazoles which are often necessary precursors for lithiation at the carbon positions [18].



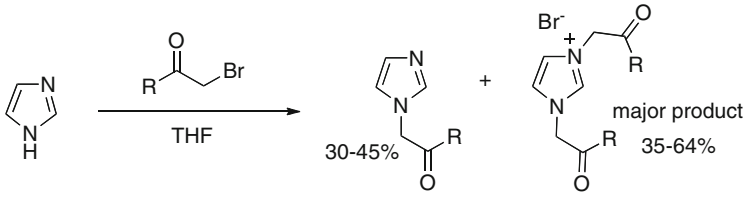
Scheme 9

Some of the substituents at N–1 that are most effective at protecting the imidazole nitrogen under lithiation conditions are presented in Scheme 10. In many cases, these substituents even facilitate lithiation via chelation/directing metalation, such as dimethylaminosulfonyl, phenylsulfonyl, 1-ethoxyethyl, dimethylaminomethyl, trimethylsilylethoxymethyl, and diethoxymethyl [18–22].



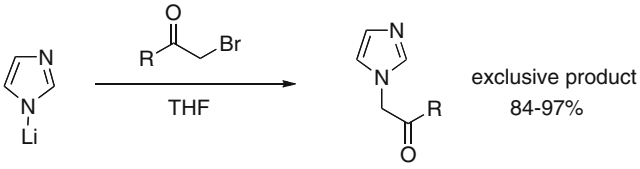
Scheme 10

While 1-substituted imidazoles can be accessed without use of base and without passing through a metalated intermediate, one of the advantages offered by use of N–1 metalated imidazoles, specifically 1-lithioimidazoles, is demonstrated in a recent paper by Wong et al. [23]. As shown in Scheme 11, treatment of imidazole with α-bromoketones produced a mixture of products, which favored formation of the undesired imidazolium salt.



Scheme 11

In contrast, use of an N–1 metalated lithium imidazolide produces exclusively the desired product (Scheme 12). In this case, formation of the N-lithioimidazole results in a reactive imidazole anion which quickly consumes the electrophile while the relatively slow-reacting neutral N–3 of the product simply spectates [23].

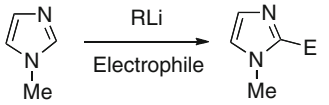


Scheme 12

3.2 Lithiation at C–2

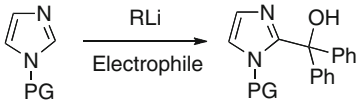
2-Lithioimidazoles are commonly prepared from N-protected imidazoles at low temperature in ethereal solvent by using lithium amides or alkyllithium reagents [24, 25]. This method has proven highly general and has demonstrated excellent results for functionalization of the 2-position with a wide variety of electrophilic reagents including alkyl, alkenyl, hydroxyalkyl, halogen, acyl, carboxyl, silyl, sulfanyl, and azido (Scheme 13) [26, 27]. However, even as recently as the past decade, several types of electrophiles continue to produce poor results when treated with 2-lithioimidazolyl salts.

The varied yields of these reactions have been explained in terms of hard–soft acid–base theory with imidazolyl carbon anions acting as hard bases. Katrizky et al. have suggested that reaction of imidazole salts with hard electrophiles produces higher yields than does reaction with comparable soft electrophiles [28].



Electrophile	Yield (%)
Me_2SO_4	68
Br_2	80
CO_2	39
DMF	65
PhN_3	70
TMSCl	56
Me_3SnCl	86
HCO_2Et	44
$ClCO_2Me$	48
cyclohexanone	56

Scheme 13

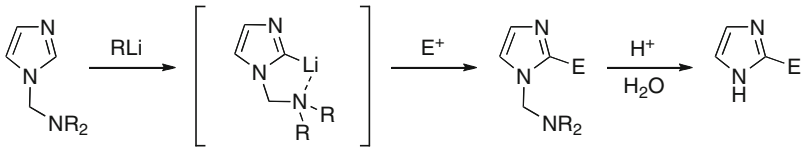


Protecting group	Yield (%)
$-CH_3$	90
$-CH_2OCH_3$	78
$-CH_2OCH_2Ph$	82
$-CH_2OCH_2OCH_3$	83
$-CH(CH_3)OCH_3$	88
$-CH_2N(CH_3)_2$	72
$-SO_2N(CH_3)_2$	60

Scheme 14

As noted above, to access the 2-position, it is first necessary to protect or block the N–1 position; Scheme 14 provides a comparison between some N–1 protectings groups [26, 27]. In addition, a host of new protecting strategies have been recently reported or improved specifically for the purpose of preparing imidazole for lithiation at C–2.

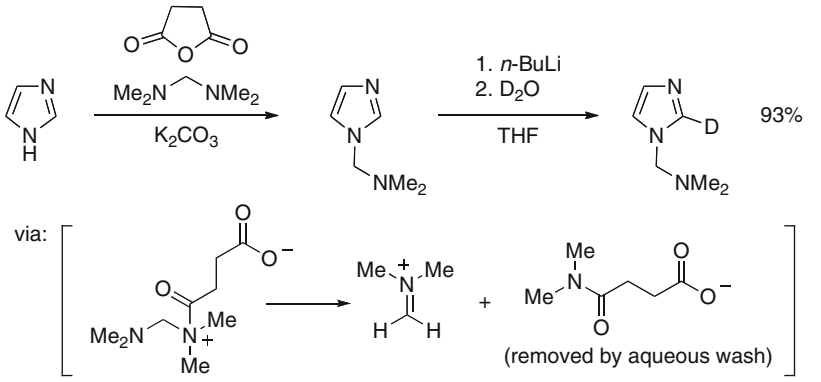
The dimethylaminomethyl group was originally devised by Katrizky et al. to facilitate lithiation at C–2 yet prove easily removable thereafter. Scheme 15 illustrates these advantages; however, initial incorporation of the group at N–1 via traditional Mannich conditions involves unfortunately lengthy reaction times [29].



Scheme 15

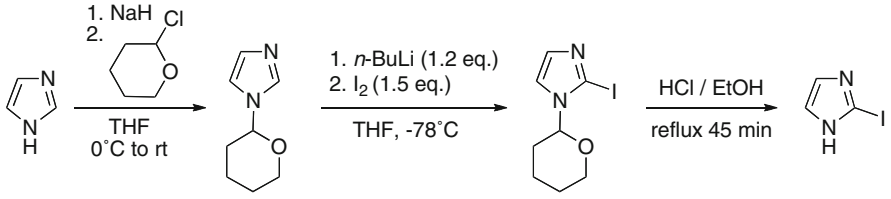
Recently, Love et al. reported a new method to improve the convenience of performing protections with dimethylaminomethyl on imidazole [30]. The novel conditions shown in Scheme 16 involve treatment of substituted aminals with

succinic anhydride to generate a quaternary trialkylacyl ammonium salt in situ which fragments to produce a Mannich reagent and water soluble by product. As a result, Love's method takes about an hour with a simple purification requiring no more than washing with aqueous base.



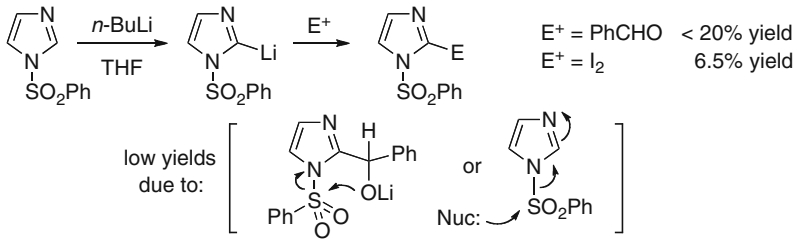
Scheme 16

Tetrahydropyran (THP) has found increased popularity as an easily removed protecting group used for protecting N–1 of imidazole during lithiation [31]. THP withstands highly basic conditions and perhaps even facilitates lithiation of N-THP-imidazole at C–2. After lithiation, the THP group can be easily removed by refluxing in HCl ethanol solution (Scheme 17).



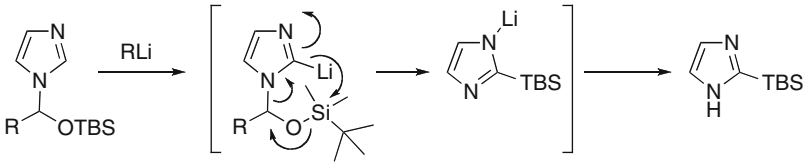
Scheme 17

Of course, not all 1-substituted imidazoles provide adequate protection. Even nitrogen protecting groups that show excellent stability with other nitrogen heterocycles can show lackluster results when used with imidazole. A protecting group like that shown in Scheme 18 which may undergo nucleophilic attack from an organolithium species can result in deprotection via nucleophilic displacement of imidazole [19]. In short, the resonance stabilized imidazolyl anion can be a surprisingly good leaving group.



Scheme 18

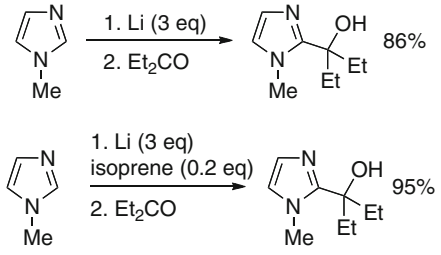
As another example, Gimisis et al. unexpectedly observed that direct lithiation of a N-(silyloxyalkyl)imidazole at C–2 resulted in an intramolecular rearrangement (Scheme 19). The nucleophilic 2-position traitorously attacks the TBDMS group at silicon to release an aldehyde and imidazolyl lithium salt [32].



Scheme 19

n-Butyllithium and LDA have long reigned as the de facto reagents for lithiation of imidazole. However, the traditional procedure for generating 2-lithioimidazoles with these reagents is not always convenient. Further, low temperature (–78°C) conditions and the use of highly reactive organolithium reagents do not produce good results with all electrophiles; enolizable carbonyl and imine compounds in particular have been especially problematic.

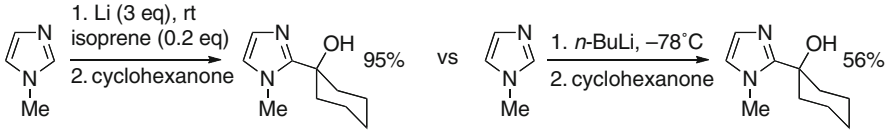
Overcoming many of these issues, Yus et al. have developed a mild room temperature method for the direct lithiation of imidazole derivatives (Scheme 20) [33].



Scheme 20

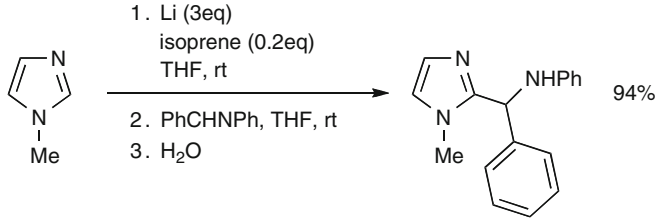
The Yus group discovered that treating N-methylimidazole with lithium metal generates 2-lithio-N-methylimidazole in high yield under mild conditions (Scheme 20). Well aware of arene-catalyzed lithiation methods, Yus et al. investigated use of electron-carrier agents including naphthalene, 4,4-di-*t*-butyl-biphenyl, and isoprene to improve their room temperature lithium metal metalation method. Where other electron-carriers showed no effect, the use of isoprene as an additive resulted in improved results. As seen above, use of isoprene raises yields from merely good to excellent.

These lithium-isoprene conditions even show improved results over traditional conditions, particularly with difficult enolizable carbonyl electrophiles. Scheme 21 emphasizes the excellent improvement realized over traditional methods.



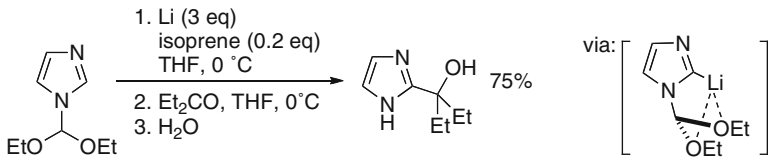
Scheme 21

In light of their success with carbonyl electrophiles, Yus et al. further investigated use of N-silylated imine electrophiles – electrophiles that had yet to find a generalized method for use with 2-lithioimidazoles (Scheme 22) [33].



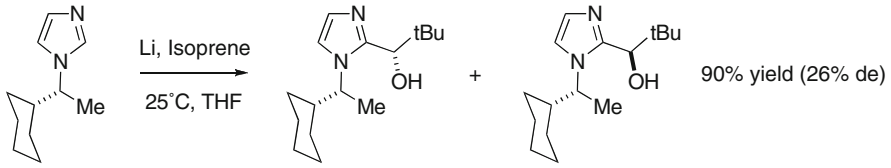
Scheme 22

However, because lithium-isoprene conditions result in a reductive system, the majority of typical protecting groups for lithiation become labile and are removed via reductive cleavage. For this reason, lithium-isoprene conditions have been limited to use with imidazoles bearing an robust alkyl or aryl group at N–1 [34]. Under the mild yet reductive lithium-isoprene conditions, trityl, allyl, benzyl, tosyl, Boc, acetyl, trimethylsilyl, and even *t*-butyldimethylsilyl groups are all removed in greater than 70% yield. While dimethylsulfonamide and vinyl groups fared slightly better, diethoxymethyl groups proved vastly superior to all other protecting groups tested. While investigating the range of N-protected imidazoles, Yus et al. devised a new approach to 2-substituted-1-unsubstituted imidazoles by a by use of a tandem lithiation-deprotection strategy using 1-(diethoxymethyl)imidazole [35].



Scheme 23

Pastor et al. investigated lithiation of imidazoles substituted at N–1 with a chiral secondary alkyl moiety – the first time this type of reaction has been investigated for 2-lithioimidazoles. Using lithium-isoprene conditions, chiral induction was observed for the C–2 bond forming reaction of the 2-lithioimidazole with pivaldehyde. Though the diasterometric excess is relatively low, the method emphasizes how mild lithium-isoprene conditions are, even at room temperature, and proves that intermolecular asymmetric induction is possible in such systems [36].



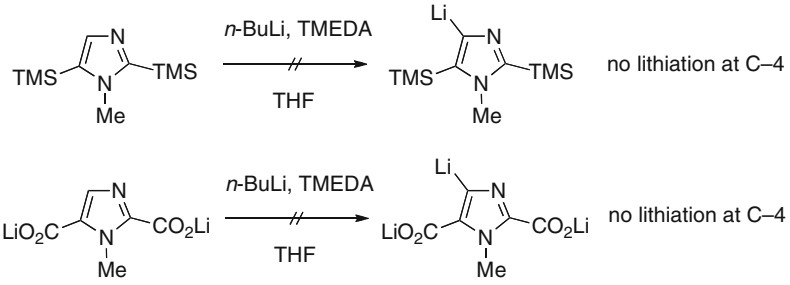
Scheme 24

The 2-lithioimidazole intermediate resulting from lithium-isoprene is a markedly different species than that generated from traditional alkyllithium or lithium amide reagents. In a recent paper, Yus et al. investigate mechanistic considerations of this reaction via computational methods, revealing an equilibrium between imidazole and isoprene anions [37].

3.3 Lithiation at C–4

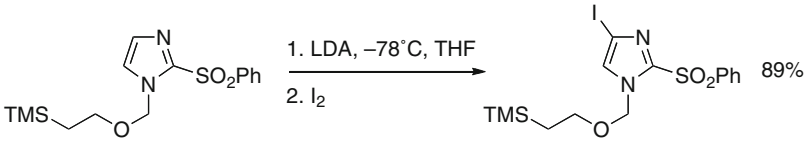
While access to 2-lithioimidazoles is relatively straightforward, lithiation at the other carbon centers requires multiple steps or blocked positions. Due to the adjacent nitrogen lone pair at N–3, the 4-position is particularly difficult to lithiate. As discussed, lithiation favors the more reactive 2-positions and 5-positions, yet even when these positions are blocked lithiation does not always proceed even with exceptionally strong bases (Scheme 23).

When both the 2-positions and 5-positions are blocked with a trimethylsilyl group, lithiation does *not* produce the expected 4-lithioimidazole (Scheme 24). Instead, upon quenching with water and workup, the 2-desilylated product is recovered [38]. Katrizky et al. also attempted direct lithiation at C–4 of 1-methylimidazole 2,5-dilithiocarboxylate to no avail, in this case producing the 2-decarboxylated product [39].



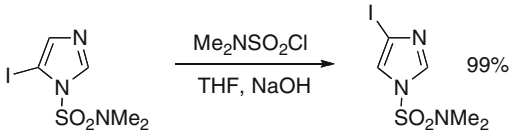
Scheme 25

Though direct lithiation of C–4 is not a general synthetically useful method, there are apparent exceptions as found in a system described by Phillips et al. Noting that 1-trityl-2-phenylimidazole is known to undergo direct lithiation at C–4 in (very) low yields, Phillips investigated the sterically analogous 1-[2′-(trimethylsilyl) ethoxymethyl]-2-phenylsulfonylimidazole system (Scheme 25). Though use of *n*-BuLi gave a mixture of 4-substituted and 5-substituted products, LDA produced exclusively the 4-substituted products in high yield [40]. However, only the product of iodination at C–4 was confirmed by X-ray crystallography.



Scheme 26

Another option for accessing 4-substituted imidazoles such as the product shown in Scheme 26 is via rearrangement of the protecting group to produce the less hindered isomer [6, 41]. Further, because 5-substituted imidazoles are easily accessed by direct lithiation, this method is remarkably straightforward and can be catalyzed with acid or base (Scheme 27) [7].

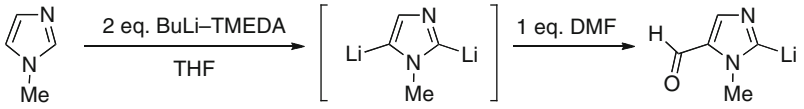


Scheme 27

Recent approaches to 4-lithioimidazoles, however, have almost unanimously favored lithium-halogen exchange to generate the species. Fortunately, this approach is quite general and incorporation of a halogen at C–4 is easily achieved even in a variety of systems [39, 42, 61, 64]. Metal-halogen exchange is discussed in Sect. 4.

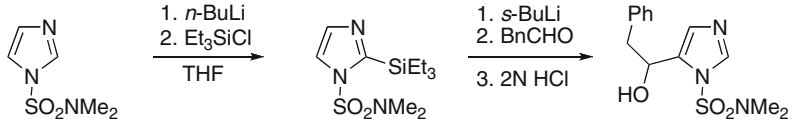
3.4 Lithiation at C–5

The 5-position is the second most acidic carbon center on imidazole though significantly less so than the 2-position. Using multiple equivalents of strong base, it is even possible to simultaneously lithiate both the 2-positions and 5-positions [39]. Further, because imidazolyl carbanions at the 5-position are significantly more reactive than those at the 2 position, 2,5-dilithioimidazoles are capable of selectively reacting with an electrophile as shown in Scheme 28 [43].



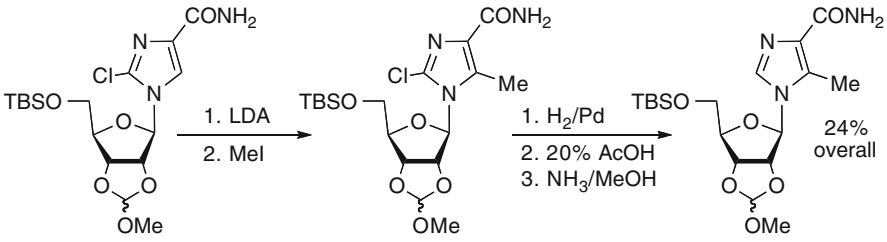
Scheme 28

When the 1-positions and 2-positions are substituted with non-labile groups, lithiation readily proceeds at the 5-position with LDA to produce 1,2,5-substituted imidazoles. In cases where it is necessary that C–2 remain unsubstituted, in situ blocking strategies have been devised to allow temporary protection of C–2 and access to 5-lithioindoles [6, 68].



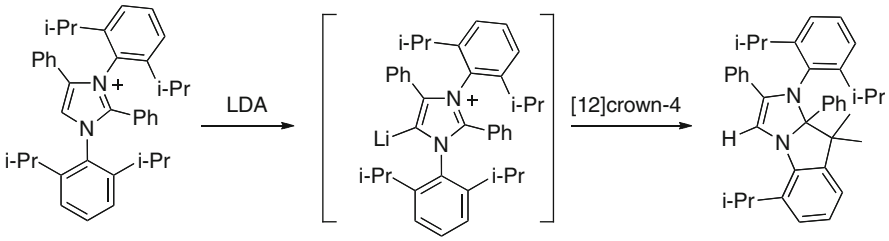
Scheme 29

Treatment of a 2-lithioimidazole with triethylsilyl chloride results in a blocked two position forcing subsequent organolithium reagents to react at the 5-position. During work-up, the triethylsilyl group is easily removed in aqueous acid as shown in Scheme 29. Other functional groups which have been used in blocking strategies include TMS, phenylsulfonyl, and chlorine (Scheme 30) [44–46, 68].



Scheme 30

By quaternizing the N–3 position, lithiation at the 5-position produces an "abnormal" C–5 deprotonated imidazolium carbene [47]. The resulting N-heterocyclic carbene may form useful complexes with metals but readily rearranges on standing when the lithium cation is sequestered by a crown ether (Scheme 31).

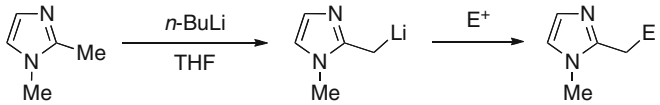


Scheme 31

As with 4-lithioimidazoles, 5-lithioimidazoles are also easily accessed via lithium-halogen exchange which is discussed in Sect. 4 of this work.

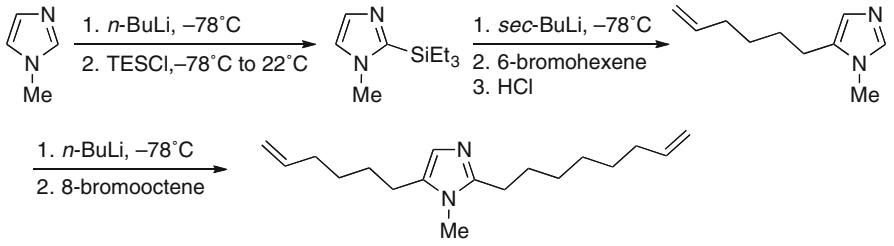
3.5 Lateral Lithiation

Extending beyond the ring positions, 2-alkyl substituted imidazoles exhibit increased acidity due to involvement of the imine-like nitrogen at C–3. NMR studies of these imidazolyllithium salts show involvement of the imidazole ring in stabilization of the alkyl anion [48]. The α-position of alkyl side-chains is deprotonated in favor over direct lithiation of the ring carbons as illustrated using 1,2-dimethylimidazole in Scheme 32. The resulting organolithium salt can be used for further homologations or other functionalizations.



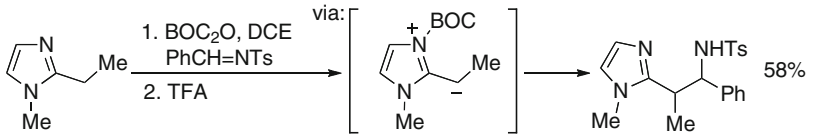
Scheme 32

Aside from the obvious utility that lithiation at this position can provide, the fact that linear alkyl chains at C–2 are not inert to lithiation can also prove inconvenient (Scheme 29). A recent paper by Ishida et al. involved a necessary synthetic detour en route toward an asymmetric 2,5-disubstituted imidazole due to the reactivity of the α-position [49]. By substituting at the 5-position first, Ishida ensures that the first side-chain is inert to lateral lithiation and able to withstand the conditions necessary for a second alkylation (Scheme 33).



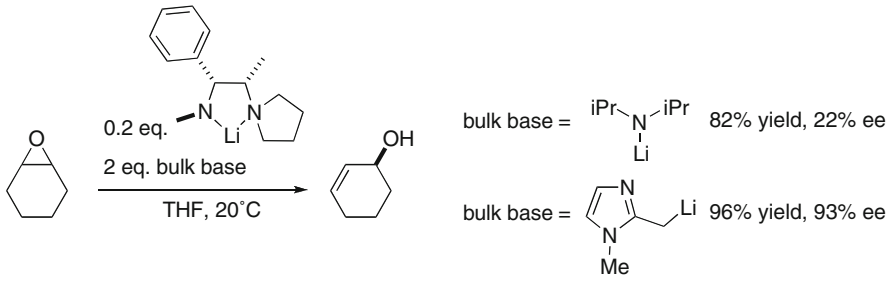
Scheme 33

The acidity of the C–2 side-chain can be further increased by quarternazation of N–3. Addition of BOC-anhydride to 2-ethyl-1-methylimidazole renders the ethyl side-chain sufficiently acidic at the α-position to readily react with Schiff bases under mild conditions [50] (Scheme 34).



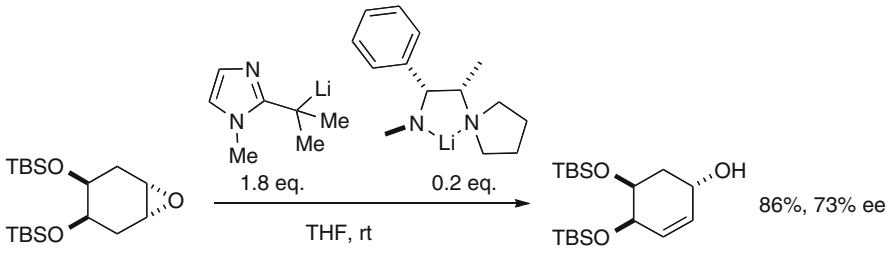
Scheme 34

Beyond providing a method for homologation of side-chains at the 2-position, lateral lithiation has also produced a uniquely functional bulky organolithium reagent. (*N*-Methylimidazole-2-yl)methyl lithium offers basicity comparable to LDA but with reduced reactivity. Ahlberg et al. report 2-(lithiomethyl)-1-methylimidazole as an efficient, nonreactive bulk base which forms a heterodimer with catalytic amounts of a chiral lithium amide [48]. Compared to LDA, 2-(lithiomethyl)-1-methylimidazole shows vast improvement in the yield and enantioselectivity of deprotonative epoxide opening reaction shown in Scheme 35, also an interesting base with advantages



Scheme 35

Oxenford et al. confirmed the unique ability of these conditions for such reactions and further investigated base-catalyzed asymmetric deprotonation. While expanding the generality of this reaction to substituted 5 and 6-membered rings, Oxenford et al. noted that nucleophilic attack on the epoxide sometimes lead to side-products. To resolve this issue, the group suggests use of the bulkier 2-(lithioisopropyl)-1-methylimidazole as shown in Scheme 36 [51].

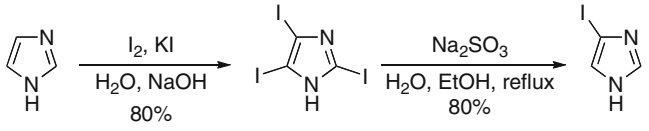


Scheme 36

4 Metal-Halogen Exchange

4.1 Lithium- and Magnesium-Halogen Exchange

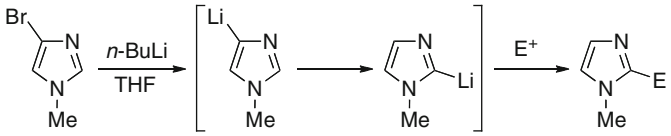
In comparison with direct lithiation, lithium-halogen exchange provides many advantages presuming an appropriately halogenated starting material is available. Positions that are otherwise inaccessible by direct lithiation (C–4, C–5) can be easily lithiated via exchange with a C–4 or C–5 halogen without requiring the use of a blocking group at C–2 [52]. Conveniently, several methods have been devised to halogenate these positions. Scheme 37 illustrates how one may incorporate halogen into the traditionally inaccessible 4-position while retaining hydrogen at N–1, C–2, and C–5 [53].



Scheme 37

Lithium-halogen exchange is an extraordinarily rapid process which allows exchange to take place on substrates that may suffer from competing or side reactions under direct lithiation conditions. Because the exchange reaction will often outcompete a direct lithiation process, lithium halogen exchange can selectively produce a carbon anion at a brominated or iodinated center even if that carbon center does not

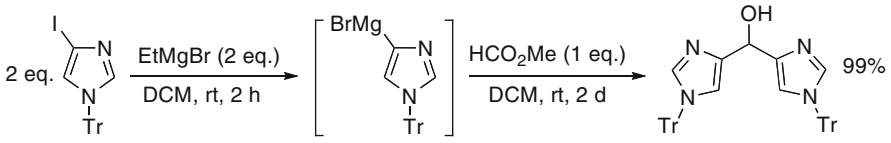
produce the most stable anion. However, such reactions must be quenched relatively quickly or at low temperature as, over time or upon heating, the resulting carbanion can rearrange to a more stable position (Scheme 38).



Scheme 38

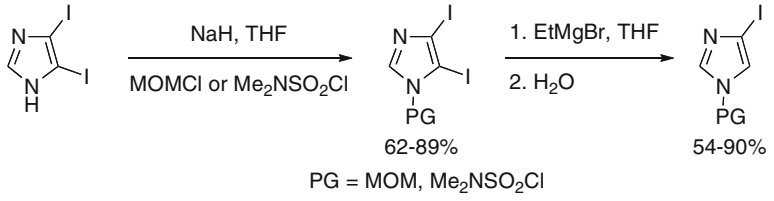
Polyhalogenated imidazoles are particularly useful substrates [54]. Even in trihalogenated imidazoles, metal-halogen exchange proceeds predictably and selectively in the same order as direct lithiation: C–2 ≫ C–5 > C–4. The halogens exchange at different rates as well: I > Br ≫ Cl. In many cases, sequential or parallel transformations can be performed in one pot.

As an alternative to using lithium, magnesium-halogen exchange can be performed under mild conditions and in many cases provides advantages. Specifically, for the preparation of bis(imidazolyl)methylenes, Lindel et al. noted that magnesium-halogen exchange was preferable over lithium-halogen exchange because the intermediate 4-metalated Grignard would not rearrange to the isomeric 2-metalated species as seen during lithium-halogen exchange [55] (Scheme 39).



Scheme 39

By exploiting the predictable regiochemistry of magnesium-halogen exchange, this method can also be used to effect reductive removal of the 5-substituent [56]. Below, Lovely et al., elect to use magnesium to safeguard against rearrangement or other side-reactions (Scheme 40) [57].

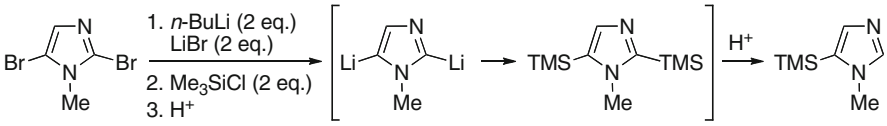


Scheme 40

4.2 Dilithio and Dimagnesioimidazoles

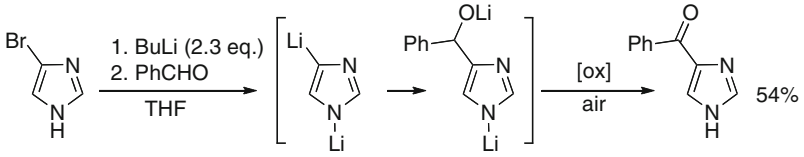
Due to the facile nature of metal-halogen exchange, these reactions play an important method for the production of dilithio- and dimagnesioimidazoles. The difference in reactivity of these positions varies considerably, and some dianions (as shown in Scheme 26 earlier) can be selectively treated with electrophiles to prepare symmetrically or asymmetrically substituted species [43].

Though dianions can be achieved via direct lithiation, the most effective approach is via metal-halogen exchange. Above, 2,5-dibromo-1-methylimidazole is doubly lithiated using *n*-butyllithium to generated the 2,5-dilithio species [38] (Scheme 41). Quenching with 2 equivalents of chlorotrimethylsilane initially results in substitution of both positions, but acid treatment can be used to produce the 5-substituted-2-unsubstituted product selectively.



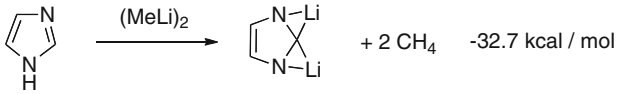
Scheme 41

Further, metal-halogen exchange allows generation of imidazolyl dianions from unprotected N–H imidazoles. In Scheme 42, lithium-halogen exchange allows substitution at C–4 without requiring the use of a protecting group at N–1 or a blocking group at C–2 [39].



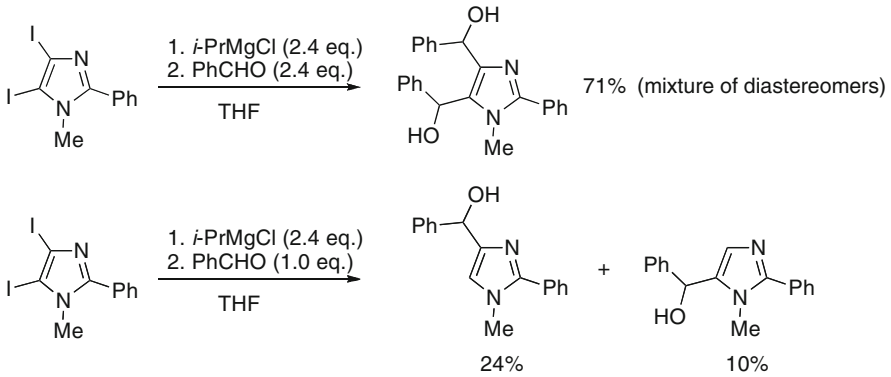
Scheme 42

In contrast to the dilithioimidazoles above, 1,2-dilithioimidazole is not a known species and has yet to be demonstrably generated and observed after either direct lithiation or lithium-halogen exchange. However, one possible structure for 1,2-dilithioimidazole was discovered computationally by accounting for the bridging proclivities of lithium. Dilithiation of imidazole has been proposed to generate the symmetrical and planar structure shown in Scheme 43. In addition, authors further examine solvation and possible configuration of dimer structures [58].



Scheme 43

Dimagnesium imidazoles, easily generated from common Grignard reagents, present another option for the production of imidazolyl dianions. As described above, organomagnesium species show greater stability adjacent to lone pairs. In the past decade, magnesium-halogen exchange has allowed the production of imidazolyl dianions with vicinal dianions [59, 60].

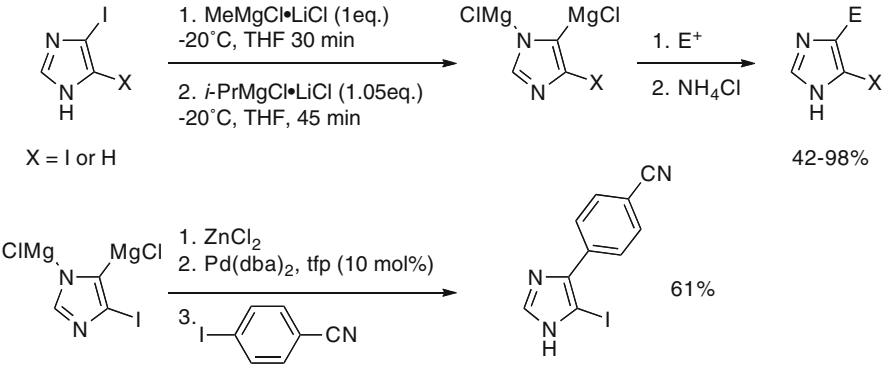


Scheme 44

Lindell et al. generated 4,5-dimagnesioimidazole by treatment of a 4,5-diiodoimidazole with multiple equivalents of isopropylmagnesium chloride at 0°C. Quenching with benzaldehyde resulted in good yields and substitution at both the 4-positions and 5-positions (Scheme 44). Curious as to whether the 4-positions and 5-positions reacted at different rates, Lindell carefully treated the dimagnesio species with a single equivalent of electrophile. Unfortunately, the results do not indicate any synthetically useful differences in reactivity between the two carbanions [59].

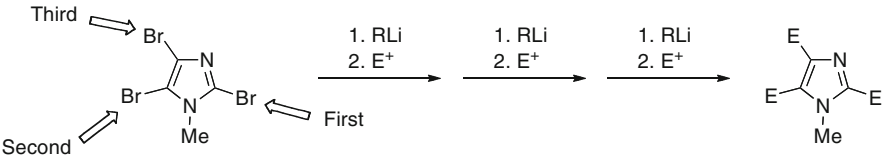
Starting from unprotected 4-iodoimidazole, Knochel et al. report generation of 1,4-dimagnesioimidazoles (Scheme 45). The resulting imidazole dianion cleanly reacts with various electrophiles in good to excellent yields allowing substitution at C–4 without the use of blocking or protecting strategies [60]. In the example below, lithium chloride is used to facilitate solubility of the organometallic species.

Demonstrating a further application, Knochel shows that the dimagnesioimidazole species readily undergoes transmetalation selectively at the more reactive carbon position with zinc chloride preparing the substrate for Negishi coupling (Scheme 45) [60].



Scheme 45

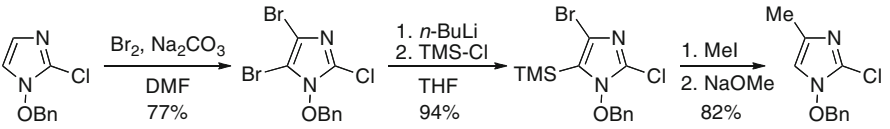
4.3 Sequential Metalation



Scheme 46

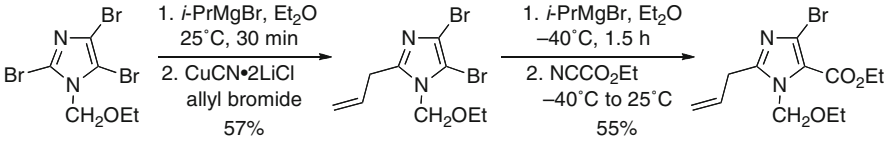
Polyhalogenated imidazoles are remarkably versatile substrates that are capable of undergoing sequential metalation-substitution reactions. Following the order of reactivity shown in Scheme 46, these powerful multistep transformations can functionalize every carbon center of imidazole in a single reaction vessel [61].

Further, the different reactivity of chlorine, bromine, and iodine, allows another layer of control allowing the order of reactivity to be manipulated into any sequence. Begtrup et al. report the synthesis of 4-substituted and 5-substituted 1-hydroxyimidazoles via metal halogen exchange [62]. As shown in Scheme 47, *n*-butyllithium will selectively exchange with bromine in preference over chlorine even if the chlorine is located at the more reactive 2-position.



Scheme 47

Likewise, polyhalogenated imidazole is an excellent substrate for magnesium-halogen exchange. Knochel's group in particular has championed use of this methodology and the topic has been the subject of review [69]. In Scheme 48, Knochel performs a magnesium-halogen exchange sequence involving transmetalation with copper to effect allylation.

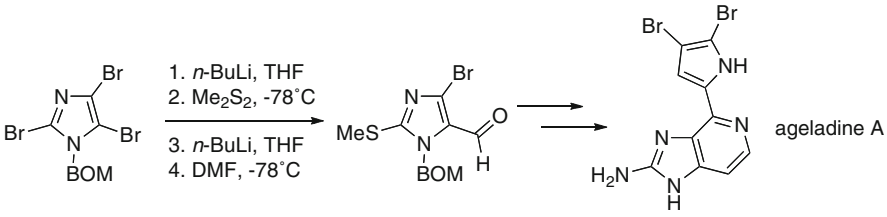


Scheme 48

Sequential metalation has been extensively used to produce highly functionalized imidazoles for the total synthesis of imidazole containing natural products [54, 69]. In many cases, this powerful methodology is used early in the synthesis to reliably furnish high yields of substituted imidazole with up to three orthogonally reactive functional groups.

5 Applications in Total Synthesis

Isolated in 2003 by Fusetani, Nakao, and coworkers, Ageladine A is an inhibitor of matrix metalloproteinases involved in metastasis and tumor angiogenesis. Containing a fused 2-aminoimidazopyridine core and a naturally halogenated pyrrole moiety, Ageladine A has been a popular synthetic target. In cooperation with Fuestani and Nakao, Weinreb et al. reported a novel synthesis this compound by powerful use of sequential lithium-halogen exchange (Scheme 49).

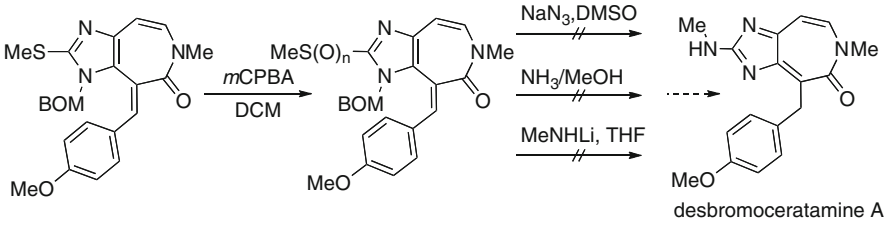


Scheme 49

From BOM-protected tribromoimidazole, treatment with a first equivalent of *n*-butyllithium selectively exchanges with the 2-position, which is subsequently trapped with dimethyl disulfide. Addition of a second equivalent of organolithium selectively lithiates the 5-position, which is treated with DMF to produce a fully substituted polyfunctional imidazole-5-carbaldehyde in 91% yield in one pot.

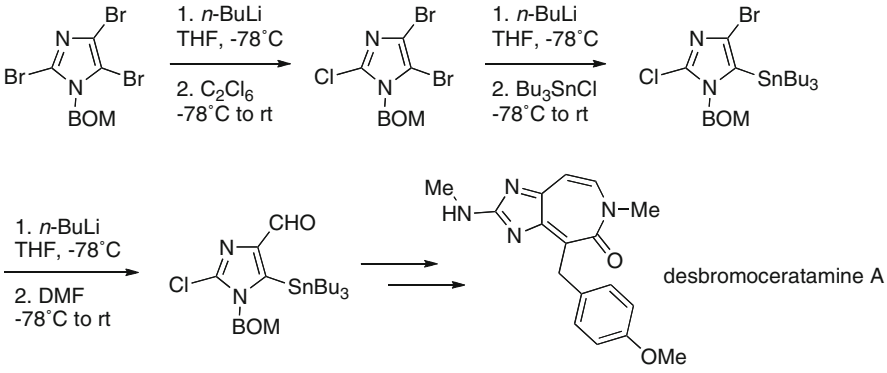
Weinreb et al., investigate various routes ultimately using the remaining bromine in another lithium-halogen exchange to quench and carboxylate the 4-position with carbon dioxide. Starting from a tribrominated imidazole, Weinreb realizes rapid introduction of complexity early, providing functional handles for both pyridine annulation and integration of the primary amine [63].

Desbromoceratamine A is a member of a family of marine alkaloids containing an unprecedented 2-aminoimidazoazepine system. Compounds containing a 2-aminoimidazole moiety are notoriously problematic due difficulties with purification and poor solubility, and consequently, it is advantageous to introduce the amino group at C–2 as late as possible.



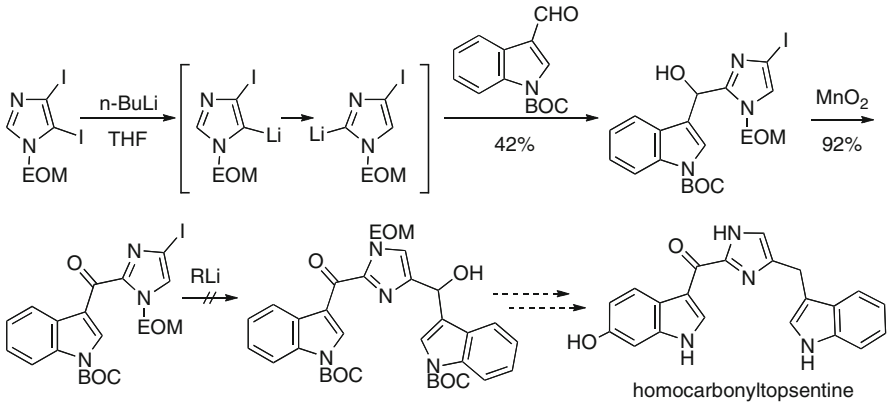
Scheme 50

Accordingly, a recent approach by Andersen et al. incorporated a methylsulfide group at C–2 anticipating a late-game displacement to generate the 2-aminoimidazole moiety necessary to complete the synthesis [64]. Unfortunately, after preparing the advanced intermediate shown in Scheme 50, it became clear that it would be necessary to use a different substituent at C–2 which was originally furnished during the first step of the synthesis. Fortunately, because Andersen's synthesis started from BOM-protected tribromoimidazole, the general synthetic route could be modified while retaining use of the same opening strategy and starting materials. The versatility of this methodology is particularly clear in Andersen's synthesis; in this case, the initial triple substitution of imidazole is simply revised to solve a problematic end game (Scheme 51).



Scheme 51

Using known BOM-protected tribromoimidazole, Andersen et al. report three sequential lithium-halogen exchange reactions in a single pot. A first lithiation was quenched with hexachloroethane to provide a proven and reliable chlorine functionality for late game amination. The 5-position was lithiated next and quenched with tributyltinchloride. Lastly, the bromine at C–4 was selectively exchanged in preference over chlorine at C–2 to be subsequently trapped with DMF to prepare the trisubstituted imidazole which successfully lead to completed synthesis of the natural product [64].

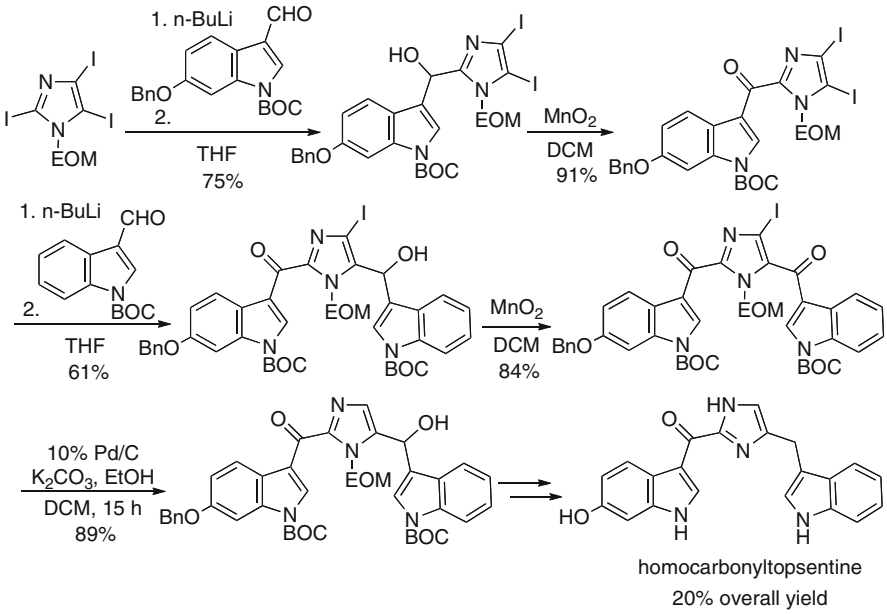


Scheme 52

Homocarbonyltopsentine is a bis-indole imidazole known to exhibit anti-inflammatory activity. A recent synthesis by Joseph et al. initially involved exploitation of a halogen dance before the synthesis was ultimately revised to benefit from the predictability of sequential-metalation [41, 65]. Halogen dance reactions are well known in heterocyclic chemistry including imidazoles [66, 67], and as discussed previously, lithioimidazoles can rearrange to produce more stable lithio species. Joseph et al. sought to achieve a 2,4-disubstituted imidazole by following the route illustrated above in Scheme 52.

Lithium-halogen exchange at C–5 isomerizes to the 2-lithio species on standing. Treatment with BOC-protected indole-3-carbaldehyde produces the 2-substituted 4-iodoimidazole. Unfortunately, neither direct lithiation with LDA at the 5-position nor lithium-halogen exchange at C–4 resulted in the expected 5-lithioimidazole.

To achieve the total synthesis of homocarbonyltopsentine, Joseph employed the powerful and reliable methodology of sequential lithiation (Scheme 53). Starting from a triodoimidazole, sequential lithiation, and electrophilic substitution proceeded as expected to substitute first at the 2-position and second at the 5-position. In this case, due to halogen-exchange with a iodine at C–5, lithiation at the 5-position was readily achieved. The final iodine was reduced using palladium in



Scheme 53

the presence of potassium carbonate. Overall, the revised route using sequential metalation achieved total synthesis of homocarbonyltopsentine in 20% overall yield [41].

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Metalation of Oxazoles and Benzoxazoles

Liangfeng Fu

Abstract Metalation of oxazoles and benzoxazoles, including synthesis of oxazoles and benzoxazoles, metal-mediated deprotonations, metal-catalyzed cross-coupling reactions, and other miscellaneous reactions are discussed and summarized.

Keywords Benzoxazole · Cross-coupling · Metalation · Oxazole · Synthesis

Contents

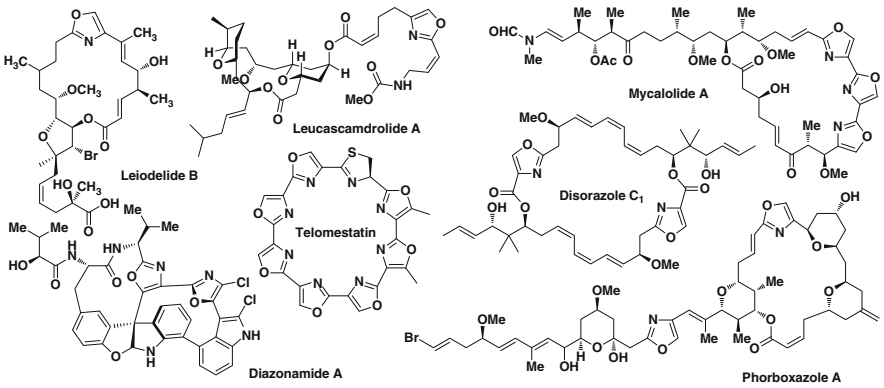
1 Introduction 103
2 Synthesis of Oxazoles and Benzoxazoles Mediated by Metals 104
2.1 Metal-Mediated Synthesis of Oxazoles 104
3 Metalation of Oxazoles and Benzoxazoles 115
3.1 Metalation of Oxazoles 115
3.2 Metalation of Benzoxazoles 121
4 Cross-Coupling Reactions 122
4.1 Oxazole-Based Cross-Coupling Reactions 122
4.2 Benzoxazole-Based Cross-Coupling Reactions 133
5 Miscellaneous Metalations 136
5.1 Aldol Reactions of Aldehydes and 5-Alkoxyoxazoles 136
5.2 Asymmetric Hydrogenation of 2-Phenyloxazoles 136
References 137

1 Introduction

Oxazole is a unique five-membered heterocycle present in many complex and biological active natural and unnatural products, such as Calyculin A [1], Chivosazole A [2, 3], Diazonamide A [4–12], Disorazole Z [13–15], Galmic [16],

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IB-01211 [17], Kabiramide C [18], Leiodelide B [19], Leucascandrolide A [20, 21], Mycalolide [22], Neooxazolomycin [23], Neopeltolide [24], Phorboxazole B [25–39], Rhizoxin D [40–42], Telomestatin [43, 44], Ulapualide A [45], etc. (Scheme 1). Benzoxazole, on the other hand, is relatively limited in both natural products and medicinal chemistry. The section on benzoxazole mainly focuses on synthetic methodology development.



Scheme 1 Representative complex oxazole-containing natural products

Metalations, with regard to oxazoles and benzoxazoles, have been widely used, especially in the last 10 years, such as synthesis of oxazoles and benzoxazoles, deprotonations and halogen–metal exchange of oxazoles and benzoxazoles, Suzuki–Miyaura, Stille, and Negishi cross-coupling reactions, and C–H activations.

In this monograph, metal-mediated synthesis of oxazoles and benzoxazoles, organometal-mediated deprotonations, halogen–metal exchange, classic cross-coupling reactions, and their corresponding applications in natural product synthesis will be discussed in detail, while C–H activations will not be covered.

2 Synthesis of Oxazoles and Benzoxazoles Mediated by Metals

2.1 Metal-Mediated Synthesis of Oxazoles

The structural diversity and complexity of naturally occurring oxazoles have fueled a continuing search for mild and efficient methods for oxazole ring construction. One method that has become particularly useful in this context is the metal-catalyzed synthesis of oxazole.

From a bond disconnection prospective, oxazole can be synthesized with **A**, **B**, **C**, **D**, or **E** bond formation, or with a combination of these bond formations (Fig. 1). In this section, synthesis of oxazoles will be discussed in a manner of bond disconnections.

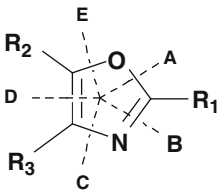
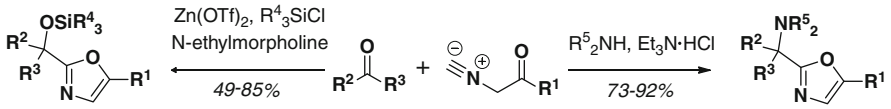


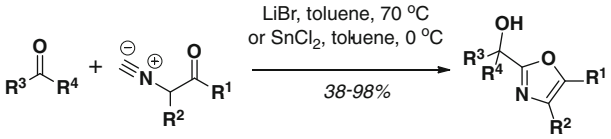
Fig. 1 Bond disconnections for oxazoles

2.1.1 A-Bond Formation

The first report of oxazole synthesis through **A**-bond formation is by Ganem and coworkers in 2002 [46, 47]. $Zn(OTf)_2$-promoted condensation of appropriately substituted isonitriles with neighboring group donation condensed with carbonyl compounds or in situ generated iminium species, followed by silylation of the resulting alcohol afforded substituted oxazoles (Scheme 2). Later on, Zhu and coworkers reported the same transformation catalyzed by LiBr [48] and $SnCl_2$ [49].



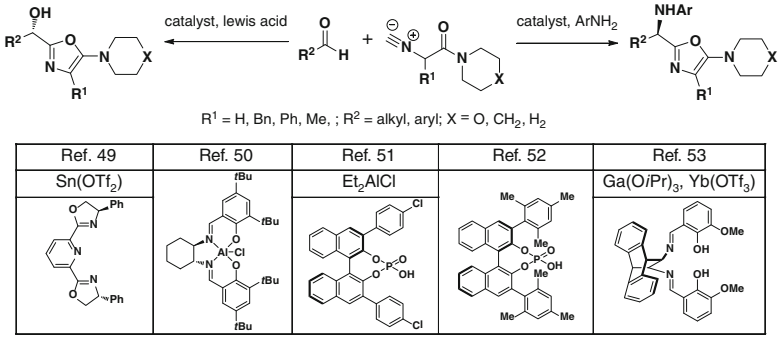
R^1 = OEt, NMe_2, morpholino; R^2COR^3 = PhCHO, $Ph(CH_2)_2CHO$, $CH_3(CH_2)_8CHO$, cyclohexanone, *p*-$MeOC_6H_4CHO$; R^4 = Me, Et; $R^5{}_2NH$ = morpholine, Me_2NH



R^1 = NEt_2, morpholino, piperidino; R^2 = Bn, H; R^3COR^4 = alkylCHO, EtO_2CCHO, $(EtO_2C)_2CO$,arylCHO, *m*-BrC_6H_4CHO; $R^5{}_2NH$ = morpholine, Me_2NH

Scheme 2 $Zn(OTf)_2$, LiBr, or $SnCl_2$-promoted formation of oxazoles

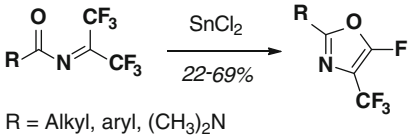
In 2007, Zhu et al. reported the first enantioselective α-addition of isocyanides to aldehydes catalyzed by chiral salen–aluminum complex [50] or $Sn(OTf)_2$-diamine complex [49] with ~80% *ee* (Scheme 3). In 2009, they introduced a chiral aluminum-organophosphate catalyst, though the selectivity has not been improved (Scheme 3) [51]. Furthermore, a three-component reaction involving α-addition of isocyanides to imines was also reported with similar enantioselectivity (Scheme 3) [52]. Independently, Shibasaki and coworkers employed a heterobimetallic Ga/Yb-Schiff base complex as catalyst, which increased the *ee* to >95% (Scheme 3) [53].



Scheme 3 Asymmetric α-addition of isocyanides to aldehdyes

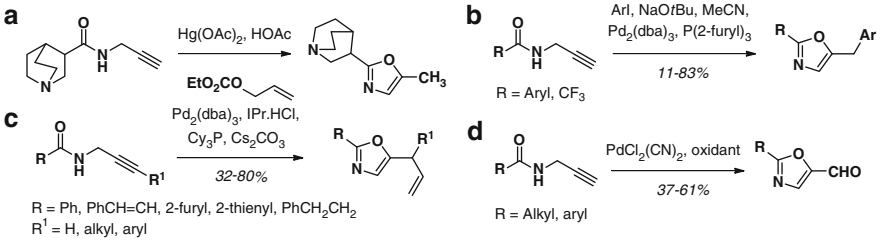
2.1.2 E-Bond Formation

In mid-1980s, Burger and coworkers introduced the first example of 5-fluoro-4-trifluoromethyloxazole synthesis with **E**-bond formation catalyzed by $SnCl_2$ (Scheme 4) [54, 55].



Scheme 4 $SnCl_2$-mediated synthesis of 5-fluoro-4-(trifluoromethyl)oxazoles

A few years later, Baker et al. reported a $Hg(OAc)_2$-promoted cyclization of *N*-propargylamide in the formation of oxazole (Scheme 5a) [56], since which synthesis of oxazoles using *N*-propargylamides has been widely used. Early 2001, Cacchi and coworkers reported a palladium-catalyzed synthesis of 2,5-disubstituted oxazoles in the presence of aryl iodide (Scheme 5b) [57].

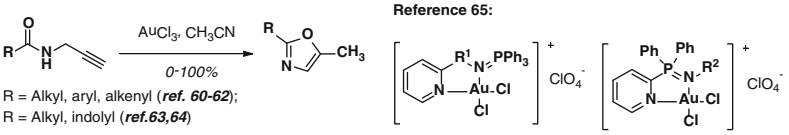


Scheme 5 Hg- and Pd-catalyzed synthesis of 2,5-disubstituted oxazoles

Very recently, Hanzawa and coworkers reported their 2,5-disubstituted oxazoles synthesis through cycloisomerization-allylation with allyl carbonates under modified conditions (Scheme 5c) [58]. In 2008, Broggini et al. introduced

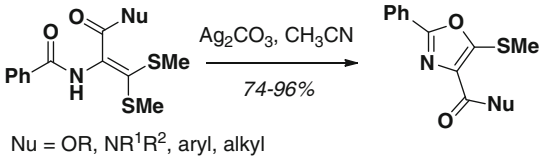
$PdCl_2(CN)_2$ as the catalyst for the same transformation in the presence of oxidants, such as 1,4-benzoquinone and $CuCl_2$ (Scheme 5d) [59]. Although only moderate yields were obtained, the 5-aldehyde was obtained instead of methyl.

In 2004, Hashmi and coworkers accomplished the similar transformation under mild conditions with the catalysis of $AuCl_3$ (Scheme 6) [60–62]; Padwa et al. applied this methodology for their synthesis of indolyloxazoles [63, 64]. In 2009, Au(III) iminophosphorane was introduced as the catalyst by Urriolabeitia et al. (Scheme 6) [65].



Scheme 6 Au-catalyzed synthesis of 2,5-disubstituted oxazoles

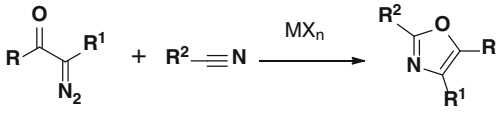
Very recently, Ila and Misra reported a Ag_2CO_3-promoted synthesis of 5-thiooxazoles from 4-bis(methythio)methylene-2-phenyloxazol-5-ones (Scheme 7) [66].



Scheme 7 Ag_2CO_3-catalyzed synthesis of 2-phenyl-4,5-functionalized oxazoles

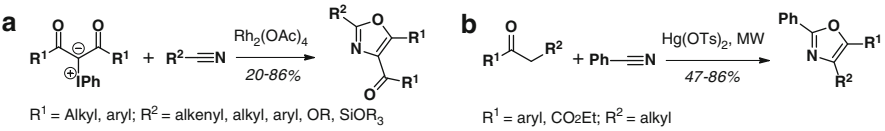
2.1.3 A-Bond and C-Bond Formation

Metal-catalyzed cyclization of α-diazocarbonyl compounds with nitriles (Scheme 8), such as WCl_6 [67], $AlCl_3$ [68], $SnCl_4$ [69], $ZrCl_4$ [69], $MoCl_5$ [69], $Cu(OTf)_2$ [70], $InCl_3$ [71], $Cu(acac)_2$ [72], $[CpRy(CH_3CN)_3][PF_6]$ [73], especially $Rh_2(OAc)_4$ [74–83], has been widely used since mid- 1970s. Synthesis of functionalized oxazoles catalyzed by $Rh_2(OAc)_4$ has been applied to many natural products synthesis, such as phorboxazole A and B [84], leucascandrolide A [85], siphonazole [86], nocardimicin B [87], and telomestatin [88].



Scheme 8 Synthesis of oxazoles from α-diazocarbonyl compounds and nitriles

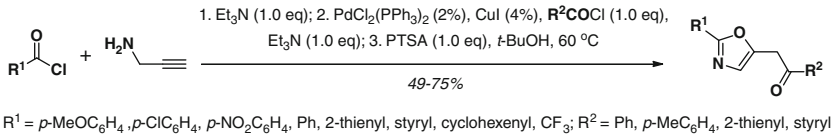
Recent discoveries in oxazole synthesis through **A**-bond and **C**-bond formation include $Rh_2(OAc)_4$-catalyzed reaction of iodonium ylides with nitriles, an alternative species to the diazocarbonyl compounds, in which the iodonium ylides are easily obtained from the corresponding carbonyl precursor (Scheme 9a) [89–91]. Lee and Song also reported a microwave assisted oxazole synthesis from aromatic ketones and nitriles with mercury(II) catalysis, no α-diazo or iodonium ylide is necessary (Scheme 9b) [92].



Scheme 9 Recently developed oxazole synthesis through **A**-bond and **C**-bond formation

2.1.4 B-Bond and E-Bond Formation

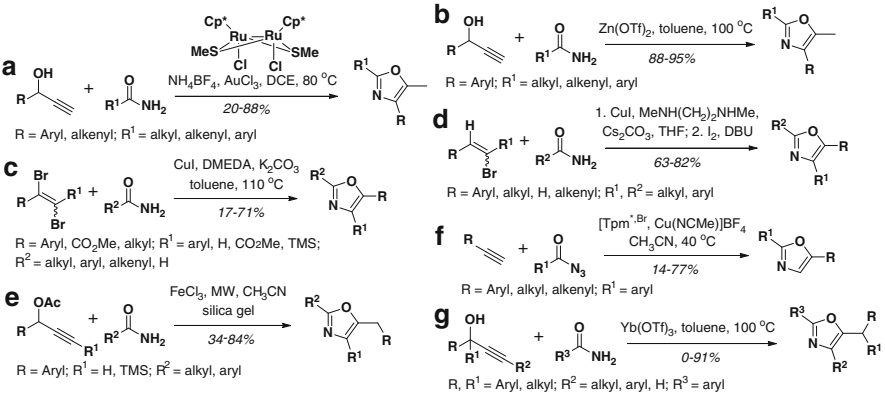
The only synthesis through **B**-bond and **E**-bond formation was reported by Müller and coworkers in 2006 [93]. The described consecutive three-component oxazole synthesis features an amidation-coupling-cycloisomerization sequence (Scheme 10).



Scheme 10 Three-component synthesis by an amidation-coupling-cycloisomerization sequence

2.1.5 C-Bond and E-Bond Formation

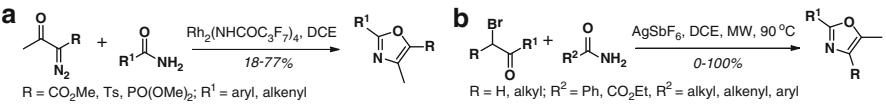
Oxazole synthesis through **C**-bond and **E**-bond formation is exemplified by transition-metal catalyzed reactions between amides and alkynes or halogenated alkenes [94–103]. In 2004, Uemura et al. introduced a sequential reaction between propargylic alcohols and amides catalyzed by ruthenium and gold (Scheme 11a) [94]. A couple of years later, Liu et al. and Chan et al. reported the same transformation catalyzed by $Zn(OTf)_2$ (Scheme 11b) [95]. In 2007, a domino copper-catalyzed C–N and C–O cross coupling between dibromoalkenes and amides was introduced by Glorius and Schuh (Scheme 11c) [96]. Buchwald et al. also reported similar copper-catalyzed vinylation/cyclization sequences (Scheme 11d) [97]. Later on, Lin et al. came up with an $FeCl_3$-catalyzed oxazole synthesis from propargylic acetates and amides with microwave irradiation (Scheme 11e) [98]. Very recently, Pérez et al. completed a similar copper-catalyzed oxazoles synthesis



Scheme 11 Metal-catalyzed synthesis of substituted oxazoles from amides

with modified acyl azides instead of amides (Scheme 11f) [99]. Chan et al. also reported a $Yb(OTf)_3$-catalyzed oxazole synthesis from tertiary propargylic alcohols with aryl amides (Scheme 11g) [100], and the results are different from secondary propargylic alcohols [94, 95].

Modified methodologies include rhodium carbene route between amides and α-diazocarbonyl compounds introduced by Moody and coworkers (Scheme 12a) [101, 102]. Moses et al. also reported a silver-catalyzed oxazole synthesis from amides and α-bromocarbonyl compounds (Scheme 12b) [103].

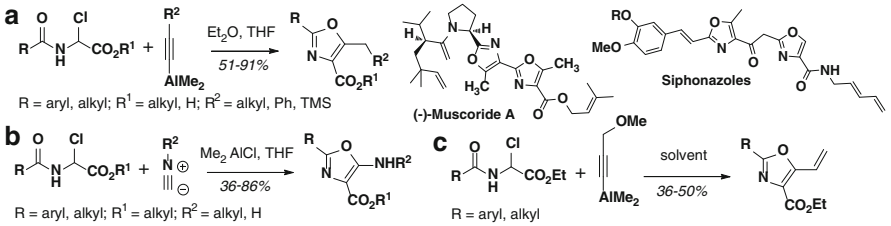


Scheme 12 Modified oxazoles synthesis from amides

2.1.6 D-Bond and E-Bond Formation

Literature related to oxazole synthesis through **D**-bond and **E**-bond formation merely comes from Ciufolini and coworkers (Scheme 13). In 2003, they initially reported the aluminum-catalyzed oxazole formation from α-chloroglycinates and aluminated alkynes, upon which they completed the total synthesis of (-)-muscoride A (Scheme 13a) [104]. In 2009, they finished their synthesis of siphonazoles using the same methodology, in which they also discussed in detail about the reaction scopes and limitations [105]. Later on, they accomplished their synthesis of 5-aminooxazole-4-carboxylates by condensation of α-chloroglycinates with isonitriles

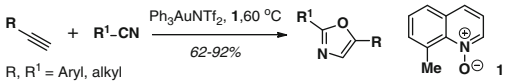
or with cyanide ion promoted by aluminum-based Lewis acid (Scheme 13b) [106], and furthermore, 2-alkyl-4-carbethoxy-5-vinyloxazoles (Scheme 13c) [107].



Scheme 13 Synthesis of 5-aminooxazoles from α-chloroglycinates

2.1.7 A-Bond, C-Bond, and E-Bond Formation

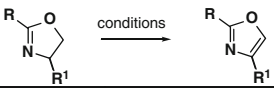
A recent publication by Zhang and coworkers features an efficient [2+2+1] synthesis of 2,5-disbustituted oxazoles via gold-catalyzed intermolecular alkyne oxidation (Scheme 14) [108]. Upon oxidation of a terminal alkyne with an oxidant catalyzed by Au, the resulting gold carbene intermediate reacted rapidly with nitrile afforded substituted oxazoles in good yields.



Scheme 14 Synthesis of 2,5-disubstituted oxazoles via gold-catalyzed alkyne oxidation

2.1.8 Partial Disconnections: Oxidation from Oxazolines

Synthesis of oxazoles from oxazolines has been a widely applied method for oxazole construction since the 1980s. Oxidants such as $CuBr_2$ [109–111], NiO_2 [112–116], and a combination of CuBr and $Cu(OAc)_2$ [117, 118], have proven their efficiency since the 1990s (Scheme 15). Other oxidants such as a combination of DDQ and MnO_2[119] and diazodinedioxide or diazodinone-mediated oxidation catalyzed by Cu(I)[120] were also reported recently for oxidation of oxazolines (Scheme 15).



	$CuBr_2$, DBU	NiO_2	CuBr, $Cu(OAc)_2$	DDQ, MnO_2	CuCl, 
R	alkyl	alkyl, alkenyl, aryl	alkyl	H	H, Ph
R^1	H, $CONR_2$, CO_2R	H, CO_2R, Ph	CO_2R	Ph	Ph
Yield	20-82%	0-73%	43-81%	86%	73-95%

Scheme 15 Synthesis of oxazoles through oxidation of oxazolines

2.1.9 Metal-Mediated Synthesis of Benzoxazoles

Similar to oxazole disconnection, the disconnection of benzoxazole is shown in Fig. 2. Although disconnection at the benzoxazole benzene ring is also possible, the literature references are rare. Thus, only disconnections on the oxazole ring are discussed in this section.

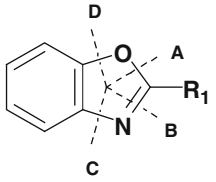
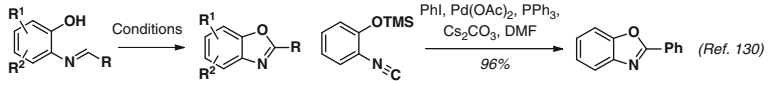


Fig. 2 Bond disconnections for benzoxazoles

2.1.10 A-Bond Formation

Benzoxazole synthesis through **A**-bond formation is exemplified by oxidative cyclization of a functionalized Schiff base; oxidative metals such as $Pb(OAc)_4$ [121–125], $Pd(OAc)_2$ [126, 127], and $Mn(OAc)_3$[128, 129] have all been proven to be efficient for this cyclization (Scheme 16). Exceptionally, Zhuravlev and Sánchez reported their palladium-catalyzed synthesis of 2-phenylbenzoxazole from 2-trimethylsiloxyphenyl isocyanide, instead of Schiff base (Scheme 16) [130].

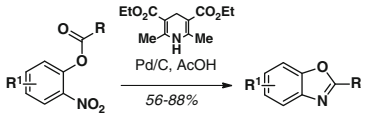


	$Pb(OAc)_4$	$Pd(OAc)_2$	$Mn(OAc)_3$
R	H, Me, Cl, Br, CF_3, OH, NO_2, NMe_2, SMe, aryl	aryl	aryl
$R^1(R^2)$	*t*Bu(*t*Bu), OR(H),	*t*Bu(H), H(H),	*t*Bu(H), Cl(H), Me(H), H(H),

Scheme 16 Synthesis of benzoxazoles through **A**-bond formation

2.1.11 B-Bond Formation

The only case through **B**-bond formation was reported by Liu et al. in 2010, in which they applied catalytic Pd/C to convert *o*-nitrobenzo-esters to benzoxazoles in the presence of the Hantzsch ester (Scheme 17) [131].

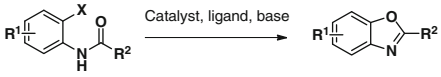


R = aryl, alkyl; R^1 = H, Me, *t*Bu, CO_2Et, OMe, CF_3

Scheme 17 Synthesis of benzoxazole through **B**-bond formation

2.1.12 D-Bond Formation

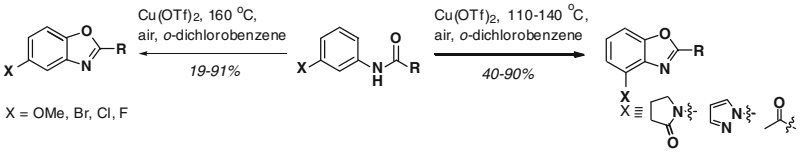
Early in 1993, Minami et al. introduced CuI-catalyzed arylation of phosphinyl-stabilized aryl iodide to produce benzoxazole derivatives (Scheme 18) [132]. Literature has evidenced wide applications recently, especially in the last few years [133–144]. In 2006, Batey and Evindar reported their benzoxazole synthesis from aryl bromide using 1,10-phenanthroline as an accelerating ligand (Scheme 18) [133]. One year later, Domínguez and coworkers developed a CuCl or $Cu(OTf)_2$-catalyzed intramolecular *O*-arylation of aryl chlorides in water (Scheme 18) [134]. In 2008, Bolm introduced environment friendly $FeCl_3$ and tetramethylheptanedione as the catalyst system (Scheme 18) [137]. Later on, other catalysts such as CuFAP [141], CuO nanoparticles [142], $Co(acac)_2$ [143], and ligand such as oxazolidin-2-one [136], thiophene-2-carboxylic acid [138], DMEDA [140], and BINAM-based ligands [144] have also been applied to this strategy (Scheme 18).



X	Catalyst	Ligand	Base	Yield	Reference
I	CuI		NaH	71%	**132**
Br/Cl	CuI	1,10-Phen	Cs_2CO_3	12-99%	**133,135**
Br/Cl	$CuCl/Cu(OTf)_2$	TMEDA	TMEDA	0-73%	**134**
I/Br/Cl	CuI	Oxazolidin-2-one	NaOMe	22-88%	**136**
I/Br/Cl	$FeCl_3$	TMHD	Cs_2CO_3	22-92%	**137**
I	CuI	TCA	K_2CO_3	15-96%	**138**
Br/Cl	CuI	DMEDA	K_2CO_3	28-91%	**140**
I/Br/Cl	CuFAP		K_2CO_3	80-96%	**141**
I/Br	CuO nanoparticles		Cs_2CO_3	60-95%	**142**
Br	$Co(acac)_2$	1,10-Phen	K_2CO_3	33-95%	**143**
I	$Cu(OTf)_2$	BINAP-based	Cs_2CO_3	20-87%	**144**

Scheme 18 Metal-catalyzed cyclization of *ortho*-halobenzanilides. Note: TCA: thiophene-2-carboxylic acid; CuFAP: copper fluorapatite catalyst

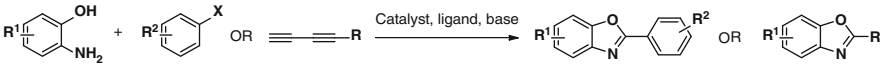
Intramolecular oxidative C–O coupling of benzanilides has also been reported by Nagasawa and Ueda (Scheme 19). Their initial 2-arylbenzoxazoles synthesis [145], followed by regioselective C–H functionalization/C–O bond formation under air atmosphere [146] were both catalyzed by $Cu(OTf)_2$.



Scheme 19 Intramolecular oxidative C–O coupling of benzanilides

2.1.13 A-Bond and B-Bond Formation

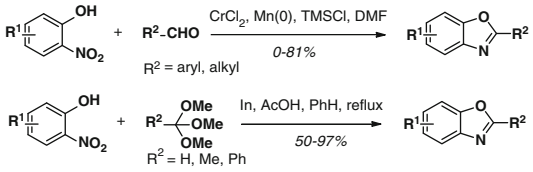
O-Aminophenols, one of the most commonly used precursors in this section, were initially introduced by Perry et al. in 1992 (Scheme 20) [147], their palladium-catalyzed carbonylation and condensation with aryl halides afforded 2-aryl benzoxazoles. In 2002, Cho et al. reported a $SnCl_2$-mediated arylation with aryl boronic acid (Scheme 20) [148]. In 2003, Yamamoto and Shimada reported a $Ru_3(CO)_{12}$-catalyzed hydroamination through C–C bond cleavage of diynes (Scheme 20) [149]. In 2006, Kidwai et al. introduced Cu-nanoparticles as an efficient catalyst for oxidative cyclization with aryl aldehydes (Scheme 20) [150], followed by Fazlinia and Mosslemin's H_2O_2/SiO_2-$FeCl_3$ system in 2010 (Scheme 20) [151], and Mamouni's $ZnBr_2$-doped animal bone meal as an efficient and reusable heterogeneous catalyst in 2011 (Scheme 20) [152]. In 2008, Simons et al. applied HgO as a catalyst by reacting with aryl isocyanate (Scheme 20) [153], Fan et al. introduced $FeCl_3$ very recently (Scheme 20) [154]. In 2009, Williams and coworkers furnished their benzoxazoles from *O*-aminophenols and alcohols or aldehydes catalyzed by ruthenium or iridium (Scheme 20) [155].



X	Catalyst, Ligand, Base	Yield	Reference
Br/I	$PdCl2(PPh_3)_2$, PPh_3, CO, DMAc, 120 °C	11-91%	**147**
CO_2H	$SnCl_2$, dioxane, 180 °C	27-73%	**148**
CHO	Cu-nano particles, K_2CO_3, O2, MeOH, 80-100 °C	69-95%	**150**
CHO	SiO_2, $FeCl_3$, H_2O_2, EtOH, r.t.	0-89%	**151**
CHO	$ZnBr_2/CuBr_2/ZnCl_2$, animal bone meal, toluene, 110 °C	83-96%	**152**
NCS	HgO, S (cat.), EtOH, reflux	77-82%	**153**
NCS	$FeCl_3.6H_2O$, H_2O, 80 °C	68-79%	**154**
CH_2OH/CHO	$(Cp^*IrI_2)_2$, toluene, reflux	52-85%	**155**
	$Ru_3(CO)_{12}$, NH_4PF_6, MeOH, 80 °C	58-98%	**149**

Scheme 20 Synthesis of benzoxazoles from 2-aminophenols

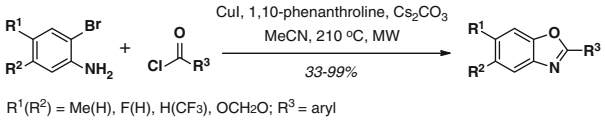
Alternatively, *o*-nitrophenols were also employed as a direct precursor for benzoxazole synthesis which requires in situ reduction to *O*-aminophenols (Scheme 21) [156, 157]. Plus, palladium-catalyzed 2-arylbenzoxazole formation from iodobenzene and 2-fluoroaniline has also been reported (Scheme 21) [158].



Scheme 21 Synthesis of benzoxazoles from *o*-nitrophenols

2.1.14 B-Bond and D-Bond Formation

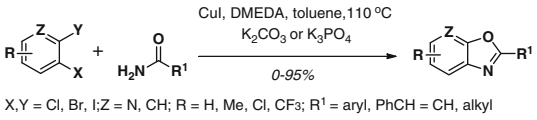
In 2008, Batey et al. reported their benzoxazole skeleton synthesis from 2-aminophenols and acyl chloride catalyzed by CuI under microwave irradiation or regular thermal conditions [159]; the scope and limitation of this reaction are shown in Scheme 22.



Scheme 22 Benzoxazole synthesis from *o*-bromoanilines and acyl chlorides

2.1.15 C-Bond and D-Bond Formation

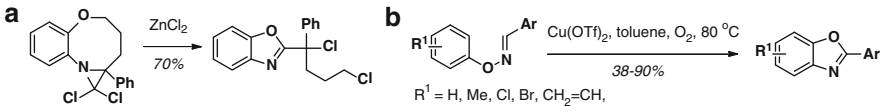
A good pathway for benzoxazole synthesis through **C**-bond and **D**-bond formation is the C–N and C–O double cross-coupling reactions from primary amides and *o*-bishalogenated benzenes. In 2004, Glorius and Altenhoff reported a CuI-catalyzed cross coupling from *o*-dibromo, dichloro, diiodo, or bromochlorobenzenes and primary amides (Scheme 23) [160]. In the same publication as **B**-bond and **D**-bond formation, similar CuI-catalyzed coupling was also detailed (Scheme 23) [159].



Scheme 23 Benzoxazole synthesis from 1,2-dihalobenzenes or pyridines and primary amides

2.1.16 Miscellaneous Methods

In addition to the above described methods, Khlebnikov et al. reported a selective transannular ring transformation catalyzed by $ZnCl_2$ to obtain benzoxazoles from aziridino-fused eight-membered *O,N*-heterocycles (Scheme 24a) [161]. Very recently, Punniyamurthy and coworkers reported their 2-arylbenzoxazole synthesis



Scheme 24 Miscellaneous metal-mediated synthesis of benzoxazoles

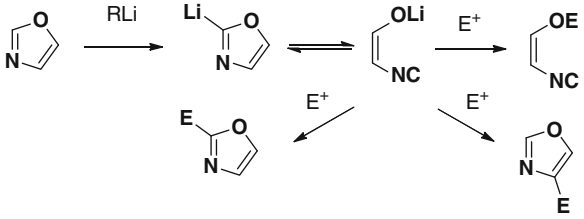
from bisaryloxime ethers (Scheme 24b) [162, 163]. The mechanism involves a Lewis acid catalyzed cascade rearrangement with C–H functionalization and C–N/C–O bond formation.

3 Metalation of Oxazoles and Benzoxazoles

3.1 Metalation of Oxazoles

3.1.1 Metalation of Oxazoles at C-2

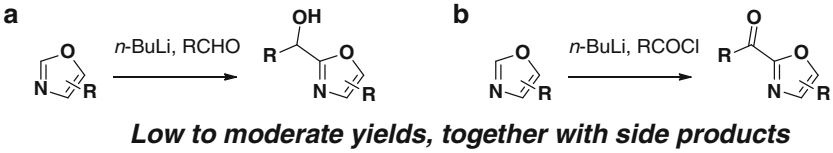
When oxazole is treated with base, such as *n*-BuLi, the most acidic C-2 proton is deprotonated and 2-lithiooxazole is generated. However, 2-lithiooxazole is not observed by NMR, only the ring opened isonitrile. Trapping of the intermediate with electrophiles affords the corresponding O-protected isonitriles [164–171], or the ring-closed 2-substituted oxazoles [164–169, 172–203], or even 4-substituted oxazoles [167, 168, 174, 176, 177], based on different reaction conditions or electrophiles (Scheme 25).



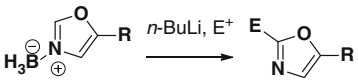
Scheme 25 Metalation of oxazole

Introduction of Electrophiles at C-2

Oxazoles, with the acidic C-2 position, present a unique challenge for metalation protecting group strategies due to this unusual behavior of the C-2 lithio anion (Scheme 25). Nevertheless, metalation at C-2 has been widely used in both organic chemistry [164–183] and medicinal chemistry[184–203] since the 1980s. Lithiation of oxazoles with *n*-BuLi followed by trapping with aldehydes or acyl halides gives the desired 2-substituted oxazoles in low to moderate yields (Scheme 25a, b). But if complexed with borane before lithiation, the desired 2-substituted oxazoles were obtained exclusively in good yields (Scheme 25c) [175]. Alternatively, trans-metalation of the initially generated 2-lithiooxazoles with $ZnCl_2$ followed by treatment with acyl chloride in the presence of cuprous iodide, the desired 2-acyloxazoles were obtained in good yields, while the corresponding O-acylated vinylisonitriles were not observed (Scheme 25d) [173].

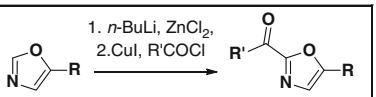


c



R	Electrophile	Yield
Ph	PhCHO	84%
Ph	$PhCH_2CH_2CHO$	84%
H	PhCHO	70%
Ph	Me_3SiCl	78%
Ph	Cl_3CCCl_3	86%
Ph	CH_3I	74%
Ph	$PhCH_2CH_2OTf$	65%

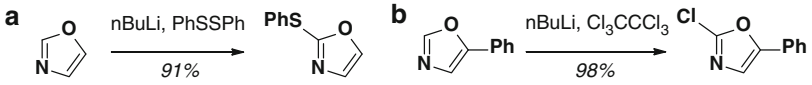
d



R	R′	Yield
Ph	Ph	70%
Ph	4-$MeOC_6H_4$	65%
Ph	4-$NO_2C_6H_4$	80%
Ph	PhCH=CH	58%
Ph	$CH_3(CH_2)_2$	67%
Ph	$(CH_3)_2CH$	67%
Ph	$(CH_3)_3C$	64%
H	Ph	74%

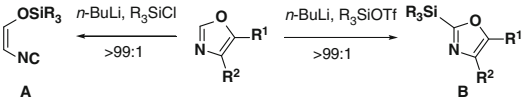
Scheme 26 Synthesis of 2-substituted oxazoles through C-2 lithiation

Electrophiles also play an important role in the outcome of this reaction. When halogen sources, such as ICH_2CH_2I, BrF_2CCF_2Br, Cl_3CCCl_3, $BrCl_2CCCl_2Br$, or PhSSPh, D_2O or DMF were imported as electrophile, the desired 2-substituted oxazoles were obtained exclusively in good yields, exemplified by the 2-phenylthiooxazole[204] (Scheme 27a) and poly-oxazole synthesis (Scheme 27b) [182].



Scheme 27 PhSSPh and Cl_3CCCl_3 act as electrophiles in 2-substituted oxazoles synthesis

A unique case for the introduction of electrophiles at oxazole C-2 is the preparation of 2-silyloxazoles. When trialkylsilyl chloride was used as the electrophile, the ring-opened vinylisonitriles were obtained as the solo product, while trialkylsilyl triflate provided 2-silyloxazoles exclusively (Scheme 28) [169].

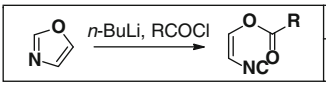


R^1	R^2	Si	Product	Yield	R^1	R^2	Si	Product	Yield
Ph	H	TBSOTf	B	93%	H	Ph	TBSOTf	B	87%
Ph	H	TBSCl	A	96%	H	Ph	TBSCl	A	90%
Ph	H	TIPSOTf	B	95%	H	Ph	TIPSOTf	B	91%
Ph	H	TIPSCl	A	95%	H	Ph	TIPSCl	A	96%
Ph	H	TMSOTf	B	90%	H	H	TIPSOTf	B	94%
Ph	H	TMSCl	A	92%	H	H	TIPSCl	A	94%

Scheme 28 Trialkylsilyl source controlled synthesis of 2-silyloxazoles

Formation of Ring Opened Products

The literature describes the easier formation of ring-opened vinylisonitriles than 2-substituted oxazoles when 2-lithiooxazoles were trapped by electrophiles. When trialkylsilyl chlorides were employed as electrophiles, vinylisonitriles were obtained exclusively (Scheme 28) [164–169]. When acyl chlorides were imported, vinylisonitriles were generally obtained in excellent yields as well (Scheme 29) [170, 171].

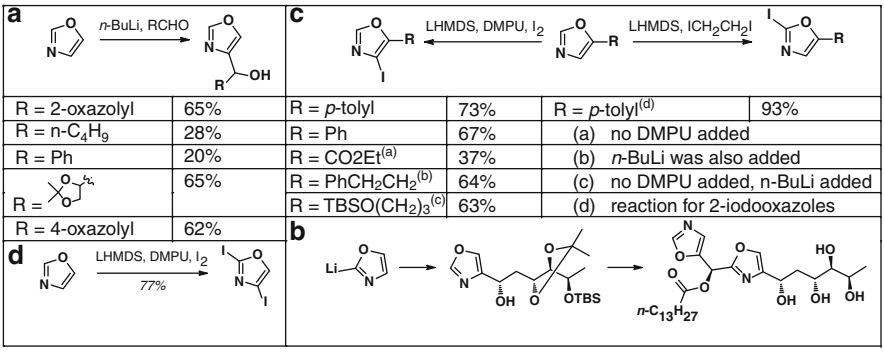


RCOCl = AcCl	75%
RCOCl = O-formylmandeloyl-Cl	95%

Scheme 29 Synthesis of unsaturated isonitrile esters

Introduction of Electrophiles at C-4

When both C-2 and C-4 are not substituted, introduction of electrophiles at C-4 induced by C-2 deprotonation can take place [167, 168, 174, 176, 177]. In 1991, Hodges et al. reported synthesis of 4-substituted oxazoles by trapping 2-lithiooxazoles with aldehydes (Scheme 30a) [167], which was applied to the synthesis of bengazole A by Molinski and coworkers (Scheme 30b) [177]. In 1999, Vedejs and Luchetta imported LHMDS as an alternative base, the 4-iodooxazoles were obtained in good yields when I_2 was introduced as the electrophile, while ICH_2CH_2I resulted in 2-iodooxazoles as the major products. In both cases, 2,4-diiodooxazoles were always a side product (Scheme 30c). Interestingly, 2,4-diiodooxazole was obtained as the major product when Greaney et al. conducted their iodination of oxazole under the same conditions (Scheme 30d) [205].



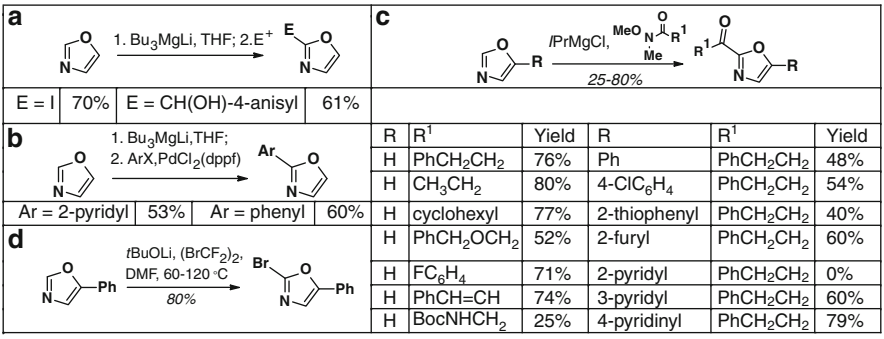
R = 2-oxazolyl	65%	R = *p*-tolyl	73%	R = *p*-tolyl[(d)]	93%
R = n-C_4H_9	28%	R = Ph	67%	(a) no DMPU added	
R = Ph	20%	R = CO2Et[(a)]	37%	(b) *n*-BuLi was also added	
R =	65%	R = $PhCH_2CH_2$[(b)]	64%	(c) no DMPU added, n-BuLi added	
		R = $TBSO(CH_2)_3$[(c)]	63%	(d) reaction for 2-iodooxazoles	
R = 4-oxazolyl	62%				

Scheme 30 Synthesis of 4-substituted oxazoles

Recently Developed Bases for Deprotonations

Besides commonly used bases such as *n*-BuLi, other bases for deprotonation at C-2 have also been developed. In 2005, lithium magnesates were introduced by Mongin

and coworkers for oxazole deprotonation, subsequent trapping with electrophiles or a cross-coupling reaction with aryl halides afforded 2-substituted oxazoles (Scheme 31a, b) [206]. In 2007, Pippel et al. reported deprotonation using isopropyl magnesium chloride, followed by trapping with Weinreb amides, 2-acyloxazoles were obtained in good yields (Scheme 31c) [207]. Early 2009, Daugulis and Do deprotonated 5-phenyloxazole with lithium *t*-butoxide in DMF at 60 °C, trapping with BrF_2CCF_2Br to afford 2-bromo-5-phenyloxazole in 80% yield (Scheme 31d) [208, 209].



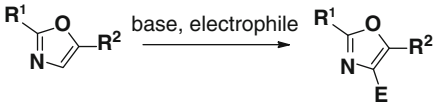
R	R^1	Yield	R	R^1	Yield
H	$PhCH_2CH_2$	76%	Ph	$PhCH_2CH_2$	48%
H	CH_3CH_2	80%	4-ClC_6H_4	$PhCH_2CH_2$	54%
H	cyclohexyl	77%	2-thiophenyl	$PhCH_2CH_2$	40%
H	$PhCH_2OCH_2$	52%	2-furyl	$PhCH_2CH_2$	60%
H	FC_6H_4	71%	2-pyridyl	$PhCH_2CH_2$	0%
H	PhCH=CH	74%	3-pyridyl	$PhCH_2CH_2$	60%
H	$BocNHCH_2$	25%	4-pyridinyl	$PhCH_2CH_2$	79%

Scheme 31 Recently developed bases for synthesis of 2-substituted oxazoles

3.1.2 Metalation of Oxazoles at C-4

Introduction of Electrophiles at C-4

When C-2 and C-5 of oxazoles are substituted, deprotonation at C-4 can take place [172, 210–213]. Treatment of 2,5-diphenyloxazole with *s*-BuLi followed by addition of CH_3I, 4-methyl-2,5-diphenyloxazole was obtained in 85% yield (Scheme 32) [172]; decent yields were also obtained for other electrophiles (Scheme 32) [210, 211]. 2-Methoxy-5-phenyloxazole[212] and 5-phenyl-2-triisopropyloxazole[213] resulted in a good outcome as well (Scheme 32).

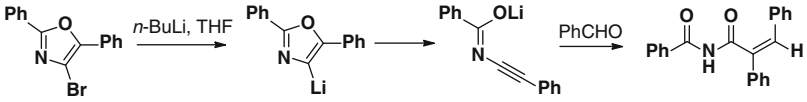


R^1	R^2	base	electrophile	yield	reference
Ph	Ph	*s*-BuLi	CH_3I	85%	172
Ph	Ph	LDA	$TMSO(CH_2)_6I$	45%	210
Ph	Ph	LDA	$TBSO(CH_2)_3CHO$	47%	210
Ph	Ph	LiTMP	DMF	33%	211
OMe	Ph	*n*-BuLi	PhCHO	54%	212
OMe	Ph	*n*-BuLi	Me_2CHCHO	65%	212
TIPS	Ph	*n*-BuLi	CH_3I	89%	213
TIPS	Ph	*n*-BuLi	PhCHO	56%	213

Scheme 32 Oxazole C-4 lithiation for synthesis of 4-substituted oxazoles

Formation of Ring Opened Products

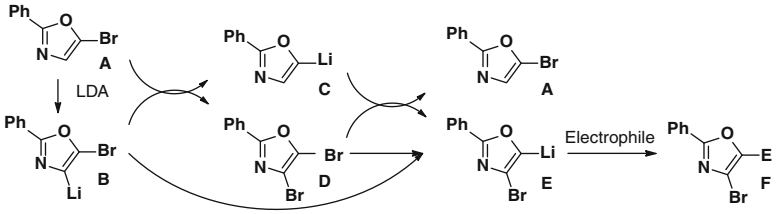
In 1976, Gilchrist and Pearson reported the only ring-opening of oxazoles induced by C-4 lithiation [214]. In their study, 4-bromo-2,5-diphenyloxazole was treated with *n*-BuLi followed by quenching with benzaldehyde in the presence of HMPA, to obtain the benzoylamide product. (Scheme 33).



Scheme 33 Oxazole C-4 lithiation induced ring opening

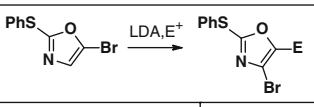
Halogen Dance Reactions

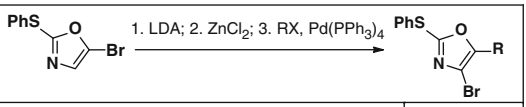
In 2005, Stanetty et al. first applied the halogen dance reaction to oxazoles [215, 216]. Lithiation of 5-bromo-2-phenyloxazoles (**A**) with LDA in the 4-position generates 4-lithioxazole (**B**), which reacts with remaining 5-bromooxazole (**A**) to form two additional intermediates, 5-lithiooxazole (**C**) and 4,5-dibromooxazole (**D**), via halogen metal exchange. The lithiated species (**B** and **C**) undergo reaction with dibromooxazole **D** to form the final 4-bromo-5-lithioxazoles **E**. Upon quenching with electrophiles, the desired 4-bromo-5-substituted oxazoles **F** were isolated (Scheme 34). Electrophiles can be H_2O, RCHO, R_3SiCl, Br_2, Cl_3CCCl_3, I_2, CO_2, $RCOR^1$, DMF, $BrCH_2CH_2Br$, $BrCl_2CCCl_2Br$, etc. [215, 216].

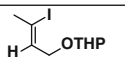
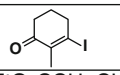
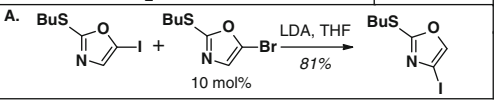


Electrophile	Yield	Electrophile	Yield	Electrophile	Yield
H_2O	60%	PhCHO	78%	TMSCl	68%
Cl_3CCCl_3	68%	$BrCl_2CCCl_2Br$	76%	I_2	66%
DMF	58%	CO_2	63%	cyclohexanone	69%

Scheme 34 Halogen dance reaction for synthesis of 4-bromo-2-phenyloxazoles





Electrophile	Yield	RX	Yield
H_2O	88%	PhI	80%
NIS	87%		67%
Bu_3SnCl	83%		
TIPSOTf	89%		72%
2-furoaldehyde	82%		
HCHO	72%	$EtO_2CCH{=}CHI$	77%
cyclopentanone	79%		
acetone	74%		

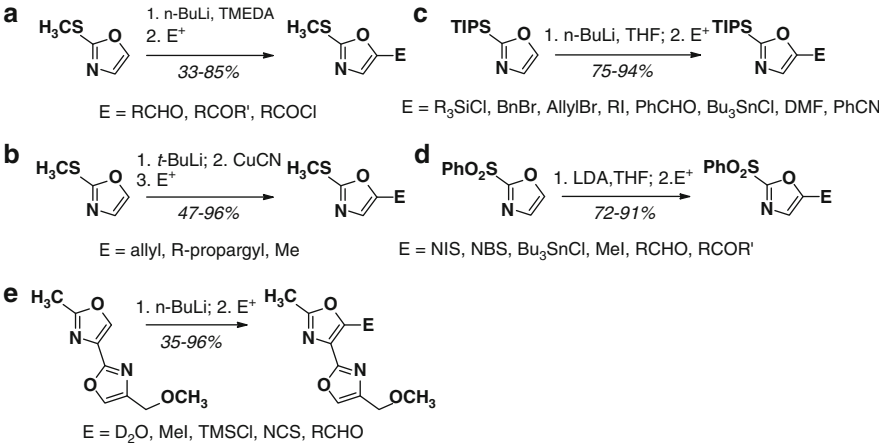
Scheme 35 Halogen dance reaction for synthesis of 4-bromo-2-phenylthiooxazoles

In 2010, Williams and Fu reported their halogen dance reaction with 5-bromo-2-(phenylthio)oxazole. Besides quenching the reaction with electrophiles, in situ transmetallation of the 4-bromo-5-lithiooxazole to the corresponding zinc chloride, followed by Negishi cross-coupling reactions afforded 4-bromo-5-substituted oxazoles (Scheme 35) [217]. Very recently, Stambuli et al. reported the halogen dance reaction using iodide instead of bromide, and optimized conditions catalyzed by bromide increased yield from 31% to 81% (Scheme 35a) [218].

3.1.3 Metalation of Oxazoles at C-5

Direct C-5 Lithiations

When oxazoles C-2 are substituted, while C-5 is not substituted [23, 196–204, 213, 219–223] or substituted with halogen [224, 225], lithiation at C-5 will take place. In 1989, Molinski and Shafer reported their direct alkylation from 2-methylthiooxazole using *n*-BuLi (Scheme 36a) [219], Marino and Ngyuen introduced copper for the C-5 allylation and propargylation (Scheme 36b) [221]. Later on, Miller et al. [213] and Williams and Fu introduced TIPS (Scheme 36c) and $PhSO_2$ (Scheme 36d) as C-2 substituents. In 1998, Williams developed a regioselective C-5 alkylation in a [2,4]-bisoxazole system (Scheme 36e) [220].

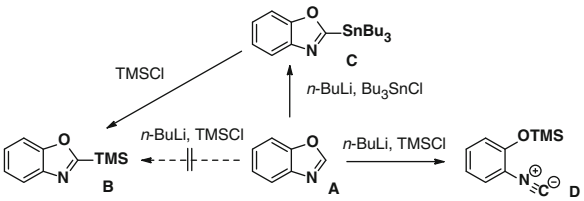


Scheme 36 Direct C-5 lithiation for synthesis of 5-substituted oxazoles

3.2 Metalation of Benzoxazoles

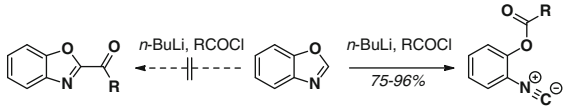
Unlike oxazoles, metalation of benzoxazoles is mainly restricted to the C-2 position. Furthermore, synthesis of benzoxazoles always results in 2-substituted benzoxazoles. Thus, compared to oxazoles, application of benzoxazole metalation is relatively limited.

Dating back to the 1980s, Whitesides and Moore reported their tentative identification of (benzoxazol-2-yl)trimethylsilane (**B**) from lithiation of benzoxazole (**A**) followed by treatment with TMSCl. But their attempt to make (benzoxazol-2-yl) phosphine from silane **B** failed when treated with PCl_3 [226]. Shortly thereafter, Jutzi and Gilge reported their synthesis of (benzoxazol-2-yl)trimethylsilane **B** and stannane **C**. Upon lithiation of benzoxazole, treatment with TMSCl, the ring-opened isonitrile **D** was obtained instead of **B**, while tributyltin chloride resulted in the formation of benzoxazole **C**, which upon treatment with TMSCl afforded silane **B** [227]. In 1989, Molloy et al. also obtained benzoxazol-2-yltributylstannane **C** following the same pathway (Scheme 37) [228].



Scheme 37 Synthesis of 2-(trimethylsilyl)benzoxazole through lithiation

In a recent application [170, 171, 206, 229–233], *Pirrung et al.* treated benzoxazole with *n*-BuLi followed by quenching with acyl chloride, unsaturated isonitriles were obtained in good yields instead of 2-acylbenzoxazoles (Scheme 38) [170, 171].

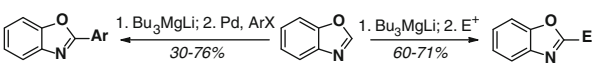


R	Yield	R	Yield	R	Yield	R	Yield
Ac	85%	MeC_6H_4	96%	$MeOC_6H_4$	96%	Ph	93%
Piv	92%	*t*BuO	83%	NCC_6H_4	90%		

Scheme 38 Metallation of benzoxazole for the synthesis of convertible isonitriles

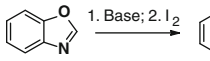
In one of the few publications by Mongin and coworkers, lithium magnesates were firstly introduced for the deprotonation of benzoxazole, upon in situ cross-coupling reactions with aryl halides or treatment with electrophiles, 2-substituted benzoxazoles were obtained in good yields (Scheme 39a) [206]. Other bases, such as mixed lithium–zinc [234], lithium–cadmium [235], lithium–indium species [236], K_3PO_4 [209], and LiO*t*-Bu[209] have also been applied in the synthesis of 2-substituted benzoxazoles from benzoxazole (Scheme 39b, c).

a



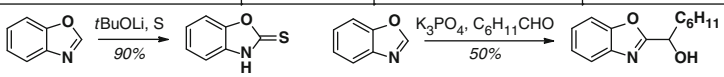
Electrophile	Yield	Ar	Yield	Ar	Yield
H_2O	68%	2-pyridyl	76%	2-thienyl	30%
I_2	60%	3-quinolyl	52%	4-(methoxycarbonyl)phenyl	52%
4-$MeOC_6H_4CHO$	70%	5-pyrimidyl	41%	4-cyanophenyl	61%
3,4,5-$(MeO)_3PhCHO$	71%	phenyl	50%		

b



Base	$ZnCl_2$.TMEDA, LiTMP	$CdCl_2$.TMEDA, LiTMP
Yield	57%	63%
Reference	I	J

c



Scheme 39 Recently introduced bases for benzoxazole deprotonation

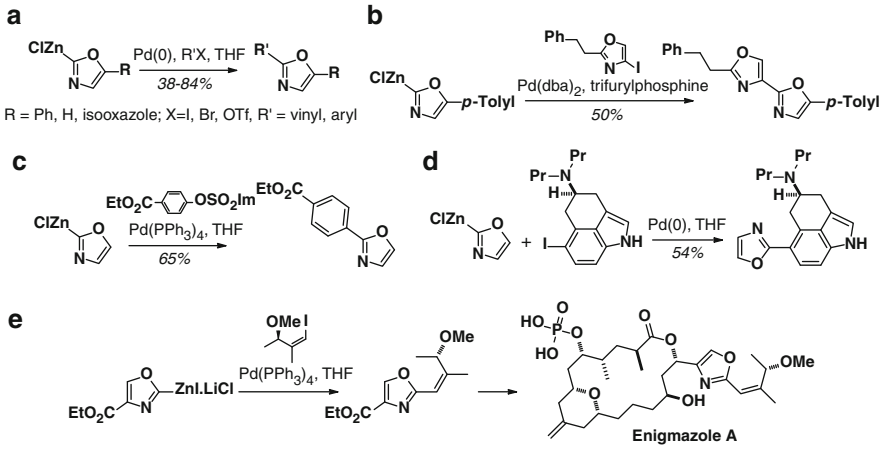
4 Cross-Coupling Reactions

4.1 Oxazole-Based Cross-Coupling Reactions

Since the 1980s, oxazole cross-coupling reactions have been widely used in synthetic organic methodology and medicinal chemistry, including Negishi coupling, Suzuki coupling, Stille coupling, Sonogashira coupling, and other novel developed methods.

4.1.1 Cross-Coupling Reactions from Oxazole Zincs

Oxazolyl zincs are generally obtained from oxazolyl lithium through transmetallation. In mid-1990s, Hughes [174] and Anderson [237] reported palladium-catalyzed coupling reactions between oxazol-2-ylzinc with vinyl halides [174], aryl halides [174, 237], and triflates (Scheme 40a) [237]. The literature contains many recent applications [238–245], such as the development of a practical and scalable procedure coupling with aryl bromides [239], coupling of oxazol-2-ylzinc with 4-iodooxazole [176] (Scheme 40b) and imidazolylsulfonate (Scheme 40c) [242], and applications to the synthesis of Ergot alkaloids [238] (Scheme 40d) and Enigmazole A [245] (Scheme 40e).



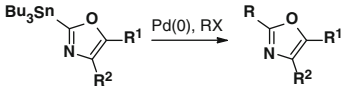
Scheme 40 Cross-coupling reactions of oxazol-2-yl zincs

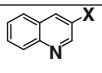
To date, there are no reports introducing oxazol-4-ylzinc cross-coupling reactions, although Williams and Fu reported an in situ generation of 5-lithiooxazoles using the halogen dance reaction, which was transmetaled to zinc, followed by coupling with halides to give trisubstituted oxazoles (Scheme 35) [217].

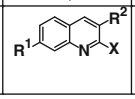
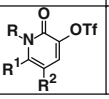
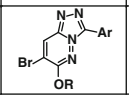
4.1.2 Cross-Coupling Reactions from Tributylstannyloxazoles

Tributylstannyloxazoles, mainly generated from lithiation of oxazoles followed by trapping with tributyltin chloride, are the most commonly used partners in oxazole cross-coupling reactions. Dating back to late-1980s, Dondoni et al. first reported cross coupling between 2-Bu_3Sn-oxazole and aryl halides in excellent yields [165]. Many other partners, such as phenyl [251, 254, 256], 2-pyridones [246], triazolo-pyridazines [247], pyrimidines [248, 252], dihydronaphthalinones [249], purines [250], azulenes [253], thiophenes [257], tetrahydroindolizinones [258], quinolines [259], indazoles [260], and others[255] have shown up to give good results in recent

publications (Scheme 41). This methodology has also been applied to the synthesis of natural products, such as ajudazol A [261].

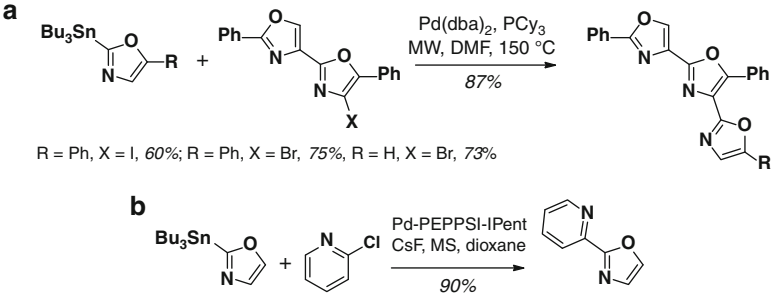


Reference	165,251,254,256	165	165	165,257	165	165	165	165
RX								

Reference	165,259	246	247	248,252	249	250	253
RX							

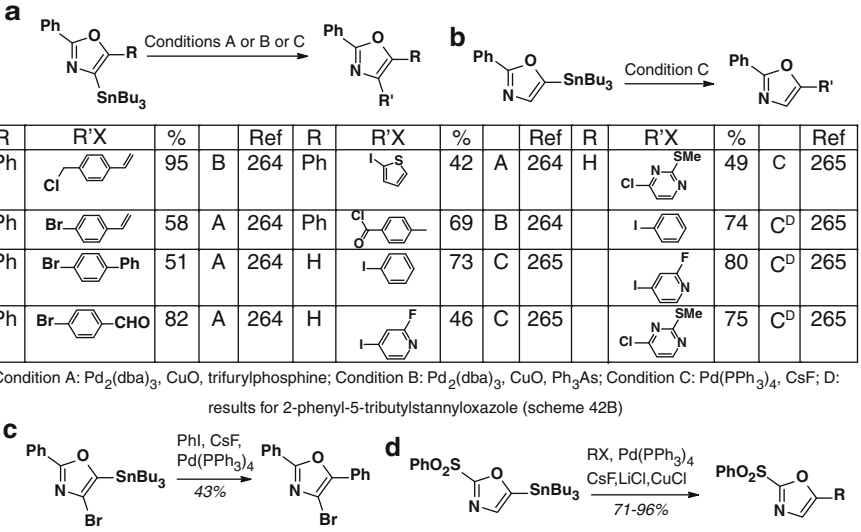
Scheme 41 Cross-coupling reactions of 2-tributylstannyloxazoles

Recent developments of special interest include synthesis of trisoxazoles through coupling of 2-stannyloxazoles and 4-halobisoxazoles reported by Greaney et al. (Scheme 42a) [262]. Very recently, Organ and coworkers also reported an efficient low-temperature Stille coupling using Pd-PEPPSI-IPent as the catalyst, in which 2-stannyloxazole coupled with 2-chloropyridine in 90% yield (Scheme 42b) [263].



Scheme 42 2-Tributylstannyloxazoles related cross-coupling reactions

Cross-coupling reactions using 4-tributylstannyl and 5-tributylstannyloxazoles have also been reported. In 2001, Sutherland and Clapham reported Stille couplings between 2,5-diphenyl-4-tributylstannyloxazole with halides catalyzed by palladium in the presence of stoichiometric quantities of CuO (Scheme 43a) [264]. In 2008, Stanetty et al. synthesized 4-aryloxazoles in moderate to good yields from 2-phenyl-4-tributylstannyloxazole and aryl halides (Scheme 43a) [265]. In the same publication, the cross-coupling reactions with 5-stannyloxazole gave much better yields (Scheme 43b), although 4-bromo-5-tributylstannyloxazole resulted in moderate yield (Scheme 43c).{216} Vedejs et al. also applied the reaction between 2-phenyl-5-Bu_3Sn-oxazole and vinyl triflate in their aziridinomitosene A synthesis [266]. In 2010, Williams and Fu reported cross coupling of with vinyl or aryl halides in good yields, the sulfone substituent at C-2 can be displaced by nucleophiles or mildly reduced to hydrogen for further C-2 modifications (Scheme 43d) [267].



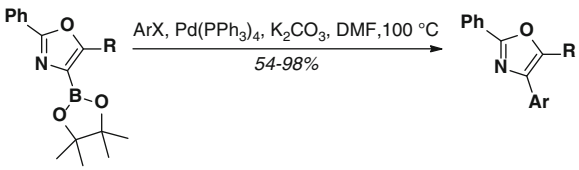
R	R'X	%		Ref	R	R'X	%		Ref	R	R'X	%		Ref
Ph		95	B	264	Ph		42	A	264	H		49	C	265
Ph		58	A	264	Ph		69	B	264			74	C^D	265
Ph		51	A	264	H		73	C	265			80	C^D	265
Ph		82	A	264	H		46	C	265			75	C^D	265

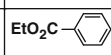
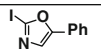
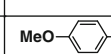
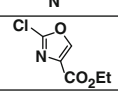
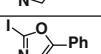
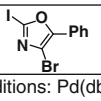
Condition A: $Pd_2(dba)_3$, CuO, trifurylphosphine; Condition B: $Pd_2(dba)_3$, CuO, Ph_3As; Condition C: $Pd(PPh_3)_4$, CsF; D: results for 2-phenyl-5-tributylstannyloxazole (scheme 42B)

Scheme 43 Stille cross-coupling of 4- and 5-tributylstannyloxazoles

4.1.3 Cross-Coupling Reactions from Oxazolylborons

Compared to oxazolylzincs and oxazolyltins, the cross-coupling reactions of oxazolylborons are relatively limited. In 2006, reported the first cross-coupling reaction of oxazol-4-ylboronates, which were obtained from oxazol-4-yltriflate through coupling with bis(pinacolato)diboron or transmetalation from 4-lithiooxazoles with triisopropylborate in pinacol [268]. In their study, 2,4-disubstituted or 2,4,5-trisubstituted oxazoles were obtained in good yields with their optimized conditions

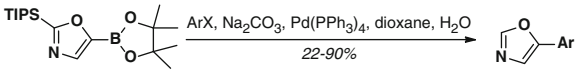


R	ArX	Yield	R	ArX	Yield	R	ArX	Yield
H		83%	H		73%	H		87%
H		56%	H Me		80% 84%	H		46%
H		54%	H Me		80% 88%	H		81%
H		65%	Me		98%	a.Conditions: $Pd(dba)_2$, PCy_3, K_2CO_3, DMF, MW, 150 °C		

Scheme 44 Cross-coupling reactions of oxazol-4-ylborates

(Scheme 44). Inoue et al. reported coupling with 2-halooxazoles for the synthesis of poly-oxazoles in 2007 [269]. Greaney et al. also reported synthesis of 2,4′-bisoxazoles by coupling with 2-iodo-5-phenyloxazole or regioselective coupling with 4-halo-2-iodo- 5-phenyloxazoles (Scheme 44) [262].

In 2009, Rault et al. reported the only cross-coupling reactions with oxazol-5-ylborates, which were prepared from 5-lithio-2-triisopropylsilyloxazole by trapping with triisopropylborate in pinacol [270]. In their study of Suzuki coupling with aryl halide, the desired 5-aryloxazoles were obtained in good yields, and the TIPS group was eliminated in the reaction as well (Scheme 45).

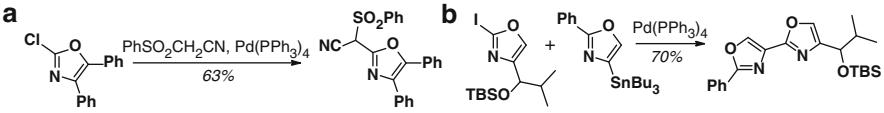


ArX	%	ArX	%	ArX	%	ArX	%	ArX	%
MeO, I	79	NC, Br	64	Br, CN	72	I, CO_2Et	53	OHC, O, Br	71
OHC, Br	71	I, MeO	90	Br, OHC	67	Br, N	69	N, EtO, N, Cl	43
H_2N, Br	62	Br, NC	75	Br, CHO	74	Br, N	42	Br, N, Boc	22

Scheme 45 Suzuki coupling reactions of oxazol-5-ylborates

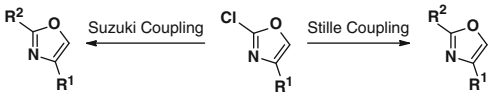
4.1.4 Cross-Coupling Reactions from Halooxazoles

Cross-coupling reactions of halooxazoles have been widely used in organic chemistry and medicinal chemistry, but not as popular as oxazolyl triflates. In 1992, Yamanaka et al. first reported the cross coupling of 2-chlorooxazole with phenylsulfonylacetonitrile catalyzed by $Pd(PPh_3)_4$ (Scheme 46a) [271]. In 1997, Barrett and Kohrt synthesized 2,4′-bisoxazole by coupling 2-iodooxazole with 4-tributylstannyloxazole in their hennoxazole A synthesis study (Scheme 46b) [272].



Scheme 46 Early reports in 2-halooxazoles cross-coupling reactions

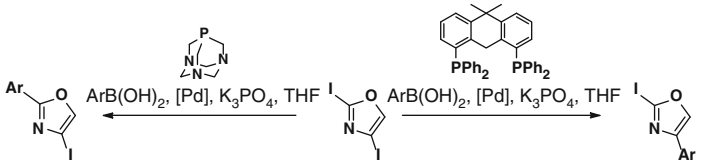
Recent applications in Suzuki and Stille coupling reactions are relatively comprehensive [273–278]. 2-Chlorooxazoles reacted well with aryl boronic acids and vinyl stannanes (Scheme 47). 2-Chloro [268], 2-bromo [268], and 2-iodooxazoles [262] also showed good results in cross-coupling reactions with oxazol-4-ylborates, including the regioselectivity over 4-iodo/bromooxazoles (Scheme 44) [262]. Negishi cross coupling between 2-pyridylzinc bromide with 2-chlorooxazole also resulted in 73% yield, but the Sonogashira coupling with phenylacetylene failed [273].



R^1	$R^2B(OH)_2$		%	Ref	R^1	R^2SnBu_3		%	Ref
CO_2Et	$PhB(OH)_2$	A	87	273,274	CO_2Et	CH_2=$CHSnBu_3$	D	84	273
Bn	$PhB(OH)_2$	B	97	275	Bn	$PhSnBu_3$	E	96	275
$PhCH$=$CHCH_2$	$PhB(OH)_2$	B	81	275	Bn	CH_2=$CHSnBu_3$	E	94	275
Bn		B	60	275	EtO_2CCH=$CHCH_2$	CH_2=$CHSnBu_3$	E	78	275
$PhCH$=$CHCH_2$		B	67	275	$PhCOCH$=$CHCH_2$	CH_2=$CHSnBu_3$	E	34	275
Ph	*o*-TolB(OH)$_2$	C	80	276	A. $Pd(PPh_3)_4$, aq. K_2CO_3, PhMe, 90 °C; B. $Pd(PPh_3)_2Cl_2$, Na_2CO_3, DME, 80 °C; C. $Pd(PPh_3)_2Cl_2$, aq. Na_2CO_3, dioxane, MW, 150 °C; D. $Pd(PPh_3)_2Cl_2$, dioxane, 100 °C; E. $Pd(PPh_3)_2Cl_2$, DMF, 100 °C				
Ph	3-FPhB(OH)$_2$	C	80	276					
Ph	*p*-TolB(OH)$_2$	C	88	276					
Ph	3-PyrB(OH)$_2$	C	91	276					
Ph	3-FurylB(OH)	C	82	276					

Scheme 47 Suzuki and Stille coupling reactions of 2-chlorooxazoles

In 2010, Strotman et al. reported regioselective Suzuki couplings of 2,4-diiodooxazole [279]. In their study, 2-aryl-4-iodooxazoles were obtained as the major products when 1,3,5-triaza-7-phosphaadamantane was used as the ligand, while xantphos gave 4-aryl-2-iodooxazoles as the major products (Scheme 48).



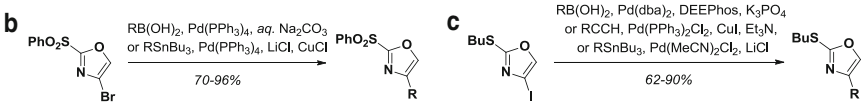
$ArB(OH)_2$							
C-2 Coupling	55%	53%	60%				
C-4 Coupling	64%	54%	44%	51%	47%	54%	58%

Scheme 48 Regioselective Suzuki coupling reactions of 2,4-diiodooxazole

Cross-coupling reactions of 4-halooxazoles have also been studied. In 1992, Yamanaka et al. first reported coupling of 4-bromo-2,5-diphenyloxazole with phenylsulfonylacetonitrile (Scheme 49a) [271], and 4-bromooxazole also coupled with tributylstannylferrocene in 89% yield (Scheme 49a) [280]. More examples were reported by Sutherland and Clapham in 2001 [264], Hodgetts and Kershaw in 2002 [271], Li et al. in 2007 [281], Stanetty et al. in 2008 [265], Greaney et al. in 2008 (Scheme 42a) [262], Boger et al. in 2008 [201], Williams and Fu in 2010 (Scheme 49b) [267], Stambuli et al. in 2011 (Scheme 49b) [282], and regioselective couplings of C-4 iodide over C-2 (Scheme 48) [279].



R	Partner		%	Ref	R	Partner		%	Ref
Ph	$PhSO_2CH_2CN$	A	85	271	H		H	81	265
Ph		B	89	280	2-NO_2Ph		I	61	281
Ph		C	98	264	2-HSPh		I	54	281
Ph		C	49	275	Condition A: $Pd(PPh_3)_4$, PhH; B: $Pd(PPh_3)_4$, CuO, DMF; C: $Pd_2(dba)_3$, trifurylphosphine, NMP; D: $Pd(PPh_3)_4$, *aq.* K_2CO_3, PhMe; E: $Pd(PPh_3)_2Cl_2$, dioxane; F: $Pd(PPh_3)_4$, THF; G: $Pd(PPh_3)_2Cl_2$, CuI, Et_3N; H: $Pd(PPh_3)_4$, CsF, PhMe; I: Pd(dppf)Cl_2, CsF, *aq.* K_2CO_3.			
Ph		C	85	275					
Ph		D	89	272					
Ph		E	83	272					
Ph		F	72	272					
Ph		G	79	272					

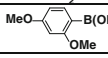


Scheme 49 Cross-coupling reactions of 4-bromooxazoles

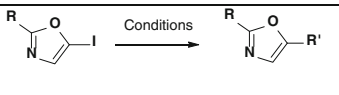
Cross couplings of 5-halooxazoles have also been explored, with initial coupling of phenylsulfonylacetonitrile in 1992 (Scheme 50a) [271]. Subsequent explorations include Suzuki, Stille, Negishi, and Sonogashira couplings of 5-bromo-4-ethoxycarbonyl-2-phenyloxazole (Scheme 50a) [272, 273], Stille couplings of 5-bromo-2-substitutedoxazoles (Scheme 50a) [196, 202, 265], Suzuki and Stille couplings of 5-iodo-2-phenylsulfonyl oxazole (Scheme 50b) [267], Suzuki, Stille, and Buchwald–Hartwig amination of 5-bromo-trisoxazoles (Scheme 50c) [283], and Suzuki, Stille, and Sonogashira coupling of 2-butylthio-4-iodooxazole (Scheme 50b) [282].

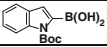
a



R	Partner		%	Ref
Ph	$PhSO_2CH_2CN$	A	85	271
CO_2Et		B	93	272
CO_2Et		B	78	273
CO_2Et		B	91	272
CO_2Et		C	82	272
CO_2Et		D	76	272
CO_2Et		E	77	272
H		F	76	265

b

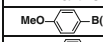
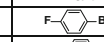
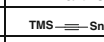
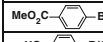
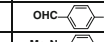
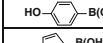
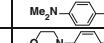
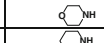
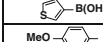
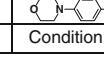
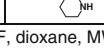
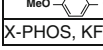


R	Partner		%	Ref
SO_2Ph		B	91	267
SO_2Ph		B	94	267
SO_2Ph		B	96	267
SO_2Ph		B	92	267
SO_2Ph		B	96	267
SO_2Ph		G	85	267
SBu		H	83	282
SBu		H	72	282
SBu		H	82	282
SBu		I	77	282
SBu	 R'' = OAc, CN, CH_2CH_3	E	63	282
		E	66	282
		E	77	282

Conditions A: $Pd(PPh_3)_4$, PhH; B: $Pd(PPh_3)_4$, *aq.* K_2CO_3, PhMe; C: $Pd(PPh_3)_2Cl_2$, dioxane; D: $Pd(PPh_3)_4$, THF; E: $Pd(PPh_3)_2Cl_2$, CuI, Et_3N; F: $Pd(PPh_3)_4$, CsF, PhMe; G: $Pd(PPh_3)_4$, LiCl, CuCl, DMSO; H: $Pd(dba)_2$, DPEEPhos, K_3PO_4; I: $Pd(CN)_2Cl_2$, LiCl, DMF;

c

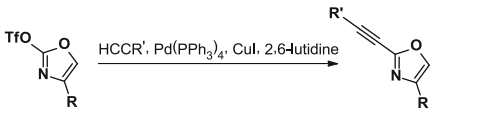


Partner		%	Ref	Partner		%	Ref	Partner		%	Ref
	J	91	283		J	80	283		L	70	283
	J	74	283		J	62	283	$CH_3(CH_2)_7NH_2$	M	70	283
	K	84	283		K	63	283		M	65	283
	K	91	283		K	68	283		M	69	283
	M	43	283	Condition J: $Pd(OAc)_2$, S-PHOS, KF, dioxane, MW, 110°C; K: $Pd(OAc)_2$, X-PHOS, KF, DME, 80 °C; L: $Pd(OAc)_2$, X-PHOS, dioxane, 60 °C; M: $Pd(OAc)_2$, X-PHOS, K_3PO_4, dioxane, 80 °C							

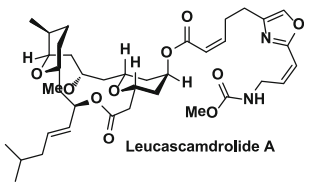
Scheme 50 Cross-couplings of 5-halooxazoles

4.1.5 Cross-Coupling Reactions from Oxazole Triflates

Oxazole triflates, a superior alternative for halooxazoles, behave very well in cross-coupling chemistry. The study of oxazol-2-yltriflates was only carried out by the research group of Panek (Scheme 51). In 2002, they reported a Sonogashira coupling of oxazol-2, 4, and 5-yltriflates with alkynes [284]. Later on, they applied the Sonogashira coupling for their total synthesis of leucascandrolide A [264, 285].

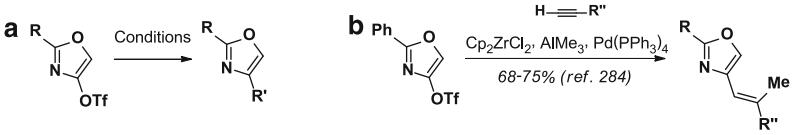


R	R'	Yield	R	R'	Yield
Ph	$Ph(CH_2)_2$	76%	Ph	$TBSOCH_2$	75%
	$BnOCH_2$	54%		MeO_2CNHCH_2	71%
$BnO(CH_2)_3$	$Ph(CH_2)_2$	83%			



Scheme 51 Cross-coupling reactions of oxazol-2-yltriflates

Oxazol-4-yltriflates evidenced wider applications than 2-triflates (Scheme 52a). Oxazol-4-yltriflates have been used as a precursor to 4-borooxazole[267, 269, 274] and 4-stannyloxazole [270]. Their direct cross couplings include palladium-catalyzed reactions with stannanes [286], vinylstannanes and alkynes [287, 288], Sonogashira coupling with alkynes (Scheme 52b) [284], and Suzuki coupling with borates [274]. Complex natural products, such as phorboxazole A[35, 289, 290] and leiodelide A [19], also utilized oxazol-4-yltriflates as key intermediates in their synthesis.



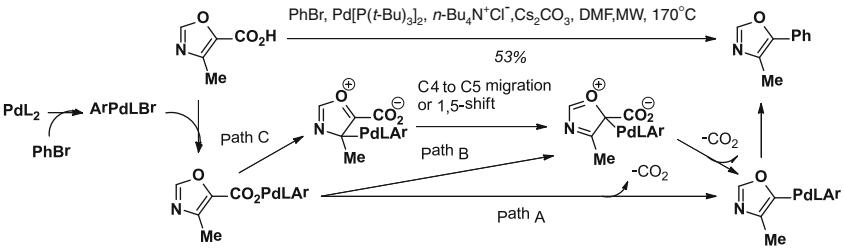
R	Partner		Yield	Ref	R	Partner		Yield	Ref
Ph	$Me_3SnSnBu_3$	A	55%	270	Ph	$PhCH{=}CHSnBu_3$	A	75%	287
Ph	pinBBpin	B	75%	267	Ph	$C_5H_{11}CH{=}CHSnBu_3$	A	80%	287
4-MeOPh	$PhSnBu_3$	A	91%	286	Ph	$AcO(CH_2)_2CH{=}CHSnBu_3$	A	84%	287
4-MeOPh	2-PyridylSnBu_3	A	85%	286	Ph	$Ph(CH_2)_2CCH$	C	86%	284
4-MeOPh	$CH_2{=}CHSnBu_3$	A	99%	286	Ph	TMSCCH	C	71%	284
4-MeOPh	$PhCCSnBu_3$	A	92%	286	Ph	*n*-PentCCH	C	69%	284
Ph	$CH_2{=}CHSnBu_3$	A	74%	288	Ph	$(CH_3)_2C(OH)CCH$	C	42%	284
Ph	4-MePhB$(OH)_2$	D	94%	274	Ph	4-MeOPhB$(OH)_2$	D	89%	274
Ph	3-NO_2PhB$(OH)_2$	D	92%	274	4-MeOPh	4-MePhB$(OH)_2$	D	82%	274
Ph	4-CF_3PhB$(OH)_2$	D	87%	274	Ph	3-FurylB$(OH)_2$	D	79%	274
Ph	2-MePhB$(OH)_2$	D	91%	274	Ph	3-PyridylB$(OH)_2$	D	73%	274
4-FPh	4-MePhB$(OH)_2$	D	75%	274	4-MeOPh	3-PyridylB$(OH)_2$	D	89%	274
4-MeOPh	3-FPhB$(OH)_2$	D	85%	274	Ph	3-FPhB$(OH)_2$	D	91%	274
	pinBBpin	B	42%	269	Ph		D	58%	274
4-FPh		D	69%	274	4-MeOPh		D	61%	274

Condition A: $Pd(PPh_3)_2Cl_2$, LiCl; B: $Pd_2(dba)_3$, PCy_3, KOAc; C: $Pd(PPh_3)_4$, CuI, 2,6-lutidine; D: $Pd(PPh_3)_2Cl_2$, *aq.* Na_2CO_3, MW.

Scheme 52 Cross-coupling reactions of oxazol-4-yltriflates

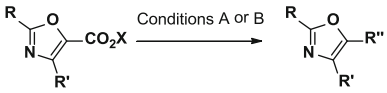
4.1.6 Cross-Coupling Reactions from Oxazole Carboxylic Acids

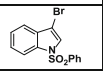
Cross-coupling reactions using oxazole carboxylic acids as coupling partners via decarboxylation were developed recently. The results were initially published by Forgione and Biodeau et al. in 2006 [291]. Coupling of 4-methyloxazol-5-ylcarboxylic acid with bromobenzene catalyzed by $Pd[P(t\text{-}Bu)_3]_2$ unexpected afforded 4-methyl-5-phenyloxazole in 53% yield [291, 292], the postulated mechanism is shown in Scheme 53.



Scheme 53 Oxazol-5-yl carboxylic acid as coupling reaction partners

In 2010, Gooßen et al. reported a low-temperature decarboxylative cross-coupling reaction of aryl triflates with aromatic carboxylate salts catalyzed by Ag/Pd, in which 5-aryloxazoles were obtained in excellent yields (Scheme 54) [293]. In the same year, Greaney and Zhang reported a decarboxylative coupling of azoyl carboxylic acids with aryl halides, in which 5-aryloxazoles were generated in good yields (Scheme 54) [294].



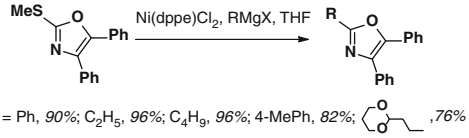
R	R'	X	Partner		Yield	Ref	R	R'	X	Partner		Yield	Ref
H	Me	K	4-ClPhOTf	A	87%	293	4-MeOPh	Me	H		B	91%	294
H	Me	K	4-MePhOTf	A	89%	293	4-MePh	Me	H		B	80%	294
Ph	H	H	4-MeOPhI	B	73%	294	Ph	H	H		B	82%	294
Me	H	H		B	63%	294	4-MeOPh	Me	H	PhI	B	90%	294
							4-MePh	Me	H	PhI	B	94%	294

Condition A: Ag_2CO_3, $PdCl_2$, PPh_3, 2,6-lutidine, NMP, 130 °C; B: Ag_2CO_3, $PdCl_2$, PPh_3, DMA, PhMe, 135 °C

Scheme 54 Examples of coupling reactions using oxazol-5-yl carboxylic acids as coupling partners

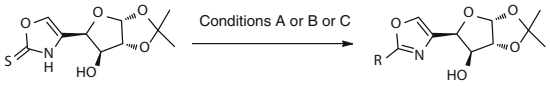
4.1.7 Cross-Coupling Reactions from Oxazole Sulfides

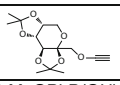
Cross-coupling reactions using sulfide instead of halides or triflates have also been studied. Early in 1984, Pridgen reported cross coupling of Grignard reagents with 2-methylthio-4,5-diphenyloxazole catalyzed by nickel, in which trisubstituted oxazoles were obtained in good to excellent yields (Scheme 55) [295].



Scheme 55 Cross-coupling reactions of 2-methylthiooxazole with Grignard reagents

Until very recently in 2008, Tatibouët et al. reported a Cu-catalyzed desulfurative Sonogashira coupling with oxazolinethiones for the synthesis of 2-substituted oxazoles (Scheme 56) [296]. The Stille and Suzuki cross-coupling reactions have also been studied using oxazoline as substrates (Scheme 56) [297]. In 2009, Roulland and Guinchard applied this methodology in their neopeltolide synthesis [298].

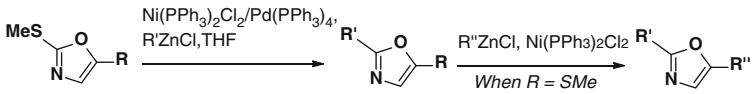


Partner		Yield	Partner		Yield	Partner		Yield
Ph—	A	77%	p-FPh—	A	42%	2-FurylB(OH)$_2$	B	61%
n-pentyl—	A	78%		A	58%	4-IPhB(OH)$_2$	B	38%
MeOH$_2$C—	A	66%				2-ThienylSnBu$_3$	C	86%
TES—	A	67%	4-MeOPhB(OH)$_2$	B	86%	CH$_2$=CHSnBu	C	72%
p-MeOPh	A	63%	3-NO$_2$PhB(OH)$_2$	B	66%			

Condition A: Pd(PPh$_3$)$_4$, CuI, CuTC, Et$_3$N, DMF, MW; B: Pd(PPh$_3$)$_4$, CuTC, THF, MW; Pd(PPh$_3$)$_4$, CuBr, THF, MW.

Scheme 56 Desulfurative cross coupling reactions of oxazolinethiones

Also in 2009, Stambuli et al. reported a regioselective coupling of 2,5-di (methylthio)oxazole with organozinc reagents, a one-pot sequential coupling for the synthesis of 2,5-disubstituted oxazoles has also been realized [299].



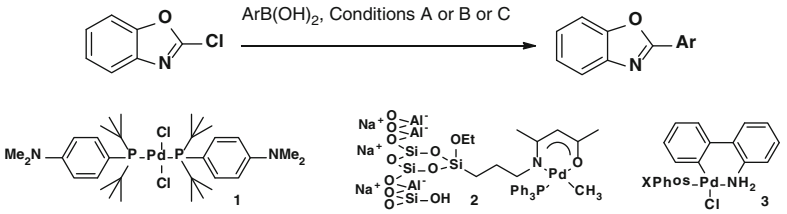
R	R'	Yield	R	R'	Yield	R	R'	R''	Yield
H	PhCH$_2$	85%	H	4-MePh	82%	SMe	Ph	3,4-(MeO)$_2$Ph	74%
H	Ph(CH$_2$)$_3$	58%	H		84%	SMe	Ph		82%
H	Ph	82%				SMe	4-CF$_3$Ph		77%
H	3,4-(MeO)$_2$Ph	81%	H	3-Pyridyl	52%				
H	4-CF$_3$Ph	88%	H	2-Thienyl	83%				
H	4-FPh	86%	H	2-Furyl	80%				
SMe	3,4-(MeO)$_2$Ph	89%	H	PhCC	56%				

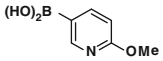
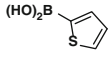
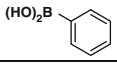
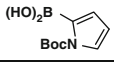
Scheme 57 Nickel-catalyzed synthesis of 2-substituted oxazoles from 2-methylthiooxazoles

4.2 *Benzoxazole-Based Cross-Coupling Reactions*

4.2.1 Cross-Coupling Reactions at C-2

Since the first introduction of benzoxazole cross-coupling reactions at C-2 in the 1980s, numerous examples have appeared including applications of conventional Stille reactions from 2-(tributylstannyl)benzoxazole and halides [300], or 2-halobenzoxazoles and stannanes; [300, 301] Negishi reactions between alkenylzincs and 2-halobenzoxazoles [302, 303], or benzoxazol-2-ylzinc and acyl chlorides;[304] and Suzuki coupling from 2-halobenzoxazole and pyrazolylborane [305]. Modifications in Negishi coupling including Mongin's introduction of lithium magnesates instead of zinc reagents, in which initial deprotonation of benzoxazole with lithium magnesates was followed by palladium-catalyzed coupling with aryl halides (Scheme 39a) [206]. Further development in Suzuki coupling includes the introduction of new catalysts, such as $PdCl_2(PR_2(Ph\text{-}R'))_2$ complex [306], MP-LTA-supported β-oxoiminatophosphanylpalladium complex [307], and XPhos-containing precatalysts (Scheme 58) [308].



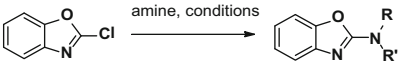
$ArB(OH)_2$		Yield	Ref	$ArB(OH)_2$		Yield	Ref
	A	88%	306		A	95%	306
	B	91%	307		C	91%	308

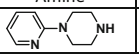
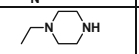
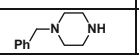
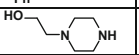
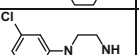
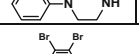
Condition A: Pd**1**, K_3PO_4/KOAc, dioxane, H_2O; B: Pd**2**, K_2CO_3, EtOH, H_2O; Pd**3**, K_3PO_4, THF.

Scheme 58 Recently developed catalysts for Suzuki coupling of 2-chlorobenzoxazole

Novel cross-coupling reactions also play an important role in recent years, such as Buchwald–Hartwig aminations. In 2003, Hartwig et al. demonstrated amination of 2-chlorobenzoxazole with morpholine in their palladium-catalyzed five-membered heterocyclic halides aminations [309], with later applications in making 2-amino- or 2-hydroxybenzoxazoles (Scheme 59) [310, 311]. In 2008, Knochel et al. reported a silane-promoted nickel-catalyzed amination of aryl chlorides including 2-chlorobenzoxazole (Scheme 59) [312]. In 2010, Murty and coworkers introduced amination of 2-chlorobenzoxazole with amines in the presence of zinc dust under solvent-free conditions (Scheme 59) [313]. In the same year, Nicasio et al. developed well-defined allylnickel chloride/*N*-heterocyclic carbene [(NHC)Ni(allyl)

Cl] complexes as highly active precatalysts for aminations, in which coupling between 2-chlorobenzoxazole and morpholine resulted in 70% yield of product (Scheme 59) [314].

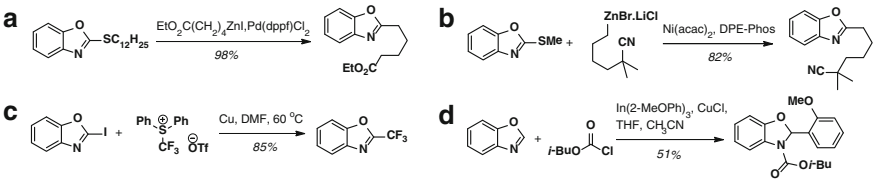


Amine		Yield	Ref	Amine		Yield	Ref	Amine		Yield	Ref
	A	51%	309		B	82%	312		B	83%	312
	C	96%	313		B	84%	312		C	89%	313
	D	70%	314		C	94%	313		C	92%	313
	C	87%	313		C	90%	313		C	85%	313
	C	88%	313		C	95%	313		C	96%	313
	C	95%	313		C	97%	313				

Condition A: $Pd(OTFA)_2$, P(*t*-Bu)$_3$, NaO*t*-Bu, PhMe; B: $Ni(acac)_2$, ligand **1**, NaO*t*-Bu, PMHS, DME, PhMe; C: Activated Zn dust, MW; D: Catalyst **2**, NaO*t*-Bu, THF.

Scheme 59 Buchwald–Hartwig aminations of 2-chlorobenzoxazole

Coupling reactions, such as palladium-catalyzed (benzoxol-2-yl)sulfide with organozinc reagents (Scheme 60a) [315], nickel-catalyzed (benzoxazol-2-yl)sulfide with organozinc reagents at room temperature (Scheme 60b) [316], copper-mediated trifluoromethylation of 2-iodobenzoxazole with trifluoromethyl sulfonium salts (Scheme 60c) [317], and copper-catalyzed multicomponent coupling of organoindium reagents with benzoxazole (Scheme 60d) [318], have also been reported.



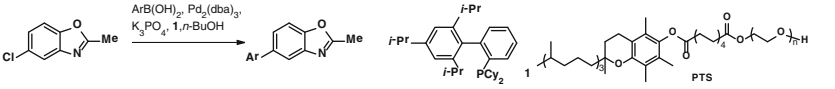
Scheme 60 Other cross-coupling reactions of benzoxazoles

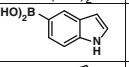
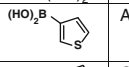
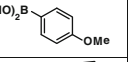
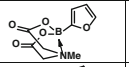
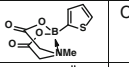
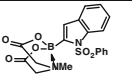
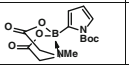
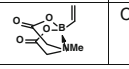
4.2.2 Cross-Coupling Reactions of the Benzene Ring

In the past ten years, conventional cross-coupling reactions, such as Suzuki, Stille, Negishi cross-coupling, have also been reported in both synthetic organic chemistry and medicinal chemistry. In 2004, Suzuki and Stille reactions were applied in the functionalization of C-7 of benzoxazole derivatives [319], formation of C-5

derivatives [320, 321], and bi-coupling at C-4 and C-7 for supramolecular organization of extended benzobisoxazole cruciforms [322].

Novel catalysts, ligands, and cross-coupling reactions have also shown up recently. In 2006, Buchwald et al. reported a palladium-catalyzed Suzuki coupling of heteroaryl halides and heteroaryl boronic acids using newly introduced monophosphine-based catalyst with high efficiency, in which 5-chlorobenzoxazole coupled with indolylboronic acid and thienylboronic acid with 91% yields (Scheme 61) [323, 324]. In 2008, palladium-catalyzed Suzuki–Miyaura coupling using PTS, a nanomicelle-forming amphiphile, in pure water under exceedingly mild conditions was introduced (Scheme 61) [325]. In 2009, Burke et al. used slow-release of air-stable *N*-methyliminodiacetic acid boronates as a source of unstable boronic acids for efficient cross-coupling reactions (Scheme 61) [326].

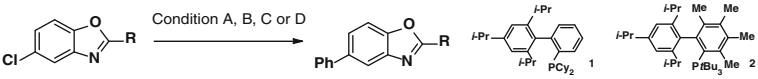


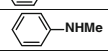
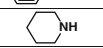
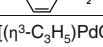
$ArB(OH)_2$		Yield	Ref	$ArB(OH)_2$		Yield	Ref	$ArB(OH)_2$		Yield	Ref
	A	91%	323		A	91%	324		B	95%	325
	C	99%	326		C	99%	326		C	93%	326
	C	98%	326		C	96%	326				

Condition A:$Pd_2(dba)_3$, K_3PO_4,**1**, *n*-BuOH; B: Pd(dtbpf)Cl_2, Et_3N, **1**, PTS, H_2O; C: $Pd(OAc)_2$, K_3PO_4,**1**, dioxane, H_2O

Scheme 61 Recently developed Suzuki cross-coupling reactions of 5-chloro-2-methylbenzoxazole.

Other types of cross-coupling reactions, such as palladium-catalyzed cross coupling between triallyl(aryl)silanes and aryl halides was reported by Hiyama et al. in 2004, in which 5-chlorobenzoxazole coupled with triallylphenylsilane to afford biaryl compound in 83% yield (Scheme 62) [327]. The Buchwald–Hartwig amination was exemplified by the synthesis of 5-aminobenzoxazole derivatives in good yields [328], 5-phenolic benzoxazole [329], and 2,5- or 2,6-diaminobenzoxazoles (Scheme 62) [330].



R	Partner		Yield	Ref	R	Partner		Yield	Ref
Me		A	83%	327	Me		C	91%	329
Me		B	83%	328			B	74%	330
Ph		B	97%	328			B	83%	330
Me		B	60%	328			B	83%	330

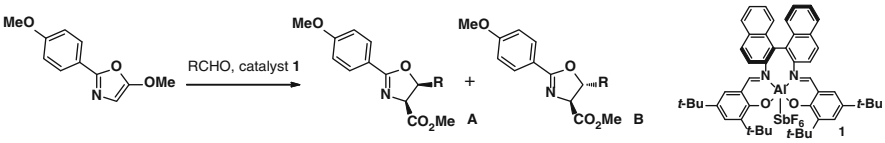
Condition A: $[(\eta^3\text{-}C_3H_5)PdCl]_2$, TBAF, ligand **1**, THF, H_2O; B: $Pd_2(dba)_3$, NaO*t*-Bu or K_3PO_4, ligand **1**, toluene; C: $Pd(OAc)_2$, K_3PO_4, ligand **2**, toluene;

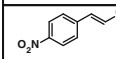
Scheme 62 Novel cross-coupling reactions of 5-chlorobenzoxazoles

5 Miscellaneous Metalations

5.1 Aldol Reactions of Aldehydes and 5-Alkoxyoxazoles

In 2001, Evans and coworkers reported a chiral salen-aluminum complexes catalyzed enantioselective aldol reactions of aldehydes and 5-alkoxyoxazoles (Scheme 63) [331]. The reactions behaved very well with aryl and alkenyl aldehydes, but aliphatic aldehydes, such as dihydrocinnamaldehyde and cyclohexane carbaldehyde, were unreactive under the standard reaction conditions. In 2005, Hutton et al. applied this chemistry for their attempted synthesis of ustiloxins A and B [332].

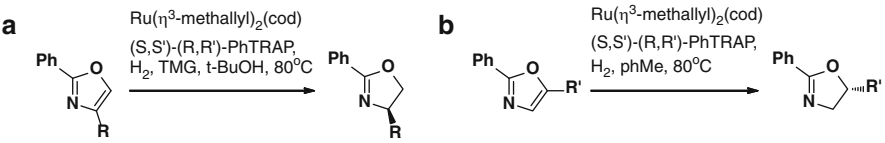


R	Yield	A:B	*ee*	R	Yield	A:B	*ee*
Ph	99%	95:5	99%	4-ClC_6H_4	93%	90:10	99%
4-FC_6H_4	98%	96:4	>99%	3-$NO_2C_6H_4$	99%	73:27	91%
4-$NO_2C_6H_4$	99%	88:12	97%	3-$MeOC_6H_4$	95%	93:7	99%
4-NCC_6H_4	96%	83:17	95%	3-MeC_6H_4	98%	95:5	98%
4-$MeO_2CC_6H_4$	98%	93:7	>99%	2-ClC_6H_4	96%	>99:1	>99%
4-$PhOC_6H_4$	89%	96:4	>99%	2-$NO_2C_6H_4$	93%	93:7	>99%
4-$AcOC_6H_4$	95%	96:4	>99%	2-Br-6$MeOC_6H_3$	98%	96:4	95%
4-MeC_6H_4	96%	92:8	96%	2-MeC_6H_4	86%	>99:1	>99%
4-PhC_6H_4	100%	96:4	99%	3-Cl-4FC_6H_4	100%	89:11	98%
	98%	96:4	99%	3-Br-4-MeO_6H_4	90%	91:9	98%
				3-NO_2-4-;C_6H_4	99%	74:26	92%
	58%	77:23	96%		97%	96:4	99%
	98%	90:10	98%		96%	90:10	98%

Scheme 63 Enantioselective aldol reactions of aldehydes and 5-alkoxyoxazoles

5.2 Asymmetric Hydrogenation of 2-Phenyloxazoles

Very recently, Kuwano et al. reported a catalytic asymmetric hydrogenation of 4-aryl-2-phenyloxazoles and 5-aryl-2-phenyloxazoles to the corresponding oxazolines (up to 99% *ee*) with a chiral ruthenium catalyst, which was generated from Ru(η^3-methallyl)$_2$(cod) and a trans-chelating bisphosphine ligand, PhTRAP (Scheme 64) [333].



R	Yield	*ee*	R	Yield	*ee*	R	Yield	*ee*
Ph	>99%	98%	*p*-$MeOC_6H_4$	93%	97%	*p*-FC_6H_4	92%	97%
Me	88%	91%	*p*-$CF_3C_6H_4$	90%	93%	*c*-C_6H_{11}	91%	88%
t-Bu			CO_2Me	89%	50%	R'	Yield	*ee*
R'	Yield	*ee*	R'	Yield	*ee*	*p*-FC_6H_4	>99%	93%
Ph	97%	97%	*p*-$MeOC_6H_4$	88%	95%	*c*-C_6H_{11}	99%	72%
Me	97%	84%	*p*-$CF_3C_6H_4$	>99%	85%	*t*-Bu		

Scheme 64 Asymmetric hydrogenation of 2-phenyloxazoles

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Metalation of Pyrazoles and Indazoles

Sudipta Roy, Sujata Roy, and Gordon W. Gribble

Abstract Metalation of pyrazoles and indazoles plays an important role in the regioselective introduction of substituents onto these ring systems. Various metalation strategies related to these heterocycles are discussed in this chapter.

Keywords Arylation · Cross-coupling · Indazole · Metalation · Pyrazole

Contents

1 Introduction 156
2 Reactions of Pyrazoles and Indazoles via *N*-Metalation 159
2.1 *N*-Alkylation of Pyrazoles via Metalation 159
2.2 *N*-Alkylation of Indazoles via Metalation 162
2.3 *N*-Arylation of Pyrazoles and Indazoles 164
2.4 Metal-Catalyzed *N*-Vinylation of Pyrazoles and Indazoles 180
2.5 Metal-Catalyzed *N*-Alkynylation of Pyrazoles and Indazoles 183
3 Reactions of Pyrazoles via *C*-Metalation 183
3.1 Metalation at C-5 of Pyrazoles 183
3.2 Metalation at C-4 of Pyrazoles 197
3.3 Metalation at C-3 of Pyrazoles 217
3.4 Sequential Multiple Metalation of Pyrazoles 224
4 Reactions of Indazoles via *C*-Metalation 231
4.1 Metalation at C-3 of Indazoles 231
4.2 Metalation at C-4 of Indazoles 236
4.3 Metalation at C-5 of Indazoles 239
4.4 Metalation at C-6 of Indazoles 243
4.5 Metalation at C-7 of Indazoles 246
4.6 General Methods for Metalation of Benzenoid Ring of Indazoles 248
References 251

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1 Introduction

Pyrazole is an important heterocycle that is frequently used in drug discovery [1–28]. Representative pharmaceutically active pyrazoles are shown in Fig. 1. Among these, celecoxib (Celebrex, Pfizer) is a COX-2 selective non-narcotic and nonsteroidal anti-inflammatory drug (NSAID) which is used in the treatment of

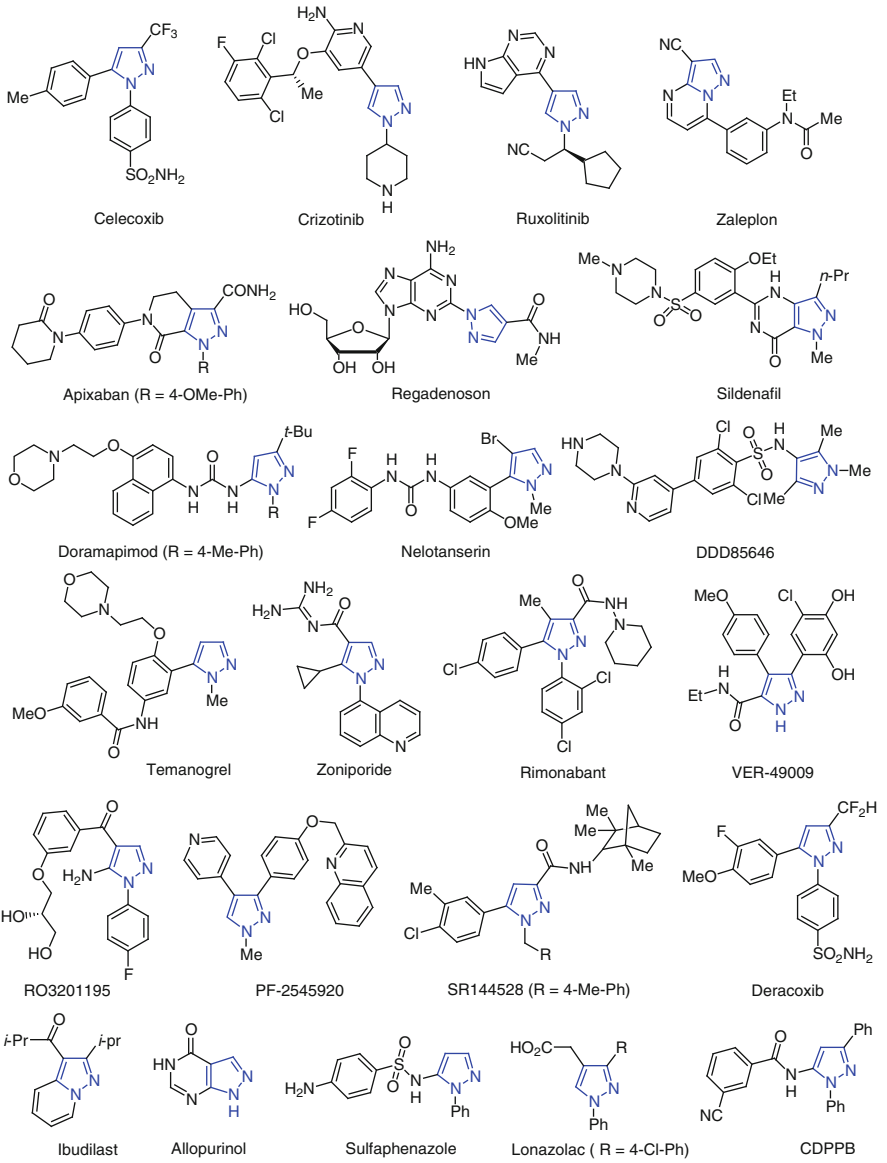


Fig. 1 Representative pharmaceuticals containing pyrazole nucleus

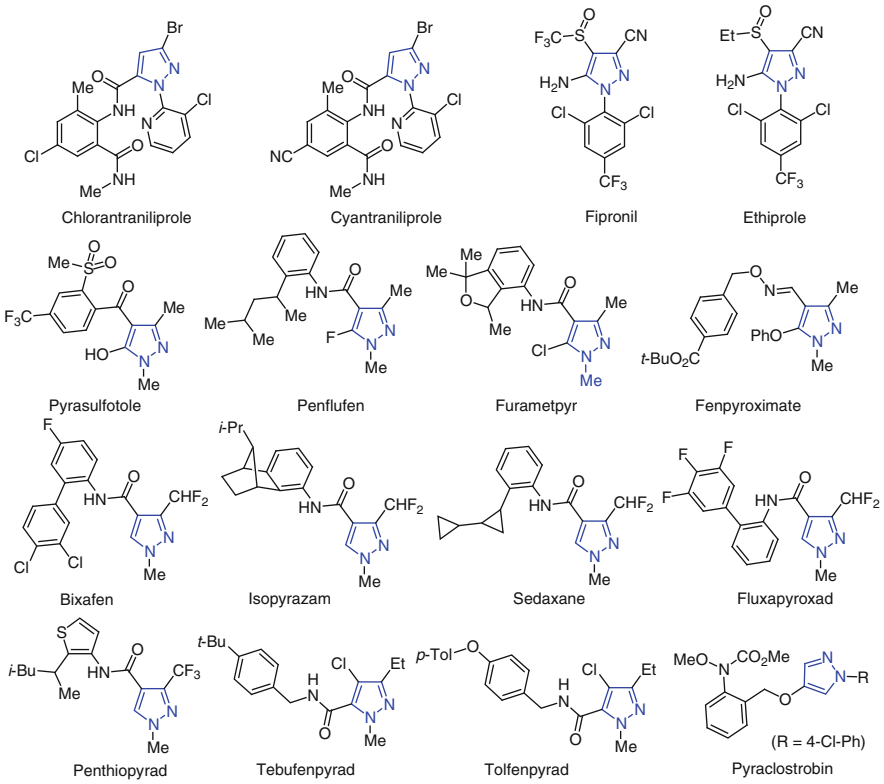


Fig. 2 Representative agrochemicals containing pyrazole nucleus

various types of arthritis and for the management of acute pain. Crizotinib (Xalkori, Pfizer), an ALK (anaplastic lymphoma kinase) inhibitor, has been recently approved for the treatment of advanced lung cancer. JAK-1/2 (janus kinase 1 and 2) inhibitor ruxolitinib (Jakafi, Incyte/Novartis) has also been approved recently for the treatment of myelofibrosis (MF), a type of blood cancer. Apixaban (Eliquis, Pfizer/BMS) is highly effective as a blood thinner/anti-coagulant. Zaleplon (Sonata, Pfizer) is used in the treatment of insomnia. Regadenoson (Lexiscan, Astellas) is used as a pharmacologic stress agent. Another coxib class of drug – deracoxib (Deramaxx, Novartis) is used for the control of pain and inflammation associated with osteoarthritis in dogs.

The pyrazole nucleus is also found in many agrochemicals (Fig. 2) [29–32]. In fact, the discovery of pyrazole-based insecticides/fungicides has gained momentum in recent years. Although the BASF's broad spectrum insecticide fipronil (Reagent) has been in the market for awhile, DuPont's new generation insecticides chlorantraniliprole (Rynaxypyr) and cyantraniliprole (Cyazypyr) have been discovered quite recently. Bayer's new fungicides penflufen and bixafen, herbicide pyrasulfotole and insecticide ethiprole also contain a pyrazole core. Syngenta's pyrazole fungicide isopyrazam and sedaxane have also made their appearance recently.

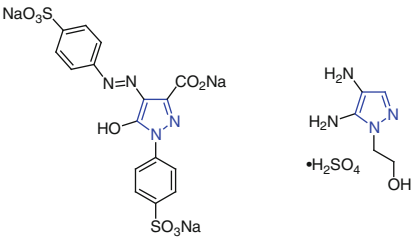


Fig. 3 Representative dyes containing pyrazole nucleus

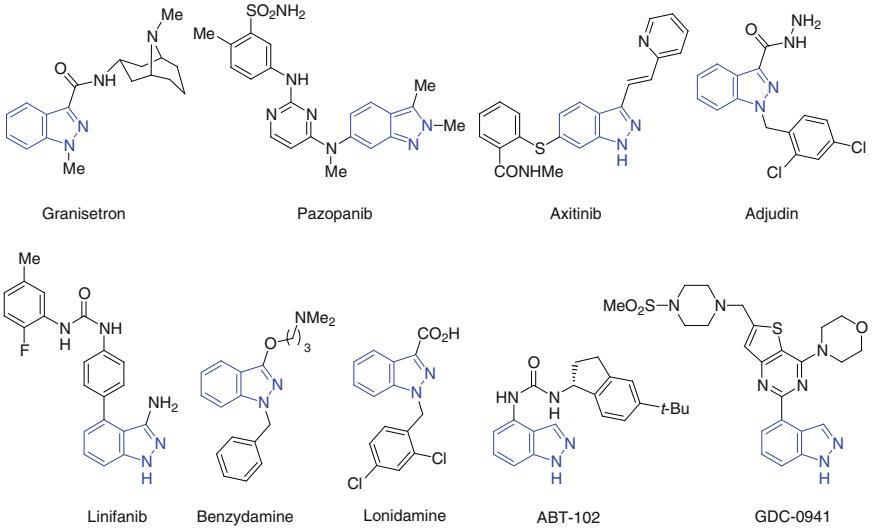


Fig. 4 Representative pharmaceuticals containing indazole nucleus

Pyrazole-based dyes are used as a coloring agent for different purposes. Tartrazine (FD&C Yellow 5) is the most common yellow dye used as a food color (Fig. 3). Pyrazole-5 (P5) dye is used as a hair coloring agent. Fujifilm and Eastman-Kodak have developed several pyrazole-based dyes in the material science area [33–37].

Indazole is another important heterocyclic scaffold often found in pharmaceutically active molecules [38–43]. For example, granisetron (Kytril, Roche), a 5-HT_3 receptor antagonist, is used as an antinauseant and antiemetic agent. Pazopanib (Votrient, GlaxoSmithKline), a tyrosine kinase inhibitor, is approved for the treatment of advanced renal cell carcinoma (RCC). Axitinib (Inlyta, Pfizer), another tyrosine kinase inhibitor, is developed by Pfizer for the treatment of renal/kidney cancer. Abbott is advancing the tyrosine kinase inhibitor linifanib for similar cancer treatment. Representative indazole-containing pharmaceuticals are shown in Fig. 4.

Although pyrazole and indazole are well-known heterocycles, a major portion of the chemistry involves the synthesis of these ring systems (and some nucleophilic reactions). For the synthesis of targeted pyrazoles and indazoles bearing a custom-substitution pattern, researchers have to rely on the suitably substituted precursors that upon condensation/cyclization would give the desired appropriately substituted compounds [44–53]. However, recent advancement in the metalation chemistry, especially in the field of metal-catalyzed cross-coupling reactions, has enabled the researchers to directly and selectively introduce the desired functionality at a specific position, thus affording the targeted products that would be difficult to synthesize otherwise. In this chapter, we have comprehensively discussed the recent examples of metalation and related chemistry of these two important classes of heterocycles.

2 Reactions of Pyrazoles and Indazoles via *N*-Metalation

2.1 N-*Alkylation of Pyrazoles via Metalation*

The pK_a of simple unsubstituted pyrazole for *N*-1 is 19.8 and *C*-5 is 35.9 (Fig. 5). The anion on nitrogen can be easily generated using bases such as KOH, KO*t*-Bu, or NaH in polar aprotic solvents such as DMSO, DMF. Thus, *N*-alkylation of pyrazole can be achieved smoothly in most cases in high yields. However, due to the tautomerization of pyrazole *NH*, there is always a possibility of obtaining a regioisomeric mixture of *N*-1- and *N*-2-substituted products from the alkylation of unsymmetrical pyrazole precursors.

Reaction of symmetrical 3,5-dimethylpyrazole with 2-chlorobenzyl chloride in the presence of KOH gave *N*-(2-chlorobenzyl)-3,5-dimethylpyrazole (Scheme 1) [54]. Similar reaction of pyrazole with *t*-butyl bromoacetate afforded the corresponding *N*-alkylpyrazole [55]. Due to intermolecular self-alkylation of the intermediates, *N*-alkylation of pyrazole using bis(2-chloroethyl)amine in the presence of KOH in DMSO produced 4-bis-(2-pyrazol-1-yl-ethyl)piperazine as the major product instead of bis(pyrazol-1-yl)alkane (Scheme 2) [56]. However, *N*-alkylation of 3,5-dimethylpyrazole under similar conditions gave the expected bis(pyrazol-1-yl)alkane. While the reaction of 3,4-diarylpyrazole with iodomethane in the presence of potassium *tert*-butoxide produced a 1:1 mixture of regiomeric *N*-substituted products, similar reaction of 3-aryl-4-bromopyrazole gave the *N*-1 alkylated product exclusively (Scheme 3) [57]. This regioselective methylation of the 3-aryl-4-bromopyrazole is useful since the desired aryl/heteroaryl group can be introduced at C-4, via the Suzuki–Miyaura coupling, at a later stage.

A strong chelating effect was observed during the *N*-alkylation of 5-carbethoxypyrazole using potassium *tert*-butoxide and chloromethyl methyl sulfide (Scheme 4) [58]. The complexation of K^+ with the nitrogen adjacent to CO_2Et reduced its availability toward electrophilic attack and, thereby, favored the

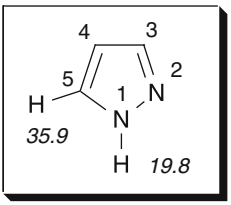
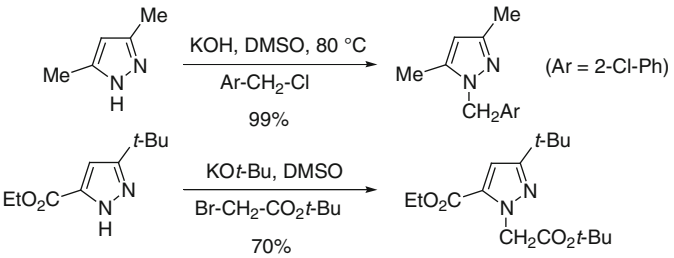
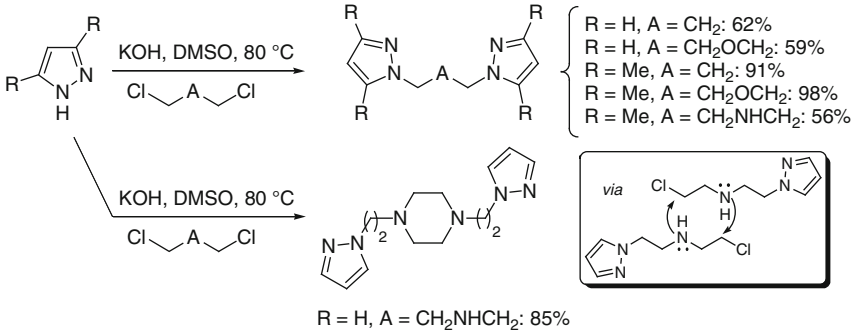


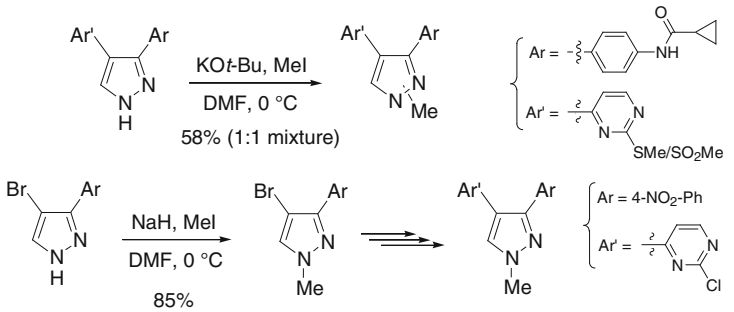
Fig. 5 pK_a's of pyrazole



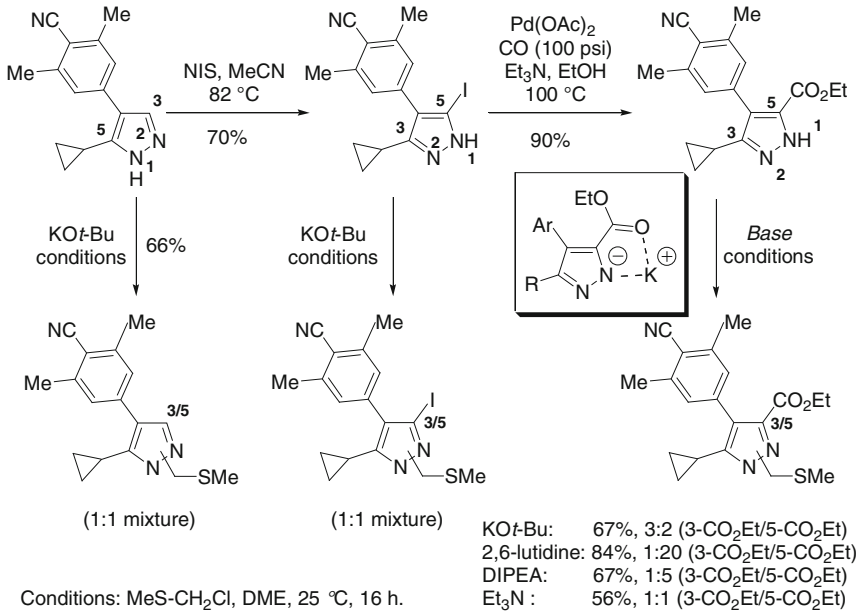
Scheme 1



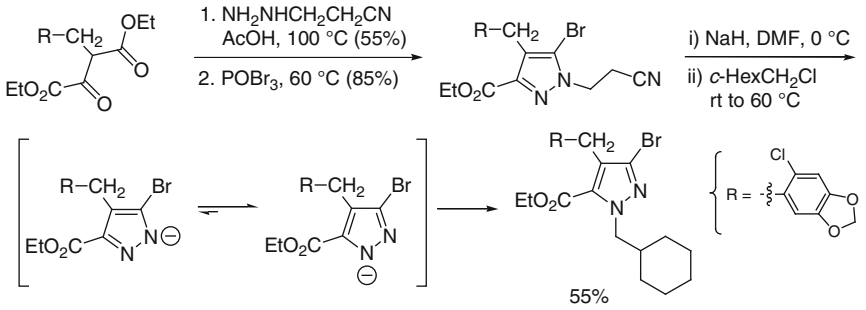
Scheme 2



Scheme 3



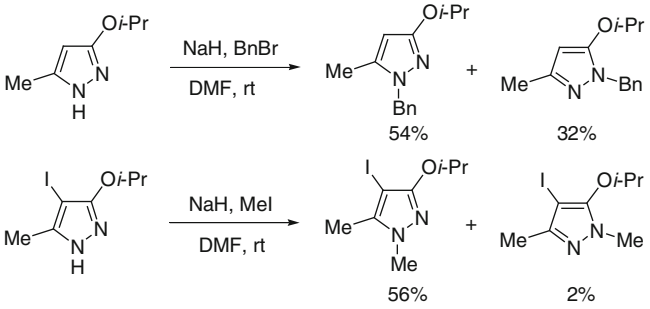
Scheme 4



Scheme 5

alkylation at the nitrogen away from the carbethoxy group to produce a 3:2 mixture of regioisomers. In contrast, the parent pyrazoles provided a 1:1 mixture of regioisomeric products under the same conditions. However, in the presence of noncoordinating, weak, and bulky 2,6-lutidine, the alkylation was favored at the nitrogen adjacent to the carbethoxy functionality presumably due to the steric effect of cyclopropyl group.

The loss of a cyanoethyl functionality, via retro-Michael type reaction, was observed from an *N*-cyanoethyl-substituted pyrazole-3-carboxylate under basic condition (Scheme 5) [59]. The resulting anionic species recaptured the electrophile through the nitrogen adjacent to CO_2Et to afford the corresponding product.



Scheme 6

Iodo-substitution at C-4 has a noteworthy effect on the *N*-alkylation of 3-alkoxy-5-methylpyrazole. While the benzylation of 4-unsubstituted 3-alkoxy-5-methylpyrazole gave a mixture of regiomers, the methylation of 4-iodo-3-isopropoxy-5-methylpyrazole afforded only the corresponding *N*-1 alkylpyrazole (Scheme 6) [60].

2.2 N-*Alkylation of Indazoles via Metalation*

Indazoles can exist in two forms, *1H*-indazoles and *2H*-indazoles, due to *NH* tautomerization (Fig. 6). The calculated energy difference between the *1H*-tautomer and *2H*-tautomer in the ground state is 2.3 kcal/mol, which indicates that *1H*-tautomer is significantly more stable than *2H*-tautomer [61]. Thus, the *N*-alkylation of 7-nitroindazoles using KOH and iodomethane afforded the corresponding 1-methyl-7-nitroindazoles (Scheme 7) [62]. Likewise, the alkylation of a 3-carbmethoxyindazole using sodium hydride and 1,4-bromobutane gave the corresponding *N*-alkylindazole (Scheme 8) [63].

The *N*-alkylation of indazole using SEM-chloride in the presence of sodium hydride produced a 7.5:1 mixture of *N*-1 and *N*-2 isomers (Scheme 9) [64]. However, weak and nonmetalating base dicyclohexylmethylamine afforded the *N*-2 isomer exclusively. In contrast to initial deprotonation of indazole by sodium hydride, nucleophilic attack on SEM-chloride by indazole occurred first in the presence of $(c\text{-hex})_2$NMe after which the *N*(1)-*H* became acidic enough to get deprotonated by the weak base. Of note, triethylamine was significantly less effective under similar conditions due to the undesired competitive reaction of SEM-chloride and Et_3N.

The reaction of 5-bromoindazole and *p*-methoxybenzyl chloride in the presence of sodium hydride gave a mixture of *N*-1 and *N*-2 regioisomers (Scheme 10) [65]. In contrast, under mildly acidic conditions (PPTS, CH_2Cl_2, 5 h), the reaction of 5-bromoindazole and dihydropyran afforded the *N*-2-substituted product exclusively. Since *N*-2 lone pair is kinetically more accessible than *N*-1 lone pair in

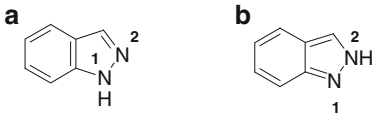
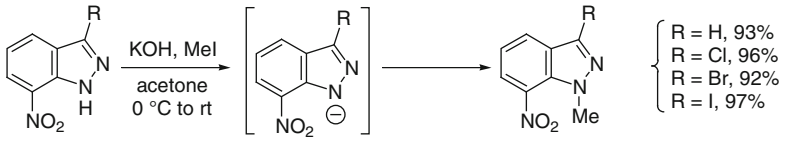
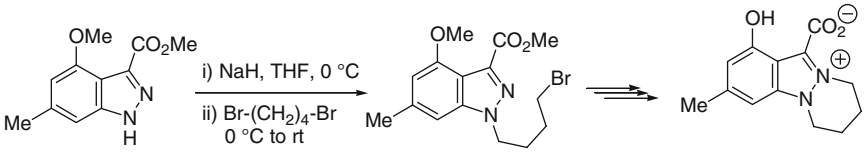


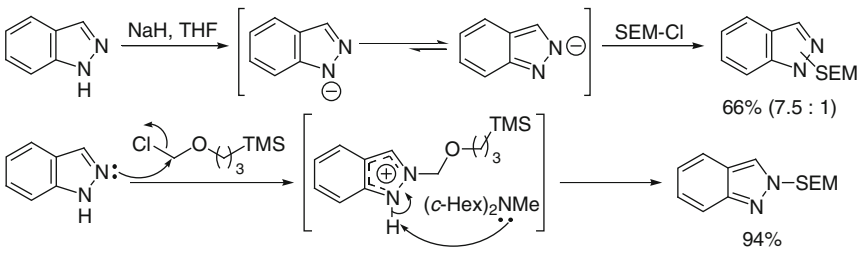
Fig. 6 Structures of *1H*-indazole (**a**) and *2H*-indazole (**b**)



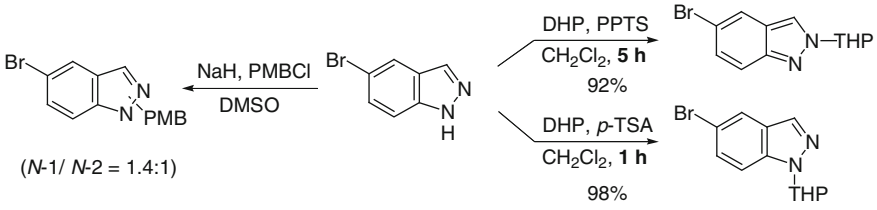
Scheme 7



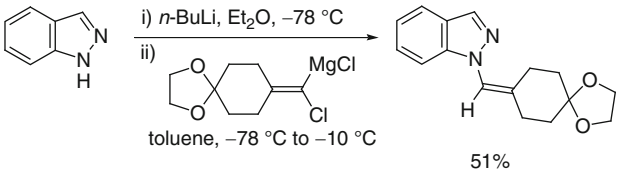
Scheme 8



Scheme 9



Scheme 10



Scheme 11

neutral indazoles [66], the *N*-2-substituted product is kinetically favored, whereas the *N*-1-substituted product is thermodynamically favored. In fact, kinetically favored *N*-2 regioisomer slowly converts to the thermodynamically favored *N*-1 regioisomer in acidic media. Thus, with an extended period of time (PPTS, CH_2Cl_2, 18 h), the reaction of 5-bromoindazole and dihydropyran provided a 3:1 mixture of regioisomeric products. Nonetheless, under relatively forcing conditions (use of *p*-TSA instead of PPTS), the same reaction rapidly provided the *N*-1-substituted indazole in nearly quantitative yield.

The *N*-alkenylation of 1-lithioindazole with the magnesium alkylidene carbenoid gave the corresponding *N*-alkenylindazole (Scheme 11) [67, 68]. However, similar transformation for pyrazole was ineffective.

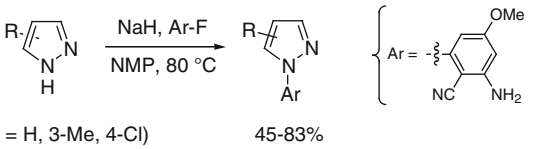
2.3 N-*Arylation of Pyrazoles and Indazoles*

The high temperature reaction of pyrazoles and indazoles with various fluoronitrobenzenes is one of the common methods for the preparation of these *N*-arylazoles [69, 70]. However, such arylations with *unactivated* aryl halides are challenging without catalytic assistance.

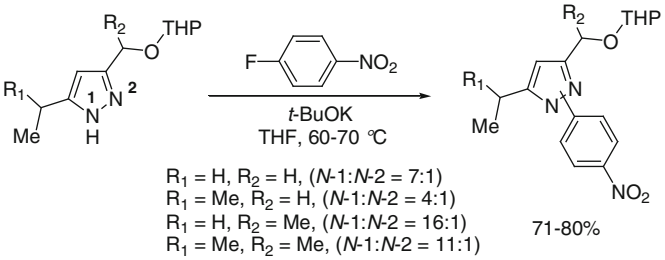
2.3.1 Anionic *N*-Arylation of Pyrazoles

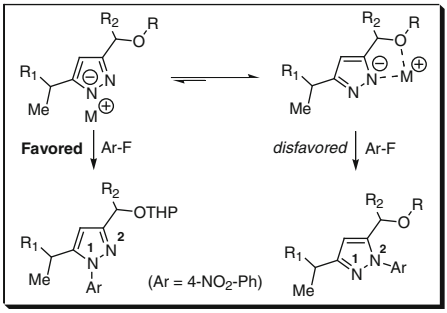
Reaction of pyrazole with 2-amino-6-fluoro-4-methoxybenzonitrile in the presence of sodium hydride gave the corresponding *N*-arylpyrazole (Scheme 12) [71].

Reaction of 5-ethylpyrazole, bearing a THP-protected hydroxymethyl functionality at C-3, with 4-fluoronitrobenzene in the presence of potassium *tert*-butoxide gave a 7:1 mixture of *N*-1: *N*-2 arylated products (Scheme 13) [72]. The chelating group at C-3 presumably hindered the access of the electrophile to the adjacent nitrogen (*N*-2) of pyrazole. Branching at the chelating scaffold dramatically enhanced the chelation due to Thorpe–Ingold effect and, thereby, largely favored the formation of *N*-1 arylpyrazole (*N*-1: *N*-2 = 16:1). Although *t*-BuOLi, NaH, and EtMgBr also favored the *N*-1 arylation, the potassium *tert*-butoxide was most effective. However, in the absence of chelation, the steric effect of C-5 aryl groups in 3-alkyl-5-arylpyrazoles governed the arylation at *N*-2 (Scheme 14) [73].

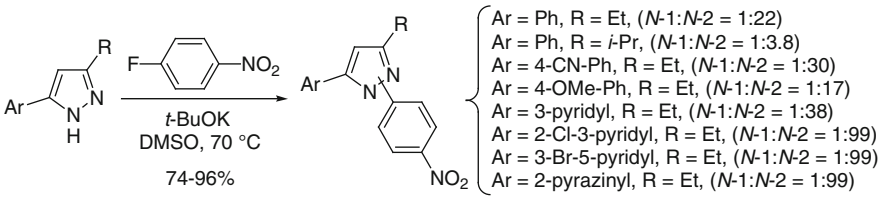


Scheme 12





Scheme 13



Scheme 14

Thus, arylation of 3-ethyl-5-phenylpyrazole using 4-fluoronitrobenzene gave a 1:22 mixture of *N*-1 and *N*-2 arylated products. Apart from steric assistance, electronic effect also played an important role in governing the regioselectivity. Electron-withdrawing aryl substituents (e.g., 4-cyanophenyl) showed high regioselectivity toward *N*-2 arylation, whereas electron-donating groups (e.g., 4-methoxyphenyl) offered low selectivity. Similarly, the electron-deficient pyridine or pyrazine at C-5 of pyrazole favored *N*-2 arylation. These chelation-controlled and steric

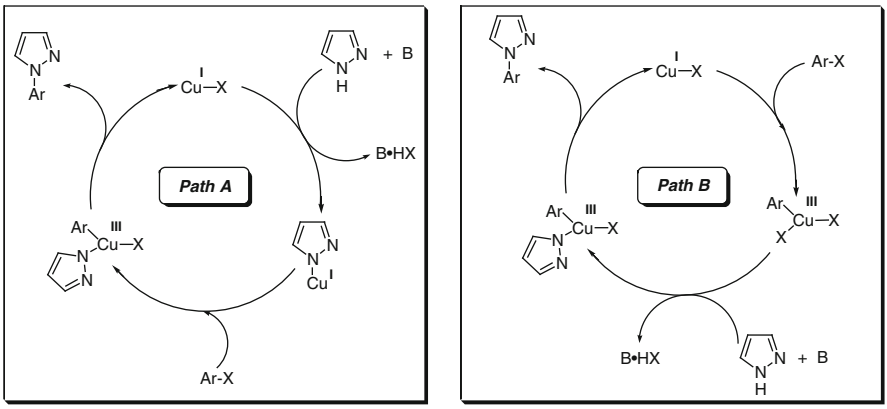


Fig. 7 Possible catalytic cycle for the copper-catalyzed arylation of pyrazole

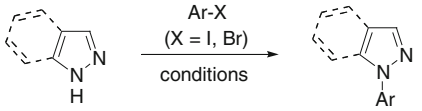
(and electronic)-controlled *N*-arylations of pyrazoles are complementary to each other and, thus, suitable choice of reaction conditions can provide the synthesis of the desired *N*-arylated products.

2.3.2 Copper-Catalyzed *N*-Arylation of Pyrazoles and Indazoles

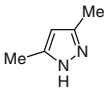
Copper-catalyzed *N*-arylation has emerged as a powerful technique to functionalize the pyrazole nitrogen. Unlike palladium-catalyzed *N*-arylation, the mechanism of copper-catalyzed *N*-arylation is not fully established. However, it is believed to proceed via the Cu(I) and Cu(III) intermediates [74, 75]. Depending on the stage of activation of aryl halides, two pathways are proposed involving the intermediacy of a Cu(III) species (Fig. 7). Pathway A, in which coordination of the pyrazole to the copper center occurs before the rate-limiting aryl halide activation step, is supported by recent studies. Choudary reported spectroscopic evidence for the preliminary coordination of an *N*-heterocycle (imidazole) to the copper center prior to oxidative addition to the aryl halide [76]. Electron-rich ligands stabilize the higher oxidation state of copper and accelerate the aryl halide activation process. In pathway B, activation of aryl halides occurs first followed by the coordination of the pyrazole nitrogen to the Cu(III) center.

Buchwald initially reported the *N*-arylation of pyrazoles using aryl iodides in the presence of catalytic CuI and *trans*-1,2-cyclohexanediamine in dioxane (Table 1, entry 1) [77]. Later, *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine was used as the ligand in toluene which offered broader substrate scope and better results (entries 2–6) [78]. In general, *N*,*N*′-dimethyl-substituted ligands are superior to their unsubstituted analogs because the increase in steric bulk at the nitrogen center tends to diminish the undesired side reaction of ligands with aryl halides. In the *N*-arylations involving sterically challenging substrates, aryl halides were used as the solvent to ensure complete consumption of the pyrazole. These conditions were

Table 1 Buchwald's copper-catalyzed *N*-arylation of pyrazoles and indazoles



Conditions: 5 mol% CuI, 20 mol% *trans-N,N'*-dimethyl-1,2-cyclohexanediamine, K_2CO_3 (2.1 eq), toluene, 110 °C, 24 h.

Entry	Pyrazole	Ar–X	Yield
1[a]		Ar–I	R = H, Ar = 3,5-diMe-Ph, 89% R = Me, Ar = 3,5-diMe-Ph, 84%
2		Ar–I	Ar = Ph, 93% (at 80°C) Ar = 3-CO_2Me-4-Cl-Ph, 89%
3		Ar–I	Ar = Ph, 98% Ar = 3-(CH_2NH_2)Ph, 71%
4		Ar–I	R = 3-Ph-5-NH_2, Ar = Ph, 88% R = 3-CF_3-4-CO_2Et, Ar = Ph, 77%
5		Ar–Br	Ar = 2-Me-Ph, 92% Ar = 2-NH_2-Ph, 91% Ar = 2-(CH_2OH)-Ph, 74% Ar = 4-COEt-Ph, 98%
6		Ar–Br	R = 3-Me, Ar = 4-OH-Ph, 78% R = 4-CO_2Et, Ar = 2-Me-Ph, 79% R = 4-CO_2Et, Ar = 4-CO_2Et-Ph, 79%
7		Ar–I	Ar = 4-Me, 85% (*N*-1: *N*-2 = 17:1) Ar = 3-OMe, 92% (*N*-1: *N*-2 = 17:1) Ar = 2-NH_2, 80% (*N*-1: *N*-2 = 20:1)
8		Ar–Br	Ar = 4-Me, 86% (*N*-1: *N*-2 = >20:1)

[a]*Trans*-1,2-diaminocyclohexane in dioxane was used

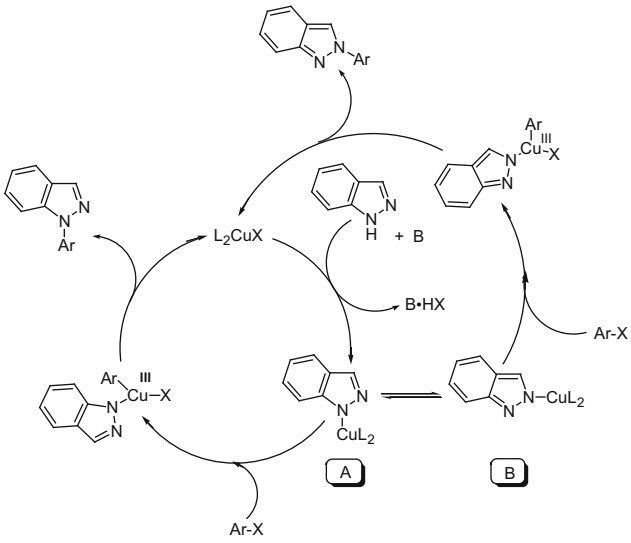


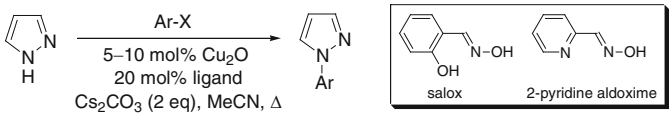
Fig. 8 Indazole *N*-arylation pathways

effective even for the electron-deficient pyrazoles as well as electron-rich aryl halides. For unsymmetrical 3,5-disubstituted pyrazoles, the *N*-arylation occurred at the sterically less hindered nitrogen. For the coupling of indazole and aryl iodides, excellent regioselectivity was observed in favor of *N*-1 arylation (entry 7). However, *N*-arylation of indazole with aryl bromides offered poor regioselectivity (*N*-1: *N*-2 = 1.4:1 to 2:1), except for 3-substituted indazoles (entry 8).

According to pathway A, as shown in Fig. 7, formation of indazole-copper complex A is kinetically favored over complex B during the *N*-arylation of indazoles; however, complexes A and B stay in equilibrium (Fig. 8). For aryl iodides, oxidative addition to complex A occurs faster than the A–B equilibrium, thereby forming *N*-1 arylindazole predominantly. However, for the aryl bromides, the rate of oxidative addition to the kinetically favored complex A is much slower, which allows formation of complex B (before reductive elimination of 1-arylindazole from Cu(III) complex obtained from A) via competitive A–B equilibrium process. Thereafter, oxidative addition of aryl bromides to this complex B followed by reductive elimination provides the *N*-2 arylated indazoles.

Taillefer identified several catalysts and ligands for the *N*-arylation of pyrazoles under relatively mild conditions. Among those, Cu_2O–salox catalyst-ligand combination was highly effective in many cases (Table 2, entries 1–3) [79]. The coupling of pyrazole with the aryl bromides required higher temperature than with the aryl iodides. Notably, a quantitative yield of *N*-phenylpyrazole was obtained only at 50°C from the coupling of pyrazole with iodobenzene (entry 3). An excellent yield of the desired product was also obtained by conducting the same reaction at room-temperature for 90 h in the presence 2-pyridine aldoxime (entry 4). Although Cu_2O was chosen as the preferred catalyst due to its lower cost and

Table 2 Temperature effect on the copper-catalyzed *N*-arylation of pyrazole

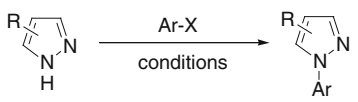


Entry	Ar–X	Ligand	Temperature (°C)	Time (h)	Yield (GC) (%)
1	Ph–Br	Salox	82	24	96
2	Ph–Br	Salox	50	90	70
3	Ph–I	Salox	50	24	100
4	Ph–I	2-Pyridine aldoxime	25	90	80

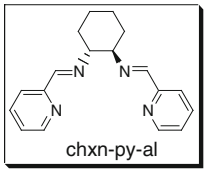
relative inertness, other copper catalysts such as CuI, CuBr, CuO, and $CuBr_2$ were also effective under similar conditions. For these *N*-arylations, Cs_2CO_3 was more effective than K_2CO_3 (or KO*t*-Bu and K_3PO_4). The superiority of Cs_2CO_3 can be explained by the higher nucleophilicity of carbonate anion due to decrease in the extent of ion-pairing between Cs^+ and CO_3^{2-}, compared to K^+ and CO_3^{2-}. Moreover, cesium salts are more soluble in the organic solvent than the potassium salts. The solubility and reactivity of economically attractive K_2CO_3 can be enhanced by conducting the reaction at a higher temperature. In fact, the coupling of pyrazole with bromobenzene in the presence of K_2CO_3 in DMF at 110°C afforded quantitative formation of *N*-phenylpyrazole. Although many oximes as well as other bidentate, tridentate, and tetradentate ligands were useful under these conditions, commonly used 1,10-phenanthroline and *trans*-1,2-diaminocyclohexane were ineffective.

Ring substituents had a relatively weak influence on the rate of these *N*-arylations. Thus, both electron-rich and electron-deficient aryl halides gave good yields for the corresponding *N*-arylpyrazoles (Table 3). Notably, acetyl, amino, and nitro functionalities were tolerated (entries 1c, 2c, 3a). The regioselective coupling of 4-bromochlorobenzene and pyrazole exclusively provided 1-(4-chlorophenyl)pyrazole (entry 1d). In the presence of salox ligand, the ester functionality did not survive and almost complete conversion of ethyl 3-bromobenzoate to 3-bromobenzoic acid was observed. However, use of an aprotic ligand (chxn-py-al) along with additional drying agent provided 50% yield of the desired product (entry 2b). Due to the steric hindrance, *N*-arylation of pyrazole with *ortho*-substituted 2-bromotoluene required either long reaction time or higher temperature (entry 3b). Reaction of unsymmetrical 3-trifluoromethylpyrazole with iodobenzene provided only *N*-1 arylated pyrazole (entry 4a). Apart from the steric effect, the −I effect of CF_3 group also favored the *N*-1 arylation (by deactivating *N*-2). For the *N*-arylation of *symmetrical* 4-methylpyrazole with iodobenzene, the desired product was obtained in nearly quantitative yield (entry 5). Although salox ligand was ineffective for the *N*-arylation 3,5-dimethylpyrazole with iodobenzene, use of chxn-py-al ligand along with higher temperature and longer reaction time afforded the desired *N*-arylpyrazole in excellent yield (entry 6).

Table 3 Taillefer's copper-catalyzed *N*-arylation of pyrazoles



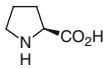
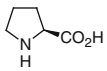
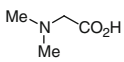
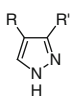
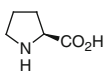
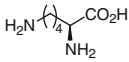
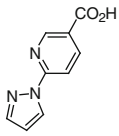
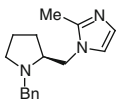
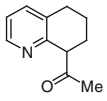
Conditions: 5 mol% Cu_2O, 20 mol% salox/ chxn-py-al, Cs_2CO_3 (2 eq), MeCN, 82 °C, 24–48 h.



Entry	Pyrazole	Ar–X, Ligand	Yield
1		Ar–Br salox	(a) Ar = 4-OMe-Ph, 93% (b) Ar = 4-CF_3-Ph, 96% (c) Ar = 4-Ac-Ph, 91% (d) Ar = 4-Cl-Ph, 93% (e) Ar = 3-pyridyl, 93%
2		Ar–Br chxn-py-al	(a) Ar = 4-CN-Ph, 91% (b) Ar = 3-CO_2Et-Ph, 50% (c) Ar = 4-NH_2-Ph, 91% (d) Ar = 4-(*N*-imidazolyl)-Ph, 92% (e) Ar = 2,4-di-Cl-Ph, 60% (at 110°C)
3		Ar–I chxn-py-al	(a) Ar = 4-NO_2-Ph, 90% (b) Ar = 2-Me-Ph, 94% (for 70 h)
4		Ar–I salox	(a) R = CF_3, Ar = Ph, 91% (b) R = Me, Ar = Ph, 71% (19% *N*-2)
5		Ar–I salox	R = Me, Ar = Ph, 98%
6		Ar–I chxn-py-al	Ar = Ph, 94% (at 110°C in DMF)

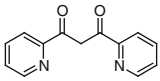
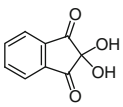
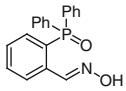
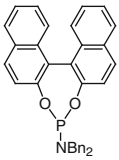
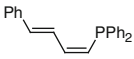
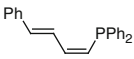
Using inexpensive natural amino acid L-proline and *N*-methylglycine as the ligand, Ma reported an efficient copper-catalyzed method for the coupling of pyrazole with aryl iodides and bromides (Table 4, entries 1–3) [80]. These conditions were successfully used for the *N*-arylation of a 3,4-di-substituted pyrazole (entry 4) [81]. L-lysine or L-glutamine ligands were also effective in the microwave-assisted "solvent-free" conditions (entries 5 and 6) [82]. L-lysine was

Table 4 *N*-Arylation of pyrazoles and indazoles under various other conditions

Entry	Pyrazole	Conditions	Ligand	Yield
1		Ar–I, CuI K_2CO_3, DMSO 90°C, 65 h		Ar = 4-OMe-Ph, 91%
2		Ar–Br, CuI K_2CO_3, DMSO 75°C, 45–48 h		Ar = 4-CN-Ph, 96% Ar = 2-pyridyl, 94%
3		Ar–Br, CuI K_2CO_3, DMSO 110°C, 45 h		Ar = 4-OMe-Ph, 71%
4		Ar–I, CuI K_2CO_3, DMSO 90°C, 8 h		Ar = 4-NO_2-Ph, 84% (R = 4-pyridyl, R′ = 3-Cl-5-OMe-Ph)
5		Ar–Br, CuI K_3PO_4, MW 150°C, 2–10 h		Ar = 3-OMe-Ph, 32% Ar = 4-OMe-Ph, 83% Ar = 4-Me-Ph, 37% Ar = 3-Ac-Ph, 44%
6		Ar–Br, CuI K_3PO_4, MW 150°C, 5 h		Ar = 4-Ac-Ph, 59%
7		Ar–Br, CuCl K_3PO_4, DMF 100°C, 24 h		Ar = Ph, 81–85% Ar = 2-pyr, 96–99% (R = H, Me)
8		Ar–Br, CuI Cs_2CO_3, DMF 110°C, 24 h		Ar = Ph, 87%
9		Ar–Br, CuBr Cs_2CO_3, DMSO 120°C, 12 h (3-NH_2-5-CF_3Ph)		88%

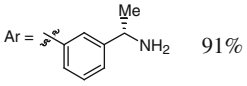
(continued)

Table 4 (continued)

Entry	Pyrazole	Conditions	Ligand	Yield
10	 (R = Me)	Ar–X, CuI K_2CO_3, DMF 90°C, 24 h		X = I, Ar = Ph, 71% X = Br, Ar = Ph, trace
11		Ar–I, Cu_2O KOH, DMSO 110°C, 24 h		Ar = Ph, 92%
12		Ar–I, Cu_2O Cs_2CO_3, MeCN 80°C, 18 h		Ar = Ph, 94% Ar = 4-OMe-Ph, 95% Ar = 3-CF_3-Ph, 81%
13		Ar–I, CuBr Cs_2CO_3, DMF 90°C, 24 h		Ar = 4-OMe-Ph, 76%
14		Ar–Br [$CuIL_2$] complex Cs_2CO_3, MeCN 82°C, 4 h		Ar = 4-CN-Ph, 97%
15		Ar–Cl [$CuIL_2$] complex Cs_2CO_3, DMF 140°C, 24 h		Ar = 4-CF_3-Ph, 70%

particularly effective for electron-rich aryl bromides, whereas L-glutamine was effective for electron-deficient aryl bromides. A copper(I) pyrazolyl-nicotinic acid system also promoted the C–N coupling between pyrazole and aryl bromides (entry 7) [83]. However, the *N*-arylation of pyrazole-4-carboxylic acid was unsuccessful under these conditions presumably due to the poor solubility of the potassium salt of pyrazole-4-carboxylic acid. The *N*-arylation of pyrazole with bromobenzene was also successful in the presence of (*S*)-pyrrolidinylmethylimidazole ligand (entry 8) [84]. An efficient coupling of 4-methylpyrazole with a bromoaniline was reported in the presence of catalytic CuBr and 1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanone ligand (entry 9) [85]. The CuI-catalyzed reaction of pyrazole and iodobenzene in the presence of a pyridine-functionalized 1,3-diketone ligand provided the corresponding *N*-arylpyrazole (entry 10) [86]. Ninhydrin was also used as a ligand for the *N*-arylation of pyrazole with iodobenzene (entry 11) [87]. Use of an oxime-phosphine

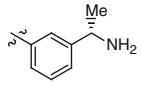
Table 5 Ligand-free *N*-arylation of pyrazoles

Entry	Pyrazole	Conditions	Yield
1		Ph–X, CuI Cs_2CO_3, DMF 120°C, 40 h	(a) X = Br, R = H, 84% (b) X = I, R = Me, 63%
2		Ar–I, Cu_2O Cs_2CO_3, DMF 100°C, 18 h	(a) Ar = Ph, 98% (b) Ar = 2-OMe-Ph, 94% (c) Ar = 4-CO_2Et-Ph, 99%
3		Ar–Br, Cu_2O Cs_2CO_3, DMF 110°C, 18 h	(a) Ar = Ph, 93% (b) Ar =2-OMe-Ph, 99% (c) Ar =3-NO_2-Ph, 98% (d) Ar = 2-thienyl, 95%
4		Ar-Cl, Cu_2O Cs_2CO_3, DMF 110°C, 18 h	(a) Ar = Ph, 0% (b) Ar = 4-CN-Ph, 98%
5		Ar–Br, CuI K_2CO_3, NMP 195°C, MW, 2 h	 91%

oxide ligand along with catalytic Cu_2O and Cs_2CO_3 in the coupling of pyrazole with aryl iodides afforded the corresponding *N*-arylpyrazoles (entry 12) [88]. These conditions were also effective in the coupling of pyrazole and iodobenzene at room temperature and thus, providing the desired *N*-phenylpyrazole in 65% yield. A phosphoramidite–copper catalytic system was successfully used for the *N*-arylation of pyrazole with 4-iodoanisole (entry 13) [89]. The CuI-(*Z*)-butadienylphosphine complex was also reported as an efficient catalyst for the *N*-arylation of pyrazole (entry 14) [90]. This catalytic system was effective even for the coupling of pyrazole with an aryl chloride (entry 15).

Examples of copper-catalyzed *N*-arylation of pyrazoles are known in literature where the reactions were performed without any additional chelating ligand (Table 5, entry 1) [91]. However, a higher temperature and longer reaction time are generally required for these ligand-free *N*-arylations. Bolm reported "ligand-free" copper-catalyzed *N*-arylation of pyrazole with representative aryl halides (entries 2–4) [92]. Although chlorobenzene did not participate in the coupling with pyrazole under these conditions, the *N*-arylpyrazole was isolated in almost quantitative yield from the coupling of electron-deficient 4-chlorobenzonitrile and pyrazole (entry 4). Notably, sterically hindered *ortho*-substituted aryl halides also afforded high yields of the corresponding products (entries 2b and 3b). Wu reported similar *N*-arylation without any additional ligand where microwave heating was used to facilitate the process (entry 5) [93].

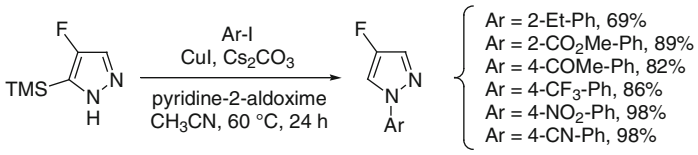
Table 6 Representative copper-catalyzed *N*-arylation of indazoles

Entry	Indazole	Conditions[a]	Yield
1		Ar–I, CuI, DMEDA[b] CsF, THF, 60°C	Ar = 4-Cl-Ph, 88%
2		Ar–I, CuI, *n*-Bu_4NBr NaOH, toluene, reflux	Ar = Ph, 50%
3		Ar–I, Cu_2O, *n*-Bu_4NBr K_3PO_4, water, 130°C	Ar = Ph, 78% Ar = 4-OMe-Ph, 83% Ar = 4-Cl-Ph, 88%
4		Ar–Br, CuI, K_2CO_3 NMP, 195°C, MW, 2 h	Ar =  72%

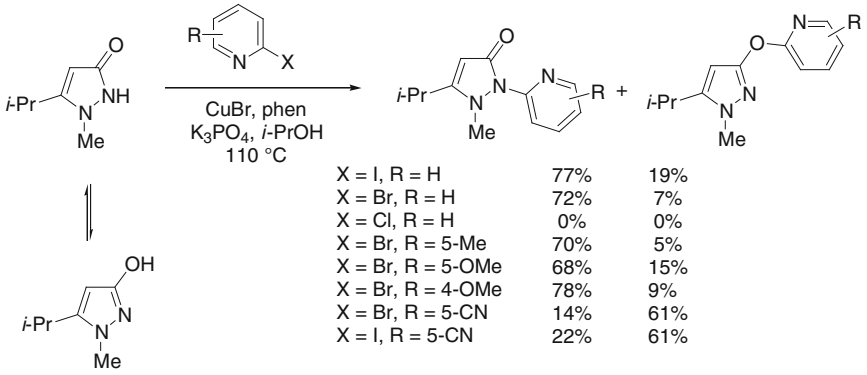
[a]Typical reaction time 18–24 h
[b]DMEDA: *N*,*N*′-dimethylethylenediamine

Phillips reported *N*-arylations of indazole with aryl iodides in the presence of CuI, *N*,*N*′-dimethylethylenediamine and CsF (Table 6, entry 1) [94]. These conditions are particularly suitable for substrates that are incompatible with commonly used bases, such as K_2CO_3, K_3PO_4 and Cs_2CO_3. The "ligand-free" *N*-arylation of indazole is also known in the literature, where catalytic *n*-Bu_4NBr was used along with the Cu-catalyst and base (entries 2 and 3) [95, 96]. Wu reported high-temperature microwave conditions for the installation of functionalized aryl moiety at *N*-1 of indazole (entry 4) [93].

An aminoarenethiolato–copper(I) catalyst has been successfully used in the coupling of pyrazole with aryl bromides to provide the corresponding *N*-arylpyrazoles [97]. Similar Cu-catalyzed coupling of pyrazole with bromobenzene also has been reported in the presence of supported amino acid ionic liquids [98]. A strong dendritic effect was observed in the *N*-arylation of pyrazole with iodobenzene in the presence of a third generation dendrimer (involving iminopyridine *N*,*N*-chelates) [99]. While the dendrimer afforded nearly quantitative formation of *N*-phenylpyrazole, the corresponding monomeric iminopyridine ligand provided <5% yield for the same reaction. Choudary reported the use of copper apatite catalysts for the *N*-arylation of chloropyrazole and fluoropyrazole [76]. Use of nanocrystalline CuO in the *N*-arylation of pyrazole with 4-chloronitrobenzene or 4-fluoronitrobenzene afforded the corresponding products in high yields [100]. A resin-supported sulfonato–Cu(salen) complex was also effective for coupling of pyrazoles with chloro and fluorobenzenes [101]. CuO hollow nanospheres (on acetylene black) have been successfully used as the catalyst for the *N*-arylation of pyrazole with iodobenzene [102]. Copper(I) thiophene-2-carboxylate (CuTC) was also effective for the coupling of pyrazole with aryl iodides and bromides [103].



Scheme 15

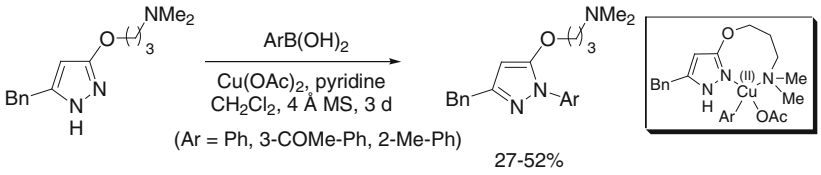


Scheme 16

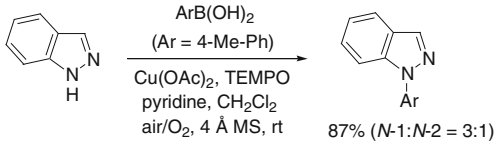
Interestingly, copper-catalyzed *N*-arylation of 4-fluoro-5-trimethylsilylpyrazole with aryl iodides afforded the corresponding *desilylated N*-arylpyrazoles as the sole product (Scheme 15) [104]. In fact, complete desilylation of the pyrazole substrates occurred prior to the *N*-arylation.

Studies on competitive *N*- versus *O*-arylations of pyrazolone with 2-iodo- and 2-bromopyridines revealed that the *N*-arylation is significantly favored over the *O*-arylation in the presence of catalytic CuBr and 1,10-phenanthroline (Scheme 16) [105]. The same trend was observed for the arylation of pyrazolone with 2-bromoquinoline. However, in the presence of electron-withdrawing cyano group in the pyridine ring, the *O*-arylation was favored. Thus, the reaction of pyrazolone with 2-bromo-5-cyanopyridine provided the *O*-arylated and *N*-arylated products in 61% and 14% yields, respectively.

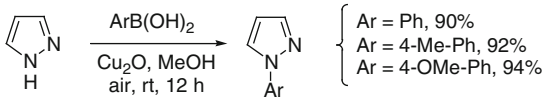
Following the Chan–Lam protocol for C–N coupling, Selwood reported the synthesis of an *N*-functionalized pyrazole library via the reaction of pyrazoles and arylboronic acids in the presence of $Cu(OAc)_2$ and pyridine in CH_2Cl_2 under air at room temperature (Scheme 17) [106]. Due to directing effect of dialkylamino functionality in 5-benzylpyrazole, bearing a 3-dimethylaminopropyloxy group, the desired arylation occurred regioselectively at the *N*-2 center; thus, affording the corresponding *N*-2 substituted products exclusively ($\geq$99:1 *N*-2: *N*-1).



Scheme 17



Scheme 18



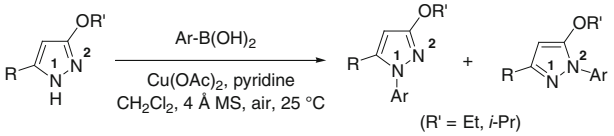
Scheme 19

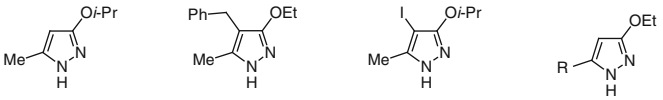
For the efficient coupling of indazole with 4-tolylboronic acid under Chan–Lam protocol, TEMPO was used as an oxidant along with catalytic $Cu(OAc)_2$ (Scheme 18) [107]. In the "base-free" version of this method, the reaction of pyrazole with arylboronic acid was carried out in methanol in the presence of catalytic Cu_2O under air (Scheme 19) [108]. Of note, air is essential for the success of these reactions.

While investigating the *N*-arylation of various 3-alkoxypyrazoles with arylboronic acids in the presence of stoichiometric amount of copper salts (Table 7) [60], Janin reported that the formation of *N*-2 arylated product (1-aryl-5-alkoxypyrazole) was slightly favored for the reaction of 3-isopropoxy-5-methylpyrazole with phenylboronic acid. Coupling of 5-phenyl and 5-trifluoromethyl substituted 3-ethoxypyrazole with 4-chlorophenylboronic acid exclusively afforded the *N*-2 arylation products due to the steric factor. In contrast, arylation of related 3-alkoxy-4-benzylpyrazole and 3-alkoxy-4-iodopyrazole with phenylboronic acid predominantly produced the corresponding *N*-1 arylation products.

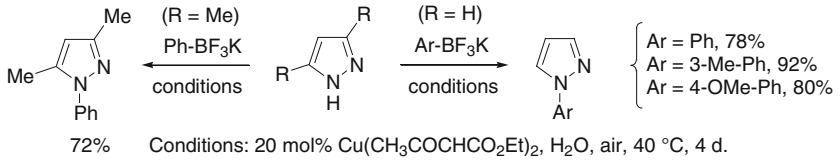
Although the "base-free" *N*-arylation of pyrazole with aryl trifluoroborates in water in the presence of catalytic copper(II) ethyl acetoacetate provided the desired *N*-arylpyrazoles in good yields, a long reaction time was required (Scheme 20) [109]. Arylation of indazole with (4-OMe)Ph-BF_3K also gave the corresponding *N*-arylindazole in 73% yield (*N*-1: *N*-2 = 57:47).

Table 7 *N*-Arylation of 3-alkoxypyrazoles





Ar	*N*-1	*N*-2	*N*-1	*N*-2	*N*-1	*N*-2	*N*-1	*N*-2
Ph	39%	53%	75%	Trace	70%	11%		
4-Cl-Ph	20%	37%	66%	<10%	69%	15%	–	R = Ph, 83% R = CF_3, 94%



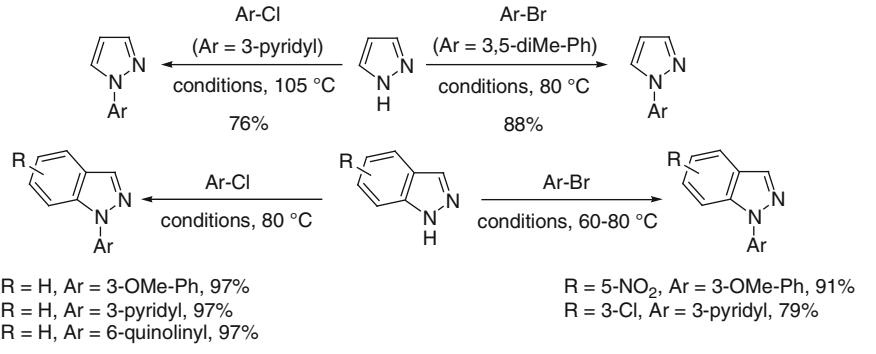
Scheme 20

2.3.3 Palladium-Catalyzed *N*-Arylation of Pyrazoles and Indazoles

Palladium-catalyzed *N*-arylations of pyrazoles and indazoles in the presence $Pd_2(dba)_3$, *t*-Bu-XPhos and NaO*t*-Bu afforded the corresponding products in high yields (Scheme 21) [110]. The mechanism of the palladium-catalyzed *N*-arylation of pyrazole is shown in Fig. 9. The faster rate of conversion from kinetically formed species A to species B over the rate of deprotonation from species A explains the selective *N*-1 arylation of indazole (Fig. 10). The direct formation of species A′ is not possible as it would disrupt the aromaticity.

2.3.4 Iron-Catalyzed *N*-Arylation of Pyrazoles

Iron–copper co-catalyzed *N*-arylation of pyrazole with aryl iodides in the presence of CuO, $[Fe(acac)_3]$ and Cs_2CO_3 afforded the corresponding products in good yields (Scheme 22) [111]. A high reaction temperature was required for the efficient coupling of electron-rich iodoanilines. Reaction of pyrazole and 4-chlorobenzotrifluoride (an activated aryl chloride) also gave the desired product, albeit in low yield. Other copper sources, such as Cu, CuI, and $[Cu(acac)_2]$, in



Scheme 21

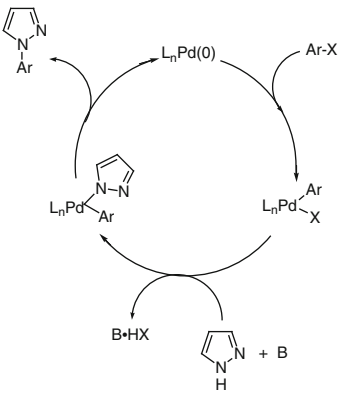


Fig. 9 Pd-Catalyzed *N*-arylation of pyrazole

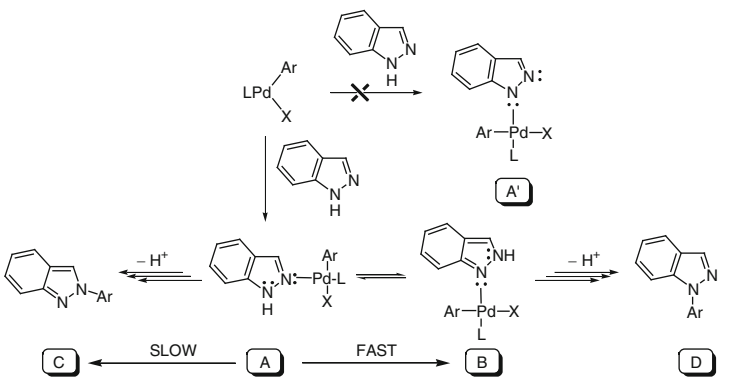
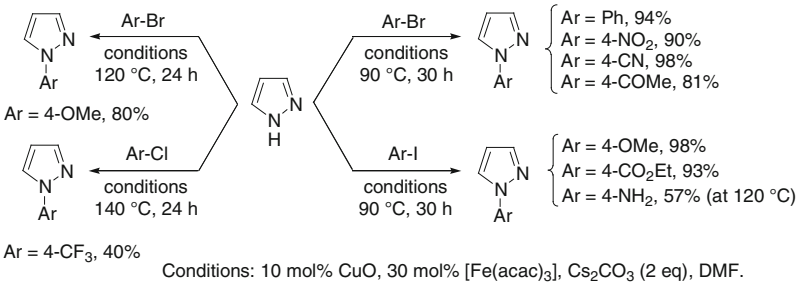
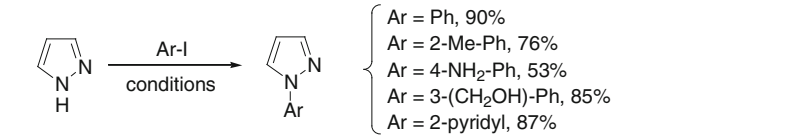


Fig. 10 Regioselectivity in Pd-catalyzed *N*-arylation of indazole



Scheme 22

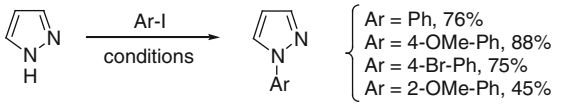


Scheme 23

combination with [Fe(acac)$_3$], were also effective. However, catalytic [Fe(acac)$_3$] in the absence of any copper source was completely ineffective. The pre-complexation of acetylacetonate ligand with iron as well as the use of an Fe(III) precatalyst (instead of a Fe(II) precatalyst) is crucial.

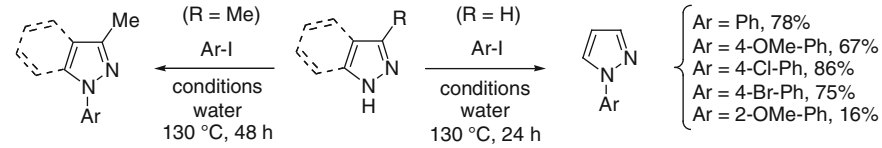
Iron-catalyzed *N*-arylation of pyrazole with aryl iodides in the presence of $FeCl_3 \cdot 6H_2O$ and a diamine ligand is also useful for the preparation of corresponding *N*-arylpyrazoles (Scheme 23) [112]. With an ideal concentration of 2–4 M, both K_3PO_4 and K_2CO_3 are suitable bases (NaO*t*-Bu is less effective) for this transformation. Use of aqueous medium and relatively inexpensive catalyst are advantages of this method. Notably, 4-iodoaniline (bearing a $-NH_2$ group), 3-iodobenzyl alcohol (bearing a $-CH_2OH$ functionality), and sterically challenging 2-iodotoluene successfully participated in *N*-arylation of pyrazole under these conditions. Likewise, coupling of pyrazole with aryl iodides in the presence of $FeCl_3$ and *N*, *N*′-dimethylethylenediamine (dmeda) in water also provided the desired products (Scheme 24) [113]. Other iron salts, such as Fe(acac)$_2$, Fe(oxalate)$\cdot 2H_2O$, Fe_2O_3 were also effective, but to a lesser extent.

A graphite-supported iron(III) acetylacetonate catalytic system can also be used for the *N*-arylation of pyrazole with aryl iodides and bromides [114]. Although an iron-catalyzed *N*-arylation procedure using $FeCl_3-$dmeda has been reported in the literature [115], the presence of trace copper impurities in the catalyst presumably played an important role in this catalysis [116].



Conditions: 10 mol% $FeCl_3$, 20 mol% *N,N'*-dimethylethylenediamine, $K_3PO_4 \cdot H_2O$ (2 eq), water, 125 °C, 36 h.

Scheme 24



Ar = Ph, 78% (90% for indazole)
Ar = 4-Cl-Ph, 72% (82% for indazole)

Conditions: 10 mol% $MnCl_2 \cdot 4H_2O$, 20 mol% *trans*-1,2-diaminocyclohexane, $K_3PO_4 \cdot H_2O$ (2 eq).
(for indazoles : 20 mol% catalyst and 40 mol% ligand)

Scheme 25

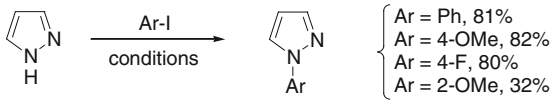
2.3.5 Other Metal-Catalyzed *N*-Arylation of Pyrazoles and Indazoles

Manganese-catalyzed coupling of pyrazole and indazole with various aryl iodides in the presence of $MnCl_2 \cdot 4H_2O$, *trans*-1,2-diaminocyclohexane and $K_3PO_4 \cdot H_2O$ afforded the corresponding *N*-arylated products in good yields (Scheme 25) [117].

Notably, the reactions proceeded efficiently only in water, and a majority of manganese salts, such as $Mn(acac)_2$, $Mn(ClO_4) \cdot H_2O$, MnF_2, $Mn(OAc)_2$, and MnO_2 were effective for this transformation. Since the reaction of pyrazole and iodobenzene with highly pure (99.99%) $MnCl_2 \cdot 4H_2O$ catalyst provided the desired product in 64% yield, the possibility of any contamination of catalyst by traces of copper salts can be ruled out. The use of $K_3PO_4 \cdot H_2O$ base was crucial for efficient coupling, whereas Cs_2CO_3 and K_2CO_3 were ineffective. A similar *N*-arylation of pyrazole in the presence of $CoCl_2 \cdot 6H_2O$ in water is also known in literature (Scheme 26) [118]. Lanthanum(III) oxide can also serve the role of catalyst in the *N*-arylation of pyrazole [119].

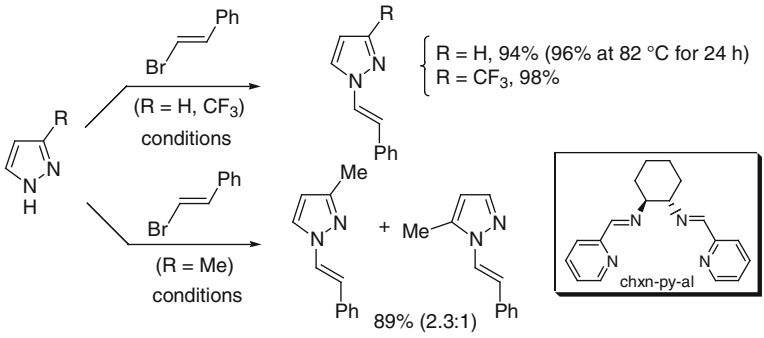
2.4 Metal-Catalyzed N-*Vinylation of Pyrazoles and Indazoles*

The copper-catalyzed *N*-vinylation of pyrazole using commercially available *β*-bromostyrene (90:10 *E*:*Z*) in the presence of a tetradentate ligand stereoselectively afforded (*E*)-*β*-styrylpyrazole in excellent yields (Scheme 27) [120]. However, *N*-vinylation of 3-methylpyrazole provided a mixture of *N*-1- and *N*-2-substituted products. Notably, 100% conversion of (*E*)-*β*-bromostyrene to



Conditions: 10 mol% $CoCl_2$•$6H_2O$, 20 mol% *N, N'*-dimethylethylenediamine, K_3PO_4•H_2O (2 eq), water, 120 °C, 36 h.

Scheme 26



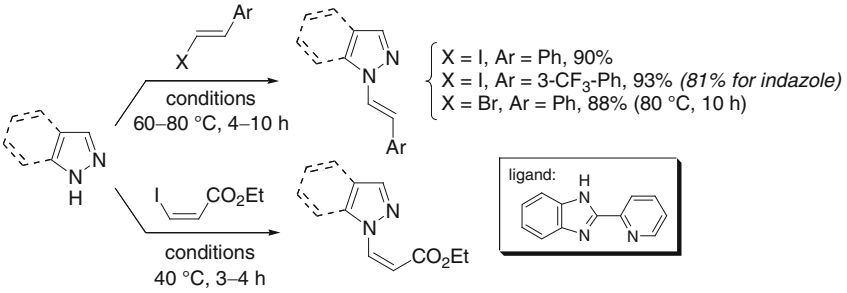
Conditions: 10 mol% CuI, 5 mol% chxn-py-al, Cs_2CO_3 (2 eq), MeCN, 50 °C, 30 h.

Scheme 27

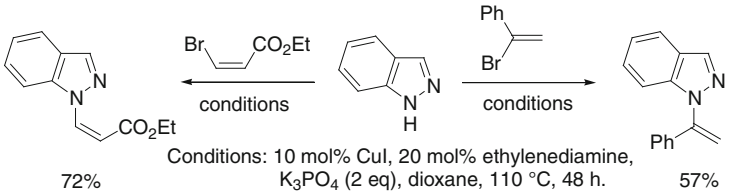
(*E*)-*β*-styrylpyrazole was observed even at 35°C (for 55 h). On the other hand, irrespective of temperature, (*Z*)-*β*-bromostyrene was converted to the phenylacetylene via a facile *E*-2-type elimination (dehydrobromination).

Cook reported 2-pyridin-2-yl-*1H*-benzoimidazole as a bidentate ligand for the copper-catalyzed *N*-vinylation of pyrazoles and indazoles (Scheme 28) [121, 122]. In a related ligand screening experiment, this pyridine–benzoimidazole ligand showed superior performance compared to structurally related 1,10-phenanthroline and similar ligands. Both, (*E*)-vinyl iodides and bromides efficiently provided the corresponding *N*-vinylated products, though higher temperature and longer reaction time were necessary for the vinyl bromides. Notably, the *N*-vinylation of pyrazole/indazole with (*Z*)-ethyl-3-iodo-acrylate produced the corresponding products (with full retention of configuration) in excellent yield, even at 40°C, and the common problem of arylacetylene by-product formation was not encountered. Notably, the TBDPS-protecting group on a phenol (Ar-OTBDPS) remained intact under these conditions; thus, providing a cleaner reaction profile and a higher yield for the desired transformation.

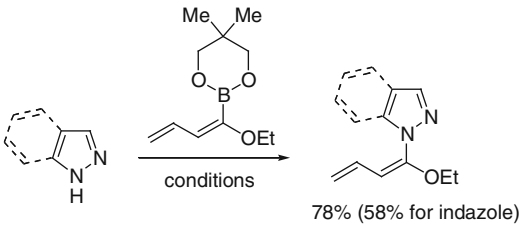
The *N*-vinylation of indazole with vinyl bromides in the presence of catalytic CuI and ethylenediamine afforded *N*-1-substituted indazoles (along with $\leq$10% of *N*-2-substituted isomer) (Scheme 29) [123]. Similarly, the room temperature coupling of pyrazole with alkoxydienyl boronic esters in the presence of $Cu(OAc)_2$, KO*t*-Bu and CsF afforded the corresponding *N*-substituted pyrazole (Scheme 30) [124].



Scheme 28



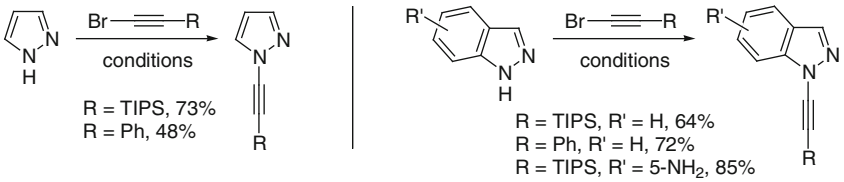
Scheme 29



Scheme 30

Related coupling of indazole and alkoxydienyl boronate gave a 3:1 mixture (*N*-1: *N*-2) of two regioisomeric products in 58% combined yield.

Copper fluorapatite-mediated coupling of pyrazole with vinylboronic acids at room temperature has also been used for the preparation of a variety of *N*-vinylpyrazoles [125].



Conditions: 5 mol% CuI, PEG-400, Cs_2CO_3, dioxane, MW, 80 °C, 90 min.

Scheme 31

2.5 Metal-Catalyzed N*-Alkynylation of Pyrazoles and Indazoles*

The microwave-assisted copper-catalyzed coupling of pyrazole with bromoalkynes in the presence of poly(ethylene)glycol (molecular weight 400) and Cs_2CO_3 conveniently afforded the corresponding *N*-alkynylated pyrazoles (Scheme 31) [126]. Additive poly(ethylene)glycol served a dual role by acting as a Cu(I) stabilizing ligand as well as a phase transfer solvent by providing a compatible reaction bridge between the hydrophobic azoles/alkynes and hydrophilic base Cs_2CO_3. The *N*-alkynylation of indazole was highly regioselective under these conditions and afforded the *N*-1 alkynylindazole exclusively.

3 Reactions of Pyrazoles via *C*-Metalation

3.1 Metalation at C-5 of Pyrazoles

The hydrogen at C-5 is the most acidic hydrogen in the *N*-protected pyrazole (Fig. 11). Typically, strong metalic bases abstract C-5 proton to generate the corresponding 5-metalopyrazole in situ. Therefore, the reaction of an *N*-alkylpyrazole with *n*-butyllithium followed by quenching of the resulting 5-lithiopyrazole with bromine or hexachloroethane afforded the corresponding 5-halopyrazoles (Scheme 32) [127]. Likewise, anionic coupling of *N*-methyl-5-lithiopyrazole with 1,2-dibromobenzene provided 5-(2-bromophenyl)-1-methylpyrazole (Scheme 33) [128]. Low-temperature addition of LDA to *N*-benzyloxy-4-methylpyrazole followed by quenching with DMF installed an aldehyde functionality at C-5 (Scheme 34) [129].

During the preparation of the insecticide Rynaxypyr, Lahm reported C-5 lithiation of *N*,*N*-dimethylsulfamoylpyrazole using *n*-butyllithium and subsequent quenching with 1,2-dibromo-1,1,2,2-tetrachloroethane to afford the corresponding 5-bromopyrazole (Scheme 35) [31, 130, 131]. Removal of the protecting group from 5-bromopyrazole by TFA produced 3-bromopyrazole. Regioselective arylation of 3-bromopyrazole followed by C-5 lithiation using LDA and subsequent addition of CO_2 gave the important 5-carboxypyrazole intermediate. Likewise, C-5 lithiation

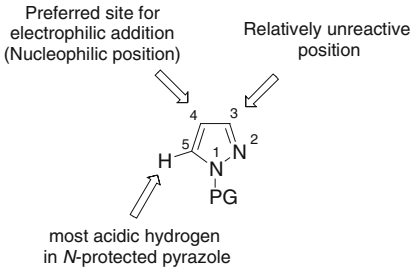
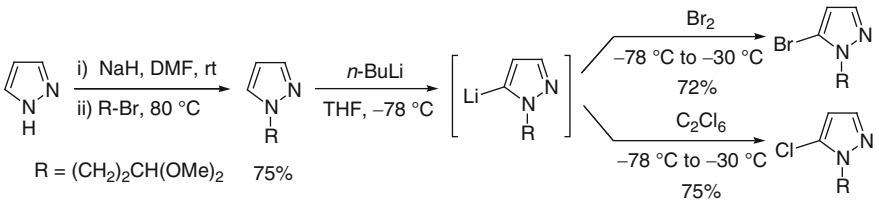
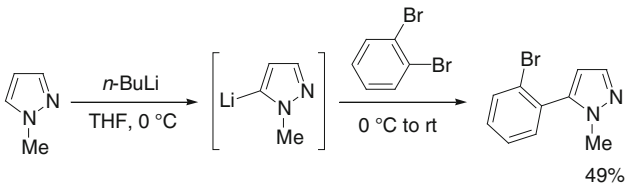


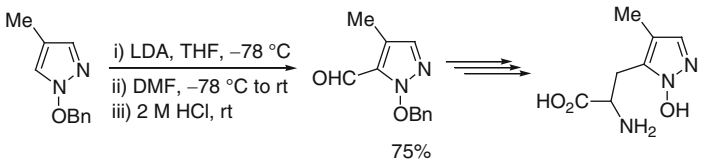
Fig. 11 Reactivity in *N*-substituted pyrazoles



Scheme 32



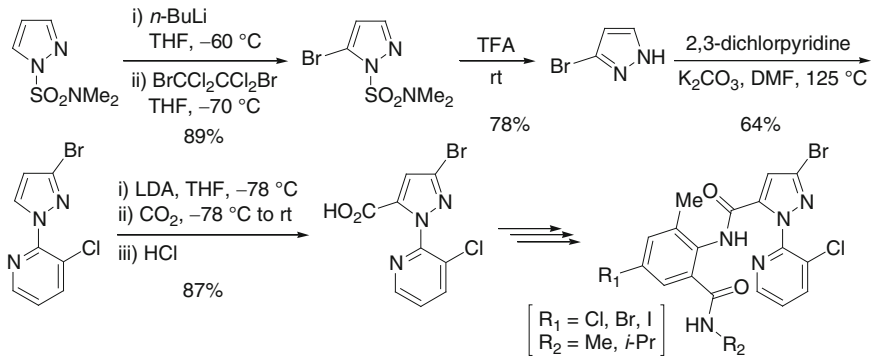
Scheme 33



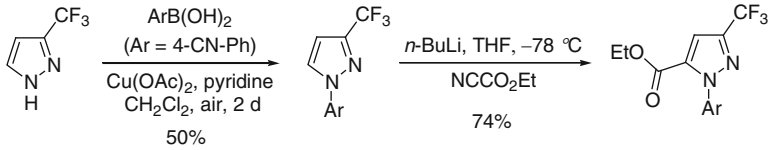
Scheme 34

of an *N*-arylated 3-trifluoromethylpyrazole followed by quenching with ethyl cyanoformate provided the corresponding 5-(carbethoxy)pyrazole (Scheme 36) [132].

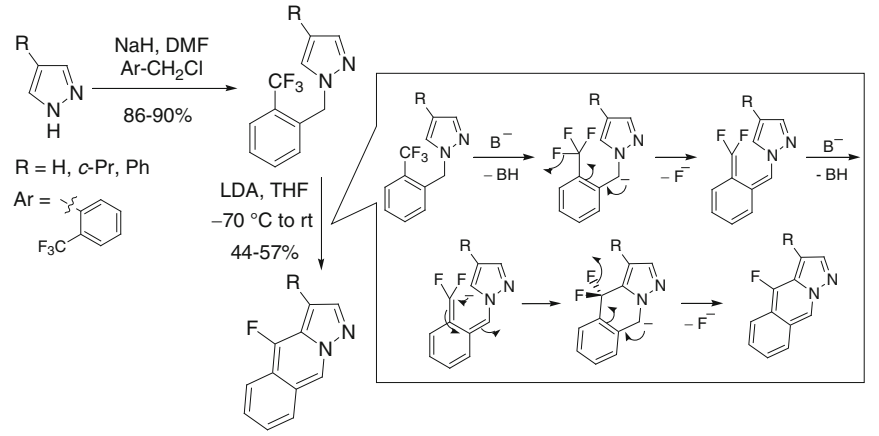
Kiselyov reported that the treatment of *N*-(2-trifluoromethylbenzyl)pyrazole with LDA (pK_a ~36) at −78°C produced fluorinated pyrazoloisoquinolines (Scheme 37) [133]. However, reactions of *N*-(2-trifluoromethylbenzyl)pyrazole with Grignard reagents gave complex mixtures along with ~15% of the desired products. Moreover, no reaction was observed using KO*t*-Bu/THF and NaOEt/EtOH.



Scheme 35

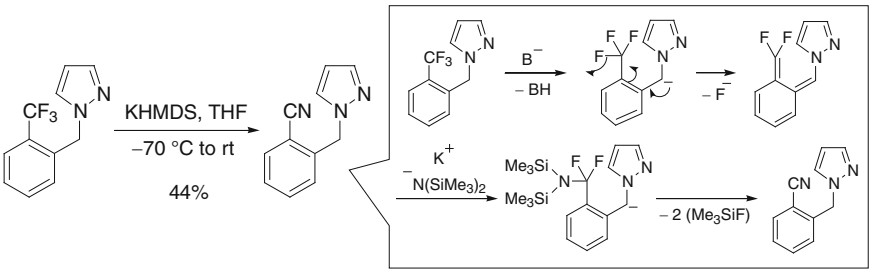


Scheme 36

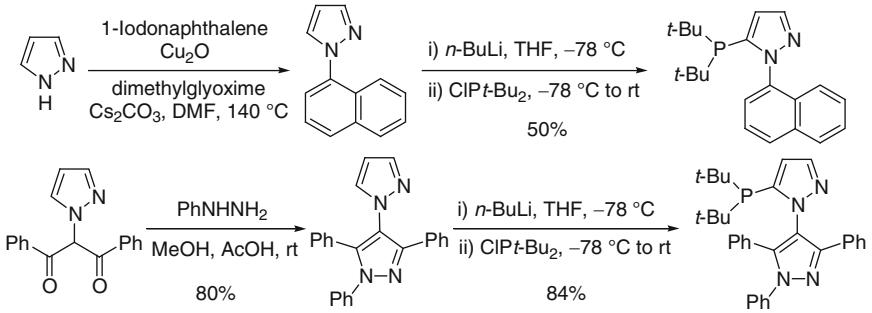


Scheme 37

Presumably, the transformation of *N*-substituted pyrazole to pyrazoloisoquinoline was initiated by the abstraction of the acidic benzylic proton of the *N*-benzylpyrazole, which subsequently afforded the highly reactive quinine methide via elimination of F^-. Thereafter, the second equivalent of base abstracted the C-5 acidic proton from the pyrazole core to provide the anion that underwent intramolecular cyclization and elimination of F^- to form the pyrazoloisoquinoline.



Scheme 38



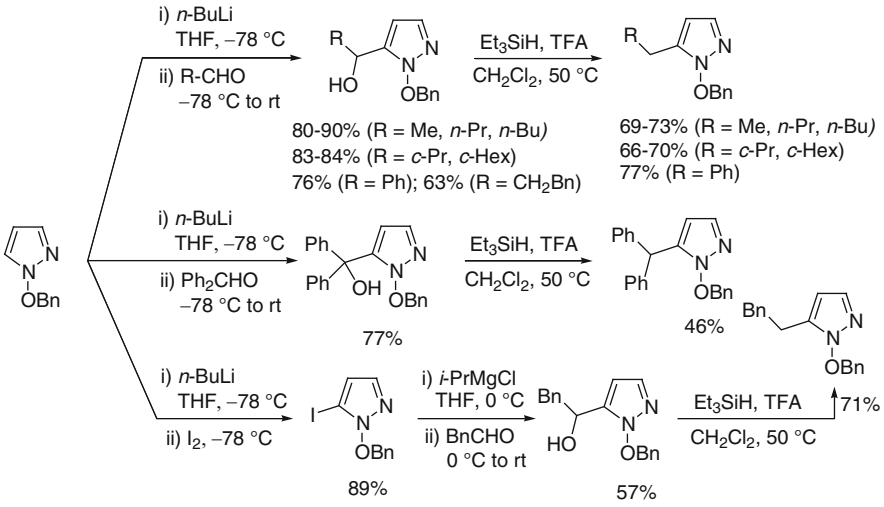
Scheme 39

Notably, the optimal amount of base required for cleaner reaction profile was 2.5 eq, which is consistent with the proposed reaction mechanism. Interestingly, treatment of *N*-(2-trifluoromethylbenzyl)pyrazole with KHMDS (pK_a ~26) under similar conditions gave *N*-(2-cyanobenzyl)pyrazole, instead of the expected fluorinated pyrazoloisoquinoline (Scheme 38). In fact, relatively weak base KHMDS nucleophilically adds to reactive quinine methide, instead of abstracting C-5 proton from pyrazole, and thereby, afforded a net conversion from trifluoromethyl to nitrile functionality on the phenyl ring.

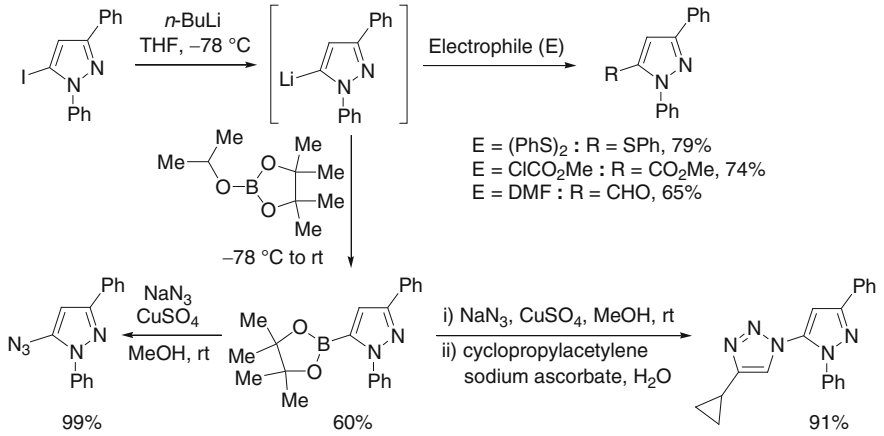
Singer reported the synthesis of few pyrazole-based phosphine ligands using regioselective C-5 lithiation of *N*-arylpyrazoles followed by the addition of di-*tert*-butylchlorophosphine to the 5-lithiopyrazoles (Scheme 39) [134].

The C-5 lithiation of *N*-benzyloxypyrazole and subsequent quenching of the resulting 5-lithiopyrazole with various aldehydes as well as benzophenone afforded the corresponding alcohols (Scheme 40) [135]. However, due to polymerization of phenylacetaldehyde under *n*-butyllithium-mediated lithiation conditions, the analogous phenylethyl alcohol derivative was synthesized via metal–halogen exchange reaction of 5-iodopyrazole using isopropylmagnesium chloride.

Harrity reported metal–halogen exchange of 5-iodopyrazole with *n*-butyllithium where 5-lithiopyrazole intermediate was subsequently quenched with diphenyldisulfide, methyl chloroformate, and DMF to furnish the corresponding C-5-



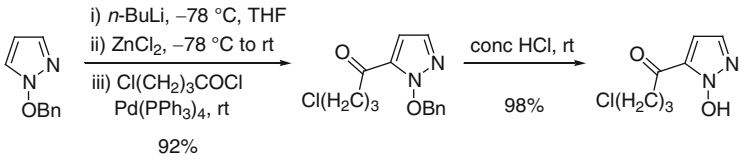
Scheme 40



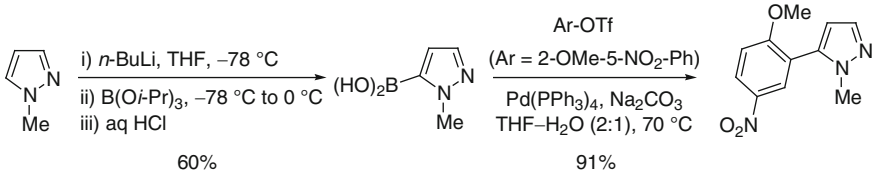
Scheme 41

substituted pyrazoles (Scheme 41) [136]. The synthetically useful pyrazole-5-boronic ester was synthesized by quenching the 5-lithiopyrazole with isopropylpinacol boronate. Copper-catalyzed coupling of the boronate with sodium azide provided the corresponding 5-azidopyrazole, which was later reduced to 5-aminopyrazole by hydrogenation. Similarly, a one-pot azidation and click chemistry on the boronate afforded the corresponding triazole derivative.

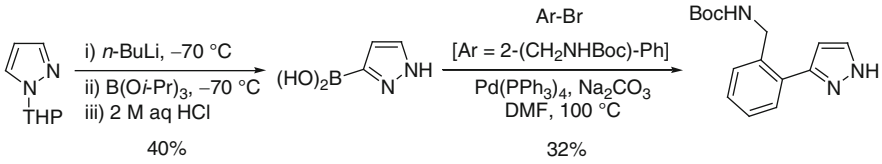
The *ortho*-lithiation of *N*-benzyloxypyrazole followed by transmetalation using $ZnCl_2$ and subsequent palladium-catalyzed coupling of the resulting organozinc with 4-chlorobutyryl chloride afforded the C-5-acylated pyrazole (Scheme 42) [137].



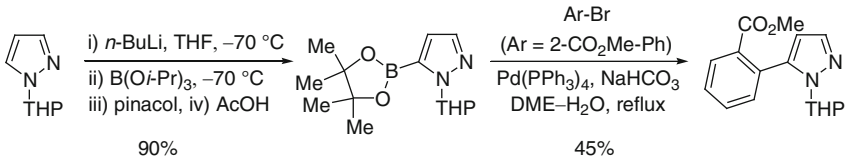
Scheme 42



Scheme 43



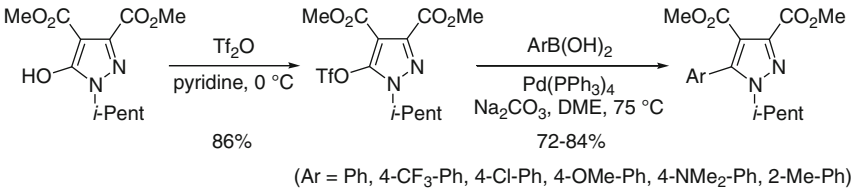
Scheme 44



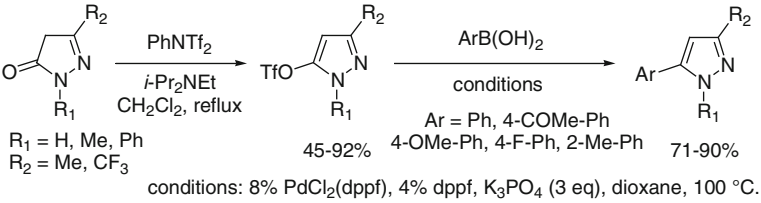
Scheme 45

Reaction of *N*-methylpyrazole with *n*-butyllithium followed by the addition of triisopropylborate provided the corresponding pyrazole-5-boronic acid (Scheme 43) [16]. Palladium-catalyzed coupling of this boronic acid with an aryl triflate introduced the aryl functionality at C-5 of pyrazole core. However, a similar synthetic sequence with THP-protected pyrazole gave 3-arylpyrazole due to the in situ deprotection of THP group and subsequent pyrazole *NH*-tautomerization (Scheme 44) [138].

Rault reported the synthesis of new pyrazoloisoindolones in which the Suzuki–Miyaura coupling of the THP-protected pyrazole-5-pinacol boronate with aryl bromides was used to prepare the 5-arylpyrazole precursor (Scheme 45) [139].



Scheme 46

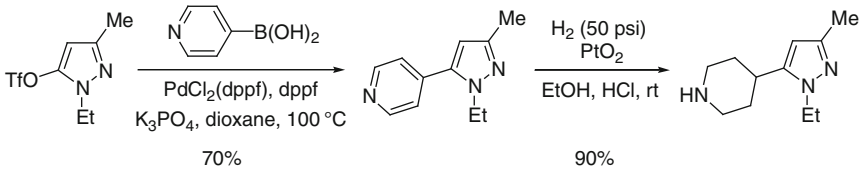


Scheme 47

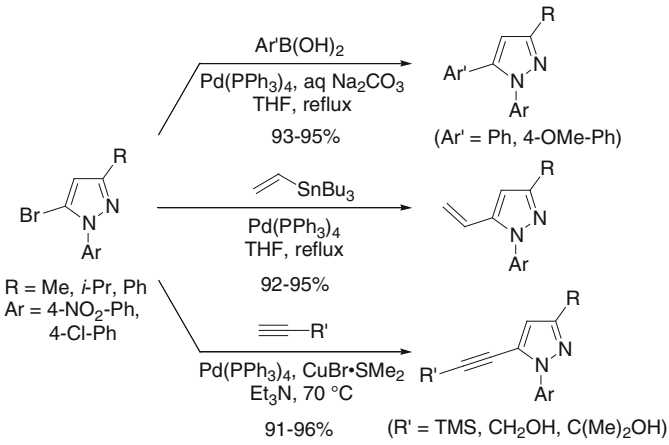
In their study on the Suzuki–Miyaura cross-coupling of pyrazole-5-triflates with arylboronic acids, Dragovich observed the formation of 5-hydroxypyrazoles, instead of the desired coupling products, due to the facile hydrolysis of pyrazole triflates under the standard literature conditions involving aqueous solvents (Scheme 46) [140]. In fact, the control experiment showed a rapid conversion of OTf → OH (100% in 4 h) upon heating the pyrazole-5-triflate at 75°C in DME−H_2O (95:5) with just 2 eq of Na_2CO_3 (without any boronic acid). Therefore, by switching to *anhydrous* conditions [$Pd(PPh_3)_4$, Na_2CO_3, DME, 75°C], a dramatic increase in yield was observed. In addition, rigorous drying of these triflates prior to use was highly recommended. Use of K_2CO_3 as the base also provided comparable yield, while Cs_2CO_3 was much less effective.

Dvorak also reported efficient coupling of pyrazole-5-triflates with arylboronic acids under anhydrous conditions (Scheme 47) [141]. In fact, use of additional dppf ligand in combination with $PdCl_2$(dppf) catalyst was highly effective. The *N*-protection of pyrazole was not absolutely necessary under these conditions as the coupling of an unprotected pyrazole-5-triflate with phenylboronic acid afforded 81% yield of the corresponding 5-phenylpyrazole. Of note, these triflates precursors were prepared from the corresponding pyrazolone derivatives using a mild triflating reagent, *N*-phenyl-bis(trifluoromethanesulfonimide). Using these conditions, Dirat also reported the coupling of a pyrazole-5-triflate with 4-pyridylboronic acid (Scheme 48) [142]. These couplings were sensitive to reaction concentration (optimum concentration ~0.15 M) and catalyst loading (8 mol% catalyst and 4 mol% of dppf).

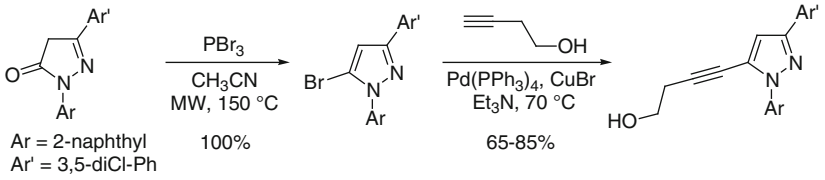
Palladium-catalyzed coupling of 1,3-disubstituted 5-bromopyrazoles with arylboronic acids, vinylstannane, and terminal alkynes afforded the corresponding 5-functionalized pyrazoles (Schemes 49 and 50) [73, 143]. Thus, these reactions are



Scheme 48



Scheme 49

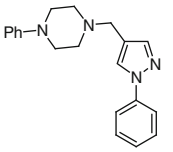
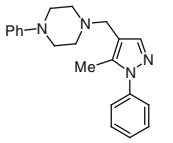
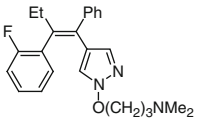
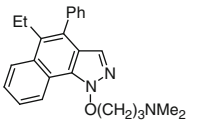
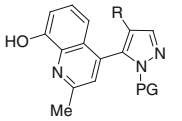
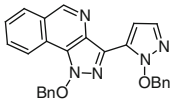
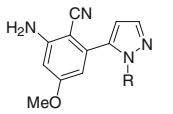
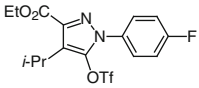
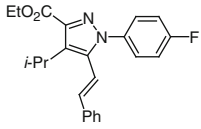


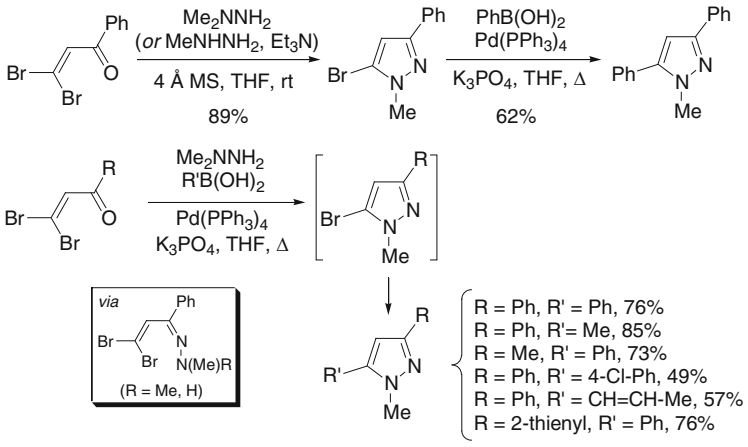
Scheme 50

useful for the preparation of *unsymmetrical* 3,5-disubstituted pyrazoles. Of note, the prerequisite 5-bromopyrazoles were made from the *β*-ketoesters using suitably substituted hydrazines followed by bromination of the resulting pyrazolones.

Regioselective C-5 lithiation of a *N*-phenylpyrazole using *n*-butyllithium followed by quenching with iodomethane afforded the corresponding 5-methylpyrazole (Table 8, entry 1) [144, 145]. Begtrup reported the synthesis of a benzoindazole via the C-5 lithiation of pyrazole followed by an intramolecular cyclization (entry 2) [146]. Likewise, regioselective C-5 lithiation of an *N*-protected pyrazoles followed by the addition of zinc chloride and subsequent palladium-

Table 8 C-5 Functionalization of pyrazoles via metalation

Entry	Pyrazole, Conditions	Products, Yields
1		
	(i) *n*-BuLi, THF, −78°C to −30°C (ii) MeI, −78°C to 0°C	62%
2		
	n-BuLi, THF, −78°C to rt	90%
3		
	(i) *n*-BuLi, THF, −78°C to −40°C (ii) $ZnCl_2$, −78°C to rt (iii) Ar-Br, $Pd(PPh_3)_4$, dioxane, 80°C	R = H, PG = BOM, 89% R = Me, PG = BOM, 87% R = Me, PG = THP, 95%
4		
	(i) *n*-BuLi, THF, −78°C (ii) $ZnCl_2$ (1 M in THF), −78°C to rt (iii) Ar-I, $Pd(PPh_3)_4$, dioxane, 80°C	63%
5		
	Ar-I, $Pd_2(dba)_3$, $P(2\text{-furyl})_3$, reflux dioxane, 2 h (*Stille*) or THF, 20 h (*Negishi*)	47% (M = $SnBu_3$, R = Me) 47% (M = ZnCl, R = CH_2OEt)
6		
	(*E*)-styrylboronic acid $PdCl_2(PPh_3)_2$, K_2CO_3, KBr toluene–*i*-PrOH–H_2O (4:1:1), 80°C, 12 h	91%

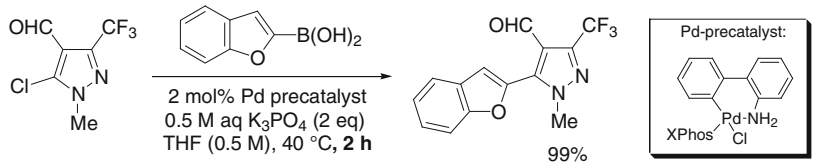


Scheme 51

catalyzed coupling of organozinc with a 4-bromoquinoline afforded the desired products in excellent yields (entry 3) [147]. The Negishi coupling was also used to introduce an azaindazole scaffold at C-5 of *N*-benzyloxypyrazole (entry 4) [148]. Fray utilized both Negishi and Stille couplings for the installation of a 2-aminobenzonitrile functionality at C-5 of pyrazole core (entry 5) [71]. The Suzuki–Miyaura coupling of a fully substituted pyrazole-5-triflate with (*E*)-styrylboronic acid in the presence of 2.5 mol% $PdCl_2(PPh_3)_2$, 20 mol% of KBr, and K_2CO_3 (3 eq) afforded the 5-styrylpyrazole that was isolated in 91% yield by the filtration of crude reaction mixture followed by crystallization (>98% purity in 3.5 kg scale) (entry 6) [149].

Taylor reported the synthesis of 3,5-disubstituted *N*-methylpyrazole from *β*,*β*-dibromo-enones using a tandem condensation and Suzuki–Miyaura reaction (Scheme 51) [150]. In a two-step process, the reaction of 3,3-dibromo-1-phenylpropenone with 2 eq of *N*, *N*-dimethylhydrazine first provided the 1,3-disubstituted 5-bromopyrazole via a condensation-demethylation-cyclization sequence, which then underwent Suzuki–Miyaura coupling with phenylboronic acid to afford the 5-phenylpyrazole. Interestingly, heating the *β*,*β*-dibromo-enone together with 2 eq of *N*, *N*-dimethylhydrazine and 2 eq of boronic acids in the presence of $Pd(PPh_3)_4$ and K_3PO_4 directly produced the desired 5-arylpyrazoles. Notably, use of 3,3-dibromo-1-phenylpropenone with methylboronic acid exclusively provided 3-phenyl-5-methylpyrazole, whereas reaction of 3,3-dibromo-1-methylpropenone with phenylboronic acid selectively produced 3-methyl-5-phenylpyrazole. This method is particularly useful for the *regioselective* synthesis of the 3,5-disubstituted *N*-methylpyrazoles because the conventional condensations of 1,3-dicarbonyl compounds (such as 1-benzoylacetone) with methylhydrazine typically produce a mixture of regioisomers.

A “fast” Suzuki-Miyaura coupling protocol was reported by Buchwald where the reaction of a 5-chloropyrazole with 2-benzofuranboronic acid in the presence of



Scheme 52

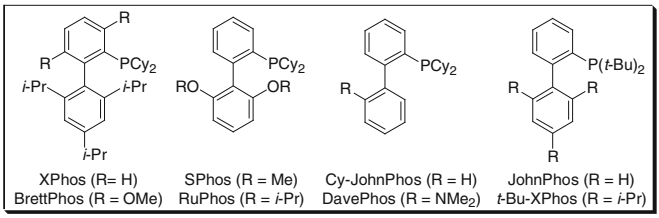
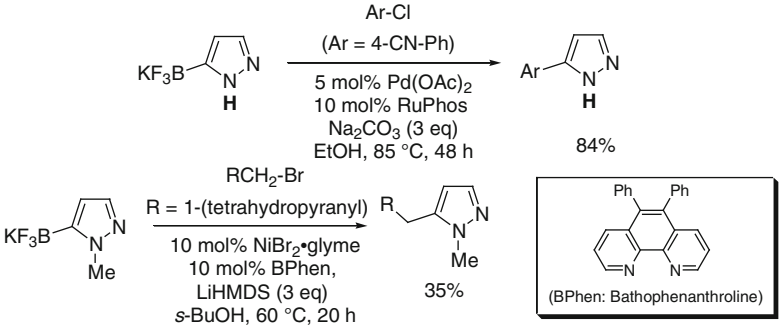


Fig. 12 Representative biarylphosphines

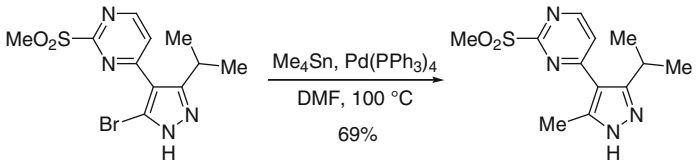


Scheme 53

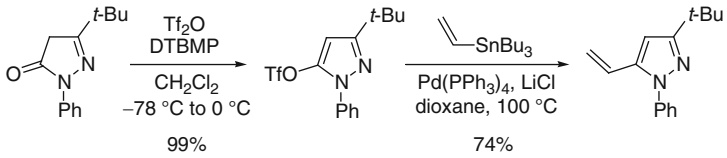
an XPhos containing Pd-precatalyst and aqueous K_3PO_4 produced the desired 5-(heteroaryl)pyrazole in 99% yield only after 2 h of heating (Scheme 52) [151].

The structures of XPhos and related biarylphosphines that are commonly used in the metal-catalyzed cross-coupling reactions are summarized in Fig. 12.

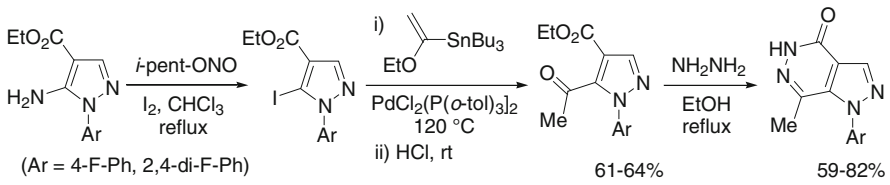
The reaction of potassium 1*H*-pyrazole-5-trifluoroborate with 4-chlorobenzonitrile in the presence of $Pd(OAc)_2$, RuPhos, and Na_2CO_3 produced the 5-arylpyrazole in excellent yield (Scheme 53) [152]. However, analogous pyrazole-4-trifluoroborate provided a low yield (37%) in the similar coupling. Likewise, nickel-catalyzed cross-coupling of *N*-methylpyrazole-5-trifluoroborate with 2-(bromoethyl)tetrahydropyran in the presence of catalytic $NiBr_2$·glyme, bathophenanthroline (BPhen), and LiHMDS provided the 5-alkylpyrazole, albeit in low yield [153].



Scheme 54



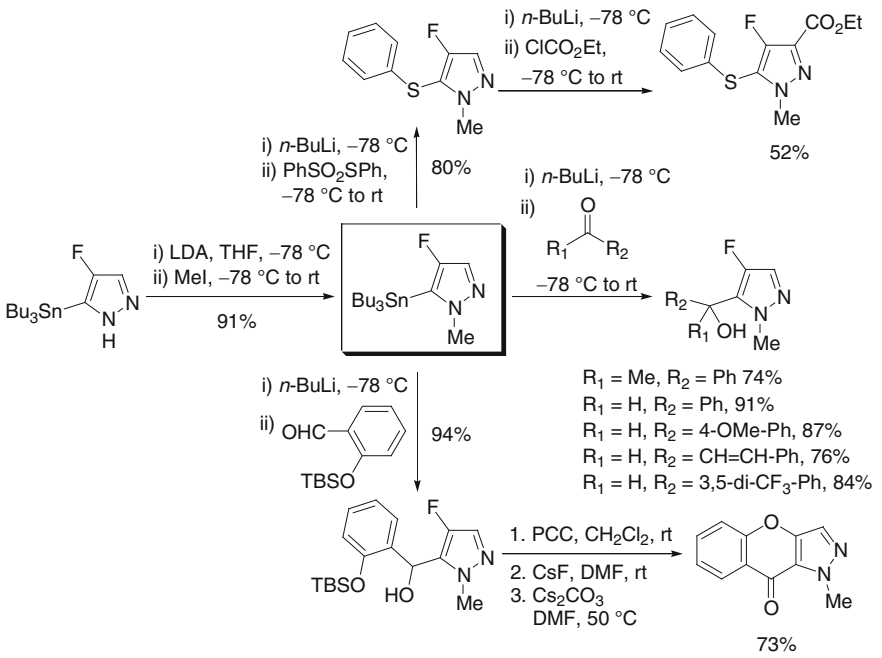
Scheme 55



Scheme 56

The Stille coupling of 5-bromopyrazole with tetramethyltin introduced a methyl group at C-5 of pyrazole (Scheme 54) [154]. The 5-bromopyrazole precursor was prepared by the regioselective bromination using NBS. Similar coupling of a pyrazole-5-triflate with tributyl(vinyl)tin afforded the 5-vinylpyrazole (Scheme 55) [155]. The triflate precursor was prepared from the corresponding pyrazolone by low-temperature addition of trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP). Likewise, the Stille coupling of 5-iodopyrazoles, prepared from the corresponding 5-aminopyrazoles via diazotization, with tributyl(1-ethoxyvinyl)tin followed by acid hydrolysis afforded the 5-acetylpyrazole (Scheme 56) [156].

Hanamoto reported transmetalation of *N*-methyl-5-tributylstannyl-4-fluoropyrazole using *n*-butyllithium. The resulting 5-lithiopyrazole that was subsequently quenched with suitable electrophiles to furnish the corresponding 5-functionalized pyrazoles (Scheme 57) [157]. The addition product formed in the coupling of 5-lithiopyrazole and TBS-protected *ortho*-hydroxybenzaldehyde was carried forward through a oxidation–deprotection–cyclization sequence to prepare an azaxanthone. Of note, the reaction of 5-lithiopyrazole with cinnamaldehyde gave only 1,2-addition product.



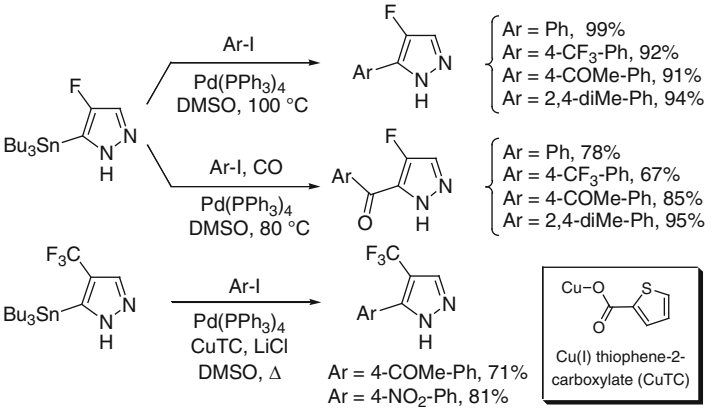
Scheme 57

The *N*-methylated pyrazole precursor was prepared with high selectivity (*N*-1: *N*-2 > 99:1) from the *NH*-pyrazole via *N*-metalation using LDA followed by the addition of iodomethane.

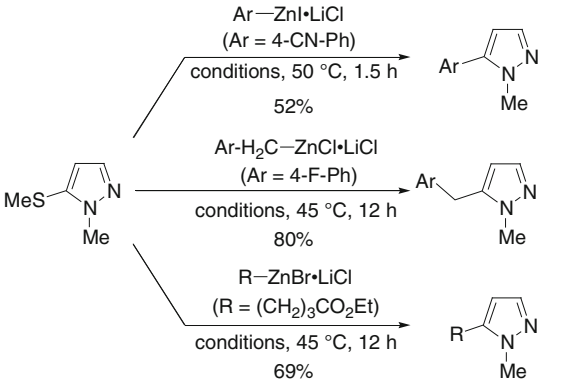
4-Fluoro-5-(tributylstannyl)pyrazole was also used in the Stille coupling with aryl iodides to afford the corresponding 5-arylpyrazoles (Scheme 58) [158–160]. Even sterically challenging *ortho*-substituted aryl iodides provided excellent yields in this reaction. 4-Fluoro-5-(tributylstannyl)pyrazole also participated in the carbonylative cross-coupling with aryl iodides in the presence of CO and catalytic $Pd(PPh_3)_4$. However, the palladium-catalyzed cross-coupling of 5-tributylstannyl-4-(trifluoromethyl)pyrazole with aryl iodides required CuTC co-catalyst (CuI was ineffective) and LiCl additive due to the steric hindrance of the CF_3 group.

The palladium-catalyzed coupling of the 5-(thiomethyl)pyrazole with arylzinc iodides, benzylzinc chlorides, and alkylzinc bromides provided the corresponding 5-aryl/alkylpyrazole in moderate to high yields (Scheme 59) [161]. An indium-mediated palladium-catalyzed coupling method has also been reported for the preparation of the 5-aryl/heteroaryl pyrazole from 5-iodopyrazole (Scheme 60) [162].

Rault reported the preparation of 3-aryl-*1H*-pyrazoles via regioselective C-5 lithiation (Scheme 61) [163]. Although a convenient method for the preparation of 3-arylpyrazoles would be the Suzuki–Miyaura coupling of 3-halopyrazoles with aryl halides, the preparation of 3-halopyrazoles (also the essential precursor for the pyrazole-3-boronic acids and esters) generally requires harsh conditions, and

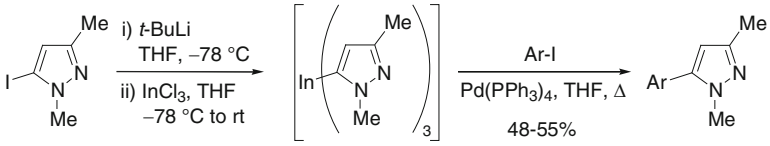


Scheme 58



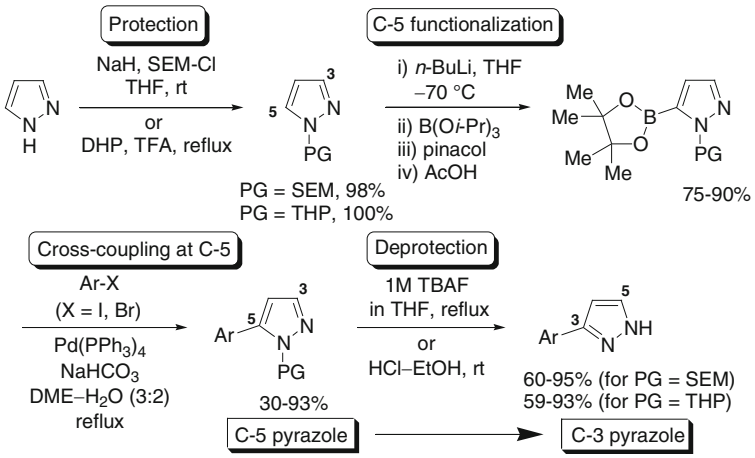
Conditions : 2.5 mol% $Pd(OAc)_2$, 5 mol% SPhos, THF.

Scheme 59



(Ar = Ph, 3-pyridyl, 2-pyridyl, 2-thienyl)

Scheme 60



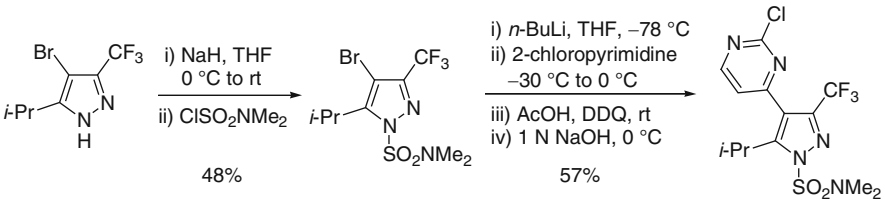
Scheme 61

therefore avoidable in most circumstances. According to this strategy, the aryl group of the targeted 3-arylpyrazole was first introduced at easily accessible C-5 position of pyrazole to afford the corresponding 5-arylpyrazole which then automatically converted into 3-arylpyrazole after *N*-deprotection due to pyrazole *NH*-tautomerization [138]. For this purpose, SEM and THP protecting groups (having oxygen atom in position to direct the lithiation α to *N*) were used for the regioselective installation of pinacol boronate at C-5. As designed, the Suzuki–Miyaura reaction and subsequent removal of SEM (using 1 M TBAF in refluxing THF) or THP (using ethanolic HCl at rt) provided the corresponding 3-arylpyrazoles.

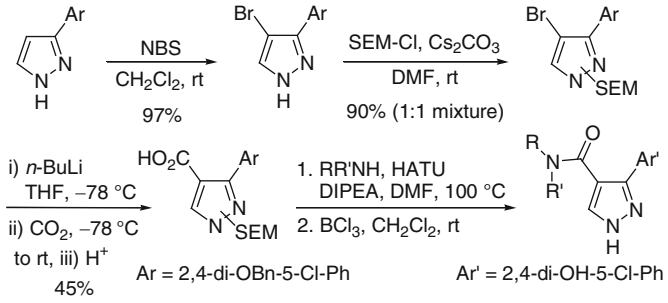
3.2 Metalation at C-4 of Pyrazoles

Metal–halogen exchange reaction of 4-halopyrazoles is the commonly used method for the preparation of 4-metalated pyrazole in situ. Using the lithium–halogen reaction of a 4-bromopyrazole, Cho reported the installation of a 2-chloropyrimidine scaffold at C-4 of pyrazole (Scheme 62) [154]. The prerequisite *N*-substituted 4-bromopyrazole was prepared from 4-bromo-1*H*-pyrazole via *N*-metalation using sodium hydride followed by quenching with *N*,*N*-dimethylsulfamoyl chloride.

Brough reported the synthesis of a few pyrazole-4-carboxamides using lithium–halogen exchange reaction as the key step (Scheme 63) [164]. The 4-lithiopyrazole was quenched with CO_2 to afford the desired carboxylic acid that was later converted to the targeted amides. The 4-bromopyrazole precursor was prepared (as 1:1 mixture *N*-1 and *N*-2 isomers) by regioselective bromination followed by SEM-protection.



Scheme 62

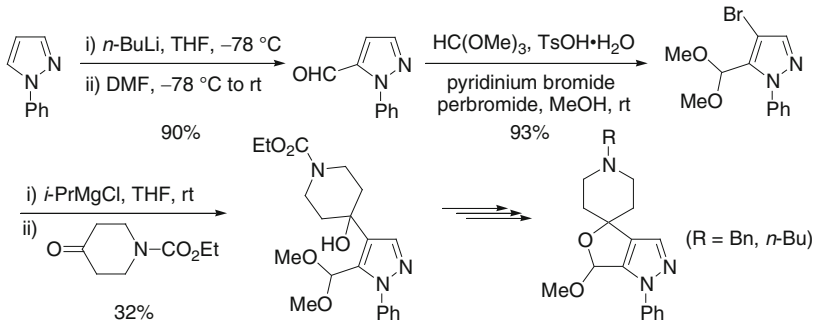


Scheme 63

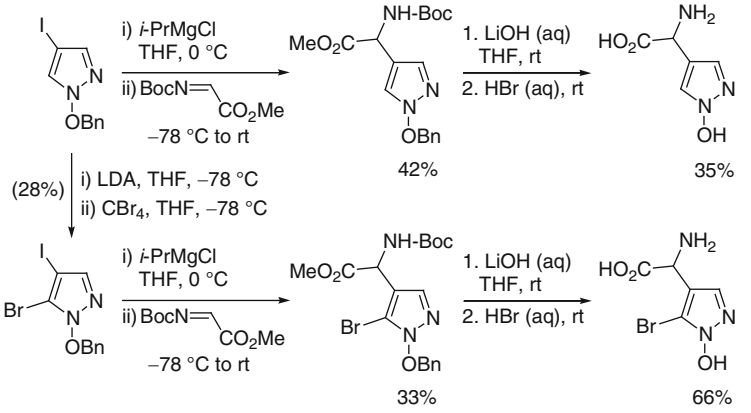
The metal–halogen exchange of a 4-bromopyrazole with isopropylmagnesium chloride generated the 4-magnesiated pyrazole which, upon quenching with *N*-carbethoxy-4-piperidone, afforded the corresponding 4-functionalized pyrazole (Scheme 64) [165]. The 4-bromopyrazole precursor was prepared from the *N*-phenylpyrazole by C-5 lithiation using *n*-butyllithium followed by addition of DMF and subsequent one-pot acetalization and bromination. Likewise, the metal–halogen exchange of *N*-benzyloxy-4-iodopyrazole using isopropylmagnesium chloride followed by quenching with an aldimine installed the amino-ester functionality at C-4 (Scheme 65) [135]. Hydrolysis of the ester functionality and Boc-deprotection provided the 4-pyrazolyl amino acid.

Treatment of *N*-benzyloxy-4-iodopyrazole with isopropylmagnesium chloride followed by the addition of *N*-carbethoxy-4-piperidone also afforded the corresponding alcohol adduct (Scheme 66) [166]. Reduction of the alcohol with TFA and trimethylsilane provided the 4-alkylpyrazole. Lithiation of the 4-substituted pyrazole using LDA followed by quenching with 2-naphthaldehyde and subsequent reduction gave the corresponding 5-(2-naphthylmethyl)pyrazole.

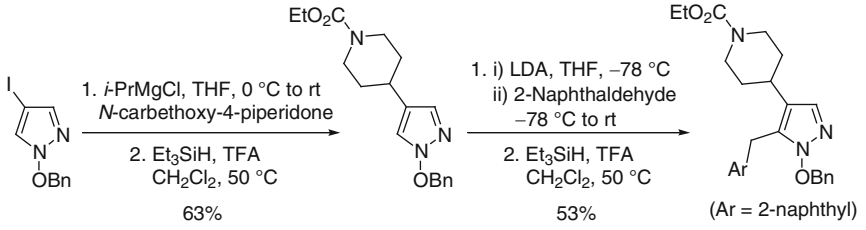
The C-4 iodination of a 5,5′-bipyrazole, prepared from *N*-benzyloxypyrazole via lithiation-transmetalation-Negishi coupling, afforded the 4,4′-diiodo-5,5′-bipyrazole (Scheme 67) [167]. Metal-halogen exchange of di-iodide using phenylmagnesium chloride generated the di-magnesium species in situ. Transmetalation of the magnesiated pyrazole using $ZnCl_2$ and subsequent Negishi coupling of the resulting organozinc with iodobenzene in the presence of $Pd(PPh_3)_4$ afforded the 4,4′-diphenyl-5,5′-bipyrazole. Alternatively, the Suzuki–Miyaura



Scheme 64



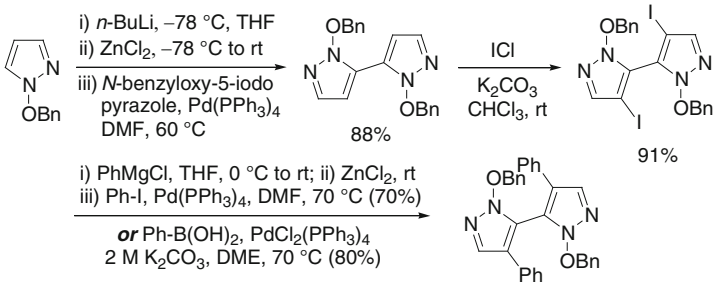
Scheme 65



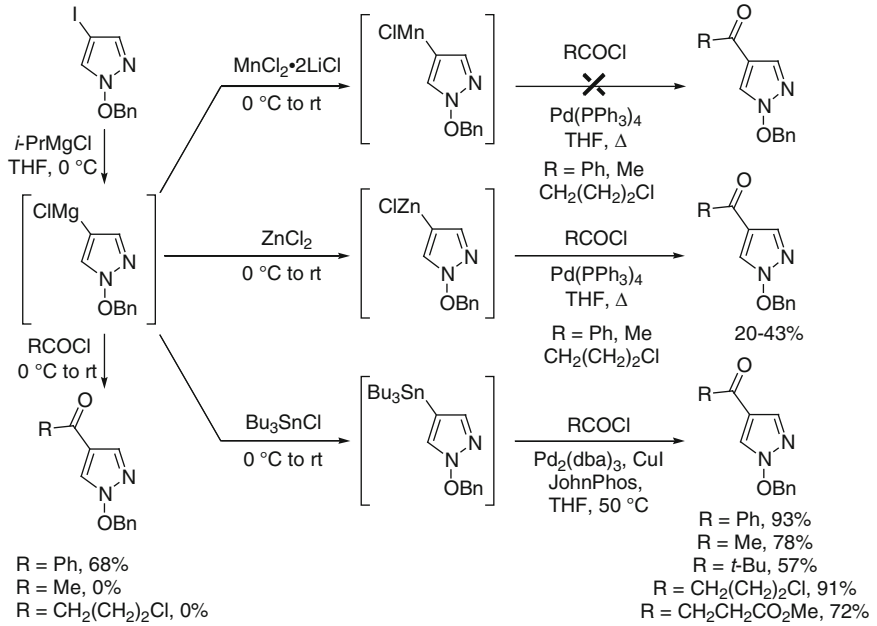
Scheme 66

coupling of the diiodide with phenylboronic acid gave the same 4,4′-diphenyl bipyrazole.

Reaction of the 4-magnesiated pyrazole, prepared by metal–halogen exchange reaction of *N*-benzyloxy-4-iodopyrazole using isopropylmagnesium chloride, with benzoyl chloride gave the corresponding 4-benzoylpyrazole (Scheme 68) [137].

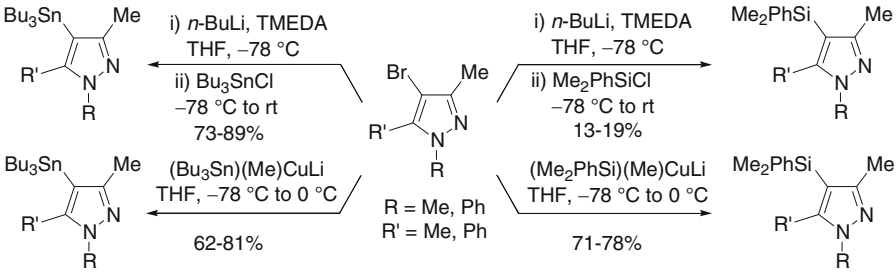


Scheme 67



Scheme 68

However, similar reaction with the aliphatic acid chlorides, such as acetyl chloride, was unsuccessful due to the abstraction of acidic α-proton from the acid chloride. Although transmetalation of 4-magnesiated pyrazole with $MnCl_2$ gave the corresponding organomanganese compound, it remained unreactive toward acid chlorides even under the Pd-assisted reaction conditions. On the other hand, transmetalation by $ZnCl_2$ and subsequent Pd-catalyzed coupling of resulting organozinc with representative acid chlorides afforded the desired products, albeit in low yields. Nonetheless, transmetalation by Bu_3SnCl followed by Pd-catalyzed coupling of the resulting organostannane with the acid chlorides in the presence of CuI and a bulky phosphine ligand provided efficient synthesis of 4-acylpyrazoles.

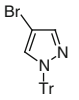
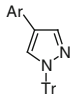
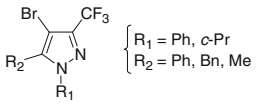
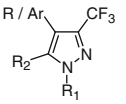
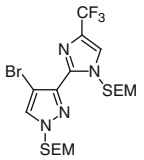
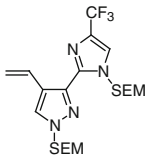
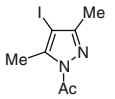
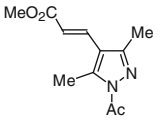
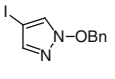
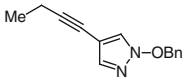


Scheme 69

The low temperature metal–halogen exchange reaction of 1,3,5-trisubstituted 4-bromopyrazole using *n*-BuLi–TMEDA followed by quenching with chlorostannanes gave the corresponding 4-stannylated pyrazoles in good yields (Scheme 69) [168]. However, similar reaction with chlorosilanes was not quite effective for the preparation of 4-silylated pyrazole. In contrast, the reaction of the 4-bromopyrazole with mixed lithium silyl- or stannylcuprates directly produced both the silanes and stannanes in good yields. The silylcupration was successfully carried out with lithium [dimethyl(phenyl)silyl]methylcuprate and even with bulky lithium [*tert*-butyl(diphenyl)silyl]methylcuprate. Likewise, lithium [tributylstannyl]methylcuprate was used for the stannylcupration. Reaction of these 4-silyl- or 4-stannylpyrazoles with suitable electrophiles, such as benzoyl chloride, afforded the corresponding 4-substituted pyrazoles. Similar carbodesilylation is also known for 5-trimethylsilylpyrazoles [169].

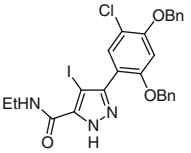
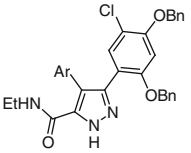
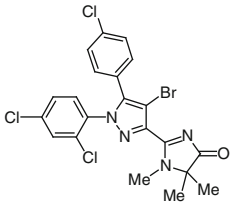
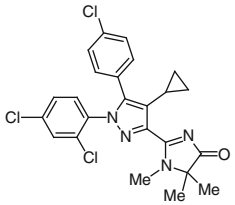
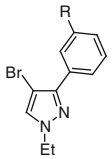
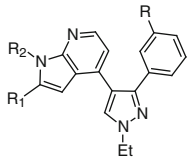
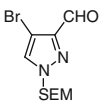
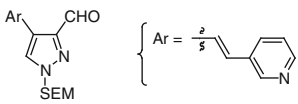
The Kumada–Corriu coupling of *N*-trityl-4-bromopyrazole with arylmagnesium bromides in the presence of 0.2 mol% $PdCl_2$(dppf) gave the corresponding 4-arylpyrazoles in excellent yields (Table 9, entry 1) [170]. Microwave-assisted Stille coupling of 3-trifluoromethyl substituted 4-bromopyrazoles with organostannanes in the presence of 5 mol% $Pd(PPh_3)_4$ also provided the 4-aryl- or 4-allylpyrazoles in high yields (entry 2) [171]. Likewise, coupling of 4-halopyrazoles with vinylstannanes gave the 4-vinylpyrazoles (entry 3) [172]. Kwok reported a preparative scale Heck reaction of *N*-acetyl-3,5-dimethyl-4-iodopyrazole with methyl acrylate in the presence of 1 mol% $Pd(OAc)_2$ and 2 mol% $P(OMe)_3$ to afford the desired product in nearly quantitative yield (entry 4) [173]. The Sonogashira coupling of *N*-benzyloxy-4-iodopyrazole and 1-butyne gave the 4-alkynylpyrazole (entry 5) [146]. Notably, the Suzuki–Miyaura coupling of unprotected 4-iodopyrazole with 3- and 4-formylboronic acids using 5 mol% $PdCl_2$(dppf) provided the corresponding products in good yields (entry 6) [174]. Similar coupling of *N*-benzyl-4-bromopyrazole with phenylboronic acid in the presence of $Pd(OAc)_2$ and SPhos (Pd–ligand ratio: 1:2.5) afforded the 4-phenylpyrazole in almost quantitative yield (entry 7) [175]. Due to partial loss of boronic acid by competitive protodeboronation, excess boronic acid was typically used in the Suzuki–Miyaura reaction to ensure complete consumption of bromopyrazole. The microwave-assisted Pd-catalyzed cross-coupling of a fully substituted 4-bromopyrazole with cyclopropylboronic acid

Table 9 C-4 Functionalization of pyrazoles via metalation

Entry	Pyrazole, Conditions	Product, Yields
1		
	Ar–MgBr $PdCl_2$(dppf), THF, reflux	Ar = Ph, 99% Ar = 4-OMe-Ph, 92% Ar = 2-OMe-Ph, 70% Ar = 4-OMOM-Ph, 86% Ar = 2-thienyl, 76%
2		
	R/Ar-$SnBu_3$, $Pd(PPh_3)_4$ MeCN, 180°, CMW	75–98% (Ar = Ph, 4-OMe-Ph) 80–97% (R = allyl)
3		
	(vinyl)$SnBu_3$ $Pd(PPh_3)_4$, DMF, 72°C	76%
4		
	methyl acrylate $Pd(OAc)_2$, $P(OMe)_3$ Et_3N, DMF, 90°C, 1 h	99%
5		
	1-butyne, $Pd(PPh_3)_4$ CuI, $K_3PO_4{\cdot}2H_2O$ DMF, −40°C to rt	86%

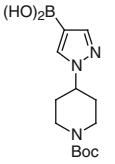
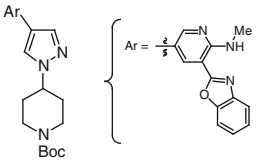
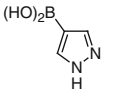
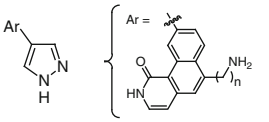
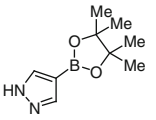
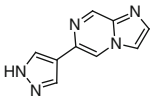
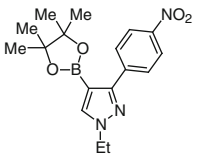
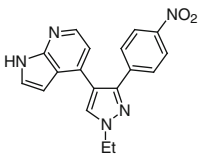
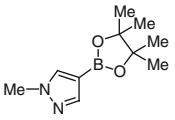
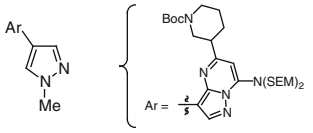
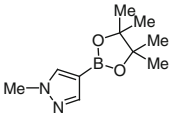
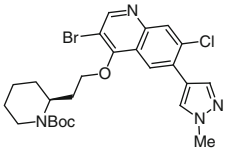
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Table 9 (continued)

Entry	Pyrazole, Conditions	Product, Yields
6		
	$Ar\text{-}B(OH)_2$, $PdCl_2(dppf)$ K_2CO_3, THF–H_2O (10:1) 160°C, MW, 10 min	Ar = 3-CHO-Ph, 71% Ar = 4-CHO-Ph, 68%
7		
	$PhB(OH)_2$, $Pd(OAc)_2$ SPhos, K_3PO_4 toluene, 100°C, 24 h	95%
8		
	c-Pr-$B(OH)_2$ K_2CO_3, $Pd(PPh_3)_4$ aq toluene, MW, 80°C, 2 h	35%
9		
	Ar-B(Pin), $Pd(PPh_3)_4$ aq Na_2CO_3, DME 120°C, MW, 1 h	R = NO_2, R_1 = H, R_2 = Ts: 88% R = NH_2, R_1 = CO_2Et, R_2 = H: 17%
10		
	$ArB(OH)_2$ $PdCl_2(dppf)\cdot CH_2Cl_2$ aq Na_2CO_3, dioxane, 120°C	72%

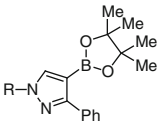
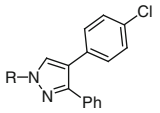
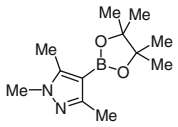
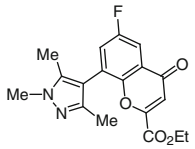
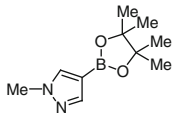
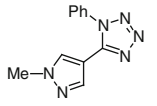
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Table 9 (continued)

Entry	Pyrazole, Conditions	Product, Yields
11		
	Ar–Br, $PdCl_2(PPh_3)_2$, aq Na_2CO_3, dioxane, reflux	91%
12		
	Ar–Br, $Pd(PPh_3)_4$ Na_2CO_3, DMF, 130°C	60–63% ($n = 2, 3$)
13		
	Ar–Br, $Pd(PPh_3)_4$ Na_2CO_3, MeCN–H_2O 150°C, MW, 20 min	73%
14		
	Ar–Br, $Pd(PPh_3)_4$ aq K_2CO_3, dioxane, 100°C	80%
15		
	Ar–I, $PdCl_2(dppf)$ K_3PO_4, DME, Δ	81%
16		
	Ar–I, $PdCl_2(dppf)$ aq Cs_2CO_3, THF 90°C, MW, 30 min	70%

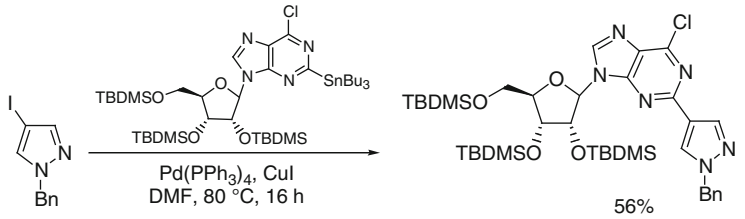
(continued)

Table 9 (continued)

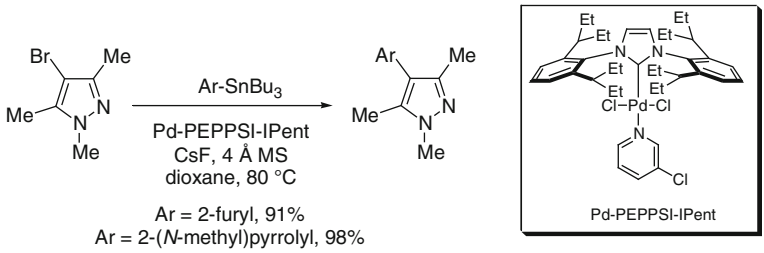
Entry	Pyrazole, Conditions	Product, Yields
17	 4-bromochlorobenzene $PdCl_2(dppf)$, K_3PO_4 dioxane, 85°C	 R = Ph, 88% R = 4-OMe-Ph, 83% R = 4-NO_2-Ph, 75%
18	 Ar–Br, $PdCl_2(PPh_3)_2$ K_2CO_3 DME-H_2O-EtOH (7:3:2) 90°C, 16 h	 58%
19	 Ar–Cl, $Pd(OAc)_2$, XPhos K_2CO_3, *n*-BuOH–H_2O (3:1) 150°C, MW, 30 min	 44%

also produced the desired product, albeit in low yield (entry 8) [176, 177]. The Suzuki–Miyaura cross-coupling of a 1,3-disubstituted 4-bromopyrazole with azaindole-derived boronic esters afforded the corresponding products; however, the yields were significantly dependent on the reactivity of the coupling partners (entry 9) [178]. Likewise, the Pd-catalyzed coupling of the pyrazole-4-boronic acids and esters with various aryl/heteroaryl iodides and bromides gave the corresponding 4-aryl/heteroaryl pyrazoles (entries 10–18) [172, 179–187]. Notably, the coupling of *N*-methylpyrazole-4-boronic acid pinacol ester with 5-chloro-1-phenyltetrazole in the presence of 5 mol% Pd catalyst, 10 mol% XPhos and K_2CO_3 afforded the corresponding product in 44% yield (entry 19) [188].

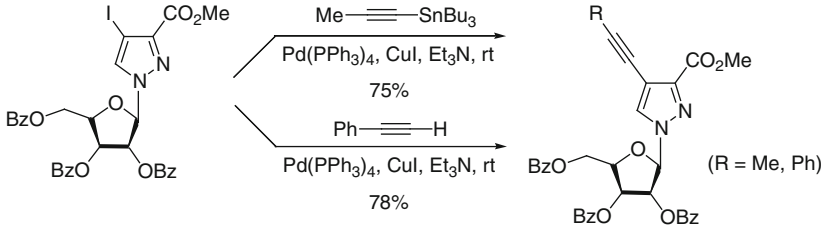
Using copper(I) iodide as a co-catalyst along with catalytic $Pd(PPh_3)_4$, Elzein reported the Stille coupling of *N*-benzyl-4-iodopyrazole with 4-chloro-2-stannyladenosine (Scheme 70) [189]. In general, copper(I) salts facilitate the Stille coupling involving sterically congested organostannanes [190]. Organ reported the Stille coupling of 4-bromo-1,3,5-trimethylpyrazole with representative organostannanes in the presence of 4 mol% Pd-PEPPSI-IPent precatalyst and CsF (2 eq) (Scheme 71) [191]. The reactions of *N*-(*β*-D-ribofuranosyl) 3-carbomethoxy-4-iodopyrazole with tributyl



Scheme 70



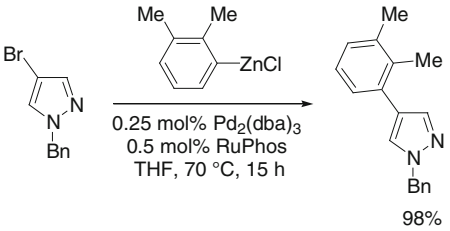
Scheme 71



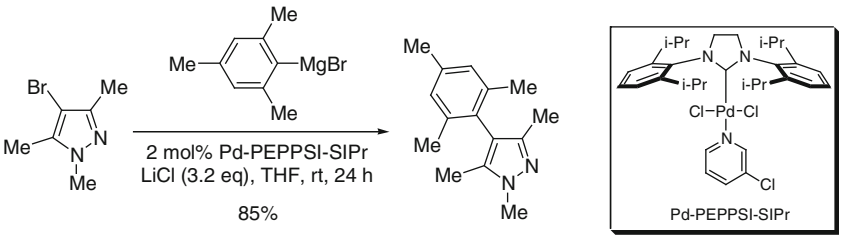
Scheme 72

(1-propynyl)tin and phenyl acetylene in the presence of catalytic $Pd(PPh_3)_4$–CuI introduced the alkynes at C-4 (Scheme 72) [192].

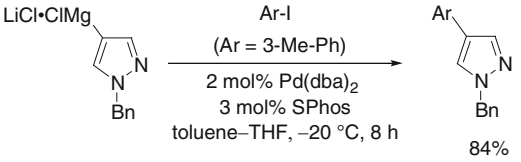
The Negishi coupling of *N*-benzyl-4-bromopyrazole with 2,3-dimethylphenylzinc chloride with an extremely low catalyst loading was reported by Buchwald (Scheme 73) [193]. In fact, 4-arylpyrazole was obtained in nearly quantitative yield in the presence of 0.25 mol% $Pd_2(dba)_3$ and 0.5 mol% RuPhos. Using an *N*-heterocyclic carbene (NHC) ligand-based Pd-precatalyst, Organ reported the coupling of 4-bromopyrazole with mesitylmagnesium bromide at room temperature (Scheme 74) [194]. The highly substituted 4-(mesityl)pyrazole was obtained in excellent yield in the presence of air-stable PEPPSI-SIPr precatalyst and LiCl. [PEPPSI: *P*yridine-*E*nhanced *P*recatalyst *P*reparation *S*tabilization and *I*nitiation].



Scheme 73



Scheme 74

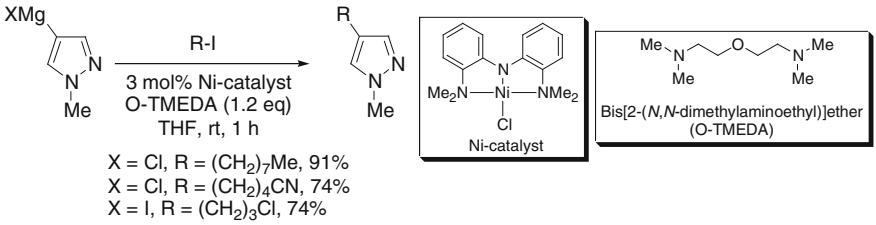


Scheme 75

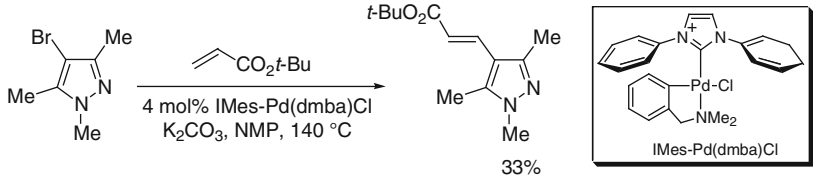
Buchwald reported a Pd-catalyzed Kumada–Corriu cross-coupling protocol where benzyl protected (4-pyrazolyl)magnesium chloride was treated with a pre-mixed solution of 3-iodotoluene, $Pd(dba)_2$, and SPhos in toluene to furnish the corresponding 4-arylpyrazole (Scheme 75) [195]. The Knochel-type Grignard reagent was prepared in situ by the magnesiation of the corresponding 4-iodopyrazole using 1 M *i*-PrMgCl·LiCl in THF at 0°C.

Using a nickel pincer complex, Hu reported the Kumada–Corriu coupling of *N*-protected (4-pyrazolyl)magnesium halides with alkyl iodides (Scheme 76) [196, 197]. Thus, the room-temperature coupling of (4-pyrazolyl)magnesium halide with excess alkyl iodides (5 eq) in the presence of Ni-catalyst and O-TMEDA additive (stabilizes the Grignard reagents and prevents homocoupling) produced the corresponding 4-alkylpyrazoles in high yields.

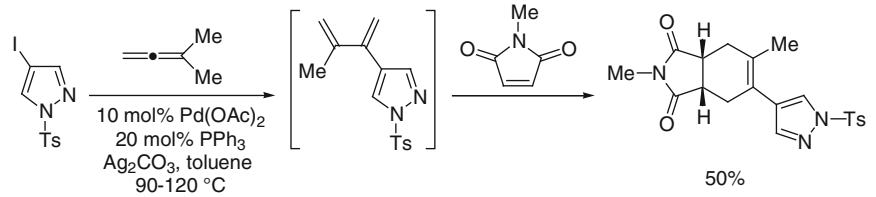
Ying reported the Heck reaction of 4-bromo-1,3,5-trimethylpyrazole with *tert*-butyl acrylate using a NHC-palladacycle (Scheme 77) [198]. The desired product was isolated in 33% yield along with 49% of unreacted bromide. Of note,



Scheme 76



Scheme 77

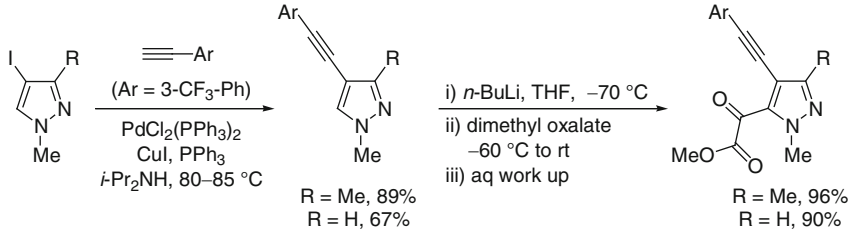


Scheme 78

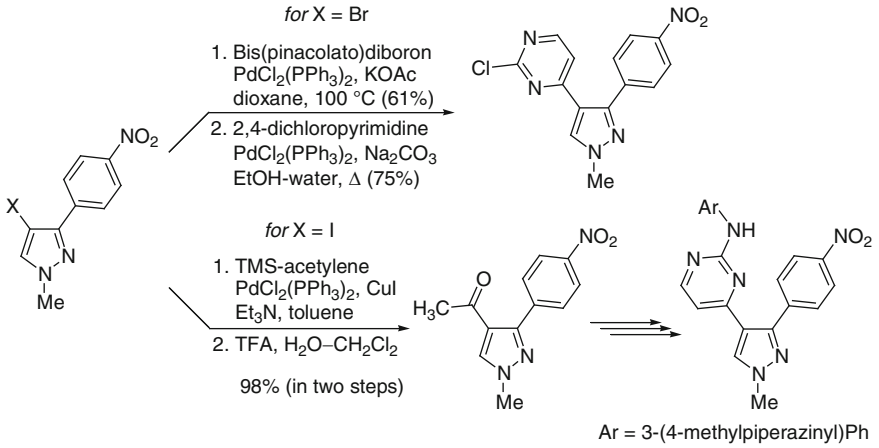
the air-stable Pd-catalyst was prepared in 90% yield (~95 g scale) using a one-pot three-component coupling of commercially available NHC-precursor IMes·HCl (IMes = 1,3-dimesitylimidazolyl-2-ylidene), dimethylbenzylamine (dmba), and $PdCl_2$ in the presence of K_2CO_3. Grigg reported a novel three-component reaction in which the initial Heck product from *N*-tosyl-4-iodopyrazole and dimethylallene was intercepted in situ by *N*-methylmaleimide to provide the Diels–Alder adduct in 50% yield (Scheme 78) [199].

Craig reported the Sonogashira coupling of 1,3-dimethyl-4-iodopyrazole and *N*-methyl-4-iodopyrazole with an arylalkyne to afford the 4-alkynylpyrazoles in 89% (12 g scale) and 67% (44 g scale) yields, respectively (Scheme 79) [200]. These *N*-protected 4-alkynylpyrazoles were further functionalized at C-5 via low-temperature lithiation followed by coupling with dimethyl oxalate.

Ralph reported the synthesis of a pyrazole-4-boronic acid pinacol ester from the corresponding 4-bromopyrazole using bis(pinacolato)diboron (Scheme 80) [57]. The boronate was subsequently used in the Suzuki–Miyaura coupling with 2,4-dichloropyrimidine. The Sonogashira reaction of an analogous 4-iodopyrazole



Scheme 79



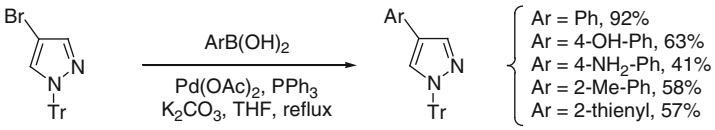
Scheme 80

with TMS-acetylene in the presence of catalytic $PdCl_2(PPh_3)_2$–CuI produced the 4-alkynylpyrazole. Acidic hydrolysis of the alkyne readily afforded the 4-acetylpyrazole.

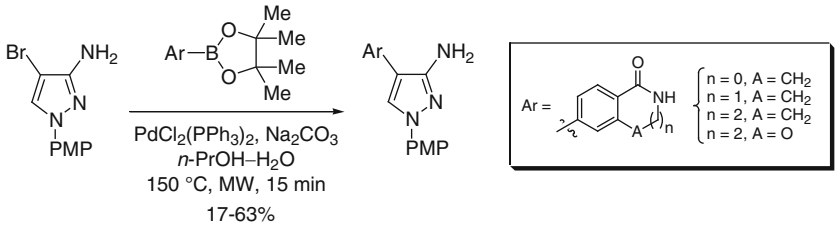
The Suzuki–Miyaura coupling of *N*-trityl-4-bromopyrazole with various arylboronic acids provided the corresponding 4-arylpyrazoles (Scheme 81) [201]. Similar microwave-assisted Pd-catalyzed coupling of *N*-protected 3-amino-4-bromopyrazole with arylboronates also afforded the 4-arylated pyrazoles (Scheme 82) [202].

A large scale Suzuki–Miyaura reaction of SEM-protected 6-chlorodeazapurine (~3.6 kg scale) with EE-protected pyrazole-4-boronic ester was reported by Lin where the desired product was isolated in 82% yield after the in situ hydrolysis (Scheme 83) [203]. The reaction was conducted using a slight excess of pinacol boronate in the presence of 0.3 mol% Pd-catalyst. The coupling of pyrazole-4-boronate with POM-protected 6-chlorodeazapurine followed by EE-deprotection also provided the 4-arylpyrazole. (EE = ethoxyethyl, POM = pivaloyloxymethyl).

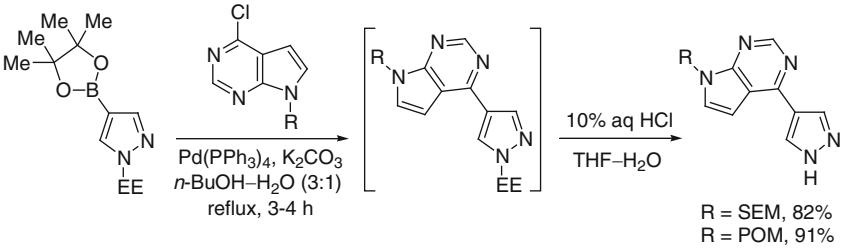
The synthesis of sterically hindered 4-(2,6-dimethoxyphenyl)-1,3,5-trimethyl-pyrazole was reported by Buchwald using the palladium-catalyzed coupling of



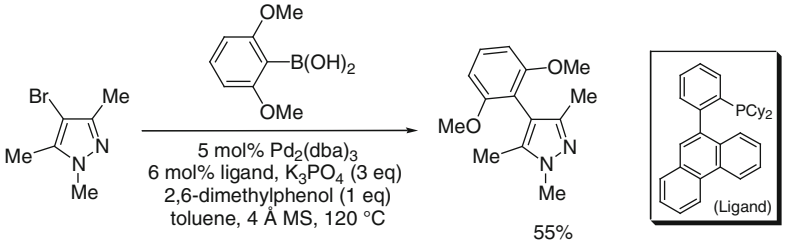
Scheme 81



Scheme 82

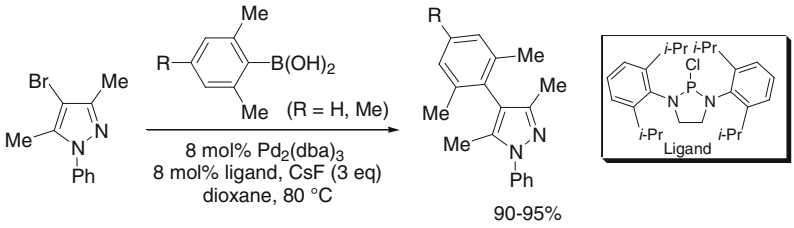


Scheme 83

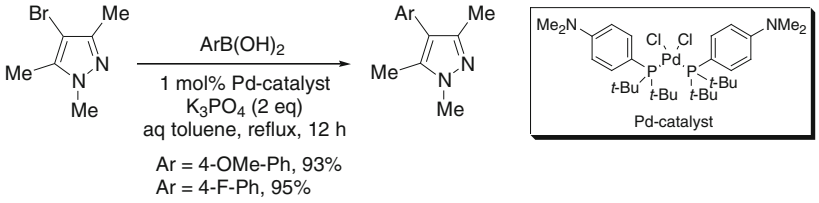


Scheme 84

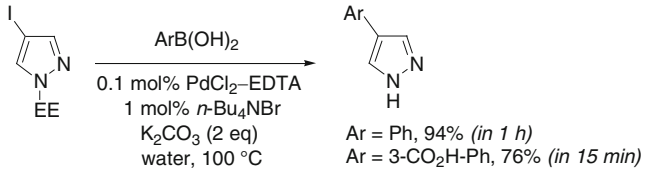
4-bromo-1,3,5-trimethylpyrazole with arylboronic acid (Scheme 84) [204]. Ackermann also reported efficient coupling of 4-bromo-3,5-dimethyl-1-phenylpyrazole with *ortho*-substituted boronic acids using a diaminochlorophosphine ligand along with $Pd_2(dba)_3$ and CsF to afford the synthetically challenging tetra-*ortho*-substituted biaryls (Scheme 85) [205].



Scheme 85



Scheme 86

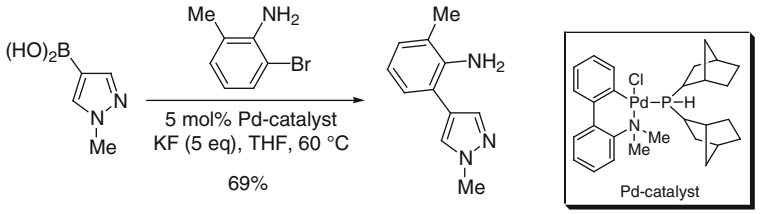


Scheme 87

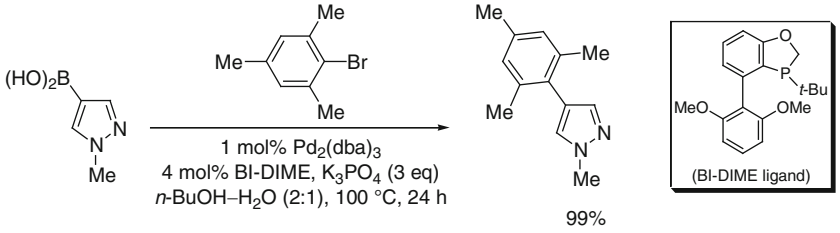
Guram reported the coupling of 4-bromo-1,3,5-trimethylpyrazole with arylboronic acids using 1 mol% $PdCl_2\{(P\textit{t}\text{-}Bu_2)\text{-}(\textit{p}\text{-}NMe_2\text{-}Ph)\}_2$ catalyst (Scheme 86) [206, 207]. Both electron-rich and electron-deficient arylboronic acids gave nearly quantitative yields of the corresponding products. Using Pd-EDTA catalyst, Bumagin reported efficient cross-coupling of 4-iodopyrazole with arylboronic acids in water (Scheme 87) [208].

Liu reported the coupling of *N*-protected pyrazole-4-boronic acid with 2-bromo-4-methylaniline using air-stable chloro(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II) (Scheme 88) [209]. Tang reported the Pd-catalyzed coupling of *N*-methylpyrazole-4-boronic acid with sterically hindered 2-bromomesitylene using an air-stable and conformationally rigid biarylphosphine ligand containing a 2,3-dihydrobenzo[*d*][1,3]oxaphosphole framework (Scheme 89) [210].

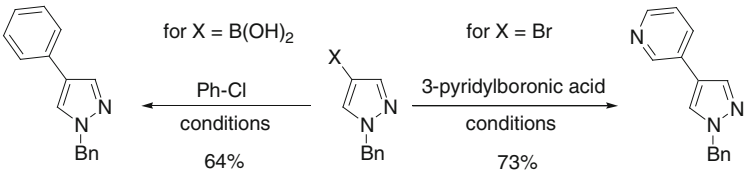
Fu reported the Suzuki–Miyaura cross-coupling of *N*-benzylpyrazole-4-boronic acid with chlorobenzene in the presence of $Pd_2(dba)_3$ and PCy_3 (Scheme 90) [211]. However, unprotected pyrazole was not suitable for this catalytic system and a trace



Scheme 88



Scheme 89

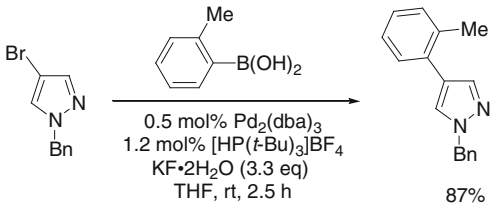


Conditions: 1 mol% $Pd_2(dba)_3$, PCy_3 (2.4 eq), aq K_3PO_4 (1.7 eq), dioxane, 100 °C, 18 h.

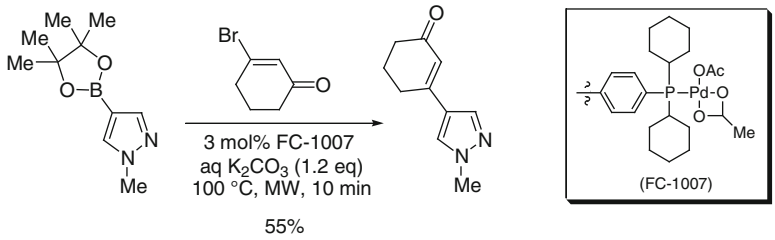
Scheme 90

amount of product was obtained from the similar coupling using *N*-unprotected pyrazole-4-boronic acid. Fu also reported cross-coupling of *N*-benzyl-4-bromopyrazole with 2-methylphenylboronic acid using a commercially available pre-made mixture of $Pd_2(dba)_3$/[$HP(t\text{-}Bu)_3$]BF_4 and 3.3 eq $KF{\cdot}2H_2O$ (Scheme 91) [212]. This pre-catalyst [Pd:P(*t*-Bu)$_3$ ratio 1:1.2] served as a convenient one-component source of palladium, and P(*t*-Bu)$_3$ and $KF{\cdot}2H_2O$ was an inexpensive alternative to anhydrous KF (a small amount of water often promotes Suzuki–Miyaura coupling).

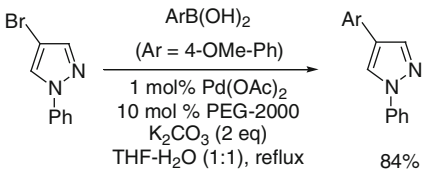
Using FC-1007 [*F*ibre*C*at: polyethylene supported palladium catalyst, Pd$(OAc)_2$/PCy_2-fibre] in aqueous K_2CO_3, Gilbertson reported the coupling of *N*-methylpyrazole-4-boronic ester with a bromoenone under microwave irradiation (Scheme 92) [213]. In general, these supported/anchored palladium catalysts (e.g., FC-1001, FC-1007, FC-1027, FC-1032) are known to provide cleaner reaction profile.



Scheme 91

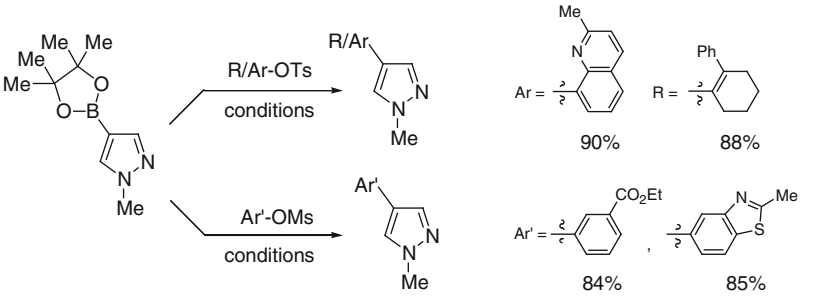


Scheme 92

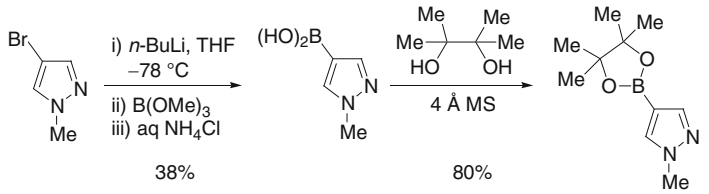


Scheme 93

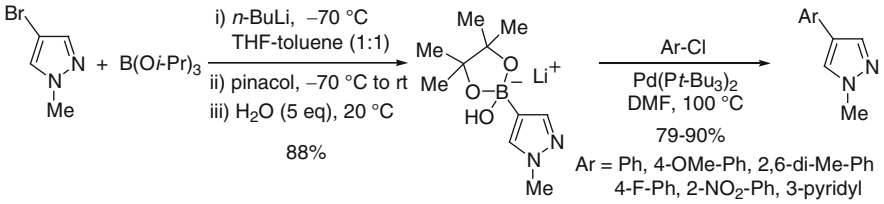
Razler reported a "ligand-free" Suzuki–Miyaura coupling of 4-bromo-1-phenylpyrazole using $Pd(OAc)_2$, PEG-2000 (polyethylene glycol 2000) and K_2CO_3 (Scheme 93) [214]. The product was isolated after dilution of the reaction mixture with ethyl acetate followed by a brine wash. Presumably, PEG phase transfer complex served the same purpose as the phosphine ligand by reducing Pd (II) to Pd(0). The formation of palladium nanoparticles with high catalytic activity was also reported for systems involving PEG solvents. However, this coupling protocol involving catalytic PEG was considerably superior to the reactions where PEG was used as a solvent mostly due to difficulty in isolating the biaryl products as well as in stirring/monitoring the reactions. Although PEG-12000 and PEG-20000 were slightly more effective than PEG-2000 for these coupling reactions, product isolation was much easier from the reaction mixture with PEG-2000. In addition, low molecular weight and lower cost of PEG-2000 offer considerable advantages over higher PEG systems in preparative scale reactions.



Scheme 94



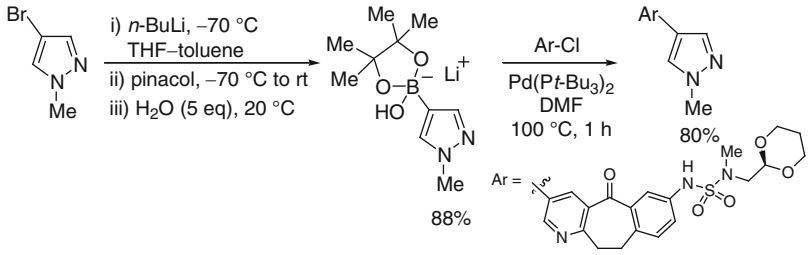
Scheme 95



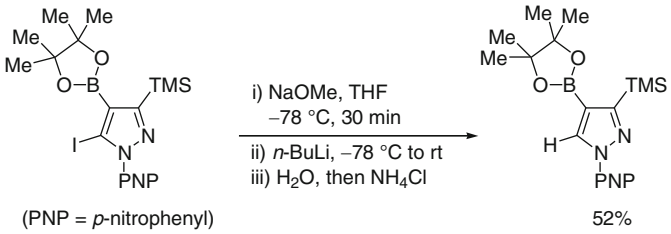
Scheme 96

The reaction of *N*-methylpyrazole-4-boronic ester with aryl (or vinyl) tosylates and mesylates in the presence of $Pd(OAc)_2$, BrettPhos, and K_3PO_4 afforded the corresponding 4-aryl- (or 4-vinyl)pyrazoles (Scheme 94) [215].

Mullens reported an improved synthesis of pyrazole-4-boronic acid pinacol ester and its lithium hydroxy "ate" complex [216]. As shown in Scheme 95, the conventional synthesis of these pyrazole-4-boronates typically involves a two-step procedure: (a) a low temperature lithium–halogen exchange of 4-bromopyrazole to generate 4-lithiopyrazole followed by quenching with trimethylborate and subsequent NH_4Cl workup to afford the boronic acid; and (b) treatment of boronic acid with pinacol in the presence of 4 Å molecular sieves to yield the boronic ester. However, Mullen used an in situ quench procedure involving the addition of *n*-butyllithium to a mixture of aryl bromide and triisopropylborate followed by the sequential addition of pinacol and water (Scheme 96). Notably, the addition of



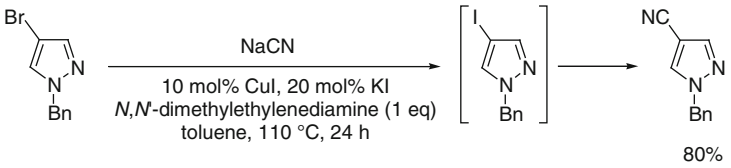
Scheme 97



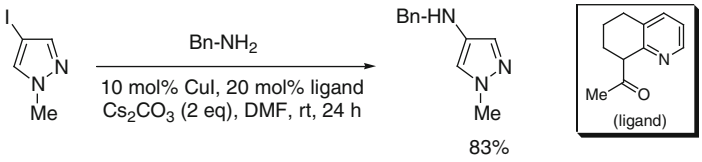
Scheme 98

5 eq of water is critical for the preparation of this lithium hydroxy "ate" complex. This one-pot procedure of synthesizing bench-stable "ate" complex is scalable to multi-kilogram quantities. Furthermore, the lithium hydroxy "ate" complex itself successfully participated in the Suzuki–Miyaura cross-coupling reactions without any external base, such as K_2CO_3, Na_2CO_3, K_3PO_4 or KF. In addition, compared to the analogous pinacol boronates, this "ate" complex showed superior performance in the coupling with aryl chlorides. In fact, more than 10 times enhancement in the reaction rate can be observed; thus, the reactions were complete in less than 2 h in most cases. Of note, neutralization of lithium hydroxy ate complex gave the pyrazole-4-boronic acid pinacol ester, thus affording a synthesis of the pyrazole-4-boronate with 70% overall yield from *N*-methyl-4-bromopyrazole compared to the 30% overall yield for conventional two-step procedure.

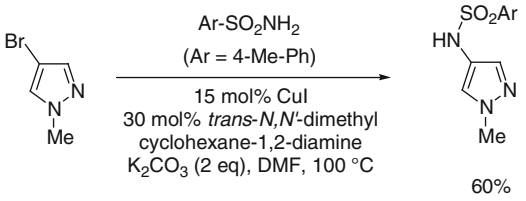
Stewart reported the coupling of the pyrazole "ate" complex (2.7 kg scale) with a heteroaryl chloride in the presence of 0.6 mol% $Pd(Pt\text{-}Bu_3)_2$ (Scheme 97) [217]. The desired product was obtained in 80% yield in an hour. Utilizing the chemistry of pyrazole "ate" complex, Harrity reported the lithium–halogen exchange reaction of a PNP-protected 5-iodopyrazole, bearing a boronic ester functionality at C-4 (Scheme 98) [218]. The pinacol boronate was first converted to the "ate" complex in situ by the addition of solid sodium methoxide at −78°C. Thereafter, lithium–halogen exchange using *n*-butyllithium and subsequent neutralization of the reaction mixture gave the desired product, without affecting the potentially labile boronic ester functionality at C-4.



Scheme 99



Scheme 100

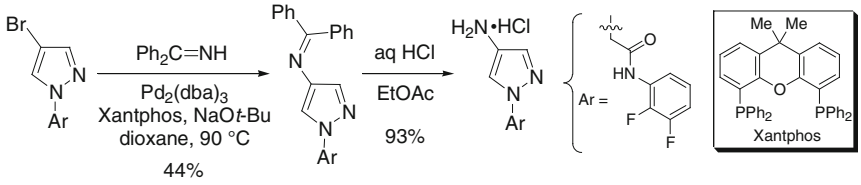


Scheme 101

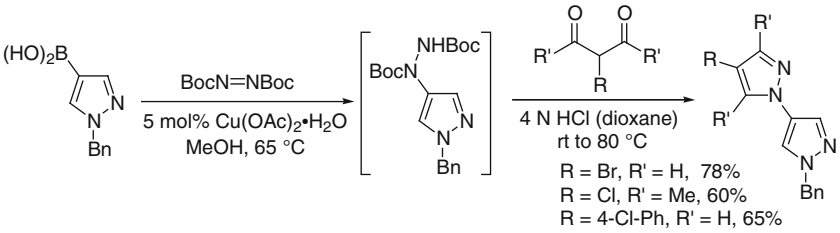
The copper-catalyzed cyanation of *N*-benzyl-4-bromopyrazole using sodium cyanide gave the 4-cyanopyrazole via the 4-iodopyrazole intermediate (Scheme 99) [219]. The rate of Br → I exchange was comparable to or exceeded the rate of cyanation of the iodo intermediate. Polar solvents such as DMF or sulfolane are not preferable as higher concentration of the dissolved cyanide in the reaction mixture strongly inhibits the essential Br → I exchange.

The Cu-catalyzed room temperature amination of *N*-methyl-4-iodopyrazole with benzylamine using 8-acetyl-5,6,7,8-tetrahydroquinoline ligand afforded the desired product in excellent yield (Scheme 100) [220]. The *β*-(2-pyridyl)ketone type ligand presumably provided the perfect bidentate angle at the chelating copper center that was crucial for the successful C–N bond-forming reaction. Likewise, copper-catalyzed coupling of 4-bromo-1-methylpyrazole with *p*-toluenesulfonamide provided the 4-(arylsulfonamido)pyrazole (Scheme 101) [221]. On the other hand, Pd-catalyzed cross-coupling of the *N*-protected 4-bromopyrazole with benzophenone imine followed by acidic hydrolysis gave the 4-aminopyrazole (Scheme 102) [222].

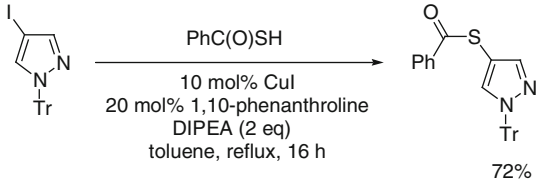
The copper-catalyzed reaction of *N*-benzylpyrazole-4-boronic acid with di-*tert* butylazodicarboxylate generated (4-pyrazolyl)hydrazine in situ which, in turn, produced the [1,4′]bipyrazolyls upon condensation with dicarbonyl compounds



Scheme 102



Scheme 103



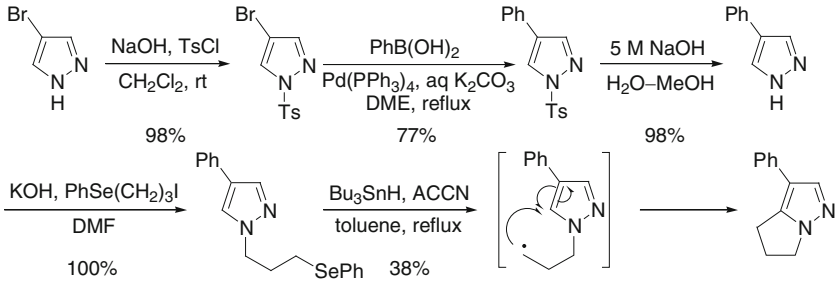
Scheme 104

(Scheme 103) [223]. Likewise, the copper-catalyzed coupling of *N*-trityl 4-iodopyrazole with thiobenzoic acid afforded the 4-substituted pyrazole (Scheme 104) [224].

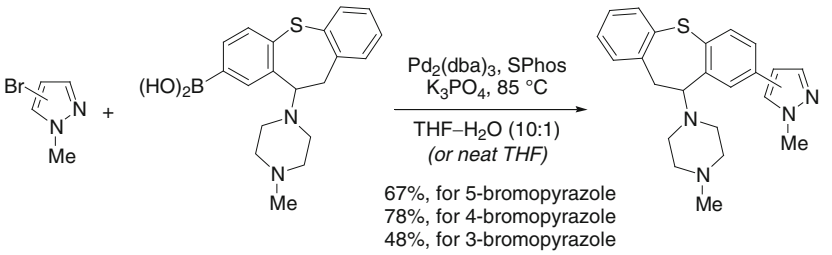
Bowman reported a short synthesis of withasomnine in which *N*-protection of 4-bromopyrazole followed by the Suzuki–Miyaura cross-coupling with phenylboronic acid gave *N*-tosyl-4-phenylpyrazole (Scheme 105) [225–227]. Tosyl removal followed by *N*-alkylation using KOH and $PhSe(CH_2)_3I$ and subsequent radical cyclization of the phenylselenyl derivative afforded withasomnine.

3.3 Metalation at C-3 of Pyrazoles

Metalation at C-3 position of *N*-1-substituted pyrazole is difficult due to the lone pair effect of the adjacent *N*-2 nitrogen [228]. Also, the preparations of 3-halopyrazoles by halogenation of pyrazoles generally require harsh conditions.



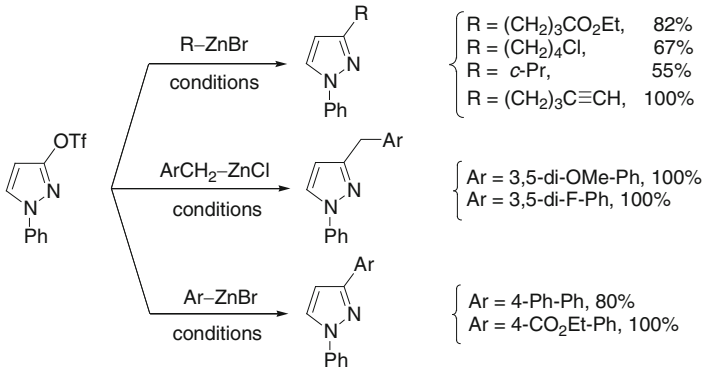
Scheme 105



Scheme 106

Furthermore, halogenation at C-3 of 4-unsubstituted pyrazole is difficult due to the preferential electrophilic attack at C-4. Historically, substitutions at C-3 have been achieved directly as a result of the cyclization of suitable precursors during the pyrazole ring-forming process. The relative difficulty of introducing substituents at C-3 is exemplified by the results reported for the Suzuki–Miyaura reactions of 5-, 4-, and 3-bromopyrazoles (Scheme 106) [229]. While the coupling of 5- and 4-bromopyrazoles with a dihydrodibenzothiepine boronic acid produced the corresponding products in 67–78% yields, only 48% yield was obtained for 3-bromopyrazole under similar conditions.

An efficient sp^2–sp^3 Negishi coupling procedure was reported by Zhang where functionalized alkyl groups were introduced at C-3 of pyrazole via Pd-catalyzed coupling of 3-[(trifluoromethyl)sulfonyl]pyrazoles with organozinc reagents (Scheme 107) [230]. These couplings are typically challenging due to the tendency of these triflates to hydrolyze, as well as the problem of β-hydride elimination from the alkyl fragments. Nonetheless, reaction of *N*-phenylpyrazole-3-triflate with excess alkylzinc reagents in the presence of catalytic $Pd(OAc)_2$ and XPhos afforded the corresponding 3-alkylpyrazoles. Although dppf, RuPhos, and SPhos were effective to a lesser extent than XPhos, electron-rich and bulky PCy_3 and P*t*-Bu_3 were completely ineffective for this transformation. Alkylzinc bromides bearing ester, alkyl chloride, alkyne and acetal functionalities were tolerated in this transformation. Moreover, use of analogous nonaflate provided relatively higher yields for the coupling in which low yields were encountered with the pyrazole-3-triflate



Scheme 107

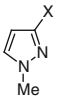
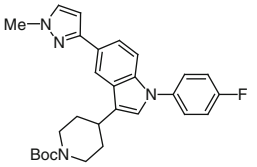
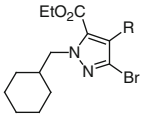
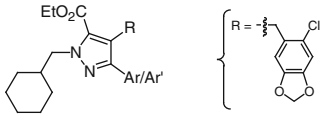
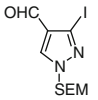
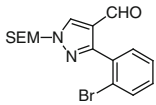
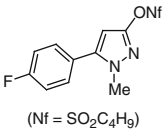
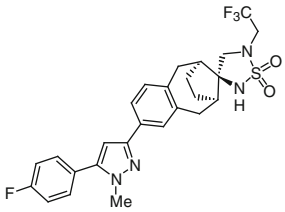
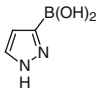
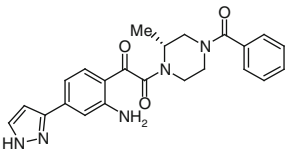
due to the better stability and higher reactivity of nonaflates compared to the triflates. Notably, this sp^2–sp^3 coupling protocol worked efficiently for the coupling of *N*-phenylpyrazole-3-triflate with both electron-rich and electron-deficient benzylzinc reagents. In addition, the sp^2–sp^2 couplings of *N*-phenylpyrazole-3-triflate with the phenylzinc bromides were also effective under these conditions.

Anderson reported the Negishi coupling of *N*-methyl-3-halopyrazoles with an organozinc to install an indolyl functionality at C-3 (Table 10, entry 1) [231]. Suzuki reported a "rapid" coupling protocol in which a large excess of (1-phenyl-3-pyrazolyl) tributylstannane was treated with iodomethane in the presence of 0.5 mol% of $Pd_2(dba)_3$, 16 eq P(*o*-tol)$_3$, CuBr (2 eq), and CsF (5 eq) for only 5 min to afford the corresponding 3-methylpyarzole in 94% yield (entry 2) [232]. Coupling of 3-bromopyrazole with organostannanes and boronic acids also gave the corresponding 3-substituted pyrazoles (entry 3) [233]. Likewise, the Suzuki–Miyaura coupling of a 3-iodopyrazole with 2-bromophenylboronic acid introduced a 2-bromophenyl scaffold at C-3 (entry 4) [234]. Coupling of a pyrazole nonaflate with an aryl boronate in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 also gave the corresponding 3-arylpyrazole (entry 5) [235]. Even the coupling of *unprotected* 3-pyrazolyl boronic acid with an aryl bromide was moderately successful (entry 6) [236]. A one-pot *N*-benzylation and Suzuki–Miyaura coupling of pyrazole-3-boronic ester is also reported for the synthesis of *N*-benzylated 3-aryl/heteroaryl pyrazoles (entry 7) [237].

Microwave-assisted double Sonogashira reaction of *N*-protected 3,4-diiodopyrazoles with excess alkyne in the presence of catalytic $PdCl_2(PPh_3)_2$ and CuI provided the corresponding 3,4-di-alkynylpyrazoles in excellent yields (Scheme 108) [238]. Of note, the bis-alkynyl pyrazoles can be converted to *2H*-indazoles via Bergman–Masamune cycloaromatization.

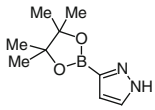
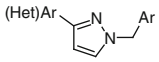
Ila and Junjappa reported nickel-catalyzed reaction of 3-(methylthio)pyrazole with alkyl/aryl Grignard reagents for C-3 functionalization (Scheme 109) [239]. This methodology is particularly useful for the regioselective synthesis of

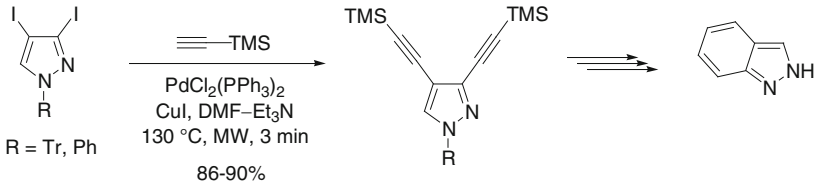
Table 10 C-3 Functionalization of pyrazoles via metalation

Entry	Pyrazole, Conditions	Product, Yields
1		
	Ar–ZnCl, $Pd(PPh_3)_4$, DMF, 80°C	(63% for X = I; 28% for X = Br)
2		
	CH_3I, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$ CuBr, CsF, NMP, 60°C, **5 min**	94%
3		
	$ArSnBu_3$, $Pd(PPh_3)_4$, toluene, Δ, 5 h **or** Ar′B(OH)$_2$, $Pd(PPh_3)_4$ K_3PO_4, DMF, Δ, 24 h	56–67% (Ar = 2-pyridyl, 3-pyridyl) 55–82% (Ar′ = 4-OMe-Ph, 2-furyl, 3-thienyl, 2-thienyl)
4		
	(2-Br)Ph-B(OH)$_2$, $Pd(PPh_3)_4$ K_2CO_3, DMF–H_2O, 80°C	75%
5		
	Ar−B(Npg), $Pd(PPh_3)_4$ Na_2CO_3, DMF, 100°C, 18 h (Npg = neopentylglycolato)	100%
6		
	Ar–Br, $Pd(PPh_3)_4$, aq Na_2CO_3 TBAB, toluene−EtOH (1:1), Δ	52%

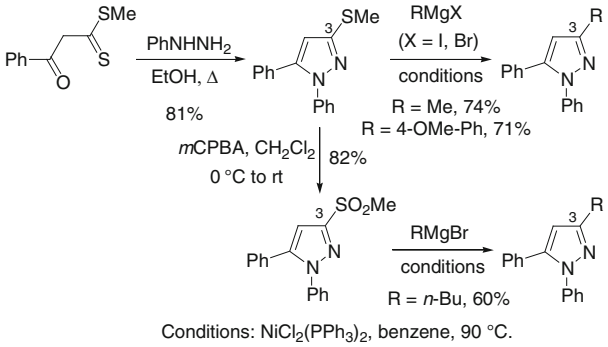
(continued)

Table 10 (continued)

Entry	Pyrazole, Conditions	Product, Yields
7		
	(i) $ArCH_2$–Br, Cs_2CO_3, MeCN, Δ (ii) (Het)Ar–Cl, $Pd(PPh_3)_4$, H_2O, Δ	27–49% Ar = 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph. (Het)Ar = 2-pyridyl, 4-pyrimidinyl.



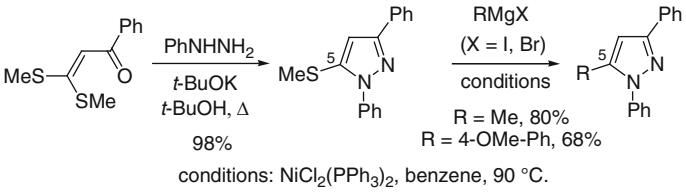
Scheme 108



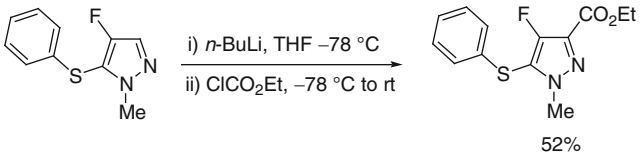
Scheme 109

differentially substituted pyrazoles. Similar coupling of 5-(methylthio)pyrazole and 5-(methylsulfonyl)pyrazole with representative alkyl/aryl Grignards also afforded the corresponding 5-substituted pyrazoles in high yields (Scheme 110).

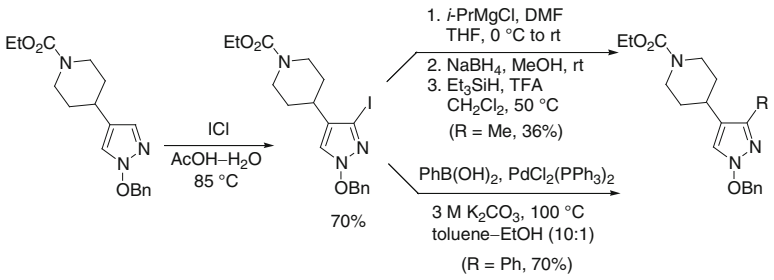
The C-3 lithiation of a fully substituted pyrazole using *n*-butyllithium followed by the addition of ethyl chloroformate introduced a carbethoxy group at C-3 (Scheme 111) [157]. Likewise, lithium halogen exchange of 3-iodopyrazole using isopropylmagnesium chloride followed by the addition of DMF and subsequent functional group manipulation afforded the 3-methylpyrazole (Scheme 112) [167]. On the other hand, the Suzuki–Miyaura coupling of the 3-iodopyrazole with phenylboronic acid gave the corresponding 3-phenylpyrazole.



Scheme 110



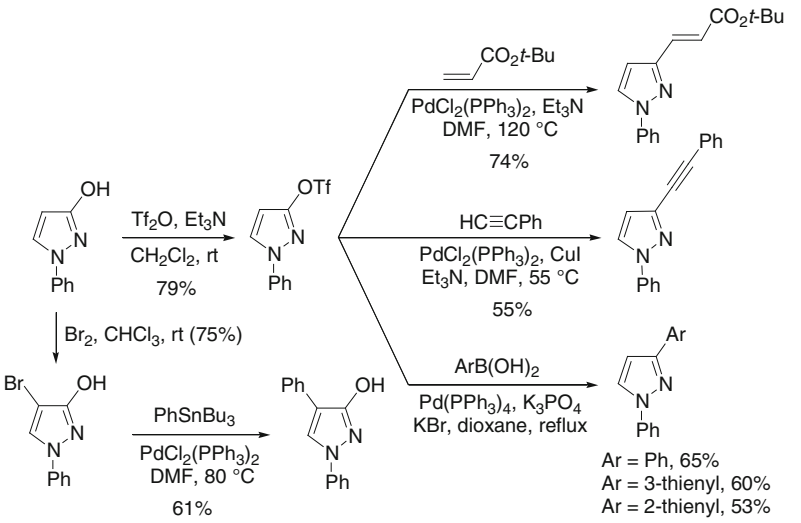
Scheme 111



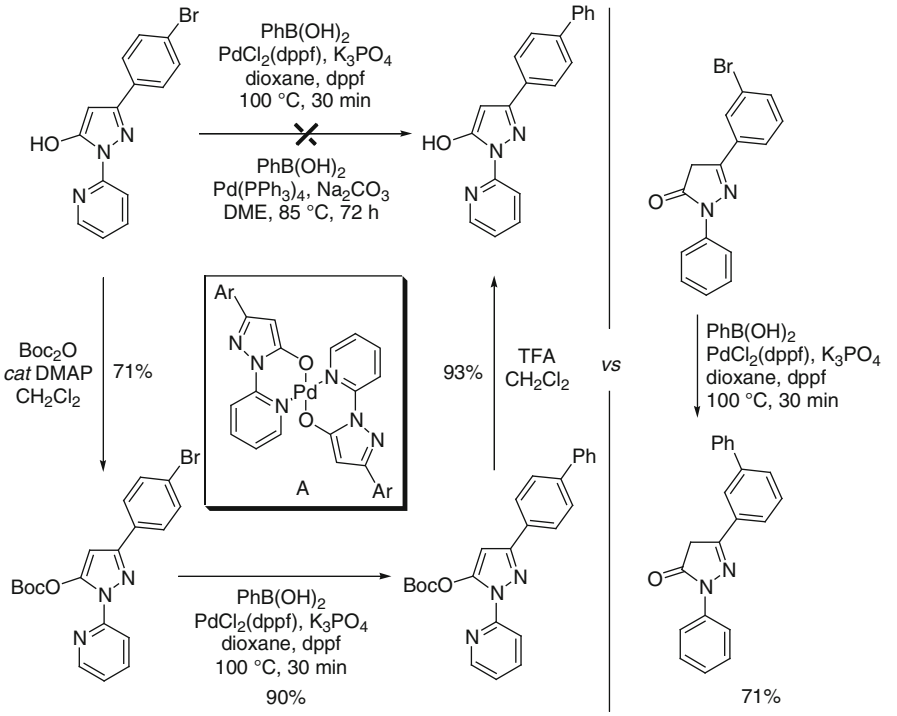
Scheme 112

Sackus reported the palladium-catalyzed coupling of pyrazole-3-triflate under the Heck, Sonogashira, and Suzuki-Miyaura coupling conditions (Scheme 113) [240]. Although 3-hydroxy-4-halopyrazole successfully participated in the Heck and Sonogashira reactions, the Suzuki–Miyaura coupling of 3-hydroxy-4-bromopyrazole with the arylboronic acids was unsuccessful. However, the Stille coupling of 3-hydroxy-4-bromopyrazole with tributylphenylstannane successfully provided 3-hydroxy-4-phenylpyrazole.

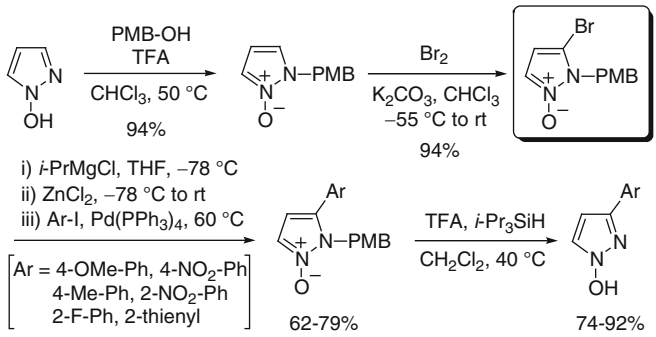
While studying the peripheral coupling of pyrazolone derivatives, Lee reported that the aryl bromide, bearing an *N*-(2-pyridyl)pyrazolone scaffold, did not participate in the Pd-catalyzed coupling with phenylboronic acid (Scheme 114) [241]. In contrast, similar coupling of an analogous aryl bromide, bearing *N*-phenylpyrazolone pendant, with phenylboronic acid furnished the desired product in 71% yield. In fact, NMR analysis indicated that *N*-(2-pyridyl)pyrazolone exists in its "enol" form whereas *N*-phenylpyrazolone stays in the "keto" form. The palladium catalyst presumably separated out from the desired catalytic cycle due to chelation with the *N*-(2-pyridyl)pyrazolone; thus, forming an inactive palladium species.



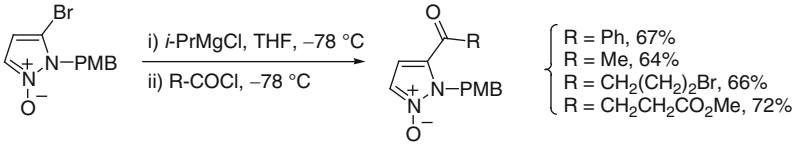
Scheme 113



Scheme 114



Scheme 115

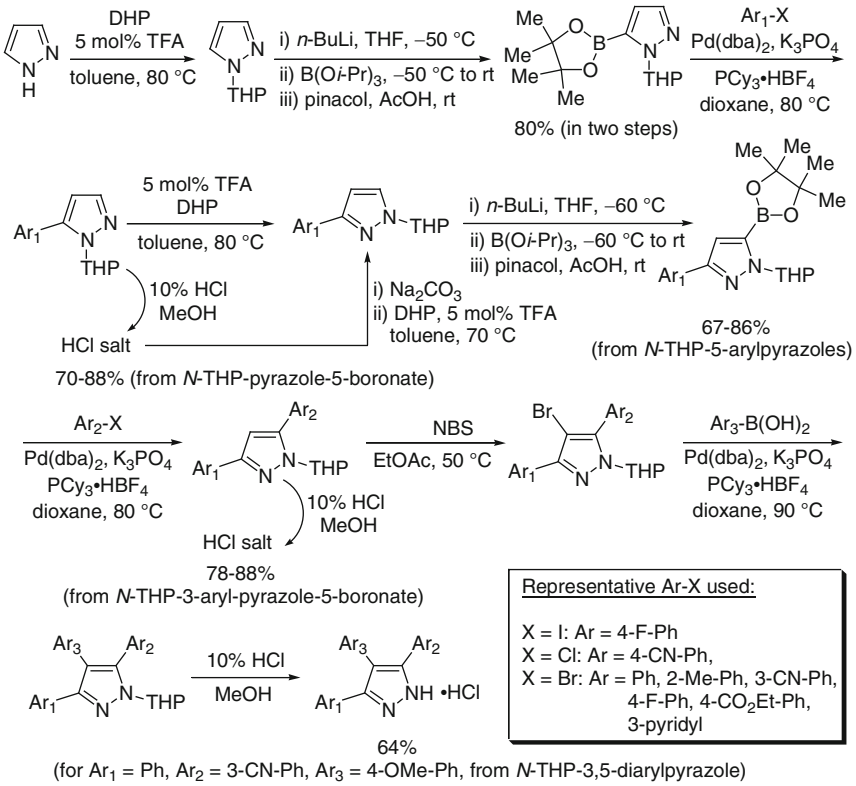


Scheme 116

Vedso reported the preparation of 3-aryl-1-hydroxypyrazoles via 3-metalated 2-PMB-substituted pyrazole-1-oxides (Scheme 115) [242]. First, the reaction of 1-hydroxypyrazole and 4-methoxybenzyl alcohol in the presence of TFA regioselectively afforded the *N*-2 alkylated pyrazole. Bromination of the resulting 2-PMB-pyrazole-1-oxide, now being activated toward the electrophilic attack at C-3, regioselectively furnished the corresponding 3-bromopyrazole. Metal–halogen exchange reaction of the 3-bromo-2-PMB-pyrazole-1-oxide using isopropylmagnesium chloride followed by transmetalation using $ZnCl_2$ and subsequent Pd-catalyzed coupling of the resulting organozinc with aryl iodides produced the corresponding 3-arylated pyrazole-1-oxides. Vedso also reported C-3 acylation of 3-bromo-2-PMB-pyrazole-1-oxide via a 3-magnesiated pyrazole intermediate (Scheme 116) [137]. Notably, acetyl chlorides bearing bromide and ester functionality successfully participated in the acylation reaction.

3.4 Sequential Multiple Metalation of Pyrazoles

McLaughlin reported a general synthesis of 3,4,5-trisubstituted pyrazoles by extending the Rault's approach for the synthesis of 3-arylpyrazoles (Scheme 117) [138, 163, 243]. The *N*-protecting THP group was used as a switchable *m*etal-*d*irecting *g*roup (MDG) to direct sequential lithiation at C-5 and C-3 positions. In this synthetic sequence, pyrazole-5-boronic ester was first prepared via the regioselective C-5 lithiation of THP-protected pyrazole and thereafter used in the Suzuki–Miyaura coupling with aryl halides to provide C-5-substituted

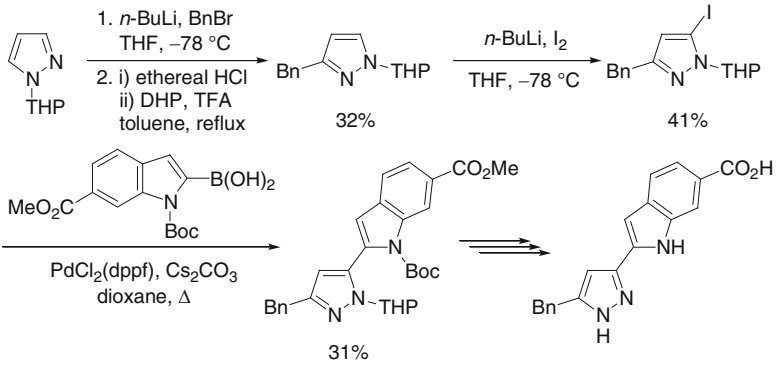


Scheme 117

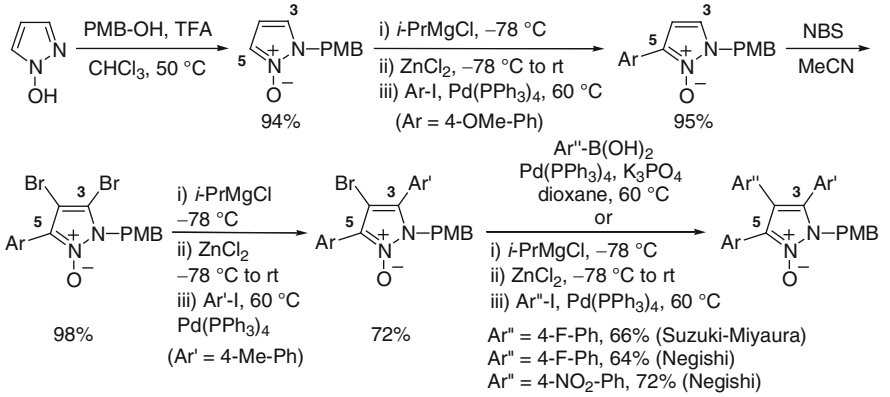
pyrazoles. THP-removal from *N*-1 position followed by re-installation at the *N*-2 position set the stage for regioselective lithiation of the neighboring C-3 ("now" C-5) position. As designed, a boronic ester functionality was introduced at this position via lithiation which thereafter participated in the Suzuki–Miyaura coupling to afford the corresponding 3,5-diarylpyrazoles. Halogenation of the remaining unsubstituted C-4 position produced the C-4-halogented pyrazole which was subsequently coupled with an arylboronic acid for the installation of the third aryl group to afford the fully substituted pyrazole.

Utilizing the THP-switching strategy, Velankar reported the synthesis of novel pyrazolyl-indoles (Scheme 118) [244]. A benzyl group was first installed at C-5 of THP-protected pyrazole via regioselective lithiation. The THP deprotection and reinstallation followed by regioselective iodination via lithiation afforded the 3-benzyl-5-iodopyrazole, which was subsequently coupled with a Boc-protected 2-indolylboronic acid.

The sequential metalation of pyrazole-1-oxide was reported by Vedso (Scheme 119) [245]. Deprotonation at C-5 of 2-PMB-pyrazole-1-oxide by isopropylmagnesium chloride (pK_a ~30) followed by transmetalation with $ZnCl_2$ and subsequent Negishi coupling with 4-iodoanisole afforded the corresponding



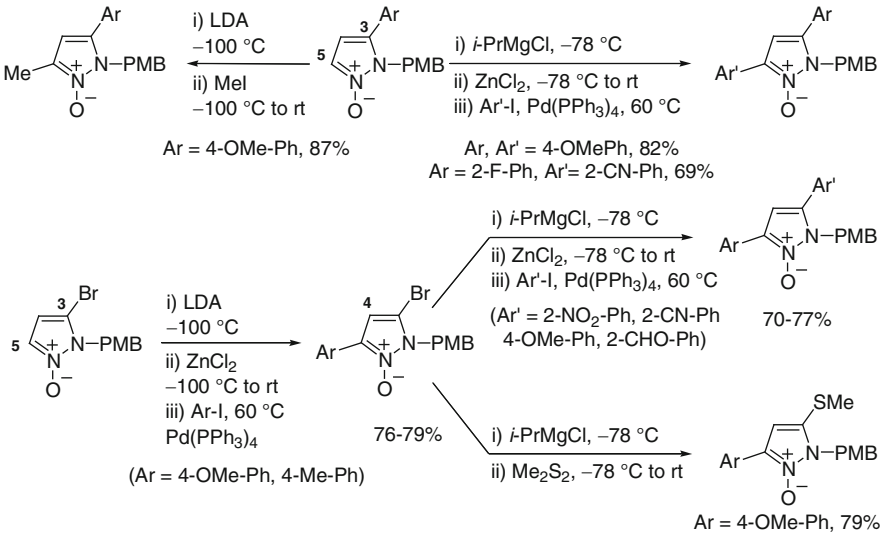
Scheme 118



Scheme 119

5-aryl-2-PMB-pyrazole-1-oxide in excellent yield. However, deprotonation by stronger lithium bases, such as LDA or *n*-BuLi, gave substantially lower yield presumably due to the instability of the 5-lithio-2-PMB-pyrazole-1-oxide, even at −78°C. Bromination of 5-substituted 2-PMB-pyrazole-1-oxide using "excess" NBS furnished the corresponding 3,4-dibromo derivative. Regioselective metal–halogen exchange at C-3 of 3,4-dibromo-5-(4-methoxyphenyl)pyrazole-1-oxide using isopropylmagnesium chloride exclusively provided the corresponding 3-magnesiated species. Transmetalation using $ZnCl_2$ followed by another Pd-catalyzed coupling of the resulting organozinc with 4-iodotoluene produced 3,5-diarylpyrazole-1-oxide. Substitution of the remaining bromine at C-4 using either Suzuki–Miyaura or Negishi cross-coupling afforded the corresponding 3,4,5-triarylpyrazole-1-oxides.

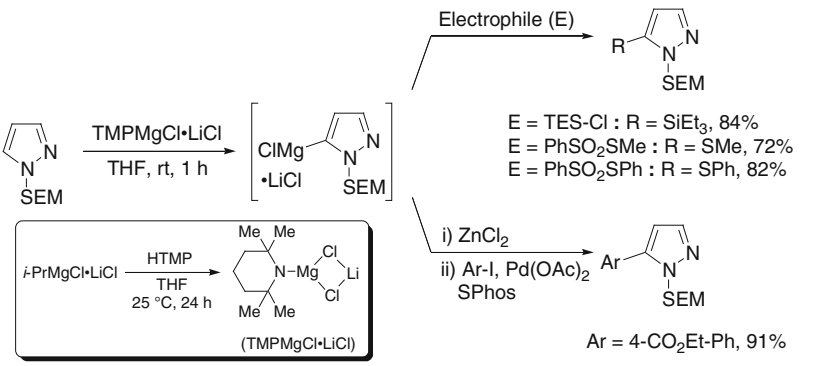
Vedso also reported the regioselective C-5 metalation of 3-aryl-2-PMB-pyrazole-1-oxide using isopropylmagnesium chloride (Scheme 120). Transmetalation of the resulting 5-magnesiated species using $ZnCl_2$ followed by the Pd-catalyzed coupling



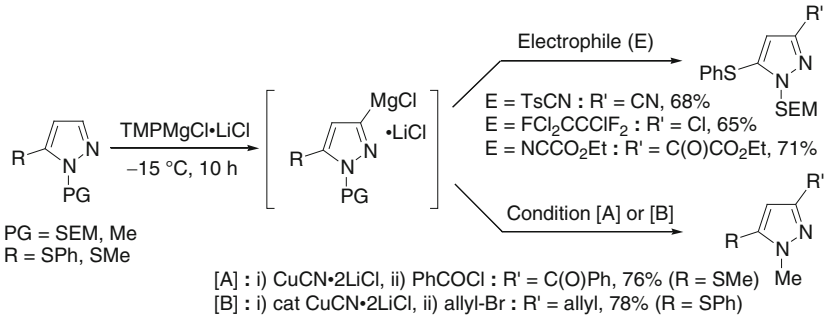
Scheme 120

with aryl iodides afforded the corresponding 3,5-diarylpyrazole-1-oxides. However, due to the instability of the C-5 lithiated 3-aryl-2-PMB-pyrazole-1-oxide, the lithiation was carried out using LDA at −100°C. Likewise, C-5 metalation of 3-bromo-2-PMB-pyrazole-1-oxide by LDA at −100°C followed by transmetalation using $ZnCl_2$ and subsequent Negishi coupling with aryl iodides provided the corresponding 5-aryl-3-bromo-2-PMB-pyrazole-1-oxides. Metal–halogen exchange of the bromine at C-3 using isopropylmagnesium chloride afforded the corresponding 3-magnesiated species, which was either used in the Negishi coupling or quenched with suitable electrophiles.

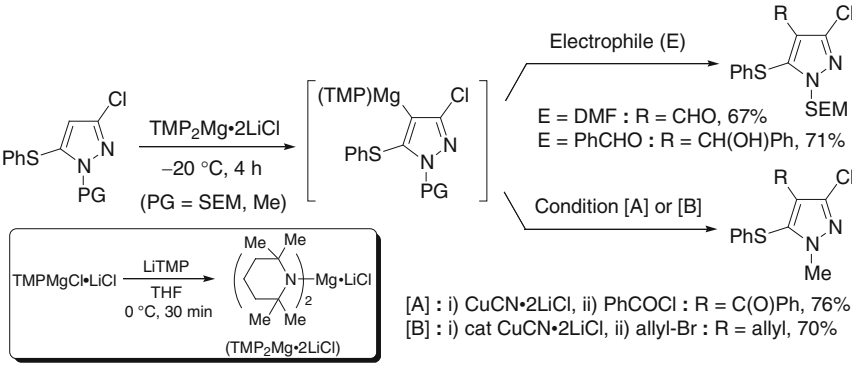
Knochel reported sequential metalation of pyrazole using mixed lithium–magnesium bases TMPMgCl·LiCl and TMP_2Mg·2LiCl (Scheme 121) [246]. Addition of TMPMgCl·LiCl to SEM-protected pyrazole generated the 5-magnesiated pyrazole in situ which was either quenched with suitable electrophiles (e. g., TES-Cl, *S*-methyl methanethiosulfonate, *S*-phenyl benzenethiosulfonate) or transmetalated with $ZnCl_2$ and subsequently used in the Pd-catalyzed Negishi coupling with aryl iodides to afford the corresponding 5-substituted pyrazoles. Of note, the relatively stable amide base TMPMgCl·LiCl was prepared from *i*-PrMgCl·LiCl and 2,2,6,6-tetramethylpiperidine (TMP) and can be stored at room temperature for over 6 months. Reaction of the representative 5-substituted *N*-protected pyrazoles with TMPMgCl·LiCl afforded the 3-magnesiated pyrazoles that were either directly quenched with suitable electrophiles or transmetalated with CuCN·2LiCl and subsequently treated with benzoyl chloride and allyl bromide to afford the corresponding 3,5-disubstituted pyrazoles (Scheme 122). Deprotonation of the remaining unsubstituted C-4 position in the 3,5-disubstituted *N*-protected pyrazoles was achieved by stronger magnesium bisamide base TMP_2Mg·2LiCl (Scheme 131). Reactions of the 4-magnesiated pyrazoles with various electrophiles afforded the corresponding 3,4,5-trisubstituted pyrazoles (Scheme 123).



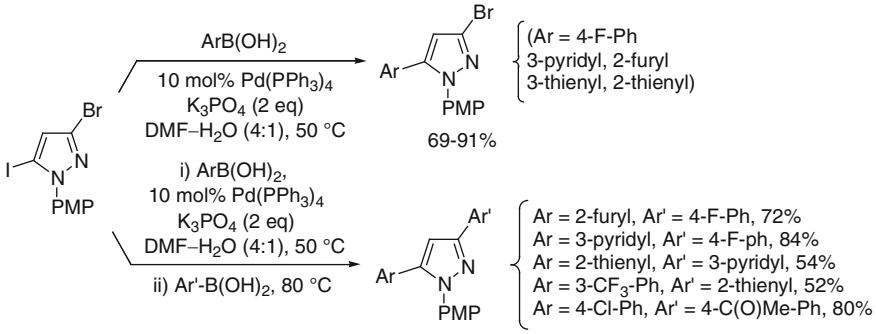
Scheme 121



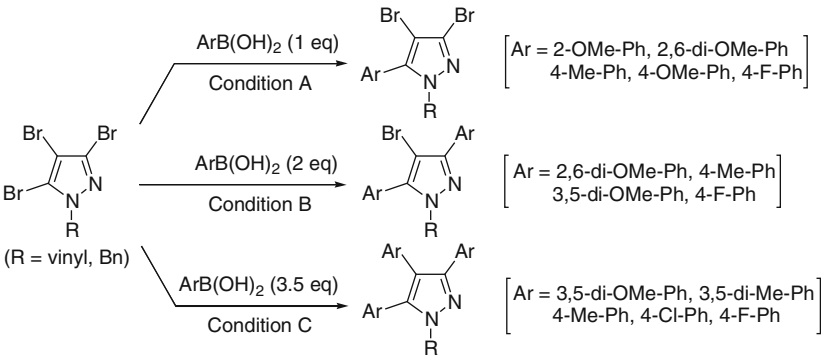
Scheme 122



Scheme 123



Scheme 124

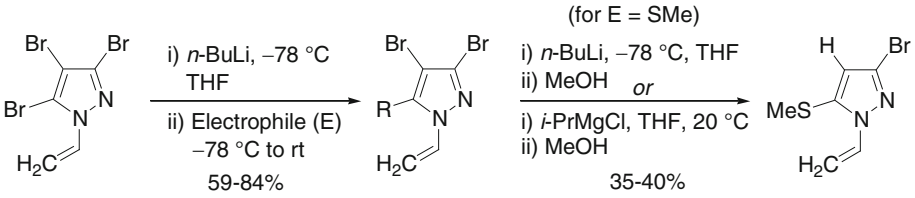


[A] : 3 mol% $Pd(PPh_3)_4$, K_3PO_4 (1.5 eq), dioxane–H_2O (4:1), 100 °C, 12 h; 66-73%
[B] : 5 mol% $Pd(PPh_3)_4$, K_3PO_4 (3 eq), dioxane–H_2O (4:1), 100 °C, 12 h; 60-74%
[C] : 10 mol% $Pd(PPh_3)_4$, K_3PO_4 (4.5 eq), dioxane–H_2O (4:1), 100 °C, 12 h; 50-76%

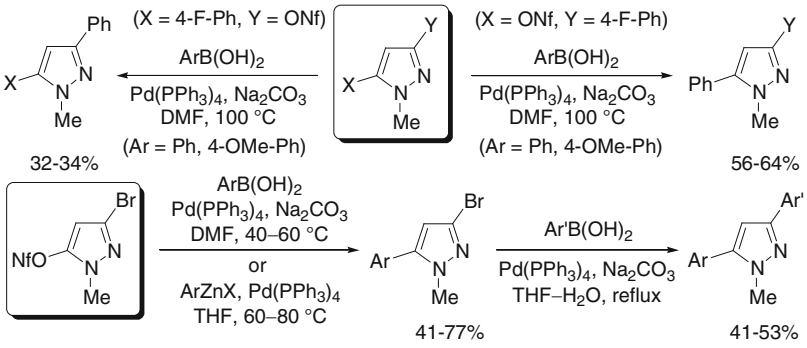
Scheme 125

The preparation of 3,5-disubstituted pyrazoles via sequential Suzuki–Miyaura coupling was reported by Monteiro and Balme (Scheme 124) [247]. The Pd-catalyzed reaction of PMP-protected 3-bromo-5-iodopyrazole with various boronic acids (1.1 eq) gave the corresponding 5-substituted 3-bromopyrazoles with high site-selectivity. Therefore, the addition of a second boronic acid to the reaction mixture after the completion of the first coupling afforded the 3,5-disubstituted pyrazoles.

Langer reported the "site-selective" Suzuki–Miyaura coupling of *N*-substituted 3,4,5-tribromopyrazoles with various arylboronic acids (Scheme 125) [248]. Reaction of the tribromopyrazole with 1 eq of boronic acids in the presence of 3 mol% $Pd(PPh_3)_4$ and K_3PO_4 (1.5 eq) regioselectively afforded the C-5 monoarylated pyrazoles. Use of 2 eq of boronic acids in the presence of 5 mol% $Pd(PPh_3)_4$ and K_3PO_4 (3 eq) gave the 3,5-disubstituted pyrazoles. Likewise, the coupling with excess boronic acids (3.5 eq) and base (4.5 eq) in the presence of 10 mol% $Pd(PPh_3)_4$ provided the 3,4,5-triarylpyrazoles.



Scheme 126



Scheme 127

The metal–halogen exchange reaction of *N*-vinyl-3,4-5-tribromopyrazole with 1.1 eq of *n*-butyllithium followed by the addition of electrophiles afforded the corresponding 5-substituted pyrazoles (Scheme 126) [249]. The second metal–halogen exchange on *N*-vinyl-3,4-dibromo-5-methylthiopyrazole predominantly occured at C-4 presumably due to the *ortho*-directing effect of the methylthio group.

Collins reported the Suzuki–Miyaura coupling of 3- and 5-(pyrazolyl)nonaflates with various arylboronic acids (Scheme 127) [250]. Although the reactions of *N*-methylpyrazole-5-nonaflate with the arylboronic acids gave the 5-arylpyrazoles in high yields, lower yields were typically obtained for the coupling of analogous pyrazole-3-nonaflate with arylboronic acids. The cross-coupling of 3-bromo-1-methylpyrazole-5-nonaflate with arylboronic acids or arylzinc reagents regioselectively afforded the 5-aryl-3-bromopyrazoles. However, coupling of these 3-bromopyrazoles with the arylboronic acid at a higher temperature introduced an aryl group at C-3. In some instances, use of arylboronic acid neopentylglycol esters instead of arylboronic acids provided higher yields in the coupling of these relatively unreactive 3-bromopyrazoles. Of note, these nonaflates were prepared conveniently from the corresponding 5- or 3-hydroxypyrazole using perfluoro-1-butanesulfonyl fluoride in the presence of NaHMDS.

4 Reactions of Indazoles via *C*-Metalation

4.1 Metalation at C-3 of Indazoles

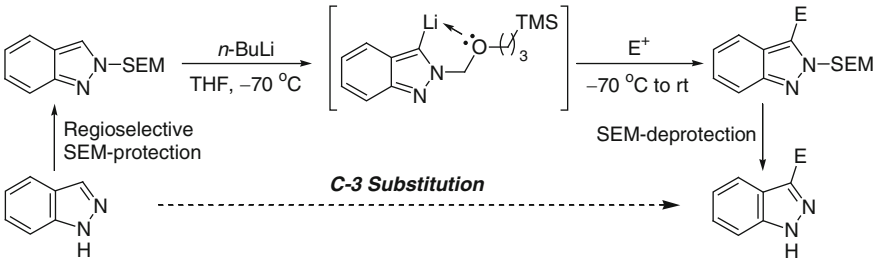
The C-3 position of indazole is significantly less nucleophilic than C-3 of indole. Therefore, Luo reported the SEM-directed C-3 lithiation to prepare 3-lithioindazole in situ which, upon the addition of suitable electrophiles, afforded the C-3 substituted indazoles (Scheme 128, Table 11) [64]. The SEM group is stable toward a variety of reaction conditions and can be conveniently removed using either basic (TBAF–THF, reflux) or acidic conditions (HCl–EtOH, reflux). The SEM-directed C-3 lithiation of indazole followed by the addition of ethyl cyanoformate to the resulting 3-lithioindazole was also successfully used in the preparation of granisetron derivatives (Scheme 129) [251].

Knochel reported an iodine–copper exchange reaction of 3-iodoindazoles using sterically hindered lithium dineophylcuprate (Scheme 130) [252, 253]. Thus, the addition of $(PhMe_2CCH_2)_2CuLi$ to *N*-benzyl-3-indazoles at 25°C furnished the corresponding lithium cuprates. However, a low temperature (−78°C) was required for successful iodine–copper exchange for the substrates bearing *N*-Boc or aryl-COEt functionality. However, the regioselective mono-exchange at C-3 in 3,5-diiodoindazole was sucessfully carried out at −10°C. In fact, after the first iodine–copper exchange, the electron density of the aromatic ring increases to such an extent that second exchange becomes unfavorable. Acylation of these indazole cuprates with the acid chlorides afforded a series of 3-acylindazoles. Knochel also reported the preparation of diindazolylzinc derivatives of *N*-benzyl-3-iodoindazoles using diisopropylzinc and catalytic lithium acetylacetonate (Scheme 131) [254]. The Pd-catalyzed coupling of bis(3-indazolyl)zinc with ethyl 4-iodobenzoate gave the corresponding 3-arylindazole. Likewise, Cu-catalyzed reaction of diindazolylzinc with allyl bromide provided 3-allylindazole.

The *one-pot* metal–halogen exchange of 3-iodoindazole with isopropylmagnesium chloride followed by transmetalation with tributyltin chloride and subsequent Stille coupling of the resulting organostannane with 2,6-dibromopyridine afforded the corresponding 3-substituted indazole (Scheme 132) [255]. The Suzuki–Miyaura reaction of Boc protected 3-iodoindazole with 4-methoxycarbonylphenylboronic acid in the presence of $PdCl_2$(dppf) also provided the corresponding 3-arylindazole [256].

Hopkins reported microwave-assisted palladium-catalyzed coupling of Boc-protected 3-iodo-5-methoxyindazole with aryl/heteroaryl boronic acids (Scheme 133) [257]. Concomitant loss of Boc-group during the course of reaction directly afforded the corresponding *NH*-free 3-arylindazoles. The copper-catalyzed *N*-arylations of these 3-arylindazoles with a variety of aryl iodides provided a diverse set of 1,3-diarylindaolzes.

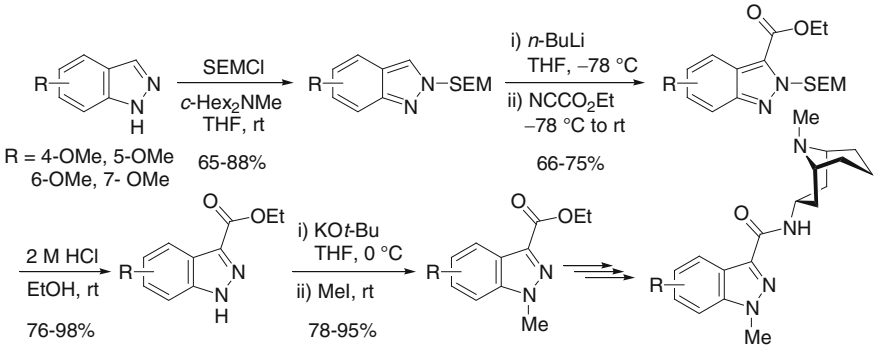
The Suzuki–Miyaura coupling is widely used for introducing aryl/heteroaryl functionalities at C-3 of indazoles (Table 12, entries 1 and 2) [62, 63, 258, 259].



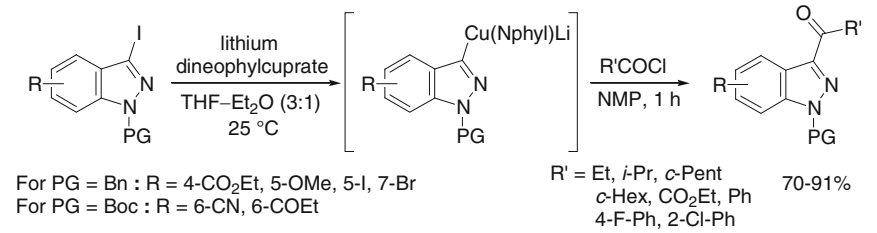
Scheme 128

Table 11 Reactions of 3-lithioindazole with various electrophiles

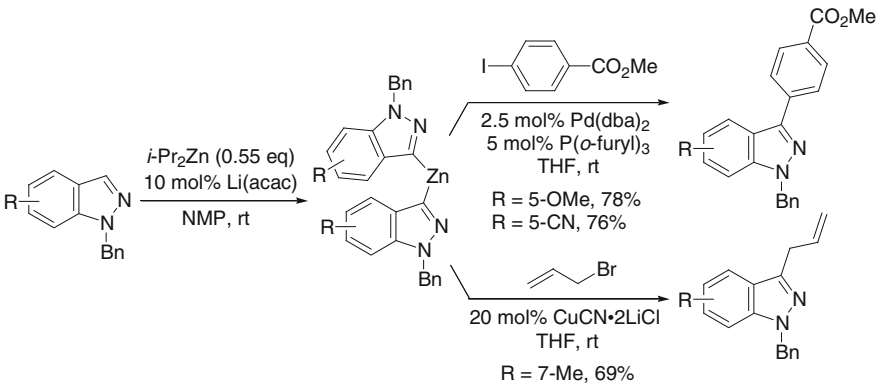
Entry	Electrophile	C-3 substitution	Yield (%)
1	Ethyl cyanoformate	$–CO_2Et$	77
2	Benzoyl chloride	–C(O)Ph	94
3	Phenyl isocyanate	–C(O)NHPh	98
4	Benzaldehyde	–C(OH)Ph	89
5	NBS	–Br	72



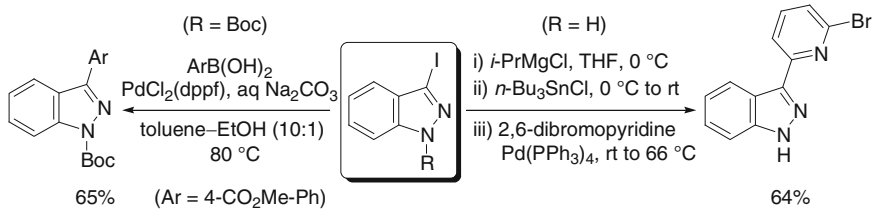
Scheme 129



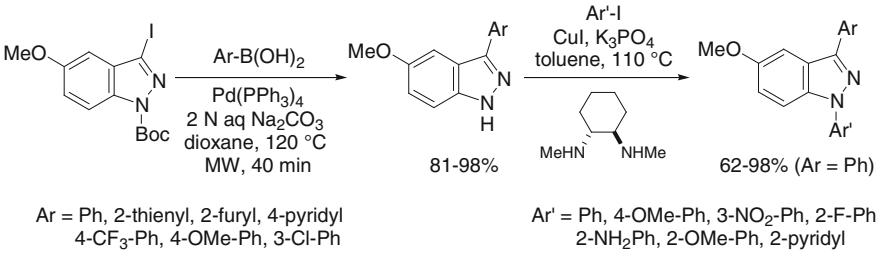
Scheme 130



Scheme 131



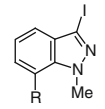
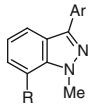
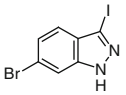
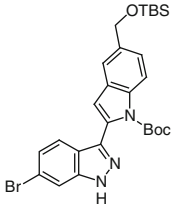
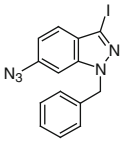
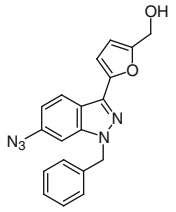
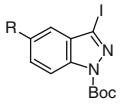
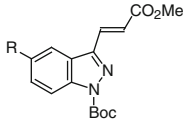
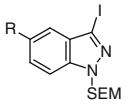
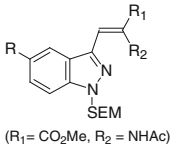
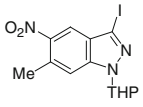
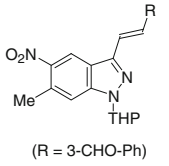
Scheme 132



Scheme 133

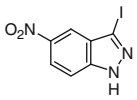
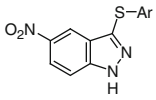
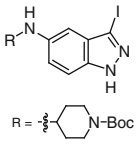
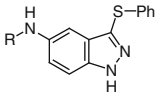
Marletta reported the installation of a furan ring at C-3 of indazole, bearing an azido group, using the Stille coupling at room temperature (entry 3) [260]. Collott and Rault reported the Heck reaction of Boc-protected 3-iodoindazole with the acrylates (entries 4 and 5) [261, 262]. While a Boc group on indazole nitrogen tolerated the Heck reaction conditions, partial loss of tosyl group was observed from related *N*-tosylindazoles under similar conditions. Of note, bromide in the benzenoid ring of indazole remained unaffected under the applied Heck conditions. For the coupling of 3-iodoindazoles with methyl 2-(acetylamino)acrylate, the corresponding (*Z*)-isomers were obtained predominantly in most cases (entry 5). The Heck reaction was also

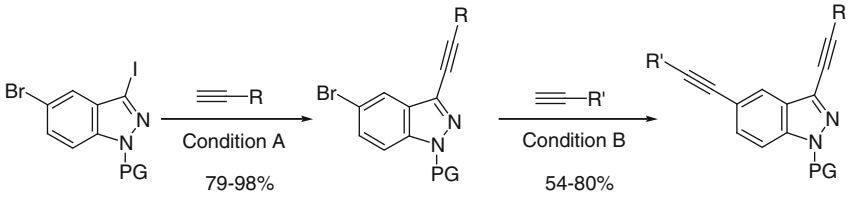
Table 12 C-3 Functionalization of indazoles via metalation

Entry	Indazole	Conditions	Product	Yield (%)
1	 R = NO_2, NHC(O)*t*-Bu	$ArB(OH)_2$ $Pd(PPh_3)_4$ Na_2CO_3 DME, Δ	 (Ar = 3-thiophen, 4-OMe-Ph)	80–81
2		$ArB(OH)_2$ $Pd(PPh_3)_4$ Na_2CO_3, LiCl dioxane, 90°C		64
3		$ArSnBu_3$ $Pd_2(dba)_3$, $AsPh_3$ DMF, rt, 3 d		89
4	 (R = H, OMe)	Methyl acrylate $PdCl_2$(dppf) Et_3N, TBAI DMF, 50°C		75–77
5	 (R = H, OMe, Br)	R_1R_2-CH=CH_2 $Pd(OAc)_2$ $NaHCO_3$, TBAB DMF, 125°C	 (R_1= CO_2Me, R_2 = NHAc)	30–54
6		R-CH=CH_2 $Pd(OAc)_2$ P(*o*-tol)$_3$, Et_3N DMF, 100°C	 (R = 3-CHO-Ph)	70

(continued)

Table 12 (continued)

Entry	Indazole	Conditions	Product	Yield (%)
7		ArSH CuI, K_2CO_3 $OH(CH_2)_2OH$ *i*-PrOH, 90°C	 (Ar = 1-naphthyl)	49
8		PhSH CuI, K_2CO_3 $OH(CH_2)_2OH$ *i*-PrOH, 100°C		100



PG = Boc, Ts R = CH_2OH, CH_2NHTs, CH_2NMe_2 R' = CH_2OH, CH_2NHTs, CH_2NMe_2

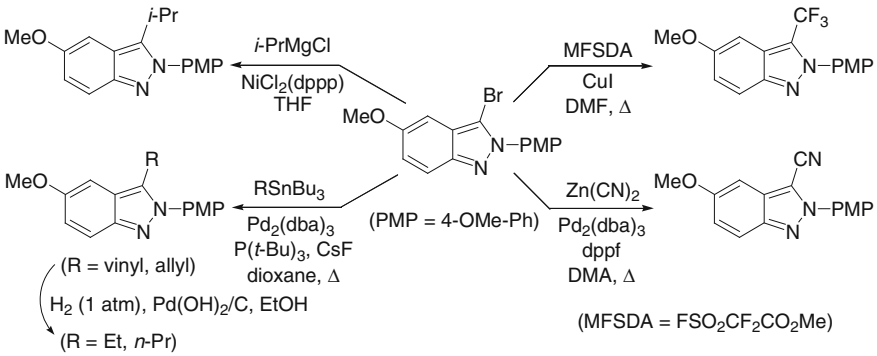
Condition A: 5 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, Et_3N–DMF (2:1), 20 °C, 12 h.
Condition B: 10 mol% $PdCl_2(PPh_3)_2$, 20 mol% CuI, 10 mol% PPh_3, Et_3N–DMF (2:1), 20 °C, 24 h.

Scheme 134

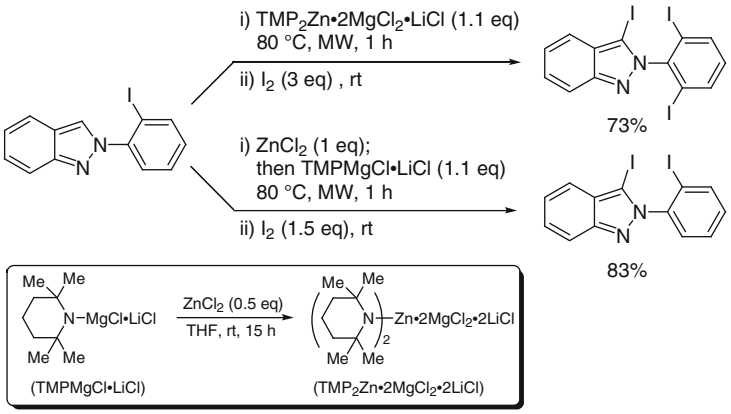
used for the coupling of a THP-protected-3-iodoindazole with 3-vinylbenzaldehyde (entry 6) [263]. The reaction of 3-iodoindazoles with thiols under the copper-catalyzed conditions afforded the corresponding sulfides (entries 7 and 8) [264].

Using sequential Sonogashira reaction, Witulski and Rault reported the preparation of *N*-protected 3,5-dialkynylindazoles from the corresponding 5-bromo-3-iodoindazoles (Scheme 134) [265, 266]. The first Sonogashira reaction at C-3 iodide with alkynes (1.2 eq) at 20°C afforded the corresponding 3-alkynyl-5-bromoindazoles. Thereafter, a second Sonogashira reaction of C-5 bromide with excess alkynes (2–3 eq) at 70°C provided the 3,5-dialkynylindazoles.

Katzenellenbogen reported metal-mediated C-3 functionalizations of PMP-protected 3-bromo-2*H*-indazole (Scheme 135) [267]. Using nickel-catalyzed Kumada–Corriu reaction, an isopropyl group was installed at C-3 of the *2H*-indazole. However, related C-3 ethyl and *n*-propyl analogs were prepared using the Stille coupling of 3-bromoindazole followed by the reduction of resulting 3-vinyl- and 3-allylindazole. Also, the copper-catalyzed trifluoromethylation and the palladium-catalyzed cyanation of 3-bromoindazole gave the corresponding 3-(trifluoromethyl)indazole and 3-cyanoindazole, respectively.



Scheme 135

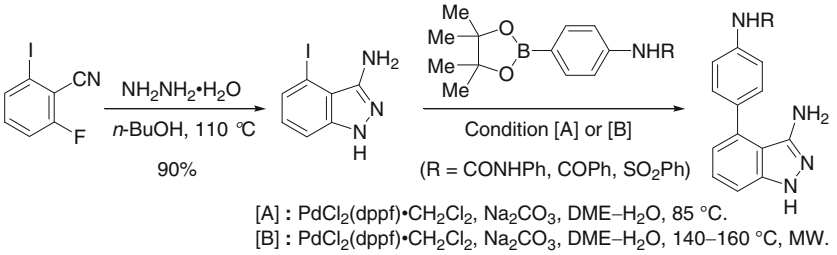


Scheme 136

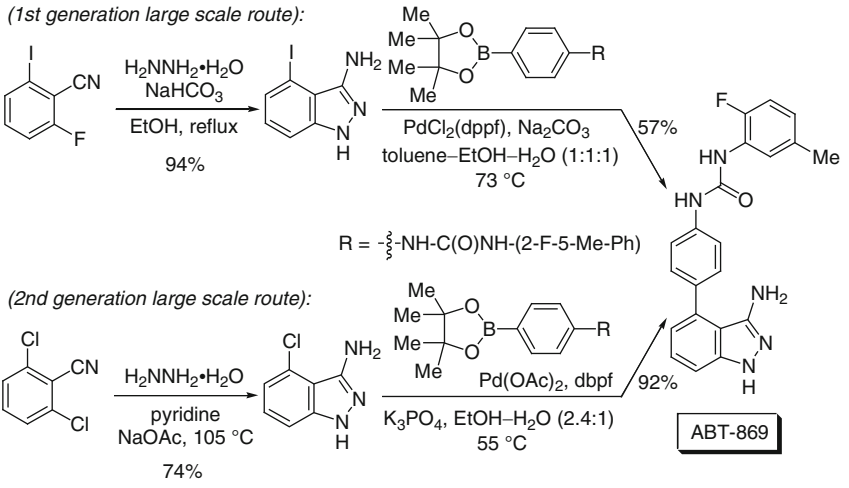
Knochel reported regioselective zincation of *2H*-indazoles (Scheme 136) [268]. The reaction of 2-(2-iodophenyl)indazole with $TMP_2Zn{\cdot}2MgCl_2{\cdot}LiCl$ (1.1 eq) followed by the addition of iodine (3 eq) afforded the corresponding 2-(2,6-diiodophenyl)-3-iodoindazole. However, selective monozincation at C-3 of 2-(2-iodophenyl)indazole was achieved by the sequential addition of $ZnCl_2$ (1 eq) followed by the addition of TMPMgCl·LiCl (1.1 eq); quenching of the resulting zincate with iodine (1.5 eq) furnished 2-(2-iodophenyl)-3-iodoindazole. Of note, $TMP_2Zn{\cdot}2MgCl_2{\cdot}$ LiCl was prepared from TMPMgCl·LiCl and $ZnCl_2$.

4.2 Metalation at C-4 of Indazoles

The palladium-catalyzed reaction of 3-amino-4-iodoindazole with arylurea boronates, prepared by the condensation of 4-aminophenyl boronates with isocyanate (or 4-isocyanatophenyl boronates with amines), gave the corresponding



Scheme 137

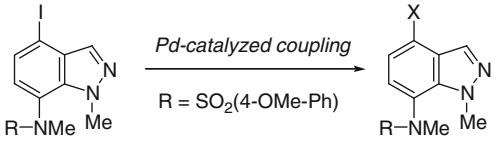


Scheme 138

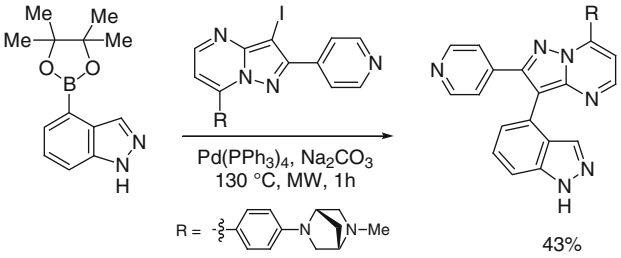
4-arylated indazoles (Scheme 137) [269]. Although the reaction of 4-iodoindazole with 4-aminophenylboronic acid pinacol ester also provided 3-amino-4-(4-aminophenyl)indazole in 60% yield, it did not serve as a suitable precursor for the preparation of urea analogs due to the competing acylation at *N*-1 of indazole.

Likewise, the Suzuki–Miyaura coupling 3-amino-4-chloroindazole with an arylurea boronate in the presence of in situ pre-complexed $Pd(OAc)_2$/dbpf afforded the corresponding 4-arylindazole (Scheme 138) [270]. Notably, in situ pre-complexed $Pd(OAc)_2$ and dbpf [1,1′-bis(di-*tert*-butylphosphino)ferrocene] was found superior to the commercially available pre-complexed $PdCl_2$(dppf). In addition, degassing the reaction solvent was extremely important for the activity of the $Pd(OAc)_2$/dbpf system in large scale. The use of 4-chloroindazole, instead of 4-iodoindazole, as the coupling partner of the arylurea boronate eliminated the fluoride-mediated glass-etching that was problematic for the large scale preparation of 4-iodoindazole from 2-fluoro-6-iodobenzonitrile.

Table 13 Pd-Catalyzed reactions of 4-iodoindazole



Entry	Coupling partner	Conditions	X	Yield (%)
1	$ArB(OH)_2$	$Pd(PPh_3)_4$, Na_2CO_3, DME, reflux	4-OMe-Ph, 3-thienyl	80–85
2	(2-furyl)$SnBu_3$	$Pd_2(dba)_3$, $AsPh_3$ dioxane, 50°C	2-furyl	82
3	HC≡C-Ph	$PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt	C≡C-Ph	71
4	CH_2=CH-CO_2Me	$PdCl_2$(dppf), TBAI, Et_3N, DMF, 50°C	CH=CH-CO_2Me	79



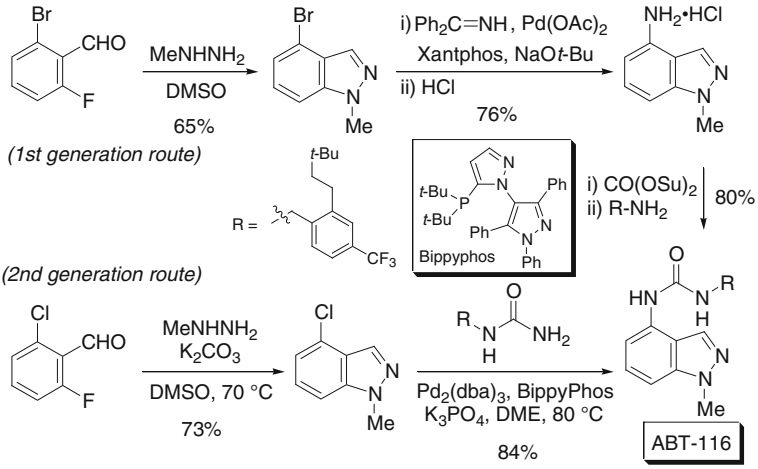
Scheme 139

Guillaumet reported various Pd-catalyzed reactions of an 4-iodoindazole for the preparation of corresponding 4-substituted indazoles (Table 13) [271].

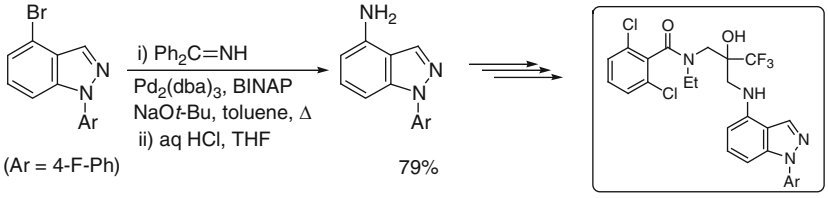
The microwave-assisted Pd-catalyzed coupling of indazole-4-boronic acid pinacol ester with the pyrazolopyrimidine iodide also afforded the C-4 functionalized indazole, albeit in low yield (Scheme 139) [272].

Yu reported palladium-catalyzed amination of 4-bromo-1-methylindazole with commercially available benzophenone imine to afford 4-amino-1-methylindazole hydrochloride (Scheme 140) [273]. Benzophenone imine serves as a convenient ammonia equivalent in the amination reaction [274]. However, due to the inherent instability 4-amino-1-methylindazole as well as the difficulty in separating this key intermediate from benzophenone by-product, an alternative Pd-catalyzed coupling involving 4-chloro-1-methylindazole and urea was later used for the synthesis of ABT-116. A pre-complexed mixture (1:2) of $Pd_2(dba)_3$ and BippyPhos was used for this coupling.

The amination of an *N*-aryl-4-bromoindazole with benzophenone imine also gave the corresponding 4-aminoindazole (Scheme 141) [275].



Scheme 140



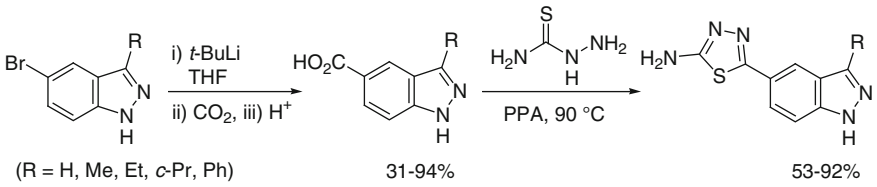
Scheme 141

4.3 Metalation at C-5 of Indazoles

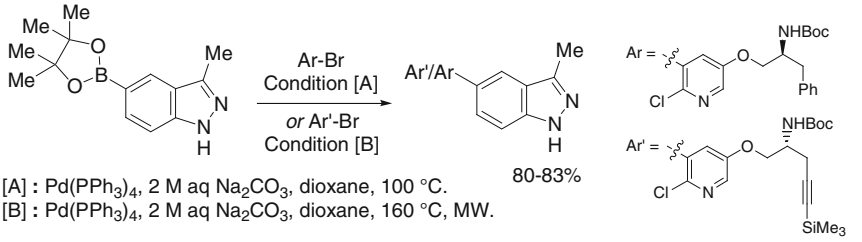
Lithiation of 5-bromoindazole using *tert*-butyllithium followed by addition of CO_2 gave the corresponding indazole-5-carboxylic acid (Scheme 142) [276]. The carboxylic acid functionality was later elaborated to a 5-aminothiadiazole scaffold using thiosemicarbazide and PPA.

The palladium-catalyzed C–C bond formation between 3-methylindazole-5-boronic acid pinacol ester with bromopyridines afforded 5-functionalized indazoles (Scheme 143) [277, 278]. Alternatively, the Stille coupling was used to introduce the functionalized pyridines at C-5 of indazole (Scheme 144) [279–281]. Thus, the organostannane, prepared from 5-bromo-3-methylindazole using hexamethyltin in the presence of 10 mol% $Pd(PPh_3)_4$, was treated with bromopyridines in the presence of 10 mol% $Pd_2(dba)_3$ and 30 mol% P(*o*-tol)$_3$.

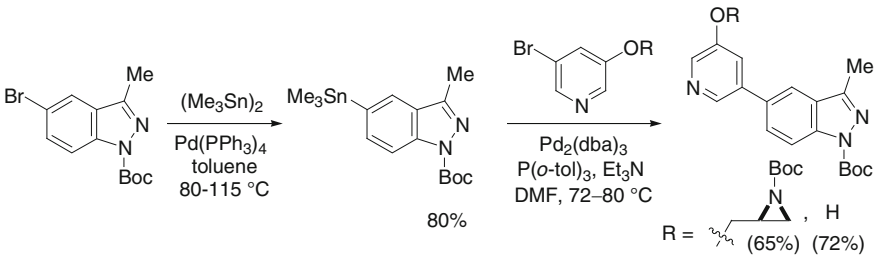
Trump also reported the preparation of 5-arylindazole utilizing the Suzuki–Miyaura reaction (Scheme 145) [282]. The Pd-catalyzed reaction of *N*-protected 5-bromoindazole with bis(pinacolato)diboron gave the indazole-5-



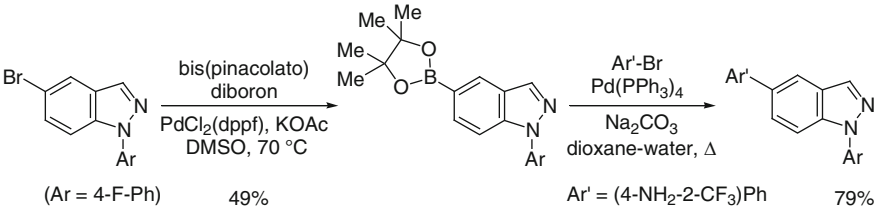
Scheme 142



Scheme 143

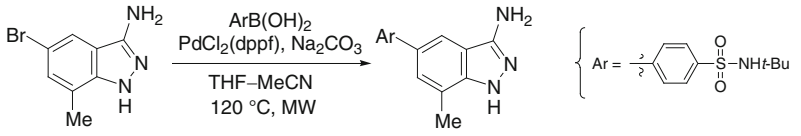


Scheme 144

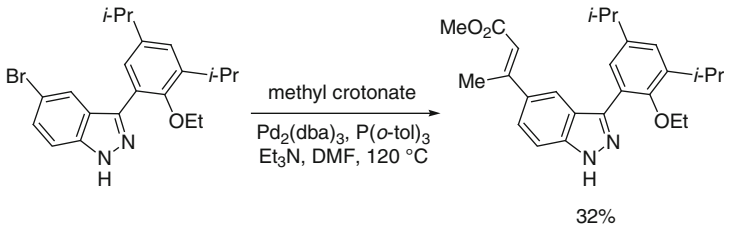


Scheme 145

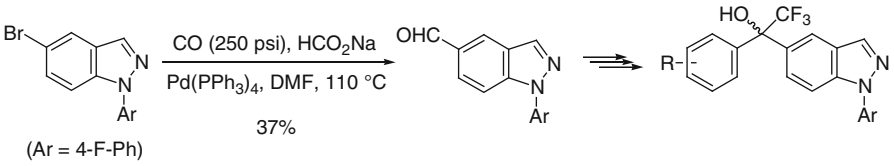
boronate which, in turn, was used in the coupling with a functionalized aryl bromide. Hirst reported similar C-5 arylation of unprotected 3-amino-5-bromoindazole with arylboronic acids under microwave irradiation (Scheme 146) [283]. Similarly, the



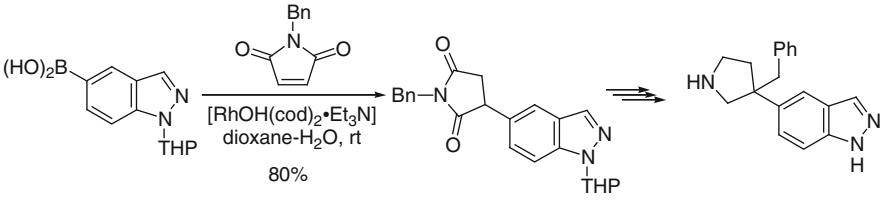
Scheme 146



Scheme 147



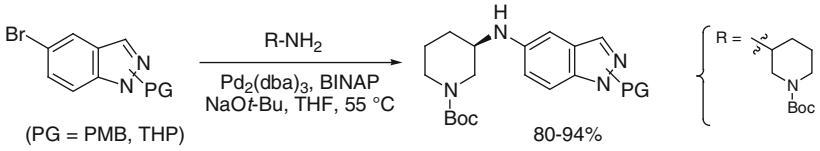
Scheme 148



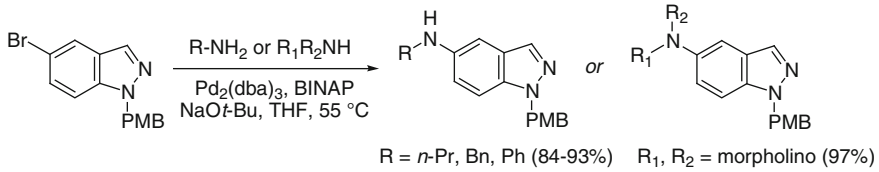
Scheme 149

Heck reaction of an unprotected 5-bromoindazole with methyl crotonate introduced a butenoic acid methyl ester at C-5 of indazole (Scheme 147) [284].

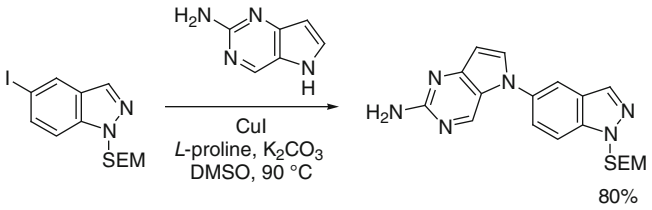
Wolf reported the palladium-catalyzed carbonylation of an *N*-aryl-5-bromoindazole for the preparation of corresponding 5-formylindazole (Scheme 148) [285]. A rhodium-catalyzed conjugate addition of an indazole-5-boronic acid to *N*-benzylmaleimide was reported by Lucas (Scheme 149) [286]. The desired C-5 functionalized indazole was obtained in high yield and subsequently converted to the targeted 3,3-disubstituted pyrrolidine.



Scheme 150



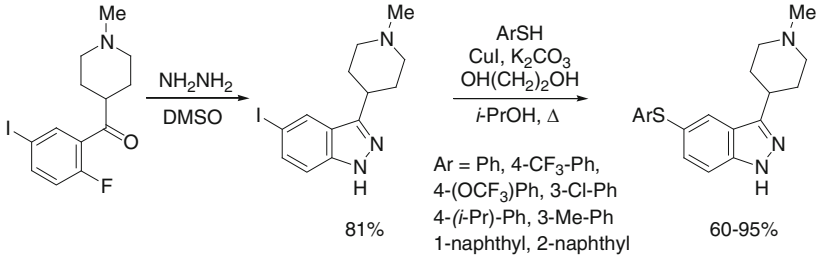
Scheme 151



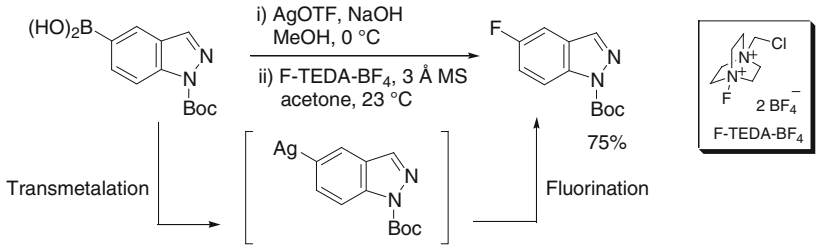
Scheme 152

The palladium-catalyzed amination of *N*-protected 5-bromoindazoles with *N*-boc-3-aminopiperidine in the presence of $Pd_2(dba)_3$, BINAP, and NaO*t*-Bu afforded the corresponding 5-substituted indazoles in excellent yield (Scheme 150) [65]. High-quality fresh sodium *tert*-butoxide and the presence of a suitable *N*-protecting group are essential for the success of this reaction. Notably, complete loss of Boc and Piv protecting groups were observed under the reaction conditions. Similar C–N bond-forming reaction of *N*-protected 5-bromoindazole with analogous amines, such as *N*-Boc-4-amino-piperidine and *N*-Boc-3-aminopyrolidines, also gave the desired products in good yields. Reactions of PMB-protected indazole with representative primary, secondary, and aromatic amines also afforded the corresponding 5-substituted indazoles, except for 3-cyanoanilne and low boiling diethyl amine (Scheme 151). In general, electron-deficient anilines provided low yields and required longer reaction time, whereas electron-rich anilines provided good yields of the corresponding products in shorter reaction time.

A copper-catalyzed C–N coupling of SEM-protected 5-iodoindazole was reported by Talanian for the C-5 functionalization (Scheme 152) [287]. Likewise, copper-catalyzed coupling of 5-iodoindazole with aryl thiols afforded the corresponding indazole sulfides (Scheme 153) [288].



Scheme 153



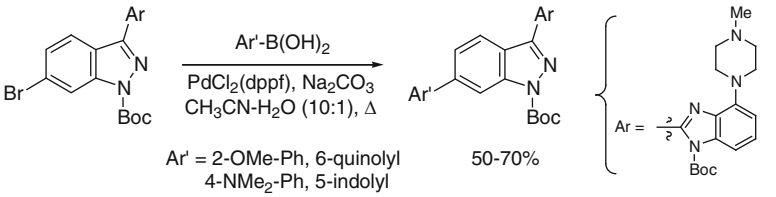
Scheme 154

A novel silver(I) triflate mediated fluorination was reported by Ritter in which *N*-Boc-protected 5-indazolylboronic acid was efficiently converted to the 5-fluoroindazole (Scheme 154) [289]. Transmetalation of boronic acid with silver (I) triflate in the presence of NaOH generated a (5-indazolyl)silver intermediate that was fluorinated in situ by F-TEDA-BF_4.

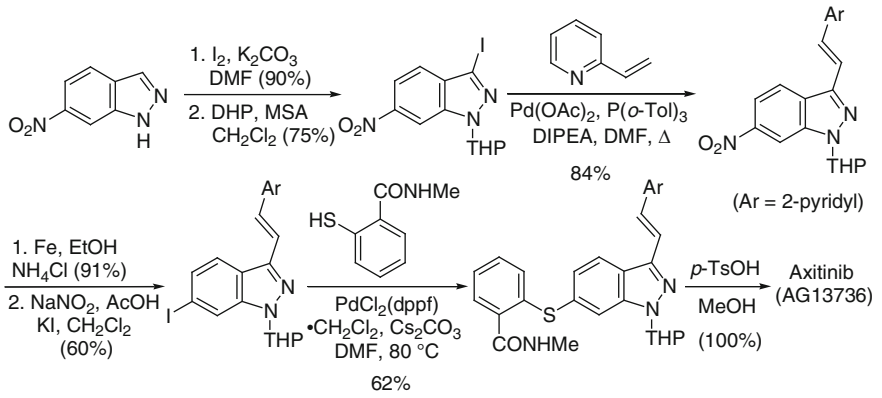
4.4 Metalation at C-6 of Indazoles

The Suzuki–Miyaura reaction of Boc-protected 6-bromoindazole with aryl/heteroaryl boronic acids afforded the 6-aryl/heteroaryl indazoles (Scheme 155) [290].

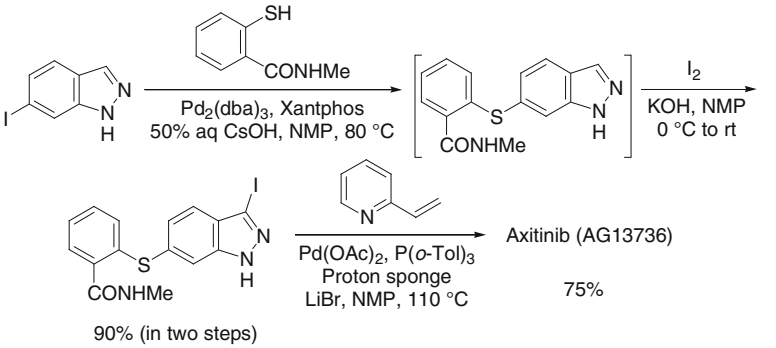
For the large-scale preparation of Axitinib (AG13736), Flahive reported a seven-step synthesis wherein two palladium-catalyzed reactions were used as key steps (Scheme 156) [291]. The C-3 iodination of 6-nitroindazole followed by THP-protection afforded the corresponding 3-iodoindazole, which was used in the Heck reaction with 2-vinylpyridine. Functional group manipulations provided the corresponding 6-iodoindazole that was subsequently used in Pd-catalyzed C–S bond forming reaction. In the second-generation manufacturing route, the synthesis of Axitinib was achieved just in three steps starting from 6-iodoindazole



Scheme 155

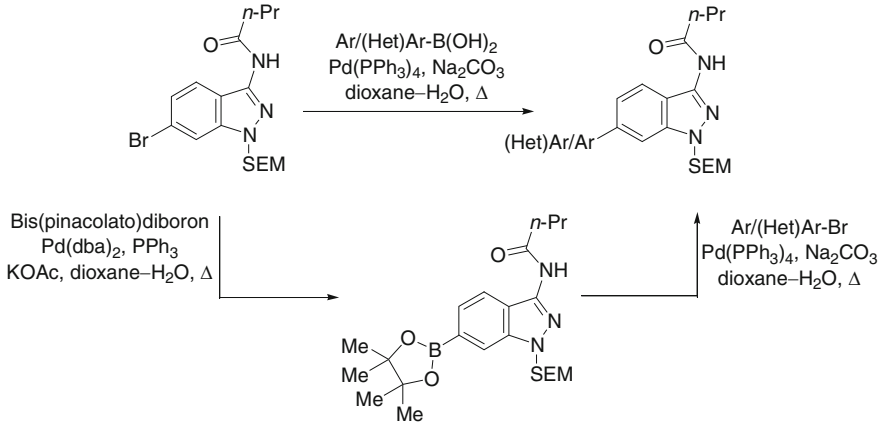


Scheme 156

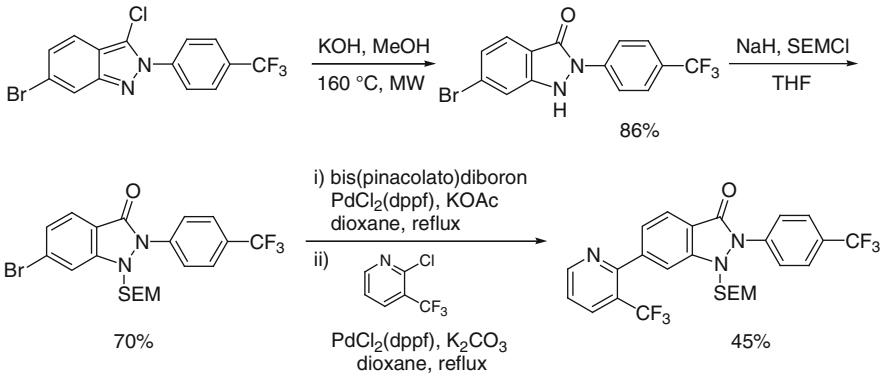


Scheme 157

(Scheme 157). The palladium-catalyzed C–S bond-formation was moved to the beginning of the synthesis and the resulting "crude" indazole sulfide was directly subjected to C-3 iodination in a one-pot fashion. The installation of vinylpyridine scaffold by the Heck reaction afforded Axitinib in 67% overall yield (compared to 19% yield in first-generation synthesis).

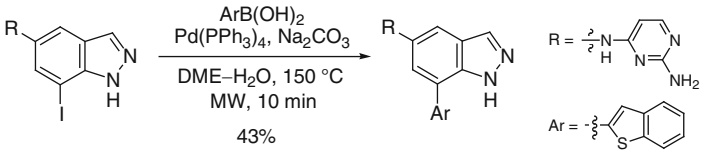


Scheme 158

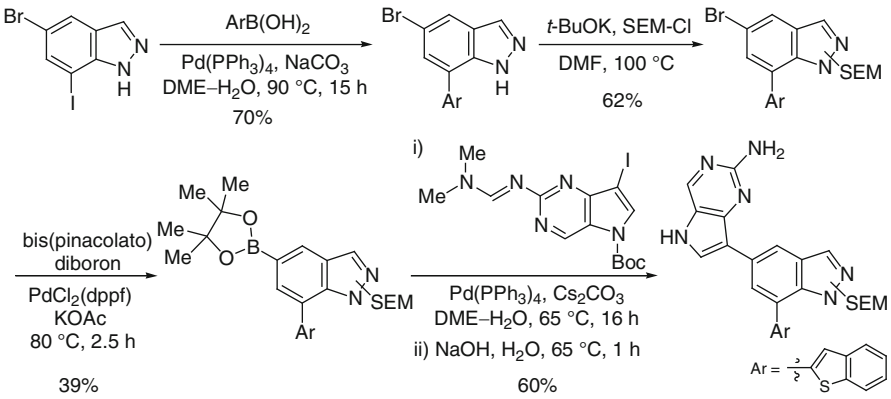


Scheme 159

Lesuisse reported the synthesis of various 6-aryl/heteroaryl indazoles wherein, depending upon the commercial availability of the boronic acids and bromides, 6-bromoindazole was either directly treated with appropriate boronic acids or converted to its boronate ester that was subsequently used for the coupling with bromides (Scheme 158) [292]. Likewise, Fletcher reported the Suzuki–Miyaura coupling of an indazolone boronate, prepared from the corresponding 6-bromoindazolone, with 2-chloro-3-(trifluoromethyl)pyridine to afford the 6-substituted indazolone (Scheme 159) [293].



Scheme 160



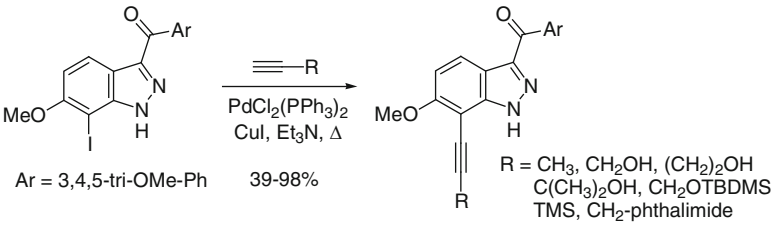
Scheme 161

4.5 Metalation at C-7 of Indazoles

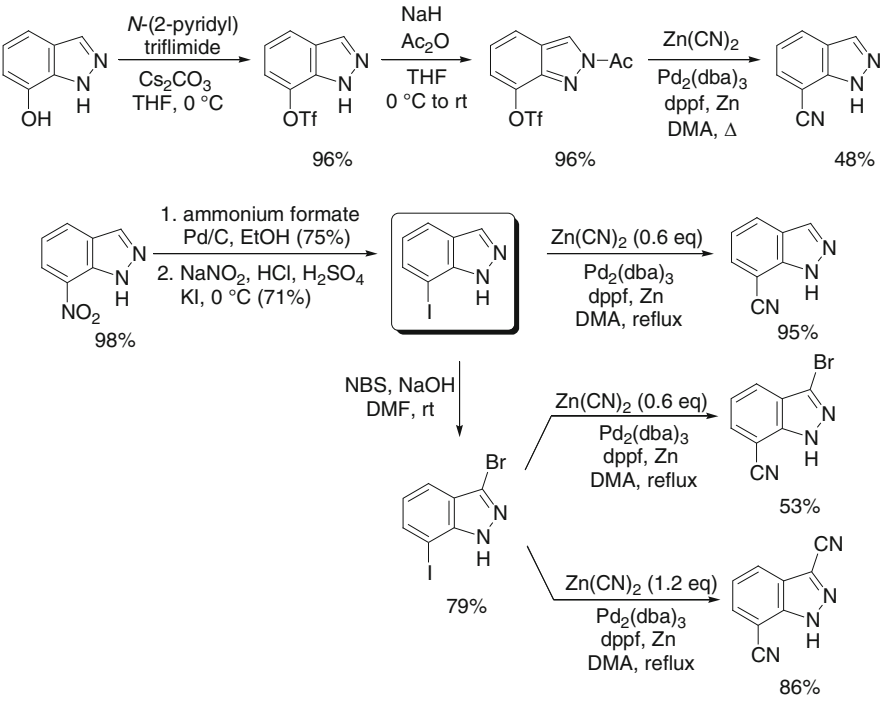
Talanian reported the Suzuki–Miyaura coupling of an unprotected 7-iodoindazole with benzothiophene-2-boronic acid under microwave to afford the C-7-substituted indazole (Scheme 160) [287]. Selective iodo-substitution in 5-bromo-7-iodoindazole was successfully achieved by conducting the Pd-catalyzed coupling at a lower temperature (Scheme 161). Deprotonation of *NH*-indazole using potassium *tert*-butoxide followed by the addition of SEM-chloride produced a mixture of *N*-1 and *N*-2 isomers, which was carried forward through the synthetic sequence for a second Suzuki–Miyaura coupling at C-5. Deprotection of SEM group provided the 5,7-disubstituted *NH*-indazole as the single product.

The Sonogashira reaction of a 7-iodoindazole with alkynes afforded the corresponding 7-alkynylindazoles (Scheme 162) [294].

Vichard reported the synthesis of 7-cyanoindazole from the corresponding triflate using palladium-catalyzed cyanation (Scheme 163) [295]. The triflate precursor was prepared from the 7-hydroxyindazole using *N*-(2-pyridine)triflimide followed by regioselective *N*-2 acylation. While the palladium-catalyzed cyanation



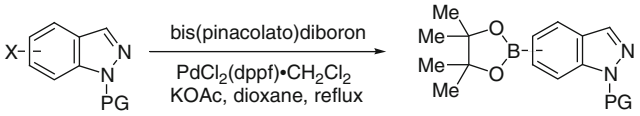
Scheme 162



Scheme 163

was unsuccessful on 7-OTf-*1H*-indazole, cyanation of *N*-acetylated 7-OTf-*2H*-indazole afforded 7-cyanoindazole after concomitant loss of acetyl group in situ. Furthermore, in contrast to the unsuccessful cyanation of unprotected indazole-7-triflate, the *unprotected* 7-iodoindazole successfully participated in the Pd-catalyzed cyanation with zinc cyanide to provide 7-cyanoindazole. Likewise, regioselective cyanation of 3-bromo-7-iodoindazole [using 0.6 eq $Zn(CN)_2$] as well as the double cyanation [using 1.2 eq $Zn(CN)_2$] was also successful without any *N*-protection.

Table 14 Preparation of *N*-substituted indazole boronates



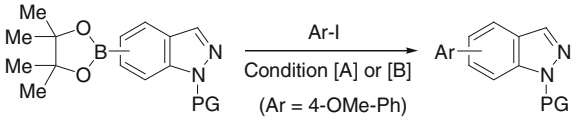
Entry	PG	Halides	Bpin	Time (min)	Yield (%)
1	SEM	4-Br	4-Bpin	45	98
2[a]	SEM	5-I	5-Bpin	15	85
3[b]	SEM	5-Br	5-Bpin	30	67
4	SEM	6-Br	6-Bpin	15	98
5	SEM	7-Br	7-Bpin	240	79
6	Ac	4-Br	4-Bpin	15	98
7[c]	Ac	5-Br	5-Bpin	240	97
8	Ac	6-Br	–	–	–
9	Ac	7-Br	–	–	–
10	THP	4-Br	4-Bpin	180	87
11	THP	5-Br	5-Bpin	180	89
12	THP	6-Br	6-Bpin	240	77
13	THP	7-Br	7-Bpin	240	18

[a]Reaction was performed at 80°C in DMSO instead of refluxing dioxane
[b]Reaction in DMSO at 80°C for 15 min gave 5,5′-bis(indazole) in 87% yield
[c]For *N*-acetyl-3-methyl-5-bromoindazole, the pinacol boronates were prepared in 90% by heating the reaction mixture at 80°C in DMSO for 24 h

4.6 General Methods for Metalation of Benzenoid Ring of Indazoles

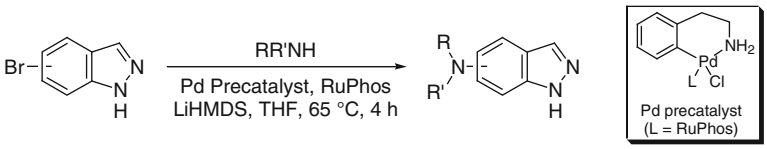
Collot reported the preparation of a variety of synthetically useful indazole boronic esters (Table 14) [296]. Reaction of bromoindazoles with bis(pinacolato)diboron in the presence of catalytic $PdCl_2(dppf)\cdot CH_2Cl_2$ and KOAc afforded the corresponding indazole boronates in good yields (entries 1–7 and 10–12); however, controlled reaction time was essential to minimize the formation of bis(indazole) byproducts. Thus, SEM-protected 5-iodoindazole gave undesired 5,5′-bis(indazole) in 85% yield when the reaction time was extended to 120 min (compared to 85% yield of the desired boronate after 15 min). However, the boronate formation completely failed for *N*-acetyl-6-bromo- and 7-bromoindazoles; the corresponding *NH*-indazoles were isolated as the major products under these conditions (entries 8 and 9). A low yield (18%) of the boronate was obtained from THP-protected 7-bromoindazole due to the steric hindrance of the THP group on C-7 of indazole (entry 13). The results for the Pd-catalyzed coupling of these boronates with 4-iodoanisole under two slightly different conditions are summarized in Table 15.

Table 15 Suzuki–Miyaura coupling of indazole boronates with 4-iodoanisole



[A] : $Pd(PPh_3)_4$, K_3PO_4, DMF, 65 °C.
[B] : $Pd(PPh_3)_4$, Cs_2CO_3, dioxane–H_2O (2:1), reflux.

Entry	Bpin	PG	Method	Yield (%)
1	4-Bpin	Ac	A	40
2	5-Bpin	SEM	A	65
3	5-Bpin	THP	A	34
4	6-Bpin	SEM	A	25
5	4-Bpin	THP	B	50
6	6-Bpin	THP	B	64
7	7-Bpin	THP	B	73
8	7-Bpin	SEM	B	37



Scheme 164

Using a RuPhos-based catalyst system (1 mol% Pd-precatalyst and 1 mol% RuPhos), Buchwald reported the amination of 4-, 5-, and 6-bromoindazoles with secondary amines to afford the corresponding aminoindazoles in high yields (Scheme 164, Fig. 13) [297]. These conditions were suitable even for the sterically challenging 7-bromoindazole, but required a longer reaction time (16 h). Since the *N*-protection of indazole often generates a mixture of *N*-1 and *N*-2 regioisomers, this amination protocol is advantageous over the other related procedures where protection of indazole nitrogen is necessary to avoid undesired homo-coupling and/or catalyst deactivation.

Similar Pd-catalyzed amination of 4-, 5-, and 6-bromoindazoles with primary amines was achieved employing a BrettPhos-based catalyst system (1 mol% Pd-precatalyst and 1 mol% Brettphos) (Scheme 165, Fig. 14) [297]. A longer reaction time (16 h) was required for the amination of 7-bromoindazole due to steric issue. Of note, 2 mol% precatalyst and 2 mol% ligand was needed to maximize the yield in the coupling of 7-bromoindazole with 3,5-dimethoxyaniline.

Notably, a *t*-BuXPhos-based catalyst system (1 mol% of Pd-precatalyst and 1 mol% of ligand) was effective for some instances, where the RuPhos and

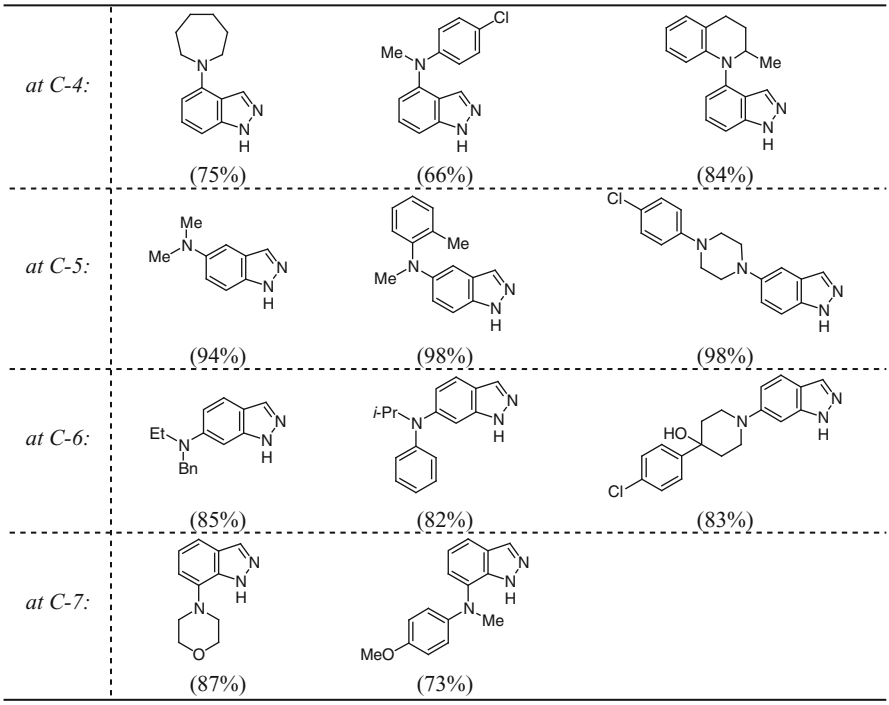
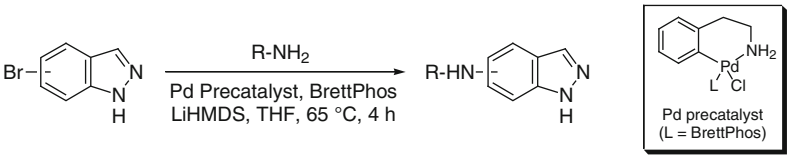


Fig. 13 Amination of 4-, 5-, 6-, 7-bromoindazoles using RuPhos-based Pd-catalyst



Scheme 165

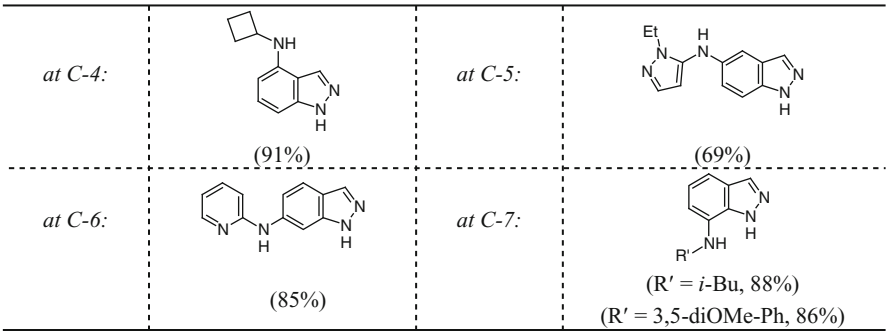


Fig. 14 Amination of 4-, 5-, 6-, 7-bromoindazoles using BrettPhos-based Pd-catalyst

BrettPhos catalyst systems failed to provide the aminoindazoles. In fact, bulky *t*-BuXPhos has the ability to facilitate the challenging (slow) reductive elimination step for the substrate with low nucleophilicity.

In conclusion, recent advances in the metalation chemistry of pyrazoles and indazoles enabled the researchers to effect regioselective functionalization of these heterocycles. Overall, these improvements have provided immense impetus to explore the diversity space in the drug-discovery landscape.

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Metalation Reactions of Isoxazoles and Benzisoxazoles

Jeanese C. Badenock

Abstract Metalation chemistry continues to play an active role in the derivatization of isoxazoles and benzisoxazoles. Some of these derivatives, which include fragmentation products, have shown their utility as supramolecular entities and pharmacologically active agents.

Keywords Benzisoxazole · Direct metalation · Grignard reagent · Halogen–metal exchange · Heck · Hiyama · Isoxazole · Lithium · Metalation · Negishi · Palladium · Songashira · Stille · Suzuki

Contents

1 Introduction 262
2 Isoxazoles 262
2.1 Metalation with Ring Cleavage 262
2.2 Direct Metalation Without Ring Cleavage 270
2.3 Halogen–Metal Exchange 271
2.4 Lateral Metalation 272
2.5 Palladium Catalyzed Coupling 276
2.6 Metal Complexes 295
3 Benzisoxazoles 295
3.1 Metalation with Ring Cleavage 295
3.2 Palladium-Catalyzed Coupling 297
References 300

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1 Introduction

Isoxazoles and their benzo-fused analogues are well represented in the literature of naturally occurring alkaloids and synthetic derived useful chemicals. Their presence in biologically active drugs [1–6], agrochemicals [7–9] and materials-based compounds [10–12] perpetuates the search for modern routes to functionalize and derivatize these heterocycles while their unique chemistry [13] continues to lead to some interesting ring-opened products. With respect to metals-based chemistry, there has been some earlier coverage of metalation and subsequent reactions of these heterocycles with particular attention being placed on lithiation and palladium catalyzed reactions [14–18].

2 Isoxazoles

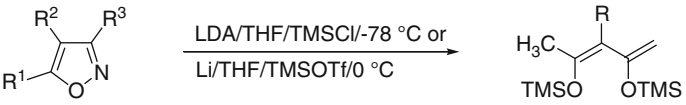
Structurally, the isoxazole ring demonstrates all the typical characteristics of an electron-rich aromatic heterocyclic compound but the weak character of the nitrogen–oxygen bond expands its utility into the realm of masked functionalities [19].

2.1 Metalation with Ring Cleavage

Metal-induced ring cleavage of isoxazoles is well documented and dates back to Claisen and Stock in 1891 [20]. Primarily, attempts at deprotonation of the C-3 proton of the ring leads convincingly to a range of ring-opened products ranging from butadienes to enaminoketones. In addition, isoxazoles substituted at the C-3 position react at the C-5 position under these conditions to generate a variety of ring fragmented and rearranged products.

2.1.1 Lithium

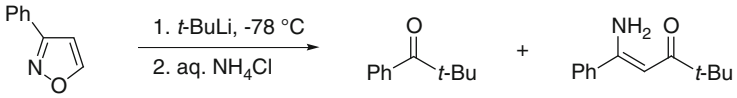
Isoxazoles have been proven to be efficient precursors in the construction of bis(siloxy)butadienes, which act as masked β-diketones and have been used as dienes in Diels–Alder reactions [21]. As such, treatment of 4-acetyl-5-methylisoxazole (**1a**) with lithium diisopropylamide (LDA) at low temperature followed by the addition of excess TMSCl and catalytic amounts of zinc chloride resulted in the formation of the cyano-bis(siloxy)butadiene **2a**. It is thought that ring cleavage occurs due to attack by LDA at the H-3 position followed by quenching of the resulting enolate with TMSCl and further generation of a silyl enol ether from the remaining 4-acetyl group. Dimethyl- and trimethyl-substituted isoxazoles **1b** and **1c**, respectively, also underwent similar cleavage with granulated lithium in wet THF followed by slow addition of excess triethylamine or trimethylsilyl triflate.



1a: R^1 = Me, R^2 = Ac, R^3 = H
1b: R^1 = R^3 = Me, R^2 = H
1c: R^1 = R^2 = R^3 = Me

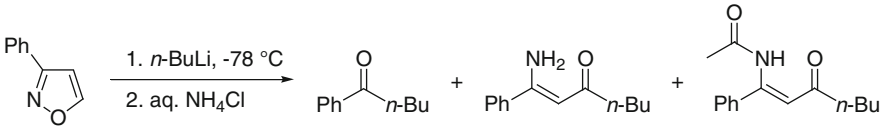
2a: R = CN (93%)
2b: R = H (91%)
2c: R = Me (87%)

Di Nunno and coworkers reported the results of a recent investigation of the reaction of 3-phenylisoxazole (**3**) with alkyllithiums [22]. This time however, treatment of **3** with *t*-butyllithium revealed the formation of *t*-butyl phenyl ketone (**4**) and enaminone **5**, as the minor product, after quenching with aqueous NH_4Cl. The mechanism for the formation of the two products is thought to first involve the H-5 abstraction and ring fragmentation of the isoxazole ring to generate benzonitrile, which further reacts with *t*-BuLi to give the phenyl ketone and the ethynolate ion – which in turn leads to the enaminone.



3 **4** (86%) **5** (14%)

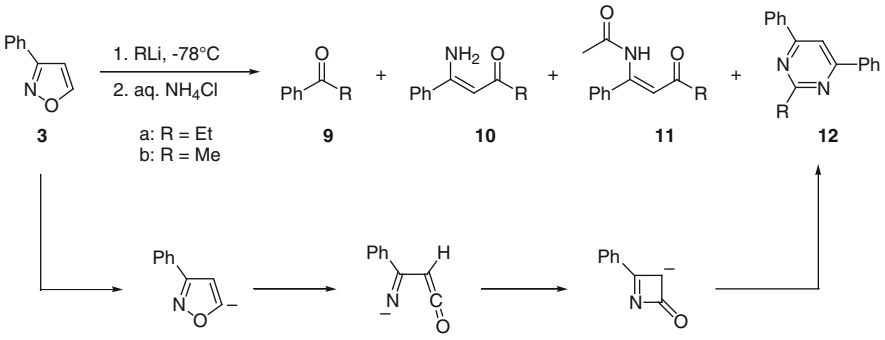
In a similarly unprecedented reaction, the addition of *n*-butyllithium to **3** generated valerophenone **6** (the ring fragmentation product), (*Z*)-1-amino-1-phenyl-1-hepten-3-one (**7**), and the *N*-acetyl derivative **8**; with increased yields of the two latter products being observed with excess *n*-butyllithium over prolonged reaction times.



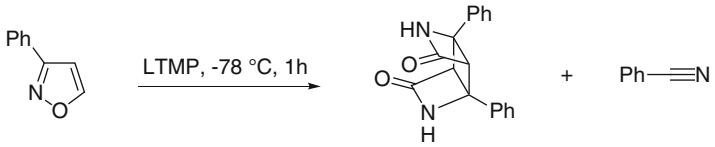
3 **6** **7** **8**

Substrate:*n*-BuLi	Time (h)	**6**	**7**	**8**
1:2	1	50%	40%	10%
1:3	1	45%	45%	10%
1:5	8	37%	43%	20%

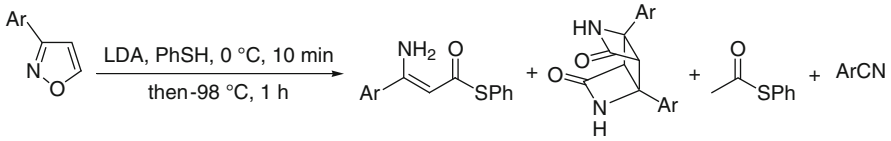
Reactions of **3** with EtLi and MeLi, however, generated 2-ethyl-4,6-diphenylpyrimidine (**12a**) and 2-methyl-4,6-diphenylpyrimidine (**12b**), respectively, as additional products. These are presumed to be formed by nucleophilic attack by the alkyllithium on an azetinone – generated by cyclization of lithium iminoketene – and subsequent reaction with benzonitrile (**14**), followed by ring-closure with aromatization.



Di Nunno also re-examined the reaction of 3-phenylisoxazole (**3**) with lithium 2,2,6,6-tetramethylpiperidide (LTMP) and extended the chemistry to other non-nucleophilic lithium amides such as LDA and lithium hexamethyldisilazide (LHMDS) [23]. In all cases, the bis-β-lactam, 2,6-diphenyl-3,7-diazatricyclo [4.2.0.0^{2,5}]octan-4,8-dione (**13**) was isolated in high yields with no trace of products of nucleophilic addition subsequent to isoxazole ring opening and ring fragmentation, as exemplified below. X-ray diffraction analysis further confirmed the *syn* geometry of **13** and gave evidence of the importance of Li^+ chelation during dimerization. This was also strengthened by a comparative analysis of the reaction of **3** with bis(trimethylsilyl)amides with different metal counterions (Na^+, K^+) – the reactivity of which paralleled the decreased binding affinity going from Li^+ to K^+. A more extensive investigation of the reaction of 3-arylisoxazoles with LDA revealed a dependence on the electronic effects of the substituent present in the aryl moiety [24].



When benzenethiolate, together with LDA, was allowed to react with 3-arylisoxazoles **15** at lower temperatures (−98°C), *N*-unsubstituted β-enamino thioesters **16** were produced, as the major product, in fair to good yields [25]. The highest yields were observed when the aryl group possessed electron-withdrawing groups in the *para*-position on the isoxazole and hence stabilized the lithium iminoketene intermediate. 3-Aryl-5-phenylthio-2-isoxazolines also reacted to form thioesters when treated with excess LDA at low temperatures. In these examples, the isoxazoline is thought to lose benzenethiol to form the arylisoxazole, which then proceeds via the iminoketene intermediate to products.



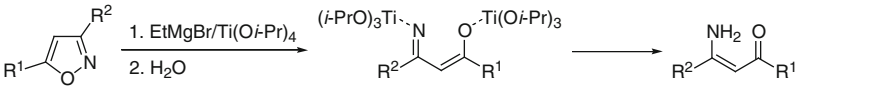
15 **16** **17** **18** **19**

Entry	Ar	**16**	**17**	**18**	**19**
1	Ph	70%	4%	9%	11%
2	4-ClC_6H_4	75%	5%	6%	10%
3	4-$CF_3C_6H_4$	72%	–	12%	15%
4	4-FC_6H_4	58%	–	12%	27%

4- and 5-Silylated isoxazolium tetrafluoroborates – formed from reaction of the corresponding silyl isoxazole and tetraethyloxonio tetrafluoroborate – underwent reductive ring-opening upon treatment with lithium dimethylcuprate to afford β-enaminoketones bearing acylsilane or α-silylketone moieties [26]. Reaction of the salts with alkyllithiums produced isoxazolines and ring-opened/rearrangement products depending on the nature of the alkyllithium.

2.1.2 Titanium

β-Enaminoketones **22** have been observed through a reductive ring cleavage of 3, 5-disubstituted isoxazoles **20** using a low-valent titanium(III) isopropoxide reagent, generated by equimolar amounts of ethyl magnesium bromide and titanium(IV) isopropoxide [27]. The intermediate bis-titanium alcoholate species (**21**) is thought to occur due to homolytic fission of the N–O bonds, which upon workup generates the enaminoketones in good yields.

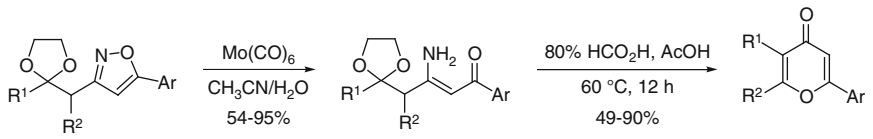


20 **21**

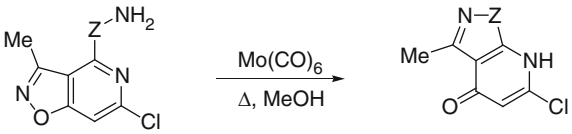
22a: $R^1 = C_4H_9$; $R^2 = C_3H_7$ (95%)
22b: R^1 = Ph; $R^2 = C_3H_7$ (71%)

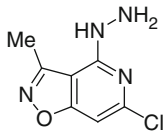
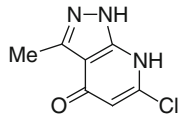
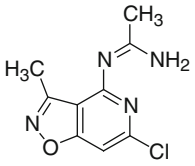
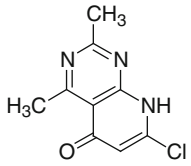
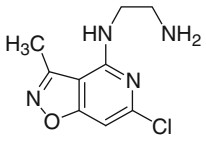
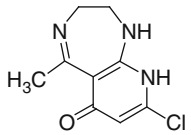
2.1.3 Molybdenum

Molybdenum hexacarbonyl induced reductive cleavage of isoxazoles has also been reported and was utilized by Li and coworkers en route to pyran-4-ones **25** [28]. Isoxazoles **23**, bearing a 2-oxoalkyl side chain on the C-3 position, converted easily to the enaminoketones upon reaction with $Mo(CO)_6$ in moist acetonitrile. Subsequent acid catalyzed cyclization proceeded without incident in moderate to good yields.

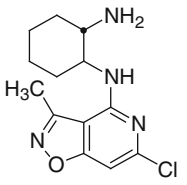
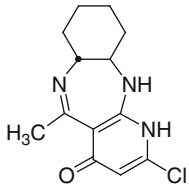
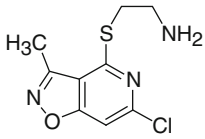
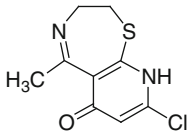
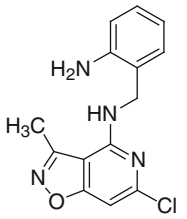
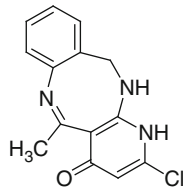


3-Methylisoxazolopyridines substituted with amino- and thio-groups on the pyridine ring underwent one-step ring-opening/ring-closure sequences in the presence of $Mo(CO)_6$ to prepare functionalized pyrido-condensed heterocycles [29]. The site-selective introduction of the nucleophiles at position 4 of the 4,6-dichloroisoxazolo[4,5-*c*]pyridine derivative proceeded to **26a–f** in good yields. Subsequent unmasking of the keto or imino groups led to nucleophilic attack by the NH_2 group to give fused heterocycles including the benzopyridodiazocine **27f**.

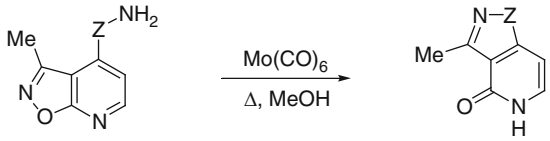


Entry	Amine	Product	%Yield
a			66
b			65
c			35

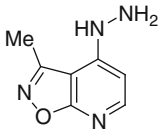
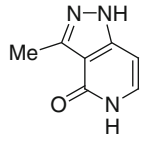
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Entry	Amine	Product	%Yield
d			41
e			67
f			46

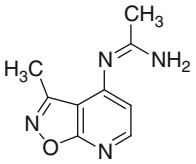
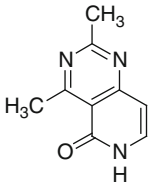
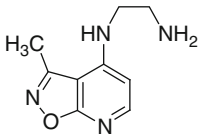
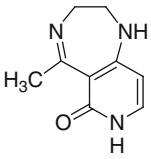
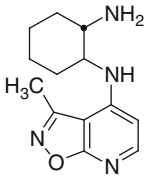
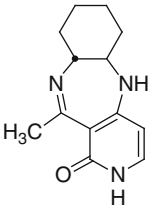
This strategy was also extended to the isoxazolo[5,4-*b*]pyridine system. Once again reaction of **28a**–**d** with $Mo(CO)_6$ resulted in good yields of the heteroaryl condensed pyridines **29a**–**d**.



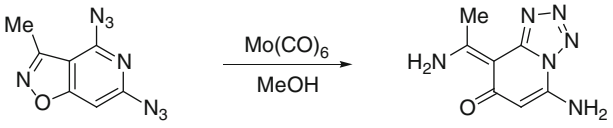
28 **29**

Entry	Amine	Product	%Yield
a			90

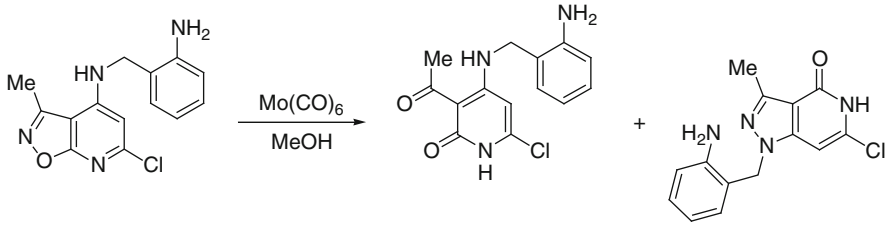
(continued)

Entry	Amine	Product	%Yield
b			65
c			55
d			75

More recently, Donati et al. explored similar reactions with isoxazole derivatives incapable of condensation with the NH_2 group [30]. As such when 4,6-diazido-3-methylisoxazolo[4,5-*c*]pyridine **30** was heated with $Mo(CO)_6$, the tetrazolo-pyridone **31** was obtained as a result of the ring opening of the isoxazole ring, selective reduction of the 6-azido group and finally tetrazole formation. Similar ring fragmentations were observed with isoxazolo[5,4-*b*]pyridine **32** but unlike the [4,5-*c*] condensed system this generated two products; the acetylpyridone **33** and the pyrazolo[4,3-*c*]pyridin-4-one **34**.

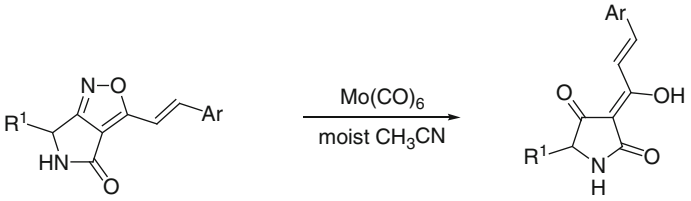


30 **31** (50%)



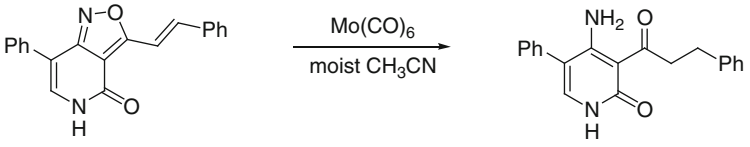
32 **33** (36%) **34** (39.5%)

The N–O bond cleavage of 3-(2-arylethenyl)isoxazole derivatives **35**, prepared from 3-methylpyrrolo[3,4-*c*]isoxazoles by deprotonation and condensation with aromatic aldehydes, occurs with $Mo(CO)_6$ in moist acetonitrile [31]. The 3-enoyltetramic acids **36a–i** were obtained in high yields (83–97%) with no indication of alkene reduction. One recent example, however, illustrated that similar treatment of 7-phenyl-3-(2-phenylethenyl)isoxazolopyridone **37** with $Mo(CO)_6$ in moist acetonitrile did result in ring cleavage but with simultaneous alkene side chain reduction [32].



35

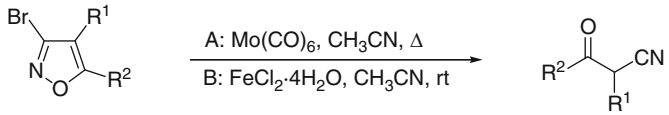
36a: R^1 = Me, Ar = Ph (92%)
36b: R^1 = Me, Ar = 4-$O_2NC_6H_4$ (83%)
36c: R^1 = Me, Ar = 4-$MeOC_6H_4$ (86%)
36d: R^1 = $CHMe_2$, Ar = Ph (97%)
36e: R^1 = $CHMe_2$, Ar = 4-$O_2NC_6H_4$ (96%)
36f: R^1 = $CHMe_2$, Ar = 4-$MeOC_6H_4$ (96%)
36g: R^1 = CH_2CMe_2, Ar = Ph (86%)
36h: R^1 = CH_2CMe_2, Ar = 4-$O_2NC_6H_4$ (95%)
36i: R^1 = CH_2CMe_2, Ar = 4-$MeOC_6H_4$ (87%)



37 **38** (50%)

Substituted 3-bromoisoxazoles **39a–h** have also been transformed into β-ketonitriles **40a–h** facilitated by either molybdenum hexacarbonyl or iron(II) chloride tetrahydrate [33]. The iron-mediated ring openings – thought to proceed through a

radical anion intermediate [34, 35] – gave better yields of the desired β-ketonitriles for most of the isoxazoles with the exception of alcohol **39d** where it is presumed that a complex forms between Fe^{3+} and the hydroxy ketonitrile **40d**, which hampers isolation of the product.

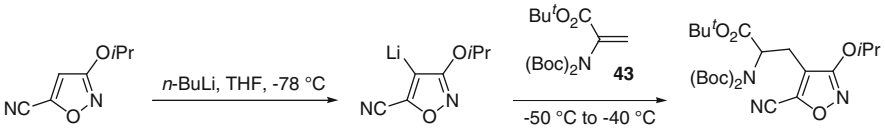


39 **40**

Isoxazole	R^1	R^2	%Yield under A	%Yield under B
39a	H	Ph	78	90
39b	H	Bu	57	86
39c	H	$AcOCH_2$	28 (38% **40d**)	72
39d	H	$HOCH_2$	76	Trace
39e	Et	Et	70	82
39f	Ph	Ph	65	70
39g	H	$NCCH_2CH_2$	82	86
39h	H	$NCCH_2CH_2CH_2$	85	95

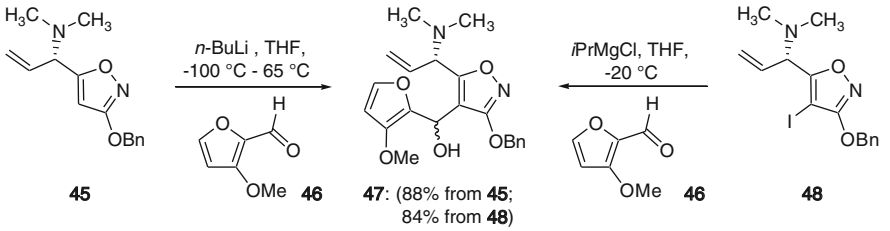
2.2 *Direct Metalation Without Ring Cleavage*

Metalation at position C-4 on the isoxazole ring has been well documented and is directly influenced by the substituents at the C-3 and C-5 positions of the ring. Earlier reports indicate that alkoxy and thioalkoxy groups, aryl groups and halogen atoms function particularly well in these positions, possibly due to their directing effects [36–38]. In an investigation of the synthesis and pharmacology of tetrazolyl analogues of 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), an ionotropic glutamate receptor antagonist, metalation at position 4 of 3, 5-disubstituted isoxazoles allowed for the introduction of a critical amino acid moiety [39]. One such example, outlined below, involved the lithiation of nitrile **41** at C-4 using *n*-butyllithium at −78°C followed by treatment of the 4-isoxazolyllithium species **42** with amino acrylate **43**. The resulting Michael reaction occurred in 45% yield with the cyano group unaltered. The 4-iododerivative of **41** was also generated in slightly better yields using a similar methodology (*n*-BuLi then I_2).



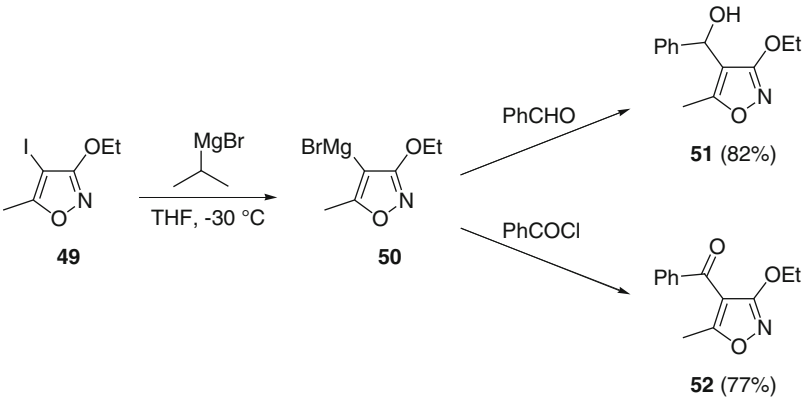
41 **42** **44** (45%)

A similar strategy was also adopted by Myers and coworkers in their synthesis of a key precursor to the tetracycline antibiotics [40]. The sequence involved the convergent coupling of the isoxazole ring of the (*S*)-allylic amine **45** – achieved via metalation using *n*-butyllithium in THF at −100°C → −65°C – and 3-methoxyfurfural (**46**). An epimeric mixture of secondary alcohols **47** was afforded in a 1.3:1 ratio with 88% overall yield. The authors also reported that higher temperatures and the use of other bases promoted allylic metalation, and further disclosed that magnesium–halogen exchange of 4-iodoisoxazole **48** led to a higher proportion of the *S*-alcohol **47** when the 4-magnesium anion was trapped with **46**.



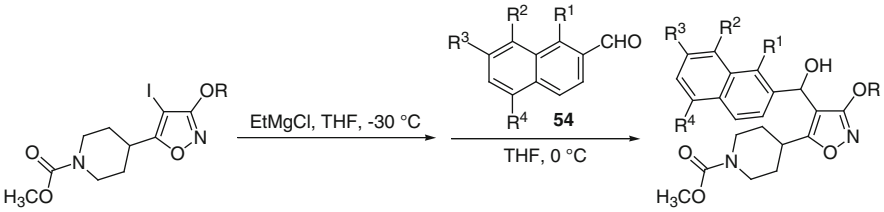
2.3 Halogen–Metal Exchange

Iodine/magnesium exchange reactions have been well established for the generation of arylmagnesium halides. Indeed 4-iodoisoxazoles have recently been converted in like manner, utilizing alkylmagnesium halides. In one such example, 3-ethoxy-4-iodo-5-methylisoxazole (**49**) converted effectively to the Grignard intermediate **50**, before reaction with benzaldehyde and benzoyl chloride to give the corresponding alcohol **51** and aldehyde **52**, in 82% and 77%, respectively [41].



In an independent investigation of competitive γ-aminobutyric acid ($GABA_A$) antagonists, Frølund et al. introduced a substituent in the 4-position of the *O*-alkylated 3-isoxazolol ring of **53a** and **53b** using a similar metal exchange protocol [42].

Hence, reaction with ethylmagnesium chloride or bromide followed by quenching with naphthalene carbaldehydes **54a–f** generated alcohols **55a–f** in 30–72% yield, which upon further modification were pharmacologically characterized.

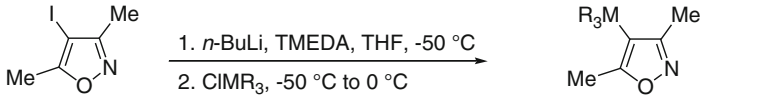


53a: R = Bn
53b: R = ^{i}Pr

55

Alcohol	R	R^1	R^2	R^3	R^4	%Yield
55a	Bn	Br	H	H	H	72
55b	^{i}Pr	H	Br	H	H	40
55c	^{i}Pr	H	H	Br	H	59
55d	^{i}Pr	H	H	H	Br	30
55e	Bn	F	H	H	H	35
55f	^{i}Pr	Cl	H	H	H	54

4-Dimethylphenylsilylisoxazole (**57a**) and 4-tributylstannyl-3,5-dimethylisoxazoles (**57b**) have also been prepared, in good yields, by an iodine/lithium exchange followed by coupling with chlorosilanes or chlorostannanes [43]. Silylcupration of 4-iodoisoxazole **56** with lithium dimethylphenylsilyl(methyl) cuprate ($PhMe_2Si(Me)CuLi$) also introduced the dimethylphenylsilyl group to the C-4 position of the isoxazole ring of **56** in 80% yield.

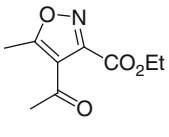


56

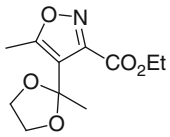
57a: $MR_3 = SiMe_2Ph$ (70%)
57b: $MR_3 = SnBu_3$ (72%)

2.4 Lateral Metalation

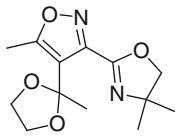
Analogues of AMPA have also been developed using lateral metalation [44]. As such, lithiation of the C5-methyl side chain of ethyl 4-acetyl-5-methyl-3-isoxazolyl carboxylate (**58**), the 1,3-dioxolanyl protected counterpart **59** and the 4′,4′-dimethyl-2-oxazolinyl protected **59** was attempted. In all cases, unidentified decomposition products or low yield of the desired products resulted.



58

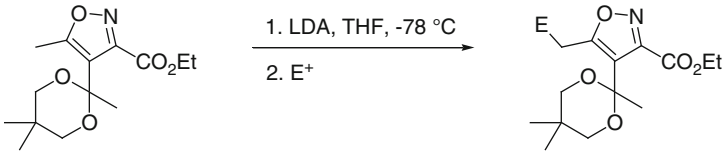


59



60

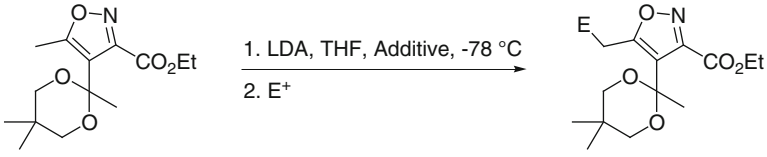
The 5,5-dimethyl-1,3-dioxanyl protected analogue **61**, however, reacted cleanly at the 5-methyl position with LDA and electrophilic quenching of the resulting anion with methyl iodide, benzyl bromide, acetone, trimethylsilyl chloride, trimethylstannyl chloride, dimethyl disulfide and phenyl isocyanate gave fair to good yields of the substituted isoxazoles **62a**–**g**. The ketone dimer, formed from the intermolecular condensation of one C-3 ester with the 5-lithio species, was also observed and characterized as the major by-product.



61 62

Entry	E^+	Product (E)	%Yield
1	CH_3I	**62a** (CH_3)	81
2	$PhCH_2Br$	**62b** ($PhCH_2$)	72
3	CH_3COCH_3	**62c** [$C(OH)Me_2$]	68
4	$(CH_3)_3SiCl$	**62d** ($Si(CH_3)_3$)	66
5	$(CH_3)_3SnCl$	**62e** ($Sn(CH_3)_3$)	42
6	CH_3SSCH_3	**62f** (SCH_3)	61
7	PhNCO	**62g** (CONHPh)	68

Optimization studies were also performed on this reaction and the effects of additives such as LiCl and the cation-complexing agent HMPA were investigated. In all instances, the addition of LiCl resulted in increased yields while HMPA addition dramatically lowered the yield of entry **3** to <10%.



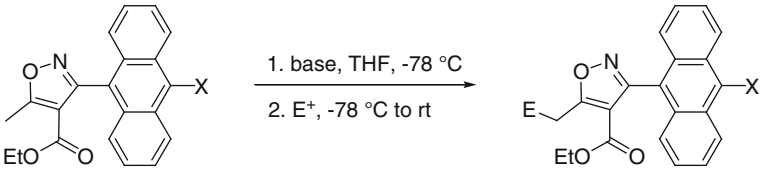
61 62

Entry	E^+	Additive	Product	Yield
1	PhCHO	None	**62h**	72%
2	PhCHO	LiCl (6 equiv.)	**62h**	95%
3	PhCHO	20% HMPA	**62h**	<10%

(continued)

Entry	E^+	Additive	Product	Yield
4	*p*-ClC_6H_4CHO	None	**62i**	67%
5	*p*-ClC_6H_4CHO	LiCl (6 equiv.)	**62i**	83%
6	Me_2CHCH_2CHO	LiCl (6 equiv.)	**62j**	79%
7	*trans*-Cinnamaldehyde	LiCl (6 equiv.)	**62k**	82%
8	EtBr	None	**62l**	65%
9	EtBr	LiCl (1.5 equiv.)	**62l**	83%
10	EtBr	LiCl (6 equiv.)	**62l**	0%

Natale and coworkers also demonstrated that lateral lithiation (LDA and *n*-BuLi) and electrophilic quenching was possible with isoxazoles **63** even in the presence of 10′-halogen groups on an anthracene ring [45]. The higher yields observed when the non-halogenated anthracenyl isoxazole ester **63a** was reacted with *n*-BuLi was attributed to a possible shielding of the ester group by the bulky anthracene group while the 10′-bromo anthracenyl isoxazole ester **63b** only retained the halogen when treated with LDA and showed overall lower yields than that observed with the 10′-chloro anthracenyl isoxazole ester **63c**.

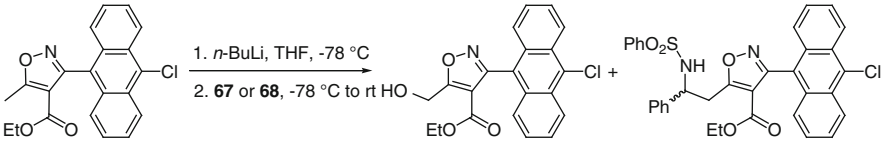


63a: X = H
63b: X = Br
63c: X = Cl

64: E = CH_3
65: E = CH_2Ph
66: E = $CH_2(OH)Ph$

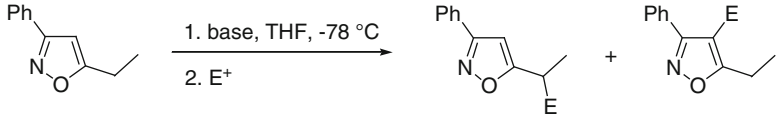
Product	X	Base	E^+	%Yield
64a	H	LDA	CH_3I	50
		n-BuLi	CH_3I	59
65a	H	LDA	$PhCH_2Br$	58
		n-BuLi	$PhCH_2Br$	68
65a	H	LDA	PhCHO	69
		n-BuLi	PhCHO	76
64b	Br	LDA	CH_3I	55
65b	Br	LDA	$PhCH_2Br$	62
66b	Br	LDA	PhCHO	70
64c	Cl	LDA	CH_3I	58
		n-BuLi	CH_3I	69
65c	Cl	LDA	$PhCH_2Br$	71
		n-BuLi	$PhCH_2Br$	75
66c	Cl	LDA	PhCHO	77
		n-BuLi	PhCHO	82

The introduction of an α-hydroxyl group at the isoxazole C-5 position of anthracenylisoxazoles, using lithium and potassium bases followed by quenching with Davis' oxaziridine (**67**) and (1R)-(−)-(10-camphorsulfonyl)oxaziridine (**68**), has also been described [46]. In one such example, highlighted below, isoxazole **63c** reacted with *n*-BuLi followed by Davis' oxaziridine **67** to generate the hydroxylated product **69** and significant amounts of the sulfonamide adduct **70**. A change to the (camphorsulfonyl)oxaziridine **68**, however, eliminated the formation of this adduct.



63c **69** (43% with **67**) (70% with **68**) **70** (36% with **67**) (0% with **68**)

Elaborations of the side chains of 3-aryl-5-alkylisoxazoles, via α-metalation, have also been reported by Natale et al. [47]. In one recent report, metalation of 3-phenyl-5-ethylisoxazole (**71**) was featured in order to determine the conditions for the regioselective incorporation of electrophiles on the α-position of the ethyl side chain [48]. Lithiation with *n*-butyllithium and *t*-butyllithium generated the 4-substituted products **73** as well as the desired side chain substituted products. This unexpected outcome was attributed to a combination of effects such as the relatively similar acidities of the C-α proton and the C-4 proton as well as the steric bulk of the *t*-BuLi. The less basic yet more sterically hindered lithium amides, LDA and LTMP, however, were more selective in their reaction with **71** and reacted solely at the side chain to give **72a** and **72b** in good yields.

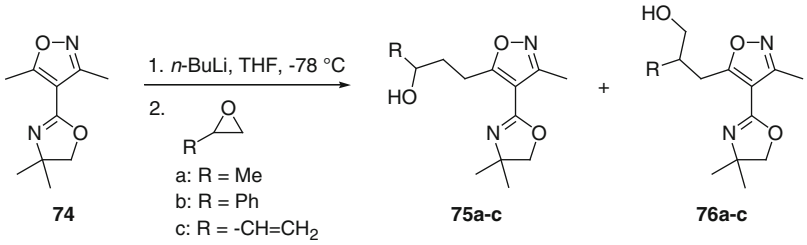


71 **72a**: E = CH_3 **72b**: E = CH_2Ph **73**: E = CH_3

Base	E^+	Substrate:E^+ ratio	% Product yields
n-BuLi	CH_3I	1:10	**72a** (40), **73** (14)
t-BuLi	CH_3I	1:10	**72a** (32), **73** (8)
LDA	CH_3I	1:10	**72a** (78)
LDA	$PhCH_2Br$	1:1.5	**72b** (81)
LTMP	CH_3I	1:10	**72a** (97)

The stabilized lithio alkyl isoxazole carbanion of **74** was also found to react, in fair to good yields, with propylene oxide regioselectively and with vinylic and benzylic epoxides in a less selective fashion – attributed to the competing steric

and electronic influences [49]. The surprising reactivity towards epoxides is thought to be due to the formation of a hemi-labile, rigid and sterically encumbered transition state, which brings the epoxide into close proximity to facilitate nucleophilic attack. Stereoselectivity was also observed upon quenching with chiral epoxides.

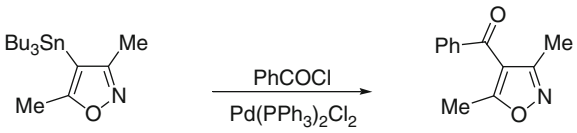


R	75:76 ratio	% Product yields
Me	100:0	66
Ph	70:30	86
–CH=CH_2	41:59	47

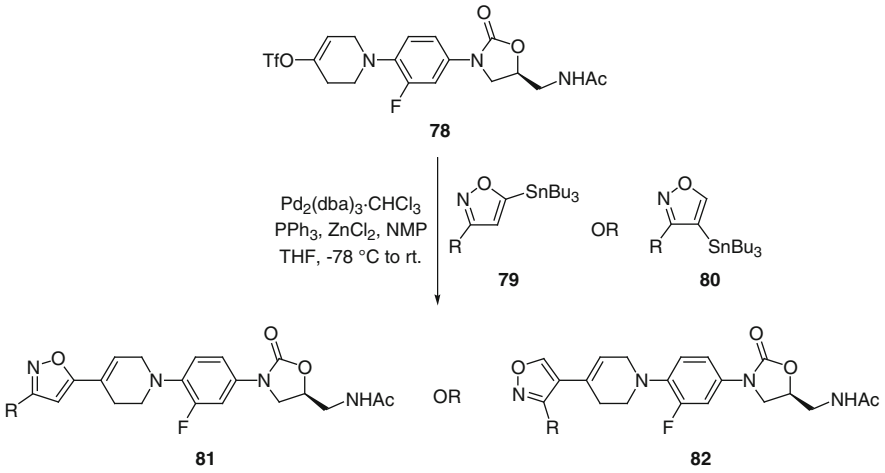
2.5 *Palladium Catalyzed Coupling*

2.5.1 Stille Reaction

A single example of a Stille coupling reaction of 4-tributylstannyl-3,5-dimethylisoxazole (**57b**), prepared by iodine/lithium exchange, with benzoyl chloride was reported [43].

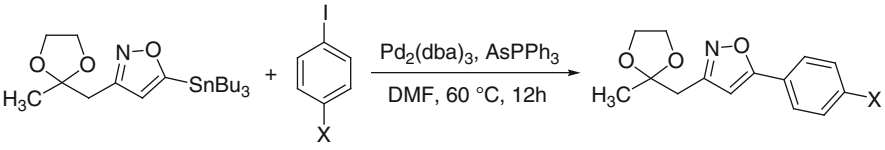


Tributylstannyl isoxazoles **79a**–**e** and **80a**, **b**, synthesized by [3+2] cycloaddition sequences, have been utilized in the synthesis of isoxazolyl tetrahydropyridinyl oxazolidinones antibacterial agents [50]. Stille coupling reactions of the isoxazoles and triflate **78** were accomplished with the palladium catalyst, tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct, triphenylphosphine and zinc(II) chloride in yields of 52–91% after 3 days. Higher yields were generally observed with 4-stannyl isoxazoles **80** than with the 5-stannyl counterparts.



Oxazolidinones	R	%Yield
81a	CH_3	86
81b	CN	58
81c	Cl	52
81d	CF_3	52
81e	CO_2Et	61
82a	Cl	93
82b	CN	91

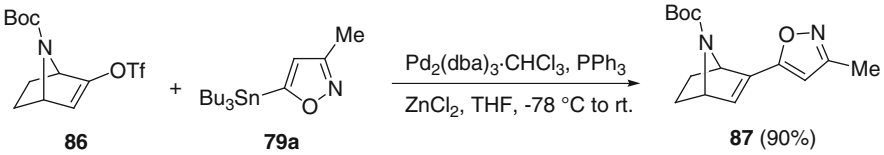
5-Stannyl isoxazole **83** has also been coupled directly with various substituted aryl iodides to afford disubstituted isoxazoles **85a–d** in moderate yields when subjected to Pd_2dba_3 and $AsPPh_3$ in hot DMF for 12 h [28].



83 **84**

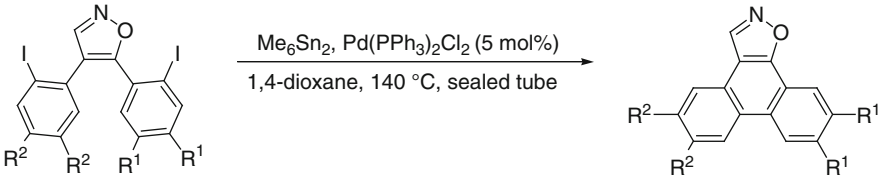
85a: X = H (31%)
85b: X = CO_2Me (60%)
85c: X = OMe (57%)
85d: X = Br (42%)

An investigation involving the synthesis and assaying for binding affinity of two major neuronal nicotinic receptor subtypes of epiboxidine and some of its analogues, employed a Stille cross-coupling reaction of 3-methyl-5-tributylstannylisoxazole **79a** and triflate **86** [51]. This account reported excellent yields of the 7-azabicyclo[2.2.1]hept-2-ene derivative **87**.



86 **79a** **87** (90%)

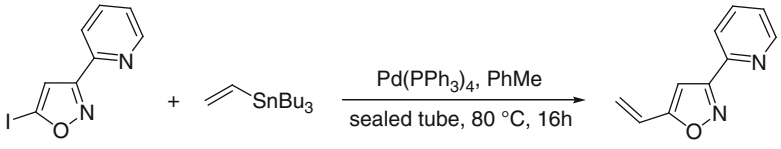
3-Ethoxy-4-iodo-5-methylisoxazole (**49**) has been coupled with 2- and 3-(tributylstannyl)pyridine in fair to excellent yields (92% and 49%, respectively) using a Stille coupling protocol [41]. Phenanthro[9,10-*d*]isoxazoles (**89**) have also been prepared through a one-pot stannylation/biaryl coupling sequence [52]. Diarylisoxazoles **88** were treated with hexamethylditin and the catalyst Pd $(PPh_3)_2Cl_2$ in 1,4-dioxane, while heating the reaction mixture at 140°C for 40 h in a sealed tube. The increased pressure proved crucial to the success of this reaction.



88 **89**

Product	R^1	R^2	%Yield
89a	H	H	89
89b	OMe	OMe	73
89c	OMe	H	81
89d	H	OMe	78

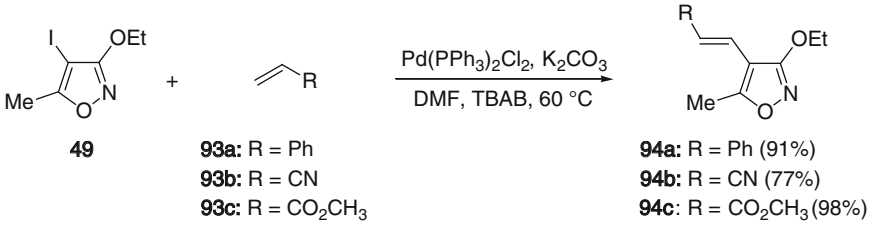
Effective Stille coupling of tributyl(vinyl)tin (**91**) and 2-(5-iodoisoxazol-3-yl) pyridine **90** is also observed using $Pd(PPh_3)_4$ in toluene at 80°C for 16 h [53].



90 **91** **92** (93%)

2.5.2 Heck Reaction

Palladium-catalyzed Heck reactions of 3-ethoxy-4-iodo-5-methylisoxazole (**49**) with styrene (**93a**), acrylonitrile (**93b**) and methyl acrylate (**93c**), using DMF as solvent, tetrabutylammonium bromide (TBAB) as the phase transfer reagent, and K_2CO_3 as base have been reported in excellent yields [41].

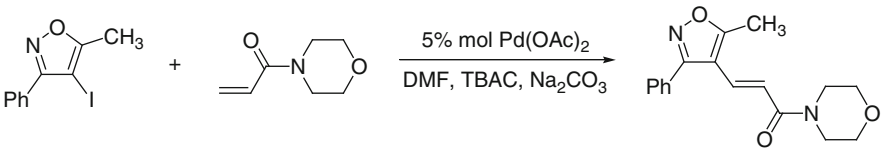


49

93a: R = Ph
93b: R = CN
93c: R = CO_2CH_3

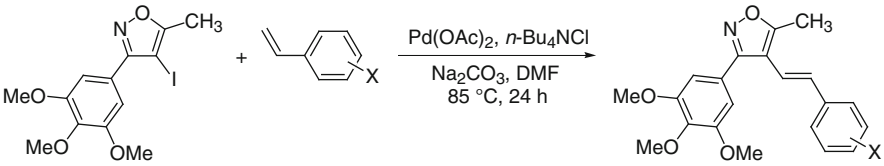
94a: R = Ph (91%)
94b: R = CN (77%)
94c: R = CO_2CH_3 (98%)

4-Iodo-5-methyl-3-phenylisoxazole (**95**), synthesized from the ICl-induced cyclization of the corresponding 2-alkyn-1-one *O*-methyl oxime [54], was allowed to react under Heck reaction conditions in the presence of *N*-acryloylmorpholine (**96**) and produced the α,β-unsaturated amide **97** in 93% yield [55].



95 **96** **97** (93%)

This methodology was further extended to create a small library of 3,4,5-trisubstituted vinyl isoxazoles using functionalized styrenes **99a–d** in a solution phase parallel synthesis approach [56]. Low yields of **100d** were obtained with 4-vinylbenzoic acid (**99d**), while the other three functionalized isoxazoles **100a–c** were obtained within the range of 60–73% yields after purification by preparative HPLC.

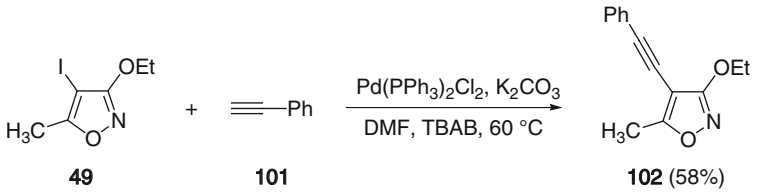


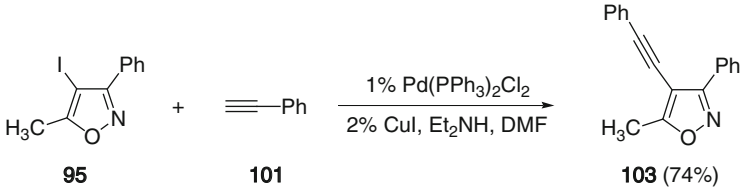
98 **99** **100**

Product	X	%Yield	%Purity
100a	4-OAc	60	94
100b	4-NH_2	67	93
100c	3-NO_2	73	95
100d	4-CO_2H	8	87

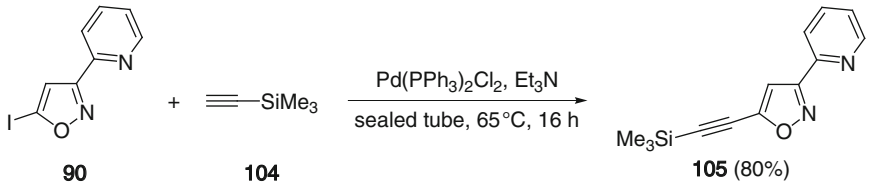
2.5.3 Sonogashira Reaction

3-Ethoxy-4-iodo-5-methylisoxazole (**49**) has been shown to undergo Sonogashira coupling with phenylacetylene (**101**) in 58% yield [41], while higher yields were reported for similar coupling of **101** with 4-iodo-5-methyl-3-phenylisoxazole (**95**) [55].

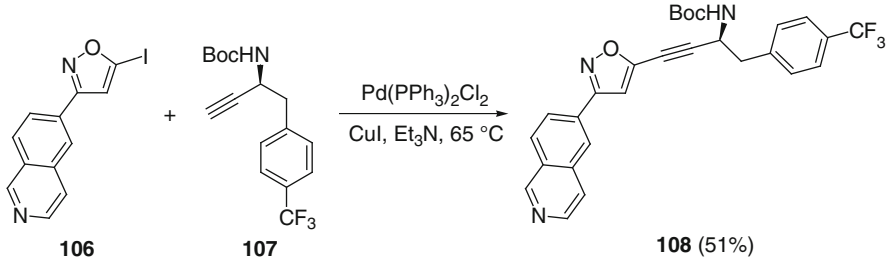




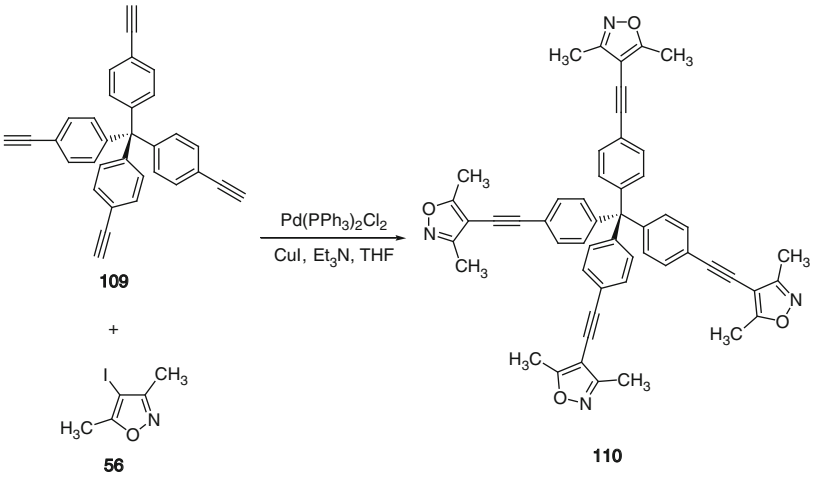
Ku et al. also reported high yielding coupling of TMS-acetylene (**104**) and 2-(5-iodoisoxazol-3-yl)pyridine **90** under Sonogashira reaction conditions using bis(triphenylphosphine)palladium dichloride as the catalyst [53].



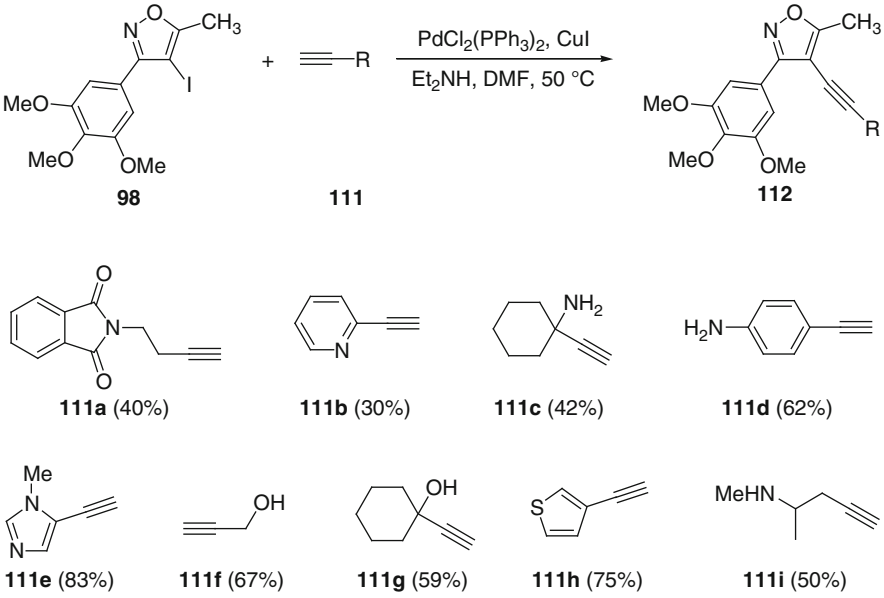
A Sonogashira coupling reaction was used to synthesize isoxazole analogues in an investigation of azole-based inhibitors of AKT/PKB for the treatment of cancer [57]. Coupling of 5-iodoisoxazole **106** with (*S*)-*tert*-butyl 1-(4-(trifluoromethyl) phenyl)but-3-yn-2-ylcarbamate (**107**) occurred in 51% yield in the presence of Pd $(PPh_3)_2Cl_2$ and copper(I) iodide.



A fourfold Sonogashira cross-coupling reaction was observed between the tetrahedral methane derivative, tetrakis(4-ethynylphenyl)methane (**109**), and 4-iodo-3,5-dimethylisoxazole (**56**) [58]. These so-called molecular tectons have potential widespread use as discrete supramolecular constructs.



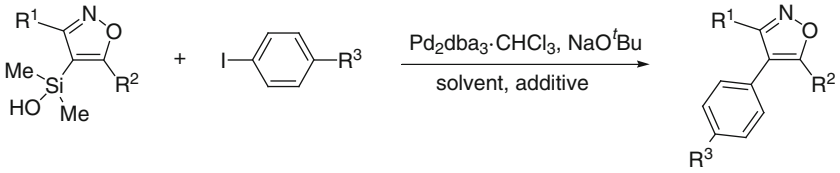
Larock and coworkers also generated a library of substituted isoxazoles using the Sonogashira coupling method [56]. As such, commercially available heteroatoms-containing acetylenes **111a–i** were selected and coupled with 3,5-disubstituted-4-iodoisoxazole **98**. High purities (94–99%) of all the products were observed while isolated yields ranged from 30% to 83%.



A single low yielding Songashira coupling reaction was reported using 3-butyl-5-isopropyl-4-iodoisoxazolines to generate a 4-alkynyl isoxazole [59].

2.5.4 Hiyama Reaction

The palladium catalyzed cross-coupling reaction of isoxazolylsilanols **113** has also been developed by Denmark et al. [60–62]. In these accounts 4-substituted silanols, along with minor quantities of the 5-substituted isomer, were prepared by a [3+2] cycloaddition between phenylethynyl silyl ether, and ethyl- or benzonitrile oxide. Subsequent cross-coupling with iodobenzenes **114** allowed for the formation of 3,4,5-trisubstituted isoxazoles **115a–l**, in optimized yields of 52–78%, under NaO^{t}Bu activation. The researchers also demonstrated that the use of copper(II) acetate not only affected the rate of the coupling reaction but also incurred desilylation of the silanol.

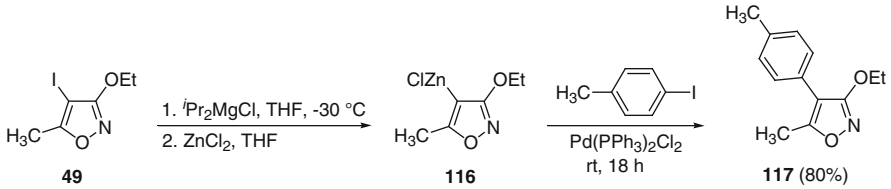


113 **114** **115**

Entry	R^1	R^2	R^3	Solvent	Additive	%Yield
a	Et	Ph	NO_2	PhMe, 40°C	$Cu(OAc)_2$	78
b	Et	Me	NO_2	PhMe, 40°C	$Cu(OAc)_2$	57
c	Et	Ph	OMe	PhMe, 80°C	$Cu(OAc)_2$	62
d	Et	Me	OMe	PhMe, 80°C	$Cu(OAc)_2$	52
e	Et	Ph	Me	PhMe, 80°C	$Cu(OAc)_2$	61
f	Et	Me	Me	PhMe, 80°C	$Cu(OAc)_2$	56
g	Ph	Ph	NO_2	Dioxane, 80°C	–	55
h	Ph	Me	NO_2	PhMe, 40°C	$Cu(OAc)_2$	63
i	Ph	Ph	OMe	Dioxane, 80°C	–	68
j	Ph	Me	OMe	Dioxane, 80°C	–	63
k	Ph	Ph	Me	Dioxane, 80°C	–	69
l	Ph	Me	Me	Dioxane, 80°C	–	60

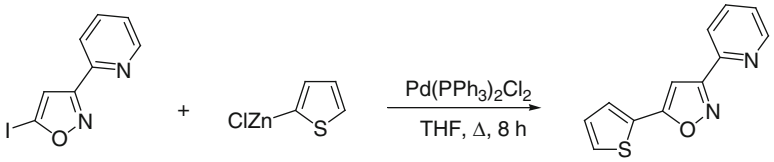
2.5.5 Negishi Reactions

Fewer examples of Negishi reactions with isoxazoles have been reported. Kromann's halogen–metal exchange/transmetalation/palladium-catalyzed coupling of 3-ethoxy-4-iodo-5-methylisoxazole (**49**) with 4-iodotoluene gave **117** in 80% yield after 18 h [41].



49 **116** **117** (80%)

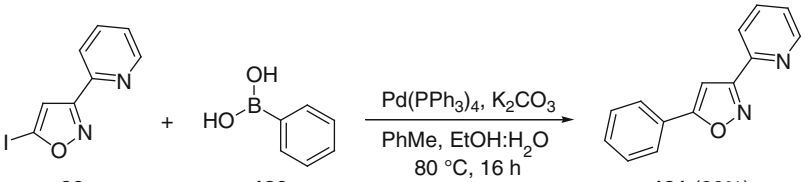
Likewise, 2-thiophenylzinc chloride (**118**) underwent Negishi coupling with 2-(5-iodoisoxazol-3-yl)pyridine (**90**) using $Pd(PPh_3)_2Cl_2$ in THF at reflux and produced the desired triaryl compound **119** in excellent yield [53].



90 **118** **119** (94%)

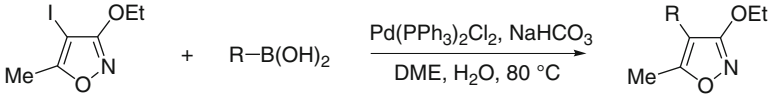
2.5.6 Suzuki Reaction

Haloisoxazoles, particularly iodoisoxazoles, have been utilized in numerous Suzuki coupling sequences with organoboronic esters and acids. 2-(5-Iodoisoxazol-3-yl) pyridine **90** was treated with phenylboronic acid (**120**), in $EtOH/H_2O$ and catalyzed by $Pd(PPh_3)_4$ at 80°C, to produce **121** in excellent yield [53].



90 **120** **121** (90%)

Kromann's initial examination of the Suzuki–Miyaura coupling between phenylboronic acid (**120**) and 3-ethoxy-4-halo-5-methylisoxazoles identified $Pd(PPh_3)_2Cl_2$ as a superior catalyst to the nickel counterpart $Ni(PPh_3)_2Cl_2$ and revealed higher % conversion with 3-ethoxy-4-iodo-5-methylisoxazole (**49**) cf. the 4-bromo counterpart [41]. A number of other arylboronic acid reagents were then coupled in high yields (76–96%) in aqueous 1,2-dimethoxyethane (DME) and basic sodium bicarbonate.

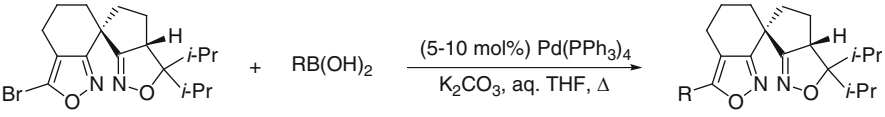


49

120: R = Ph
122b: R = 1-Naphthyl
122c: R = 2-Naphthyl
122d: R = 2-$PhOCH_3$
122e: R = 3-$PhOCH_3$
122f: R = 4-$PhOCH_3$
122g: R = 4-Pyridyl

123a: R = Ph (84%)
123b: R = 1-Naphthyl (85%)
123c: R = 2-Naphthyl (88%)
123d: R = 2-$PhOCH_3$ (80%)
123e: R = 3-$PhOCH_3$ (76%)
123f: R = 4-$PhOCH_3$ (90%)
123g: R = 4-Pyridyl (96%)

Enatiomerically pure chiral (isoxazole–isoxazoline) hybrid ligands based on an unsymmetrical spiro[4.5]decane backbone were successfully synthesized via the Suzuki–Miyaura cross-coupling reaction of arylboronic acids **125** and 3-bromo-3′,3′-diisopropyl-3′,3a′,4′,5,5′,6-hexahydro-4*H*-spiro[2,1-benzisoxazole-7,6′-cyclopenta[*c*]isoxazole] (**124**) [63]. The highest yields were obtained for ligands with a *para*-substituted phenyl group while lower yields were obtained for naphthyl substituted analogues. Substitution, however, of DME and $Ba(OH)_2{\cdot}8H_2O$ for THF and Na_2CO_3 allowed for the effective preparation of spiro hybrids possessing 9-anthryl, 2,6-xylyl-, 2-biphenyl-, 2-trifluoromethylphenyl-, and 3,5-bis(trifluoromethyl)phenyl groups in excellent yields.



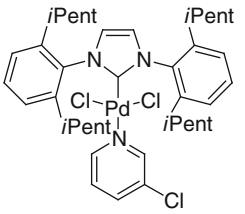
124 **125** **126**

Entry	R	Time (h)	% Yield
1	Ph	24	94
2	4-$MeOC_6H_4$	24	92
3	4-$MeSC_6H_4$	22	99
4	4-$Me_2NC_6H_4$	22	78
5	4-$MeOCOC_6H_4$	21	97
6	4-FC_6H_4	14	99
7	1-Naphthyl	24	43
8	2-Naphthyl	24	27
9[a]	9-Anthryl	24.5	57
10[a]	2,6-Xylyl	30	95
11[a]	2-Biphenyl	32.5	97
12[a]	2-$CF_3C_6H_4$	21	97
13[a]	3,6-$(CF_3)_2C_6H_3$	25.5	89

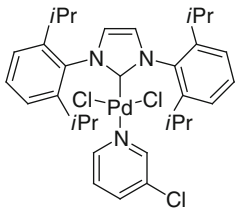
[a]DME and $Ba(OH)_2{\cdot}8H_2O$ were used instead of THF and K_2CO_3, respectively

A new monoligated Pd-N-heterocyclic carbene (Pd-NHC) complex, Pd-PEPPSI-IPent (**127**) (Pd-*P*yridine-*E*nhanced *P*recatalyst *P*reparation *S*tabilization and

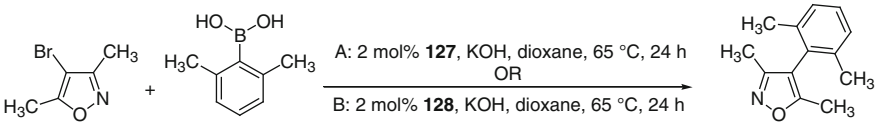
*I*nitiation-IsoPentyl) has been recently evaluated as a catalyst in the Suzuki–Miyaura coupling with a view to explore the effect of catalyst bulk on biaryl formation [64]. Generally, when compared to the less bulky Pd-PEPPSI-IPr (**128**), **127** was found to be more efficient and produced higher yields in most of the coupling sequences attempted. With 4-bromo-3,5-dimethylisoxazole (**129**), however, the trisubstituted isoxazole **131** was realized upon coupling with boronic acid **130**, in 87% yield, using catalyst **128**, and only 69% with catalyst **127**.



127

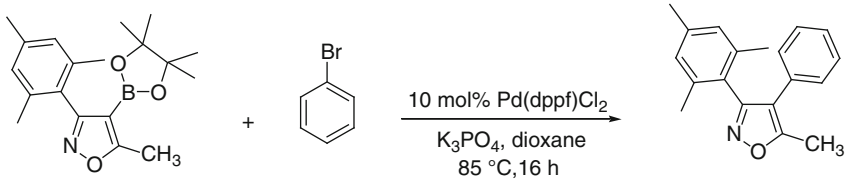


128

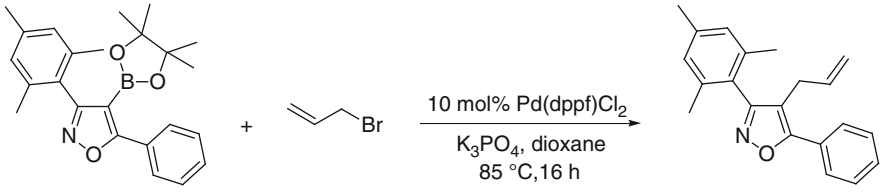


129 **130** **131 A**: 69%; **B**: 87%

Isoxazoleboronic esters have also been synthesized – mainly through [3+2] cycloaddition protocols – and coupled with alkyl- and arylhalides. An efficient palladium-catalyzed coupling of isoxazole 4-boronic esters was explored by Davies and coworkers in their synthesis of trisubstituted isoxazoles [65]. Bromobenzene (**133**) and allyl bromide (**136**) were treated with boronic esters **132** and **135**, respectively, to give very high yields of the coupled products **134** and **137** after 16 h at reflux.

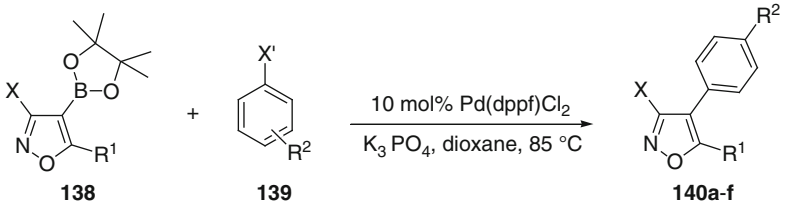


132 **133** **134** (97%)



135 **136** **137** (96%)

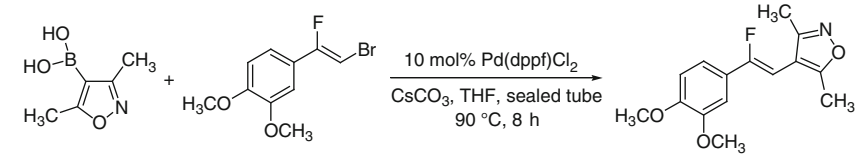
Harrity and coworkers have also used Suzuki coupling reactions to selectively functionalize the 4-position of 3-haloisoxazole boronic esters **138** [66]. Coupling with bromobenzene gave a modest yield (47%) of **141a** (R^1 = *n*-Bu; R^2 = H; X = Br) along with minor amounts of protodeboronated isoxazole (entry **1**). Increased yields of **140**, however, were observed with iodobenzene (entry **2**) and with other similarly activated systems.



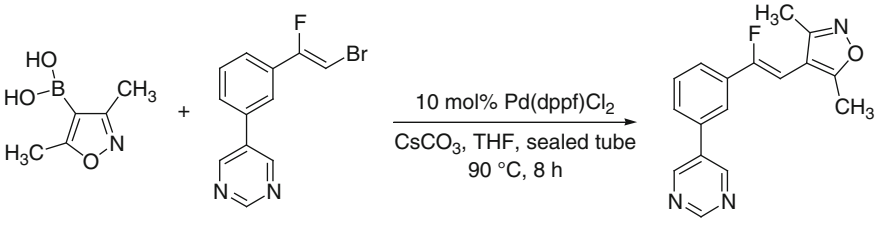
138 **139** **140a-f**

Entry	R^1	X	R^2	X′	%Yield
1	*n*-Bu	Br	H	Br	47
2	*n*-Bu	Br	H	I	98
3	Me	Br	H	I	89
4	*n*-Bu	Br	4-NO_2	I	73
5	*n*-Bu	Br	2-NO_2	I	87
6	*n*-Bu	Br	4-OMe	I	70
7	*n*-Bu	Cl	H	I	99
8	*n*-Bu	Cl	4-NO_2	I	92

Research focused on the design of conformationally restricted peptidomimetics utilized palladium cross-coupling reactions with arylboronic acids [67]. (*Z*)-1-Fluoro-2-bromostyrenes **142** and **144** underwent reaction with isoxazole 4-boronic acid **141** in resealable Carius tubes in refluxing THF at 90°C for 8–12 h in the presence of 10 mol% Pd(dppf)Cl_2 and $CsCO_3$. All of the reactions investigated proceeded with complete retention of the *Z*-stereochemistry in the coupled 1-fluorostilbenes.

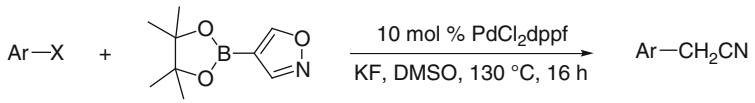


141 **142** **143** (50%)

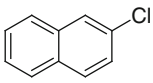
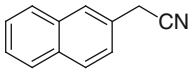
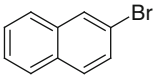
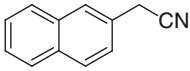
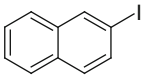
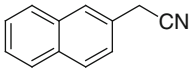
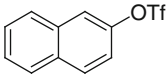
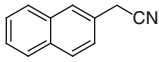
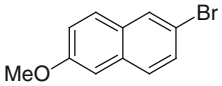
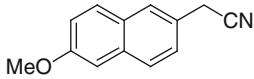
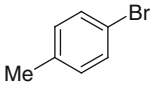
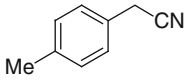
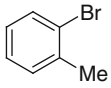
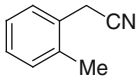


141 **144** **145** (73%)

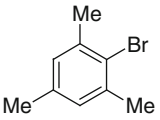
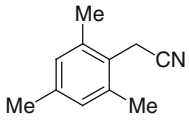
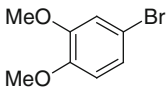
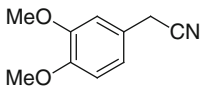
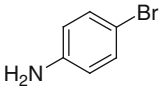
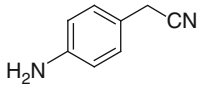
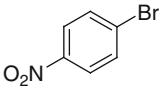
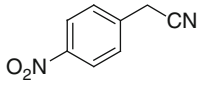
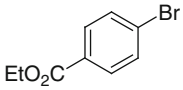
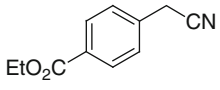
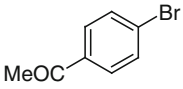
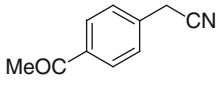
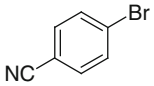
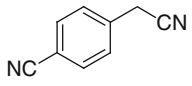
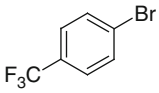
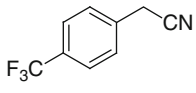
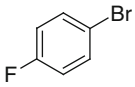
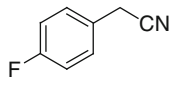
Velcicky, Schmalz and coworkers recently reported a palladium-catalyzed cyanomethylation of aryl halides with isoxazole-4-boronic acid pinacol ester (**147**) [68]. This sequence, which is thought to involve an initial Suzuki coupling reaction followed by a base-induced isoxazole fragmentation, gave highest yields of the cyanomethylated products when reaction conditions of $PdCl_2$dppf, KF, DMSO, 130°C were utilized.



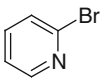
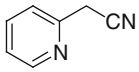
146 **147** **148**

Entry	Ar–X	$ArCH_2CN$	%Yield
1			3
2			88
3			90
4			66
5			74
6			82
7			69

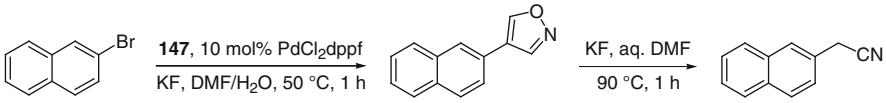
(continued)

Entry	Ar–X	$ArCH_2CN$	%Yield
8			64
9			84
10			74
11			49
12			71
13			86
14			72
15			68
16			81

(continued)

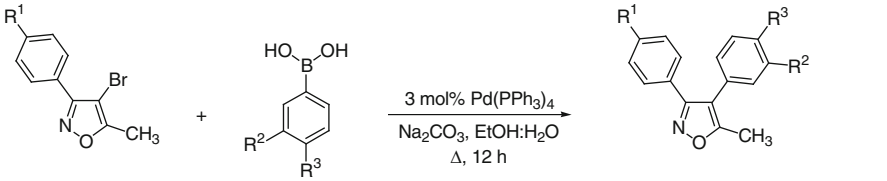
Entry	Ar–X	$ArCH_2CN$	%Yield
17			65

The mechanism was further investigated through an independent synthesis of the presumed key intermediates, and it was shown that the fragmentation sequence could be suppressed under milder Suzuki coupling conditions to give coupled arylisoxazoles. In turn, this intermediate could be heated in the presence of aqueous base to give the cyanomethylated product. One such example is displayed below.



146b **149** **148a**

Suzuki coupling reactions have also been used by a number of researchers in search of a viable synthesis of 3,4-diarylisoxazoles of pharmacological interest such as the non-steroidal anti-inflammatory drug (NSAID) valdecoxib (**156a**), and its analogues [69]. Toyokuni and coworkers also manipulated this cross-coupling reaction to synthesize highly potent COX-2 selective inhibitors [70]. Initial exploration revealed that 3-aryl-4-bromo-5-methylisoxazoles **150** and **151** underwent coupling in a facile manner with commercially available arylboronic acids **152a–c** using 3 mol% $Pd(PPh_3)_4$ as catalyst and Na_2CO_3 as base. Attempts to synthesize the valdecoxib analogue, **153c**, were less successful and resulted in only 10% isolated product.



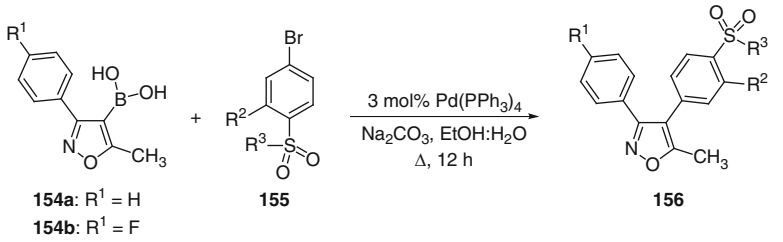
150: R^1 = H
151: R^1 = F

152a: R^2 = H; R^3 = F
152b: R^2 = R^3 = H
152c: R^2 = F; R^3 = SO_2NHDMT

153a: R^1 = H; R^2 = H; R^3 = F (60%)
153b: R^1 = F; R^2 = H; R^3 = H (65%)
153c: R^1 = H; R^2 = F; R^3 = SO_2NH_2 (10%)

A reverse coupling strategy was then attempted and as such, (3-aryl-4-isoxazolyl)boronic acids **154a** (R^1 = H) and **154b** (R^1 = F) – generated by a bromine/lithium exchange followed by treatment with triisopropylborate – were coupled with aryl bromides **155** containing 4-sulfonamide or 4-methylsulfonyl groups. Valdecoxib (**156a**) and its analogues were obtained in 30–75% yield

while coupling of **154b** with 5-bromopyrimidine (**157**) successfully resulted in **158** in good yield.

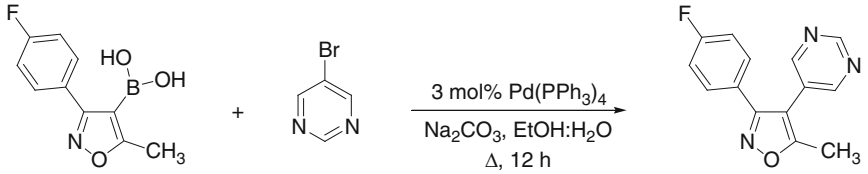


154a: R^1 = H
154b: R^1 = F

155

156

Product	R^1	R^2	R^3	%Yield
156a	H	H	NH_2	70
156b	H	F	NH_2	75
156c	H	NO_2	NH_2	30
156d	H	H	CH_3	50
156e	F	H	NH_2	60
156f	F	F	NH_2	55
156g	F	H	CH_3	59

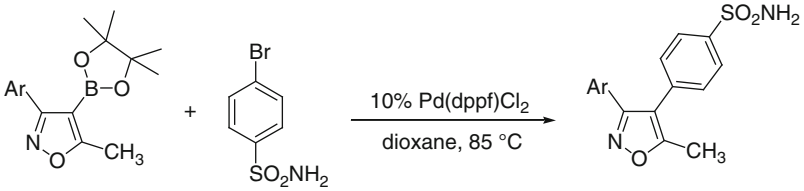


154b

157

158 (60%)

Isoxazoleboronates **133** and **159**, synthesized by a [3+2] cycloaddition of the requisite alkyne with benzonitrile oxide, were found to be a viable precursors of the valdecoxib (**156a**) and the mesityl-substituted analogue **161** [71].

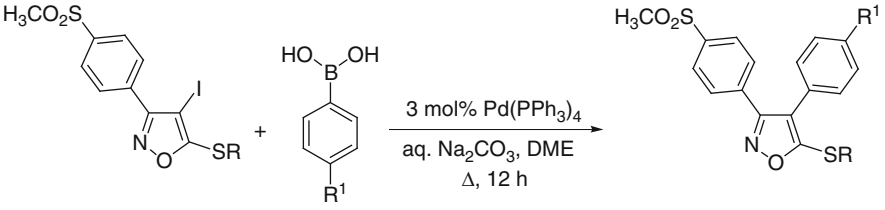


159: Ar = Ph
133: Ar = Mes

160

156a: Ar = Ph (100%)
161: Ar = Mes (78%)

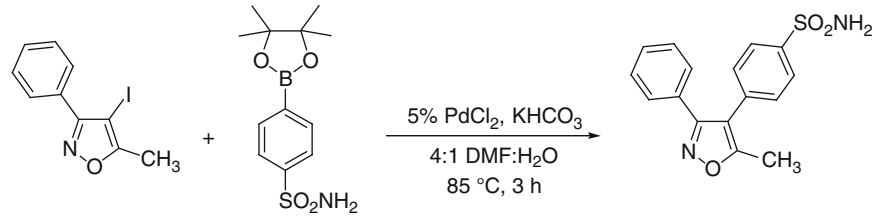
5-Alkylthio-4-aryl-3-(4-methylsulfonylphenyl)isoxazoles (**164a–f**), synthesized from the corresponding 4-iodoisoxazoles **162** via Suzuki coupling reactions, have also been shown to exhibit excellent activity as selective, anti-inflammatory COX-2 inhibitors [72]. These compounds reduced inflammation by 75–85% and 63–82% at 3 and 5 h post drug administration, respectively, relative to the reference drug celecoxib administered at the same dose.



162 **163** **164**

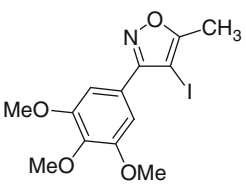
Product	R	R^1	%Yield
164a	CH_3	F	94
164b	CH_2CH_3	H	88
164c	CH_2CH_3	F	92
164d	CH_2CH_3	Br	81
164e	CH_2CH_3	CH_3	80
164f	CH_2CH_3	CH_2CH_3	85

Waldo and Larock reported an alternative Sukuki–Miyaura coupling reaction to generate valdecoxib (**156a**) using 4-iodo-5-methyl-3-phenylisoxazole (**95**) and the commercially available benzenesulfonamide-4-boronic acid pinacol ester (**165**). In this experiment, reaction conditions included 5 mol% $PdCl_2$ catalyst, 1.4 equiv. of $KHCO_3$ in 4:1 DMF:H_2O at 85°C for 3 h and generated **156a** in 81% yield [55].

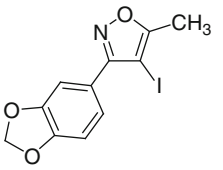


95 **165** **156a** (81%)

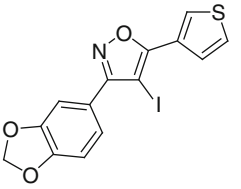
Commercially available boronic acids **169a–i** were also coupled with 4-iodoisoxazoles **98** and **166–168** to synthesize a 27-member library of 3,4,5-trisubstituted isoxazoles [56]. Coupling with boronic acids **169d** and **169g** gave low or no yield of the desired products while 4-iodoisoxazole **167** generated the highest overall yields of coupled products.



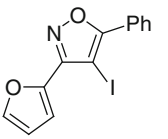
98



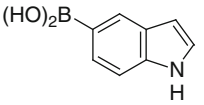
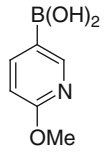
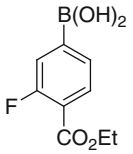
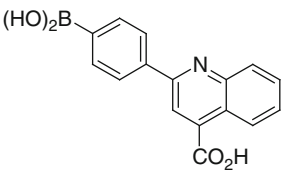
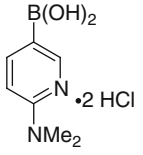
166



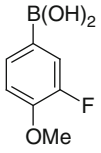
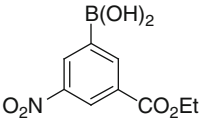
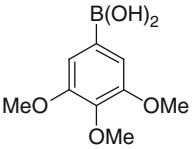
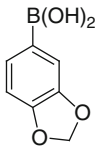
167



168

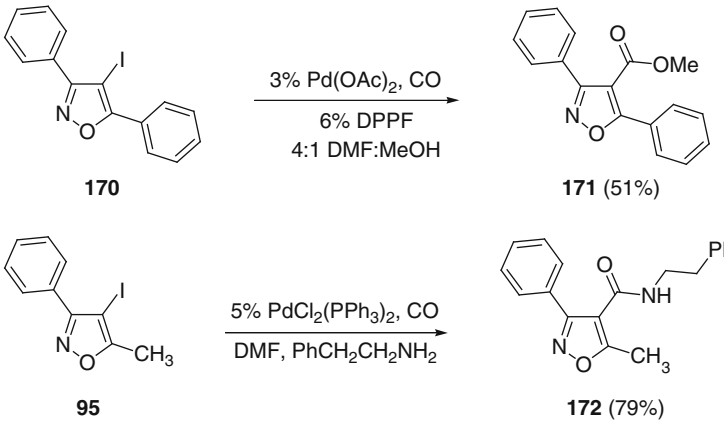
Boronic acid	%Yields			
	98	**166**	**167**	**168**
 **169a**	24	51	79	75
 **169b**	29	26	81	16
 **169c**	53	26	73	64
 **169d**	5	0	57	7
 **169e**	22	7	85	20

(continued)

Boronic acid	%Yields			
	98	**166**	**167**	**168**
 **169f**	58	46	73	60
 **169g**	44	0	–	0
 **169h**	–	–	44	53
 **169i**	–	–	–	44

2.5.7 Other Palladium Catalyzed Coupling

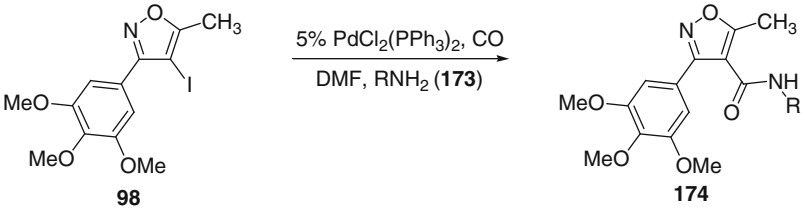
Larock and coworkers have also shown the utility of other palladium catalyzed coupling sequences with isoxazoles. Using catalytic amounts of $Pd(OAc)_2$ plus the ferrocene ligand DPPF, carbon monoxide, and methanol, 4-iodo-3,6-diphenylisoxazole (**170**) was converted to the methyl ester **171** in 51% yield [55]. Additionally, 4-iodo-5-methyl-3-phenylisoxazole (**95**) was converted, in higher yield, to the corresponding phenethylamide **172** using a similar approach, which involved treatment with $PdCl_2(PPh_3)_2$, carbon monoxide and 2-phenethyl amine.



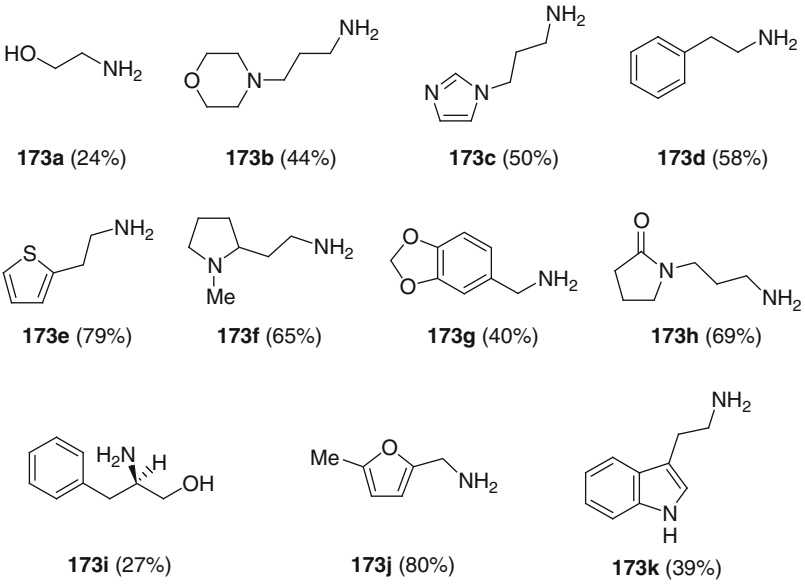
170 **171** (51%)

95 **172** (79%)

A library of isoxazole amides **174a**–**k** was also prepared in high purity using this methodology from amines **173a**–**k** in yields ranging from 24% to 80%.



98 **174**



173a (24%) **173b** (44%) **173c** (50%) **173d** (58%)

173e (79%) **173f** (65%) **173g** (40%) **173h** (69%)

173i (27%) **173j** (80%) **173k** (39%)

2.6 Metal Complexes

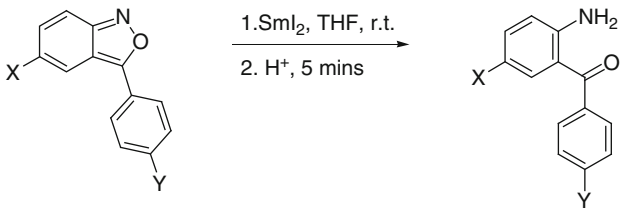
Often overlooked, metal complexes and chelates have been documented in the recent literature. Isoxaline[60]fullerene platinum and iridium complexes have been synthesized and their properties have been investigated with the intent to extend into the sphere of supermolecular and materials chemistry [73]. Other metal complexes such as $[Fe(isoxazole)_6]^{2+}$, $[Fe_3O(OAc)_6(isoxazole)_3][ClO_4]$, [Fe(3-amino-5-methylisoxazole)$_2$(H_2O_2)][ClO]$_2$, [Pd(3,5-dimethyl-isoxazole)$_2$(Cl_2)], [Pt(5-methylisoxazole)$_2$(Cl_2)], [Zn(3-amino-5-methylisoxazole)$_2$(Cl_2)] and more recently aquabis(5-methylisoxazole-3-carboxylato-*O*,*N*)copper(II) monohydrate have also been reported [74–79]. A pyridine-bis(ferrocene-isoxazole)Pd(II) complex was also synthesized through coordination of 2,6-bis-(5-ferrocenylisoxazole-3-yl)ligand and palladium(II) acetate and shown to exhibit good catalytic activity in the Songashira cross-coupling reactions of terminal alkynes with iodides and bromides under copper- and phosphine-free reaction conditions [80].

3 Benzisoxazoles

The chemistry of 1,2-benzisoxazoles and 2,1-benzisoxazoles has been recently reviewed [81, 82]; however, far fewer metalation sequences have been reported with these heterocycles.

3.1 Metalation with Ring Cleavage

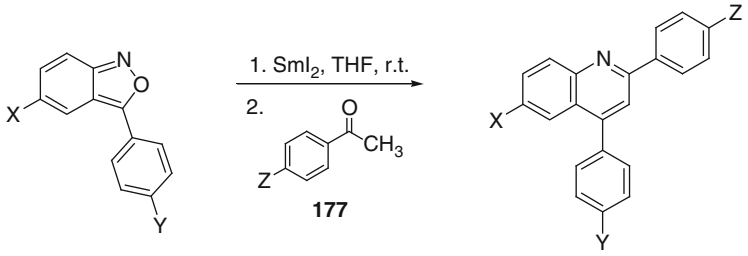
Fan and Zhang extended the use of samarium(II) iodide (Kagan's reagent) from isoxazoles [83] to benzisoxazoles in a one-pot preparation of 2,4-diarylquinolines from 3-aryl-2,1-benzisoxazoles [84]. The facile reductive cleavage of the N–O bond in 3-aryl-2,1-benzisoxazoles **175** was completed in minutes, as detected by TLC, to give 2-aminobenzophenones **176**, upon acid workup in good yields.



175 **176**

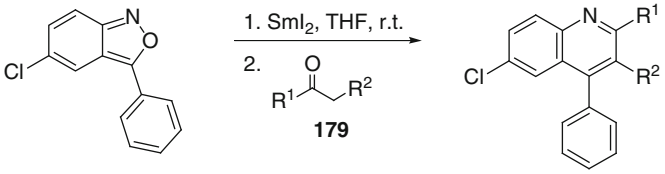
Entry	X	Y	Product	%Yield
1	Cl	H	**176a**	90
2	Cl	Br	**176b**	84
3	Cl	Cl	**176c**	82
4	Cl	OCH_3	**176d**	85
5	Br	H	**176e**	86
6	Br	Cl	**176f**	78

When a variety of substituted acetophenones **177a–d** were added to the reaction mixture containing the benzisoxazole and SmI_2, 2,4-disubstituted quinolines **178** resulted within 1–2 h at room temperature – through what maybe an intermediate formed in situ from the N–O bond cleavage.



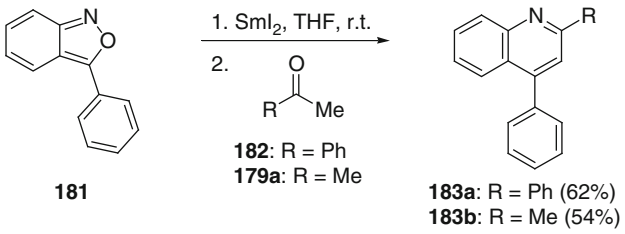
Entry	X	Y	Z	Product	%Yield
1	Cl	H	H	**178a**	62
2	Cl	H	CH_3	**178b**	70
3	Cl	H	Cl	**178c**	72
4	Cl	H	Br	**178d**	70
5	Cl	Cl	Br	**178e**	62
6	Cl	OCH_3	H	**178f**	65
7	Cl	OCH_3	CH_3	**178g**	68
8	Cl	OCH_3	Cl	**178h**	66
9	Cl	OCH_3	Br	**178i**	56
10	Cl	Br	Br	**178j**	52

2,3,4-Trisubstituted quinoline derivatives were also prepared from **175a** and aliphatic ketones possessing one or two α-methyl or methylene groups [85]. Indeed, acetone (**179a**), methyl ethyl ketone (**179b**), 3-pentanone (**179c**) and cyclohexanone (**179d**) converted in good yields to quinolines **180a–d**.



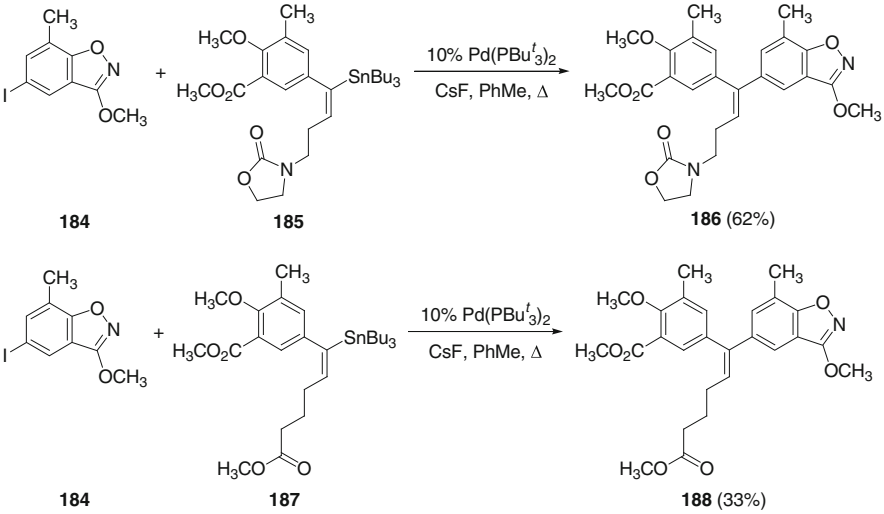
Entry	R^1	R^2	Products	%Yield
1	CH_3	H	**180a**	68
2	CH_3	CH_3	**180b**	65
3	C_2H_5	CH_3	**180c**	70
4	$-(CH_2)_4-$		**180d**	71

More recently, Driver and coworkers elaborated 2,1-benzisoxazole **181** into quinolines **183a–b** in the presence of acetophenone (**182**) or acetone (**179a**) [86].

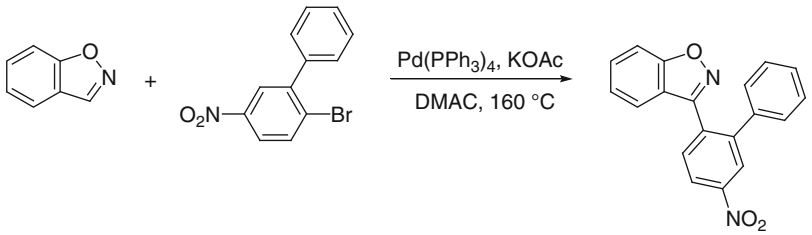


3.2 *Palladium-Catalyzed Coupling*

Although not as common as those with isoxazoles, examples of palladium-catalyzed coupling reactions with benzisoxazoles have been reported. Recently, Cushman and coworkers utilized a Stille cross-coupling sequence while investigating a series of alkenyldiarylmethanes (ADAMs) as HIV-1 non-nucleoside reverse transcriptase inhibitors with anti-HIV activity [87]. In order to fully examine the structure–activity relationship of the benzo[*d*]isoxazole ADAMs under consideration, ADAM **186** and **188**, differing at the side chain, were synthesized using this methodology.

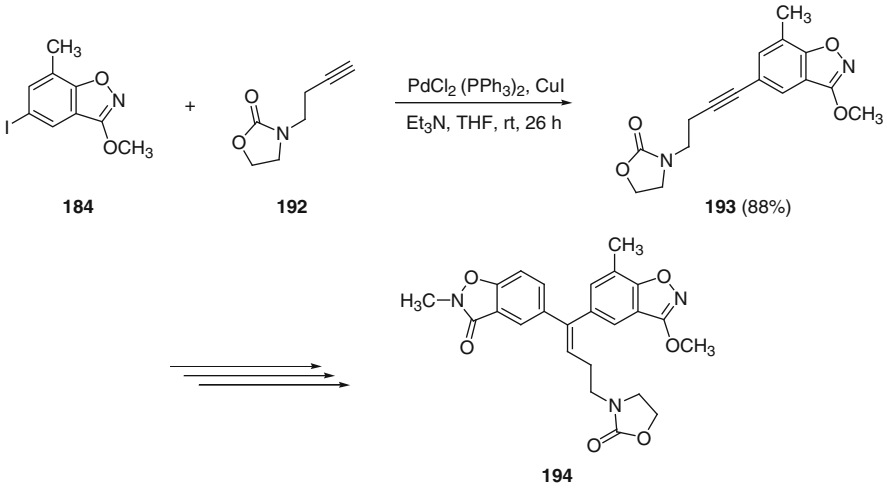


Heck coupling of 1,2-benzisoxazole (**189**) with 2-phenyl-4-nitrobromobenzene (**190**) in the presence of $Pd(PPh_3)_4$, potassium acetate and *N*,*N*-dimethylacetamide was reported by Gelb and coworkers [88]. The coupled product, 3-(5-nitro-biphenyl-2-yl)-benzo[*d*]isoxazole (**191**), was characterized by ^{1}H NMR spectroscopy and used without further purification in the synthesis of dialkylimidazole inhibitors of *Trypanosama cruzi* lanosterol-14α-demethylase (L14DM).



189 **190** **191**

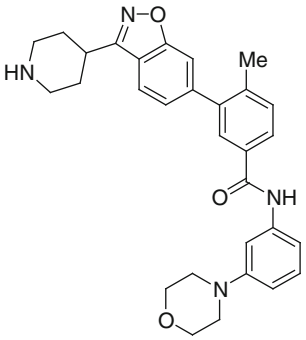
Sonogashira coupling of 5-iodo-3-methoxy-7-methylbenzo[*d*]isoxazole (**184**), with 3-but-3-ynyl-1,3-oxazolidine-2-one (**192**) has also been employed in the pursuit of novel ADAMs designed to replace the metabolically labile methyl ester moieties [89]. The resultant alkyne **193** underwent hydrostannylation and subsequent Stille coupling to create ADAM **194**, which was found to be the most stable of all the ADAMs studied but lost the ability to inhibit the cytopathic effect of the HIV virus at noncytotoxic concentrations.



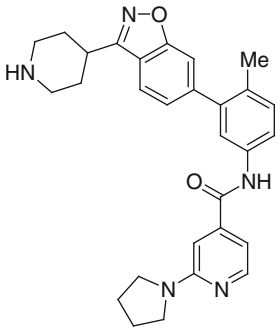
184 **192** **193** (88%)

194

Bamborough and coworkers reported the use of Suzuki catalyzed coupling in order to generate potential kinase inhibitors designed to bind in the purine subpocket of the ATP-site [90]. While the details of the coupling were not reported, it was observed that benzisoxazoles **195** and **196** were shown to be the most potent. This high activity was attributed to the additional bulk in the outer lipophilic pocket region.

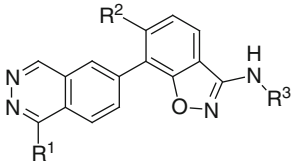


195



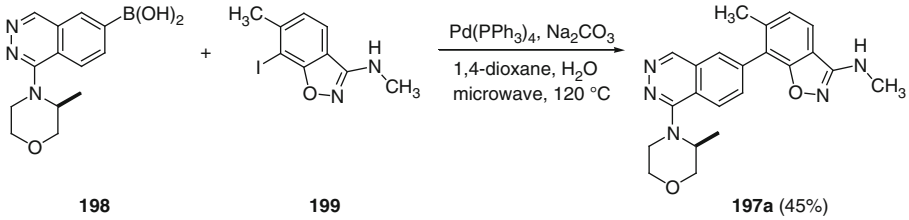
196

A novel class of 3-amino-7-phthalazinylbenzoisoxazole derivatives (**197**) was designed as inhibitors of p38 mitogen-activated protein kinase (MAPK), shown to play a crucial role in regulating the biosynthesis of many proinflammatory pathways [91].



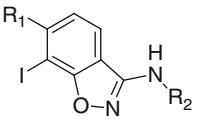
197

The key step of the synthesis of these derivatives involved the Suzuki coupling of the 7-iodobenzo[*d*]isoxazole-3-amine precursor with the required boronic acid using $Pd(PPh_3)_4$ and sodium carbonate in 1,4-dioxane in a sealed tube and heating in a microwave at 130°C. The synthesis of the lead compound, benzoisoxazole **197a**, which displayed the highest efficacy ($EC_{50} = 0.05$ mg/kg) in the rat collagen-induced arthritis (CIA) model is displayed below.

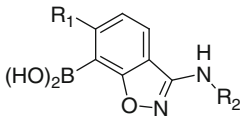


198 199 **197a** (45%)

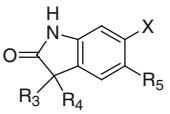
Eastwood and coworkers also recently designed substituted benzisoxazole derivates as indolin-2-one p38α inhibitors using a Suzuki coupling strategy [92]. In this description, coupling of the iodobenzisoxazole **200** or the boronic acid **201** with the appropriate indolin-2-ones **202** using $PdCl_2dppf{\cdot}CH_2Cl_2$ generated the bicyclic aromatic derivatives **203** with good potency at the nanomolar level. The full synthetic details of this procedure were not disclosed in this paper.



200



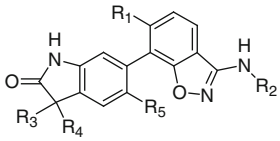
201



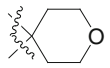
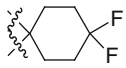
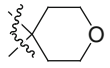
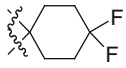
202

+ **200-201**

$PdCl_2dppf{\cdot}CH_2Cl_2$
2M Cs_2CO_3
1,4-dioxane, 100-110 °C



203

Entry	R_1	R_2	R_3, R_4	R_5
1	Me	cyc-Pr	$-(CH_2)_4-$	H
2	H	cyc-Pr	$-(CH_2)_4-$	H
3	H	cyc-Pr	$-(CH_2)_4-$	Cl
4	Me	cyc-Pr	Me, Me	H
5	Me	cyc-Pr		H
6	Me	cyc-Pr		H
7	Me	H	Me, Me	H
8	Me	H		H
9	Me	H		H

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Thiazoles and Benzothiazoles

Yong-Jin Wu

Abstract This chapter highlights the recent developments in the metalation of thiazoles and benzothiazoles as well as the reactions of the resulting metalated species (2000 to present). Metalation reactions consist of lithiation (including halogen dance reactions), magnesation, zincation, caldation, boronation, and silylation, while application of the metalated thiazoles focuses on nucleophilic additions and metal-catalyzed cross-coupling reactions (Stille, Negishi, and Suzuki). The power of these metalated reactions is amply demonstrated in the total synthesis of the thiazolyl peptide GE2270A.

Keywords Addition reaction · Benzothiazoles · Cross-coupling · Halogen dance reaction · Metalation · Thiazoles

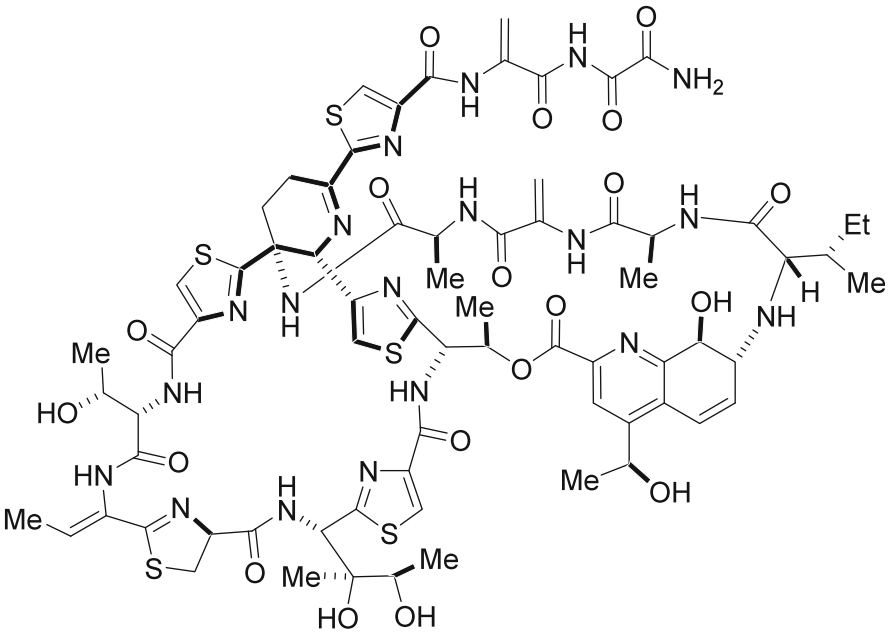
Contents

1 Introduction 308
2 Lithiation 311
2.1 C-2 Lithiation 311
2.2 C-5 Lithiation 312
2.3 Halogen Dance Reaction 314
3 Magnesation 315
3.1 C-2 Magnesation 315
3.2 C-5 Magnesation 317
4 Stannylation 317
5 Zincation and Caldation 320
6 Boronation 323
7 Silylation 324
8 Conclusion 325
References 326

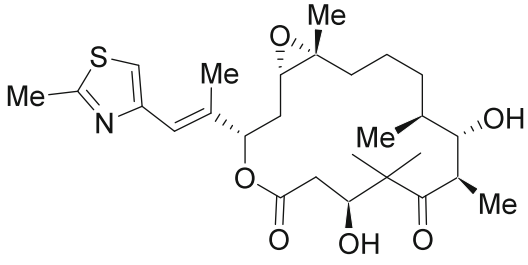
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1 Introduction

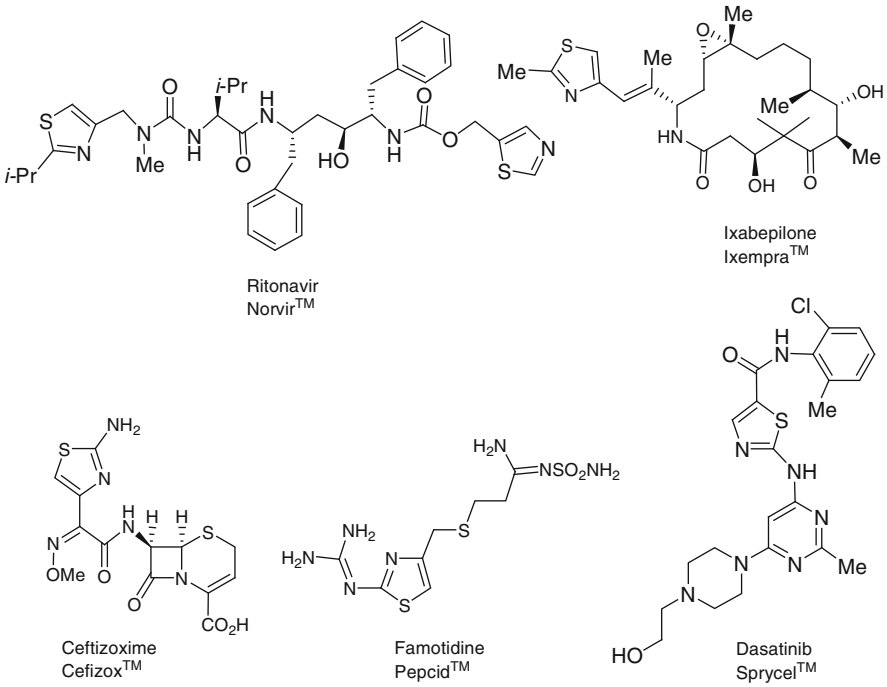
Thiazole ring system is ubiquitous in biologically active natural products and pharmaceutically important compounds [1–11]. Representatives of well-known thiazole-containing natural products are antibiotics thiostrepton, GE2270A [12], amythiamicin C and D [13], and antitumor agent epothilone. Thiazole-containing drugs include ritonavir (antiviral), ixabepilone and dasatinib (both antitumor), ceftizoxime (antibacterial), and famotidine (histamine H2-receptor antagonist).



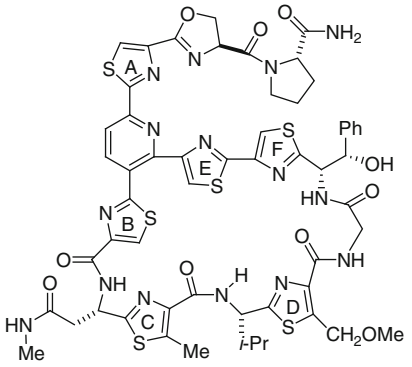
Thiostrepton



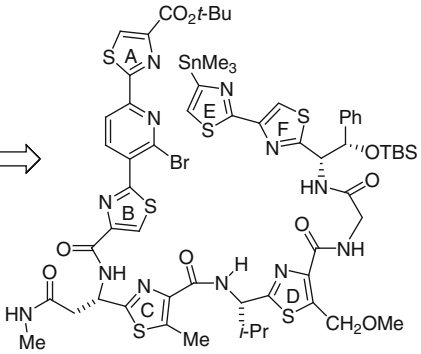
Epothilone



Due to the importance of the thiazole ring system in biologically active natural products and modern drug discovery, numerous methodologies have been developed for the synthesis of thiazole-containing compounds. These methods can be broadly classified into two categories: (1) thiazole synthesis per se; (2) functionalization and incorporation of existing thiazoles. Since there are a variety of thiazole building blocks either commercially available or readily prepared, the latter has attracted significant attention. Among various approaches to functionalize and incorporate the diazole ring system, metalation is most widely utilized. A recent elegant total synthesis of GE2270A is a case in point [14–17]. In this work, three of the six thiazoles (A, E, and F) are assembled through reactions of the appropriated metalated thiazoles **1**–**6**, and the methoxymethyl group attached to the D ring thiazole is introduced via lithiated thiazole **7**. These metalated intermediates **1**–**7** will be detailed in the following sections. A similar strategy has been applied to the synthesis of amythiamicin C and D [18]. This review chapter focuses on the syntheses and reactions of the metalated thiazoles and benzothiazoles (reported during the past decade).

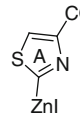


GE2270A

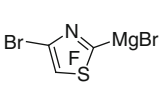


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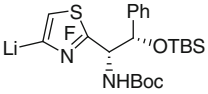




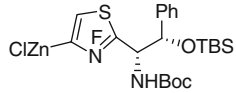
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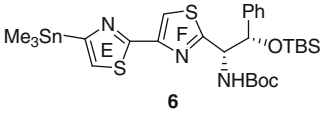
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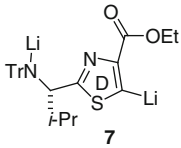
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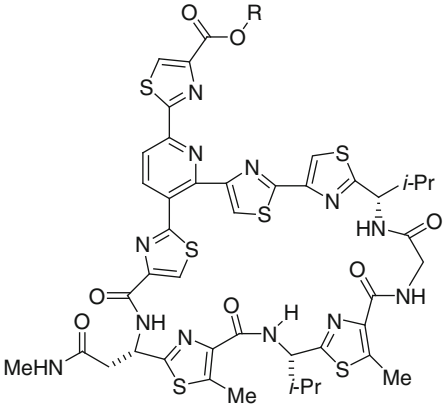
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6

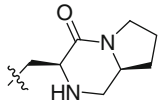


7



Amythiamicin C:

R =



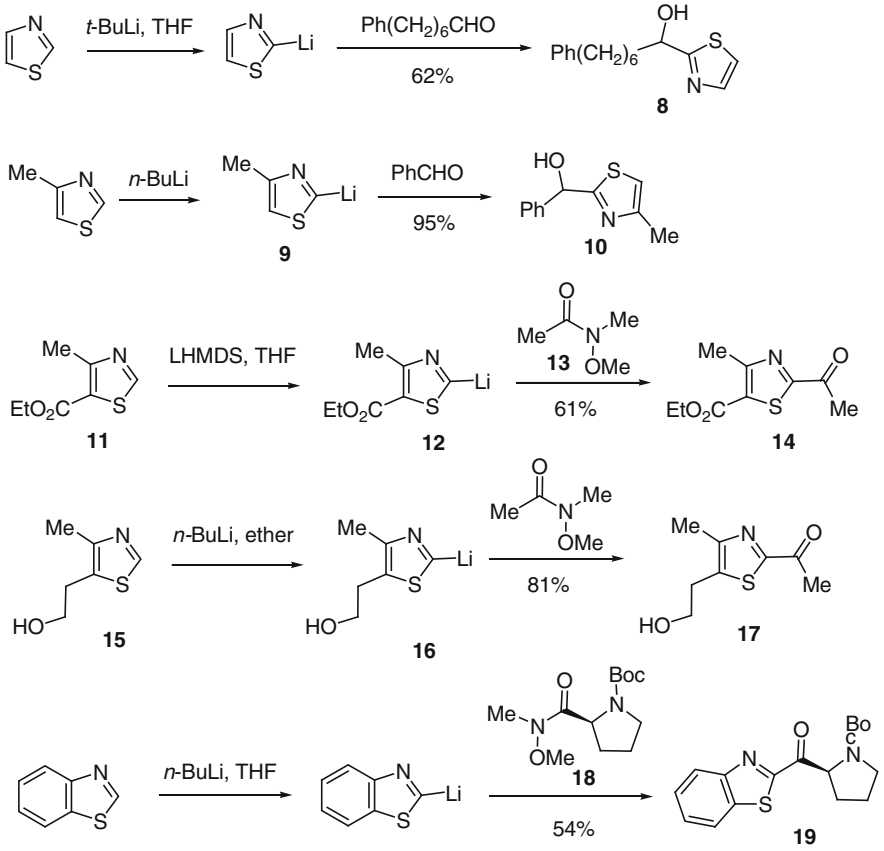
Amythiamicin D:

R = Me

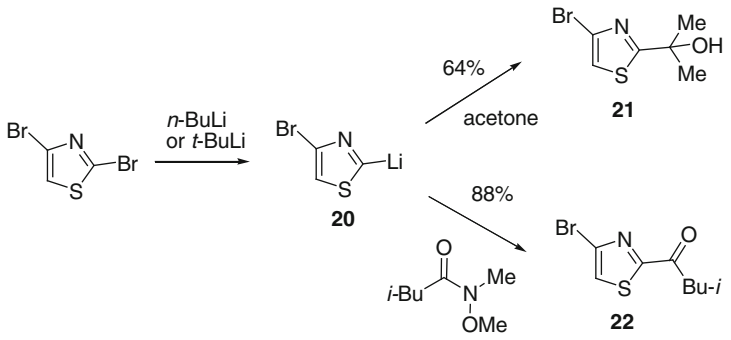
2 Lithiation

2.1 C-2 Lithiation

The regiochemistry of lithiation reactions of thiazole depends on the acidity of thiazole protons: H2 > H5 ≫ H4. Thus, 2-thiazolyl lithium reagents are conveniently prepared via direct lithiation with strong bases. For example, reaction of thiazole with *tert*-BuLi generates 2-thiazolyl lithium, which is trapped with 7-phenylheptanal to give adduct **8** [19]. Lithiation of 4-methylthiazole occurs exclusively at C-2, and the resulting lithium reagent **9** undergoes nucleophilic addition with benzaldehyde to furnish phenyl(thiazol-2-yl)methanol **10** in good yield [20]. The C-2 lithiation conditions are relatively mild, and a variety of functional groups are well tolerated including ester group [21]. Thus, ethyl 4-methylthiazole-5-carboxylate **11** undergoes smooth lithiation, and the resulting lithium reagent **12** reacts with *N*-methoxy-*N*-methylacetamide **13** to give methyl ketone **14** in good yield. The same transformation has also been carried out on 2-(4-methylthiazol-5-yl)ethanol **15**. Lithiation of benzothiazole gives benzo[*d*]thiazol-2-yllithium, which is converted to ketone **19** upon addition with the Weinreb amide **18** [22].

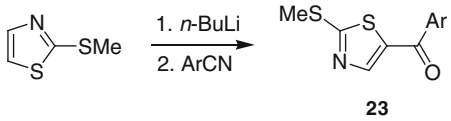


The total synthesis of the antifungal agent cystothiazole B involves a regioselective bromine–lithium exchange reaction of 2,4-dibromothiazole [23]. Treatment of 2,4-dibromothiazole with either *n*- or *tert*-BuLi brings about regioselective bromine–lithium exchange to give 4-bromo-2-thiazolyl lithium **20**, which adds to acetone to provide the tertiary alcohol **21**. When *N*-methoxy-*N*,3-dimethylbutanamide is added instead of acetone, ketone **22** is obtained in good yield [24].

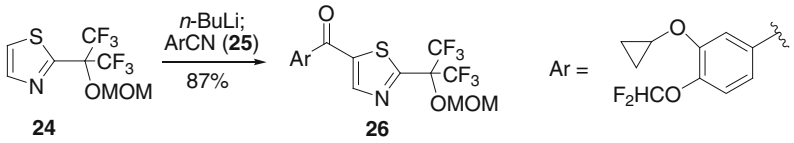


2.2 C-5 Lithiation

Lithiation of 2-(methylthio)thiazole with *n*-BuLi occurs exclusively at C-5, and subsequent quenching with aromatic nitrile yields 5-thiazolyl ketone **23** [25].

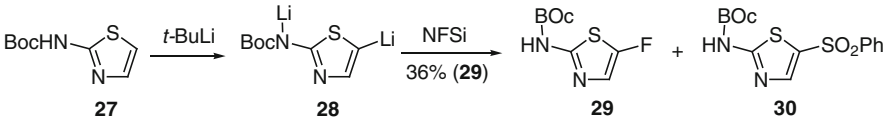


A practical synthesis of L-869,298, a potent phosphodiesterase-4 (PDE4) inhibitor, features a regioselective deprotonation of thiazole **24** at the 5-position [26]. Exposure of **24** to *n*-BuLi followed by the addition of nitrile **25** furnishes ketone **26**, a key intermediate for the synthesis of L-869,298.

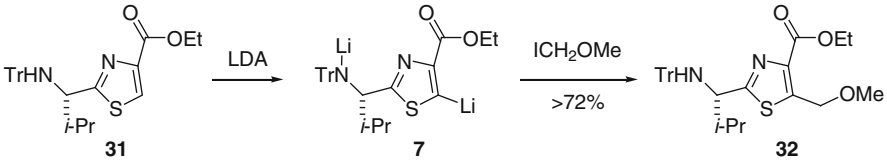


The first practical, large-scale synthesis of 2-amino-5-fluorothiazole **29** makes use of the reaction of dilithiated 2-butoxycarbonylaminothiazole **28** with *N*-fluorobenzenesulfonimide (NFSi) [27]. This reaction generates a 70:15 mixture of the desired fluorinated thiazole **29** and the sulphone **30**, and after three

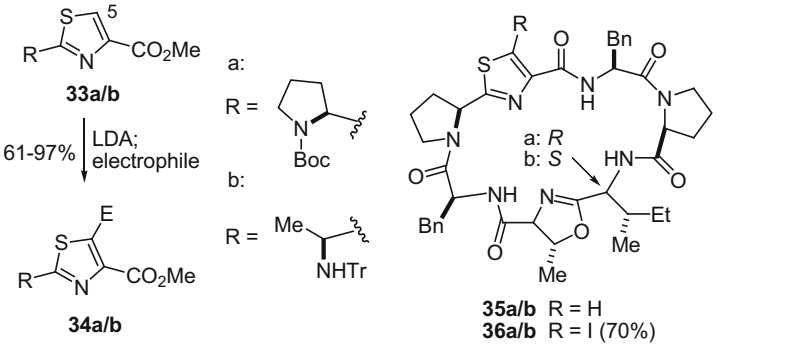
consecutive recrystallizations thiazole **29** is isolated in 35–40% yield. This procedure has been utilized to prepare multikilogram quantities of **29**, which is a heterocyclic amine component of a series of glucokinase inhibitors.



Reaction of chiral thiazole **31** with LDA at −78°C for 1 min results in clean lithiation at C-5 without racemization, and the resulting 5-lithiated thiazole **7** is quenched with iodo(methoxy)methane to give the 5-substituted thiazole **32** in good yield. This trisubstituted thiazole is a building block in the total synthesis of GE2270A [14].

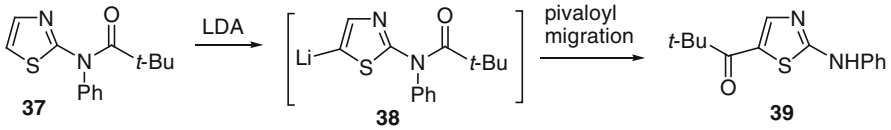


Direct lithiation of peptide thiazoles provides an efficient C-5 diversification strategy [28]. Thus, treatment of thiazoles **33a/b** with 1.05 eq. LDA, followed by reaction with a variety of electrophiles, affords 5-substituted thiazoles **34a/b** without racemization. Of special note is that 1.05 eq. LDA is sufficient even with *N*-trityl L-alanine-based thiazole **33b** where a secondary amine is present. The thiazole lithiation approach even works in complex systems. For example, lithiation of ceratospongamide **35a** and its epimer **35b** with 4.2 eq. LDA, followed by quenching with iodine, affords the 5-iodo thiazole adducts **36a** and **36b**, respectively, again without epimerization.



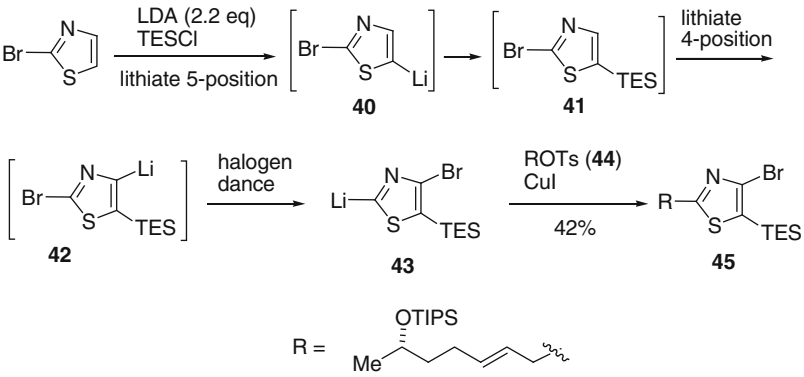
The pivaloyl group in 2,2-dimethylpropanamide **37** shows a great tendency to migrate into the 5-position of the thiazole ring under lithiation conditions even at low temperatures to form amide **39** via 5-lithiated thiazole **38** [29]. This migration must be an intermolecular process since for steric reasons an intramolecular migration is

not possible. This represents the first intermolecular migration of a pivaloyl group whereas intramolecular migrations have been known in the literature.



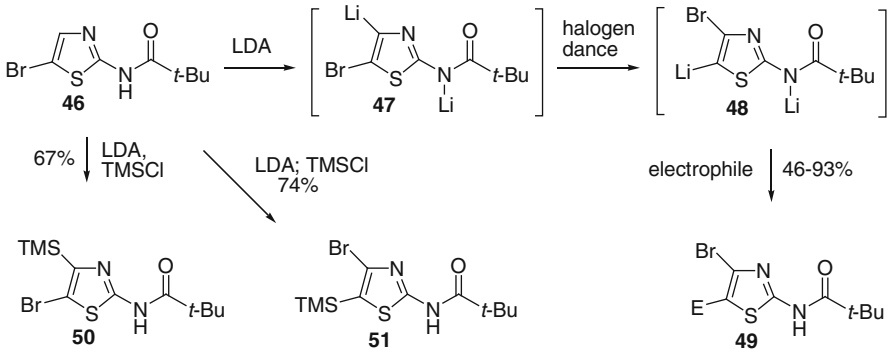
2.3 Halogen Dance Reaction

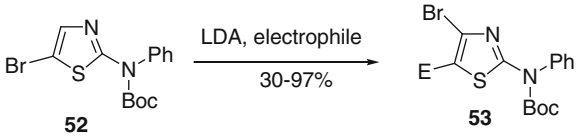
The halogen dance reaction on thiazoles has been elegantly applied to the total synthesis of the pyridine-thiazole-containing natural product WS75624B [30]. Treatment of 2-bromothiazole with 2.2 eq. LDA at −78°C in the presence of 1 eq. TESCl results in the formation of 2-thiazolyl lithium **43**, which undergoes copper(I)-catalyzed coupling reaction with allylic tosylate **44** to give **45**. The remarkable generation of 2-thiazolyl lithium **43** likely proceeds via intermediates **40**–**42**. Presumably, the first equivalent of LDA deprotonates 2-bromothiazole at the more acidic 5-position to produce 5-lithio-2-bromothiazole (**40**), which is trapped with TESCl to give 5-triethylsilyl-2-bromothiazole (**41**). This intermediate is deprotonated by the second equivalent of LDA to generate the substituted 4-lithothiazole **42**, which undergoes a 1,3-halogen dance reaction to furnish **43**.

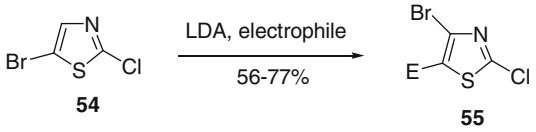


Easy access to a series of 5-substituted 4-bromo-2-thiazolamine derivatives **49** is based on the halogen dance reaction [29]. Addition of 3.3 eq. LDA to 4-bromothiazole **46** at 0°C results in full conversion to the halogen dance product **48**, which is trapped with various electrophiles to give the 5-substituted thiazoles **49**. For example, 4-bromo-5-trimethylsilylthiazole **51** is obtained in 74% yield when **46** is exposed to LDA followed by the addition of TMSCl as the electrophile. Interestingly, the halogen dance reaction is completely blocked when thiazole **46** is added to a solution of 3.3 eq. LDA in the presence of TMSCl at −80°C, and the corresponding

normal, anti-halogen dance product **50** is formed exclusively. Bromothiazoles **52** and **54** undergo analogous halogen dance reactions to afford **53** and **55**, respectively [31, 32]. Two reviews on halogen dance reaction have appeared [33, 34].



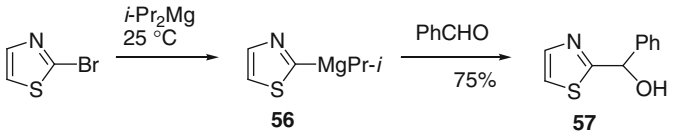




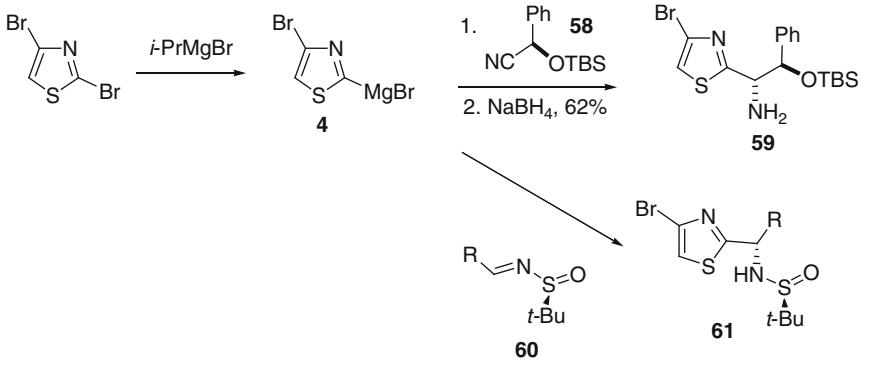
3 Magnesation

3.1 C-2 Magnesation

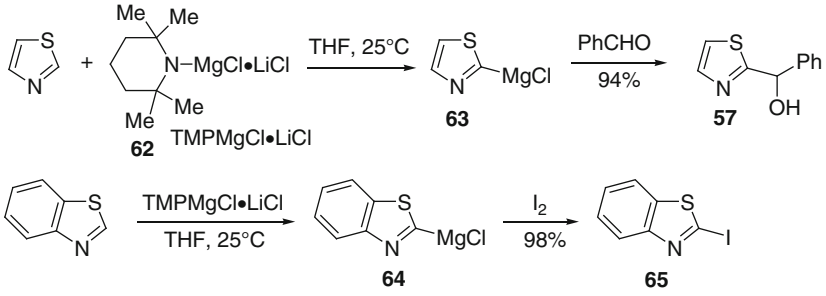
The unfunctionalized 2-bromothiazole undergoes bromine–magnesium exchange reaction only at room temperature and requires the use of diisopropylmagnesium, and the corresponding addition product from benzaldehyde **57** is obtained in good yield [35].



4-Bromo-2-thiazolyl lithium **20** is successfully used in the total synthesis of cystothiazole B (vide supra); however, it is unstable at 0°C or higher. The alternative reagent is 2-thiazolyl magnesium **4**, which is stable at ambient temperature. This reagent is readily prepared from 2,4-dibromothiazole using a regioselective bromine–magnesium exchange. Addition of **4** with nitrile **58** yields an intermediate imine, which is directly reduced with sodium borohydride to afford amine **59**. Bromothiazolyl magnesium bromide **4** is also subjected to the Ellman reaction with chiral imine **60**, but only modest diastereoselectivity is obtained.

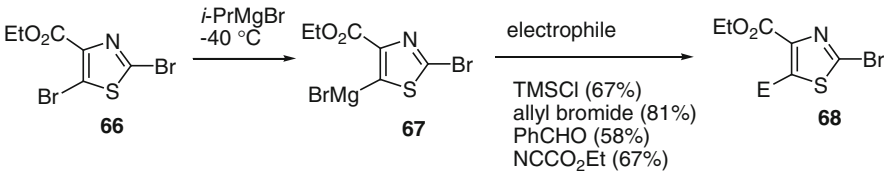


A regioselective generation of thiazol-2-yl and benzo[*d*]thiazol-2-yl magnesium chlorides (**63** and **64**) uses 2,2,6,6-tetramethylpiperidyl MgCl•LiCl (TMPMgCl•LiCl), readily available by reacting *iso*-propyl MgCl•LiCl with 2,2,6,6-tetramethylpiperidine [36-38]. This mixed Mg/Li amide, which has excellent solubility in THF (1.2 M) and is stable for more than 6 months as THF solution at 25°C, allows the regioselective functionalization of various aromatic and heteroaromatic compounds. Thus, both thiazole and benzothiazole undergo smooth C-2 magnesation with TMPMgCl•LiCl at 25°C, and the resulting magnesium chlorides are trapped with benzaldehyde and iodine, respectively, to furnish adducts **57** and **65**.



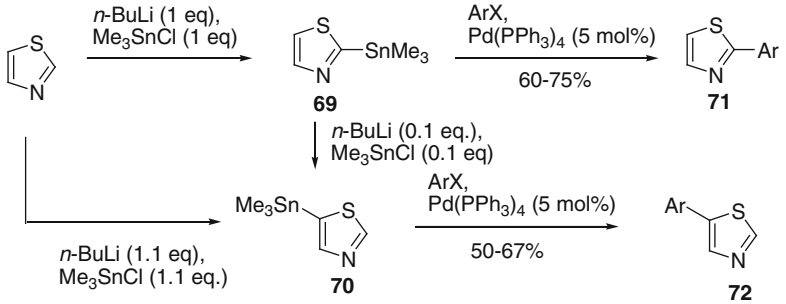
3.2 C-5 Magnesation

Dibromothiazole **66** bearing an ester functional group undergoes selective bromine–magnesium exchange reaction at C-5 when treated with isopropylmagnesium bromide or diisopropylmagnesium at −40°C, and the resulting magnesium bromide **67** reacts with a variety of electrophiles to afford 2-bromo-5-substituted thiazoles **68** in good yields [35].

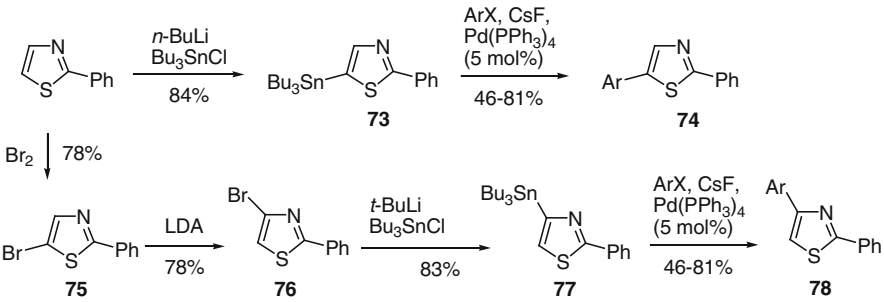


4 Stannylation

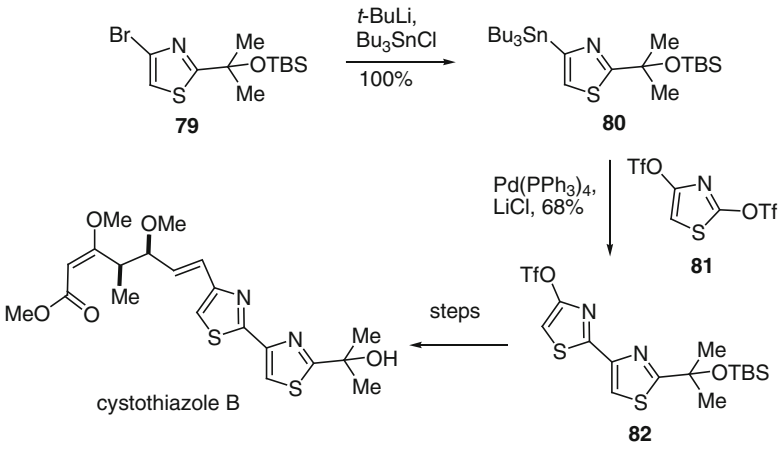
2-(Trimethylstannyl)thiazole **69** is generated from thiazole by the addition of 1 eq. *n*-BuLi and 1 eq. Me_3SnCl. On the other hand, the generation of 5-(trimethylstannyl) thiazole **70** requires the metal–halogen exchange reactions of 5-halogenated thiazoles, which are not easily accessible. To this end, an efficient, alternative approach to the 5-substituted thiazole **70** has been developed [39]. Treatment of thiazole with 1.1 eq. *n*-BuLi and 1.1 eq. Me_3SnCl generates the 5-trimethylstannyl thiazole **70** instead of the 2-substituted thiazoles **69**. The 5-trimethylstannyl thiazole **70** is also prepared from the 2-trimethylstannyl counterparts **69** upon treatment with 0.1 eq. *n*-BuLi and 0.1 eq. Me_3SnCl. The formation of the 5-substituted thiazoles involves a novel metallotropic rearrangement of Me_3Sn groups around the thiazole ring from C-2 to C-5. The observed migration of Me_3Sn around thiazole ring is similar to the base-catalyzed halogen dance reaction, in which a halogen substituent moves to a new position on an aromatic ring system. The proposed mechanism for the metallotropic rearrangement also parallels with that of halogen dance reaction. The 2- and 5-trimethylstannylthiazoles **69** and **70** are readily coupled with various boronic acids to provide the 2- and 5-aryl thiazoles **71** and **72**, respectively.



The 5-(tributylstannyl)-2-phenylthiazole **73** is readily prepared from 2-phenylthiazole via lithiation and subsequent quenching with tributyltin chloride [40]. The synthesis of the 4-(tributylstannyl)-2-phenylthiazole **77** requires a three-step sequence: direct bromination, halogen dance reaction, and metal–halogen exchange followed by quenching with tributyltin chloride. Both 4- and 5-(tributylstannyl)-2-phenylthiazoles, **73** and **77**, undergo Stille cross-coupling reactions to give 4- and 5-aryl thiazoles, **74** and **78**, respectively.

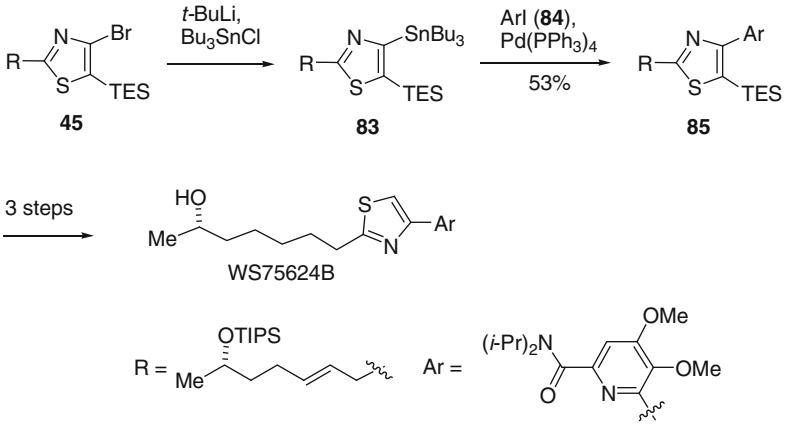


A regioselective Stille cross-coupling reaction is used in the total synthesis of the antifungal agent cystothiazole B [23]. The required 4-tributylstannylthiazole **80** is prepared from **79** through bromine–lithium exchange followed by quenching with tributyltin chloride. Stille cross-coupling reaction of **80** with ditriflate **81** proceeds regioselectively to give bis(thiazole) triflate **82**. This triflate is converted into cystothiazole B in a few steps.

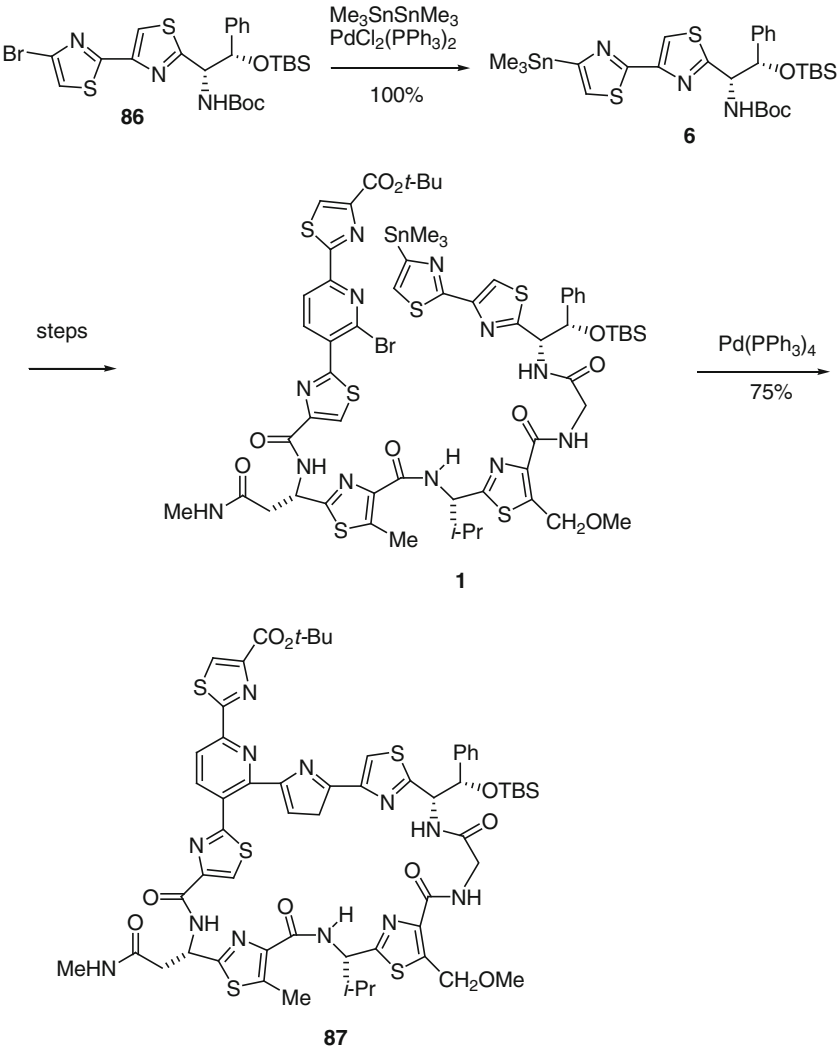


The total synthesis of the pyridine-thiazole-containing natural product WS75624B involves the 3-tributylstannylthiazole **83** [30]. Bromide **45** is converted into tributylstannylthiazole **83** under standard conditions, and Stille

coupling of **83** with iodopyridine **84** provides pyridyl thiazole **85**, which is converted to WS75624B in three steps.

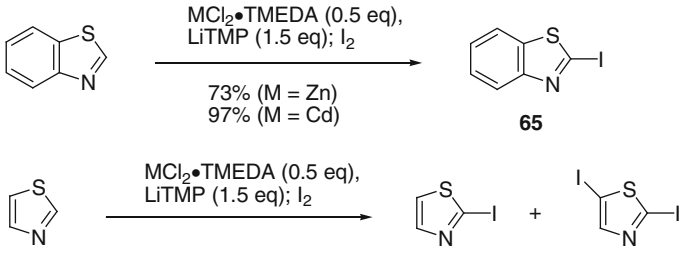


Stannylation of thiazoles can also be carried out by palladium-catalyzed reaction of bromothiazoles with hexaalkylditin reagents as demonstrated in the total synthesis of GE2270A [14]. Standard stannylation of 4-bromo-2,4′-bithiazole **86** with hexamethylditin affords 4-(trimethylstannyl)-2,4′-bithiazole **6**, which leads to the Stille coupling precursor **1** via a multistep sequence. Macrocyclization of **1** under palladium-catalyzed cross-coupling conditions proceeds smoothly to give the macrocycle **87**, which is only four steps away from DE2270A. An analogous Stille coupling reaction has been utilized in the total synthesis of thiopeptides amythiamicin C and D [18].

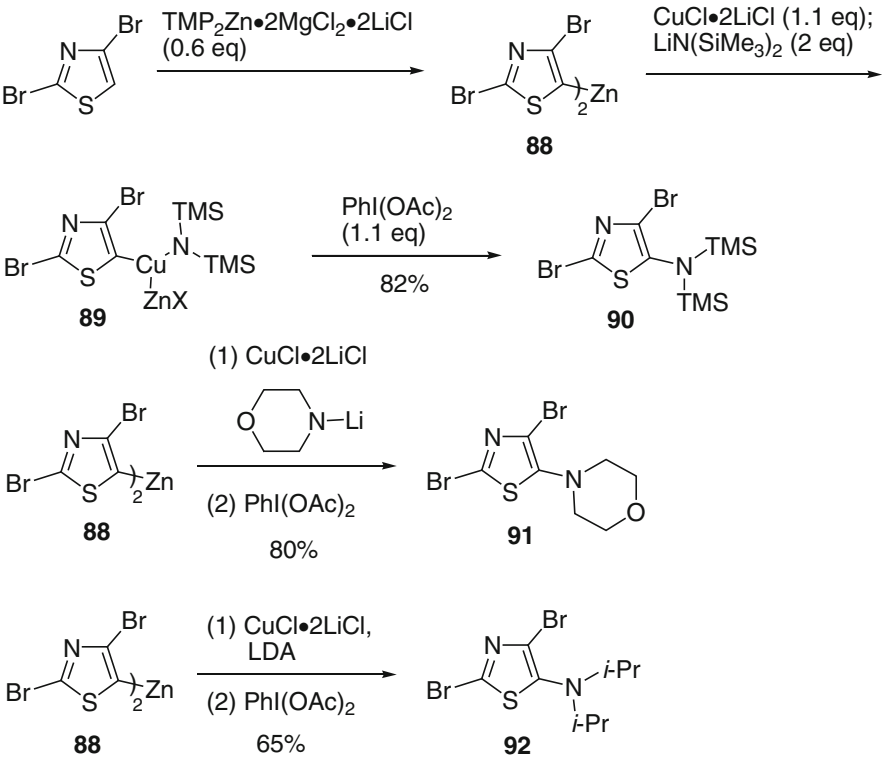


5 Zincation and Caldation

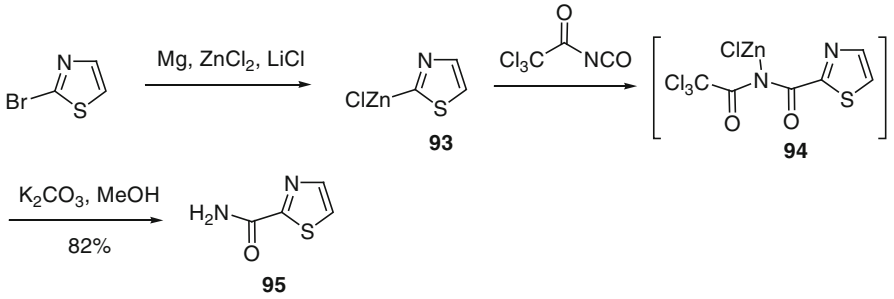
2-Iodobenzothiazole **65** is prepared from benzothiazole by deprotonation using an in situ mixture of $ZnCl_2$•TMEDA and lithium 2,2,6,6-tetramethylpiperidine (LiTMP) followed by trapping with iodine [41–44]. When $CdCl_2$•TMEDA is used instead of $ZnCl_2$•TMEDA, the yield is increased to 97%. However, a mixture of 2-iodothiazole and 2,5-diiodothiazoleis obtained from simple thiazole.



Functionalized thiazolyl amines are made by the oxidative coupling of polyfunctional zinc amidocuprates using (diacetoxyiodo)benzene ($PhI(OAc)_2$) as oxidant [45, 46]. The required organozinc reagent **88** is obtained by direct zincation of 2,4-dibromothiazole with $TMP_2Zn•2MgCl_2•2LiCl$ (TMP = 2,2,6,6-tetramethylpiperidyl). This zinc reagent is treated with the THF soluble complex CuCl•2LiCl and $LiN(TMS)_2$ to afford the corresponding zinc amidocuprate **89**. Subsequent oxidation of **89** with (diacetoxyiodo)benzene furnishes the heterocyclic amine **90** in 82% yield. Amines **91** and **92** are obtained from the zinc reagent **88** when lithium morpholin-4-ide and lithium diisopropylamide are used, respectively.

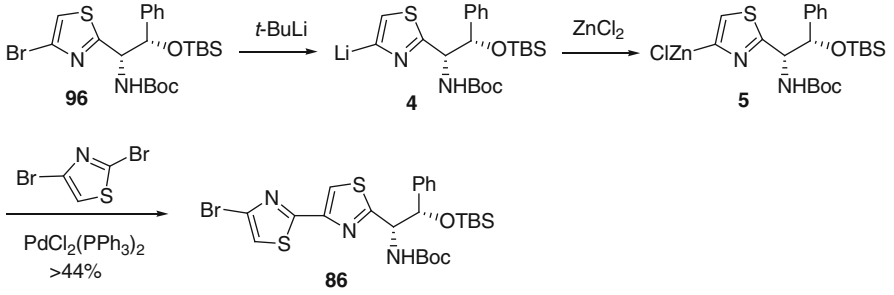


The functionalized organozinc halides can also be converted to primary amides [47]. Thus, organozinc chloride **93**, which is readily prepared by halogen–magnesium exchange and subsequent transmetalation with zinc chloride, reacts with trichloroacetyl isocyanate to give the corresponding primary amide **95** after hydrolysis under basic conditions.



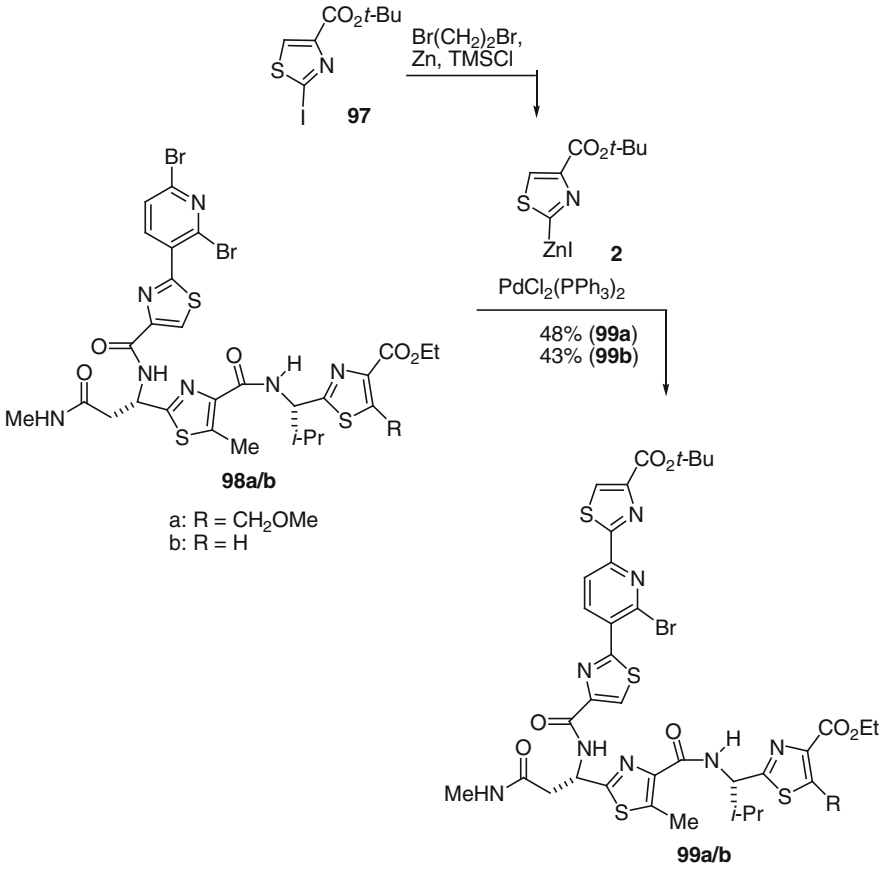
93 **94** **95**

The 4-thiazolylzinc **5** required for the Negishi reaction in the total synthesis of GE2270A is prepared by low temperature lithium–bromine exchange of bromothiazole **96** and subsequent transmetalation to zinc [15]. Addition of 2,4-bromothiazole and $PdCl_2(PPh_3)_2$ catalyst to a solution of the 4-thiazolylzinc **5** yields the desired 2,4′-bithiazole **86** in moderate yield.



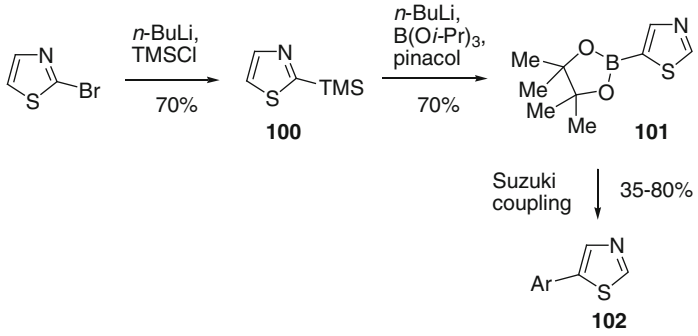
96 **4** **5** **86**

Dibromopyridines **98a/b** undergo regioselective Negishi cross-coupling reactions with the 2-zincated *tert*-butyl thiazole-5-carboxylate **2** (readily prepared from iodide **97**) to give pyridyl tri(thiazoles) **99a/b**, which serve as advanced intermediates to GE2270A [15] and amythiamicin C/D [18], respectively.

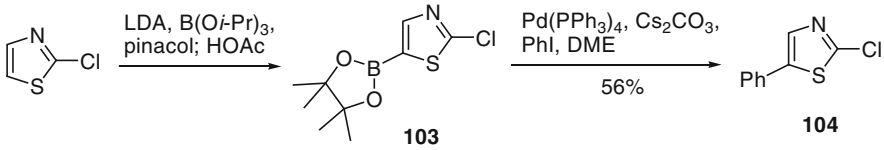


6 Boronation

A facile synthetic route to the thiazol-5-ylboronic acid pinacol ester **101** has been established [48]. 2-Bromothiazole undergoes halogen lithium exchange to give 2-trimethylsilylthiazole **100**. Lithiation at C-5 with *n*-BuLi, boronation with triisopropyl borate, and transesterification with pinacol in the presence of acetic acid generate the stable pinacol ester **101** directly. The trimethylsilyl group is cleaved during the workup process. Compound **101** is coupled with various aryl halides under typical Suzuki conditions to give the 5-arylthiazoles **102**.

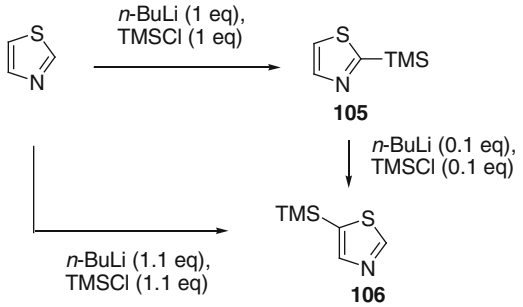


5-Thiazoleboronic acid pinacol ester **103** is prepared in high yield using a water-free workup procedure followed by distillation [49]. Due to its instability in aqueous media, the Suzuki coupling reactions of **103** with various aryl halides are preformed under water-free conditions to furnish the desired products in moderate to high yields.

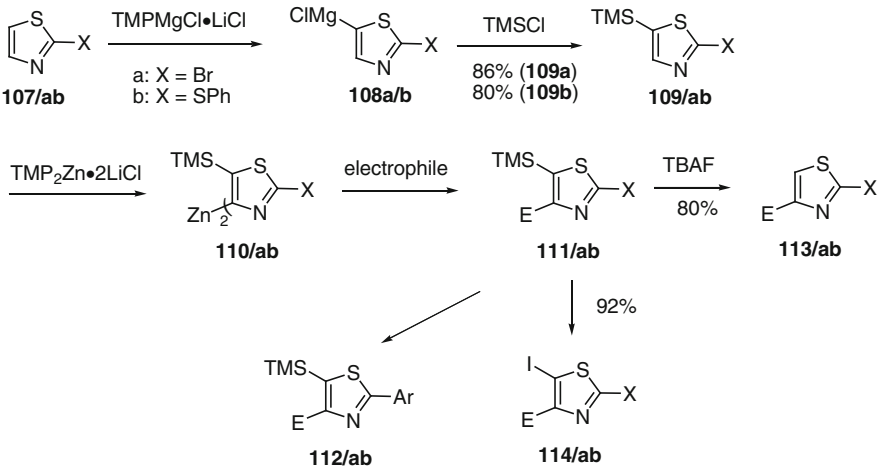


7 Silylation

2-(Trimethylsilyl)thiazole **105** is generated from thiazole by the addition of 1 eq. *n*-BuLi and 1 eq. TMSCl. 5-(Trimethylsilyl)thiazole **106** can be prepared directly from thiazole in the same fashion as 5-trimethylstannyl thiazole **70** (vide supra) [39]. Treatment of thiazole with 1.1 eq. *n*-BuLi and 1.1 eq. TMSCl generates the 5-trimethylsilylthiazole **106** instead of the 2-substituted thiazoles **105**. The 5-trimethylstannyl thiazole **106** is also prepared from the 2-trimethylsilyl counterpart **69** upon treatment with 0.1 eq. *n*-BuLi and 0.1 eq. TMSCl. The formation of the 5-substituted thiazoles involves a novel metallotropic rearrangement of TMS group around the thiazole ring from C-2 to C-5.



Thiazole silylation is an important tool in the regioselective functionalization of the thiazole scaffold [50]. For example, the commercially available 2-bromothiazole (**107a**) and 2-(phenylthio)thiazole (**107b**) undergo regioselective magnesation at C-5 using TMPMgCl•LiCl, and the resulting thiazol-5-ylmagnesium chlorides **108a/b** are exposed to TMSCl to give 5-(trimethylsilyl)thiazoles **109a/b** in good yields. With the 5-position protected with a TMS group, a subsequent zincation is carried out with TMP_2Zn•2LiCl. The zincated species **110a/b** react with various electrophiles to give the trisubstituted thiazoles **111a/b**, which are versatile synthetic intermediates. The Ni-catalyzed cross-coupling of the 2-thiophenyl thiazole **111b** with arylzinc chloride provides 2-aryl thiazoles **112b**, and the 2-bromothiazole **111a** can be converted to 2-aryl thiazole **112a** via palladium-catalyzed coupling reactions. Deprotection of the TMS group in **111a/b** with TBAF affords the 2,4-difunctionalized thiazole **113a/b**. Alternatively, addition of iodine chloride to **111a/b** results in 5-iodothiazols **114a/b** in good yields.



8 Conclusion

As thiazole metalation becomes one of the most important tools in the functionalization and incorporation of thiazole scaffold, significant efforts have gone into the development of metalated thiazoles and their reactions. These efforts have culminated in the concise total syntheses of thiazole-containing natural products, thiopeptides GE2270A and amythiamicin C and D. Future efforts will be directed to the search for new, stable, and multifunctionalized metalated thiazoles as well as for mild conditions to carry out their cross-coupling reactions such as room temperature and aqueous media.

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Isothiazoles and Benzisothiazoles

Charles F. Nutaitis

Abstract In this study, metalation chemistry of isothiazoles, benz[*c*]isothiazoles, and benz[*d*]isothiazoles is discussed, and examples of ring metalation, lateral metalation, and utilization of metalated isothiazoles in transition metal-catalyzed coupling reactions are presented.

Keywords Benz[*c*]isothiazole · Benz[*d*]isothiazole · Isothiazole · Metalation

Contents

1 Introduction 329
2 Ring Metalation 330
2.1 Isothiazole 330
2.2 Benz[*d*]isothiazole and Benz[*c*]isothiazole 335
3 Lateral Metalation 337
4 Coupling Reactions 339
4.1 Isothiazole 339
4.2 Benz[*d*]isothiazole 341
5 Conclusion 342
References 342

1 Introduction

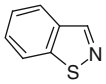
The chemistry and properties of isothiazole (**1**) as well as the two isomeric benzo-analogs, benz[*d*]isothiazole (**2**) and benz[*c*]isothiazole (**3**), have been extensively investigated, and reviews have been previously published [1–6]. It should be noted

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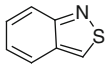
that the benzo-analogs are often named as 1,2-benzisothiazole (**2**) and 2,1-benzisothiazole (**3**) in the literature.



1



2



3

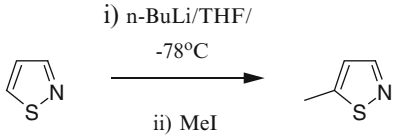
Interest in isothiazoles arises from the varied biological activities attributed to compounds incorporating this ring system. Molecules possessing isothiazole components have been shown to have antiviral, antibacterial, anticancer, and antifungal activities and have also been demonstrated to be drug candidates for the treatment of a number of diverse conditions such as depression, schizophrenia, Alzheimer's, insomnia, pain, type 2 diabetes, diabetic retinopathy, rheumatoid arthritis, and psoriasis ([4]; for representative examples and leading references see [7–18]).

Despite this great and varied potential, reports of successful metalations for the elaboration of these ring systems, in particular the benzo-analogs, are scarce when compared to other heterocycles. This review will primarily focus on reports published since 2001, but will also briefly discuss earlier literature to provide appropriate background and context.

2 Ring Metalation

2.1 Isothiazole

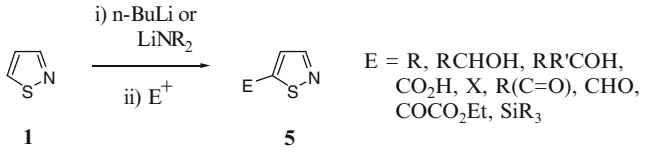
In 1964, it was determined that direct lithiation of isothiazole with *n*-butyllithium occurs at C-5 [19]. The position of lithiation was established by quenching the lithiated intermediate with methyl iodide to provide 5-methylisothiazole (**4**), a known compound, in 40% yield.



1 **4**

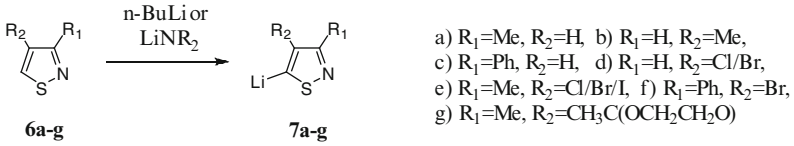
After this initial report, it was subsequently shown that lithiation of isothiazole occurs at C-5 with a high degree of selectivity upon treatment with alkyllithium reagents or lithium dialkylamides such as LDA. The intermediate lithiated species can be trapped with a variety of electrophiles, including other alkyl halides as well

as carbon dioxide, halogens, esters, nitriles, aldehydes/ketones, DMF, and silyl chlorides, affording a number of different types of substituted isothiazoles [20–31].

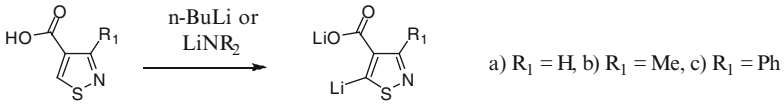


1 **5**

It was also found that substituents at the C-3 and C-4 positions do not generally interfere with C-5 lithiation, even when the substituent present is protic, provided excess base is utilized [19, 20, 22–24, 26, 29, 31].

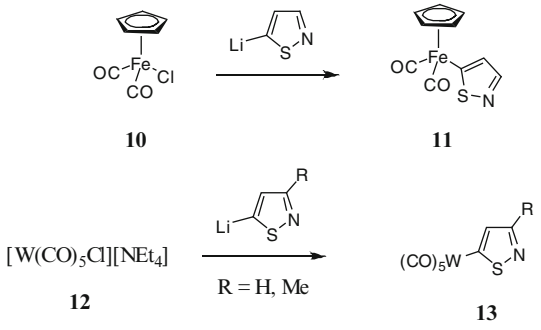


6a-g **7a-g**



8a-c **9a-c**

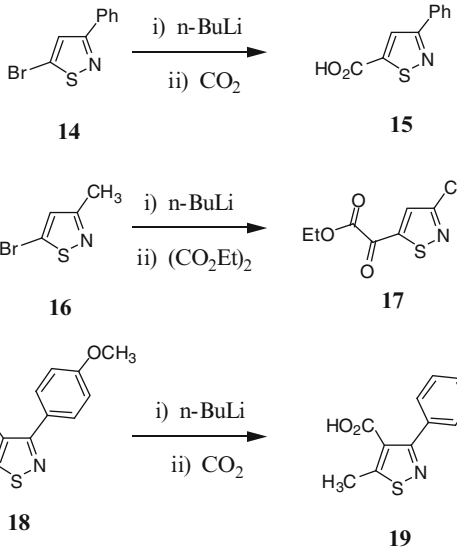
Transition metal-substituted derivatives have also been prepared from 5-lithioisothiazoles, as shown below [32, 33].



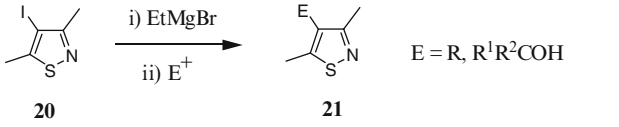
10 **11**

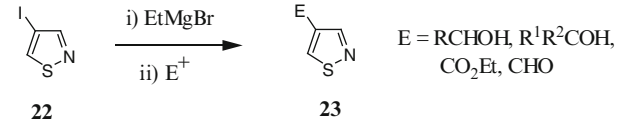
12 **13**

The propensity for lithiation at C-5 is so great that it occurs as a major pathway even over halogen–metal exchange, when a halogen (Cl, Br, I) is present at C-4 (see examples **6d–f** above) [19, 22]. However, halogen–metal exchange occurs as expected at the C-5 position, or at the C-4 position when both C-3 and C-5 are substituted [20, 22, 26].

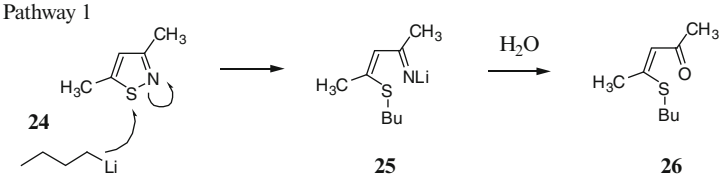


Preparation of C-4 isothiazolyl Grignard reagents has been accomplished by the treatment of the appropriate 4-iodoisothiazole with ethylmagnesium bromide. Quenching with a variety of electrophiles affords 4-substituted isothiazoles [34, 35].

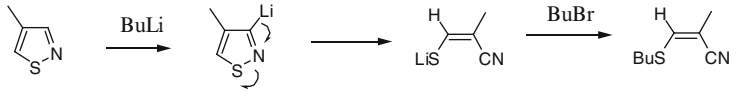




Although not always seen, ring opening side reactions have occasionally been reported when isothiazole is treated with alkyllithium reagents [19, 24]. Two different types of ring decomposition have been observed and have been explained by either attack of butyllithium at sulfur (Pathway 1) or by lithiation at C-3 followed by ring opening (Pathway 2).

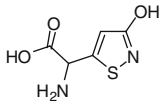


Pathway 2



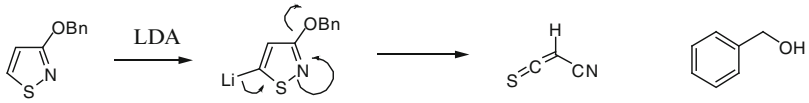
6b **27** **28** **29**

More recently, the first direct functionalization of a 3-oxygenated isothiazole was reported during the synthesis of thioibotenic acid (**30**) [36]. Thioibotenic acid is the sulfur analog of ibotenic acid, a neurotoxic natural product found in certain mushrooms.



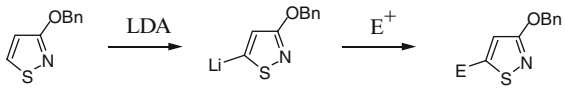
30

Thus, lithiation of 3-benzyloxyisothiazole (**31**) was investigated, and it was found that metalation occurs smoothly at C-5 with LDA in diethyl ether at −78°C, but fails completely with *n*-butyllithium. Additionally, diethyl ether was found to be preferred over THF as the solvent for these reactions. When diethyl ether was used, the intermediate lithium salt immediately precipitated from the solvent and was found to be highly stable, whereas precipitation did not occur from THF, and decomposition was noted to occur over time. Upon analysis of the byproducts, only benzyl alcohol (**34**) could be conclusively identified, suggesting ring fragmentation, a process which had been previously observed in other isothiazole systems [19, 24].



31 **32** **33** **34**

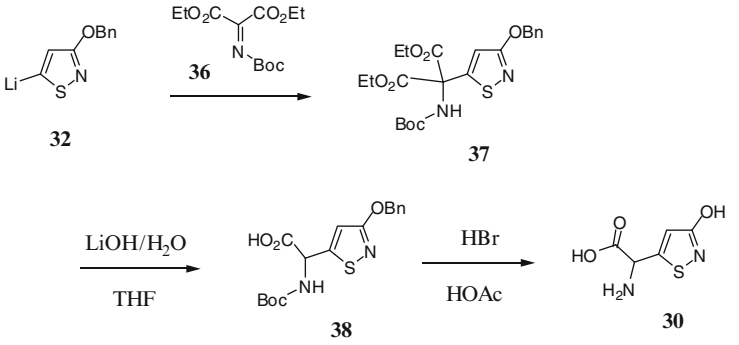
Subsequent reaction of 3-benzyloxy-5-lithioisothiazole (**32**) with a variety of electrophiles proved successful, affording 5-substituted-3-benzyloxyisothiazoles **35** in 54–68% yield. Attempts to incorporate a benzoyl group via this methodology, however, failed.



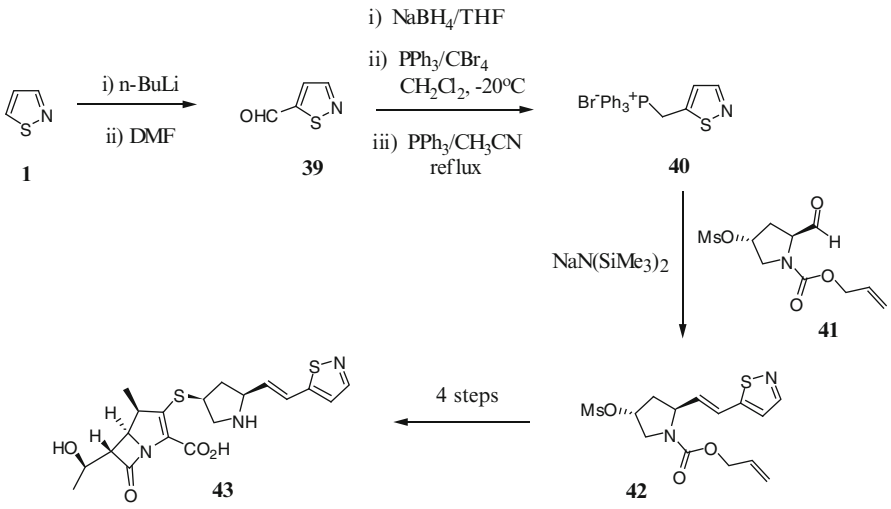
31 **32** **35**

E = RCHOH, R^1R^2COH, CO_2R, CHO

To complete the synthesis of the natural product analog, 3-benzyloxy-5-lithioisothiazole (**32**) was treated with imine **36** to afford the protected aminodiester **37**. Ester hydrolysis with lithium hydroxide followed by concomitant decarboxylation afforded the carboxylic acid **38**. Treatment of **38** with HBr/acetic acid resulted in both benzyl and Boc deprotection to provide thioibotenic acid (**30**).

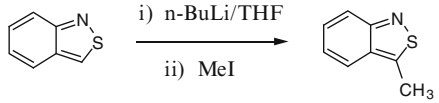


Lithiation of isothiazole was utilized in the synthesis of the 1β-methylcarbapenem **43**, a compound which exhibits activity against both Gram-negative and Gram-positive bacteria. Thus, treatment of 5-lithioisothiazole (generated from isothiazole (**1**) and *n*-butyllithium) with DMF provided 5-formylisothiazole (**39**), which was converted in three steps to the Wittig reagent **40**. Treatment of **40** with formylpyrrolidine **41** and sodium bis(trimethylsilyl)amide gave alkene **42**, which was transformed in four subsequent steps to the target 1β-methylcarbapenem **43** [37].



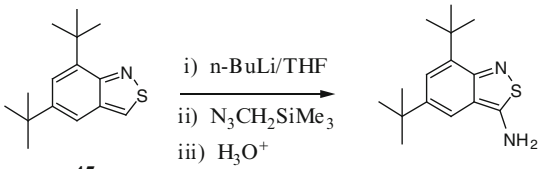
2.2 *Benz[*d*]isothiazole and Benz[*c*]isothiazole*

Very few reports regarding the metalation of the two benzo-analogs of isothiazole have appeared in the literature. Metalation of benz[*c*]isothiazole (**3**) with *n*-butyllithium occurs at C-3, and the resulting anion has been converted to 3-methylbenz[*c*]isothiazole (**44**) upon quenching with methyl iodide [38].



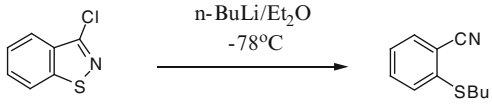
3 **44**

Similarly, treatment of 5,7-di-*tert*-butylbenz[*c*]isothiazole (**45**) with *n*-butyllithium followed by trimethylsilylmethyl azide and acid hydrolysis yields 3-amino-5,7-di-*tert*-butylbenz[*c*]isothiazole (**46**) [39].



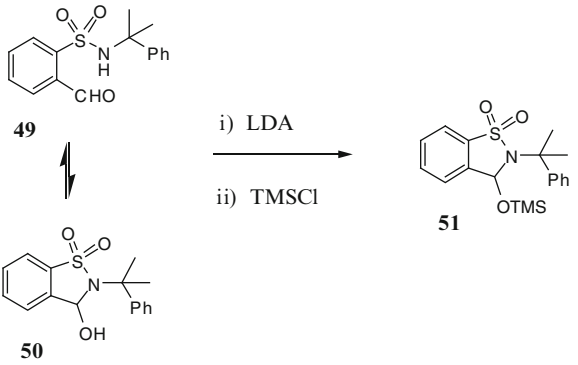
45 **46**

Utilization of metalated benz[*d*]isothiazoles for the preparation of substituted analogs has not been accomplished, likely due to ring fragmentation, as illustrated by the reaction of 3-chlorobenz[*d*]isothiazole (**47**) with *n*-butyllithium to afford nitrile **48** [40].

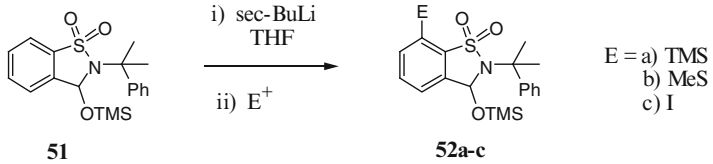


47 **48**

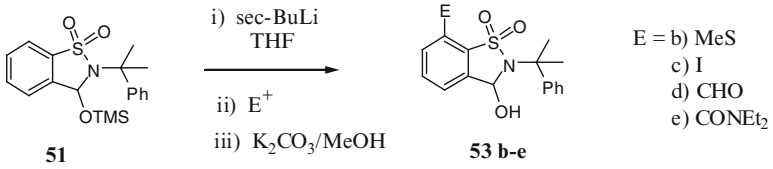
Directed *ortho*-metalation of the 3-silyloxy sultam **51** was found to be a convenient method for the preparation of 7-substituted saccharin derivatives [41]. Compound **51** can be prepared upon treatment of the equilibrium mixture of **49**:**50** with LDA and trimethylsilyl chloride. However, it was found that the product was unstable over time, degrading back to **49**:**50** upon desilylation.



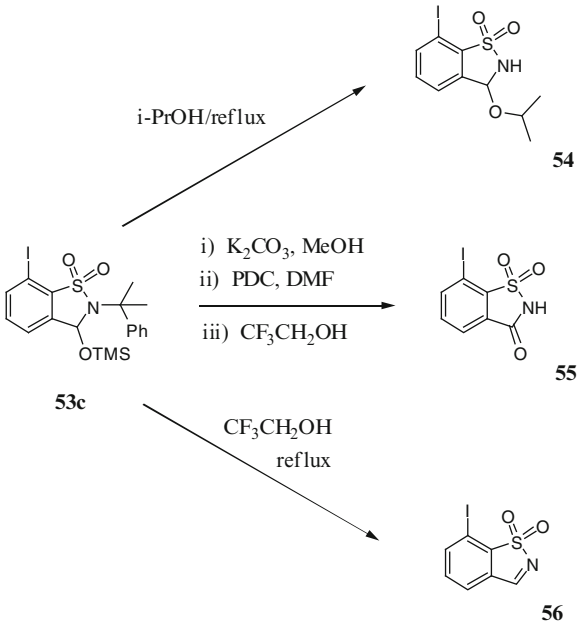
Nevertheless, treatment of **51** with *sec*-BuLi/TMEDA followed by a variety of electrophiles provided the 7-substituted sultams **52** in moderate to good yield. It was found that employment of two equivalents of *sec*-BuLi/TMEDA provided better yields of **52** than did one equivalent.



Furthermore, if the metalation reaction is followed by a methanolic potassium carbonate workup, desilylation can be effected to provide the carbinols **53**.

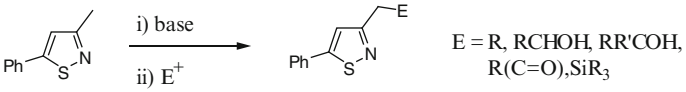


It was also demonstrated that the 7-iodosultam **53c** could be converted to several other potentially useful derivatives, as illustrated below.

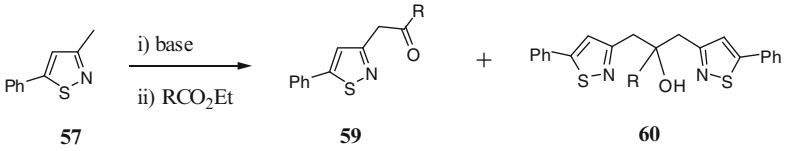


3 Lateral Metalation

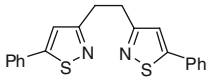
Lateral metalation at all three positions (C-3, C-4, and C-5) of the isothiazole ring system has been reported. Treatment of 3-methyl-5-phenylisothiazole (**57**) with *n*-butyllithium, lithium isopropylcyclohexylamide (LICA), or LICA–TMEDA results in metalation of the C-3 methyl group. Reaction of the anionic intermediate with alkyl halides, aldehydes, ketones, nitriles, and chlorosilanes occurred as expected to provide the substituted products **58** [42, 43].



Reaction with esters formed a mixture of the ketone **59** and tertiary alcohol **60** products [43].

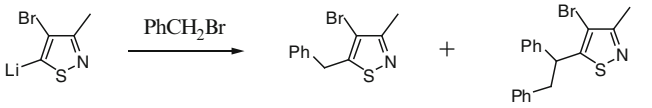


The dimeric product **61** was also observed in all metalation reactions of 3-methyl-5-phenylisothiazole (**57**) and is presumed to arise via a free radical coupling mechanism.



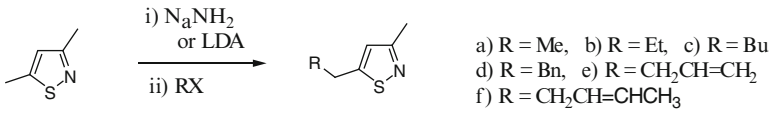
61

Lateral metalation at C-5 was reported to occur as a side reaction (10%) in the benzylation reaction between 4-bromo-5-lithio-3-methylisothiazole (**62**) and benzyl bromide [19].



62 **63** (13%) **64** (10%)

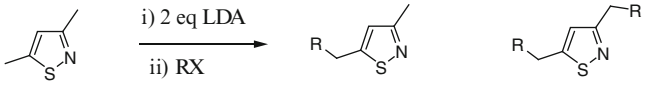
Lateral metalation can be made to be the major reaction pathway as demonstrated by lithiation of the 3,5-dimethylisothiazole (**24**) system [44]. Treatment of **24** with either sodium amide or LDA and quenching of the intermediate anion with alkyl or allyl halides results in selective α-alkylation at C-5, providing the products **65** in 21–57% yield when sodium amide is used, and in 53–88% yield when LDA is used.



a) R = Me, b) R = Et, c) R = Bu
d) R = Bn, e) R = $CH_2CH{=}CH_2$
f) R = $CH_2CH{=}CHCH_3$

24 **65a-f**

When the metalation is carried out with two equivalents of LDA and excess alkyl halide, a mixture of 5-alkyl **65b–f** and 3,5-dialkyl **66b–f** products is formed, with mono-alkylation at C-5 dominating.

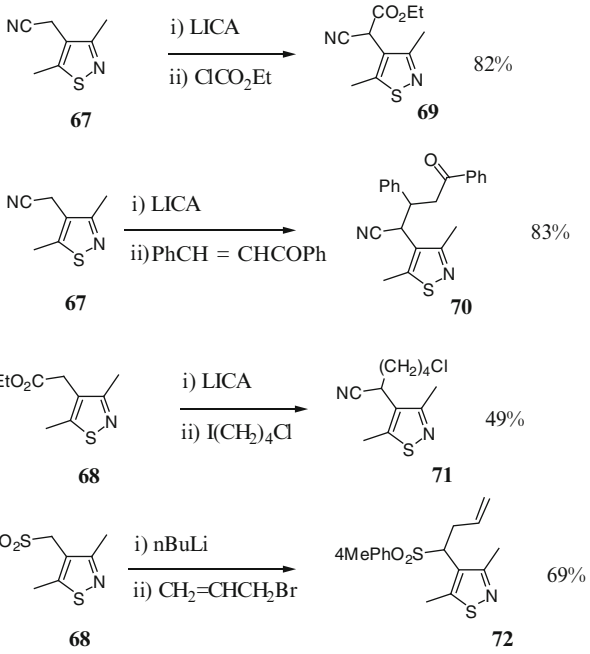


24 **65b-f** **66b-f**

Although the authors attribute the presence of **66** to possible formation of the C-3/C-5 dianion, no evidence is presented to conclusively support concomitant lithiation at both sites.

Lateral metalation at C-4 of an isothiazole system has been accomplished when the molecule also contains a resonance-stabilizing electron withdrawing group at the C-4 α-position in order to overcome the propensity of isothiazoles to preferentially undergo α-metalation at C-5. The metalation has been accomplished with

several different strong bases (LDA, LTMP, $NaNH_2$, LICA, or *n*-butyllithium), and a variety of electrophiles have been utilized to trap the intermediate anion. Representative examples are illustrated below [45].



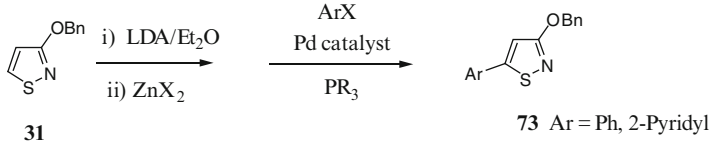
4 Coupling Reactions

4.1 Isothiazole

Transition metal-catalyzed cross-coupling reactions are an important tool in the arsenal of the organic chemist (for recent reviews, see [46–48]), and since 2003, isothiazoles have been utilized in this regard. However, most often the isothiazole has served as the electrophilic reactant of the coupling reaction, generally in the form of an isothiazolyl halide [49–58]. Relatively few reports of successful cross-couplings in which the isothiazole system functions as the metalated nucleophilic component have appeared in the literature.

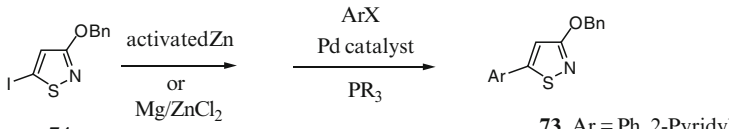
In an attempt to prepare isothiazole-based ligands for the 4-aminobutanoic acid (GABA) and the (*S*)-glutamate (Glu) receptors, which could be potential drug candidates for the treatment of pain and insomnia, cross-coupling reactions of 3-benzyloxyisothiazole (**31**) were investigated [52]. Initially, a Negishi

cross-coupling strategy involving preparation of the required organozinc reagent was explored. Lithiation of **31** at C-5 with LDA followed by transmetalation with zinc chloride or zinc bromide, and subsequent reaction under a variety of conditions, however, led to extensive decomposition. In all cases, less than 5% of the expected coupling products **73** were observed.



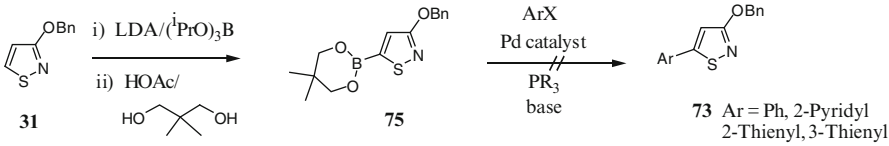
31 **73** Ar = Ph, 2-Pyridyl

Negishi cross-coupling of 3-benzyloxy-5-iodoisothiazole (**74**), prepared upon treatment of **31** with LDA and molecular iodine, was also attempted. Reaction of **74** with either activated zinc or magnesium/zinc chloride, followed by a variety of typical Negishi-style coupling conditions, once again resulted in low yields (<35%) of the expected products **73**; 3-benzyloxyisothiazole (**31**) was the major product in all reactions.



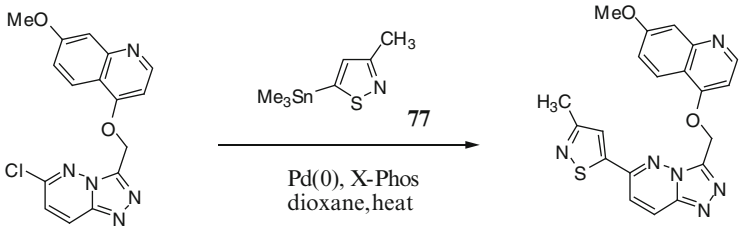
74 **73** Ar = Ph, 2-Pyridyl
2-Thienyl

In this same report, Suzuki cross-couplings of **75**, prepared by treating 3-benzyloxyisothiazole (**31**) with LDA/triisopropylborate followed by 2,2-dimethylpropane-1,3-diol/acetic acid, were also investigated. Under all conditions studied, deboronation to regenerate **31** was the major pathway, with no coupling products being detected. Deboronation was attributed to instability of **75** at elevated temperatures when in solution.



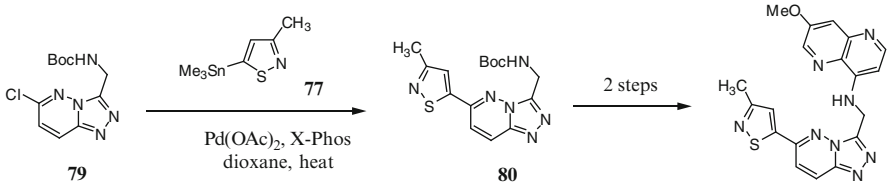
31 **75** **73** Ar = Ph, 2-Pyridyl
2-Thienyl, 3-Thienyl

During a study on the preparation and evaluation of small molecule inhibitors of the tyrosine kinase receptor (c-Met), for the treatment of human cancers, a successful Stille cross-coupling utilizing an isothiazole nucleophilic species was realized in 2008 [59]. Treatment of **76** with 3-methyl-5-trimethylstannylisothiazole (**77**), Pd (0), and X-Phos, in dioxane, afforded the coupled product **78**. No information with regard to the reaction yield was provided by the authors.



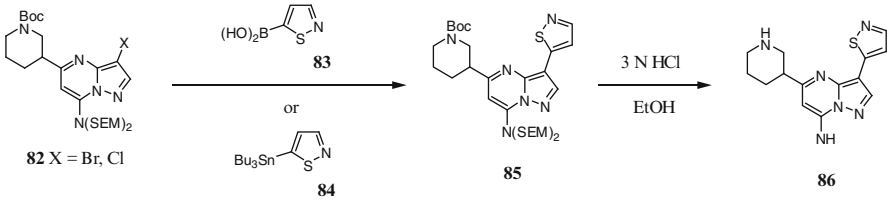
76 **78**

In a subsequent study targeting **81** as a potential c-Met inhibitor, an additional Stille coupling between 3-methyl-5-trimethylstannylisothiazole (**77**) and the triazolopyridazine **79** was reported to occur in 33% yield to afford **80**. Conversion of **80** to the **81** was accomplished in two additional steps [60].



79 **80** **81**

Molecules that inhibit checkpoint kinase 1 (CHK1) have been found to enhance the effect of other cytotoxic agents in the treatment of cancer [61–63]. During the screening of potential CHK1 inhibitors, the isothiazolyl-substituted triazolo[1,5-*a*] pyrimidine **86** was prepared utilizing a coupling reaction between the halide **82** and either 5-isothiazolylboronic acid (**83**) or 5-tributylstannylisothiazole (**84**) in the reaction sequence. The authors did not provide details as to whether a Suzuki or Stille coupling strategy was used for this particular analog [64].

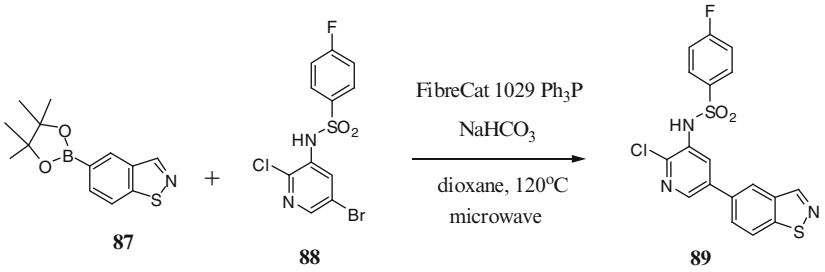


82 X = Br, Cl **85** **86**

*4.2 Benz[*d*]isothiazole*

For evaluation as an anticancer agent, via the inhibition of phosphoinositide 3-kinases (P13Ks), the benz[*d*]isothiazolylpyridyl sulfonamide **89** was prepared

in 48% yield by the Suzuki cross-coupling between benz[*d*]isothiazolyl boronic ester **87** and the pyridylsulfonamide **88** [65].



87 **88** **89**

5 Conclusion

The metalation of isothiazoles is anything but a mature field of study. Although progress has been made to some extent, particularly for isothiazole, much work remains to be done. Simple isothiazoles are, to a limited extent, understood. It has been shown that metalation can be readily made to occur selectively at C-5, and in certain cases at C-4 via halogen–metal exchange, but metalation at C-3 remains unrealized. Furthermore, although a variety of electrophiles have been utilized for quenching of successfully generated isothiazole anions, the metalation of relatively few isothiazole systems has been studied. Ring openings noted by some researchers remain capricious, and more work is needed to determine when and why these generally unwanted side reactions occur. Recently, progress has been made on the utilization of metalated isothiazoles as nucleophiles in transition metal-catalyzed cross-coupling reactions, but the full potential of these reagents remains to be unveiled. Lateral metalations have been successfully effected in all three positions of isothiazole, but further research is needed to fully explore the scope and limitations of this strategy for elaboration of the isothiazole system.

Reports on the metalation of the benzo-analogs of isothiazole are even more limited than for the parent isothiazole itself. Although it appears that benz[*c*] isothiazole is lithiated at C-3 selectively, only two electrophiles have apparently been utilized as quenching reagents for the anions; successful trapping by an electrophile of a C-3 metalated benz[*d*]isothiazole has not been reported. A directed *ortho*-metalation of the carbocyclic ring of a sultam system has also been accomplished.

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Recent Advances in the Synthesis of Thiophenes and Benzothiophenes

Edward R. Biehl

Abstract The use of thiophenes in medicinal chemistry and materials sciences has grown enormously during the past several years. For example, thiophene is the backbone of several important pharmaceuticals such as Reloxifen, duloxetine (Cymbalta), tiotropium (Spiriva), Cosopt (dorzolamide), etc. Importantly, the syntheses the aforementioned drugs use simple thiophenes as starting materials. The quest for these exotic small molecules has been brought forth by either modification of classical methods and, more importantly, novel synthesis by highly creative synthetic chemists. Likewise attention has been drawn to the efficient synthesis of thiophenes-containing organic materials due to the importance of atom-economics and green chemistry. Due to the facile synthesis of thiophene derivatives much progress has been made in thiophenes containing organic materials with respect to light-emitting diodes, firld-effect transistors, solar cells, etc. This report details the major synthetic methods for the synthesis of thiophenes and benzo[*b*]thiophenes including Gewald reaction, Wilgerodt-Kindler reaction, Paul-Knorr reaction, fluorous synthetic protocol, sulfur-assisted reactions, electrophilic cylization and direct arylation methods. Where possible, the reactions will be categorized. However, in several cases major overlapping of two or more synthetic methods have prevented such categorizations.

Keywords Benzo[a}thiophenes · Direct arylation of thiophenes · Electrophilic cyclization of alkynes · Fluorous synthetic protocol · Gewald reaction · Paul-Knorr condensation · Synthesis · Sulfur-assisted synthesis · Thiophenes · Wilgerodt-Kinler reaction

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Contents

1 Introduction 348
2 Synthesis of Thiophenes 348
2.1 Gewald Reaction 348
2.2 Willgerodt–Kindler Reaction 354
2.3 Paal–Knorr Cyclocondensation Reaction 356
2.4 Fluorous Synthetic Protocol 359
2.5 Sulfur-Assisted Synthesis of Thiophenes 359
2.6 Synthesis of Thiophenes Involving Electrophilic Cyclization of Alkynes 364
2.7 Direct Arylation of Thiophenes 368
References 377

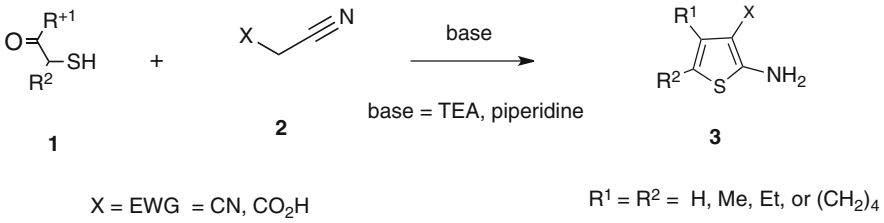
1 Introduction

The use of thiophenes in medicinal chemistry and materials sciences has grown enormously during the past several years. For example, thiophene is the backbone of several important pharmaceuticals such as Reloxifen, duloxetine (Cymbalta), tiotropium (Spiriva), and Cosopt (dorzolamide). Importantly, the syntheses of the aforementioned drugs use simple thiophenes as starting materials. The quest for these exotic small molecules has been brought forth by either modification of classical methods and, more importantly, novel synthesis by highly creative synthetic chemists. Likewise attention has been drawn to the efficient synthesis of thiophenes-containing organic materials due to the importance of atom-economics and green chemistry. Due to the facile synthesis of thiophene derivatives, much progress has been made in thiophene-containing organic materials with respect to light-emitting diodes, field-effect transistors, solar cells, etc. This report details the major methods for this important class of five-membered heterocycles. Where possible, the reactions will be categorized. However, in several cases major overlapping of two or more synthetic methods will prevent this.

2 Synthesis of Thiophenes

2.1 Gewald Reaction

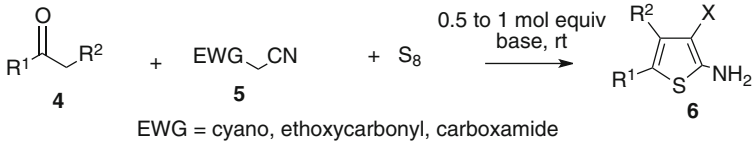
In 1961, Gewald [1] reported a simple three-component (G-3CR) reaction in which 2-aminothiophenes **3** were prepared by treating an α-mercaptoaldehyde or ketone **1**, prepared by the reaction of sulfur and carbonyl compound, with an activated nitrile **2** in the presence of a base. The first version of the Gewald reaction is shown in Scheme 1. As shown in Table 1, the reactions between **1** and **2** containing electron-releasing groups such as alkyl and cycloalkyl chains at C-4 and C-5 positions gave 2-amino derivatives **3** in yields ranging between 45% and 80%. Interestingly, nonactivated nitriles such as cyanoacetic acid do not undergo this version of the Gewald reaction.



Scheme 1 First version of Gewald reaction

Table 1 Selected syntheses of 2-aminothiophenes using first version of Gewald reaction

R^1	R^2	X	**3** Yield (%)	Reference
Me	Et	CN	51	[1]
Me	Me	CN	70	[1]
$(CH_2)_4$		CN	70	[2]
Me	Me	CO_2Me	45	[3]
$(CH_2)_4$		CO_2Et	80	[4]



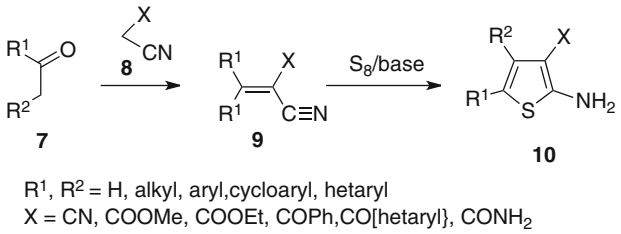
Scheme 2 Synthesis of 2-aminothiophenes **6** by second version of the Gewald reaction

Because of the instability and difficulty in preparing α-sulfanylcarbonyl compounds **1**, the first version of the Gewald reaction is limited in scope. Since then three major versions of the Gewald reaction (referred to as second, third, and fourth versions) have been developed. These improved methods have allowed the facile synthesis of multisubstituted 2-aminothiophenes many of which have major importance in combinatorial and medicinal chemistry. The Gewald multicomponent reaction has been exhaustively reviewed by Doemling [5] and Vegh [6] and will only be mentioned briefly here. In addition, application of 2-aminothiophenes to synthesis of condensed heterocycles and in drug design, optoelectronics and dyes has been reviewed by Vegh [6] and will be discussed in a later section of this review.

The second version of the Gewald reaction is probably the most elegant and consists of one-pot condensation (see Scheme 2) involving three component – α-methylene carbonyl compound **4,** α-activated acetonitrile **5**, and sulfur (referred to as MCR III) at room temperature in the presence of a relative large amount of amine (0.5–1 molar equiv). The most important nitrile components are: malonodinitrile, cyanoacetic ester, primary cyanoacetamide, and ω-cyanoacetophenone [7]. The corresponding 2-aminothiophenes **6** are formed in higher yields than those prepared by the original version (Table 2).

Table 2 Selected syntheses of 2-aminothiophen es using second version of Gewald reaction

R^1	R^2	X	**6** Yield (%)	Reference
$(CH_2)_4$		CN	90	[7]
$(CH_2)_4$		CO_2Et	91	[7]
$(CH_2)_4$		$CONH_2$	71	[7]
Me	CO_2Et	CO_2Et	60	[7]
SO_2Ph	4-BrC_6H_4	CN	84	[7]

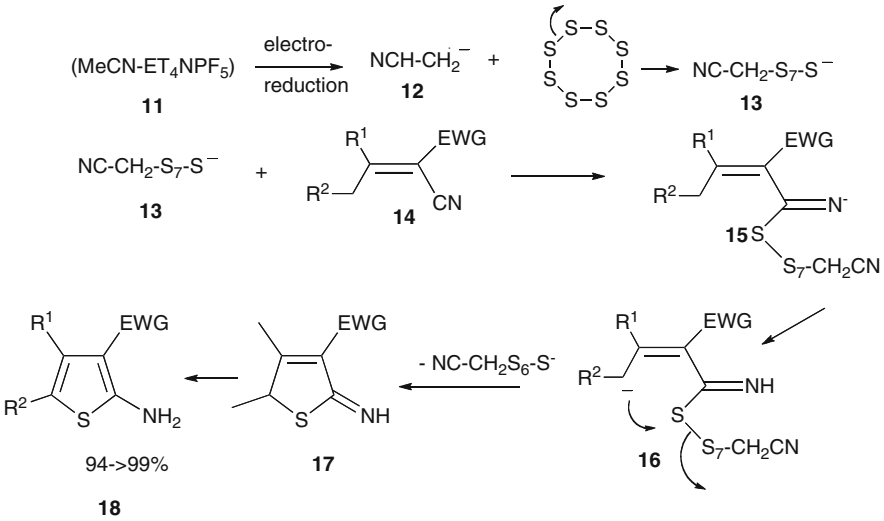


Scheme 3 Third version of Gewald reaction

The third version involves a two-pot synthesis of 2-aminothiophenes **10** by the reaction of a α,β-unsaturated nitrile **9**, prepared by a Knoevenagel condensation of **7** and **8**, which is then treated with sulfur and an amine. Alkyl aryl ketones and some cycloalkyl ketones that cannot be obtained by the first or second version of the Gewald reaction are readily prepared by the third version shown in Scheme 3.

The advances that have been made in the Gewald synthesis of thiophenes in the past decade have involved improvements in the second and particularly in the third version, the three-component reaction. These improved methods have allowed the facile synthesis of multisubstituted 2-aminothiophenes, many of which have major importance in combinatorial and medicinal chemistry. These multicomponent Gewald reactions have been exhaustively reviewed by Huang and Doemling [5, 8], Vegh [9], and Sabnis [10] and thus will only be mentioned briefly here. The most recent review (2011) by Huang and Doemling [8] which also includes isocyanide-based reactions such as the Ugi and Passerine reactions involving Gewald multicomponent reactions (MCR), reports on the synthesis of a diverse variety of highly substituted 2-aminothiophene derivatives and their many applications in combinatorial and medicinal chemistry.

Due to space limitation, this report will concentrate on a few important examples of Gewald type reactions. Although the mechanism of the Knoevenagel variations of the Gewald reaction is not fully understood, it is known that elemental sulfur does react when activated [9]. Such activation, until recently, was accomplished by adding base, usually an amine, to the reaction mixture. Support for this comes from reports (not associated with the Gewald reaction) that sulfur reacts with amines to yield polysulfide anions [10]. Recently, an elegant method (see Scheme 4) was reported by Feroci et al. [11] for activating elemental sulfur in the Knoevenagel version of the Gewald reaction using electrogenerated cyanomethyl anion **12** (easily prepared by galvanostatic reduction of acetonitrile-tetraethylammonium fluorophosphates **11**).



Scheme 4 New protocol for the synthesis of 2-aminothiophenes via Gewald reaction under solvent-free condition

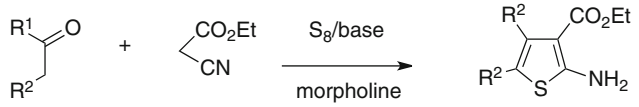
The activated sulfur **13** then reacted with substituted malonitriles **14** to give substituted 2-aminothiophenes **18** in excellent yields (94% to >99%) most likely by the successive conversion of the initial adduct **15** to intermediates **16** and then **17**.

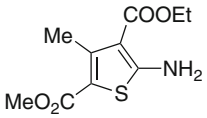
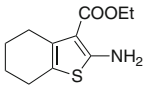
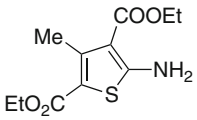
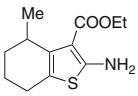
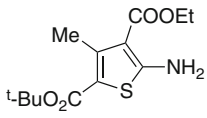
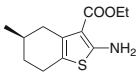
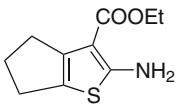
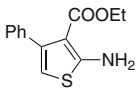
Recently, a new protocol for the synthesis of 2-aminothiophenes through the Gewald reaction in solvent-free condition run at room temperature was reported [12]. As shown in Table 3, the multisubstituted 2-aminothiophenes were formed in a single step and in good yields. 4-Phenyl-2-aminothiophene ester (Entry 8) was prepared previously in lower yields, required two sequential steps, and was run under an argon atmosphere [13].

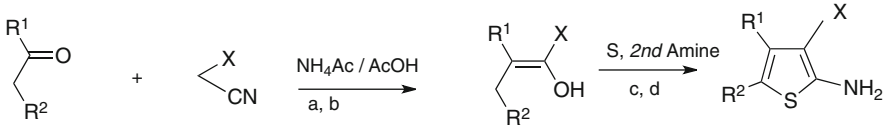
Generally, the Gewald reaction with aldehyde, methyl ketones, and acetoacetic ester occurs in an efficient manner to give 2-aminothiophenes. However, when applied to specific methyl ketones such as acetophenone, 4-methylacetophenone, and 4-chloroacetophenone, a two-step process must be used. The first step involves the slow formation (8–18 h) of the required alkylidene intermediate **21** from the reaction of methyl ketone **19** and nitrile **20** in refluxing toluene. The second step involves adding sulfur and a second amine and stirring the resulting mixture at 50°C for 6–8 h. However, Kathiravan et al. [14] have shown that the overall rate of formation of aminothiophenes in the two-step reaction can be greatly accelerated by use of microwave heating (MWH). This is shown in Scheme 5 in the reaction times for the MWH two steps are 7–24 min and 2 min, respectively.

In the past, the scope of the Gewald-3CR was hampered by the use of structurally simple nitrile components. However, recently Doemling et al. [15] were able to increase the scope of the reaction to include the use of cyanoacetamides **23**. As shown in Scheme 6, general protocols were established for the synthesis of an array of 2-aminothiophene-3-carboxamides (40 compounds) **24** from cyanoacetamides **23**, aldehydes, or ketones, and sulfur via a 3-component Gewald-3CR variation.

Table 3 Gewald synthesis of 2-aminothiophenes under solvent-free conditions

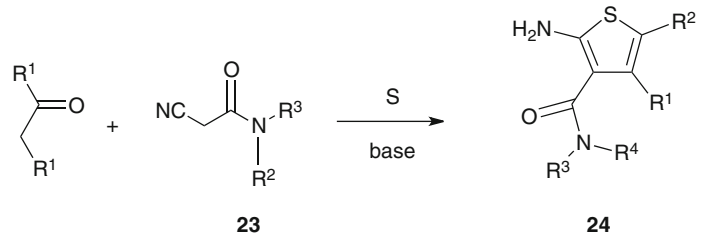


Entry	2-Amino-thiophene	Yield(%) Time (h)	Entry	2-Amino-thiophene	Yield (%) Time (h)
1		82(14)	5		75(14)
2		70(14)	6		100(14)
3		78(14)	7		77(14)
4		60(24)	8		51(25)

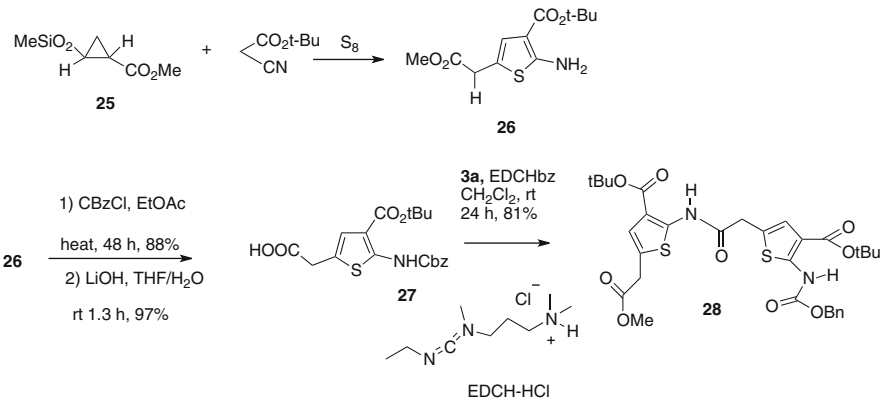


Scheme 5 (*a*) 8–18 h reflux in PhMe, (*b*) 7–24 min MWH, (*c*) 6–8 h at 50°C (50–78%), (*d*) 2 min MWH (60–80%)

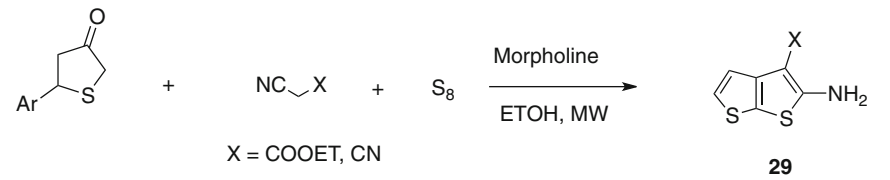
3-Bromobenzo[*b*]-5-aminothiophene carboxylic esters were also prepared by a modified Gewald reaction by the reaction of a novel siloxycyclopropane with preparation of new macrocyclic peptidomimetics. A typical example is shown in Scheme 7 in which the siloxy compound **25** is condensed with *t*-butyl cyanoacetate



Scheme 6 General protocol for preparation of 2-aminothiophene-3-carboxamides



Scheme 7 Typical example of novel preparation of macrocyclic peptidomimetics **28**



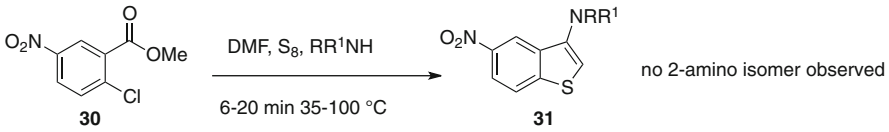
Scheme 8 Synthesis of 2-amino-5-arylthieno[2,3-*b*]thiophenes **29**

to give the 2-amino thiophene derivative **26** which after protection with CBz and saponification yields **27**. Compound **27** is subsequently converted to the dimer **28** by treatment with EDCHbz.

Another example of the synthesis of thiophene by a Gewald reaction is that reported by Balamurugan et al. [16] who used a facile domino protocol for the regioselective synthesis and discovery of potential antimycobacterial agents, i.e., 2-amino-5-arylthieno-[2,3-*b*]thiophenes **29**. The 2-amino derivatives **29** were prepared by the reaction of 5-aryldihydro-3 (2*H*)-thiophenes, ethyl cyanoacetate/

Table 4 Synthesis of 2-amino-3-arylthieno[2,3-*b*]thiophenes **29**

Compound	Ar	X	Rx time		Yield% of **29**	
			Reflux (h) (80°C)	MW (min) (140°C)	Reflux	MW
29a	C_6H_5	CO_2Et	12	25	65	77
29b	*p*-MeC_6H_4	CO_2Et	12	25	60	74
29c	*p*-ClC_6H_4	CO_2Et	12	25	62	75
29d	*p*-PrC_6H_4	CO_2Et	12	25	65	70
29e	1-Naphthyl	CO_2Et	12	25	63	69
29f	C_6H_5	CN	15	30	68	73
29g	*p*-MeC_6H_4	CN	15	30	62	71
29h	*p*-ClC_6H_4	CN	15	30	67	76
29i	*p*-PrC_6H_4	CN	15	30	61	68
29j	1-Naphthyl	CN	15	30	57	69



Scheme 9 Synthesis of 3-aminobeno[2,3a]thiophenes 31

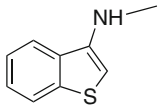
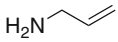
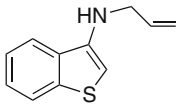
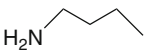
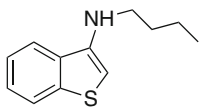
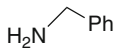
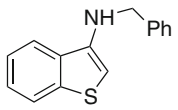
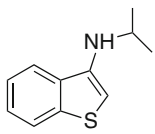
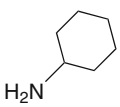
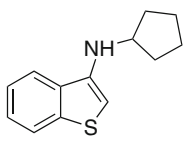
malononitrile, and sulfur in the presence of morpholine under both thermal and MWH (Scheme 8). The yields of 2-amino-5-arylthieno-[2,3-*b*]thiophenes (65–77%) and reaction times (25–30 min) obtained by MWH were significantly higher than those (57–68% and 12–15 h, respectively) obtained using conventional thermal heating. This reaction most likely occurs by a domino Gewald reaction-dehydrogenation sequence (Table 4).

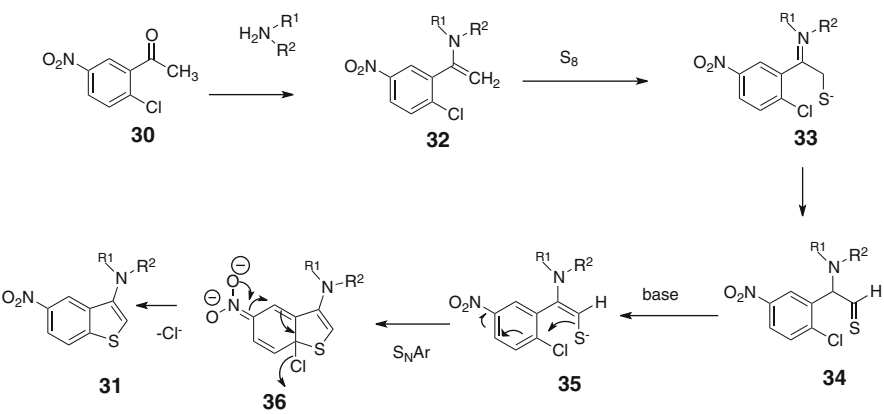
2.2 Willgerodt–Kindler Reaction

In its general form the Willgerodt–Kindler (W–K) reaction [17, 18] is a well-used method for the synthesis of thioamides from aryl ketones in the presence of a base and sulfur. Recently, Solovyev and coworkers [19] reported a new entry into the synthesis of aminobenzo[*b*]thiophenes by treating 2-chloro-5-nitrophenyl ethanone under W–K conditions (S_8 and primary or secondary amines). As will be discussed shortly, the products were formed in yields ranging from 4% to 47%, however they were incorrectly identified as 2-amino-5-nitrobenzo[*b*]thiophenes. No mechanism was proposed, but interestingly, reactions of ketones lacking a 5-nitro group failed indicating stabilization of a key intermediate are required.

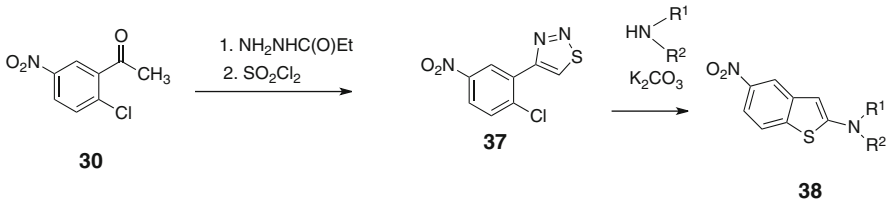
Androsov et al. [20] later found, based on NOE and X-ray analysis, that the products were in reality 3-amino-5-nitro[*b*]thiophenes **31** (see Scheme 9). The results are listed in Table 5.

Table 5 Synthesis of 3-aminobenzo[2,3*a*]thiophenes **31**

Entry	Amine	Product **31**	Yield (%)
1	$-NH_2$		46
2			47
3			36
4			30
5			14
6			40



Scheme 10 Proposed mechanism for formation of 3-aminothiophenes **31**



Scheme 11 Synthesis of 2-amino-5-nitrobenzo[2,3-*b*]thiophenes **38**

A two-part mechanism was proposed, which is shown in Scheme 10. The first part of the mechanism involves a W–K pathway in which ketone **30** in converted to the aminothio aldehyde **34** via successive formation to enamine **32** then to enaminium thiolate **33**. The second part involves a base deprotonation of the α-ring hydrogen of **33** yielding the nucleophilic thiolate intermediate **35**, which then undergoes a S_NAr intramolecular cyclization to give the Meisenheimer complex **36**. This intermediate would be expected to be stabilized by thru-resonance between the resulting ring carbanion and 5-nitro group. The loss of chloride ion and aromatization of **35** then affords the 3-amino product **31.**

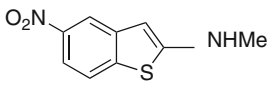
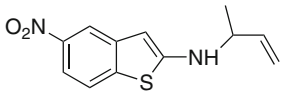
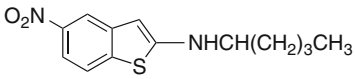
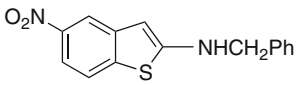
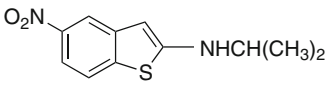
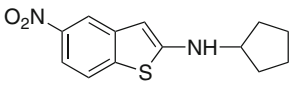
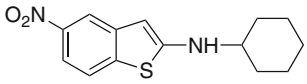
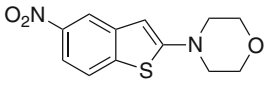
To confirm that 2-amino derivatives **38** were misidentified in original work [19], authentic samples of 2-amino derivatives **38** were prepared by a new W–K type reaction. This synthesis involved two steps described in Scheme 11. The first step involves the synthesis of a 1,2,3-thiadiazoles **37** from ethanone **30** by a Hurd–Mori reaction [21]. Compound **37** is then alkylaminated with a variety of primary and secondary amines to yield, unexpectedly, the 2-amino derivatives **38** in 7–63% as evidence by spectroscopic analysis. Selected product yields are shown in Table 6.

A possible mechanism for the synthesis of **38** is shown in Scheme 12. GC/MS confirmed the intermediate **44** (m/z = 286), whereas the other intermediates **39**–**43** are consistent with data documented in the literature.

2.3 Paal–Knorr Cyclocondensation Reaction

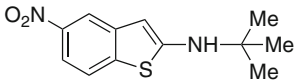
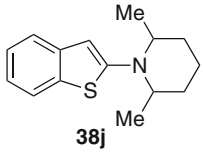
The Paal–Knorr cyclocondensation of 1,4-diketones with Lawesson's reagent and is a well-established and valuable tool for the preparation of thiophenes [21]. The 1,4-dicarbonyl compound provides four atoms (with their substituents) and the sulfur atom supplies the fifth atom. The drawback of this reaction is the harsh conditions required. This obstacle was overcome by the work of Taddei et al. [22] who developed a three-step regiocontrolled microwave-assisted Paal–Knorr reaction. As shown in Scheme 13, starting from commercially or easily prepared by β-keto esters, functional homologation provides 1,4-diketones that are treated with Et_2Zn R^2CHO followed by PCC oxidation to give the methoxycarbonyl intermediates **45** that are treated with Lawesson's reagent under MWH to give methoxycarbonyl thiophenes **46** that undergoes usual functionalization to carboxylic acids, amines, and amides **47**.

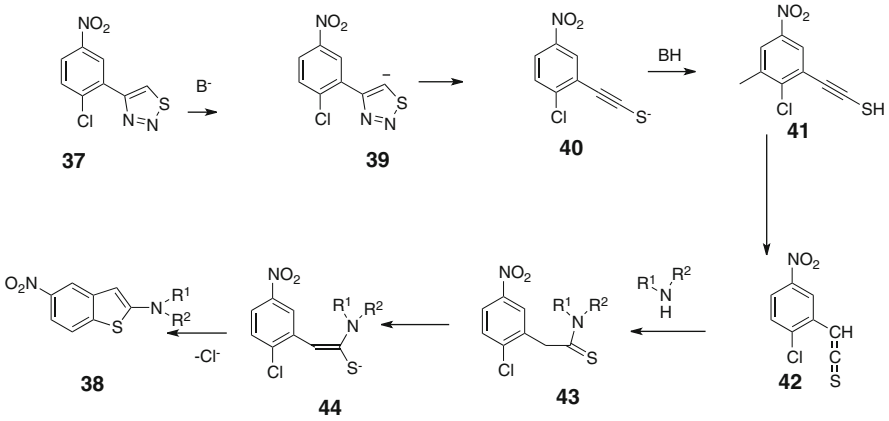
Table 6 Synthesis of 2-amino-5-nitrobenz[*b*]thiophenes **38**

Entry	Amine	Product **38**	Yield (%)
1	Methylamine-HCl	 **38a**	6
2	3-Amino-1-butene	 **38b**	42
3	*n*-Butylamine	 **38c**	44
4	Benzylamine	 **38d**	33
5	Isopropylamine	 **38e**	29
6	Cyclopentylamine	 **38f**	7
7	Cyclohexylamine	 **38g**	17
8	Morpholine	 **38h**	49

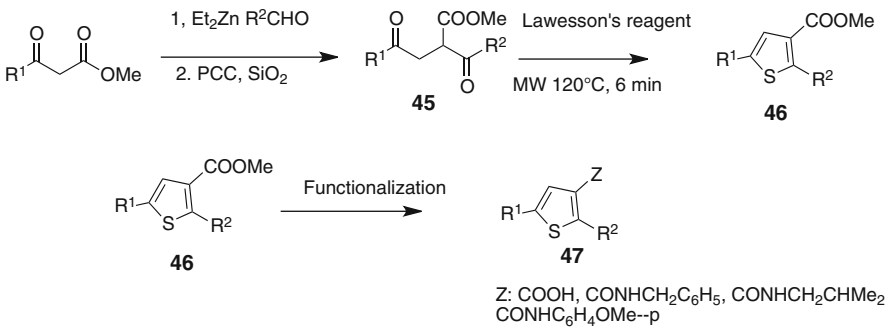
(continued)

Table 6 (continued)

Entry	Amine	Product **38**	Yield (%)
9	*t*-Butylamine	 **38i**	39
10	2,6-Dimethylpiperidine	 **38j**	63



Scheme 12 Mechanism for formation of **38**



Scheme 13 Preparation of 3-functionalized thiophenes **47**

2.4 Fluorous Synthetic Protocol

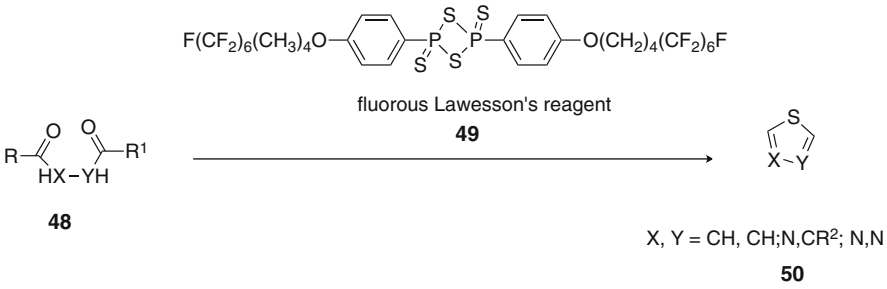
Fluorous synthetic protocols have been developed over the past few years [23]. This protocol has been applied to several well-known organic reactions such as Swern [24] and Baeyer-Villiger [25]. Subsequently, this fluorous protocol was applied to the Paal–Knorr thionation of 1,4-diketones **48** with fluorous Lawesson's reagent **49** thiophenes and other five-membered heterocycles **50** in high yields [26] (see Scheme 14). Moreover, in most cases the products are obtained in high purity by simple filtration.

2.5 Sulfur-Assisted Synthesis of Thiophenes

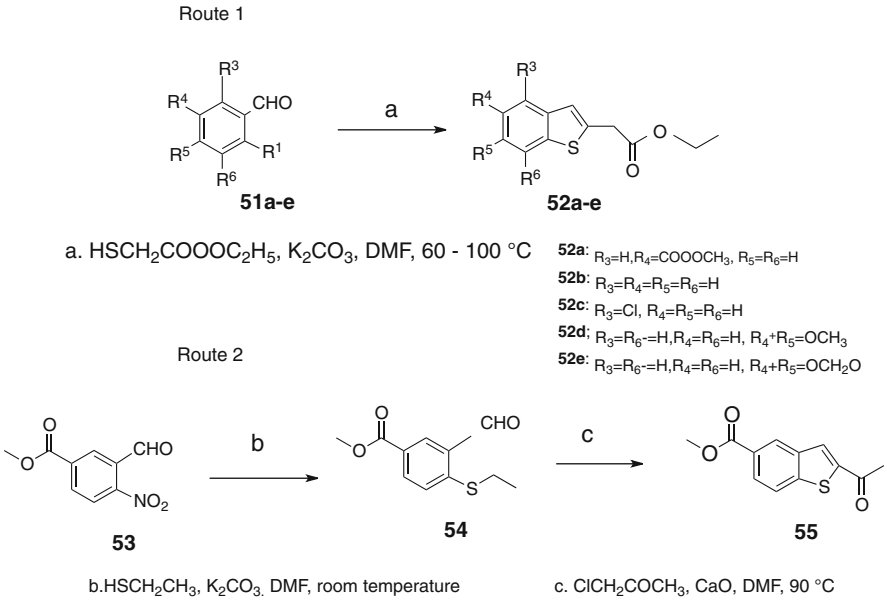
Three routes were used to prepare several substituted benzothiophenes. Due to space considerations, only the two routes that involve a sulfur-assisted reaction are given in Scheme 15 [27]. Route 1 involves the reaction of multisubstituted benzaldehydes **51a–e** with ethyl thiogylcolate to give the ethyl benzo[*b*]thiophene-2-carboxylates **52a–e** and Route 2 consists of treatment of a 2-nitrobenzaldehyde methyl ester **53** with ethyl sulfide to give 2-ethyl sulfide thiophenecarbaldehyde **54** that is then treated with $ClCH_2COCH_3$ to give the 2-acetylthiophene **55**. Several compounds represent potential leads in the development of a new class of anabolic agents.

2.5.1 Sulfur-Assisted Synthesis of Thiophenes Using Propargylic Compounds

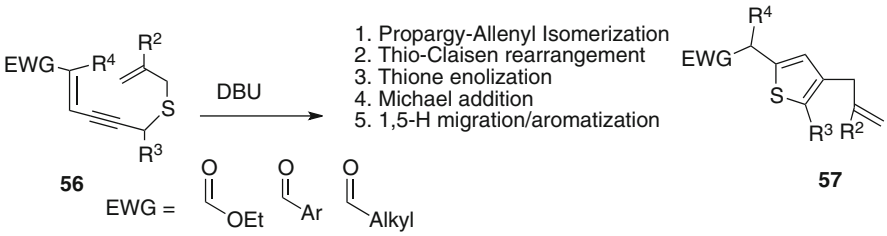
During the last 10 years much progress has been made in the synthesis of five-membered heterocyclic compounds by transition metal-catalyzed cyclization of propargylic compounds. This chemistry has been reviewed by Hao and Zhan [28] and thus will briefly reported here. The focus of this review will be on the synthesis of thiophenes by sulfur-assisted progargyl reactions.



Scheme 14 Synthesis of thiophenes and other five-membered heterocycles **50** using fluorous Lawesson's reagent



Scheme 15 Synthesis of substituted benzothiophene derivatives

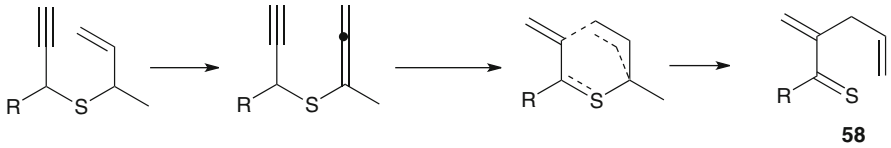


Scheme 16 Sulfur-assisted five-cascade sequential syntheses of allyl thiophen-2-yl derivatives **57**

A sulfur-assisted five-cascade sequential reaction for the convenient and efficient synthesis of allyl thiophen-2-yl acetates, propionates and ketones **57** reported by Zhou et al. [29] is shown in Scheme 16. A sulfur-assisted reaction involving an in-situ generation of an allenyl allyl sulfide **58** (for recent allene reviews, see [30–33], see also [6] in reference [36] for comprehensive list of reports) shown in Scheme 17 was proposed. The intermediate **58** then undergoes thio-Claisen rearrangement, intramolecular Michael addition, and 1,5-proton migration/aromatization to give the observed allyl thiophenes **57**.

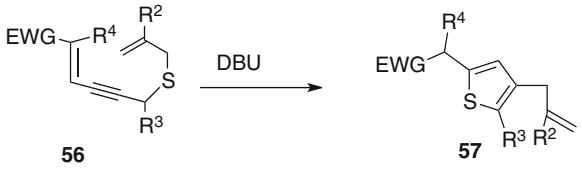
Selected syntheses of allyl thiophenes are shown in Table 7.

A facile, sulfur-assisted, metal-free propargyl-allenyl isomerization and intramolecular cyclization for the synthesis of tricyclic thiophenes derivatives 60 from diynes **59** has been developed [34]. As shown in Scheme 18 and Table 8, compounds **60** were obtained in modest to good yields. Due to the ready availability



Scheme 17 In situ-generation of allenyl allyl sulfide **58**

Table 7 Synthesis of allyl thiophenes **57**[a]



Entry	R^1	R^2	R^3	R^4	Yield[b] % **57**
1	OEt	H	Me	H	**57a** (63)
2	Ph	H	Me	H	**57b** (68)
3	Ph	H	*N*-Pr	H	**57c** (65)
4	*N*-Pr	H	Me	H	**57d** (60)
5	*N*-Pr	H	*n*-Pr	H	**57e** (70)
6	OEt	Me	Me	H	**57f** (73)
7	Ph	Me	Me	H	**57g** (62)
8	*n*-Pr	Me	Me	H	**57h** (71)
9	OEt	Me	*n*-Pr	H	**57i** (80)

[a]Standard condition: **56** (0.5 mmol) and DBU (0.6 mmol) in THF at room temperature for 1 h under nitrogen atmosphere
[b]Isolated yields

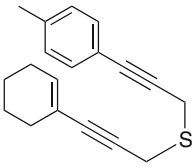
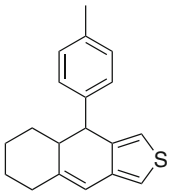
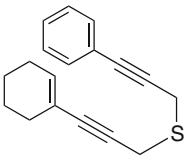
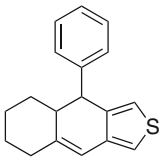
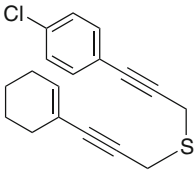
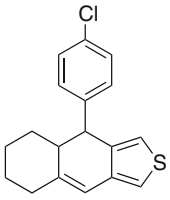
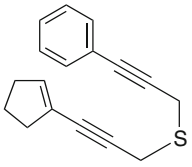
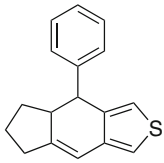
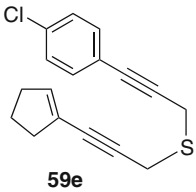
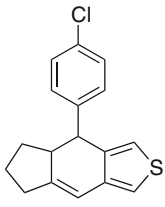


Scheme 18 Synthesis of tricyclic thiophenes derivatives by sulfur-assisted propargyl-allenyl isomerization reaction

of the starting materials and convenient procedure, the authors suggested that this reaction has great potential utility in organic synthesis. Table 8 depicts yields of selected products formed.

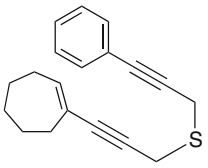
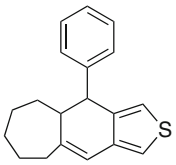
As shown in Scheme 19, a mechanism was proposed that involves a sulfur-assisted isomerization to give a tricyclic thiophene isomerization to a diallene

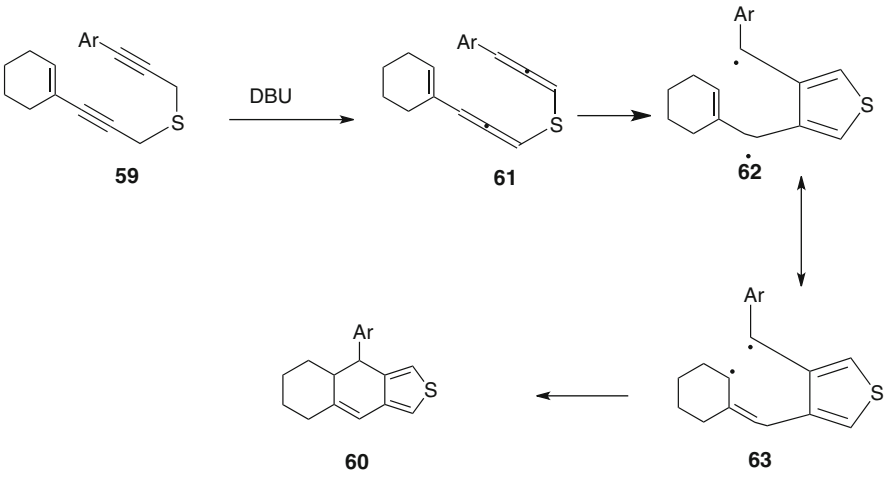
Table 8 Synthesis of tricyclic thiophenes derivatives **60**

Substrate	Time (h)	Product **60**	Yield (%)
 **59a**	12	 **60a**	82
 **59b**	10	 **60b**	75
 **59c**	12	 **60c**	82
 **59d**	10	 **60d**	73
 **59e**	10	 **60e**	71

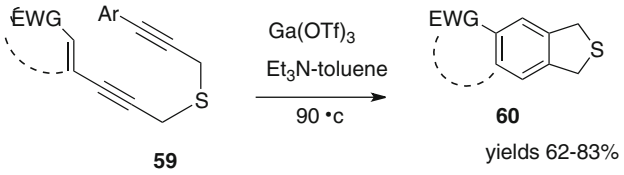
(continued)

Table 8 (continued)

Substrate	Time (h)	Product **60**	Yield (%)
 **59f**	10	 **60f**	71



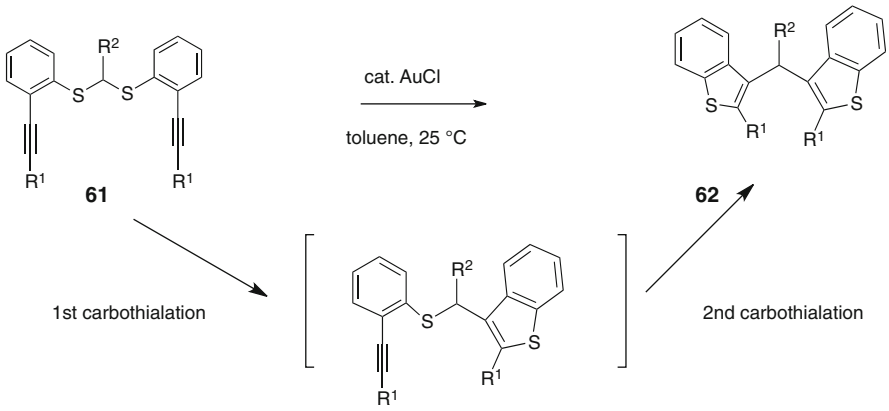
Scheme 19 Proposed mechanism for the conversion of **59** to **60**



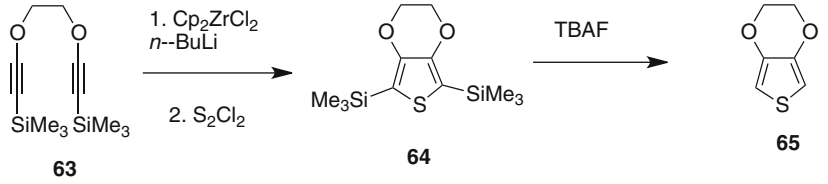
Scheme 20 Conversion of **59** to **60** using $Ga(OTf)_3$

intermediate **61** [35]. Intermediate **61**, on the basis of isotopic labeling experiments, then is thought to undergo a nontraditional bis-allene diradical cyclization, rather than the previously proposed [4 + 2] cycloaddition pathway [36].

In a previous paper, Zhou et al. [36] demonstrated that 1,3-dihydrobenzo[*c*] thiophene **60** can be prepared from **59** in yields ranging from 62% to 83% using Ga $(OTf)_3$ (see Scheme 20). The authors chose metal triflates to examine this reaction



Scheme 21 Synthesis of bis(benzo[*b*]thiophenyl)methanes **62**



Scheme 22 Synthesis of 3,4-alkyldioxythiophenes

because of their stability to Lewis bases (for reviews of bifunctional catalysis of cooperative Lewis acid/base systems, see [37, 38]).

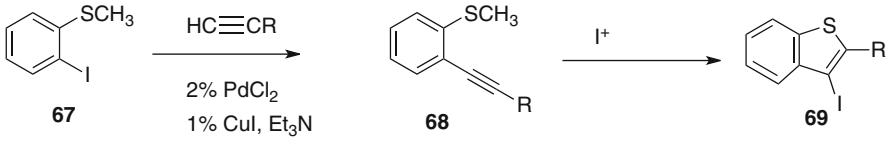
An interesting synthesis of bis-(benzo[*b*]thiophenyl)methanes **62** by gold-catalyzed double carbothiolation of diyne **61** is shown in Scheme 21 (see, for example, [39, 40]). The reaction proceeded through two successive intramolecular carbon–sulfur bond additions, i.e., carbothialation steps.

An intriguing synthesis of EDOT (3,4-ethylenedioxythiophene) **65**, an important precursor to polymers that are very useful for numerous electronic devices (see, for example, [39, 40]) is shown in Scheme 22. As shown **65** is easily prepared by treating **63** successively with zirconocene dichloride followed by S_2Cl_2 to give **64**. Intermediate **64** then was desilylated by TBAF to give EDOT [41].

2.6 Synthesis of Thiophenes Involving Electrophilic Cyclization of Alkynes

Electrophilic cyclization of alkynes possessing tethered heteroatom nucleophiles in the presence of various catalytic reagents has found extensive use in the synthesis of

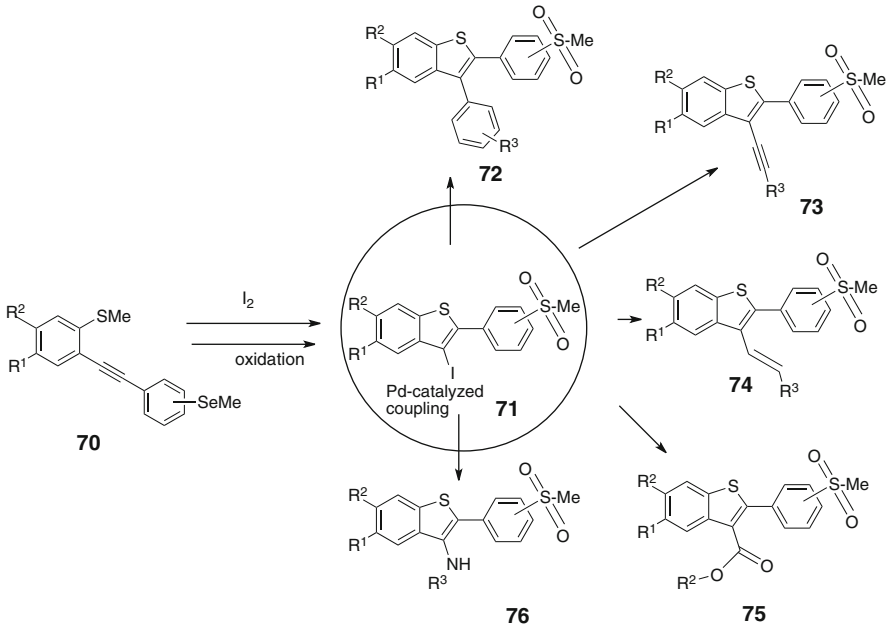
Table 9 Synthesis of benzo[b]benzothiophenes by PdCu catayzed crossed-coupling/iodine electrophilic cyclization reactions



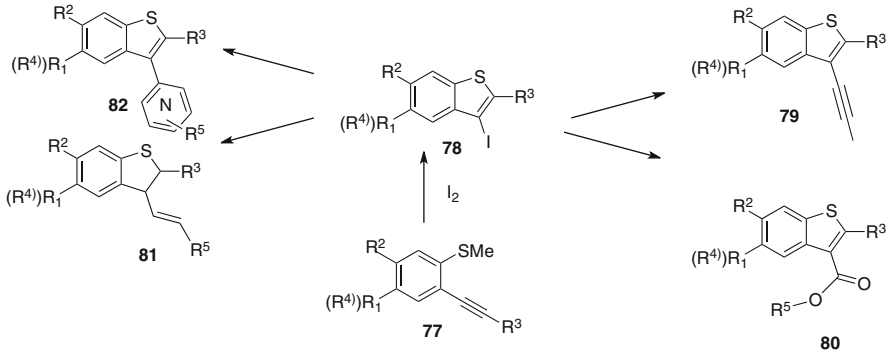
Alkyne	E^+	% Yield
68a	I_2	100
68b	I_2	100
68c	I_2	97
68a	Br_2	91
68b	Br_2	92
68c	Br_2	–
68c	NBS	74
68a	*p*-$O_2NC_6H_4SCl$	70
68b	*p*-$O_2NC_6H_4SCl$	97
68c	*p*-$O_2NC_6H_4SCl$	95
68a	PhSeCl	91
68b	PhSeCl	100
68c	PhSeCl	97

heterocycles including benzothiaphenes. Over the past 10 years, halogens have been particularly attractive because of their ease of polarization by alkenes and alkynes. In particular, iodine has received the most attention since it is an inexpensive, nontoxic, safe to handle, and readily available reagent. Recently, the synthesis of five membered heterocycles via electrophilic cyclization of alkynes has been extensively reviewed [42]. A slightly earlier review on this topic; however the major emphasis in this review was on the synthesis of nitrogen-containing and oxygen-containing heterocycles; only four examples on the synthesis of thiophenes were cited [43]. Because of this extensive coverage, this report will concentrate mainly on recent coverage of this chemistry.

As early as 2001, Larock and Yue [44] synthesized a wide variety of benzo[*b*] thiophene by Pd/Cu-catalyzed cross coupling of commercially available *o*-iodoanisole and terminal alkynes followed by electrophilic cyclization using iodine, bromine, NBS, *p*-$O_2NC_6H_4SCl$, or PhSeCl. As shown in Table 9 the use of iodine gave 3-iododerivatives **69a–c** in best yields (97–100%). The other E^+ groups, Br_2, $pO_2NC_6H_4SC$, and PhSeCl with few exceptions gave slightly lower but still excellent yields. The authors realized that enormous synthetic potential of this reaction by noting the many ways to transform the resulting 3-substituents. The 3-iodo-substituted thiophenes would be strong candidates for palladium catalyzed cross-coupling reactions such as Sonogashira and Suzuki. In fact, combined iodocyclization/palladium

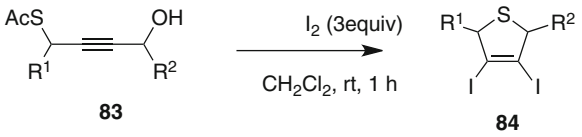


Scheme 23 Synthesis of diverse methyl sulfone-containing benzo[*b*]thiophenes

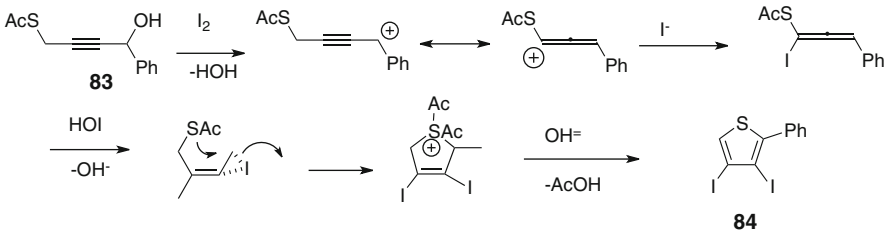


Scheme 24 Synthesis of multisubstituted benzo[*b*]thiophenes

catalyzed reactions have emerged as important methods for synthesizing important heterocycles. For example, a parallel solution-phase method for a diverse 72-membered benzo[*b*] library was developed by Larock et al. [45] and is shown in Scheme 23. The appropriate 3-iodothiophene **71** was prepared by the iodine-catalyzed cyclization of alkyne **70**. Subsequent palladium-catalyzed substitution of **71** by Suzuki-Miyaura, Sonogashira, Heck, carboalkylation, and aminocarbonylation chemistry gave **72**, **73, 74**, **75**, and **76**, respectively.



Scheme 25 Synthesis of 3,4-diiododihydrothiophenes **84**



Scheme 26 Possible mechanism for the synthesis of 3,4-diiodo-2-phenyl thiophenes **84** from yne-ols **83**

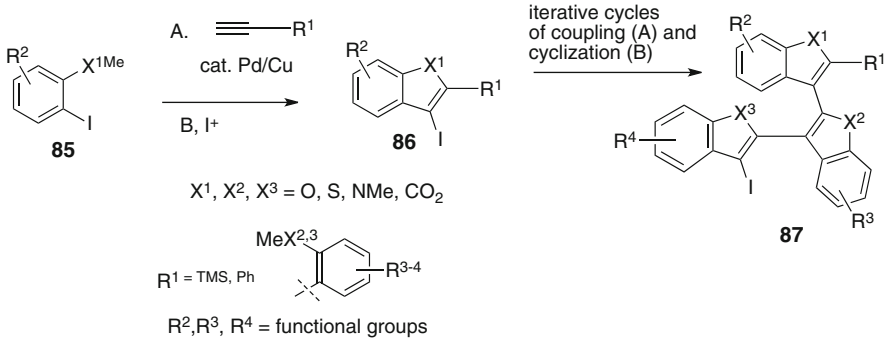
Similarly, a multisubstituted benzo[*b*]thiophene library (Scheme 24) was synthesized from 2,5,6-trisubstituted 3-iodobenzo[*b*]thiophenes **78** prepared from the alkyne **77** [46].

As before, heteroaromatic carbon–iodine bond allowed further diversification by various palladium-catalyzed crossed coupling reactions.

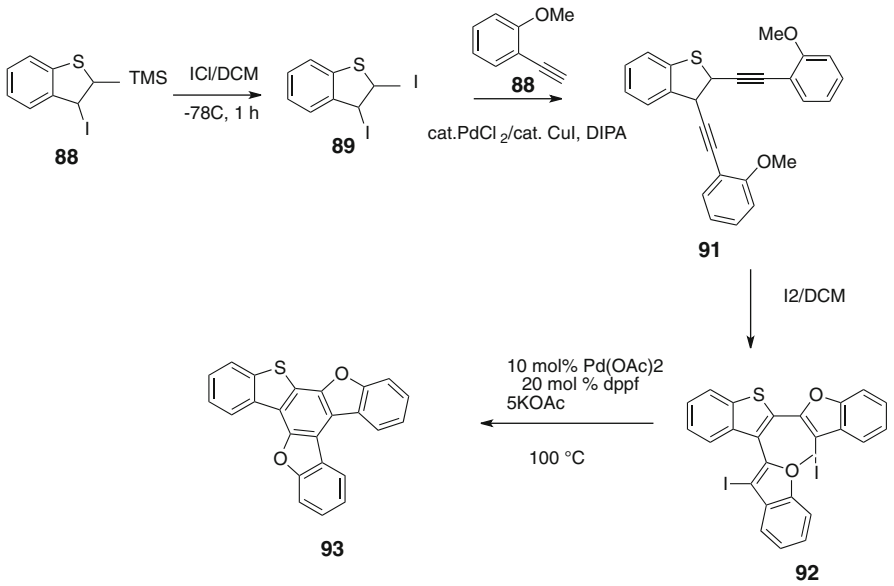
Recently, 3,4-diiododihydrothiophenes **84**, one of the most important classes of heterocycles intermediates in the synthesis of important natural and unnatural products, was reported [47]. As shown in Scheme 25, 3,4-diiodo derivatives **84** were prepared in 1 h at room temperature in good to excellent yields via electrophilic iodocyclization of the respective yne-ols **83**. Prior to this study, the synthetic methods available for preparing dihydrothiophenes such as Birch reduction [48] and McIntosh cycloaddition of mercapto ketones or aldehydes [49] required harsh conditions. An interesting mechanism shown in Scheme 26 was proposed.

Interesting iterative cycles of cross coupling and cyclization were reported for the rapid synthesis of a wide variety of polyheterocyclic compounds (PHCs) [50] (see Scheme 27). As shown the synthesis of PHCs **87** involves iterative cycles of palladium-catalyzed Sonogashira couplings (**85**–**86**), followed by iodocyclization using iodine or iodochloride (ICl). Several variations of this strategy, e.g., click chemistry followed by iodo-desilyation and double Sonogashira coupling, followed by double iodocyclization, and elaboration or Ullmann reaction of the iodine-containing compounds afforded a variety of linked and fused PHCs.

The synthesis of the fused heterocycle **93** was accomplished by a double Sonogashira coupling followed by double iodocyclization then Ullmann reaction and is shown in Scheme 28. Similar fused heterocycles have been shown to exhibit interesting electronic and luminescent properties [51].



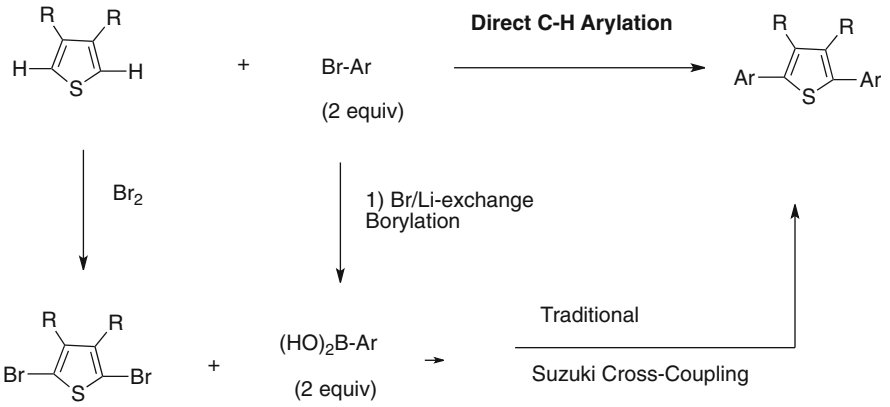
Scheme 27 Synthesis of polyheterocyclic compounds



Scheme 28 Iterative synthesis of tricyclic heterocyclic **93**

2.7 Direct Arylation of Thiophenes

As seen in the previous section, palladium-catalyzed cross-coupling reactions (Suzuki, Heck, Sonogashira, Negishi, etc.) have been important reactions in the synthesis of multisubstituted thiophenes. However, these reactions have several drawbacks including the generation of stoichiometric amounts of waste metal which may be toxic, difficulties in handling, lower catalyst loading, higher yields, and/or requiring several steps. An alternate method is now available which in the

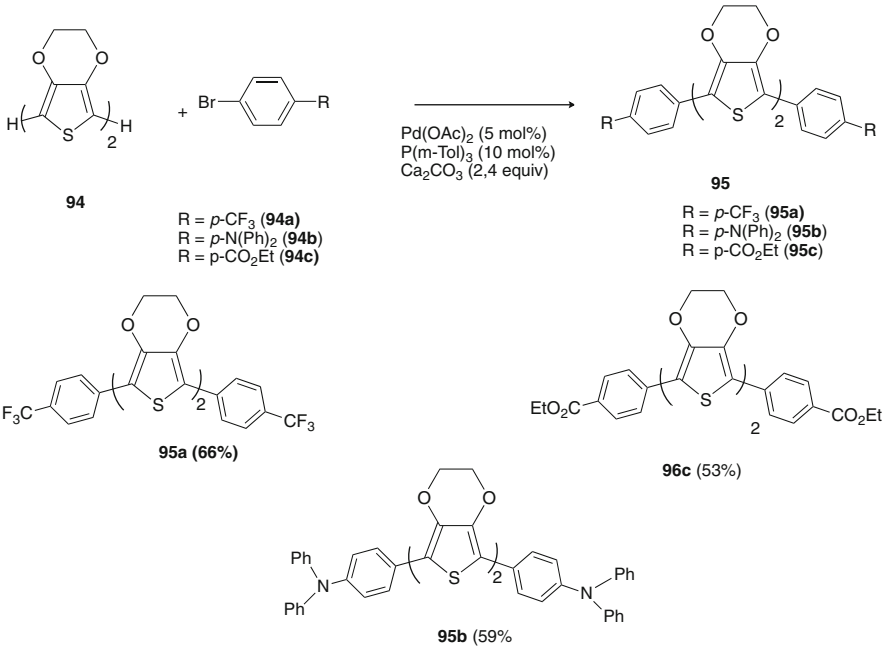


Scheme 29 Comparison of direct C–H arylation and traditional cross-coupling reactions

organometallic has been replaced by a simple arene. This was first shown by Ohta and coworkers [52] who reported the first direct arylation of aryl halides via C–H functionalization using palladium catalyst. A comparison between these two reactions is shown in Scheme 29. Since that time direct arylation syntheses has exploded. Two excellent reviews have been reported. The first is a critical review that covers the literature until November 2006 and has 117 references [53], and the other review covers the literature until December 2010 [54]. We will focus here on some recent reports on the application of direct arylation in material sciences.

As stated by IF Perepichta and DF Perepichta, "synthesis and applications of thiophenes-based organic electronic materials have been widely investigated in recent years, and their importance cannot be overemphasized" [55]. For example, a variety of 3,4-ethylenedioxythiophene (EDOT)-based π-conjugated molecules **95** were synthesized from the reaction of **94** and **94a–c** in good yields through Pd-catalyzed direct C–H bond arylation [56]. A few interesting products and yields from the arylation of EDOT are shown in Scheme 30 [57].

Schipper and Fagnou also showed that thiophenes based on organic electronic material can be carried out in high yields using simple materials by using palladium-mediated direct arylation [57]. In a *tour-de force* study, a wide variety of traditional syntheses used to prepare important organic electronic materials were carried out using direct arylation Pd-catalyzed reactions. In all cases, the direct arylation protocol proved superior to the traditional method. In fact, in large scale reactions the direct arylation gave products that required no chromatograpic clean up. In the interest of space only two formal syntheses are presented below. Scheme 31 illustrates the formal synthesis of **96** which is the precursor to the star molecule **101** which is an effective donor material in heterojunction solar cells [58]. As shown, the key intermediate **100** was prepared by Stille coupling between **96** and **97** followed by a Vilsmeier-Haack formylation in 77% overall yield. However,



Scheme 30 Synthesis of EDOT-based functional π-conjugated molecules through direct C–H bond arylation

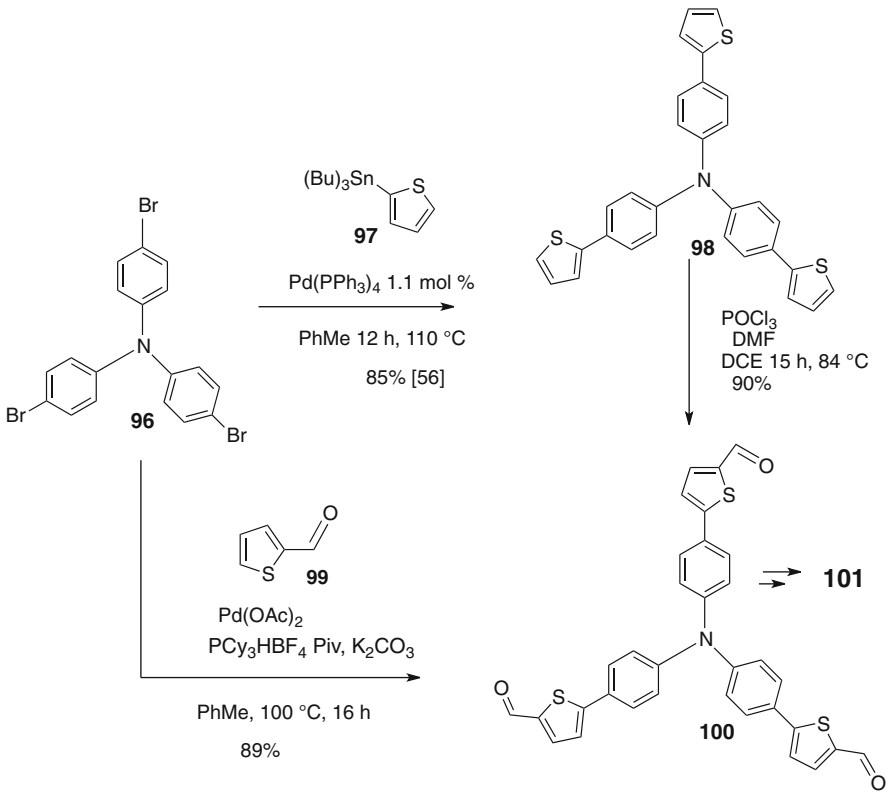
the direct arylation method gave **100** in one step and in 89% yield using **96** and 2-thiophenecarboxaldehyde **99**.

Scheme 32 depicts the formal synthesis of synthesis of 5,5′-bis (4-hexylphenyl)-2,3′-bithiophene **105**. Marks [59] has pioneered the use of **105** in organic field-effect transitors. As shown, the bithiophene **105** is prepared by converting **97** to the bisstannane **103** which is then subjected to Stille coupling affording **105**. However, in the direct arylation procedure **105** can be made in one step and in 87% yield from commercially available **102.**

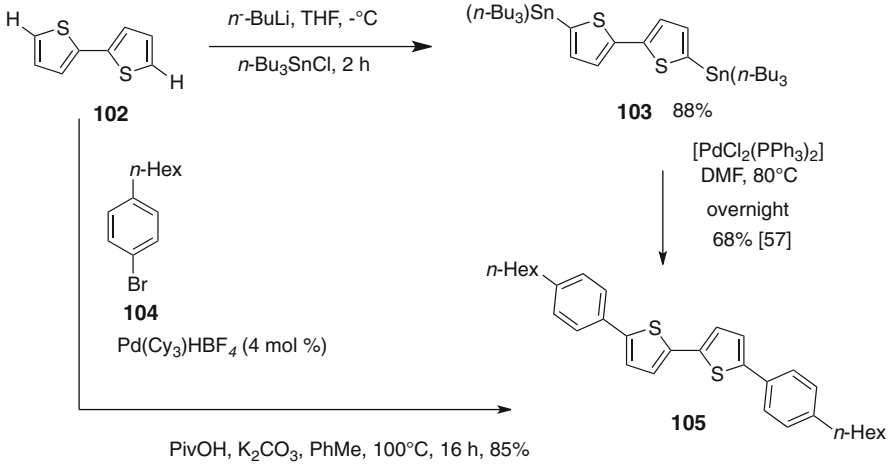
It should be mention that reference [57] has a large number of citations concerning direct arylation of thiophenes.

As so often the case, the use of MWH results in faster reaction times and lower reaction temperatures than those carried out with conventional heating. This can be seen in a very recent report on the versatile and rapid microwave-assisted procedure for the palladium-catalyzed direct arylation of heterocycles by aryl bromides and heteroaryl bromides [60]. This procedure reduces the coupling times by 10–60 min and lowers catalytic loadings (to 1%), and allows the successful arylation of previously reported unreactive heterocyclic substrates. Table 10 lists selected arylated heterocycles that were formed in yields ranging from 55% to 80%.

In addition, direct arylation of heterocycles with heteroaryl bromides were successfully carried out; the results are shown in Table 11.

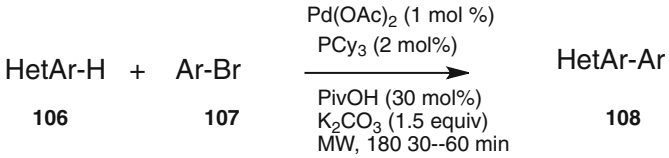


Scheme 31 Formal synthesis of key intermediate **100**



Scheme 32 Formal synthesis of 5,5'-bis (4-hexylphenyl)-2,3'-bithiophene **105**

Table 10 Synthesis of HetAr–Ar by direct arylation of heterocycles **106** with aryl bromides **107**



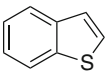
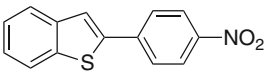
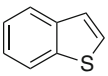
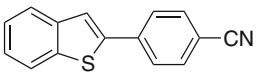
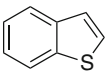
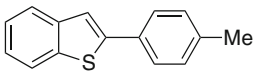
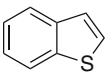
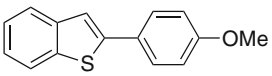
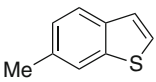
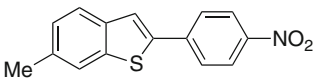
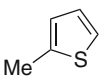
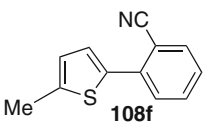
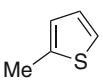
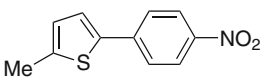
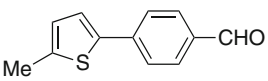
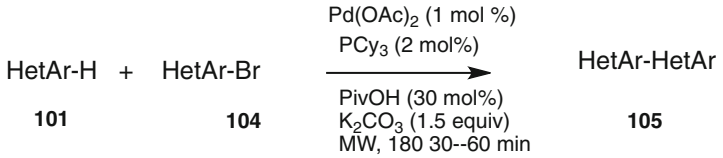
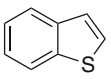
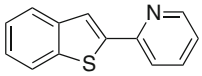
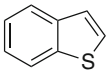
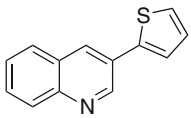
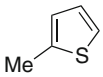
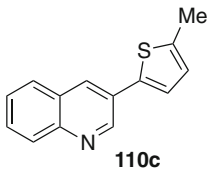
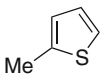
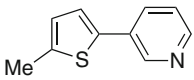
Entry	**106**	**108**	Time (min)	Yield (%)
1	 **106a**	 **108a**	10	75
2	 **106a**	 **108b**	10	80
3	 **106a**	 **108c**	30	80
4	 **106a**	 **108d**	60	55
5	 **106b**	 **108e**	10	85
6	 **106b**	 **108f**	10	85
7	 **106b**	 **108g**	30	60
8	 **106c**	 **108h**	10	84

Table 11 Synthesis of HetAr–HetAr **110** from HetAr–H **106** and HetAr=Br **109**

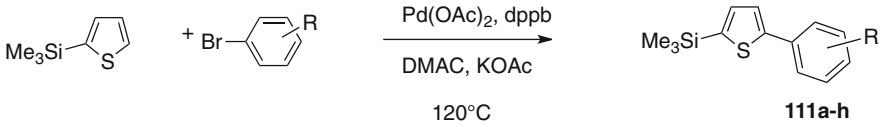


101 **104** **105**

Entry	**101**	**110**	Time (min)	Yield (%)
1	 **106a**	 **110a**	60	55
2	 **106a**	 **110b**	30	65
3	 **106b**	 **110c**	30	58
4	 **106b**	 **110d**	60	64

The data in Tables 10 and 11 show that the C–H arylation of a wide variety of hetaryl and aryl bromides occur within a short period of time (10–60 min) which compares very favorable with the long reaction times for the Fagnou protocol (1.5–74 h). Of particular importance is the greater reactivity of electron deficient aryl and hetaryl bromides in microwave-assisted reactions. Thus, by carrying out the microwave reactions at 180°C, it is possible to increase the reactivity of some substrates dramatically and allows the preparation of arylated products that could not be prepared by previously published methods [61, 62]. For example, the

Table 12 Synthesis of 5-aryl-2-trimethylsilylthiophenes **111a–h**



Entry	R or aryl bromide	Product	Time/h	Yield (%)
1	4-CN	**111a**	5	65
2	4-COEt	**111b**	7	75
3	4-CHO	**111c**	6	72
4	4-CF_3	**111d**	11	52
5	4-Cl	**111e**	4	78
6	4-Me	**111f**	23	40
7	2-Bromonaphthalene	**111g**	15	63
8	3-Bromopyridine	**111h**	15	72

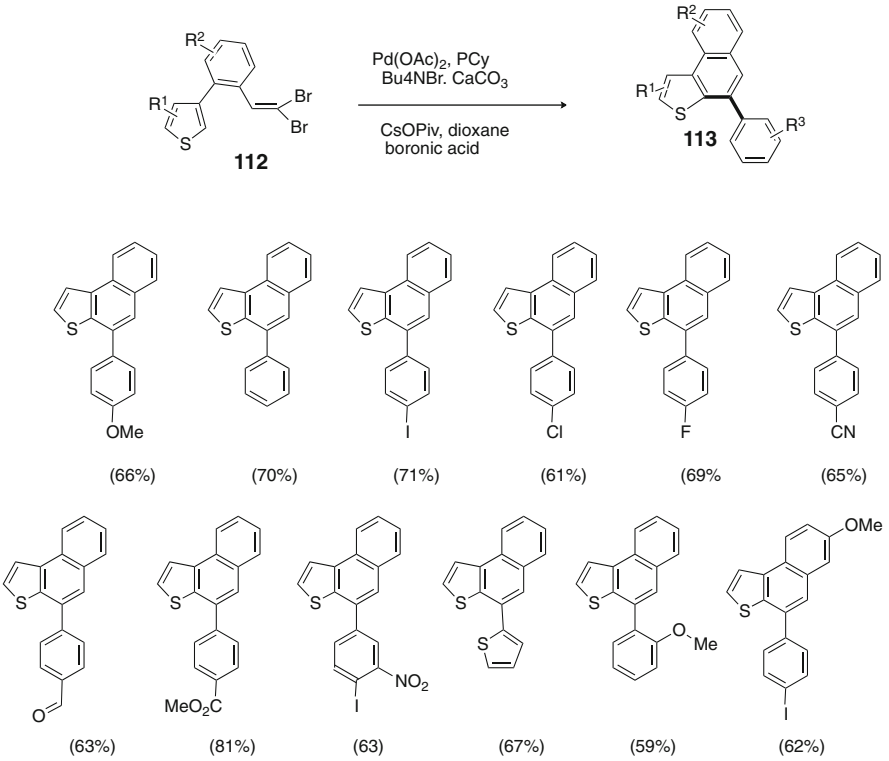
yield of **108a** (Entry 1, Table 10) was 75%, as compared with the 5% yield of **108a** using conventional heating; the yield of **108b** (Entry 2, Table 10) was 80% as compared with 15% using conventional heating; and the yield of **110a** (Entry 1, Table 11) was 55% as compared with the <5% yield using conventional heating. Another aspect of the microwave-assisted direct arylation is the wide range of substituents tolerated. Interestingly, the aldehyde derivative **108h** was formed in 84% in 10 min.

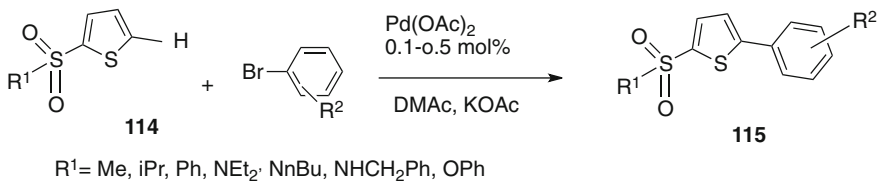
5-Aryl-2-silylated thiophene-containing polymers have been used as dye-sensitized solar cells [63]. They also exhibit fluorescent [64] and other optical properties [65]. To tune the optical properties requires a variety of 5-aryl 2-trimethylsilylthiophenes that, until recently, were prepared in the traditional way, i.e., Suzuki, Negishi, or Stille cross coupling in the key step of the protocol; no straightforward general method of synthesis was available at that time. In a recent paper a palladium-catalyzed direct arylation of 2-(trimethylsilyl)-thiophenes *via* C–H functionalization resulted in the synthesis of arylated silylthiophenes **111a–h** in only one step [66]. The results are shown in Table 12.

A recent paper described a short and highly modular three-step synthesis of a new class of substituted naphthothiophenes **113** that exhibits a Pd-catalyzed tandem direct arylation/Suzuki transformation in the key step [64]. The yields are up to 91%. This approach has several advantages since it significantly improves the efficiency, atom economy, and the modular of the synthesis. Due to the simplicity and superior overall yields of this approach, a generation of novel polyaromatic thiophenes relevant to applications in biology and material science appears imminent (Table 13).

The palladium-catalyzed direct arylation of SO_2R-substituted thiophene derivatives (shown in Scheme 33) was found to proceed regioselectively at C-5 in

Table 13 Synthesis of a wide variety of novel thiophenes relevant to applications in biology and material sciences



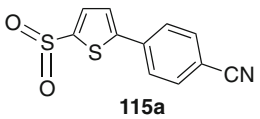
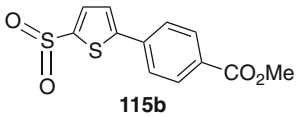
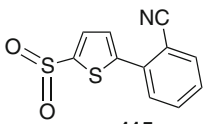
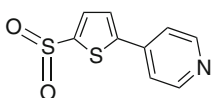
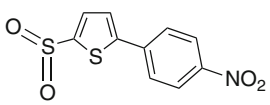
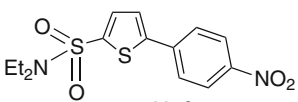
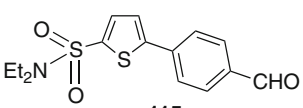


Scheme 33 Synthesis of 5-arylated SO_2R-substituted thiophenes **115**

high yields using various aryl bromides and extremely low (0.5–0.1 mol%) of phosphine-free $Pd(OAc)_2$ as catalyst [65]. Arylation of thiophenes-containing sulfonyls, sulfonamides, and sulfonic acid phenyl esters was accomplished. Some typical results are shown in Table 14. This new procedure is better than the previously reported Suzuki coupling method using halothiophenes [66] or the

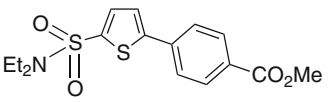
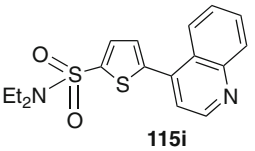
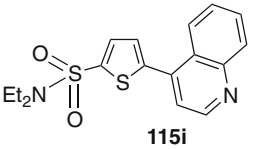
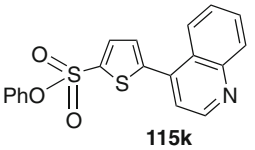
reaction of arylthiophenes with sulfuric acid [67] since the former requires the synthesis of an arylboronic acid and provides an organometallic salt as bi-product and the latter requires very stable reactants.

Table 14 Synthesis of SO_2R substituted thiophenes **115**

Entry	R or aryl bromide	R^1	Product	Yield (%)
1	4-CN	CH_2Ph	 **115a**	71
2	4-CO_2Me	CH_2Ph	 **115b**	66
3	2-CN	CH_2Ph	 **115c**	74
4	4-Bromopyridine hydrochloride	CH_2Ph	 **115d**	73
5	4-NO_2	CH_2Ph	 **115e**	60
6	4-CN	NEt_2	 **115f**	79
7	4-CHO	NEt_2	 **115g**	87

(continued)

Table 14 (continued)

Entry	R or aryl bromide	R^1	Product	Yield (%)
8	4-CO_2Me	NEt_2	 **115h**	75
9	4-Bromoisoquinoline	NEt_2	 **115i**	86
10	4-CN	OPh	 **115i**	72
11	4-Bromoisoquinoline	OPh	 **115k**	83

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Mesoionics

Justin M. Lopchuk

Abstract Metalation and metal-mediated reactions of various mesoionic heterocycles including sydnones, münchnones, and isomünchnones are reviewed through early 2012. The monograph is divided into sections by heterocycle; subdivisions cover direct metalation with lithium or magnesium, transmetalation to other metals such as copper and zinc, cross-coupling chemistry, and the metal-mediated synthesis of various mesoionic systems.

Keywords Cross-coupling · Gold catalysis · Grignard formation · Isomünchnone · Lithiation · Münchnone · Sydnone

Contents

1 Introduction 382
2 Sydnones 383
2.1 Lithiation at C4 383
2.2 Grignard Formation at C4 384
2.3 Transmetallation of Lithiated Sydnones 385
2.4 Zinc-Mediated Debromination of Sydnones 386
2.5 Lithiation of the N3 Side Chain 386
2.6 Uses of Lithiated Sydnones 387
2.7 Cross-Coupling of Sydnones 390
3 Sydnone Imines 395
4 Sydnone *N*-Oxides and Sydnone Iminium *N*-Oxides 397
5 Münchnones 399
5.1 Silicon-Mediated Chemistry 399
5.2 Silver-Mediated Chemistry 400
5.3 Gold-Mediated Chemistry 400
5.4 Palladium-Mediated Chemistry 401

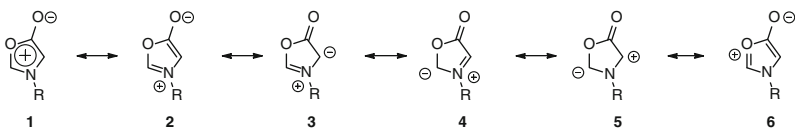
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6 Münchnone Imines 402
7 Isomünchnones 404
7.1 Copper-Mediated Diazo Decomposition 404
7.2 Rh-Mediated Diazo Decomposition 404
8 Oxamünchnones 407
9 Thioisomünchnones 407
References 408

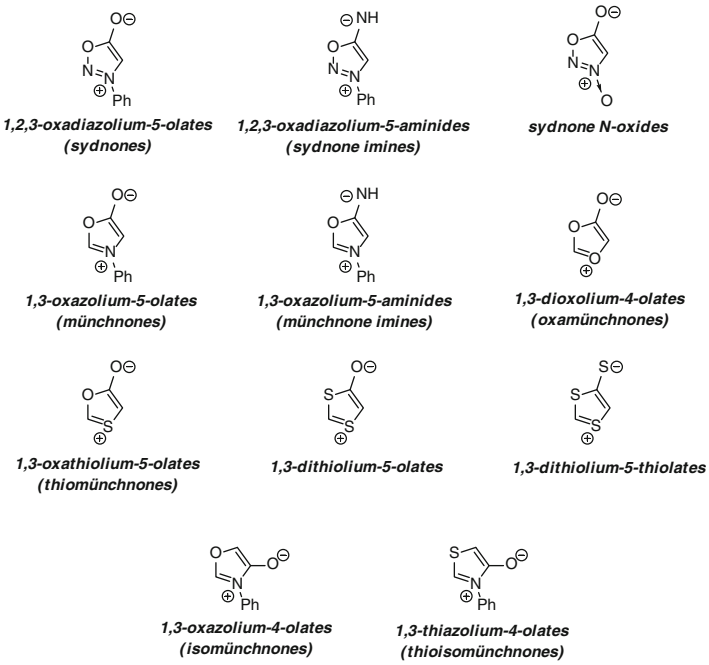
1 Introduction

"Mesoionic heterocycles" is a general term which comprises many different types of dipolar five-membered heterocycles. Significant investigations into this class of compounds began in the early 1930s with the work of Earl and Mackney, and Schonberg, continued in the 1940s with Baker and Ollis (who coined the term mesoionic as a combination of mesomeric and ionic), and was furthered by Huisgen in the 1960s who worked extensively on the dipolar cycloadditions of münchnones [1]. The generally accepted definition of mesoionic heterocycles states that "a compound may be appropriately called mesoionic if it is a five-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the five atoms comprising the ring [2]." This definition leaves the mesomeric betaines as a separate class of compounds which will not be considered herein [3]. As a consequence of their dipolar structure, a wide variety of resonance structures can be drawn for a given mesoionic species (Scheme 1). As there is no consensus regarding a preferred structure, they will be used interchangeably throughout this monograph.

The most commonly utilized mesoionic heterocycles (Scheme 2) in synthesis are sydnones, münchnones, and isomünchnones [4, 5]. These heterocycles are most often considered useful for their facile ability to undergo 1,3-dipolar cycloadditions with alkynes and alkenes which typically yield pyrazoles, pyrroles, and furans, respectively [6]. Due to the variations in reactivity and stability among the mesoionic ring systems, this monograph is divided into sections by ring system. Each section is further divided as needed to discuss direct metalation, reactions of the organometallic derivatives, cross-coupling, and synthesis of the mesoionic ring systems. Mesoionic heterocycles have a rich history and many reviews have been written over the past 40 years. These are noted where applicable and the reader is encouraged to visit them, especially where chemistry other than metalation is concerned.



Scheme 1 Münchnone resonance structures



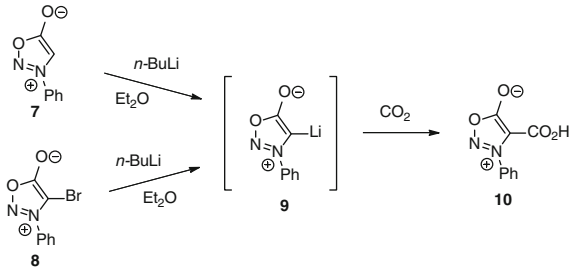
Scheme 2 Some common mesoionic heterocycles

2 Sydnones

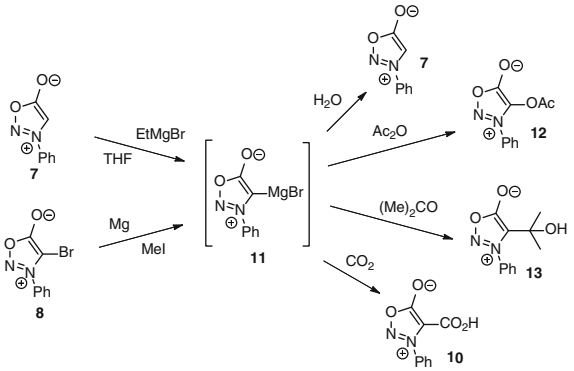
Discovered in 1935 by Earl and Mackney [7], sydnones (1,2,3-oxadiazolium-5-olates) have received the most attention of all the mesoionic compounds [8–10]. This is in no small part due to their relative stability, straightforward synthesis, and the ease with which many of them can be isolated. Although a major use for sydnones is in the preparation of pyrazoles via 1,3-dipolar cycloadditions, their stability allows for the ring to be deprotonated with organometallic reagents such as organolithium and Grignard reagents. Such manipulations allow for the elaboration of the sydnone ring system after its initial synthesis. This can be highly useful both for synthesizing pyrazoles and for the sydnones themselves which have been found useful as a core structure in bioactive compounds [11]. Metalation has also been used to determine the acidity of the C4 position of sydnone. Greco and O'Reilly estimated the acidity of 3-phenylsydnone ($pK_a = 18–20$) by reaction with a wide variety of Li^+, Mg^{2+}, and Na^+ organometallic salts [12].

2.1 Lithiation at C4

The only ring position available for the lithiation on the sydnone is at C4. Kato and Ohta generated lithio sydnone **9** [13] via halogen–metal exchange; 4-bromo-3-phenylsydnone **8** was treated with *n*-BuLi in ether and the resulting



Scheme 3 C4 lithiation of sydnones

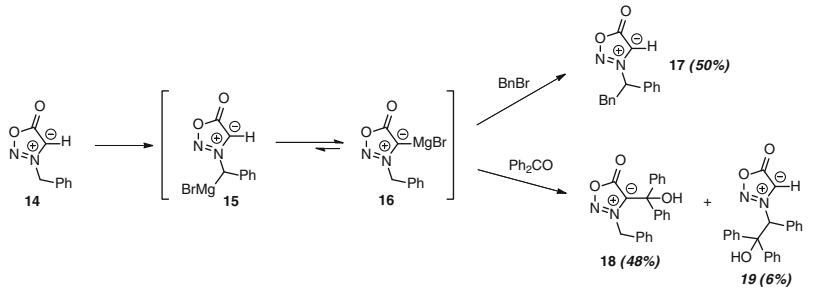


Scheme 4 C4 Grignard formation and reaction in sydnones

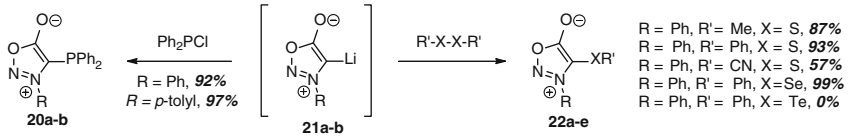
lithio species was quenched with CO_2 to yield the corresponding acid (**10**) (Scheme 3). Greco and coworkers later showed that the direct deprotonation of sydnones was possible under similar conditions (**7** → **9**) [14], thereby avoiding the need for an extra halogenation step (Scheme 3).

2.2 Grignard Formation at C4

Kato and Ohta first reported the formation of a Grignard reagent (**11**) from sydnone **8** by insertion of Mg into the C–Br bond in the presence of methyl iodide [15]. It was noted that the use of Mg alone failed to promote the desired reaction. The subsequent addition of water decomposed **11** to yield **7** (Scheme 4). Additionally, sydnone **8** failed to react in the presence of silver nitrate, sodium nitrite, sodium phenolate, acetyl nitrate, guanidine, or sodium iodide indicating both the aromatic character of the sydnone ring and the relative stability of the C–Br bond. Grignard



Scheme 5 Grignard regioselectivity



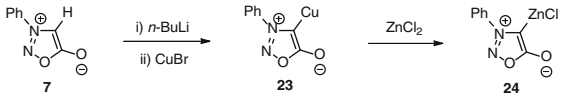
Scheme 6 Quenching of lithiated sydnones with phosphorus, sulfur, and selenium

reagent **11** behaves as fairly typical organometallic reagent and can be trapped with electrophiles such as water, acetic anhydride, acetone, and carbon dioxide (Scheme 4). Although it was initially reported that CO_2 failed to react with **11** [15], a later report detailed the successful reaction [16].

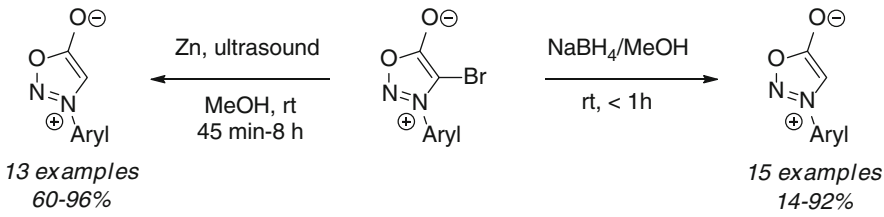
Greco and O'Reilly later studied the alkylation of 3-benzylsydnone [17]. Upon treatment of **14** with excess ethylmagnesium bromide, an equilibrium is formed between **15** and **16**. Quenching of the Grignard reagent with benzyl bromide results in reaction on the N–Bn (**17**), while quenching with benzophenone results (**18**, **19**) in reactivity primarily at C4 (Scheme 5). The observed results from the reaction of benzyl bromide can be explained by considering the greater acidity of the C4 proton which would result in poorer nucleophilicity of the corresponding C4 Grignard reagent. However, the reaction with benzophenone may be reversible and thermodynamically controlled. This would lead to **18** as the major product. Similar reactions were attempted with N3-methylsydnone, but failed to show any detectable product indicating the lack of acidity of the methyl groups.

2.3 Transmetallation of Lithiated Sydnones

Fuchigami and coworkers treated 4-lithio sydnones with a variety of sulfur, selenium, phosphorus, and arsenic compounds to yield heteroatom-substituted sydnones (Scheme 6). Although similar reactions with silyl compounds were successful, analogous reactions with tin and antimony compounds failed to deliver



Scheme 7 Lithium, copper, and zinc sydnones



Scheme 8 C4 debromination of sydnones

the desired products indicating the lithio sydnone is less nucleophilic than typical phenyllithium species which are known to react with these electrophiles [18, 19].

Kalinin and coworkers demonstrated that sydnone **7** could be lithiated with *n*-BuLi, transmetalated with copper, and once again with zinc. Both the copper sydnone **23** and zinc sydnone **24** were able to engage in cross-coupling chemistry (vide infra) [20] (Scheme 7).

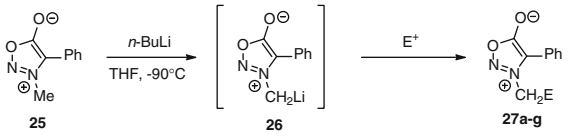
2.4 Zinc-Mediated Debromination of Sydnones

Although debromination of 4-bromosydnone can be accomplished by quenching of the corresponding organometallic derivatives with water [13–16], the zinc-mediated debromination of a wide variety of 4-bromosydnones, which can be accelerated by ultrasound, was reported by Tien et al. [21]. These conditions proved to be mild, quick, and high yielding for a variety of substrates. The same transformation can be accomplished in variable yields with sodium borohydride (Scheme 8) [22].

2.5 Lithiation of the N3 Side Chain

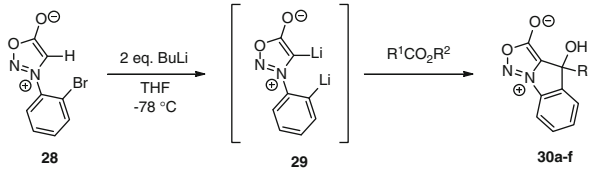
The methyl group of 3-methyl-4-phenylsydnone can be readily deprotonated with butyllithium. The addition of a suitable electrophile gives sydnones with modified side chains at the 3-position (Table 1) [23, 24].

Table 1 N3 side chain lithiation of sydnone



Entry	E^+	Compound	Yield (%)
1	AllylBr	**27a**	67
2	$ClCO_2Me$	**27b**	21
3	TMSCl	**27c**	36
4	CO_2	**27d**	70
5	*p*-ClPhCHO	**27e**	80
6	PhCOMe	**27f**	12
7	PhCOPh	**27g**	70

Table 2 Dilithiation of sydnone

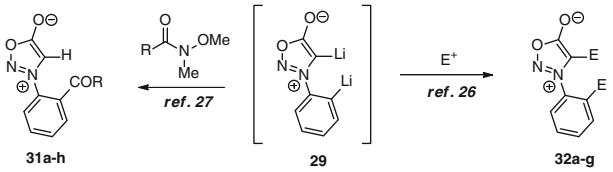


Entry	R^1	R^2	Compound	Yield (%)
1	Me	Et	**30a**	71
2	Et	Et	**30b**	76
3	*i*-Pr	Me	**30c**	93
4	*t*-Bu	Me	**30d**	95
5	Bn	Et	**30e**	80
6	Ph	Et	**30f**	86

2.6 Uses of Lithiated Sydnones

A novel dilithiation of 3-(2-bromophenyl)sydnone to yield sydnoindoles was reported by Turnbull and Krein (Table 2). The dilithio species was generated at high dilution with 2 eq. of *n*-BuLi and quenched with various esters; the best yields came from the most hindered esters which mostly likely favored the intramolecular reaction [25].

Table 3 Trapping of dilithium species with electrophiles or Weinreb amides



Entry	R	Compound	Yield (%)	Entry	R	Compound	Yield (%)
1	Me	**31a**	84	**9**	TMSCl	**32a**	93
2	CH_2Cl	**31b**	86	**10**	$HCONMe_2$	**32b**	89
3	Ph	**31c**	90	**11**	PhCHO	**32c**	86
4	Bn	**31d**	40	**12**	I_2	**32d**	92
5	*p*-BrPh	**31e**	88	**13**	PhSSPh	**32e**	88
6	*p*-ClPh	**31f**	88	**14**	MeI	**32f**	85
7	*p*-MePh	**31g**	70	**15**	Br_2	**32g**	91
8	*p*-OMePh	**31h**	75				

This work was extended by generating the dilithio species with *n*-BuLi/TMEDA; herein the sydnone ring acted as an *ortho*-lithiation director. The dilithio species was trapped with 2 eq. of a variety of electrophiles [26] to give the resulting products in high yield (Table 3, entries **9**–**15**). This chemistry was further tuned by quenching the sydnone **29** with Weinreb amides [27]. The reactions proceeded with complete regioselectivity to yield the *ortho*-acylation products in excellent yields (Table 3, entries **1**–**8**).

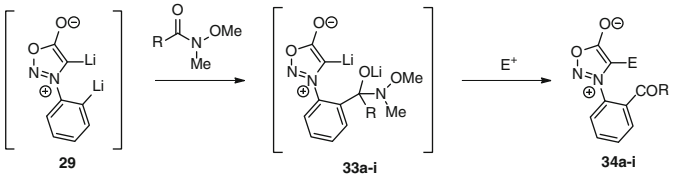
Turnbull and Krein later found that dilithiosydnone **29** could be differentially substituted by first adding an equivalent of Weinreb amide (which quenches the more nucleophilic *ortho*-anion) followed by an addition of a second electrophile (which quenches the C4 anion). This preparation provides a convenient method for accessing functionalized sydnones in high yields from simple starting materials (Table 4) [28].

One limitation of Turnbull's Weinreb amide chemistry is that stronger electrophiles cannot be used to quench the *ortho*-anion. To circumvent this issue, Turnbull and Krein found that LDA could be used to deprotonate sydnone **28**; the resulting anion was quenched with various silyl chlorides. Treatment of **35** with *n*-BuLi induced halogen–metal exchange at the ortho position followed by silyl rearrangement to give **36** (Scheme 9) [29].

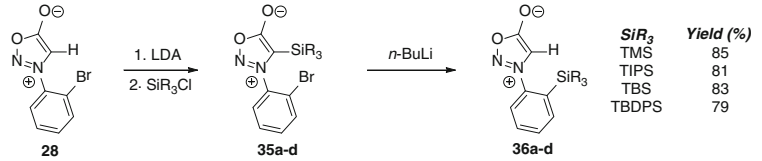
Turnbull and Nashashibi extended the usefulness of their silicon rearrangement methodology by intercepting anion **37** with various electrophiles [30]. The resulting substituted sydnones **38a**–**h** were isolated in good to excellent yields (Table 5).

Turnbull's dilithio intermediate **29** was also utilized in the synthesis of oligomeric areneynes. Trapping of **29** with I_2 gave the diiodide. Na_2SO_3 was used to selectively remove the iodine from the sydnone ring; subsequent Sonogashira couplings yielded the desired products [31].

Table 4 Differential trapping of dilithio sydnone with Weinreb amides and electrophiles

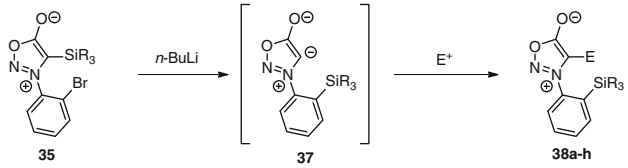


Entry	R	E^+	Compound	Yield (%)
1	Ph	TMSCl	**34a**	71
2	*p*-BrPh	TMSCl	**34b**	61
3	*p*-OMePh	TMSCl	**34c**	63
4	Me	TMSCl	**34d**	59
5	CH_2Cl	TMSCl	**34e**	57
6	Ph	Br_2	**34f**	84
7	Ph	I_2	**34g**	74
8	Ph	PhSSPh	**34h**	82
9	Ph	DMF	**34i**	86

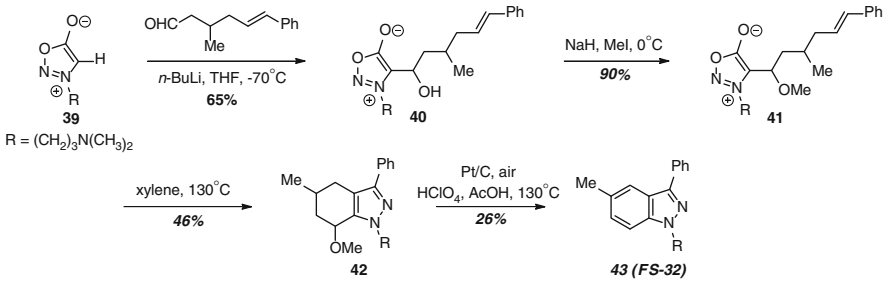


Scheme 9 Silicon migration from C4 to *ortho*-phenyl

Table 5 Silicon migration and C4 substitution of sydnones



Entry	SiR_3	E^+	Compound	Yield (%)
1	TMS	I_2	**38a**	73
2	TMS	TMSCl	**38b**	80
3	TMS	TBDMSCl	**38c**	84
4	TIPS	I_2	**38d**	70
5	TIPS	TMSCl	**38e**	74.5
6	TIPS	TBDMSCl	**38f**	41
7	TBS	I_2	**38g**	88.5
8	TBS	TMSCl	**38h**	66.5



Scheme 10 Yeu's total synthesis of FS-32

Yeu and coworkers reported a short synthesis of FS-32, an antidepressant drug candidate (Scheme 10). Direct lithiation of the sydnone ring with *n*-BuLi followed by condensation with the aldehyde gave alcohol **40**. This set the stage for an intramoleculation cycloaddition which generated the core structure **42** [32].

2.7 Cross-Coupling of Sydnones

2.7.1 Copper- and Zinc-Mediated Methods

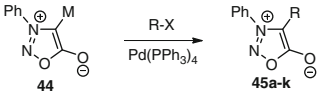
Kalinin and coworkers utilized 4-copper-3-phenylsydnones (prepared from a lithiosydnone, vide supra) with aryl and vinyl halides in the presence of Pd $(PPh_3)_4$ to effect cross-coupling reactions in moderate to excellent yields. This chemistry was extended by the same group to include the coupling of alkynes and heteroaryl groups. Transmetalation of the lithiosydnones with $ZnCl_2$ gave zincates which were found to be more stable and less reactive than the Li analogs. Cross-coupling of the zincates only worked well with *p*-nitroiodobenzene and β-bromostyrene (Table 6) [20, 33].

Kalinin and coworkers furthered their cross-coupling chemistry by synthesizing a series of 4-alkynyl-substituted sydnones [34]. Deprotection of **46** with TBAF revealed the terminal acetylene which was then subjected to the requisite halide and catalyst system (Scheme 11).

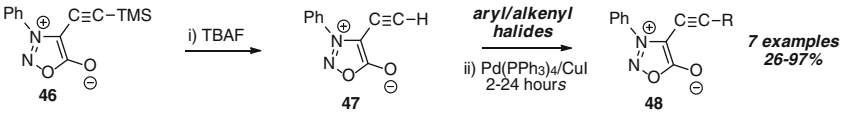
2.7.2 Palladium-Mediated Methods

A more direct route to 4-alkynyl-substituted sydnones was reported by Turnbull and coworkers which began with the readily available 4-bromo-3-phenylsydnone. Upon subjecting sydnone **8** to standard Sonogashira coupling conditions, products **49a–h** were isolated in high yield (Table 7). It was noted, however, that alkyl acetylenes did not react well under these conditions [35].

Table 6 Cross-coupling of sydnone cuprates and zincates

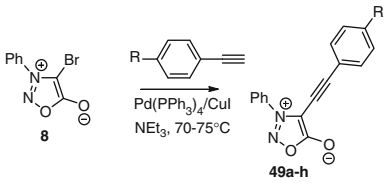


Entry	R	X	Compound	Yield (%) M = Cu	Yield (%) M = ZnCl
1	Ph	I	**45a**	90	27
2	*p*-NO_2Ph	I	**45b**	92	98
3	CH═CHPh (*E*/*Z*)	Br	**45c**	86	86
4	C≡CPh	Br	**45d**	71	3
5	C≡CC_5H_{11}	Br	**45e**	83	–
6	C≡$CC_{10}H_{21}$	Br	**45f**	42	–
7	C≡C-TMS	Br	**45g**	Nr	–
8	2-Pyridyl	I	**45h**	85	–
9	2-Thienyl	I	**45i**	98	10
10	2-Furyl	I	**45j**	80	
11	5-Furfuryl	I	**45k**	51	2



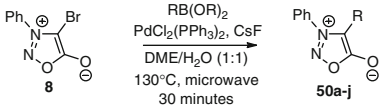
Scheme 11 Synthesis of 4-alkynyl-substituted sydnones

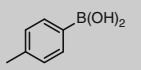
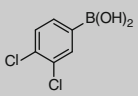
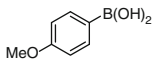
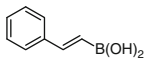
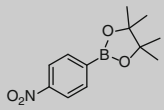
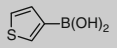
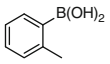
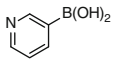
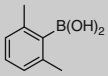
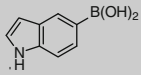
Table 7 Sonogashira coupling of 4-bromo-3-phenylsydnone



Entry	R	Compound	Yield (%)
1	H	**49a**	79
2	Me	**49b**	89
3	Et	**49c**	86
4	OMe	**49d**	89
5	OEt	**49e**	92
6	Cl	**49f**	94
7	NMe_2	**49g**	82
8	OTHP	**49h**	89

Table 8 Suzuki coupling of 4-bromo-3-phenylsydnone

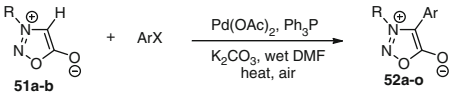


Entry	RB(OR)2	Compound	Yield (%)	Entry	RB(OR)2	Compound	Yield (%)
1		**50a**	93	**6**		**50f**	69
2		**50b**	71	**7**		**50g**	79
3		**50c**	86	**8**		**50h**	75
4		**50d**	56	**9**		**50i**	78
5		**50e**	0	**10**		**50j**	82

This work was added to by Harrity and coworkers who subjected 4-bromo-3-phenylsydnone to Suzuki cross-coupling conditions [36]. Under these conditions (Table 8), a variety of aryl and alkenyl boronates successfully coupled with sydnone **8**. The reaction failed only with the sterically congested substrate (entry **5**). The elaborated sydnones were then subjected to 1,3-dipolar cycloadditions with various alkynes to provide a flexible route to substituted pyrazoles.

The direct arylation of sydnones was recently reported by Moran and Rodriguez (Table 9). This useful protocol avoids the need for activating the sydnone via halogenation or conversion into an appropriate organometallic species. Either phenyl or methyl substituents are tolerated at N3 of the sydnone as well as a wide variety of electron-rich, electron-poor, or heterocyclic aryl iodides or bromides as coupling partners. Aryl chlorides are not sufficiently activated to react under the reported conditions [37].

Table 9 Direct arylation of sydnones

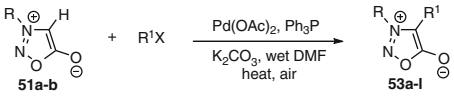


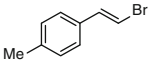
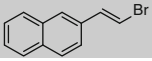
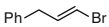
Entry	R	Ar	X	Temperature (°C)	Compound	Yield (%)
1	Ph	Ph	I	120	**52a**	81
2	Ph	*m*-NO_2Ph	I	120	**52b**	79
3	Ph	*p*-NO_2Ph	I	120	**52c**	85
4	Ph	*p*-OMePh	I	120	**52d**	77
5	Ph	Ph	Br	120	**52e**	62
6	Ph	*p*-MePh	Br	120	**52f**	53
7	Ph	*p*-AcNHPh	Br	120	**52g**	92
8	Ph	1-Naphthyl	Br	120	**52h**	73
9	Ph	2-Pyridyl	Br	120	**52i**	61
10	Ph	Ph	Cl	120	**52j**	0
11	Me	Ph	I	80	**52k**	60
12	Me	*m*-NO_2Ph	I	80	**52l**	19
13	Me	*p*-NO_2Ph	I	80	**52m**	57
14	Me	*p*-OMePh	I	80	**52n**	53
15	Me	1-Naphthyl	Br	80	**52o**	55

Moran and coworkers extended their direct arylation chemistry to include the direct alkenylation and alkynylation of sydnones at the C4 position (Table 10). Yields were moderate to good for a variety of aryl-substituted vinyl bromides. It is notable that alkyl-substituted vinyl bromides failed to react (entries **7** and **8**), while an alkyl-substituted vinyl iodide was successful (entry **9**). The first example of the direct coupling of an alkynyl bromide was reported in modest yield [38].

The direct alkynylation was expanded upon by Larock and coworkers (Table 11). Extensive optimization of the conditions was required in order to avoid, chiefly, the oxidative dimerization of the terminal alkyne. Fully optimized conditions required lower temperatures (e.g., 75°C vs. 90–110°C) and slow addition of the alkyne (syringe pump over 6 h) which was further followed by slow addition of more catalyst and alkyne. Although somewhat tedious to perform, these conditions allow for the direct coupling of a variety of alkynes to unactivated sydnones and compares favorably to other approaches to 4-alkynyl-substituted sydnones. 2-Ethylyl pyridine (entry **13**) underwent 1,3-dipolar cycloaddition (Scheme 12) as opposed to alkynylation; the reaction appears to be promoted by the various metals as no reaction was seen in the absence of Pd, Cu, and Ag [39].

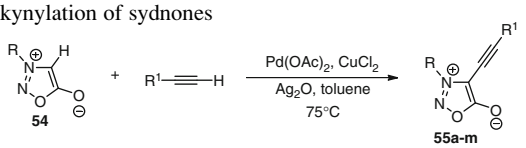
Table 10 Direct alkenylation of sydnones



Entry	R	R^1	Temperature (°C)	Compound	Yield (%)
1	Ph		120	**53a**	78
2	Ph		120	**53b**	76
3	Ph		120	**53c**	74
4	Ph		120	**53d**	62
5	Ph		120	**53e**	65
6	Ph		120	**53f**	42
7	Ph		120	**53g**	0
8	Ph		120	**53h**	0
9	Ph		120	**53i**	57
10	Me		80	**53j**	51
11	Me		80	**53k**	46
12	Ph		120	**53l**	34

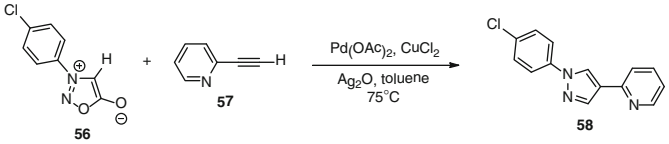
Although not a direct cross-coupling of sydnones, Harrity and coworkers reported the 1,3-dipolar cycloaddition of iodosydnones with alkynes to yield functionalized pyrazoles primed for further cross-coupling chemistry [40]. Additionally, Balme and coworkers similarly reported the cycloaddition of iodosydnones with bromoacetylene. This yields a differentially halogenated pyrazole which can undergo sequential and selective cross couplings [41, 42].

Table 11 Direct alkynylation of sydnones



Entry	R	R^1	Compound	Yield (%)
1	*p*-ClPh	Ph	**55a**	69
2	Ph	Ph	**55b**	72
3	*p*-MePh	Ph	**55c**	69
4	3,4-(OCH_2O)-Ph	Ph	**55d**	72
5	*p*-BrPh	Ph	**55e**	60
6	*p*-NO_2Ph	Ph	**55f**	0
7	Me	Ph	**55g**	29
8	*p*-ClPh	*m*-OMePh	**55h**	73
9	*p*-ClPh	*p*-MePh	**55i**	78
10	*p*-ClPh	*p*-AcPh	**55j**	76
11	*p*-ClPh	*m*-ClPh	**55k**	66
12	*p*-ClPh	2-Thiophenyl	**55l**	38
13	*p*-ClPh	2-Pyridyl	[a]	25[a]
14	*p*-ClPh	CO_2Me	**55m**	33

[a]Expected sydnone not isolated; isolated compound had undergone 1,3-dipolar cycloadditions (see Scheme 12)

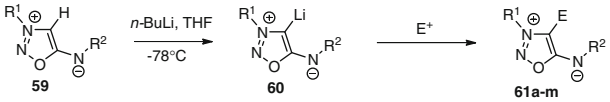


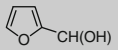
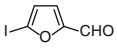
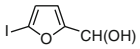
Scheme 12 Unexpected cycloaddtion (from Table 11, entry **13**)

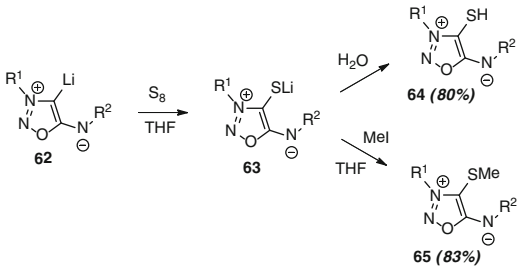
3 Sydnone Imines

While they have not received the same attention as sydnones, sydnone imines can also be directly lithiated (however, they cannot successfully undergo halogen–metal exchange when a halogen is installed on C4). Lithio sydnone **60** appears to have a modest nucleophilicity and this limits the range of electrophiles which can be utilized (electrophiles such as TMSCl, methyl iodide, and allyl bromide failed to react). In addition, the lithiated species is thermally unstable above −78°C (Table 12). However, **60** can be transmetallated with CuBr; the resulting cuprate is found to be stable to higher temperature and successfully

Table 12 C4 lithiation of sydnone imines



Run	R^1	R^2	E^+	E	Compound	Yield (%)
1	Cy	C(O)*t*-Bu	PhCHO	PhCH(OH)	**61a**	53
2	Cy	C(O)*t*-Bu	*p*-ClPhCHO	*p*-ClPhCH(OH)	**61b**	63
3	Cy	C(O)*t*-Bu			**61c**	53
4	Cy	C(O)*t*-Bu			**61d**	33
5	Cy	C(O)*t*-Bu	AcOCl	MeOC(O)	**61e**	83
6	Cy	C(O)Ph	PhCHO	PhCH(OH)	**61f**	45
7	Cy	$C(O)CF_3$	PhCHO	PhCH(OH)	**61g**	47
8	Cy	C(O)Me	PhCHO	PhCH(OH)	**61h**	30
9	Cy	CO_2Me	PhCHO	PhCH(OH)	**61i**	65
10	Cy	Ts	PhCHO	PhCH(OH)	**61j**	44
11	1-Morpholine	C(O)Ph	PhCHO	PhCH(OH)	**61k**	62
12	1-Morpholine	C(O)Ph	AcOCl	MeOC(O)	**61l**	60
13	1-Morpholine	C(O)Ph	CH_2O	CH_2OH	**61m**	36



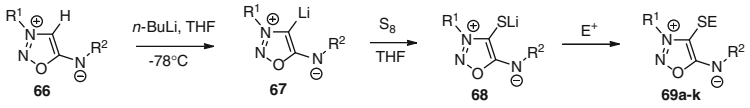
Scheme 13 C4 thiolation of sydnone imines

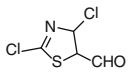
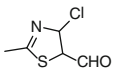
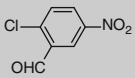
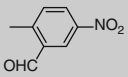
undergoes palladium-catalyzed cross-coupling with vinyl bromides, aryl iodides, and acid chlorides in moderate yields [43].

A unique route to 4-thiosydnone imines was reported by Kalinin et al. (Scheme 13). Treatment of lithio sydnone **62** with elemental sulfur gives the intermediate lithium thiolate; trapping with water yields the free thiol while addition of methyl iodide yields the corresponding methyl sulfide [44].

A wide variety of 4-thiolated sydnone imines can be generated in good yield with this reaction sequence (Table 13) [44].

Table 13 Synthesis of 4-thiolated sydnone imines



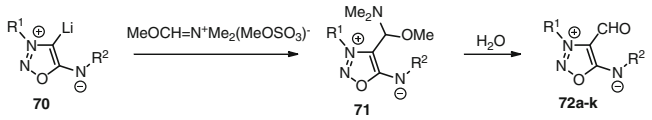
Entry	R^1	R^2	E^+	E	Compound	Yield (%)
1	*n*-Bu	C(O)Ph	MeI	Me	**69a**	68
2	*n*-Bu	$C(O)CF_3$	MeI	Me	**69b**	58
3	*n*-Bu	C(O)*t*-Bu	MeI	Me	**69c**	70
4	NMe_2	C(O)Me	MeI	Me	**69d**	83
5	NMe_2	C(O)Ph	MeI	Me	**69e**	68
6	*i*-Pr	C(O)Me	MeI	Me	**69f**	54
7	*i*-Pr	C(O)Ph	MeI	Me	**69g**	83
8	*i*-Pr	C(O)Ph	$PhCH_2Br$	$PhCH_2$	**69h**	75
9	*i*-Pr	C(O)Ph			**69i**	89
10	*i*-Pr	C(O)Ph			**69j**	83
11	*i*-Pr	C(O)Ph			**69k**	76

Recently Kalinin and coworkers reported the conversion of 4-lithiosydnone imines into the corresponding formyl derivatives (Table 14). Attempts to promote the reaction with dimethylformamide resulted in decomposition of the sydnone imine, so (methoxymethylidene)dimethylammonium methyl sulfate was utilized. This reagent is much more electrophilic and often utilized with organometallic reagents which have poor reactivity. Products **72a–k** were obtained in modest to good yield; the presence of methoxy groups on N3 (entries **7** and **8**) has significantly reduced yields possibly due to intramolecular chelation of the lithio intermediate [45].

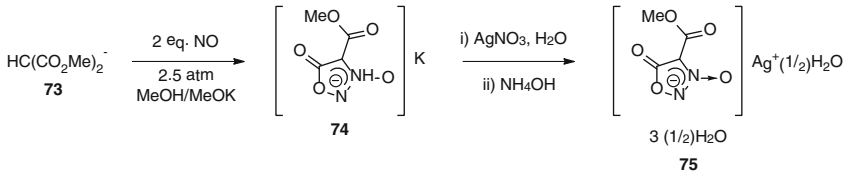
4 Sydnone *N*-Oxides and Sydnone Iminium *N*-Oxides

Sydnone *N*-oxides have been recently described [46, 47] by Bohle and coworkers (they were originally described by Traube in 1895, but were misidentified). They are synthesized (Scheme 14) by the addition of 2 eq. of nitric oxide to the anion of

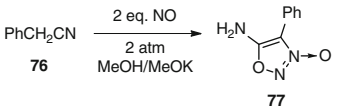
Table 14 Synthesis of 4-formylsydnones



Entry	R^1	R^2	Compound	Yield (%)
1	Me	COPh	**72a**	61
2	CH_2Me	COPh	**72b**	64
3	CH_2Me	COMe	**72c**	45
4	$CHMe_2$	COMe	**72d**	64
5	$CHMe_2$	COPh	**72e**	91
6	$CHMe_2$	Ts	**72f**	83
7	$(CH_2)_2OMe$	COPh	**72g**	38
8	$(CH_2)_2OMe$	Ts	**72h**	10
9	NMe_2	COMe	**72i**	41
10	NMe_2	Ts	**72j**	64
11	$CHMe_2$	$COCF_3$	**72k**	62



Scheme 14 Synthesis of sydnone *N*-oxides



Scheme 15 Synthesis of sydnone iminium *N*-oxides

dimethylmalonate [46]. Compared to other sydnones, these compounds are uniquely stable to acid and base and soluble in water. A variety of salts have been prepared, including potassium, silver, and tetrabutylammonium, the latter of which was found to be soluble in a range of organic solvents [48]. Methylation on the *N*-oxide is accomplished with dimethyl sulfate while methyl iodide alkylates on N2 instead [49].

The sydnone iminium *N*-oxides are prepared in an analogous fashion with the addition of 2 eq. of nitric oxide to benzylcyanide in basic methanol (Scheme 15) [50].

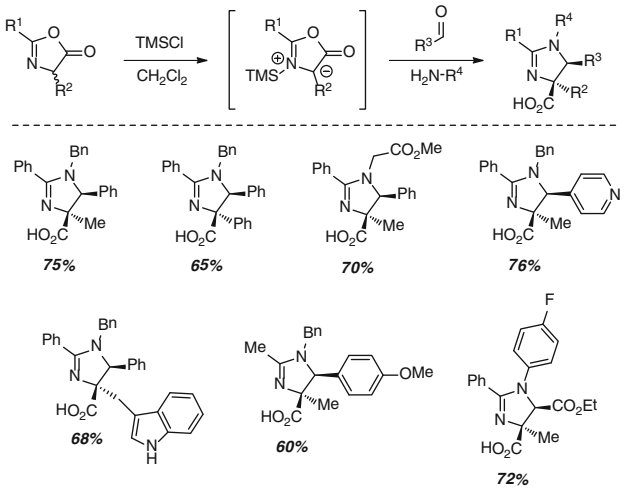
5 Münchnones

Münchnones (1,3-oxazolium-5-olates) were discovered and extensively investigated by Huisgen and coworkers. In stark contrast to sydnones, münchnones are generally too unstable to be isolated or metalated directly. Their chemistry is generally restricted to 1,3-dipolar cycloadditions which yield pyrroles or similar compounds depending on the dipolarophile [51].

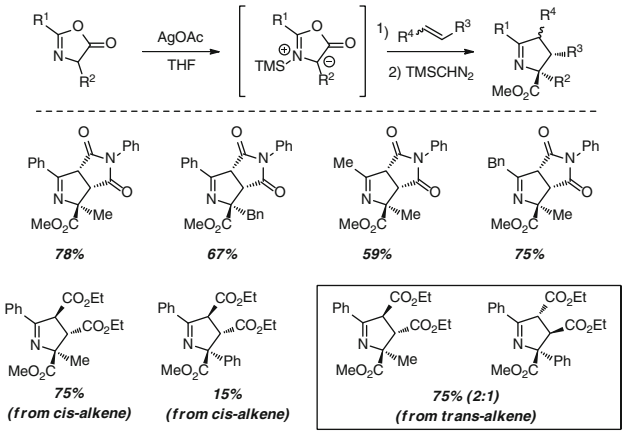
5.1 Silicon-Mediated Chemistry

In 2002, Tepe and coworkers reported a multicomponent synthesis of unsymmetrical imidazolines from oxazolones, TMSCl, aldehydes, and amines (Scheme 16). The münchnones were generated in situ by the interaction of oxazolones and TMSCl; the mesoionic species subsequently cyclized with the imine to yield the imidazolines. The products were isolated as single anti-diastereomers in high yield and tolerated a wide range of aryl, acyl, alkyl, and heterocyclic substituents [52].

A wide variety of catalysts were screened under the reaction conditions including $TiCl_4$, $SnCl_4$, $ZnCl_2$, CuCl, and AgOTf; however, the silyl chlorides proved the optimum choices [53]. In addition, Tepe and Sharma devised a route which provides primarily the *syn*-diastereomeric imidazolines by altering the substituents in the oxazolone [54].



Scheme 16 Tepe's silicon-mediated münchnone reactions



Scheme 17 Tepe's silver-mediated münchnone reactions

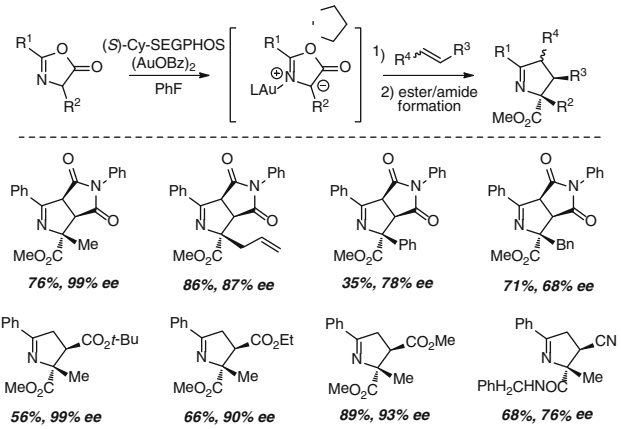
5.2 Silver-Mediated Chemistry

Tepe and Peddibhotla reported an extension to their silicon-mediated chemistry which utilized silver acetate and oxazolones to generate the münchnones in situ; subsequent addition of various alkenes yielded pyrrolines after the requisite 1,3-dipolar cycloadditions (Scheme 17). The reactions are limited to electron-deficient alkenes (as is typically of münchnone-based cycloadditions) and smoothly deliver the *exo* products. This provides a complementary methodology to azomethine ylides which usually give *endo*-selective cycloadditions [55].

Tepe and coworkers utilized this chemistry in the synthesis of imidazolines which were shown to have a symbiotic effect with camptothecin and cisplatin in the treatment of cancer cell lines [56, 57].

5.3 Gold-Mediated Chemistry

Toste and coworkers developed a gold-catalyzed reaction with electron-deficient alkenes which is analogous to Tepe's silver acetate chemistry (Scheme 18). Münchnone formation is achieved in situ from an oxazolone and one of a variety of gold catalysts. Addition of an electron-deficient alkene leads to the regioselective formation of pyrrolidines via a 1,3-dipolar cycloaddition. The use of chiral catalysts (i.e., (*S*)-Cy-SEGPHOS(AuOBz)$_2$) allowed for the generation of the pyrrolidines in fairly high enantioselectivity (68–99% ee) [58].



Scheme 18 Toste's gold-catalyzed münchnone reactions

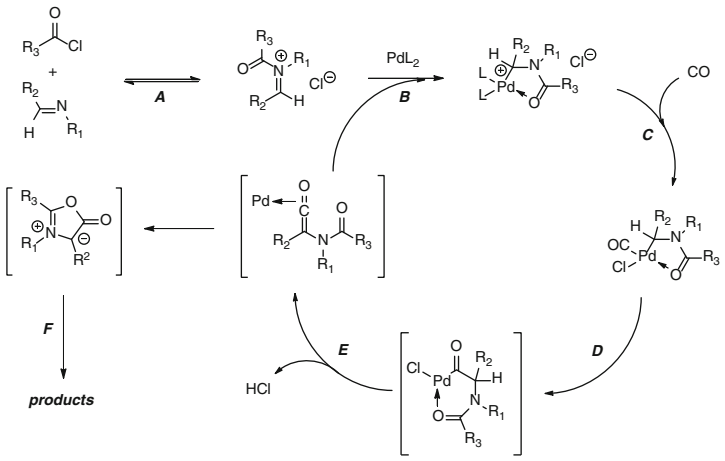
5.4 Palladium-Mediated Chemistry

One traditional limitation to münchnone chemistry is the synthesis of the münchnones themselves. The most common route for their preparation involves the synthesis of amino acid precursors and subsequent dehydration/cyclization in situ to yield the mesoionic heterocycles. This usually involves three to five steps (although they steps are often high yielding) [51]. The oxazolone chemistry (Sects. 5.1–5.3) also involves precursors that are not commercially available.

Arndtsen and coworkers developed a versatile multicomponent synthesis of münchnones which uses a wide variety of imines, acid chlorides, carbon monoxide, and a palladium catalyst (Scheme 19) [59–61]. The reaction mechanism likely proceeds with the coupling of the imine and acid chloride (**A**), insertion of the iminium species into the Pd-catalyst (**B**), coordination of carbon monoxide (**C**), insertion (**D**), β-hydride elimination and cyclization (**E**), and finally trapping with alkynes or alkenes (to yield heterocycles) or alcohols (to yield amino acid derivatives) (**F**).

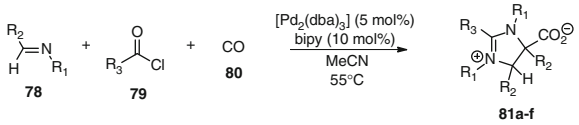
If excess imine is used in the reaction sequence (Table 15), highly substituted imidazolinium salts are obtained. Although the variety of substituents is limited by using the same imine for both generating the münchnone and trapping it, the products are generated efficiently and in high yield from simple and readily available starting materials.

Arndtsen and Dhawan extended the scope of the palladium-catalyzed multicomponent reactions by trapping the münchnone with alkynes to yield a wide array of tetra-substituted pyrroles (Scheme 20). The reactions proceed in moderate to excellent yield and tolerate a wide range of substituents (although the alkynes are generally limited to ones that are electron deficient) [62].



Scheme 19 Proposed mechanism of palladium-catalyzed münchnone formation

Table 15 Palladium-catalyzed imidazolium salt formation

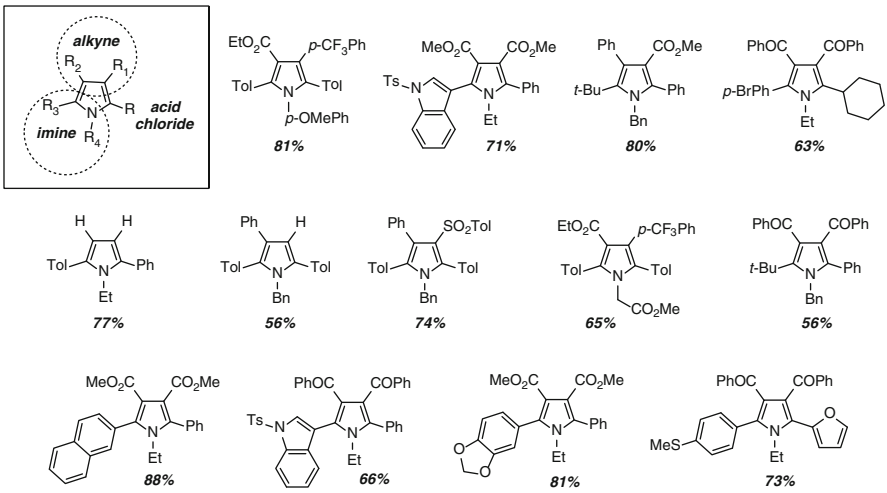


Entry	R_1	R_2	R_3	Compound	Yield (%)
1	Bn	*p*-MePh	Ph	**81a**	82
2	Me	*p*-MePh	Ph	**81b**	92
3	Bn	*p*-SMePh	Ph	**81c**	73
4	Bn	*p*-ClPh	Ph	**81d**	62
5	CH_2CH_2OMe	*p*-MePh	Ph	**81e**	78
6	Bn	*p*-MePh	Me	**81f**	70

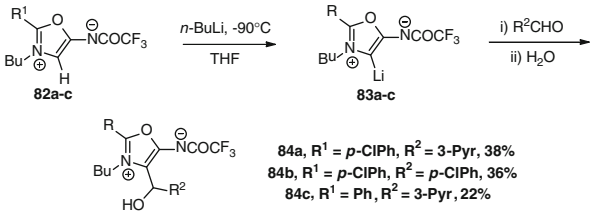
Further extensions of this chemistry have been applied to the synthesis of imidazoles [63] and β-lactams [64].

6 Münchnone Imines

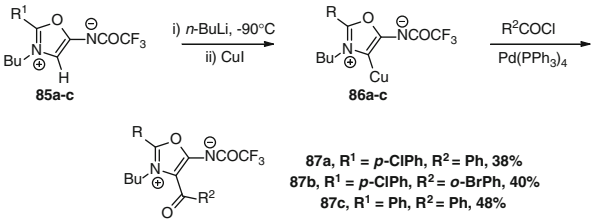
Metal-based reactions of münchnone imines have received little attention over the years. Unlike münchnones, however, münchnone imines can be stable enough to undergo lithiation. Kalinin and coworkers used *n*-BuLi to deprotonate münchnone



Scheme 20 Palladium-catalyzed pyrrole formation



Scheme 21 Lithiation of münchnone imines



Scheme 22 Transmetalation of lithio münchnone imines to cuprates

imine **82** at C4; the resulting intermediate was trapped with aldehydes to give the corresponding carbinols in low yield (Scheme 21) [65].

The lithiated münchnone imines could be transmetalated to their respective cuprates with CuI. These compounds were successfully subjected to palladium-catalyzed cross-coupling conditions with acid chlorides (Scheme 22) [65].

7 Isomünchnones

Isomünchnones have become quite popular in the literature over the last 20–25 years with the advent of mild Rh-mediated synthesis of the ring system. Although generally not isolable, these mesoionic heterocycles tend to partake in 1,3-dipolar cycloadditions with great efficiency and yield furans or bicyclic furan-like adducts. Isomünchnones can be synthesized by cyclization without metals or one can use phosphorus, copper, or ruthenium. Most notably, Padwa and coworkers have used isomünchnones to great effect in the synthesis of complex molecules. A number of extensive reviews have been published [66–72].

7.1 Copper-Mediated Diazo Decomposition

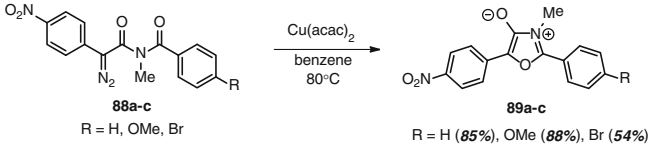
The isomünchnone ring system was first synthesized and isolated by Ibata in 1974 via the $Cu(acac)_2$ catalyzed decomposition of diazo compounds **88** (Scheme 23) [73]. These systems were found to react readily with a variety of acetylenic dipolarophiles which yielded either a substituted furan or bicyclic adduct [74].

The copper-catalyzed decomposition of diazo compounds was also utilized to create fused isomünchnones [75–78]. Bien and coworkers conducted a screen of decomposition catalysts which included $Pd_2Cl_2(C_3H_5)_2$ (which gave an extremely complex mixture of products) as well as $(Et_3)P{\cdot}CuCl$ or $Rh_2(OAc)_4$ [79]. The latter two catalyst systems gave clean reactions and easily isolable products; this marked the starting point for the tremendous increase in the use of Rh catalysts for the generation of isomünchnones.

7.2 Rh-Mediated Diazo Decomposition

Padwa and coworkers initially utilized $Rh_2(OAc)_4$ to generate various six-membered carbonyl ylides for use in dipolar cycloadditions [80–82]. This work led to the development of using isomünchnones to construct more complex polycycles. Maier (Scheme 24) and Padwa (Scheme 25) independently reported Rh-mediated intramolecular dipolar cycloadditions of isomünchnones and pendant alkenes [83, 84].

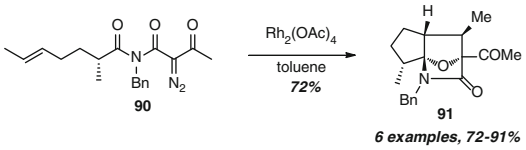
The many examples of isomünchnone synthesis and use [85–118] from 1991 to 2000 have been exhaustively reviewed in a number of places [66–72] and thus will not



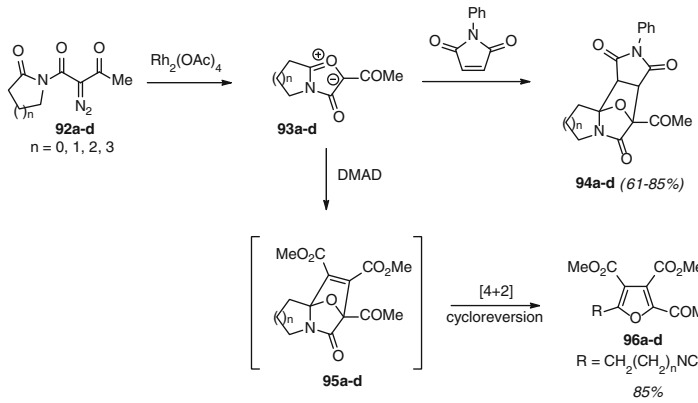
88a-c
R = H, OMe, Br

89a-c
R = H (***85%***), OMe (***88%***), Br (***54%***)

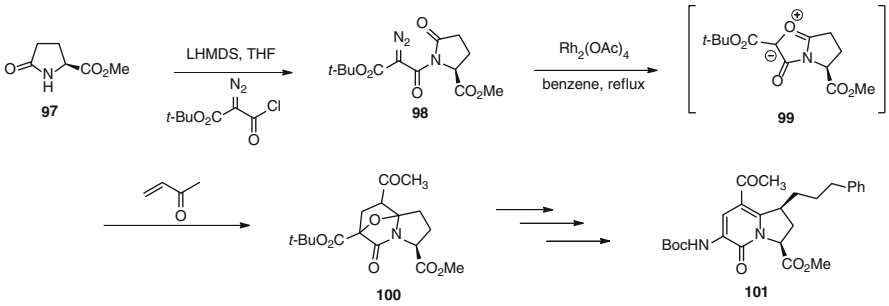
Scheme 23 Copper-mediated synthesis of isomünchnones



Scheme 24 Maier's original synthesis of isomünchnones



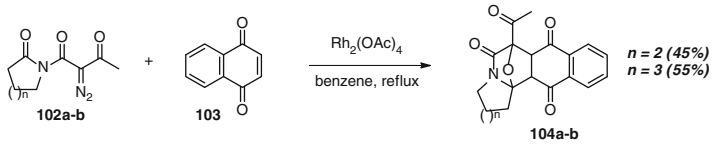
Scheme 25 Padwa's original synthesis of isomünchnones



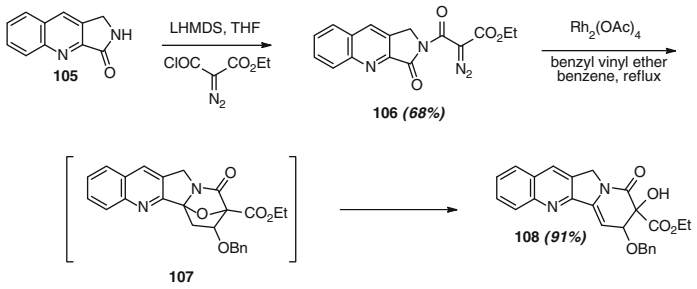
Scheme 26 Zhangs's synthesis of peptidomimetics

be duplicated here. More recently, Zhang and coworkers utilized the Rh-mediated decomposition of diazo compound **98** to generate a fused isomünchnone (**99**) which was trapped with methyl vinyl ketone to yield adduct **100**. This compound was further elaborated to yield highly functionalized indolizinecarboxylic acids which served as peptidomimetics (Scheme 26) [119].

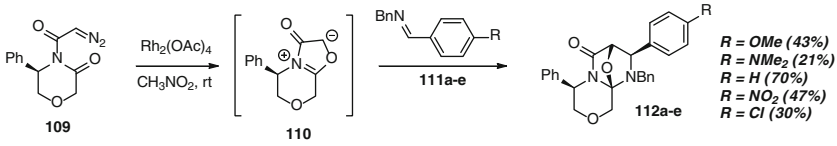
Nair and coworkers provide a similar example of using fused isomünchnones. Here they are combined with 1,4-quinones which ultimately yield azapolycycles in moderate yield (Scheme 27) [120].



Scheme 27 Nair's synthesis of novel azapolycycles



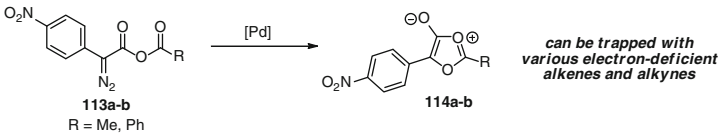
Scheme 28 Kanazawa's synthetic route toward camptothecin



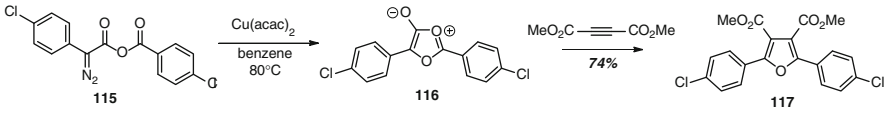
Scheme 29 Harwood's chiral isomünchnones

Precursor **106** was treated with $Rh_2(OAc)_4$ to generate a fused isomünchnone that was trapped with benzyl vinyl ether. Adduct **107** was reduced in situ to give advanced intermediate **108**. Kanazawa and coworkers further elaborated this compound to give camptothecin (Scheme 28) [121].

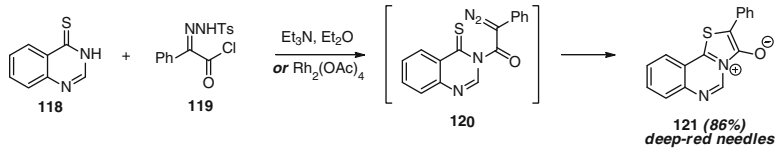
A dramatic solvent effect was seen by Harwood and coworkers while investigating the 1,3-dipolar cycloaddition of fused isomünchnone **110** (Scheme 29). The solvent screen including CH_2Cl_2, THF, EtOAc, $CHCl_3$, MeOH, and CH_3NO_2 and only nitromethane provided the desired product in a yield greater than 12%. Interestingly, each cycloaddition occurred with excellent diastereofacial- and *exo*-selectivity. The obtained products from this key step were utilized in the synthesis of enantiomerically pure α-amino-β hydroxy acids [122].



Scheme 30 Palladium-mediated synthesis of oxamünchnones



Scheme 31 Copper-mediated synthesis of oxamünchnones



Scheme 32 Potts and Murphy's synthesis of thioisomünchnones

8 Oxamünchnones

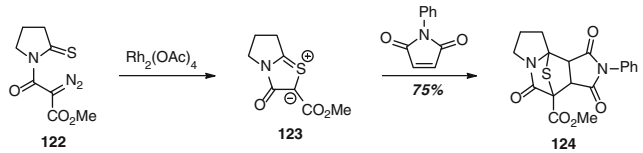
Although they are seldom encountered in the literature, oxamünchnones (1,3-dioxolium-4-olates) can be made in a similar manner as isomünchnones. Hamaguchi and Nagai treated diazo compounds **113** with a π-allyl palladium complex to yield oxamünchnones **114** (Scheme 30) [123].

While $Cu(acac)_2$ was unsuccessful in decomposing **113**, it worked well for diazo compound **115**. This in turn generated oxamünchnone **116** which was trapped with dimethyl acetylenedicarboxylate to yield furan **117** [124] (Scheme 31).

9 Thioisomünchnones

Though not as common as isomünchnones, thioisomünchnones can be quite useful for generating various fused ring systems [125–131]. They can be made in a similar way as isomünchnones and oxamünchnones (via decomposition of the appropriate diazo compounds). Potts and Murphy were the first to synthesize this class of compounds [132]. They found that diazo compound **120** could be decomposed with either Et_3N or $Rh_2(OAc)_4$ to yield isolable fused thioisomünchnone **121** (Scheme 32).

Similar chemistry was used by Padwa and coworkers to generate fused thioisomünchnones which were further elaborated to yield various heterocycles (Scheme 33) [133].



122 123 124

Scheme 33 Padwa's use of thioisomünchnones for the synthesis of heterocycles

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Azoles with 3-4 Heteroatoms

Justin M. Lopchuk

Abstract Direct metalation of various 1,2,3-triazoles, 1,2,4-triazoles, tetrazoles, and 1,3,4-oxadiazoles is reviewed through early 2012. The monograph is divided into sections by heterocycle; the most attention is paid to lithiation chemistry, however, transmetalation, directed *ortho*-lithiation, and other applications are noted where applicable.

Keywords 1,2,3-Triazole • 1,2,4-Triazole • 1,3,4-Oxadiazole • Directed-ortho metalation • Grignard formation • Lithiation • Tetrazole

Contents

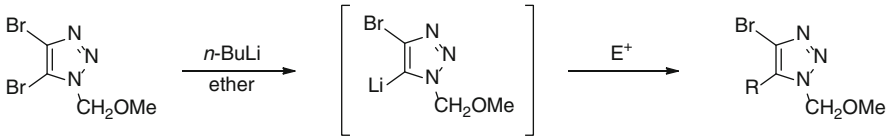
1 Introduction 415
2 1,2,3-Triazoles 416
3 1,2,4-Triazoles 424
4 Tetrazoles 428
5 Oxadiazoles 433
References 437

1 Introduction

This review covers the metalation chemistry of a variety of heterocycles with 3 or 4 heteroatoms including 1,2,3-triazoles, 1,2,4-triazoles, tetrazoles, and 1,3,4-oxadiazoles. Due to the scope of the topic and page limitations, this review is not intended to be comprehensive and will highlight selected examples of direct metalation, transmetalation, and directed *ortho*-lithiation through 2011. The chemistry of

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Table 1 Halogen–metal exchange of 4,5-dibromo-1*H*-1,2,3-triazoles [9]



1 **2** **3a-f**

Entry	E^+	R	Cmpd	Yield (%)
1	H_2O	H	**3a**	84
2	CO_2	COOH	**3b**	72
3	Ph_2CO	$C(OH)Ph_2$	**3c**	93
4	MeSSMe	SMe	**3d**	87
5	PhSSPh	SPh	**3e**	71
6	DMF	CHO	**3f**	~5

these heterocycles (synthesis of the ring systems, reactions, etc.) has been reviewed extensively, and these reviews will be noted in the appropriate sections of the text.

2 1,2,3-Triazoles

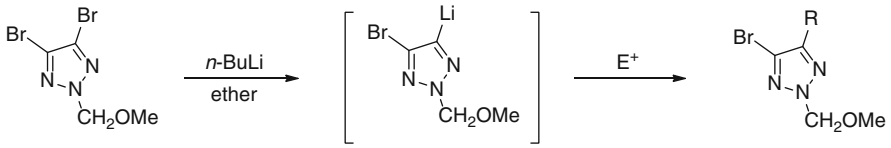
1,2,3-Triazoles are a staple of organic chemistry from their use in "click chemistry" and inclusion in potential drug molecules. They have been the subject of many recent review articles [1–8]. 4,5-Dibromo-1*H*-1,2,3-triazoles (**1**) are readily prepared in high yield by treating the parent triazoles with elemental bromine. While a variety of protected dibromotriazoles can be subsequently synthesized, smooth halogen–metal exchange occurs with *n*-BuLi on N-methoxymethyl compounds **1**. The lithio intermediates (**2**) can be quenched with a variety of electrophiles (Table 1); however, attempts to prepare aldehydes from DMF resulted only in very low yields and complex mixtures [9]

In an analogous manner, 4,5-dibromo-2*H*-1,2,3-triazoles can be lithiated to yield substituted triazoles **6a–f**. In addition, treatment of **4** with anhydrous magnesium bromide yielded the expected Grignard reagent via lithium–magnesium exchange [9] (Table 2).

Benzyl protected triazole **7** was generated with a 95:5 ratio of Br:I at the C-5 position [10]. The mixture of compounds was treated directly with *n*-BuLi and the resulting lithiated heterocycle quenched with benzaldehyde to yield a series of trisubstituted 1,2,3-triazoles (Scheme 1).

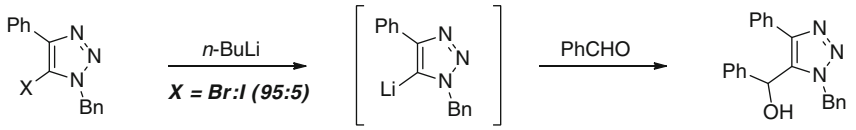
Ohta and coworkers investigated the alkylation and acylation of N-methyl-1,2,3-triazole with a variety of organolithium bases and electrophiles [11]. The reaction proceeds smoothly with *n*-BuLi, *t*-BuLi, lithium diisopropylamide (LDA), and lithium 2,2,6,6-tetramethylpiperidide (LTMP). Nearly all electrophiles tested

Table 2 Halogen–metal exchange of 4,5-dibromo-2*H*-1,2,3-triazoles [9]



4 **5** **6a-f**

Entry	E^+	R	Cmpd	Yield (%)
1	H_2O	H	**6a**	91
2	CO_2	COOH	**6b**	71
3	Ph_2CO	C(OH)Ph2	**6c**	77
4	MeSSMe	SMe	**6d**	76
5	PhSSPh	SPh	**6e**	75
6	DMF	CHO	**6f**	~5



7 **8** ***9 (90%)***

Scheme 1 Synthesis of trisubstituted 1,2,3-triazoles [10]

quenched the in situ generated lithio species in moderate to high yield. The notable exception was entry **11** where treatment of **11** with DMF yielded product **13** in 33% yield (Table 3).

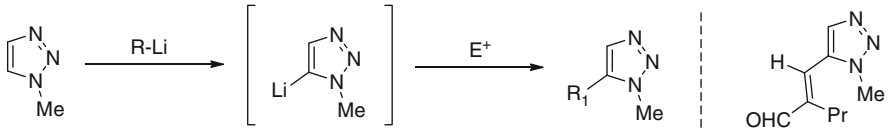
With the C-5 position of **14** protected with a TBDMS group, lithiation with LTMP resulted in deprotonation of the N-methyl side chain instead of the triazole ring [11]. The anion was successfully quenched to yield ketone **16** (Scheme 2).

In contrast to the aforementioned deprotonation in Scheme 2, substitution of the triazole ring at C-5 with a thiol derivative allowed for selective lithiation of C-4 instead of the side chain (Table 4). Lithio species **18** were then quenched with aldehydes and amides in high yield [11].

Holzer and Ruso prepared a series of 5-substituted-1,2,3-triazoles by treating SEM-protected triazoles **20** with *n*-BuLi (Table 5). The protecting group was subsequently removed by treatment with dilute hydrochloride acid or tetrabutylammonium fluoride (TBAF) [12].

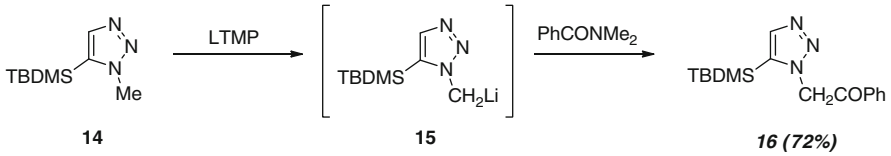
While developing structure–activity relationships among a series of 1,2,3-triazole-based HIV type 1 protease inhibitors, Fokin and coworkers discovered that late-stage functionalization of the triazoles at C-5 greatly improved their

Table 3 Some common mesoionic heterocycles [11]



10 **11** **12a-r** **13**

Entry	R	E^+	R_1	Cmpd	Yield (%)
1	*n*-Bu	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$	**12a**	51
2	*t*-Bu	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$	**12b**	57
3	LDA	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$	**12c**	62
4	LTMP	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$	**12d**	64
5	LTMP	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$	**12e**	63
6	*n*-Bu	PhCHO	PhCH(OH)	**12f**	61
7	*n*-Bu	*p*-ClPhCHO	*p*-ClPhCH(OH)	**12g**	62
8	*n*-Bu	$PhCONMe_2$	PhCO	**12h**	62
9	*n*-Bu	*p*-$ClPhCONMe_2$	*p*-ClPhCH(OH)	**12i**	67
10	LTMP	MeCON(Me)OMe	MeCO	**12j**	78
11	*n*-Bu	DMF	–	**12k**	33
12	*n*-Bu	MeI	Me	**12l**	56
13	*n*-Bu	EtI	Et	**12m**	54
14	*n*-Bu	$PhCOCH_2Br$	$PhCOCH_2$	**12n**	66
15	*n*-Bu	PhSSPh	PhS	**12o**	78
16	*n*-Bu	TBSCl	TBS	**12p**	84
17	*n*-Bu	Br_2	Br	**12q**	46
18	*n*-Bu	D_2O	D	**12r**	83



14 **15** ***16 (72%)***

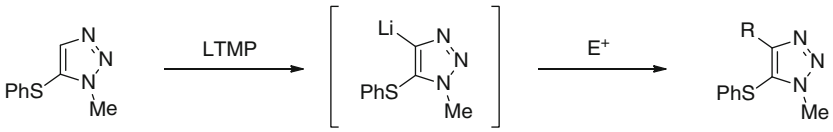
Scheme 2 Selective lithiation of the N-methyl side chain [11]

activity [13]. The lithio anions were generated from **23** with *n*-BuLi and quenched with various aldehydes or TMSCl in low to moderate yields (Table 6).

Konig and coworkers utilized the direct metalation of triazoles during the development of a series of triaryl α-helix mimetics [14]. The synthetic route is particularly well suited for library development; selective functionalization of the triazole allows for the installation of a side chain at C-5 of the ring (Scheme 3).

A series of 1-hydroxy-1,2,3-triazoles (**33a–l**) was prepared from the corresponding 1-(benzyloxy)-1,2,3-triazoles (Table 7). Lithiation occurs exclusively at C-5 (α to the

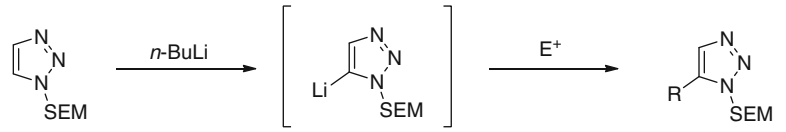
Table 4 Selective lithiation at C-4 of the triazole ring [11]



17 **18** **19a-d**

Entry	E^+	R	Cmpd	Yield (%)
1	PhCHO	PhCH(OH)	**19a**	86
2	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$	**19b**	71
3	PhCONMe2	PhCO	**19c**	73
4	MeCON(Me)OMe	MeCO	**19d**	82

Table 5 Lithiation of N-SEM-1,2,3-triazole [12]



20 **21** **22a-f**

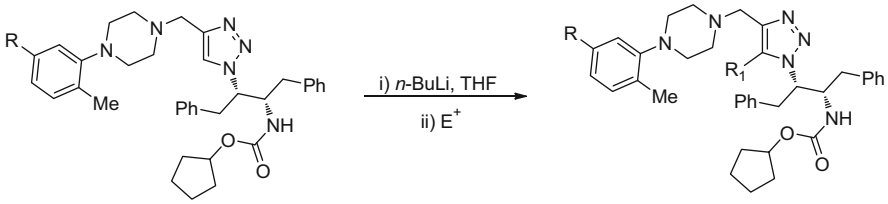
Entry	E^+	R	Cmpd	Yield (%)
1	PhCHO	PhCH(OH)	**22a**	45
2	$PhCO_2Et$	PhCO	**22b**	21
3	MeI	Me	**22c**	30
4	PhSSPh	PhS	**22d**	80
5	Cl_3CCl_3	Cl	**22e**	50
6	TMSCl	TMS	**22f**	37

benzyloxy group). A wide variety of electrophiles were used which gave C-5 substituents including halogen, silyl, tin, sulfur, and carbon groups in high yield. The 1-hydroxy group was revealed by treatment of **33a–l** with H_2 and Pd/C or concentrated hydrochloride acid [15].

Interestingly, if lithio triazole **32** is permitted to warm up above −78°C or react longer than 5 min, the anion rearranges to give **34** which decomposes to give 1,2,3-triazole **37** and alcohol **38** (Scheme 4) [15].

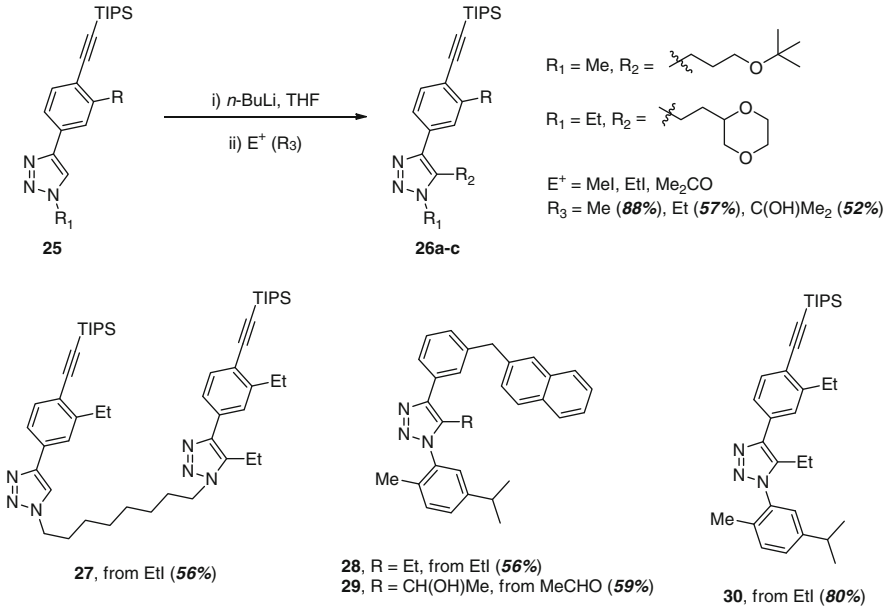
Begtrup and coworkers demonstrated that lithio triazoles **32** can be transmetalated to the corresponding tin and zinc species [16]. The stannyl derivatives could be coupling with various acyl chlorides under palladium-catalyzed conditions by failed to react with aryl iodides. However, coupling with aryl and heteroaryl iodides was

Table 6 Lithiation of HIV type 1 protease inhibitors [13]



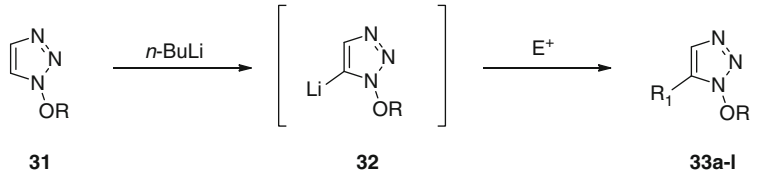
23 **24a-i**

Entry	R	E^+	R_1	Cmpd	Yield (%)
1	Me	TMSCl	TMS	**24a**	58
2	Me	HCHO	CH2OH	**24b**	53
3	Me	MeCHO	(*S*)-CH(OH)Me	**24c**	65
4	Me	MeCHO	(*R*)-CH(OH)Me	**24d**	23
5	Me	EtCHO	(*S*)-CH(OH)Et	**24e**	45
6	Me	EtCHO	(*R*)-CH(OH)Et	**24f**	15
7	Cl	HCHO	CH2OH	**24g**	38
8	Cl	MeCHO	(*S*)-CH(OH)Me	**24h**	58
9	Cl	MeCHO	(*R*)-CH(OH)Me	**24i**	16



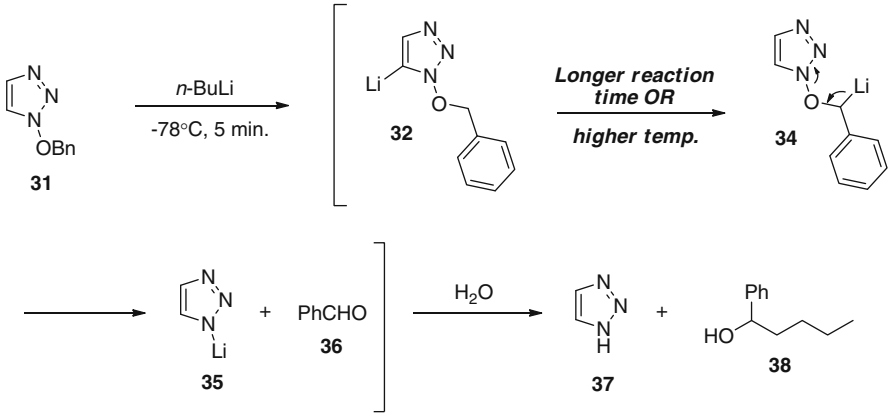
Scheme 3 Synthesis of triaryl α-helix mimetics [14]

Table 7 Lithiation of 1-hydroxy-1,2,3-triazoles [15]



31 **32** **33a-l**

Entry	R	E^+	R_1	Cmpd	Yield (%)
1	Bn	D_2O	D	**33a**	90
2	Bn	MeI	Me	**33b**	93
3	Bn	DMF	CHO	**33c**	87
4	Bn	MeCOOCl	COOMe	**33d**	76
5	Bn	Me_2NCOCl	$CONMe_2$	**33e**	97
6	Bn	Cl_3CCCl_3	Cl	**33f**	88
7	Bn	Br_2	Br	**33g**	86
8	Bn	I_2	I	**33h**	96
9	Bn	MeSSMe	MeS	**33i**	67
10	Bn	TMSCl	TMS	**33j**	93
11	Bn	Bu_3SnCl	Bu_3Sn	**33k**	91
12	$CONEt_2$	I_2	I	**33l**	87

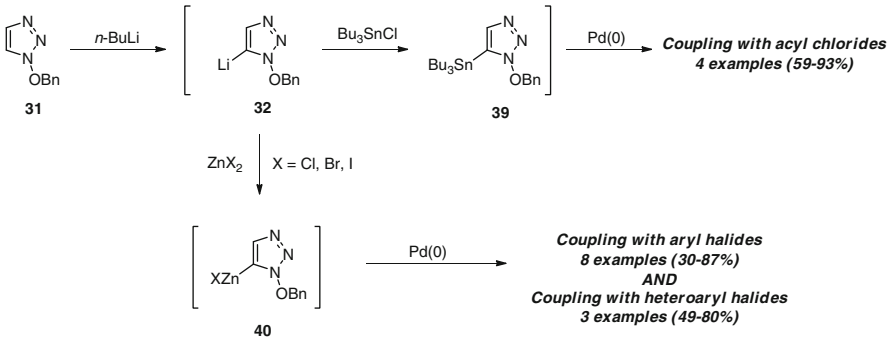


31 **32** **34** **35** **36** **37** **38**

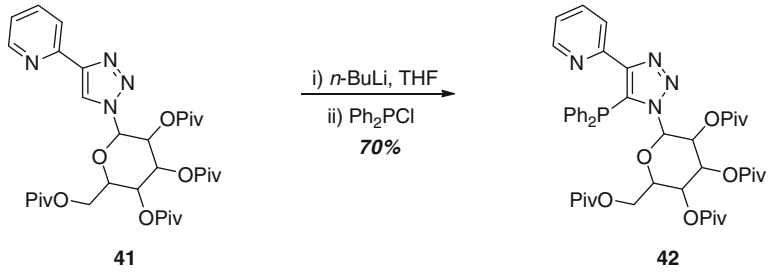
Scheme 4 Rearrangement of lithiated 1-hydroxy-1,2,3-triazole [15]

successfully achieved instead through the zincate **40** in moderate to high yield (Scheme 5).

Phosphorus-based electrophiles typically work well in quenching lithiated intermediates. During their synthesis of 1-glycosyl-1*H*-triazoles, Chen and coworkers found that the pyridine substituent at C-4 was crucial in the installation



Scheme 5 Tin and zinc triazole derivatives [16]



Scheme 6 Synthesis of 1-glycosyl-1*H*-triazoles [17]

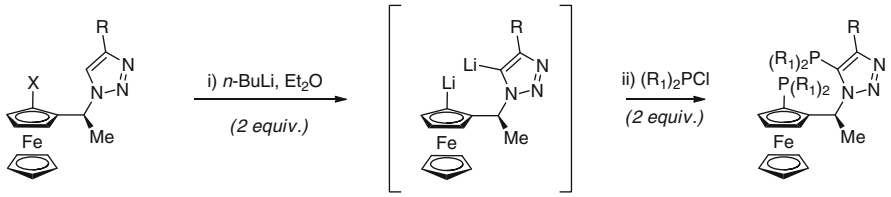
of the phosphorus side chain (Scheme 6). A variety of C-4 aryl groups failed to give the desired products of type **42** [17].

During their synthesis of the ClickFerrophos ligands, Fukuzawa and coworkers showed that ferrocene-triazole **43** could be converted to dilithio species **44** with 2 equiv. of *n*-BuLi; this species could be quenched with phosphoryl chlorides to yield the desired chiral ligands (Table 8) [18, 19].

Sequential lithiation is an alternative method for preparing differentially substituted ClickFerrophos ligands (Table 9). Treatment of triazole **46** with *n*-BuLi gives selective lithiation at C-5 of the ring, which was quenched with a variety of electrophiles to yield compounds **48a–k** [18–20].

Trudell and coworkers showed that Grignard reagent **49** is generated in situ and allowed to react with ammonium chloride or methyl chloroformate; triazoles **50a–d** are isolated in high yield and further elaborated to give a series of compounds which demonstrated an affinity for CB1 cannabinoid receptors (Table 10) [21].

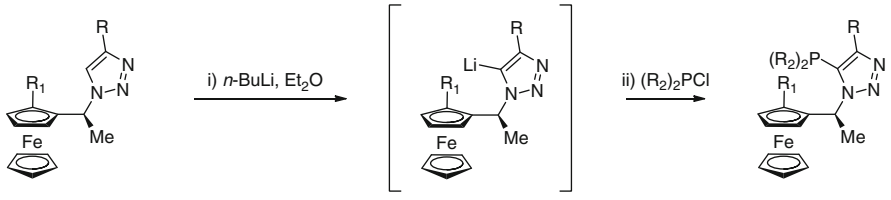
Table 8 Synthesis of the ClickFerrophos ligands by dilithiation [18, 19]



43 **44** **45a-h**

Entry	X	R	R_1	Cmpd	Yield (%)	Ref.
1	I	Ph	Ph	**45a**	42	[18]
2	Br	Ph	Ph	**45b**	81	[19]
3	Br	*o*-MePh	Ph	**45c**	77	[19]
4	Br	*o*-FPh	Ph	**45d**	74	[19]
5	Br	H	Ph	**45e**	73	[19]
6	Br	Ph	3,5-xylyl	**45f**	63	[19]
7	Br	*o*-FPh	3,5-xylyl	**45g**	51	[19]
8	Br	Ph	Cyclohexyl	**45h**	71	[19]

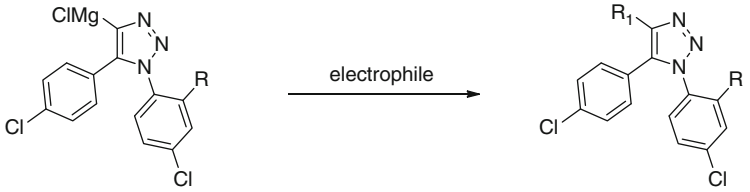
Table 9 Synthesis of the ClickFerrophos ligands by sequential lithiation [18–20]



46 **47** **48a-k**

Entry	R	R_1	R_2	Cmpd	Yield (%)	Ref.
1	Ph	Ph	Ph	**48a**	38	[18]
2	Ph	Ph	Cy	**48b**	55	[18]
3	Ph	Ph	3,5-xylyl	**48c**	37	[19]
4	Ph	Ph	3,5-(CF_3)Ph	**48d**	44	[19]
5	Ph	Ph	Cy	**48e**	Not given	[19]
6	Ph	Ph	Ph	**48f**	39	[20]
7	Ph	*p*-MePh	Ph	**48g**	67	[20]
8	Ph	*p*-ClPh	Ph	**48h**	68	[20]
9	Ph	Cy	Ph	**48i**	36	[20]
10	Ph	Et	Ph	**48j**	75	[20]
11	H	Et	Ph	**48k**	74	[20]

Table 10 Grignard formation [21]



49 **50a-d**

Entry	R	Electrophile	R_1	Cmpd	Yield (%)
1	H	NH_4Cl	H	**50a**	85
2	Cl	NH_4Cl	H	**50b**	87
3	H	$MeCO_2Cl$	CO_2Me	**50c**	67
4	Cl	$MeCO_2Cl$	CO_2Me	**50d**	61

3 1,2,4-Triazoles

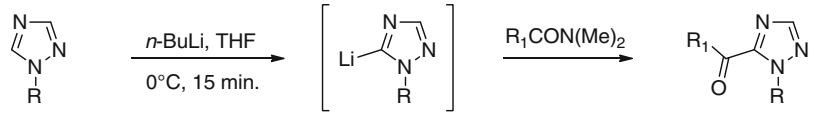
Although they receive less coverage in the literature compared to 1,2,3-triazoles, 1,2,4-triazoles are also readily metalated and find applications in materials and pharmaceuticals [6, 8, 22]. Ohta and coworkers synthesized a comprehensive series of 5-acyl-1,2,4-triazoles via lithiation with *n*-BuLi [23]. The triazoles were protected at N-1 with alkyl groups (Me, Et, *i*-Pr, *n*-hexyl) or benzyl groups. A wide variety of electrophiles (R-groups = aryl, alkyl) reacted successfully and in high yields (Table 11).

Use of a formal protecting group at N-1 can be avoided by treating the unprotected 1,2,4-triazole (**54**) with ethyl orthoformate followed by *n*-BuLi and the electrophile of choice (Table 12). Diethoxymethyl triazole **55** is formed in situ, converted to lithiated heterocycle **56** and then quenched with various N,N′-dimethylamides and water to yield unprotected 1,2,4-triazoles **57a–f**. The reactions proceed in one-pot are high yielding and provide an operationally simple method for the synthesis of unprotected triazoles [23].

3-Substituted-1,2,4-triazoles can be synthesized by treatment of **58** with *n*-BuLi and diphenylsulfide which serves as a blocking group for the C-5 position (Table 13). Subsequent lithiation of **59** with LTMP/TMEDA gives exclusive lithiation at C-3; the anions are then quenched with electrophiles [23]. Treatment with Raney nickel facilitates desulfurization to give 3-substituted-1,2,4-triazoles (not shown).

During the course of their studies on the synthesis of 2-cyanoimiadazoles, Dudfield and coworkers found that their methodology works equally well for 3-aryl-1,2,4-triazoles (Scheme 7). The C-5 anion formed by treatment with *n*-BuLi in THF was trapped with phenyl cyanate. Upon workup with water, compound **64** is isolated in 75% yield [24].

Table 11 Lithiation of N-protected 1,2,4-triazoles [23]



51a-q **52a-q** **53a-q**

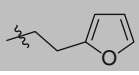
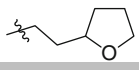
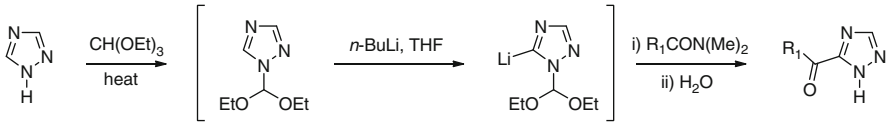
Entry	R	R_1	Cmpd	Yield (%)
1	Me	Me	**53a**	82
2	Me	Ph	**53b**	62
3	Me	Et	**53c**	98
4	Me	*n*-Hexyl	**53d**	91
5	Me	Cy	**53e**	78
6	Me	*t*-Bu	**53f**	49
7	Me	Bn	**53g**	60
8	Me	*p*-ClPhCH$_2$	**53h**	43
9	Me		**53i**	85
10	Me		**53j**	70
11	Me	*p*-ClPh	**53k**	56
12	Me	2,4-ClPh	**53l**	78
13	Me	*p*-OMePh	**53m**	83
14	Et	Me	**53n**	81
15	*i*-Pr	Me	**53o**	94
16	*n*-Hexyl	Me	**53p**	98
17	Bn	Me	**53q**	99

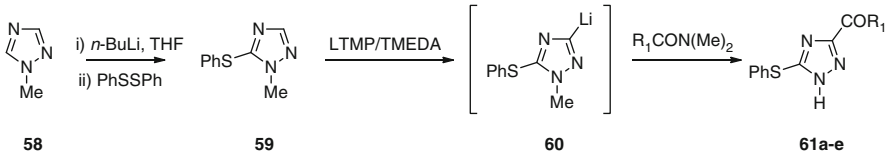
Table 12 Lithiation of in situ protected 1,2,4-triazoles [23]



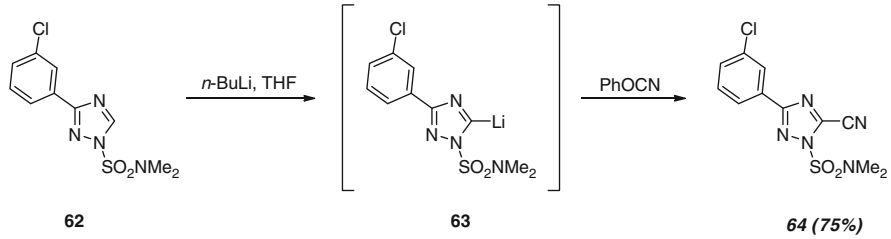
54 **55** **56** **57a-f**

Entry	R_1	Cmpd	Yield (%)
1	Me	**57a**	96
2	Ph	**57b**	61
3	*n*-Hexyl	**57c**	85
4	*p*-ClPh	**57d**	58
5	2,4-ClPh	**57e**	48
6	*p*-OMePh	**57f**	53

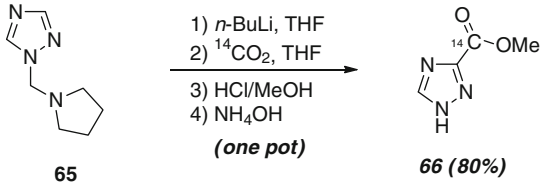
Table 13 Synthesis of 3-acyl-1,2,4-triazoles [23]



Entry	R_1	Cmpd	Yield (%)
1	Me	**61a**	35
2	Ph	**61b**	57
3	Et	**61c**	67
4	*n*-Hexyl	**61d**	55
5	*t*-Bu	**61e**	55



Scheme 7 Synthesis of 5-cyano-1,2,4-triazoles [24]

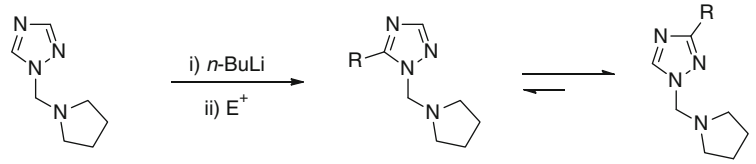


Scheme 8 Synthesis of radiolabeled acyl triazoles [25]

As part of their synthesis of levovirin and a levovirin valinate pro-drug [25], de Keczer and coworkers generated ^{14}C radiolabeled **66** by one-pot sequential treatment of **65** with *n*-BuLi, $^{14}CO_2$, HCl/MeOH, and NH_4OH (which served to deprotect the triazole). The desired 3-acyl-1,2,4-triazole was isolated in 80% yield and with a total activity of 168 mCi (Scheme 8).

Katritzky and coworkers reported that treatment of 1,2,4-triazole **65** with *n*-BuLi resulted in initial formation of the C-5 anion; however upon treatment with a number of electrophiles, the isolated products tended to be substituted at C-3

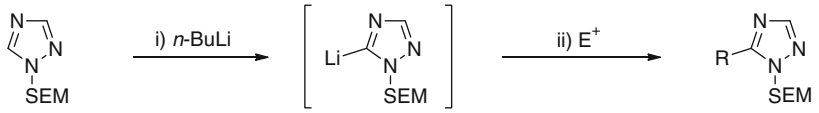
Table 14 Rearrangement of 3(5)-substituted-1,2,4-triazoles [26]



65 **67a-g** **68a-g**

Entry	E^+	R	Cmpd	Yield (%)
1	Cyclohexanone	$(CH_2)_5COH$	**68a**	83
2	D_2O	D	**68b**	90
3	MeI	Me	**68c**	95
4	$(Me)_3CNCO$	$(Me)_3CNHCO$	**68d**	86
5	PhCHO	PhCHOH	**68e**	87
6	*p*-MePhCHO	*p*-MePhCHOH	**68f**	78
7	PhNCO	PhNHCO	**68g**	91

Table 15 Lithiation of N-SEM-1,2,4-triazoles [27]



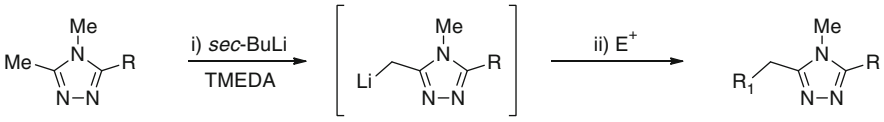
69 **70** **71a-e**

Entry	E^+	R	Cmpd	Yield (%)
1	PhCOCl	PhCO	**71a**	30
2	PhCHO	PhCHOH	**71b**	39
3	PhSSPh	PhS	**71c**	57
4	Cl_3CCCl_3	Cl	**71d**	41
5	MeI	Me	**71e**	35

(Table 14). The rearrangement in the product is presumably driven by steric interactions from the N-1 protecting group [26].

Much like the isomeric 1,2,3-triazoles, SEM-protected 1,2,4-triazoles are readily lithiated at C-5 with *n*-BuLi. The 5-substituted products **71a–e** are isolated in moderate yield [27]. As opposed to the rearrangement observed in Table 14, coordination with the SEM group may help favor substitution at the 5-position (Table 15).

Table 16 Side chain lithiation of 1,2,4-triazoles [28]



72 **73** **74a-i**

Entry	R	E^+	R_1	Cmpd	Yield (%)
1	Ph	BnBr	Bn	**74a**	61
2	Ph	PhCO2Me	PhCO	**74b**	63
3	Ph	Cyclohexanone	Cyclohexanol	**74c**	20
4	Ph	PhSSPh	PhS	**74d**	25
5	Ph	Diethyl chlorophosphate	Diethyl phosphate	**74e**	20
6	Ph	Allyl bromide	Allyl	**74f**	79
7	*p*-(Me)2NPh	BnBr	Bn	**74g**	75
8	*p*-NO2Ph	BnBr	Bn	**74h**	0
9	4-Pyridyl	BnBr	Bn	**74i**	12

Treatment of **72** with *sec*-BuLi gave selective deprotonation of the C-2 alkyl side chain; addition of various electrophiles yielded α-substituted 1,2,4-triazoles **74a–i** in low to moderate yields (Table 16) [28].

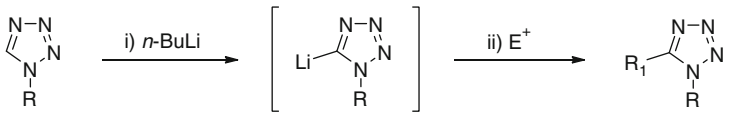
4 Tetrazoles

Tetrazoles are utilized most often in organic synthesis as reagents in olefination reactions (e.g., Julia-type olefinations) and as a bioisosteric replacement for carboxylic acids in drug discovery [29–31]. The only available ring position for lithiation on tetrazole is at C-5. As shown in Table 17, N-protected (Bn, BOM, PMB) tetrazoles are smoothly lithated with *n*-BuLi; the resulting anion can be quenched with a wide variety of electrophiles to yield compounds **77a–u** in moderate to high yields [32–36].

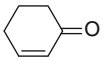
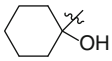
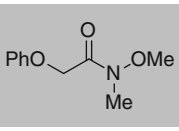
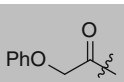
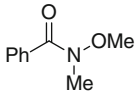
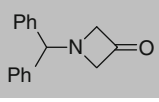
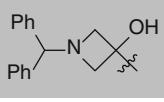
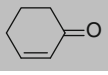
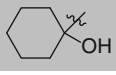
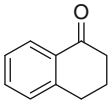
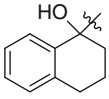
While studying analogs of pregabalin at Pfizer, Schwartz and coworkers added lithiated tetrazole **78** to nitroalkene **80**; subsequent reduction with H_2 and Pd/C yielded **82**. This compound served as bioisotere of pregabalin which served as a lead compound for further studies (Scheme 9) [37].

Alkyl side chains connected to the C-5 position of tetrazoles can usually be deprotonated with organolithium reagents and functionalized. A series of tetrazolo [1,5-*a*]-α-cycloalkanes were lithiated α to the tetrazole and the anion was quenched with benzaldehyde (Scheme 10). These compounds were converted to the corresponding acetates and on to the tetrazolo[1,5-*a*]-α-cycloalkanones over a few more steps [38].

Table 17 Lithiation of N-protected tetrazoles [32–36]

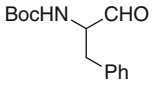
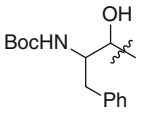
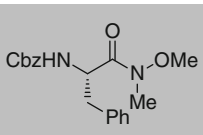
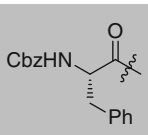


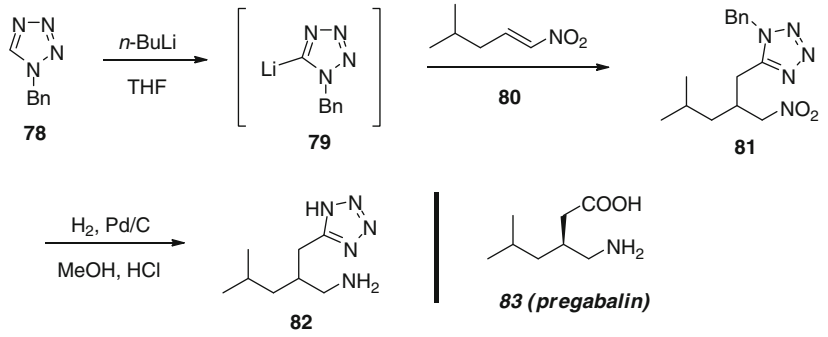
75 **76** **77a-u**

Entry	R	E^+	R_1	Cmpd	Yield (%)	Ref.
1	Bn	Br2	Br	**77a**	82	[32]
2	BOM	Bu_3SnCl	Bu_3Sn	**77b**	67	[33]
3	Bn	$PhCH_2CH_2CHO$	$PhCH_2CH_2CHOH$	**77c**	71	[34]
4	PMB	$PhCH_2CH_2CHO$	$PhCH_2CH_2CHOH$	**77d**	73	[34]
5	Bn	PhCHO	PhCHOH	**77e**	70	[34]
6	PMB	PhCHO	PhCHOH	**77f**	80	[34]
7	Bn	Cycloheptanone	Cycloheptanol	**77g**	78	[34]
8	PMB			**77h**	93	[34]
9	PMB			**77i**	52	[34]
10	PMB			**77j**	62	[34]
11	PMB	I_2	I	**77k**	84	[34]
12	PMB	$ClPO(OEt)_2$	$PO(OEt)_2$	**77l**	68	[34]
13	PMB			**77m**	63	[36]
14	BOM	PhCHO	PhCHOH	**77n**	71	[35]
15	BOM	$PhCH_2OCH_2CHO$	$PhCH_2OCH_2CHOH$	**77o**	65	[35]
16	BOM	Cyclopentanone	Cyclopentanol	**77p**	56	[35]
17	BOM			**77q**	60	[35]
18	BOM			**77r**	57	[35]
19	BOM	I_2	I	**77s**	54	[35]
20	BOM			**77t**	27	[35]

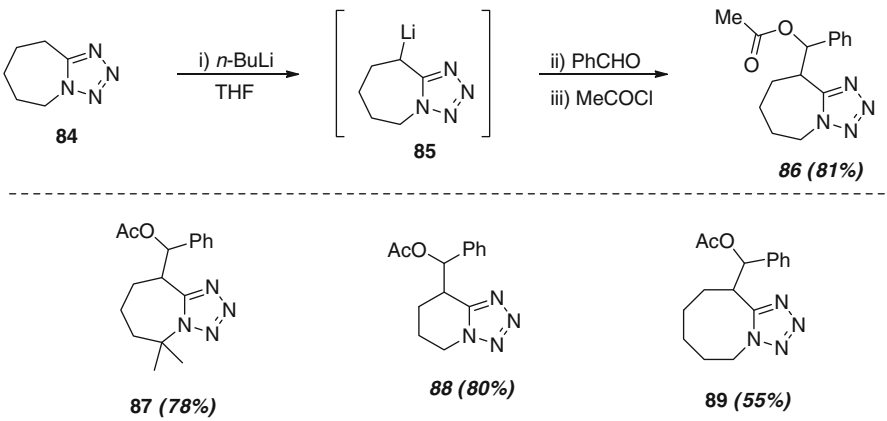
(continued)

Table 17 (continued)

Entry	R	E^+	R_1	Cmpd	Yield (%)	Ref.
						
21	BOM			**77u**	65	[35]

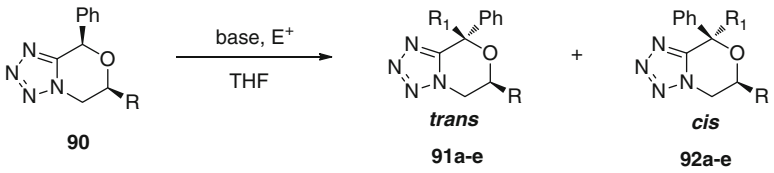


Scheme 9 Synthesis of pregabalin bioisosteres [37]

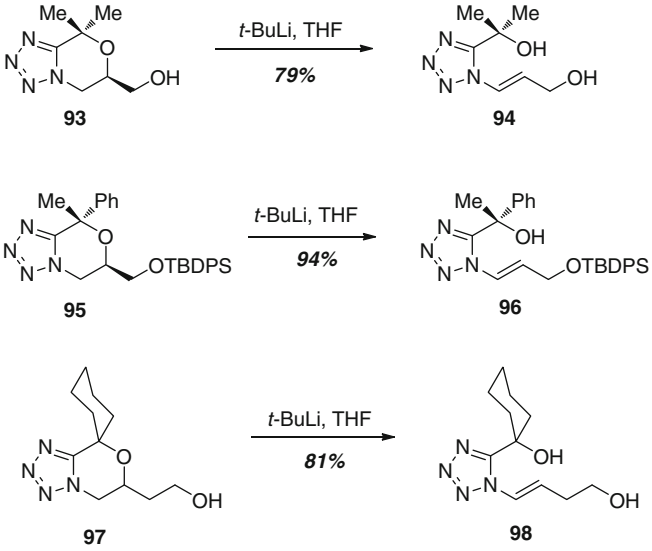


Scheme 10 Synthesis of tetrazolo[1,5-*a*]-α-cycloalkanes [38]

Table 18 Lithiation of oxabicyclic tetrazoles [39]



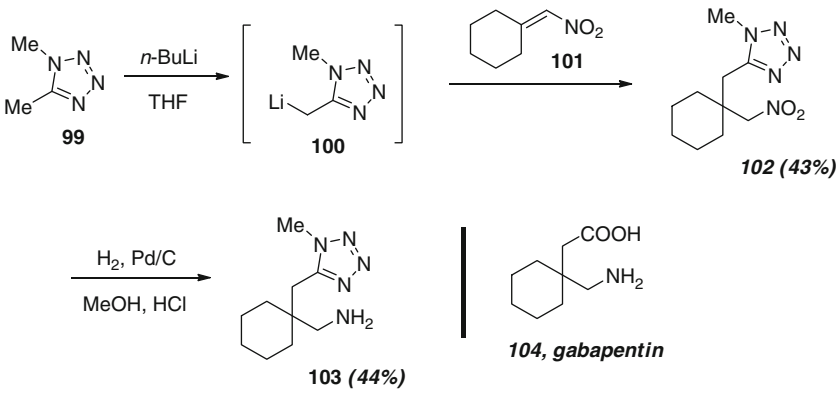
Entry	Base	R	E^+	Temp (°C)	Cmpd	*Trans*/*cis*	Yield (%)
1	NaH	$CH_2OTBDPS$	BnBr	−5	**91a:92a**	86:14	97
2	LiHMDS	$CH_2OTBDPS$	BnBr	−78	**91b:92b**	96:4	87
3	LiHMDS	Me	BnBr	−78	**91c:92c**	95:5	94
4	LiHMDS	$CH_2OTBDPS$	MeI	−100	**91d:92d**	75:25	94
5	LiHMDS	$CH_2OTBDPS$	Allyl-I	−100	**91e:92e**	63:37	95



Scheme 11 Fragmentation reactions of oxabicyclic tetrazoles [39]

Hanessian and coworkers synthesized a series of oxabicyclic tetrazoles by treatment of **90** with either NaH or LiHMDS and trapping the resulting anion with BnBr, MeI, or allyl iodide. The optimal conditions were found to be LiHMDS at −78°C; these conditions selectively gave the trans products in the highest yield (Table 18) [39].

These oxabicyclic tetrazoles fragmented upon being treated with *t*-BuLi which yielded vinyl tetrazoles **94**, **96**, and **98** (Scheme 11) [39].



Scheme 12 Synthesis of gabapentin bioisosteres [40]

In an analogous study as shown above (Scheme 9), Schwarz and coworkers generated the lithio anion of tetrazole **100**; this anion added to nitroalkene **101** and subsequent reduction gave a bioisostere of gabapentin (Scheme 12) [40].

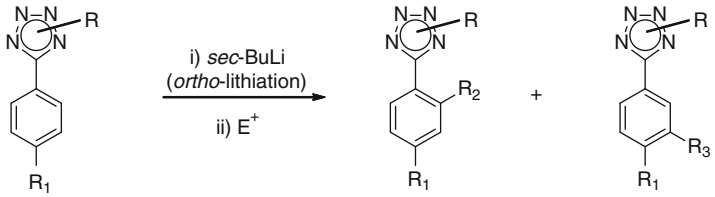
Tetrazoles can serve as effective ortho-directors for lithiation. In an initial study (Table 19, entries **1**–**8**), Wensbo found that 2-trityl (2-Tr) was the most effective ortho director; sequential treatment with *sec*-BuLi and MeI gave **106b** in 88% yield. Interestingly, placement of BOM groups at either the 1 or 2 position failed to give any of the desired product (entries **7** and **8**). A competition study (Table 19, entries **9**–**19**) was designed to determine the relative strength of ortho directors (tetrazole, 2-Tr-tetrazole, OMe, N,N′-diethylamide, *t*-butylamide, and N,N′diethylcarbamate). Differentially substituted starting materials **105i–s** were treated with *sec*-BuLi and methyl iodide; the ratio of products **106:107** was measured. The ortho directors, in order of increasing strength, were found to be OMe < tetrazole < $CONEt_2$ < 2-Tr-tetrazole < NHCO*t*-Bu = $OCONEt_2$ [41].

1-Hydroxy5-aryltetrazoles **108** were treated with 2 equiv. of *n*-BuLi/TMEDA to form dilithio anions **109**. The second anion forms exclusively as the ortho position; quenching with electrophiles gives good to high yields of substituted 1-hydroxytetrazoles (Table 20) [42].

Boronic acid **112** was utilized for a synthesis of losartan by chemists at Merck [43]. The trityl-protected tetrazole served as an ortho director upon treatment with *n*-BuLi and $B(O\text{-}iPr)_3$; workup with ammonium chloride gave the boronic acid in 89% yield (Scheme 13).

A further example of tetrazoles as ortho directors of lithiation was disclosed by Frejd and coworkers [44]. Tetrazoles **113** and **114** were deprotonated with *sec*-BuLi/TMEDA; the anions were quenched with alkyl bromides or aldehydes to yield compounds **117**–**121** (Scheme 14).

Table 19 Tetrazoles are *ortho*-directors for lithiation [41]



105 **106a-s** **107a-s**

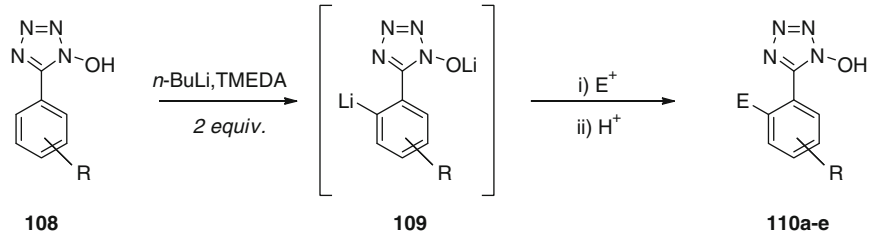
Entry	R	R_1	E^+	R_2	R_3	Temp (°C)	Cmpd	Yield (%)	Ratio (X:X)
1	H	H	MeI	Me	–	−30	**106a**	83	–
2	2-Tr	H	MeI	Me	–	−30	**106b**	88	–
3	2-Tr	H	BnBr	Bn	–	−30	**106c**	38	–
4	2-Tr	H	BnBr	Bn	–	−78	**106d**	42	–
5	2-Tr	H	*i*-PrI	*i*-Pr	–	−30	**106e**	0	–
6	H	H	*i*-PrI	*i*-Pr	–	−78	**106f**	0	–
7	1-BOM	H	–	–	–	–	**106g**	–	–
8	2-BOM	H	–	–	–	–	**106h**	–	–
9	H	OMe	MeI	Me	Me	−78	**106i:107i**	62	85:15
10	H	OMe	MeI	Me	Me	−30	**106j:107j**	53	90:10
11	2-Tr	OMe	MeI	Me	Me	−78	**106k:107k**	88	90:10
12	2-Tr	$CONEt_2$	MeI	Me	Me	−78	**106l:107l**	53	95:5
13	H	$CONEt_2$	MeI	Me	Me	−78	**106m:107m**	10	<5:>95
14	H	$NHCOCMe_3$	MeI	Me	Me	−78	**106n:107n**	Trace	–
15	H	$NHCOCMe_3$	MeI	Me	Me	−30	**106o:107o**	Trace	–
16	2-Tr	$NHCOCMe_3$	MeI	Me	Me	−30	**106p:107p**	25	<5:>95
17	2-Tr	$NHCOCMe_3$	MeI	Me	Me	−78	**106q:107q**	12	<5:>95
18	2-Tr	$OCONEt_2$	MeI	Me	Me	−78	**106r:107r**	26	<5:>95
19	H	$OCONEt_2$	MeI	Me	Me	−78	**106s:107s**	–	<5:>95

Tetrazole **122** was converted to the corresponding dilithio species **123** by treatment with 2 equiv. or *sec*-BuLi. Subsequent addition of electrophiles gave compounds **124a–c** in moderate to high yield (Scheme 15). Similar chemistry was performed to functionalize the side chain of tetrazole **125** [45].

5 Oxadiazoles

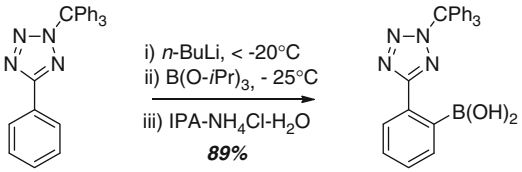
1,3,4-Oxadiazoles are increasingly common heterocycles in medicinal chemistry and drug design [46, 47]. Oxadiazole **128** was deprotonated with *n*-BuLi and $MgBr_2$ and its anion was added to Boc-Valinal (**129**) to give amino acid **130** in 79% yield

Table 20 Dilithiation of 1-hydroxy5-aryltetrazoles [42]



108 **109** **110a-e**

Entry	R	E^+	E	Cmpd	Yield (%)
1	H	MeSSMe	MeS	**110a**	85
2	H	MeI	Me	**110b**	83
3	H	TMSCl	TMS	**110c**	62
4	2-Cl	MeI	6-Me	**110d**	68
5	3-Cl	MeSSMe	MeS	**110e**	80



111 **112**

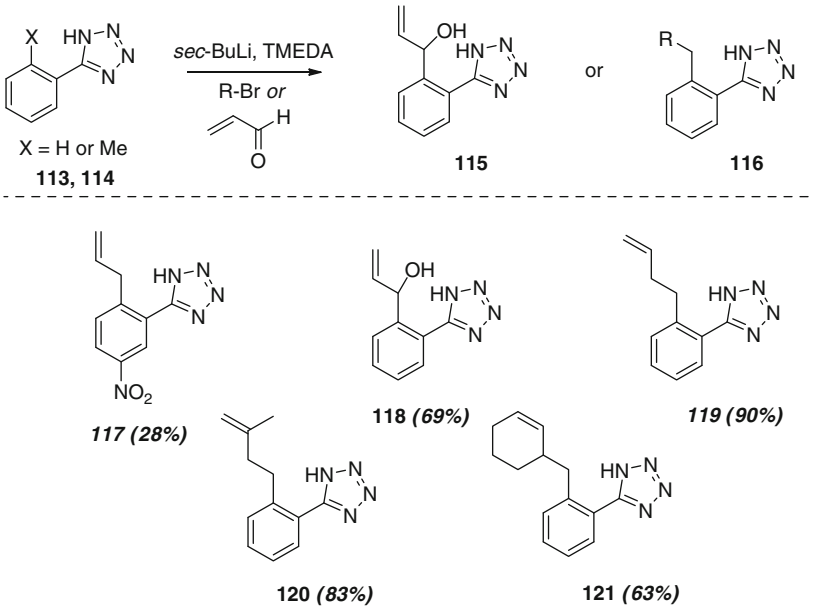
Scheme 13 Synthesis of a tetrazole boronic acid [43]

(Scheme 16). Aside from the *t*-butyl group, a variety of alkyl, cycloalkyl, aryl, and heteroaryl groups were successfully utilized while developing a series of human neutrophil elastase inhibitors [48].

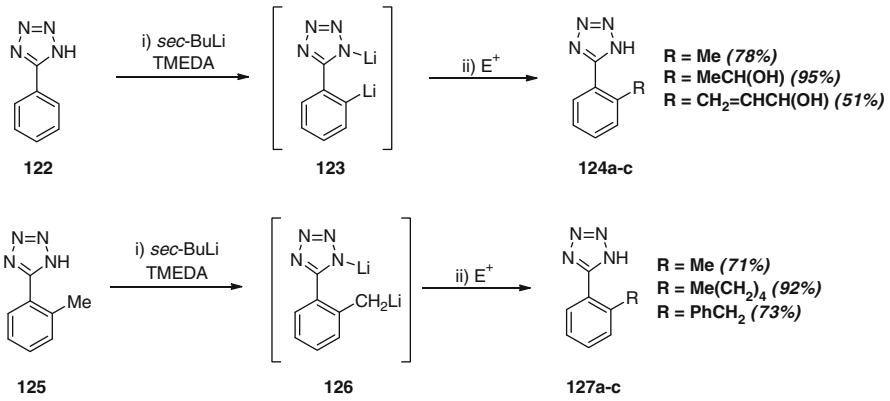
Rydzewski and coworkers utilized similar chemistry for the development of 2-keto-1,3,4-oxadiazoles as proteasome inhibitors [49]. Oxadiazole **131** was lithiated with *n*-BuLi/$MgBr_2$ and added to aldehyde **132**. The resulting adduct (**133**) was converted over a series of steps to inhibitor **134** (Scheme 17).

An impressive showcase of lithiated 1,3,4-oxadiazoles was reported by Shin and coworkers during the development of a kilogram-scale synthesis of *cis*-LC15-0133 tartrate (**137**) [50]. Oxadiazole **128** was lithiated on a 1.9 kg scale and added to Weinreb amide **135**; chiral ketone **136** was isolated in 67% yield (Scheme 18).

Knochel and coworkers have developed a series of chemoselective bases which have found many uses in functionalizing a wide variety of sensitive arenes and heteroarenes [51]. These metalation reactions have been run at scales as high as 50 mmol [52]. Two bases which have been used for azoles are $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**145**) and $(tmp)_4Zr{\cdot}4MgCl_2{\cdot}6LiCl$ (**146**). 2-Phenyl-1,3,4-oxadiazole was converted to

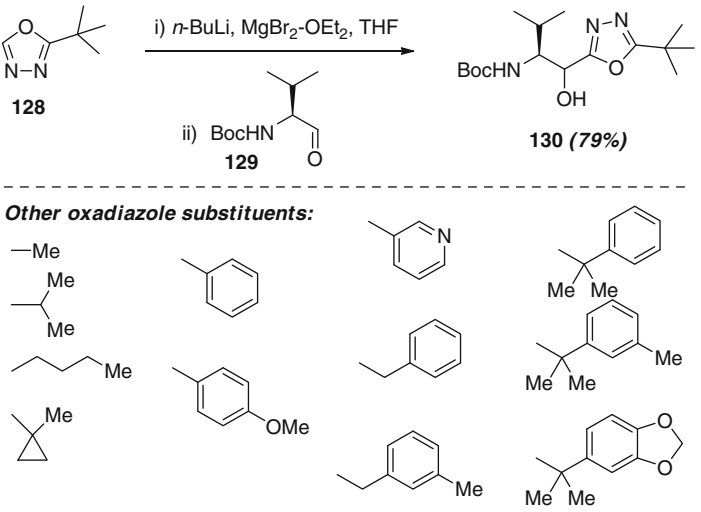


Scheme 14 Ortho lithiation of aryltetrazoles [44]

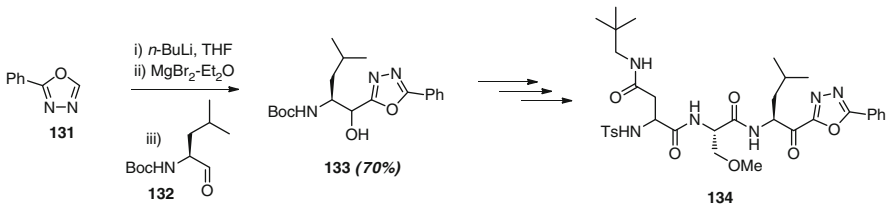


Scheme 15 Dilithiation of aryltetrazoles [45]

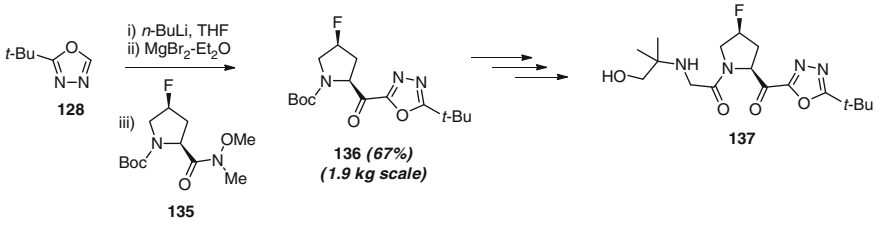
the C-5 zincate by treatment with **145**. Addition of $PhSSO_2Ph$ gave thioether **139** in 75% yield. Similarly, 1,2,4-triazole **140** was allylated by sequential treatment with **145** and allyl bromide [53, 54]. Zirconium base **146** was used to facilitate the allylation of 1,3,4-oxadiazole **131** in 79% yield (Scheme 19) [55].



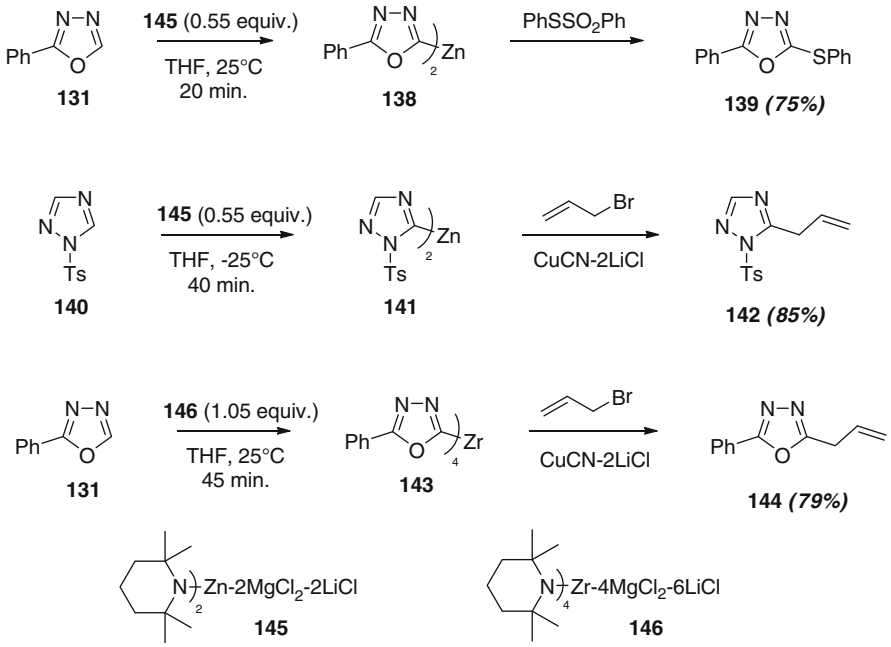
Scheme 16 Synthesis of a series of 1,3,4-oxadiazole-containing human neutrophil elastase inhibitors [48]



Scheme 17 Synthesis of 2-keto-1,3,4-oxadiazoles [49]



Scheme 18 Kilogram-scale synthesis of *cis*-LC15-0133 tartrate [50]



Scheme 19 Metalation with Knochel's $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ and $(tmp)_4Zr{\cdot}4MgCl_2{\cdot}6LiCl$ [53–55]

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Index

A
Addition reactions, 47, 307
Ageladine A, 6, 35, 97
Ajudazol A, 124
Alkenyldiarylmethanes (ADAMs), 297
Alkynes, electrophilic cyclization, 347
2-Amino-5-arylthieno[2,3-*b*]thiophenes, 353
2-Aminobenzophenones, 295
2-Amino-5-fluorothiazole, 312
Aminoimidazoazepines, 98
3-Amino-7-phthalazinylbenzoisoxazole derivatives, 299
2-Aminothiophenes, 349
Amythiamicin C/D, 308, 322
Apixaban, 157
Arylalkynyl-calix[4]pyrroles, 21
N-Aryl azoles, 3
5-Aryloxazoles, 131
Atorvastatin, 18
Axitinib, 158
Azoles, metalation, 415

B
Benzisothiazoles, metalation, 329
Benzisoxazoles, 261, 295
Benzofurans, boronated, 59
  magnesation, 52
  metalation/lithiation, 47, 50
Benzothiadiazole-based polymers, 19
Benzothiazoles, metalation, 307
Benzothiophenes, 347
Benzoxazoles, cross-coupling reactions, 134
  metalation, 103, 121
N-Benzyl-3,4-dibromopyrrole, 16
Bipinnatin J, Negishi coupling, 59
Bis(pyrrol-2-yl)arenes, 29
Bis(siloxy)butadienes, 262
Bixafen, 157
N-Boc pyrrole-2-boronic acid, 35
BODIPY dyes, 1, 21
Boronation, 323
2-Borylpyrrole, Suzuki–Miyaura coupling, 29
3-Bromobenzo[*b*]-5-aminothiophene carboxylic esters, 352
Bromooxazoles, 128
4-Bromo-2-phenylbenzofuran, lithium–bromide exchange, 52
4-Bromopyrrole-2-carboxylates, 26
3-Bromo-2-triisopropylsilyloxyfuran, 49
Butenolides, 49

C
Cadmium, 9, 57, 122
Calcium, 2, 19
Caldation, 320
Calix[4]pyrrole[2]carbazole, 19
Calixpyrroles, 19
Calyculin A, 103
Camptothecin, Kanazawa's synthetic route, 406
Carbazole, 19
Ceftizoxime, 308

Celecoxib, 156
Chettaphanin, 49
Chivosazole A, 103
Chlorantraniliprole, 157
5-Chlorobenzoxazoles, cross-coupling reactions, 135
p-Chloronitrobenzene, 5
Chlorooxazoles, 126
4-Chloro-2-phenylbenzofuran, nickel-catalyzed Kumada coupling, 56
3-Chloropyrrole, 17
3-Chloro-1-tosylpyrrole, lithiation, 13
p-Chlorotrifluoromethylbenzene, 5
ClickFerrophos ligands, 422
Copper thiophenecarboxylate (CuTC), 17
Cosopt, 348
Crizotinib, 157
Cross-coupling reactions, 1, 47, 103, 122, 155, 307, 381
  benzoxazole-based, 133
Cup-shaped molecules, 17
Cyano-bis(siloxy)butadiene, 262
7-Cyanoindazole, 246
Cyantraniliprole, 157
Cycloheptylprodigison, 37
Cystothiazole B, 316

D
Dasatinib, 308
Davis' oxaziridine, 275
Deracoxib, 157
Desbromoceratamine A, 98
Dialkylimidazole inhibitors, 298
Diaryl pyrrole, 30
Diazonamide A, 103
Dibromopyrroles, 32
Dibromothiazole, 317
Dicytodendrin B, 34
Diiododihydrothiophenes, 367
Diiodooxazoles, 117
Dilithioimidazoles, 94
Dimagnesioimidazoles, 94
4-Dimethylphenylsilylisoxazole, 272
Dipyrromethanes, alkylation, 15
Disorazole Z, 103
Dragmacidin F, 26
Duloxetine, 348

E
Enigmazole A, 123
Epothilone, 308
Ergot alkaloids, 123
Ethiprole, 157
3-Ethoxy-4-iodo-5-methylisoxazole, 271

F
Famotidine, 308
Fipronil, 157
Fluoride, 2, 19
Fluorous synthetic protocol, 347
Frondosin B, 68
Furans, boronated, 59
  magnesation, 52
  metalation/lithiation, 47, 50
2-Furylcerium, 68
Furylmethyl ethers, deprotonation, 51

G
Gabapentin bioisosteres, 432
GABA receptor ligands, 36
Galmic, 103
GE2270A, 308, 319
Gewald reaction, 347, 348
1-Glycosyl-1*H*-triazoles, 422
Gold catalysis, 381
Granisetron, 158
Grignard formation, 381, 415
Grignard reagent, 7, 261

H
Halitulin, 22, 39, 40
Halogen dance reaction, 307, 314
Halogen–metal exchange, 1, 261, 271
Haloindolizines, 41
Halooxazoles, 126
Heck coupling, 1, 23, 261, 278
Hennoxazole A, 126
Histamine, 78
Histidine, 79
HIV-1 non-nucleoside reverse transcriptase inhibitors, 297
Hiyama reaction, 261, 282
Homocarbonyltopsentine, 99

I
IB-01211, 104
Ibotenic acid, 333
Imidazoles, metalation/lithiation, 77, 81
Imidazolium salts, 80
Imidazolylidene carbenes, 80
Indazoles, metalation, 155
  N-alkylation, 162
  N-arylation, 164
  N-vinylation, 180
Indolizine-5,8-diones, 2
Indolizines, metalation, 1
  Suzuki reaction, 41
Iodine/magnesium exchange, 271
4-Iodoanisole, 5
Iodobenzene, 5
2-Iodobenzothiazole, 320
Ionic liquids, 80, 174
Isoindoles, 25
Isomünchnones, metalation, 381, 404
Isonitrile esters, unsaturated, 117
Isopyrazam, 157
Isothiazole, metalation, 329
Isoxazole, metalation, 261
Ixabepilone, 308

K
Kabiramide C, 104

L
L-869, 298, 312
Lamellarins, 12, 16, 22
Leiodelide B, 104
Leucascandrolide A, 104, 129
Levovirin, 426
Linifanib, 158
Liphagal, 48
Lithiation, 1, 11, 47, 77, 261, 381, 415
2-Lithio-3,4-bistrimethylsilylpyrroles, 11
2-Lithiofuran, retro-Brook rearrangement, 52
Lithioimidazoles, 81
Lithium–halogen exchange, 92
Lukianol A, 32

M
Magnesation, 47, 52, 77, 307, 315, 325
Magnesium, 17, 381
Magnesium dibenzofuranylboronate, Suzuki–Miyaura coupling, 55
Magnesium–halogen exchange, 92
Marinopyrrole A, 6
Mesoionics, metalation, 381
Metalation, directed, 1, 261
Metal–halogen exchange, 16
4-Methoxy-2,2'-bipyrrole-5-carboxyaldehde, 37
2-(4-Methoxyphenyl)sulfinyl-5-trimethylsilylfuran, magnesation, 54
Methyl 5-bromofuran-2-carboxylate, 54
N-Methyl pyrrole, 10
Molybdenum, 265
Münchnone imines, 402
Münchnones (1,3-oxazolium-5-olates), metalation, 381, 399
Mycalazal 2, 18
Mycalolide, 104

N
Negishi coupling, 1, 22, 261, 282
Neooxazolomycin, 104
Neopeltolide, 104
Ningalin B, 34
2-Nitrobenzofuran, zincation, 56

O
Organocadmium reagents, 9
Organosilanols, 42
Organotrifluoroborates, 37
Oscarella lobularis, 16
Oxabicyclic tetrazoles, 431
8-Oxabicyclooctane, 18
Oxadiazoles, metalation, 415, 433
Oxamünchnones, 407
Oxazole carboxylic acids, 131
Oxazole, metalation, 103
Oxazole sulfides, 131
Oxazole triflates, 129

Oxazolines, 136
  oxidation, 110
Oxazolinethiones, 132
Oxazolylborons, cross-coupling reactions, 125
Oxazol-4-yltriflates, 130
Oxazolyl zincs, 123

P

Paal-Knorr cyclocondensation, 347, 356
Palladium, 1, 18, 42, 99, 111, 133, 261, 365, 401
Pazopanib, 158
Pd-PEPPSI-IPent, 20, 58
Penflufen, 157
Peptidomimetics, 352
Permethylstorniamide A, 27
3-Phenylbenzofuran, dilithiation, 51
2-Phenyloxazoles, asymmetric hydrogenation, 136
N-Phenylpyrrole, 9
N-Phenylsulfonyl-3,4-dibromopyrrole, 30
3-Phenylsulfonylpyrroles, 14,
Phorboxazole A, 130
Phorboxazole B, 104
Phosphodiesterase-4 (PDE4) inhibitor, 312
Phosphoinositide-3-kinase α inhibitor, 48
Pinacolboranate ester, 39
p38 mitogen-activated protein kinase (MAPK) inhibitors, 299
Polycitones, 28
Polyheterocyclic compounds, 367
Pregabalin, 428
Progesterone receptor modulators, 36
Proton abstraction, 1
Pyrasulfotole, 157
Pyrazole-5, 158
Pyrazoles, metalation, 155
  N-alkylation, 159
  N-arylation, 164
  C-metalation, 183
  N-vinylation, 180
Pyrrole boronic acids/esters, 35
Pyrrole pinacolboranate ester, 39, 41
Pyrroles, diarylation, 30
  metalation, 1
  mono-arylation, 26
  palladium cross coupling, 18
Pyrrolidinylmethylimidazole, 4
Pyrrolnitrin, 39
Pyrrolo[1,2-*a*][4,1]benzoxazepine, 12
Pyrroloisoquinolines, 25
Pyrrol-2-yl-boronic acid, 36
Pyrrolyl Grignards, 7
Pyrrolyl triflates, 34
Pyrrolyl zinc bromide, 10
Pyrrolyl zinc chlorides, 23

R

Regadenoson, 157
Reloxifen, 348
Rhaziniliam, 25
Rhizoxin D, 104
Rigidin, 28
Ritonavir, 308
Roseophilin, 13
Ruxolitinib, 157
Rynaxypyr, 183

S

Salvileucalin B, 48
Sedaxane, 157
Serotonin selective uptake inhibitors, 18
Silylation, 13, 49, 105, 324
Sodium dimethyl(2-furyl)silanolate, 62
Sonogashira coupling, 1, 21, 261, 279
Stannylation, 317
Stannyl pyrroles, 18
Steglich synthon, 28
Stilbenzylpyrrole, 18
Stille coupling, 1, 18, 261
Storniamide, 30, 34
Styrylfurans, lithiation, 50
Sulfur-assisted synthesis, 347
Suzuki coupling, 1, 34, 261, 283
  halopyrroles, 26
Sydnone imines, 395
Sydnone *N*-oxides, 397
Sydnones, metalation, 381, 383

T

Tartrazine, 158
2-TBS-3-formylfuran, 51
Telomestatin, 104
Tetrazoles, metalation, 415, 428
Tetrazolo[1,5-*a*]-α-cycloalkanones, 428

Thiazoles, metalation, 307
Thiazol-5-ylboronic acid pinacol ester, 323
Thieno[3,2-*b*]furan, lithiation, 71
Thioethers, 43
Thioibotenic acid, 333
Thioisomünchnones, 407
Thiophenes, 13, 123
  direct arylation, 347, 368
Thiostrepton, 308
Tiotropium, 348
Titanium, 265
Triaryl α-helix mimetics, 420
Triazoles, metalation, 415
Tributylstannyl isoxazoles, 176
Tributylstannyloxazoles, 123
Trypanosama cruzi lanosterol-14α-demethylase (L14DM), 298

U
Ulapualide A, 104

V
Verrucarin E, 16

W
Willgerodt-Kindler reaction, 347, 354
WS75624B, 314, 319

Z
Zaleplon, 157
Zinc, 9
Zincation, 46, 56, 236, 320, 326, 390