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Metalated Heterocycles and Their Applications in Synthetic Organic Chemistry

Rafael Chinchilla,* Carmen Nájera,* and Miguel Yus*

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Universidad de Alicante, Apartado 99, 03080 Alicante, Spain

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Contents

* To whom correspondence should be addressed. Phone: +34 965903548. Fax: +34 965903549. E-mail: chinchilla@ua.es (R.C.); cnajera@ua.es (C.N.); yus@ua.es (M.Y.). URL: www.ua.es/dqorg.

1. Introduction

The presence of heterocyclic moieties in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is sufficiently known to deserve more comment.[1] Among all the possible ways of introducing a heterocyclic moiety into a more complex structure, the use of an organometallic formed by metalation of a heterocycle is probably one of the most direct.[2−4] Epecially in the last several years, the use of transition metals, particularly palladium, as catalysts for achieving coupling reactions which involve metalated species has increased the use of heterocyclic organometallics in all kinds of organic transformations.[2−4]

This review deals with heterocyclic systems applicable to organic synthesis where the presence of a carbon−metal bond can be found; therefore, metalated species where the metal atom can be more appropriately situated near a more electronegative atom, generally after metalation α to a delocalizing functionality, such as a carbonyl, imine, sulfone, and so on, are excluded. Since this review can be considered a rather practical tool, only metalated heterocycles which have found applicability in synthesis will be considered, organometallics prepared for theoretical or mechanistic considerations being excluded. In addition, transient metalated species forming part of a catalytic cycle or metallacyles will also not be considered.

The review is organized by the type of metal and subdivided by the type of metalated heterocycle, including methods for their preparation and their synthetic uses, although other possible divisions may have been considered. For example, another suitable classification for such a wide topic could have been based on reaction type. Thus, considering the most important methodologies leading to metalated heterocycles, a suitable classification for their preparation could be (Figure 1) as follows. (a) *Dehydrometalations*: For this reaction to proceed, the acidity of the generated R−H from R−M should lower that of Het−H. This is a very direct method being used mainly

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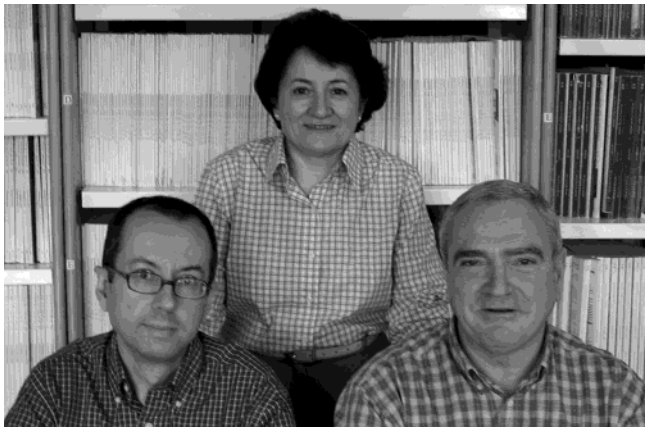


Rafael Chinchilla (left) was born in Alicante and graduated in chemistry (1985) and obtained his doctorate (1990) from the University of Alicante. After a period (1991–1992) at the University of Uppsala, Sweden, as a postdoctoral fellow, he moved back to the University of Alicante, where he was appointed Associate Professor in 1997. His current research interest includes asymmetric synthesis, amino acid and peptide synthesis, and solid-supported reagents.

Carmen Nájera (middle) was born in Nájera (La Rioja) and graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979 under the supervision of Profs. J. Barluenga and M. Yus. She spent postdoctoral stays with Prof. D. Seebach at the ETH (Zurich), Prof. J. E. Baldwin at the Dyson Perrins Laboratory (Oxford), Prof. E. J. Corey at Harvard University, and Prof. J.-E. Bäckvall at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and full Professor in 1993 at the University of Alicante. She is coauthor of more than 160 papers and 15 reviews. Her current research interest is focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis, peptide coupling reagents, solid-phase synthesis, asymmetric catalysis, and palladium catalysis.

Miguel Yus (right) was born in Zaragoza in 1947. He received B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoc at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo, where he became Associate Professor in 1977, being promoted to full Professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante. Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities at Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris VI, and Strasbourg. He is a member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland, and United States. He is coauthor of more than 300 papers mainly in the fields of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry, the use of active metals, and asymmetric catalysis. Among others, he has recently received the Spanish-French Prize (1999), the Japan Society for the Promotion of Science Prize (2000), and the Stiefvater Memorial Lectureship Award (2001). He belongs to the advisory board of the journals *Tetrahedron*, *Tetrahedron Letters*, and *European Journal of Organic Chemistry*.

(but not exclusively) for the preparation of heterolithiums employing lithium alkyls. (b) *Dehalometalations*: This is a metal−halogen exchange methodology also used mainly for organolithiums, being a rather fast reaction favored at low temperatures (kinetic control). The reaction is shifted to the right if Het is superior to R in stabilizing a negative charge, therefore being especially suitable for aryl halides (X = I, Br, rarely Cl, almost never F). (c) *Transmetalations*: The reaction lies on the side of the products if M^1 is more electropositive than M^2. As usual, M^1 = Li, heterocyclic organolithiums being considered a gate to many other organometallics. (d) *Oxidative additions*: The generation of M−C bonds

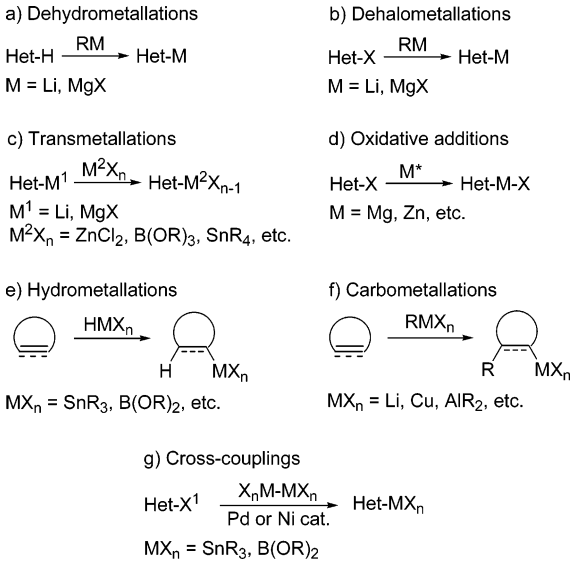


Figure 1.

by means of the addition of R−X to a metal such as Mg is an old procedure, although not so frequently used for heteroaromatics due to problems related to the presence of basic nitrogens, some "active" metals (M*) usually being employed. (e) *Hydrometalations*: This reaction is essentially the addition of M−H across a double bond, and can be used for the preparation of organometallics with less electropositive metals such as B or Si. (f) *Carbometalations*: In contrast with the previous M−H, insertions into M−C bonds proceeds if M is rather highly electropositive. (g) *Cross-couplings:* Similarly to the C−C bond-forming reactions promoted by transition metals, heterocyclic tin or boron derivatives can be obtained from heterocyclic halides and ditin or diboron reagents under mainly palladium catalysis. Even considering the former classification, we have preferred to divide this review by metals because it can be considered a more instructive way for connecting them and their reactivity.

The literature covered by this review begins mainly in 1996 because previous years have been comprehensively compiled, although older works can be commented on if necessary.[1a] However, in the case that some reviews on particular related topics have been more recently published, only the literature after them will be considered.

2. Group I Metal-Containing Heterocycles

2.1. Lithium Heterocycles

Organolithiums are beyond any doubt the most useful metalated heterocycles. Usually they are prepared by direct deprotonation[5,6] of acidic hydrogens using strong bases or, particularly useful in the case of the less acidic sites in aromatic rings, by halogen exchange[5,7] between a halogenated heterocycle and an organolithium compound or lithium metal. Another frequent alternative is the so-called *ortho*-lithiation or "directed *ortho*-metalation" (DoM), which is the metalation of an aromatic ring adjacent to a heteroatom-containing functional group by providing the lithium base with a point of coordination,

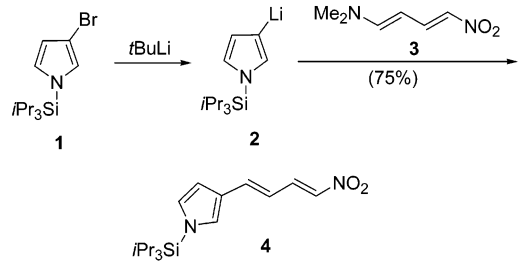
thus increasing reactivity close to the coordination site.[6,8] The lithiated species generated by all these methods are able to react with all kinds of electrophiles,[5−9] also being a source of a huge array of other metalated heterocycles from less electropositive metals.

2.1.1. Aromatic Five-Membered Rings

As a rule of thumb, the electron-rich five-membered aromatic heterocycles *N*-substituted pyrrole, furan, and thiophene are lithiated at C-2 by direct deprotonation with a lithium-containing base, whereas the lithiation at C-3 is achieved generally by a halogen (bromine or iodine)−lithium exchange by means of an alkyllithium, the lithiation agent usually being *n*-, *sec*-, or *tert*-butyllithium, although LDA has also been employed.

As mentioned, the 2-position of heteroaromatics such as *N*-substituted pyrroles is the easiest to deprotonate by a base and, therefore, to functionalize. Lithiated *N*-alkylpyrroles are sufficiently nucleophilic to attack even highly hindered carbonyl groups such as in di(1-adamantyl) ketone,[10] or in camphor or fenchone.[11] There are also examples of directed lithiation of *N*-methylpyrrole, as well as furan, thiophene, and *N*-methylindole, bearing carboxamido and carboxylic acid functions.[8b] In addition, examples of the synthetic use of the halogen−lithium exchange methodology can be found in the condensation reaction of the 3-lithiated pyrrole **2** [prepared from 3-bromo-*N*-(triisopropylsilyl)pyrrole (**1**)] with the nitrodienamine **3**, to give pyrrole derivative **4** (Scheme 1).[12] Moreover, 2,5-dibrominated pyrroles have been

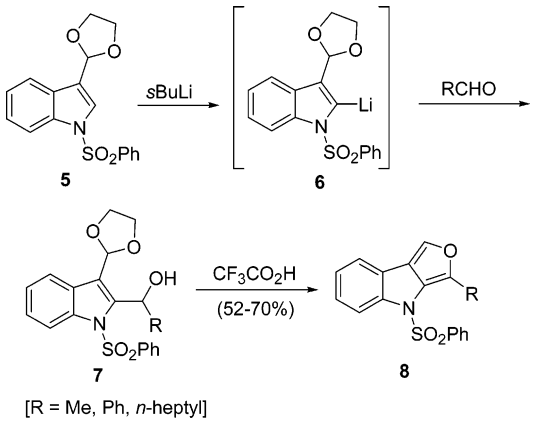
Scheme 1



used for consecutive 2,5-dilithiation and reaction with electrophiles, examples being the synthesis of pyrrole−sulfur oligomers[13] and the total synthesis of the antitumor marine sponge metabolite agelastin A.[14]

Indoles are directly lithiated at either C-2 or C-3 according to the *N*-substitution. Thus, the presence of a nonbulky alkyl or a coordinating group at the nitrogen atom drives the lithiation at C-2, whereas bulky noncoordinating groups, such as the triisopropylsilyl group,[15] direct the lithiation at C-3. Examples of the use of nucleophilic indolyllithiums are frequent, because the indole framework has been widely accepted as a pivotal structure in numerous natural products and medicinal agents.[16] Thus, indol-2-yllithiums have been used recently in different reactions such as epoxide ring openings[17] or additions to carbonyl compounds[18] as in the reaction shown in Scheme 2, where acetal **5** is lithiated at C-2 using *s*BuLi and reacts with aldehydes to give furo[3,4-*b*]-indoles **8** after acid treatment, intermediates **6** and

Scheme 2

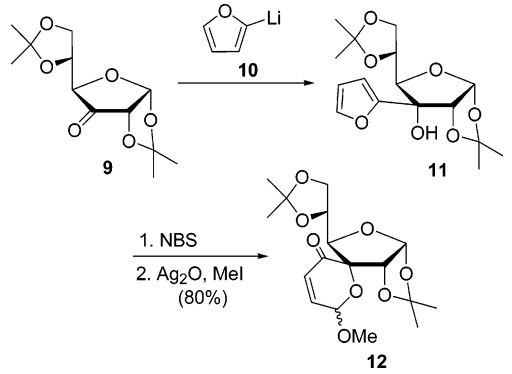


7 probably being involved in the process.[19] There are also recent reports on the reaction of 2-lithiated indoles with elemental sulfur for the formation of pentathiepinoindoles,[20] or with dinitrogen tetroxide for the synthesis of 2-nitroindoles.[21]

2-Lithioindoles have also been generated by halogen−lithium exchange,[22] also being generated selectively from 2,3-dibromo-*N*-methylindole, which allows the regioselective synthesis of 2,3-disubstituted indoles after a sequential 3-bromine−lithium exchange.[23] In addition, 3-lithioindoles with a trialkylsilyl *N*-protection have been frequently prepared by bromine−lithium exchange using *tert*-butyllithium,[24] although with some stabilizing *N*-protecting groups, such as phenylsulfonyl, very low temperatures are necessary to avoid rearrangement to the more stable intermediate lithiated at the 2-position.[25] These 3-lithioindoles have been recently used in the synthesis of different *N*-isoprenylindole alkaloids by reaction with methyl chloroformate,[26] with *N*-tosylimines, generating aminomethylindoles,[25] and with epoxides and aziridines.[27] Similarly, lithiated deazapurines have also been used in the addition to cyclic imines for the synthesis of the purine nucleoside phosphorylase (PNP) inhibitors immucillins.[28]

The introduction of the furan moiety into a system has a particular interest, not only for the activity of the furan ring on its own, but also due to the variety of useful functional groups which can be obtained through a one- or two-step procedure from the heterocycle.[29] Therefore, lithiation of the furan system followed by using the lithiated species as a nucleophile has been a frequently employed synthetic method. Thus, 2-lithiofurans prepared by direct deprotonation have been used in the last several years in alkylation reactions for the synthesis of (+)-patulolide,[30] (−)-pyrenophorin,[31] (+)-aspicilin,[30b] and arachidonic or linoleic esters of 2-lysophosphatidylcholine.[31] In addition, they have been employed in addition reactions to aldehydes in alaninals,[32] to benzaldehyde for the synthesis of oxyporphyrin building blocks using 2,5-dilithiated furans,[33] and to dialdoses[34] and other aldehydes for the synthesis of some natural products.[35] Different ketones have been used as electrophiles, such as cyclobutenones,[36] the glucofuranoulose **9** for the preparation of pyranosides **12** [after reaction with **10** and oxidative ring opening of the furan ring in derivative **11** with *N*-bromo-

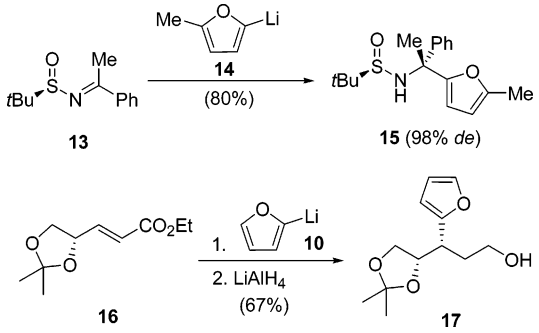
Scheme 3



succinimide (NBS) and final methylation] (Scheme 3)[37] and in the synthesis of polyquinane ring systems,[38] diterpene skeletons,[39] or diarylanthrones.[40] Moreover, other ketones have been used, as in studies toward the total synthesis of zaragozic acid[41] or the preparation of quinuclidinone analogues.[42]

2-Lithiofurans have also been added to the carbonyl group of isoxazol-5-ones to give isoxazoles,[43] to the carbonyl group of mannonolactones,[44] to imines,[45] or to chiral sulfinyl ketimines such as compound **13**, affording the furan derivative **15**, after treatment with the intermediate **14**, being subsequently oxidized to a carboxylate functionality to give protected α,α-disubstituted amino acids such as, in this case, butylsulfinyl-protected α-methylphenylglycine (Scheme 4).[46] In addition, examples of the reaction of 2-furyl-

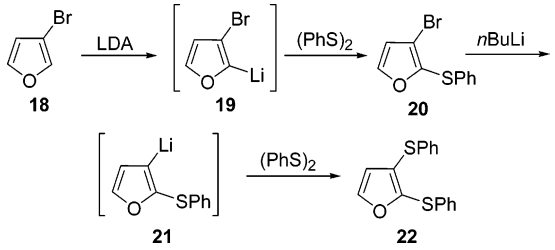
Scheme 4



lithiums such as **10** with lactones,[47] amides[48] including Weinreb amides,[49] nitrones,[50] and α,β-unsaturated esters have been reported, that in the case of D-(−)-mannitol-derived ester **16** affords the Michael addition adduct (>20:1 dr), which gives the alcohol **17** after reduction (Scheme 4).[51] Moreover, 5-bromo-2-lithiofuran, prepared from 2,5-dibromofuran by bromine−lithium exchange, has been employed for the addition reaction to an aldehyde in a synthesis of the marine metabolites eleuthesides.[52] Furthermore, silicon−lithium exchange using LDA has also been used as a way of generating bromine-substituted 2-furyllithiums, which have been used for the synthesis of *C*-aryl glycosides.[53]

As mentioned, 3-lithiofurans are mainly prepared by reaction of 3-halogen (frequently bromine)-substituted furans with an alkyllithium. A recent example showing the selectivity in the lithiation of 3-bromofuran using this methodology, together with *ortho*-lithiation, is shown in Scheme 5, where 3-bromo-

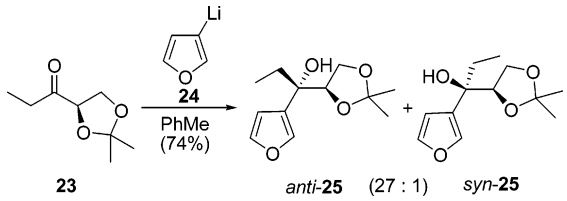
Scheme 5



furan (**18**) is lithiated preferentially at C-2 using LDA to give intermediate **19**, which reacts with diphenyl disulfide, affording (phenylsulfanyl)furan **20**, which suffers bromine−lithium exchange using *n*-butyllithium, affording 2,3-bis(phenylsulfanyl)furan (**22**) through intermediate **21**.[54] Other examples starting from 3,4-dibromofuran and also using LDA as base for *ortho*-lithiations and an alkyllithium for a bromine−lithium exchange have been reported,[55a] as in the case of the synthesis of dopamine D1-selective agonists.[55b]

3-Lithiofurans have been used as nucleophiles, as can be seen in recently reported additions to aldehydes, as in the synthesis of the tetracyclic decalin part of azadirachtin[56] and cyclic terpenoids,[57] or to ketones, as in the reaction between 3-furyllithium (**24**) and the chiral pentanone **23** in studies toward the synthesis of marine natural products plakortones. The reaction shows a high dependence of the solvent, toluene affording the *anti*-diastereomer **25** as the major one (Scheme 6), whereas when the addition is

Scheme 6

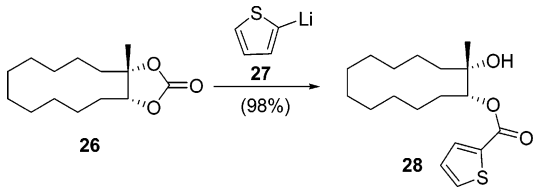


performed in diethyl ether the *syn*-isomer is predominantly obtained.[58] Moreover, addition to lactones[51] and (η^3-dihydropyridyl)molybdenum complexes[60] and formylation reactions have also been reported.[61]

2-Lithiated thiophenes have found frequent applications reacting as nucleophiles, for example, with aldehydes in the synthesis of core-modified porphyrins[62] or azanucleosides,[63] and with ketones for the synthesis of bithiophene-containing calixpyrrole analogues,[64] sulfur-containing heteroaromatics,[65] angular triquinanes,[38b] heteroaryl-substituted zirconium complexes,[66] or some carboranylbutenolides.[36] There are also examples of reactions of 2-thienyllithiums with esters,[67] amides[68] (including Weinreb amides[69]), the carbonyl group of 2-pyrrolidinones,[70] the Vilsmaier reagent,[71] and carbon dioxide[72] or the regioselective synthesis of esters by addition of the organolithium **27** to cyclic carbonates such as compound **26**, which affords the corresponding ester **28** as the only isomer, used in studies on taxoids (Scheme 7).[73]

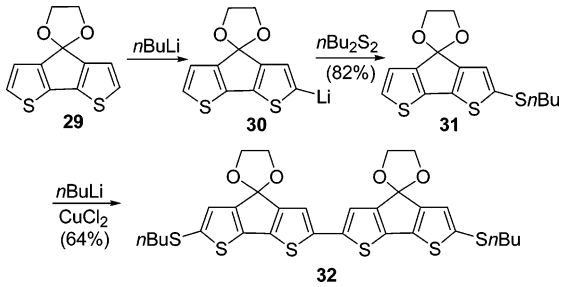
Thiophene oligomers are among the most promising organic materials for electronic and electrooptical uses,[74] numerous methodologies being developed to achieve their preparation. Thus, the copper-mediated

Scheme 7



coupling reaction of the methyl ester of 2-bromothiophene-3-carboxylate,[75] by LDA-promoted deprotonation at C-2 and bromination, affords 3-substituted bithiophenes. Another example is the synthesis of compound **32** by the copper-promoted oxidative coupling of dithiophene **31**, prepared from **29** by lithiation to give **30** and further reaction with dibutyl disulfide (Scheme 8).[76] Moreover, related poly[bis(2-

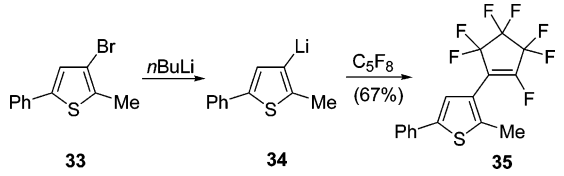
Scheme 8



thienyl)ethenes] have also been obtained.[77] In addition, 2-thienyllithiums have been used in other transformations, such as reactions with dinitrogen tetroxide,[78] with pyrylium salts for the synthesis of polyenes,[79] and with ammonium thioate inner salts,[80] as well as for the synthesis of diphosphathienoquinones,[81] diphenylphosphino derivatives of bi- and terthiophene,[82] and dyes such as tris-(2-thienyl)-methinium perchlorate.[83]

As mentioned above, 3-thienyllithiums are normally generated by alkyllithium-promoted halogen (mainly bromine)−lithium exchange. An example of their generation and synthetic use is the reaction of the 3-lithiothiophene **34**, prepared from bromothiophene **33**, with perfluorocyclopentene, which affords the thiophene derivative **35**, which has been used for the preparation of novel photochromic compounds (Scheme 9),[84a] other thiophenes also being

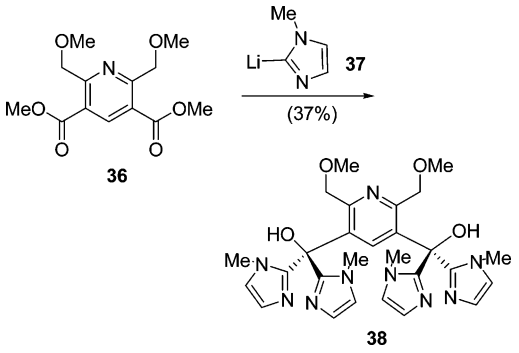
Scheme 9



used with this methodology.[84b] Recent examples of reactions of 3-thienyllithiums with tosyl azide for the synthesis of 3-azidothiophenes[85] or with ethyl chloroformate for the synthesis of thiophene linkers[86] have also been reported.

1,3-Azoles tend to lithiate at C-2, but if this position is already occupied, lithiation occurs at C-5. When a C-4-metalation is required, usually the halogen−lithium exchange methodology is employed, the combination of all these techniques allowing the selective lithiation at any position in the azole nucleus, even in azaindolizines with bridgehead nitrogen such as imidazo[1,2-*a*]pyrazines. 2-Lithiated *N*-substituted imidazoles such as 2-lithio-*N*-methylimidazole (**37**), prepared by direct deprotonation using *n*-butyllithium, have been recently used in reaction with a diester such as compound **36** for the preparation of ligands for zinc catalysts such as compound **38** (Scheme 10).[87b] Interestingly, this organolithium has

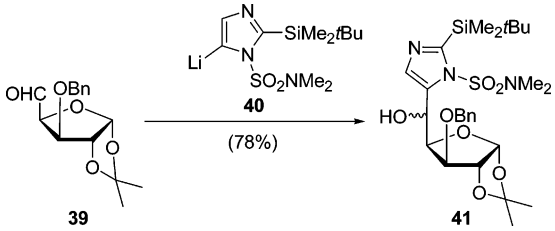
Scheme 10



been employed as a base in chiral lithium amide-catalyzed deprotonations.[88] Other 5-substituted lithiated analogues have also been used in the construction of ligands for mimics of cytochrome C oxidase[89] or copper-promoted dimerization reactions for the formation of oligoimidazoles.[90]

As mentioned above, 5-lithioimidazoles can be generated by direct deprotonation with an alkyllithium if the C-2-position of the ring is blocked. When the substituent at C-2 is a trialkylsilyl group, introduced previously by deprotonation and reaction with a trialkylsilyl halide, lithiation at C-5 occurs and the silyl group can be easily removed once the reaction with the electrophile at C-5 takes place. Examples of the use of these 2-silylated imidazol-5-yllithiums can be found in the synthesis of imidazolosugars,[91] which are potential glycosidase inhibitors, and in the reaction between the lithium species **40** and dialdofuranose **39** to afford the furanose **41** (Scheme 11).[91b] This silylated lithium intermediate

Scheme 11



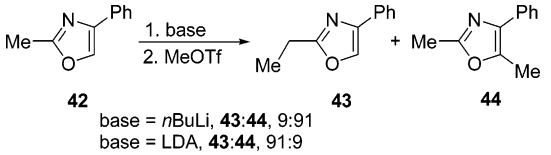
40 has also been used in additions to aldehydes for the synthesis of histamine H_3 agonists[92] or nucleosides.[93] Following this methodology, 5-lithio-*N*-methyl-2-(triethylsilyl)imidazole has been employed for the synthesis of the marine alkaloid xestomanzamine A.[94]

As in the case of any 1,3-azole, oxazoles are readily lithiated at C-2.[95a] However, attemps to trap 2-lithioxazoles with electrophiles must contend with compli-

cations due to the ring opening of the anion to produce an enolate which recloses after the *C*-electrophilic attack, therefore affording mixtures of C-2- and C-4-substituted oxazoles.[95] In this electrophilic ring opening, solvent locks the electron pair at the oxazole nitrogen by complexation with a Lewis acid such as borane, thus allowing C-2-lithiation.[96]

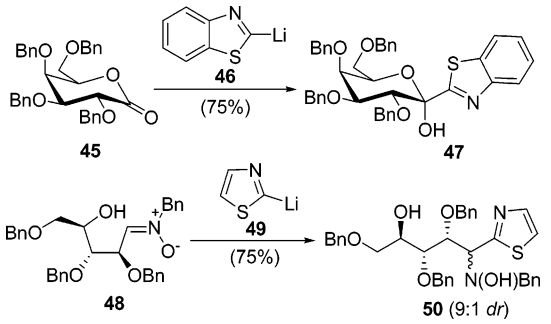
In C-2-substituted ozaxoles, direct C-5-lithiation can be carried out, allowing further reaction with electrophiles,[97a] although the bromine−lithium exchange methodology has also been used.[97b] It is remarkable that, in C-2-methylated C-4-substituted imidazoles such as **42**, a selectivity for lithiation at C-5 to give compound **44**, versus lithiation at the methyl group to give compound **43**, has been observed depending on the lithium base (Scheme 12).[98a] 5-Lithiation of 2-substituted oxazoles has also been achieved by *ortho*-lithiation to a triflate group.[98b,c]

Scheme 12



2-Lithiothiazoles have been used as nucleophiles, the thiazole moiety being considered as a formyl equivalent,[99,100] for example, in addition reactions to lactones as well as in the synthesis of antimalarial trioxane dimers.[101] Benzothiazole has also been used as a formyl equivalent, and has been added to galactonolactone **45** as 2-lithiobenzothiazole (**46**) (Scheme 13)[102] in saccharide chemistry (for instance,

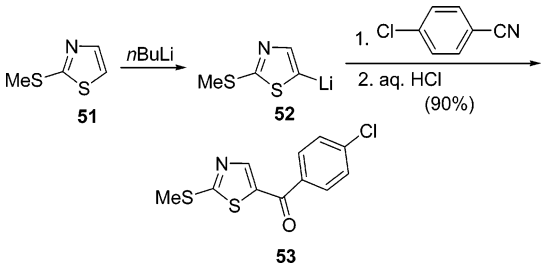
Scheme 13



to give compound **47**), with some advantages related with the easy crystallinity of the products. In addition, 2-lithiothiazole has been used in reactions with nitrones for the synthesis of amino sugars,[50,100,103] as in the reaction between nitrone **48** and 2-lithiothiazole (**49**) to give a diastereomeric mixture of *N*-benzylhydroxylamines **50** (Scheme 13).[103b] Furthermore, there are also examples of the use of 2-lithiothiazole in addtions to imines,[104] and in reactions with Weinreb amides.[49b]

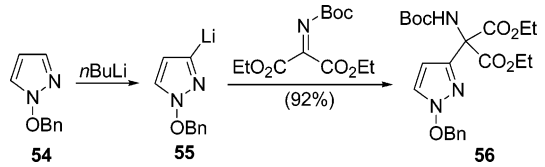
Lithiation at the C-5-position in thiazoles takes place directly if the C-2-position is blocked, an example being the lithiation of 2-(methylthio)thiazole (**51**) to give intermediate **52**, which can react further with a nitrile such as *p*-chlorobenzonitrile, affording 5-(arylcarbonyl)thiazole **53** after hydrolysis (Scheme 14).[105] However, 4-lithiated thiazoles have been generated usually by bromine−lithium exchange, a recent example of their use being the synthesis of some photochromic dithiazolylethenes.[106]

Scheme 14



N-Substituted pyrazoles can be directly lithiated at C-3 using alkyllithiums,[107a] a recent example being the deprotonation of *N*-benzyloxypyrazole (**54**) and the further reaction of the lithiated intermediate **55** with diethyl *N*-Boc-iminomalonate (Boc = *tert*-butoxycarbonyl) as an electrophilic glycine equivalent for the subsequent synthesis of *N*-hydroxypyrazole glycine derivatives such as compound **56** (Scheme 15).[107b] Moreover, different electrophiles have been introduced in the 4-position of *N*-substituted pyrazoles via bromine−lithium exchange.[108]

Scheme 15



The lithiation of isoxazoles[109] and isothiazoles[110a] at C-3 by deprotonation leads to ring-opening reactions, direct lithiation to the next more acidic C-4-position being possible if a substituent is already at C-3.

Another use of lithiated azoles is the generation of carbene complexes. Thus, heterocyclic carbene complex formation can be achieved by transmetalation of lithioazoles by means of a variety of transition-metal complexes followed by protonation or alkylation.[110b]

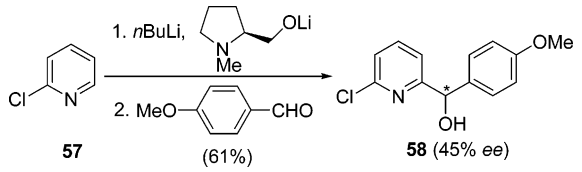
2.1.2. Aromatic Six-Membered Rings

Electron-deficient six-membered aromatic heterocycles can be deprotonated with lithium amides, whereas alkyllithiums, frequently used for five-membered heteroaromatics, prefer addition to the electron-deficient ring over deprotonation. Even the lithiated ring is able to attack the starting heterocyle, giving rise to coupling products. Alkyllithium-sensitive heterocycles such as pyridines can be deprotonated at C-2 using a "superbase" created by association of *n*-butyllithium and lithium diethylamino ethoxide (LiDMAE) in an apolar solvent, which increases the basicity/nucleophilicity ratio of *n*-butyllithium.[111] Moreover, 2-hetero-substituted pyridines, such as chloropyridine, which reacts with alkyllithiums, leading to the loss of the chlorine atom, and with LDA, affording *ortho*-metalation, can be metalated at the unusual C-6 position using this combination.[111a,112] As the most stable pyridinyllithi-

ums are those bearing the lithium atom at C-3 or C-4, due to the destabilizing effect of the lone pair of the nitrogen on an anion formed at the adjacent carbon, this selectivity to C-2 using this superbase arises by the formation of a stabilized complex beween LiDMAE and 2-pyridinyllithium.[111,113] The C-2-lithiation of 3- and 4-chloropyridines,[114] 2-phenylpyridine,[115a] and 3,5-lutidine[115b] has also been recently studied using this base.

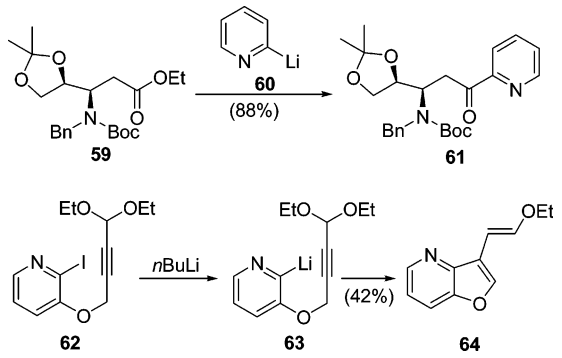
Chiral aminoalkoxides have also been used for the formation of the superbases. Thus, the combination of *n*-butyllithium and lithium (*S*)-*N*-methyl-2-pyrrolidine methoxide promotes not only the regioselective C-6-lithiation of pyridines, but also the asymmetric addition to aldehydes, as in the case of the lithiation of 2-chloropyridine (**57**) and further reaction with *p*-methoxybenzaldehyde, affording the final alcohol **58** in 45% ee (Scheme 16).[116]

Scheme 16



Due to the mentioned problems related to the addition of alkyllithiums to pyridines, the most simple unsubstituted pyridinyllithiums are generated normally by halogen−lithium exchange. Thus, 2-lithiopyridine is obtained usually by treatment of 2-bromopyridine with *n*-butyllithium at low temperature, although naphthalene-catalyzed lithiation on chloropyridine has also been used.[117a] The lithiated species have been used frequently as nucleophiles, for example, in addition reactions to aldehydes in nucleoside chemistry,[117b,118] or to ketones in (+)-camphor, (−)-fenchone,[11] or (+)-isomenthone derivatives.[119] 2-Lithiopyridine has also been used to obtain tris(2-pyridyl)carbinol by addition to bis(2-pyridyl) ketone,[120] as well as bis(2-pyridyl)carbinols by reaction of 2 equiv of the organolithium with esters,[121] whereas only attack of 1 equiv of an organolithium such as **60** has been observed in the reaction with the chiral *β*-amino ester **59** to give the ketone **61** (Scheme 17).[67a]

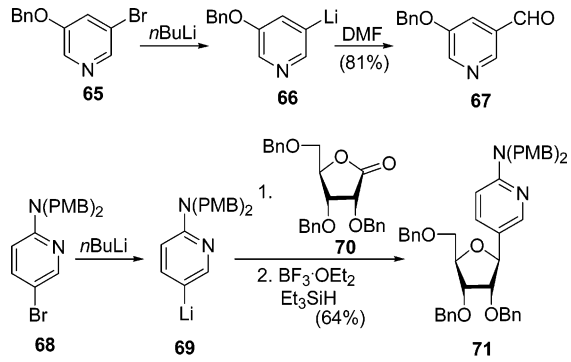
Scheme 17



Furthermore, there are examples of opening of cylic carbonates for the synthesis of taxoids,[73] additions to chiral *tert*-butylsulfinimines,[122] or the synthesis of vinylfuro[3,2-*b*]pyridines such as compound **64**, prepared by iodine−lithium exchange on pyridine **62**, followed by anionic cascade through a 5-*exo*-*dig* addition on the triple bond in derivative **63** (Scheme 17).[123]

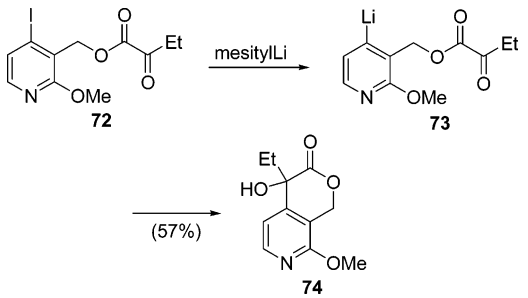
The halogen−lithium exchange is the method frequently employed for the generation of 3- and 4-lithiopyridines. Examples of the use of 3-lithiopyridines, generated by this methodology, are the additions to aldehydes[124] as in the total synthesis of the fungus metabolite pyridovericin,[125] to ketones,[124,126] to esters,[127a] or to the Vilsmaier reagent,[124,127b] as in the preparation of aldehyde **67** from bromopyridine **65** via lithiated species **66**, a compound which is an intermediate in the total synthesis of the alkaloid toddaquinoline (Scheme 18).[128] In addition, 3-lithiopyridine has been added to chiral *N*-(*tert*-butylsulfinyl)ketimine[129a] and a cyclic imine in the preparation of an inhibitor for *N*-riboside hydrolases and transferases,[129b] whereas *p*-methoxybenzyl-protected aminobromopyridine **68** has been lithiated to give the intermediate **69** and reacted then with the lactone **70** to give the nucleoside derivative **71** as a single isomer, after reduction of the initially formed hemiacetal (Scheme 18).[130]

Scheme 18



Examples of the use of 4-lithiopyridines, obtained by halogen−lithium exchange, can be found in additions to aldehydes such as propanal in a synthesis of alkaloids such as mappicine and the mappicine ketone.[131] There are also recent examples of intramolecular additions to ketones such as compound **72**, which, after lithiation at C-4 by iodine−lithium exchange using mesityllithium as a selective lithiating agent, gives the intermediate **73**, which cyclizes, giving the camptothecin precursor **74** (Scheme 19),[132] a compound which has been obtained enantiomerically enriched by intermolecular reaction of

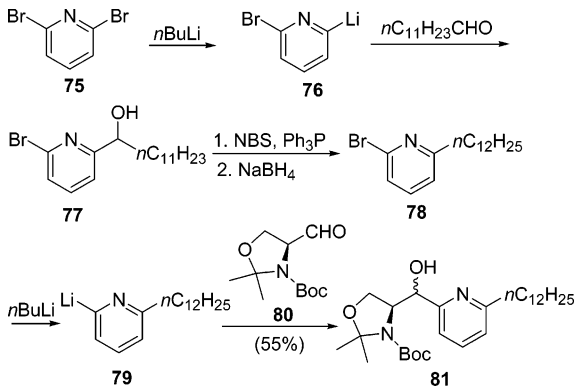
Scheme 19



a 3-lithiopyridine with a chiral oxoester.[133] Furthermore, reactions of 4-lithiopyridine with other electrophiles such as dinitrogen tetroxide for the synthesis of 4-nitropyridine have also been reported.[78]

The monolithiation of dihalopyridines such as 2,6-dibromopyridine is an interesting process because 2-bromo-6-lithiopyridine is an important building block in a number of syntheses of biologically interesting compounds,[134a] also being a key intermediate in the synthesis of oligopyridines.[134b] The main difficulty in this process resides in controlling the extent of lithiation, a monolithiation in THF being obtained by inverse addition of the dibrominated compound to 1 equiv of *n*-butyllithium,[135] although the use of dichloromethane as solvent allows monolithiation even with excess *n*-butyllithium.[136] The monolithiated species can therefore react with electrophiles,[136] although keeping an additional bromine atom which can be subsequently metalated.[135] An example of the application of this bisfunctionalization methodology is illustrated in Scheme 20, which shows the mono-

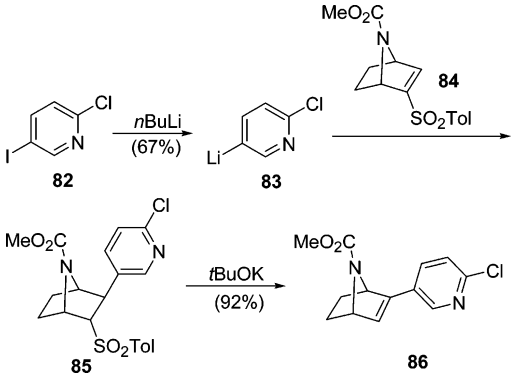
Scheme 20



lithiation of the dibromopyridine **75** to give the intermediate **76**, which, after addition to dodecanal and reduction of the resulting alcohol **77** via the corresponding bromo derivative, affords the bromopyridine **78**, which is lithiated again to give **79**, reacting with the aldehyde **80** to afford compound **81**, the precursor of a ceramide analogue.[137] There are also examples of reactions leading to β-pyridyl-β-amino acid derivatives,[138] ligands for carbonic anhydrase mimicry,[139] or metal complexes.[140] Even examples of monolithiations of 2-bromo-6-chloropyridine can be found, in this case the bromine−lithium exchange being preferential,[141a] extensive studies also being made on dichloropyridines, where the lithiation position depends largely on the choice of the reagents.[141b]

Also interesting is the case of the selective monolithiation of 2,5-dibromopyridine by bromine−lithium exchange, where the crucial influence of the solvent can be seen. 2-Bromo-5-lithiopyridine, which is the most stable species, can be generated by lithiation of 2,5-dibromopyridine using *n*-butyllithium in ether as solvent, the use of THF affording complex mixtures.[142] However, 5-bromo-2-lithiopyridine can be obtained by reaction of 2,5-dibromopyridine with *n*-butyllithium in toluene as solvent (up to 34:1 selectivity ratio), reacting then with different electrophiles.[143] This study shows that coordinating solvents and higher concentration favor lithium−halogen exchange at the 5-position while noncoordinating solvents and lower concentration favor lithiation at the 2-position.[143] As in the case of lithiation of 2,6-dibromopyridine, lithiation of 2,5-dibromopyridine allows the introduction of two different electrophiles into the 2- and 5-positions of the pyridine nucleus.[142] Thus, the monolithiation of differently halogenated 2,5-halopyridines at C-5 allows the generation of 2-halopyridinyl nucleophiles, which have been used in a recent synthesis of the analgesic alkaloid epibatidine, as shown in Scheme 21 with the

Scheme 21

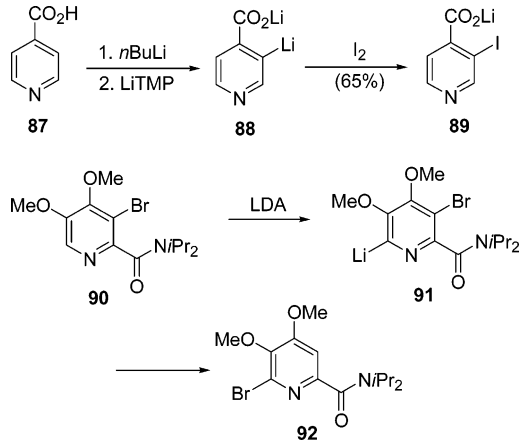


metalation of pyridine **82** to give the monolithiated 2-chloropyridine **83**, which reacts with the alkenyl sulfone **84**, affording the corresponding adduct **85**, which gives the epibatidine precursor **86** after sulfinate elimination.[144] Other epibatidine analogues have been obtained following similar methodologies involving a 5-lithiopyridine.[145]

The DoM reaction in π-deficient heterocycles has recently been extensively reviewed.[6d−f] The process can be carried out with alkyllithiums if the directing group is not very suitable for halogen exchange and the substrate is not prone to undergo nucleophilic additions, the process proceeding under kinetic control via the most acidic hydrogen. On the contrary, less basic lithium amide bases are used if halogen−lithium exchange on the substrate is suitable or nucleophilic addition is possible, the process now being controlled thermodynamically via the higher stabilization of the generated anion.[6d] Very recent examples of the use of the DoM reaction in pyridines involve the direct lithiation of unprotected pyridinecarboxylic acids such as isonicotinic acid **87**, which is transformed into its lithium salt using *n*-butyllithium and in situ metalated at C-3 using lithium 2,2,6,6-tetramethylpiperidine (LiTMP) to give intermediate **88**, which affords iodopyridine **89** after reaction with iodine (Scheme 22).[146] This DoM reaction using a 2-amidopyridine such as **90** to give **91**, combined with a "halogen dance" reaction [a process that rearranges the position of a halogen on a deprotonated arene ring that contains an exchangeable halogen (typically Br or I) and a nonexchangeable directing group], has been used in the synthesis of the bromopyridine **92**, an intermediate in the synthesis of caerulomycin C.[147]

Lithiated pyridines via the DoM reaction have also been used, for example, in the synthesis of iodo-

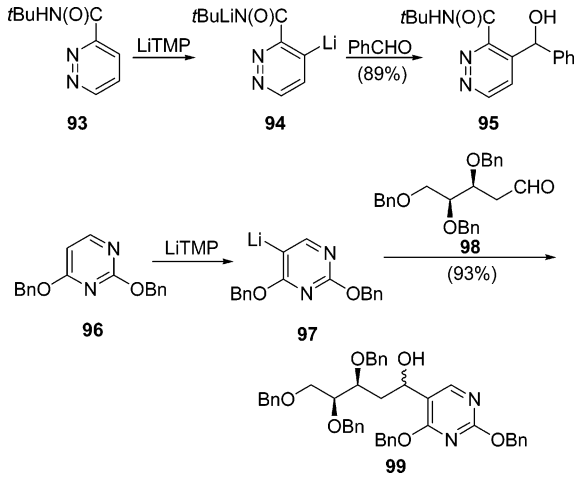
Scheme 22



pyridines from 3-cyanopyridine,[148] in the total synthesis of marine metabolite variolin B via addition to a ketone,[149] or in reaction with the Vilsmaier reagent for the synthesis of dendrimers,[150] as well as in the preparation of nicotine analogues.[151] In addition, trifluoromethyl-substituted pyridines[152] and quinolines[152,153] have been obtained following this type of lithiation.

The three parent diazines can be lithiated adjacent to the nitrogen (at C-4 for pyrimidine) using nonnuclephilic lithium amides such as LiTMP, although the lithiated species are rather unstable and usually form dimeric species by self-condensation. However, if the metalation time is very short or when the electrophile is present during the metalation step (Barbier conditions), the expected products can be obtained. Other positions can be metalated by halogen−lithium exchange,[154] even using an arene-catalyzed lithiation,[117a] under sonication,[155] or using an *ortho*-metalation procedure.[6] Recent examples of the synthetic uses of lithiated diazines can be found in the reaction of the lithiopyridazine **94**, generated by a DoM reaction of LiTMP with amidopyridazine **93**, with benzaldehyde to give alcohol **95** (Scheme 23).[156] However, the reaction of 3-(methylthio)-4-

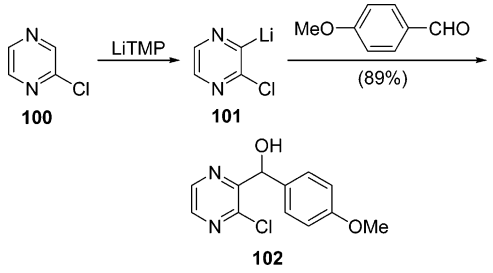
Scheme 23



lithiopyrimidine with diethyl carbonate in an attempted synthesis of variolin B was hampered due to the instability of the lithiated species.[149] Better results have been achieved in the DoM reaction as in the case of the 5-lithiopyrimidine **97**, prepared from pyrimidine **96**, which has been used, for example, in the addition to the aldehyde **98** to give compound **99**, a precursor of the uracil nucleus in a synthesis of azaribonucleosides (Scheme 23).[157]

Recently, 2-chloropyrazine (**100**) has been lithiated via a DoM reaction to give the intermediate **101**, reacting then with aldehydes such as *p*-methoxybenzaldehyde to give alcohol **102** in a route to the wheat disease impeding growth agent septorin (Scheme 24).[158] Regioselective metalation has also been per-

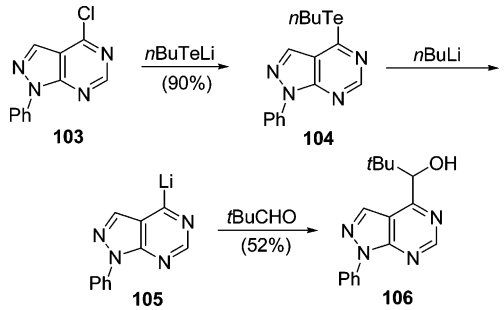
Scheme 24



formed with 2-fluoropyrazine.[159] 2,6-Dichloropyrazine has been dilithiated using LiTMP, reacting subsequently with different electrophiles for the one-pot synthesis of multisubstituted pyrazine *C*-nucleosides.[160]

Purines, *N*-substituted at N-7- and N-9-positions, lithiate preferentially at C-8, the metalation at other positions being possible via halogen−lithium exchange with alkyllithiums, although always at low temperature to avoid equilibration to the most stable organolithium.[161] As the rate of the tellurium−lithium exchange is much faster than that of the halogen−lithium exchange, the former reaction can be interesting for a rapid organolithium formation and reaction with an electrophile, thus avoiding equilibration. Thus, reaction of the chloropyrazolo[3,4-*b*]pyrimidine **103** with lithium *n*-butyltellurolate, obtained from the reaction of tellurium and *n*-butyllithium, gave telluride **104**, which was subsequently converted into the alcohol **106** after successive treatment with *n*-butyllithium and pivalaldehyde, via intermediate **105** (Scheme 25).[162] However, when the same methodology was applied to an analogous chloropurine, products from an equilibration lithiation at C-8 were obtained.[162]

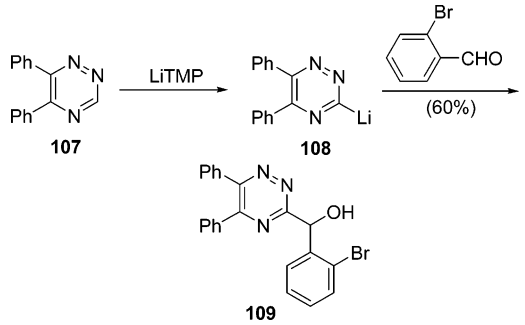
Scheme 25



Triazines show a high susceptibility toward nucleophilic addition. However, LiTMP has been used

for the lithiation of 5-methoxy-1,2,4-triazine to give the corresponding 6-lithio-1,2,4-triazine derivative using a DoM to give triazine-derived aldehydes when reacted with *N*-formylpiperidine or ethyl formate.[163] In addition, 5,6-disubstituted-1,2,4-triazines such as **107** have been lithiated at C-2 to give in this case intermediate **108**, for the reaction with different aldehydes such as *o*-bromobenzaldehyde to give the alcohol **109**, in a methodology useful for the preparation of 1-azafluorenones (Scheme 26).[164] Furthermore,

Scheme 26



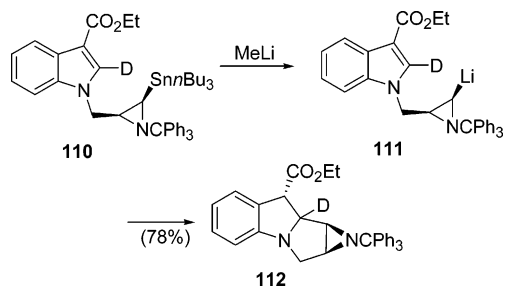
3-aryl-1,2,4,5-tetrazines have been lithiated with LiTMP and react with aldehydes and benzophenone to give the corresponding alcohols. However, with these highly π-deficient substrates, byproducts arising from the lithium amide addition to the heterocycle and also from a ring opening are also obtained.[165]

2.1.3. Nonaromatic Heterocycles

The first part of this section will deal with lithiated aziridines, oxiranes, and thiiranes acting as reagents while keeping their three-membered structure intact. These lithiated heterocycles, specially derived from aziridines and oxiranes, are nowadays finding more applications in synthetic organic chemistry, being able to introduce the azirinidyl and oxiranyl moieties as configurationally stable nucleophiles, as well as being implied intermediates in the formation of carbenes, especially in the case of nonstabilized oxiranyl anions, all these uses already having been reviewed.[166]

Nonstabilized aziridinyllithiums have been obtained via sulfoxide−metal exchange using *tert*-butyllithium at low temperature,[167] and also by tin−lithium exchange[168] as can be seen in Scheme 27, where (tri-*n*-butylstannyl)aziridine **110** suffers a tin−lithium transmetalation using methyllithium at −65 °C to give aziridyllithium **111**, which affords the tricyclic derivative **112** after intramolecular Michel

Scheme 27

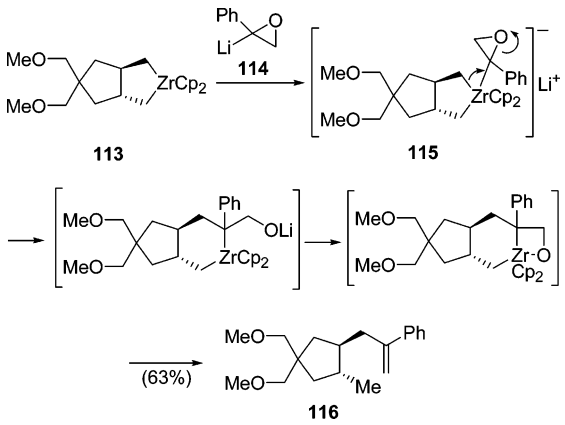


addition, in recent studies toward aziridinomitosene antibiotics.[169a] In addition, Lewis acid activators such as borane can be used with aziridines, thus facilitating α-metalation as well as controlling the stereochemistry of both the metalation and electrophilic quenching.[169b,c]

Recently, nonstabilized oxiranyllithiums have been generated through direct lithiation at the less hindered side of terminal epoxides, using *sec*-butyllithium in the presence of diamines at −90 °C, and react with chlorosilane as an electrophile.[170] In addition, they have been generated by desulfinylation of the corresponding precursors using *tert*-butyllithium at −100 °C,[171] or by a cyclization−lithiation sequence from dichlorohydrins using *n*-butyllithium at −98 °C.[172]

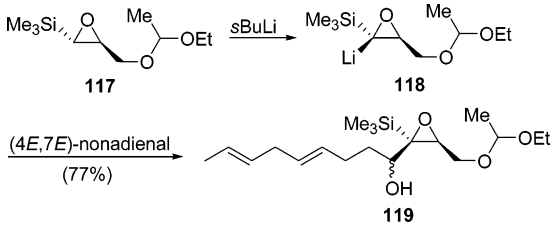
The formation and use of stabilized oxiranyllithiums is perhaps more frequent. Thus, styrene oxide can be deprotonated with *tert*-butyllithium in the presence of *N*,*N*,*N*′,*N*′- tetramethylethylenediamine (TMEDA) to give the lithiated epoxide **114**. This species inserts into zirconacycles such as **113** via a 1,2-metalate rearrangement to form intermediate **115**, which eliminates $Cp_2Zr(R)O^-$ (Cp = cyclopentadienyl), affording substituted alkene **116** (Scheme 28).[173] The same reaction has also been carried out with lithiated epoxynitriles and epoxysilanes.[173]

Scheme 28



The trialkylsilyl group in the above-mentioned lithium epoxysilanes has been used as a group for the stabilization of an anion in oxiranyllithiums,[166] examples being the deprotonation at −116 °C of the silylated epoxide **117** to give lithiated species **118**, followed by reaction with nonadienal to give alcohols **119**, which are intermediates in a synthesis of the antimicrobial (+)-cerulenin (Scheme 29),[174] or the lithiation of α,*β*-epoxy-*γ*,*δ*-vinylsilanes.[175] Moreover, the sulfonyl group has also been used as a stabilizing

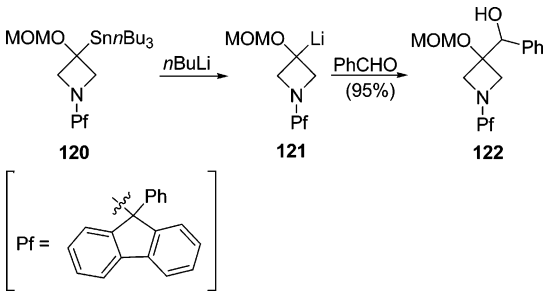
Scheme 29



group for an oxiranyllithium, an example being its use in a strategy for the iterative synthesis of *trans*-fused tetrahydropyrans.[176]

N-Protected azetidines lithiated at C-3 are elusive compounds, as any polar organometallic compound possesing a leaving group β to the anionic center.[166c,177] A recent example shows the generation and reactivity of a 3-lithioazetidine stabilized by an alkoxy group.[178] Thus, stannane **120** (prepared by addition reaction of lithium tri-*n*-butylstannilide to the corresponding azetidin-2-one followed by MOM protection) suffers tin−lithium exchange to give intermediate **121**, which reacts with electrophiles such as benzaldehyde to give the alcohol **122** and no traces of ring-opening products (Scheme 30). Cyclic amines with different

Scheme 30

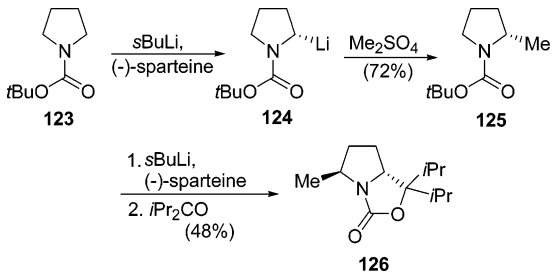


ring sizes have been lithiated by this methodology, and their β-eliminative decomposition has been studied according to the microscopic reversibility principle along with Baldwin's rules, concluding that their stability would decrease with increasing ring size.[178]

α-Lithiated pyrrolidines, like other α-aminoorganolithiums,[166c,179] are configurationally stable in more or less extension depending of the ability of the organolithium for achieving stabilization. Thus, the nonstabilized α-aminoorganolithiums derived from *N*-alkylpyrrolidines present surprising configurational stability up to −40 °C due to internal Li−N bridging,[180] whereas their corresponding carbamate or amide dipole-stabilized counterparts need lower temperatures to prevent racemization.[166c,179,181] However, the electrophile employed also plays an important role in the possible final racemization or even inversion of the stereochemistry, probably due to different operating SETs of polar mechanisms,[182] as well as solvation and aggregation of the lithiated species.[183]

The most used methods for generating these pyrrolidinyllithiums are deprotonation and transmetalation by tin−lithium exchange.[166c,179] Both methods are complementary: deprotonation can be made stereoselective when the lithiating base is combined with (−)-sparteine,[184] whereas tin−lithium exchange provides access to species not accessible due to a kinetic barrier. Furthermore, since metal exchange usually proceeds with retention of the configuration, organolithiums of a known absolute configuration can be achieved. An example of the use of this enantioselective deprotonating methodology is shown in Scheme 31, where *N*-Boc-pyrrolidine (**123**) is treated with *sec*-butyllithium in the presence of (−)-sparteine to give the methylated pyrrolidine **125**, after treatment with dimethyl sulfate and through lithiated

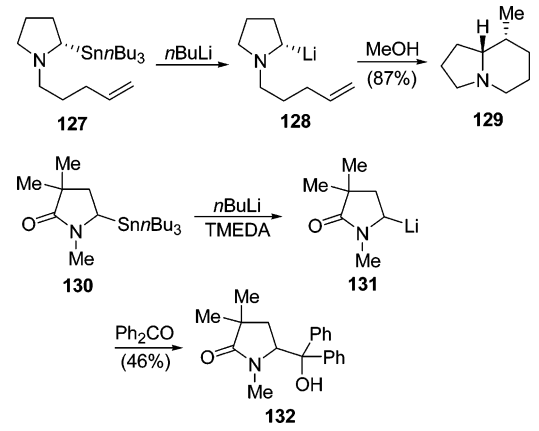
Scheme 31



species **124**. Further deprotonation under the same reaction conditions, and reaction with diisopropyl ketone afforded the *trans*-oxazolidinone **126**.[185] This methodology has also been applied to *N*-Boc-pyrrolidine for the preparation of chiral diamines.[86]

Recent examples of the generation of α-lithiopyrrolidines by tin−lithium exchange are the transmetalation of *N*-alkenyl-2-(tri-*n*-butylstannyl)pyrrolidines, obtained by enantioselective deprotonation of the corresponding pyrrolidine and reaction with chlorotri-*n*-butylsilane, which cyclize to give pyrrolizidine and indolizidine derivatives.[187] Thus, transmetalation of the stannylpyrrolidine **127** with *n*-butyllithium gave the expected organolithium intermediate **128**, which after cyclization and quenching with methanol yielded the indolizidine **129** in 90% de (Scheme 32).[187b] In addition, the 7-azabiciclo[2.2.1]-

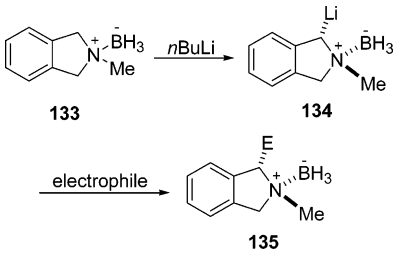
Scheme 32



heptane ring system has also been obtained following this methodology, but starting from 2-allyl-5-(tri-*n*-butylstannyl)pyrrolidines.[188] Moreover, the stannylated lactam **130** can be transmetalated to species **131**, which reacts with electrophiles in low yields, the highest one being obtained using benzophenone to give the corresponding alcohol **132** (Scheme 32).[189]

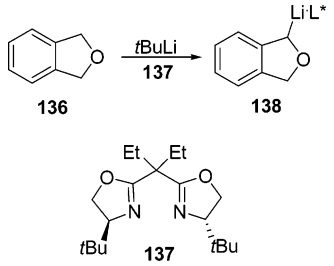
N-Boc-protected α-lithiopyrrolidines experience copper cyanide-catalyzed palladium coupling with aryl iodides or vinyl iodides.[190] In addition, and similarly to aziridines, *N*-methylisoindole reacts with borane to form an amine−borane complex (**133**) which facilitates the lithiation to give intermediate **134**, the following quenching with the electrophile being *syn* to the BH_3 group to give compounds **135** (Scheme 33).[191] Moreover, *N*-Boc-protected 2,3-dihydro-1*H*-pyrrole has been lithiated at the vinylic α-position by treatment with *tert*-butyllithium and used as a nucleophile in the synthesis of polyquinanes.[192]

Scheme 33



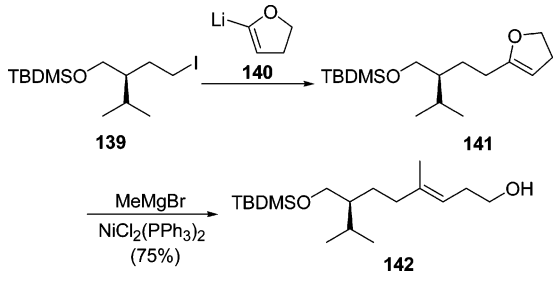
2-Lithiotetrahydrofuran, once formed by deprotonation of oxolane with alkyllithium or using lithium and a catalytic amount of an electron carrier such as naphthalene,[193] slowly decomposes at room temperature through a [3 + 2]-cycloreversion into ethene and the lithium enolate of acetaldehyde, this instability largely preventing its use for actual synthesis.[194a] However, phthalan (**136**) has been α-lithiated with *tert*-butyllithium in the presence of the chiral bis(dihydrooxazole) **137** to give the corresponding lithiated species **138**, which is able to react with electrophiles, achieving enantioselectivities up to 97% ee (Scheme 34).[194b]

Scheme 34



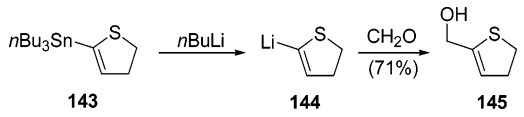
2,3-Dihydrofuran has been α-lithiated using *tert*-butyllithium at 0 °C, although starting from more substituted dihydrofurans, the tin−lithium exchange methodology is more frequent, the resulting lithio derivatives being used as nucleophiles.[166c,195] A recent example of the use of these lithiated derivatives can be seen in the substitution reaction of 5-lithio-2,3-dihydrofuran (**140**) with the iodide **139**, providing the 5-substituted dihydrofuran **141**, which can be subjected to a nickel(0)-catalyzed coupling and ring opening with methylmagnesium bromide to furnish compound **142**, an intermediate in the total synthesis of (−)-1(10),5-germacradien-4-ol (Scheme 35).[196]

Scheme 35



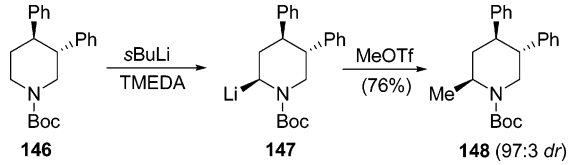
Tetrahydrothiophene can be efficiently α-lithiated using the combination *n*-butyllithium/potassium *tert*-butoxide at −40 °C and can react with trialkylstannyl chlorides or trialkylsilyl chlorides, affording the corresponding α-silylated or -stannylated products.[197] In addition, α-lithiated 2,3-dihydrothiophene **144** can be generated by treating the tri-*n*-butylvinylstannane **143** with *n*-butyllithium, and reacts with formaldehyde to give alcohol **145** (Scheme 36),[198] as well as with cyclobutanone to achieve spirocyclization compounds.[199]

Scheme 36



N-Boc-protected piperidine can be α-lithiated similarly to its corresponding five-membered pyrrolidine counterpart (see above),[182,185] as can be seen in a recent example where a 3,4-disubstituted *N*-Boc-piperidine (**146**) is lithiated using *sec*-butyllithium in the presence of TMEDA to give the lithio intermediate **147**, which can be regio- and diastereoselectively alkylated to piperidine **148** using methyl triflate (Scheme 37).[200] Other examples include the dia-

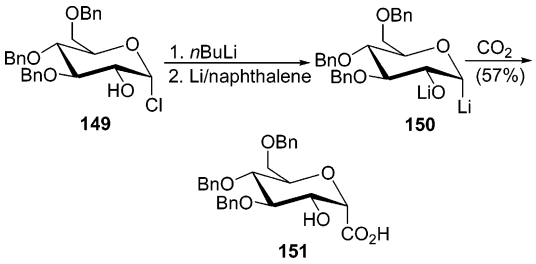
Scheme 37



stereoselective synthesis of analogues via lithiation−electrophilic quenching of *N*-Boc-bispidines,[201] or the lithiation at the 1-position of the amine−borane complex from *N*-methyltetrahydroisoquinoline.[202]

Tetrahydropyrans have been α-lithiated mainly by tin−lithium transmetalation (see below), although other methods can be used, such as the reductive lithiation of α-chlorotetrahydropyrans[203] or α-cyanotetrahydropyrans[204] using lithium naphthalenide or lithium 4,4′-di-*tert*-butylbiphenylide, respectively. An example is shown in Scheme 38, where the chlori-

Scheme 38

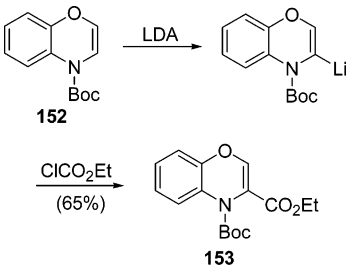


nated glycoside **149** is lithiated using lithium naphthalenide, after deprotonation of the alcohol functionality, giving the intermediate **150**, which reacts with electrophiles such as carbon dioxide to give the α-heptonic acid **151**.[203a] In addition, tetrahydrothiophene can be α-lithiated using *n*-butyllithium/potassium *tert*-butoxide.[197] Moreover, the reaction of 2,3-dihydro-2*H*-pyran with *n*-butyllithium affords the corresponding 6-lithio-2,3-dihydro-2*H*-pyran, although the tin−lithium transmetalation has also been

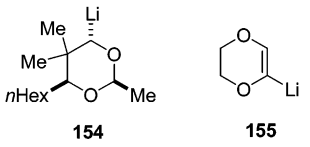
frequently employed with substituted dihydropyrans.[166c,195]

N-Boc-substituted 4*H*-1,4-benzoxazines such as compound **152** can be lithiated at C-3 using LDA at −78 °C to give a lithiated species which is able to react with electrophiles such as ethyl chloroformate, affording the ester **153** (Scheme 39).[205] In addition,

Scheme 39



configurationally defined 4-lithio-1,3-dioxanes such as **154** have been generated by reductive lithiation of 4-(phenylthio)-1,3-dioxanes using lithium di-*tert*-butylbiphenylide.[206] Moreover, 2-lithio-5,6-dihydro-1,4-dioxine (**155**) has been obtained by direct lithiation using *tert*-butyllithium,[207] whereas 2-lithio-1,3-dithianes have been extensively used in synthetic organic chemistry and have been reviewed recently,[208] a recent example being their S_N2' addition to 3,3,3-trifluoropropene derivatives.[209]



2.2. Sodium Heterocycles

Despite the low cost of metallic sodium, in general organosodium compounds have not been considered so far as valuable organometallic reagents for organic synthesis, due to their poor stability. Recently, heterocyclic systems such as thiophene and benzofuran have been successfully α-metalated using sodium sand dispersion in the presence of 1-chlorooctane.[210] However, other heteroaromatics bearing electron-withdrawing groups, such as oxazolines, failed to undergo metalation using this procedure.

3. Group 2 Metal-Containing Heterocycles

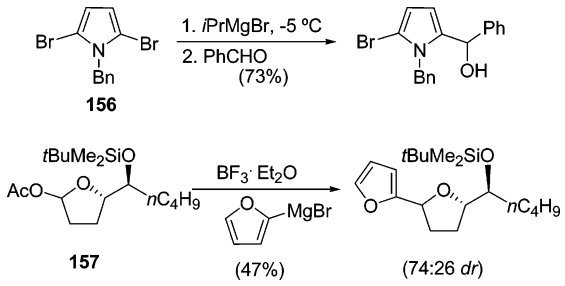
3.1. Magnesium Heterocycles

The direct preparation of heterocyclic organomagnesium reagents using the standard reaction between a halogenated derivative and magnesium is sometimes rather difficult, mainly in the case of basic nitrogen-containing heterocycles. In these cases, the usual preparative procedure is to treat the heterocycle with an alkyl Grignard reagent (generally EtMgBr, *i*PrMgBr, or *i*Pr_2Mg) or to perform a halogen−magnesium exchange by treating bromo and iodo heterocycles with the mentioned alkyl Grignards,[211,212] this procedure tolerating the presence of other functionalities.[212] Moreover, the preparation of the organolithium derivative followed by interchange using magnesium dibromide can also be used.[211] In addition to the usual applications of arylmagnesium reagents, reacting with all kinds of electrophiles, these organomagnesium derivatives can also be used in nickel- and palladium-catalyzed cross-coupling reactions (the so-called Kharasch or Kumada coupling).[213]

3.1.1. Aromatic Five-Membered Rings

The use of the usual metalating methodology with alkyl Grignards also shows chemoselectivity, and only the monoexchange is achieved by working with dibrominated heterocycles, as in the case of the benzylated pyrrole **156** shown in Scheme 40, the

Scheme 40

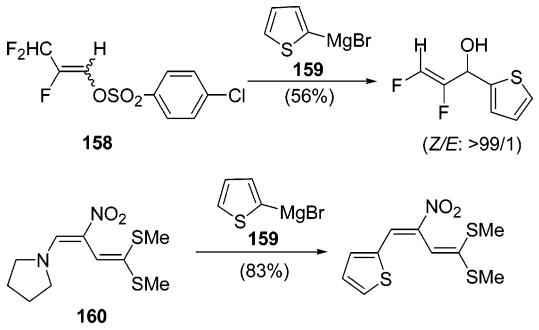


corresponding metalated species reacting further with benzaldehyde to give the corresponding alcohol.[213a] Another example is the use of an *N*-protected indole Grignard reacting with a substituted bromomaleimide, employed for the total synthesis of staurosporine and *ent*-staurosporine.[214]

An example of lithium−magnesium exhange is the use of 3-furylmagnesium bromide, prepared from its corresponding furyllithium, for the synthesis of a chiral sulfoxide by addition to a chiral sulfinamide,[215] or for the preparation of a diarylmethylamine by addition to a chiral sulfinimine.[216] In addition, 2-furylmagnesium bromide, similarly prepared from the corresponding heteroaryllithium, has recently been employed in a diastereoselective addition to cyclic oxocarbenium ions, obtained from glycosyl acetates such as **157**, to afford the corresponding 2,5-disubstituted tetrahydrofuran (Scheme 40),[217] or in another case involving an addition to pyridinium salts.[218]

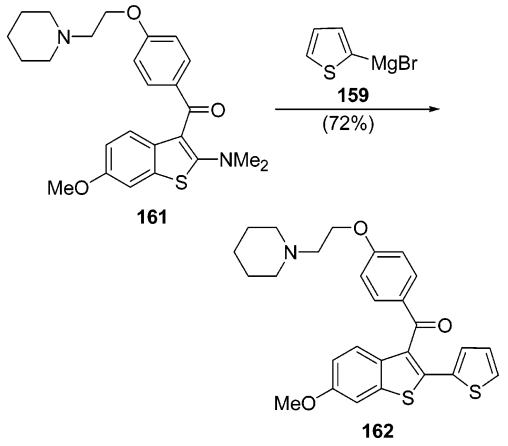
2-Thienyl Grignard reagents have been prepared by the usual halogen−metal exchange using magnesium turnings, and have been employed as nucleophiles in reactions such as additions to the carbonyl functionality in steroids,[219] riboses,[220] pyranones,[221] trifluoromethylated phosphonates,[222] ester groups,[223] lactams for the synthesis of aminoribonucleosides,[224] and Weinreb amides.[225] There are also examples of their use in addition reactions to fluorinated enamines[226] and fluorinated enol sulfonates such as compound **158**, which reacts with 2-thienylmagnesium bromide (**159**), affording the corresponding difluorinated alcohol (Scheme 41), probably via the generation of a transient fluorinated enolate.[227] In addition, 2-thienylmagnesium bromide (**159**) has also been employed in different substitution reactions on estrogenic and antiestrogenic isoflav-3-enes,[228] chlorinated oxathianes,[229] oxazolidines,[230] nitrovinyl sys-

Scheme 41



tems [such as compound **160** to give the corresponding diene (Scheme 41)[231]], 2-perfluoroalkylanilines (for the preparation of molecular propellers[232]), fluorovinadiminium salts,[233] and aminated benzothiophenes [such as **161** for the preparation of compounds such as **162** (Scheme 42) related to raloxifene, an

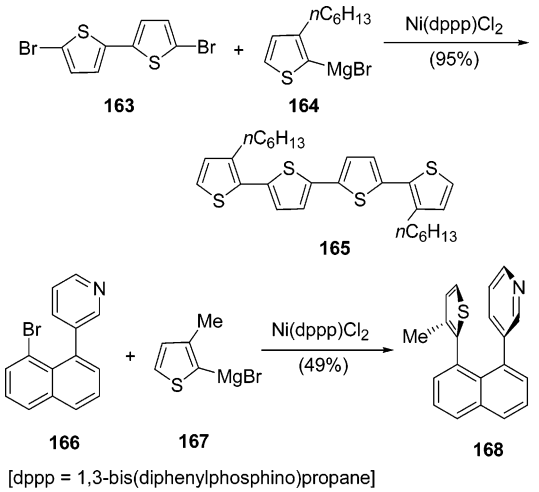
Scheme 42



estrogen receptor modulator[234]]. 3-Thienylmagnesium bromide is difficult to prepare from, for example, 3-bromothiophene using the above-mentioned methodology applied to its 2-metalated counterpart, the halogenated heterocycle being rather unreactive toward magnesium, a problem which can be solved using the reaction of the active metal with 3-iodothiophene.[235]

Among the methodologies developed for achieving the synthesis of electronically interesting oligo- and polythiophenes, transition-metal-catalyzed cross-coupling using thiophene-derived organometallics has probably been one of the most successful (see other metals below). Related to this chemistry, the use of thiophene-derived magnesium reagents in the Kumada cross-coupling reaction has been frequent in the last several years,[236,237] as in the case shown in Scheme 43 with the nickel(0)-promoted coupling between the 2-thienylmagnesium derivative **164** and the dibrominated bithiophene **163** to give quaterthiophene **165**.[236] Related couplings have been reported for the preparation of extended di(4-pyridyl)-thiophene oligomers,[238] thiophene-derived solvatochromic chromophores,[239] and dithienylcyclopentene optical molecular switches.[240] In addition, the Kumada reaction using thiophene-derived Grignard reagents such as **167** has been employed with brominated naphthalenes such as compound **166** for the

Scheme 43

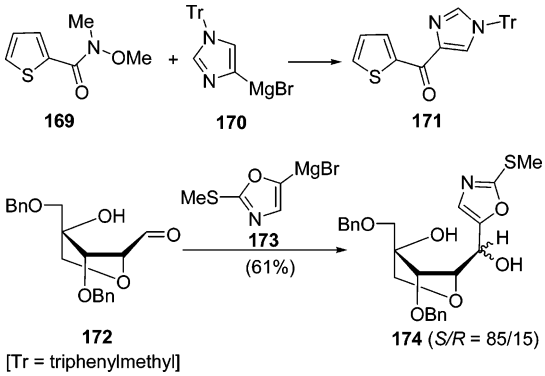


synthesis of 1,8-di(hetero)arylnaphthalene **168**, an interesting compound for nonlinear optics (Scheme 43),[241] and pyridine−thiophene alternating assemblies.[242] Iron salts have also been used as precatalysts in cross-coupling reactions, the real catalysts being reduced iron species created by the Grignard reagent.[243]

2-Thienylmagnesium bromide (**159**) has also been used in some other metal-catalyzed transformations such as cobalt-mediated radical cyclizations,[244] nickel(0)-mediated synthesis of ketones from acyl bromides,[245] or copper-catalyzed reactions with benzyl iodides for the synthesis of precurors of lipoxygenase inhibitors.[246]

Brominated or iodinated *N*-protected imidazoles have been transformed into the corresponding heterocyclic Grignards by the mentioned treatment with an alkyl organomagnesium.[211,212b] The generated imidazolylmagnesium halide has been employed in addition reactions to carbonyl compounds for the preparation, for example, of ligands for the α_{2D} adrenergic receptor,[247] sugar-mimic glycosidase inhibitors,[248] or *C*-nucleosides.[118,249] It has also been used in acylation reactions with esters in the synthesis of pilocarpine analogues,[250] or Weinreb amides, as shown in Scheme 44 for the reaction between

Scheme 44



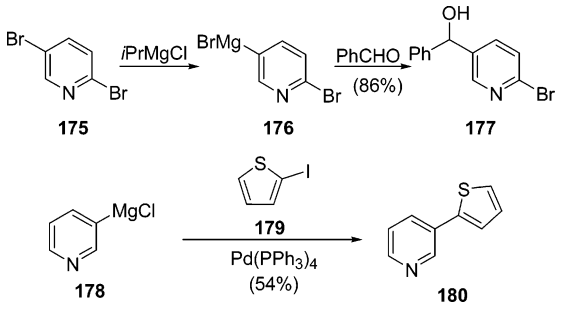
N-tritylimidazolylmagnesium bromide **170** and the thiophene amide **169** to give compound **171**, which is an intermediate in the synthesis of an α_2 adrenoceptor agonist.[251] In addition, examples of the use of

oxazolylmagnesiums can be found in the addition of 2-(methylthio)-5-oxazolylmagnesium bromide (**173**) to the aldehyde **172** to give compound **174** (Scheme 44), employed for the synthesis of conformationally locked *C*-nucleosides.[252] Moreover, thiazolylmagnesiums metalated at C-2 have been used in addition reactions to nitrones,[100] examples of the use of isothiazol-4-ylmagnesiums having also been reported.[253] Furthermore, and as an example of the use of 1,2-azoles, 4-pyrazolylmagnesiums have been used as nucleophiles in additions to *N*-Boc-iminomalonate for the synthesis of pyrazole-substituted glycines.[107b]

3.1.2. Aromatic Six-Membered Rings

Although pyridyllithiums tend to decompose even at low temperatures,[1] the corresponding Grignard reagents are stable up to room temperature and even higher. However, magnesiopyridines are difficult to generate from the corresponding halide and magnesium metal, the formation of pyridyl Grignards via direct reaction with alkyl or aryl Grignard reagents being much more convenient due to the mild conditions employed.[213,254] However, halogenopyridines, as well as halogenated pyrazolopyrimidines or quinoxalines, have been transformed into the corresponding Grignards by oxidative magnesiation using active magnesium, generated from magnesium dichloride in the presence of lithium naphthalenide.[255] The differently obtained pyridyl Grignards have been used recently as nucleophiles in reactions with aldehydes,[118,220,254,255] ketones,[254,255] carbon dioxide,[256] carbon disulfide,[257] Weinreb amides,[258] or fluorinated enol sulfonates.[227] Interestingly, the magnesiation reaction of dibromopyridines generally takes place with rather high selectivity; for example, 2,6-dibromopyridine reacts with *i*PrMgBr to give a single exchange reaction, even in the presence of an excess of the alkyl Grignard.[254b] 2,3- and 3,5-dibromopyridines also easily monometalate at C-3, whereas 2,5-dibromopyridine (**175**) metalates at C-5 to give the intermediate **176**, as shown in Scheme 45, reacting then with benzaldehyde to give the expected compound **177**.[254b]

Scheme 45

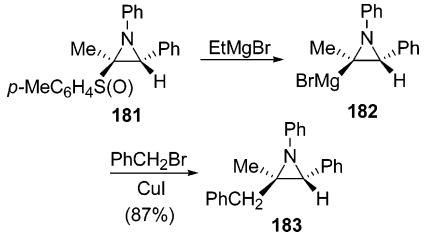


Pyridylmagnesiums have also been used in the transition-metal-catalyzed Kumada cross-coupling reactions. For example, heteroaromatic halides such as 2-iodothiophene (**179**) have been coupled with 3-pyridylmagnesium chloride (**178**) under palladium catalysis to give compound **180**, whereas, with Grignards derived from chloroquinolines and chloropyrazines, a nickel(0) catalysis proved to be more efficient.[259a] In addition, 6-magnesiated purines have been recently prepared by reaction of the corresponding iodopurines with isopropylmagnesium chloride, reacting further with aldehydes.[259b]

3.1.3. Nonaromatic Heterocycles

Configurationally stable nonstabilized aziridinylmagnesiums, such as **182**, have been generated from sulfinylaziridines such as **181** with ethylmagnesium bromide by sulfoxide−magnesium exchange (Scheme 46).[260] Subsequent copper(I) iodide-catalyzed reaction

Scheme 46



of the aziridinylmagnesium **182** with an alkyl, allyl, or benzyl halide such as benzyl bromide gave alkylated aziridine **183**. In addition, *N*-alkylated 4-piperidinylmagnesium reagents have been employed in the synthesis of farnesyl protease inhibitors,[261] whereas a 4-tetrahydropyranylmagnesium has been employed for the synthesis of a leukotriene biosynthesis inhibitor.[262]

4. Group 3 Metal-Containing Heterocycles

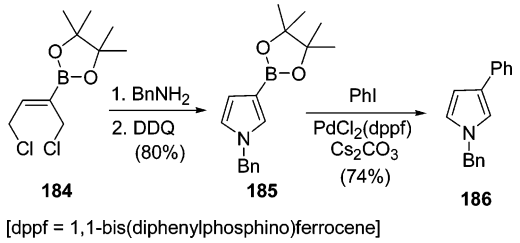
4.1. Boron Heterocycles

The most general preparative method for the synthesis of heterocyclic boronic acid derivatives is the reaction of a heterocyclic organolithium or magnesium with a trialkylborate,[263,264] although other recent methods such as the iridium-catalyzed carbon−hydrogen coupling reaction of heteroaromatics with bis(pinacolborane) have been reported.[265] These organoborons have been used mainly for the palladium-catalyzed cross-coupling reaction (the so-called Suzuki−Miyaura coupling reaction).[263,264] Compared to other organometallics employed in related couplings (see below), boron derivatives present, in addition to their tolerance of a variety of functional groups, air stability and rather low toxicity.

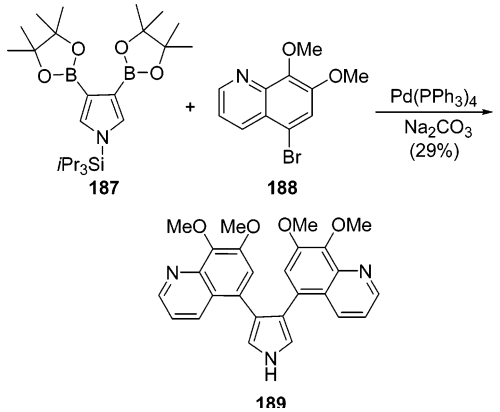
4.1.1. Aromatic Five-Membered Rings

The synthesis and applications of heteroarylboronic acids have been reviewed recently.[264] An example of the use of the Suzuki−Miyaura cross-coupling methodology is the palladium-promoted coupling reaction of *N*-Boc-protected pyrrol-2-ylboronic acids with aryl bromides and iodides,[266] or the coupling between the pyrroleboronate **185** [prepared by cyclization of olefin **184** followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)] and iodobenzene to give pyrrole **186** (Scheme 47).[267] Moreover, the polycyclic framework **189** of the cytotoxic marine alkaloid halitulin has also been obtained via cross-coupling

Scheme 47



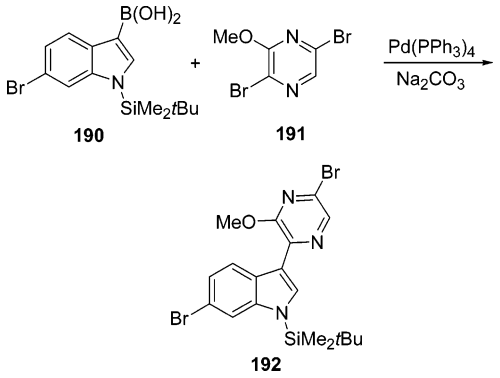
Scheme 48



of the bis(pinacolborane)pyrrole **187** with the bromoquinoline **188** (Scheme 48).[268]

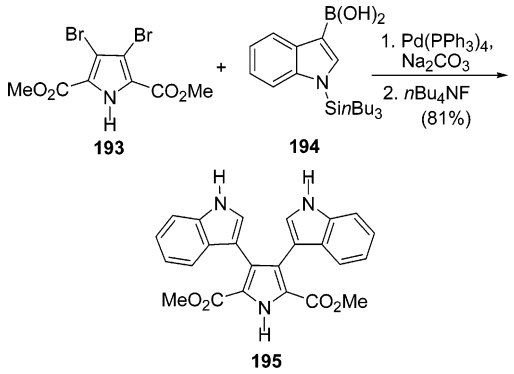
The Suzuki−Miyaura coupling has been frequently employed in indole chemistry, recent examples being the coupling of the indol-3-ylboronic acid **190** with dibromopyrazine **191** to give compound **192** (Scheme 49), in a method to construct the skeleton of drag-

Scheme 49



macidin D,[269] a bis(indole) marine alkaloid also prepared recently via cross-coupling using an indol-3-yl(pinacolboronate),[270a] so other 2-bis(indoles) are obtained.[270b,c] Furthermore, an indol-3-ylboronic acid (**194**) has been coupled to the pyrrole **193** in the total synthesis of the lycogalic acid methyl ester **195**, an alkaloid isolated from the mycomycete *Lycogala epidendrum* which exhibits some anti-HIV I activity (Scheme 50),[271] an *N*-tosylated analogue having been used in the synthesis of *dl*-cypridina.[272a] Other boron-containing heterocycles have been used as precursors in the enantioselective synthesis of methyltryptophan[272b] and a 3-(1′-isoquinolyl)indole,[272c] in arylation studies toward the synthesis of simplified eastern subunits of macropolypeptides chloropeptin and

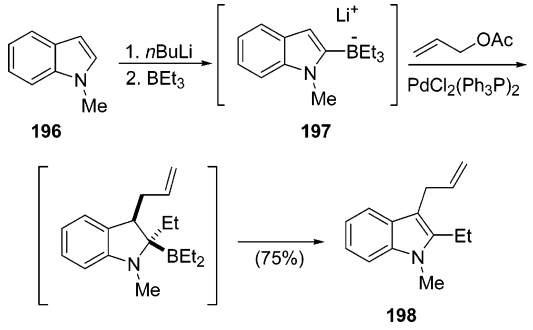
Scheme 50



kistamycin,[272d] and in the total synthesis of the tremorgenic alkaloid (−)-21-isopentenylpaxilline.[272e]

Lithium indolylborates of the type **197**, prepared by lithiation of indole **196** and reaction of the corresponding indolyllithium with a trialkylborane, undergo the familiar, in organoboron chemistry, intramolecular migration reaction of an alkyl group from boron to carbon.[273] An example of the synthetic use of this reaction is shown in Scheme 51, where the

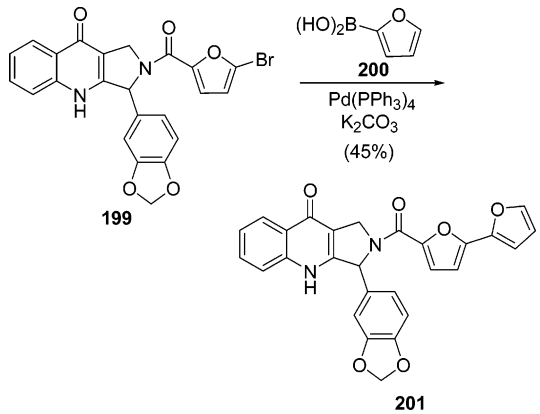
Scheme 51



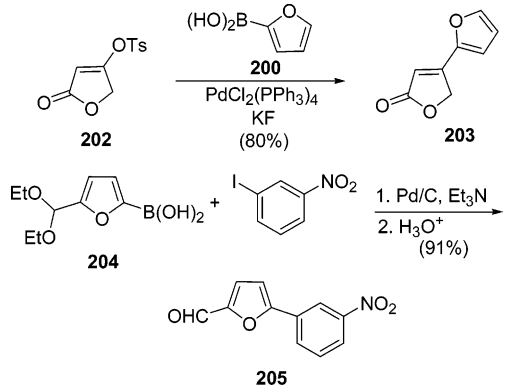
borate **197** reacts with an in situ generated π-allylpalladium species, finally affording the corresponding substituted indole **198**.[274]

Furylboronic acids have also often been employed in the Suzuki−Miyaura cross-coupling reaction.[264] Very recent examples are the use of 2-furylboronic acid (**200**), which is coupled with the aryl bromide **199**, either for the synthesis of furoylpyrroloquinolones [such as compound **201**, which acts as a potent and selective PDE3 inhibitor for treatment of erectyle dysfunction (Scheme 52)[275]] or for coupling with

Scheme 52



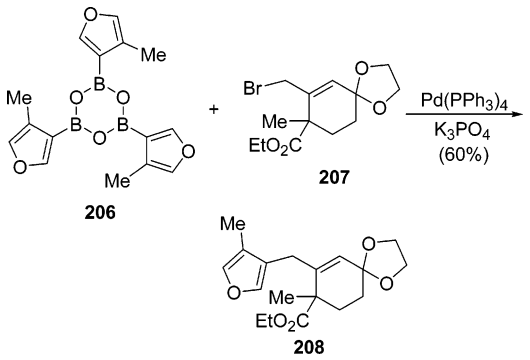
Scheme 53



tosylated systems such as 4-tosyloxy-2-(5*H*)furanone (**202**) (Scheme 53),[276a] which acts as a β-acylvinyl cation[276b] to afford compound **203**. Moreover, 5-(diethoxymethyl)-2-furylboronic acid (**204**) has been used for the synthesis of 5-aryl-2-furaldehydes such as compound **205** (Scheme 53), although using in this case palladium on carbon as catalyst, which facilitates the removal of traces of the metal, something especially valuable when working with pharmaceuticals.[277]

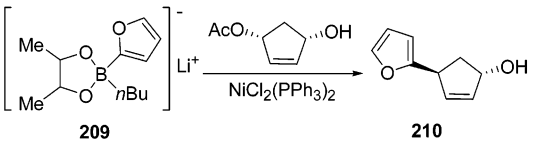
4-Methyl-3-(trimethylsilyl)furan can be transformed into the boroxine **206** according to a silicon−boron exchange using boron trichloride followed by hydrolysis (see below). This boroxine **206** has been employed recently in the palladium-catalyzed coupling with the bromoketal **207** to give the furan derivative **208**, used in model approaches toward sesquiterpenoid furanoeudesmanes (Scheme 54).[278]

Scheme 54



Lithium organoborates, which can be obtained by reaction of an alkyllithium reagent with the corresponding boronate, have been used in nickel(0)-catalyzed coupling reactions where aryl, alkenyl, or furyl groups can be transferred.[279] An example of this methodology is the furyl-derived borate **209**, which reacts with the monoacetate of *cis*-cyclopent-4-ene-1,3-diol to furnish stereo- and regioselectively the *trans*-product **210** (Scheme 55).[279b] This product has

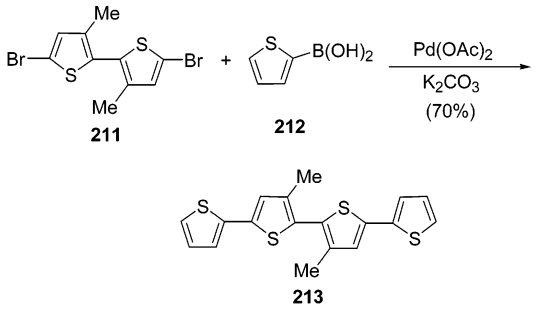
Scheme 55



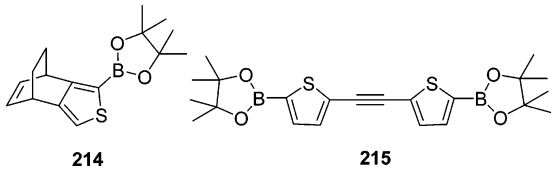
a furyl group which can act as a synthetic equivalent of the hydroxymethyl group, producing the key diol in the synthesis of (−)-aristeromycin, a carbocyclic analogue of adenosine. Zinc borates of this type have also been employed.[280] On the other hand, a furaldehyde bearing a chiral boronate group at the furan C-3-position has been used in diastereoselective additions[281] and aldol reactions.[282]

The Suzuki−Miyaura reaction has found a logical application in the coupling of thiophene boronic acid derivatives with thiophene halides for the synthesis of interesting thiophene oligomers. Thus, recently the bithiophene **211** has been coupled with 2-thiophene boronic acid (**212**), affording quaterthiophene **213** (Scheme 56), which can be brominated with *N*-

Scheme 56



bromosuccinimide, thus allowing a further coupling and chain enlargement,[283] a process also performed under microwave irradiation.[284] In addition, trimers have been prepared by Suzuki−Miyaura coupling between boronate **214** and a structurally related diiodide, these compounds being precursors of benzo[*c*]thiophene, generally called isothianaphthene.[285] Moreover, diboronic ester **215** has been employed in the synthesis of chiral polybinaphthyls with conjugated chromophores,[286] and boronic acids such as 2-thienylboronic acid have been immobilized onto a dendritic polyglycerol,[287a] amorphous molecular materials also being obtained following this methodology.[287b]

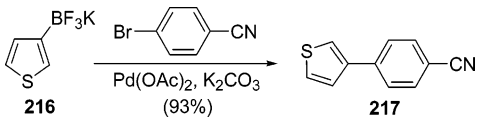


Apart from the typical palladium-catalyzed cross-coupling with aryl halides,[263,264] thienylboronic acids have been recently coupled with imidoyl chlorides,[288] halo-*exo*-glycals,[289] and carboxylic acid anhydrides.[290] In addition, 2- and 3-benzo[*b*]thiophene boronic acids have been coupled with *N*-Boc-β-bromodehydroalanine esters for the preparation of sulfur analogues of dehydrotryptophan.[291] Moreover, a sulfur analogue of tryptophan has also been prepared recently via Petasis boronic acid−Mannich reaction of substituted hydrazines using 2-benzo[*b*]thiophene boronic acid.[292]

Heteroaryl trifluoroborates, easily prepared by reaction of the corresponding boronic acids with KHF_2, couple well with diaryliodonium ions under palladium catalysis even in the presence of halogen

functionalities on the substrates.[293] This reaction has also been carried out with aryl bromides using a ligandless Suzuki−Miyaura methodology, as shown in Scheme 57 for the reaction between the trifluoroborate **216** and *p*-bromobenzonitrile to give the thiophene derivative **217**.[294] Furthermore, very recently, a rhodium-catalyzed cross-coupling of cinnamyl alcohol with 2-thienylboronic acid has been described.[295]

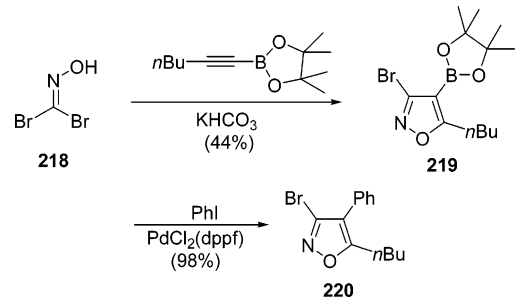
Scheme 57



216 **217**

Examples of the use of *N*-substituted pyrazolyl-5-boronic acids (prepared by hydrolysis of the corresponding borate after a favorable direct C-5-lithiation) for palladium-catalyzed Suzuki−Miyaura cross-coupling reactions have been reported,[296] for instance, producing cyclic HIV protease inhibitors.[297] Recently, some 3-aryl-substituted isoxazolyl-4-boronic acids, prepared by bromine−lithium exchange, have been used in Suzuki couplings for the synthesis of cyclooxygenase-2 (COX-2) inhibitors.[298] Moreover, isoxazolyl-4- and isoxazolyl-5-boronic esters have also been obtained by 1,3-dipolar cycloaddition reactions between alkynyl boronates[299] and nitrile oxides, which can also be generated in situ from the oxime **218**,[300] as shown in Scheme 58 for the synthesis of the bromoisoxazole boronic ester **219**, being used in palladium-catalyzed cross-coupling reactions to afford the isoxazole **220**.

Scheme 58

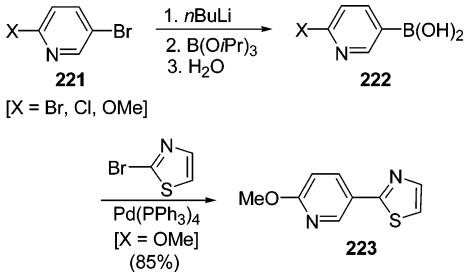


218 **219** **220**

4.1.2. Aromatic Six-Membered Rings

Boronated pyridines are prepared via the usual lithium− or magnesium−boron transmetalation[264] which, combining direct deprotonation, halogen−metal exchange, and the DoM methodology, allows the entry to boronation in any ring position. Boronated pyridines have been used mainly for the Suzuki−Miyaura palladium-catalyzed cross-coupling reaction, giving rise to all kinds of substituted pyridines. Thus, through this tandem lithium−boron exchange−cross-coupling reaction methodology, monobrominated pyridines gave almost all possible disubstituted pyridines.[264,301,302] As an example, 2-bromo-, 2-chloro-, and 2-methoxypyridylboronic acids **222** [which have been prepared from the corresponding 2-substituted 5-bromopyridines **221** by bromine−lithium exchange followed by reaction with triisopropyl borate and further hydrolysis] have been employed in Suzuki−Miyaura couplings with brominated heterocycles such as 2-bromothiazole to give the adduct **223** as shown in Scheme 59.[301f] In addition, thioethers have also been used in cross-coupling reactions with 3-pyridylboronic acids,[303] amidines also being obtained in a different process.[304]

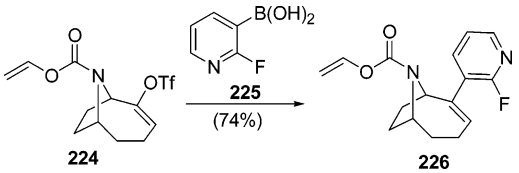
Scheme 59



221 **222** **223**

Other recent examples of the use of pyridylboronic acids in Suzuki−Miyaura cross-coupling reactions can be found in the synthesis of blockers of the voltage-gated potassium chanel Kv1.5,[305] polymerase-1 inhibitors,[306] or metacyclophanes,[307] as well as in the synthesis of analogues of the azabicyclic alkaloid anatoxin-a such as compound **226**,[308] obtained by palladium-catalyzed reaction between the fluoropyridylboronic acid **225** and enol triflate **224** (Scheme 60).[308b]

Scheme 60



224 **226**

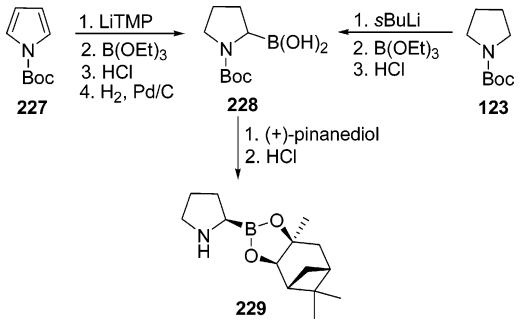
Recent examples of the use of 2-pyridylboronic esters in homocoupling reactions can be found,[309] as well as 4-pyridylboronic esters in the cross-coupling reaction applied to pyridine-derived metal-coordinating ligands.[310] In addition, pyridylboronates have been cross-coupled using copper(II) acetate.[311a] Recently, pyridylboranes, also employed in cross-coupling reactions, have been prepared by reaction of the corresponding pyridylmagnesium chlorides with diethylmethoxyborane.[311b]

4.1.3. Nonaromatic Heterocycles

N-Boc-protected pyrrolidine boronic acid **228** can be prepared by a lithiation−boronation−reduction sequence from *N*-Boc-pyrrole (**227**), or by lithium−boron exchange from *N*-Boc-pyrrolidine (**123**) (Scheme 61).[312] The boronic acid **228** can be resolved[313] using (+)-pinanediol to give the enantiomerically pure boronate **229**, which has been used for the preparation of boronic acid dipeptides, which are potent serine protease dipeptidyl peptidase inhibitors.[312] In addition, an analogue of the *N*-acetylkainic acid with a boronic acid at the 2-position has been prepared enantioselectively following a cyclization strategy, also using (+)-pinanediol as a chiral auxiliary.[314]

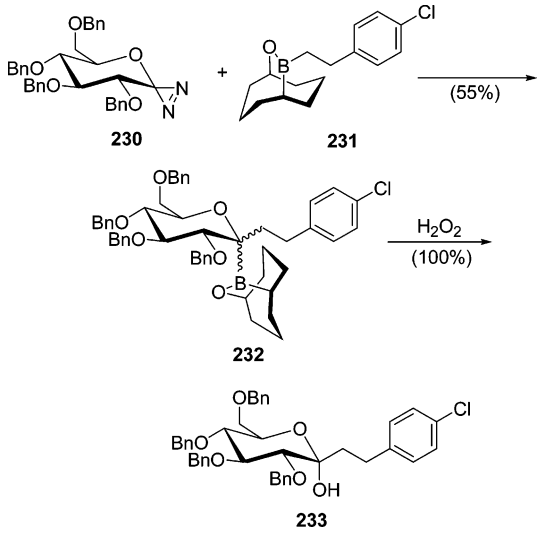
2-Quinolone derivatives with a boronic acid at the 3-position have been obtained by *n*-butyllithium-

Scheme 61



promoted deprotonation and reaction with trimethyl borate, being used for the synthesis of quinoline alkaloids.[315] In addition, glycosylidene carbenes, generated from glycosylidene diazirines such as compound **230** by thermolysis or photolysis, insert into the boron−carbon bond of triethylboron, leading to unstable glycosylboranes, while insertion into a boron−carbon bond of borinic esters such as **231** gives stable glycosylborinates **232**,[316] which can be transformed into the single hemiacetal **233** by treatment with hydrogen peroxide (Scheme 62).[316b] Moreover, a 6-boronic acid prepared from 2,3-dihydropyran has been used for palladium-catalyzed Suzuki cross-coupling reactions, although with moderate yields.[317]

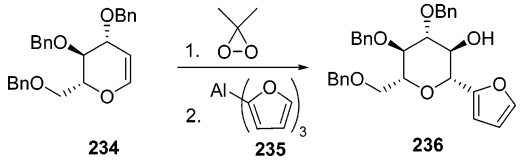
Scheme 62



4.2. Aluminum Heterocycles

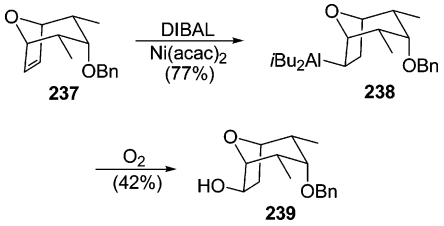
Heteroarylaluminum reagents can be prepared by coupling aluminum chlorides with the appropriate heteroaryllithiums or -magnesiums,[318,319] although starting from other heteroarylmetals such as heteroarylmercurials is possible, as was reported in the transmetalation of 2,3-bis(chloromercurio)-1-indole using trimethylaluminum.[320] Although the use of these organoaluminums in synthetic organic chemistry is rather limited, there are examples of the use of dimethyl[2-(*N*-methylpyrrolyl)]aluminum and (2-furyl)dimethylaluminum (obtained by reaction of the corresponding lithiated heterocycles with diethylaluminum chloride) in coupling reactions with glycopyranosyl fluorides.[318] Recently, tri(2-furyl)aluminum (**235**) has been used in the regio- and stereoselective ring opening of the dimethyldioxirane-promoted in situ generated epoxide from glycal **234** to give compound **236** (Scheme 63).[319] In addition, examples of the use of diethyl(thiazol-2-yl)aluminum in addition reactions to nitrones are also reported.[100]

Scheme 63



An example of an aluminated tetrahydrofuran can be seen in the nickel-catalyzed hydroalumination of the oxabicyclo[3.2.1]alkene **237** using DIBAL, giving rise to the organoalane **238**, which upon exposure to oxygen affords the *exo*-alcohol **239** (Scheme 64).[321]

Scheme 64



5. Group 4 Metal-Containing Heterocycles

5.1. Silicon Heterocycles

Heterocyclic silanes are usually prepared by reaction of the corresponding heterocyclic organolithiums with alkylhalosilanes;[322a,b] even organosilicon dendrimers derived from thiophene have been obtained using this methodology.[322c] Moreover, the formation of some heterocycles with hydridosilyl substituents has also been reported,[322d] as well as the synthesis via palladium(0)-catalyzed silylation of heteroaryl iodides and bromides with triethoxysilane.[323] The use of these organosilicon compounds in palladium-catalyzed cross-couplings with organic halides (the so-called Hiyama coupling)[324] is a very interesting alternative to the use of other organometallic derivatives. Silicon is environmentally benign, since organosilicon compounds are oxidized ultimately to biologically inactive silica gel. In these reactions, the presence of fluoride ions is essential for accelerating the transmetalation step, whereas a remarkable feature of this process is that functionalities such as carbonyl groups on both coupling partners tolerate the reaction conditions.[324]

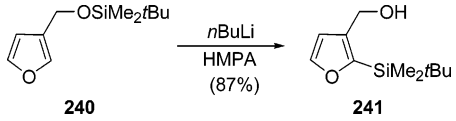
Heteroaryl derivatives of silicon (and boron or tin) also suffer *ipso*-substitution by electrophiles due to a large β-effect via a mechanism analogous to other aromatic substitutions although generally at a much faster rate.[325] In addition, the silyl group has also been employed as an easily removable protecting group for acidic hydrogens.

5.1.1. Aromatic Five-Membered Rings

2-Silyl-substituted *N*-protected pyrroles, furans, and thiophenes are usually obtained by direct lithia-

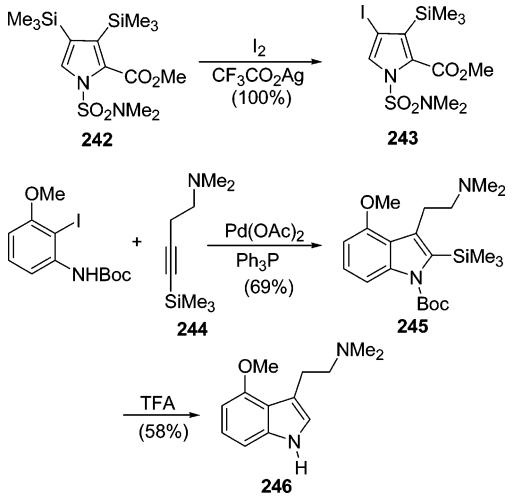
tion followed by reaction with a silylation reagent.[322a,326] In the case of 3-silyl heterocycles, the synthesis is generally carried out via halogen−lithium−silicon exchange.[322a,326] Other methods have also been developed for the preparation of 3,4-bis(silylated) pyrroles,[327a,b] furans, and thiophenes.[327c] In addition, silylated furan rings such as compound **241** have also been obtained by oxygen-to-carbon retro-Brook silyl migration from the lithiation of silyl ethers such as in the case of starting material **240** (Scheme 65).[328]

Scheme 65



Perhaps the most frequent use of a silyl group on a nitrogen-containing heterocycle has been the *ipso*-substitution reaction.[325] Thus, mono-*ipso*-iodination at the most nucleophilic C-4 of bis(trimethylsilyl)-pyrrole **242** to give the pyrrole **243** has been carried out using iodine and silver trifluoroacetate (Scheme 66), in a formal total synthesis of the marine natural

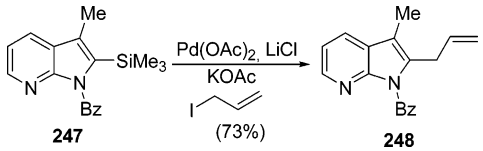
Scheme 66



product lukianol A.[329] This kind of *ipso*-halogenation has been profusely used in indole transformations such as palladium-catalyzed couplings, due to the importance of this heterocyclic system in natural product chemistry.[330−336] In addition, the protodesilylation[337−340] or fluoride-promoted elimination[341,342] have also been employed on indoles and related systems as a way of removing an auxiliary silyl group, as shown in Scheme 66 for the synthesis of compound **245**, which has been obtained via a palladium-catalyzed cyclization using the silylacetylene **244**, being a precursor of a scaffold of psilocin.[343] Moreover, there are also examples of palladium-catalyzed coupling reactions, such as the coupling of the 2-silylpyrrolopyridine **247** with allyl iodide to give the derivative **248** (Scheme 67).[344]

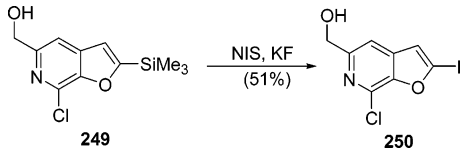
The *ipso*-silyl substitution has also been employed on silylated furan rings.[326] Thus, 2-(trimethylsilyl)-furopyridine **249** has been transformed into 2-iodo-furopyridine **250**, suitable for palladium-catalyzed

Scheme 67



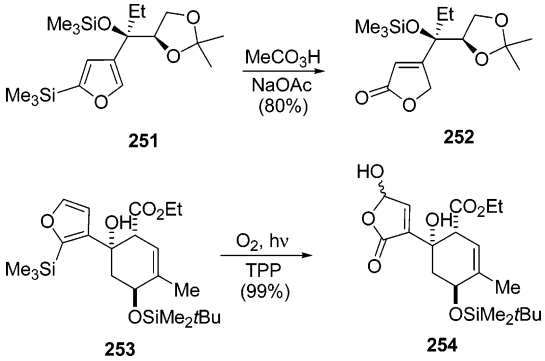
couplings, after treatment with *N*-iodosuccinimide (NIS) (Scheme 68).[345] This *ipso*-iodination, but using iodine, has also been used in the preparation of polysubstituted furans such as rosefuran.[346] This electrophilic substitution has also been carried out on 4-methyl-3-(trimethylsilyl)furan with an electrophile such as boron trichloride, affording a key intermediate in studies toward eudesmanes.[278]

Scheme 68



2-Silylated furan rings can be regiospecifically converted into butenolides or 5-hydroxybutenolides, in which the carbonyl group is attached to the carbon atom where the silyl group was originally, after treatment with either a peracid or singlet oxygen, respectively.[326] This methodology has been profusely applied to the synthesis of numerous natural products. Thus, chiral butenolide **252** has been prepared by treating the silylfuran **251** with 40% peracetic acid (Scheme 69), in an enantioselective synthesis of

Scheme 69

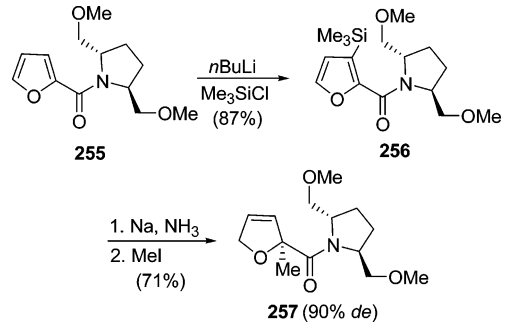


plakortones, which are cardiac sacroplasmic reticulum Ca^{2+}-pumping ATPase activators.[347] In addition, 5-hydroxybutenolide **254**, generated from furan **253** after oxygen was bubbled under UV irradiation in the presence of tetraphenylporphyrin (TPP), has been used as an intermediate toward the total synthesis of milbemycin E[348] (Scheme 69) and G.[349] Other examples where these synthetic procedures have been applied are the synthesis of an analogue of the carbenolide ouabain,[350] the carotenoid peridinin,[351] the alkaloid norzoanthamine,[352] the terpenoid acuminolide,[353] (−)-spongianolide A,[353,354] the frameworks of CP-225,917 and CP-263,114,[355] a fragment of rapamycin,[356] and sphydrofuran.[357]

An example of the use of the silyl group bonded to the furan ring as an easily removed auxiliary[326] is a recent stereoselective synthesis of 2-furoic acids.

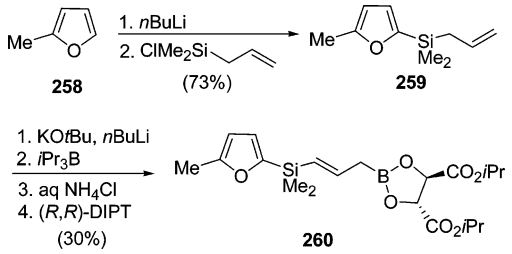
Thus, the silylated system **256** is prepared from compound **255** following a conventional *ortho*-lithiation procedure and suffers Birch reduction followed by diastereoselective alkylation and silyl removal to afford the 2-furoic acid derivative **257** (Scheme 70).[358] In addition, the Birch reduction of 2-(trialkylsilyl)-3-furoic acids is known to affect only the silyl-carrying double bond.[359]

Scheme 70



α-Silylated furans have also been used for the preparation of chiral reagents for the *anti*-α-hydroxyallylation of aldehydes, due to the easier protodesilylation of the furylsilane compared to, for instance, allylsilane. Thus, 2-methylfuran (**258**) is lithiated and reacts with allyldimethylchlorosilane, affording the metalated furan **259**, which was transformed into the corresponding boronic acid and esterified with (*R,R*)-diisopropyl tartrate (DIPT), giving the chiral silyl boronate **260** (Scheme 71). This compound has been

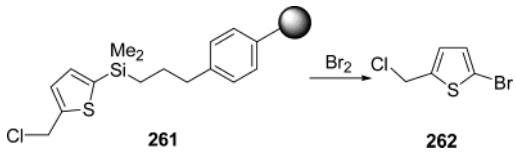
Scheme 71



employed, for instance, in the enantioselective synthesis of (−)-swainsonine.[360] There are also examples of the use of silylfurans as dienes in different intermolecular[361] and intramolecular[362] Diels−Alder reactions.

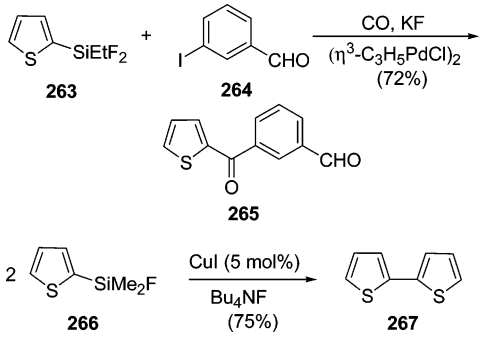
The *ipso*-silicon−halogen substitution reaction has also been used on silylthiophenes,[363] a recent example being the cleavage of a resin-bound compound (**261**) with bromine to give the bromothiophene **262**, in studies on heteroaromatic linkers for solid-phase synthesis (Scheme 72).[364]

Scheme 72



One example which shows the applicability of the palladium-catalyzed coupling reaction of silylated thiophenes is the carbonylative coupling of 2-(ethyldifluorosilyl)thiophene (**263**) (prepared by reaction of 2-thienyllithium with ethyltrichlorosilane and further treatment with SbF_3) with the aldehyde **264** to afford compound **265** (Scheme 73).[365] Similar cou-

Scheme 73



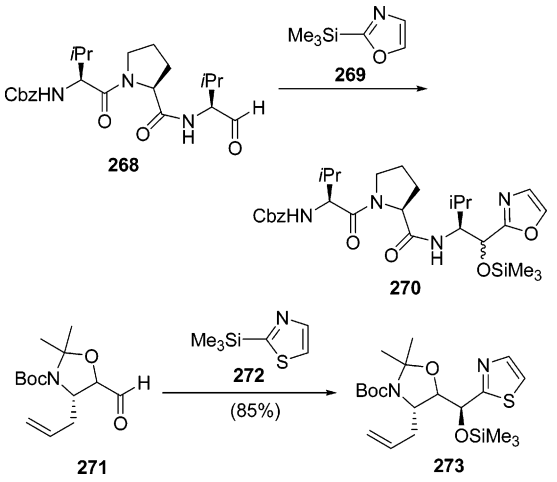
plings are described using 2-(fluorodimethylsilyl)-thiophene (**266**),[366] which has been homocoupled using copper(I) iodide as the catalyst to afford the bithiophene **267** (Scheme 73).[367] A similar homocoupling has been performed starting from 2-(methoxydimethylsilyl)thiophene or its *N*-methylpyrrole analogue, although in this case no addition of a fluoride ion source was necessary.[368] Homocoupling of silylated dithienylbenzo[*c*]thiophenes toward oligothiophene derivatives, which exhibit promising electrochemical, optical, and electronic effects (see above), has also been recently performed using iron(III) chloride.[369]

The introduction of a silyl group at the 2-position in *N*-protected imidazoles has been used as a logical way of changing the acidic proton by an easily removable group, thus allowing deprotonation at C-5 and further transformations. Examples are 2-silylated imidazoles, which are lithiated at C-5 and act as nucleophiles.[370]

The preparation of 2-silylated oxazoles is not obvious, since the usual 2-lithiation−silylation sequence drives the above-mentioned ring opening to give an isocyano enolate (see above) after the lithiation step. This problem has been overcome by *O*-silylation of the isocyano enolate followed by a base-promoted insertion to give the corresponding 2-silyloxazole.[371] The procedure can be simplified by a heat-induced cyclization in the final distillation step.[372] These 2-silylated oxazoles can be used as nucleophiles in additions to aldehydes, as shown in Scheme 74 for the addition of 2-(trimethylsilyl)oxazole (**269**) (and many other metalated heterocycles) to the tripeptide-derived aldehyde **268** to give peptidyl α-hydroxyalkyloxazole **270**, which after oxidation gives a peptidyl α-ketooxazole inhibitor of human neutrophil elastase.[372] Recently, 4-(triethylsilyl)oxazoles have been prepared by treatment of (triethylsilyl)diazoacetates with rhodium(II) octanoate and nitriles, being precursors of 4-halogenated oxazoles after treatment with *N*-halosuccinimides.[373]

2-(Trimethylsilyl)thiazole (**272**), which is prepared by the conventional lithiation−silylation sequence, has been frequently used for addition reactions to aldehydes,[374,375] mainly for chain elongation due to the consideration of the thiazole moiety as an equiva-

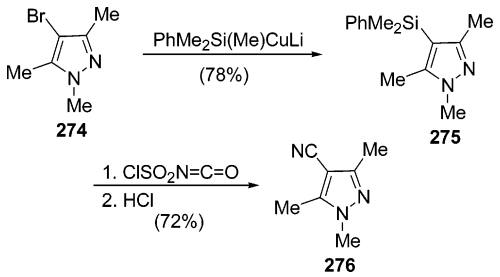
Scheme 74



lent of the formyl synthon. The reaction, as in the case of 2-silyloxazoles, is orbital-symmetry-forbidden, but ab initio calculations showed results consistent with a termolecular mechanism.[376] An example of the use of **272** is its diastereoselective addition to the chiral aldehyde **271**, yielding the protected alcohol **273**, an intermediate in the synthesis of the pseudopeptide microbial agent AI-77-B (Scheme 74).[374h] Although the addition to aldehydes is well documented, the less known reaction with ketones[377] and some acid chlorides[378] has also been reported. Other examples of the use of 2-(trimethylsilyl)thiazole are the ring expansion of a cyclopropanated carbohydrate,[379] the copper(I) salt-mediated coupling to iodobenzene,[380] or the *ipso*-substitution with iodine.[381]

4-Silylated pyrazoles and isoxazoles can be synthesized by silylcupration from 4-haloazoles,[382] whereas the 5-silylated analogues have been prepared by reaction of 5-unsubstituted pyrazoles with LDA and further treatment with chlorosilanes.[382] An example of the former methodology is the synthesis of the 4-silylpyrazole **275** from bromopyrazole **274**, which can be used in *ipso*-substitution reactions using, for example, chlorosulfonyl isocyanate to give the cyanopyrazole **276** (Scheme 75).[382] In addition,

Scheme 75

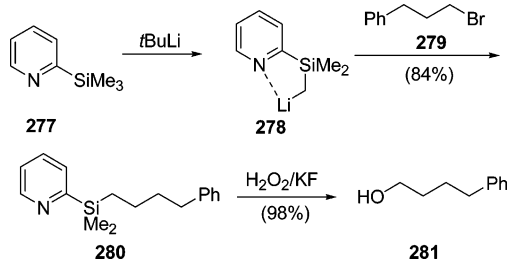


1-hydroxypyrazoles have been silylated at C-5 via the usual lithiation−silylation sequence, thus allowing further metalation at C-4,[108] whereas other silylpyrazoles have been recently obtained from silylated β-enaminones[383] or from lithiated (trimethylsilyl)diazomethane.[384] Moreover, 3,5-disubstituted isoxazoles and isothiazoles can be silylated at C-3 after lithiation with different alkyllithiums.[385]

5.1.2. Aromatic Six-Membered Rings

2-(Trimethylsilyl)pyridine (**277**), which is easily prepared from 2-bromopyridine by a tandem lithiation−silylation sequence, has found very interesting applications for the generation of the corresponding α-silyl carbanion **278** after reaction with *tert*-butyllithium or LDA (Scheme 76).[386] This easy α-lithiation

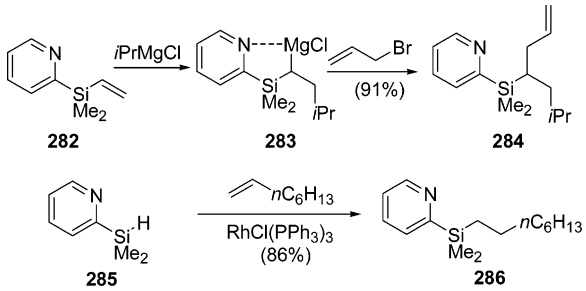
Scheme 76



is based on the intramolecular pyridyl group coordination to stabilize further the α-silyl carbanion via CIPE (complex-induced proximity effect).[387] The metalated species **278** reacts with electrophiles and can be oxidized to the corresponding alcohols, as shown in Scheme 76 for the reaction of the intermediate **278** with an alkyl halide such as **279**, affording compound **280**, which is transformed into alcohol **281**.[388] Thus, the (2-pyridyldimethylsilyl)methyllithium can be considered as a hydroxymethyl anion equivalent.[389] When (pyridyldimethylsilyl)methyllithium (**278**) reacts with dimethyl(pyridyl)silane, a dimeric bis(2-pyridyldimethylsilyl)methane is obtained, which is suitable for lithiation, affording $(2\text{-PyMe}_2\text{Si})_2\text{CHLi}$, reacting then with electrophiles.[390]

The 2-pyridyldimethylsilyl group in vinylsilanes, such as compound **282**, acts as a directing group in carbomagnesiation reactions, giving the α-silyl organomagnesium compound **283** after reaction with *i*PrMgCl and, in the presence of an electrophile such as allyl bromide, affords adduct **286** where the 2-pyridyldimethylsilyl group can be oxidatively removed as was previously mentioned (Scheme 77).[391]

Scheme 77



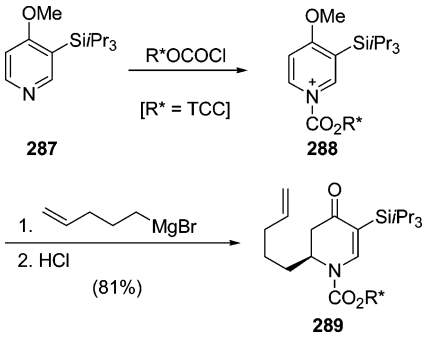
In addition, more uses of this 2-pyridyldimethylsilyl moiety as an activating and directing removable group can be found in the silver acetate-catalyzed aldehyde allylation using allyldimethyl(2-pyridyl)silane,[392] or in the metal-catalyzed hydrosilylation of alkenes and alkynes using dimethyl(pyridyl)silane (**285**),[393] an example of this use being shown in Scheme 77 for the rhodium-catalyzed hydrosilylation of 1-octene to afford compound **286**.[393b] The mentioned silyl group has also been used as a removable

hydrophilic group in aqueous Diels−Alder reactions[394] and in intermolecular Pauson−Khand processes.[395] In addition, there are numerous examples of the use of this pyridylsilyl group as a directing group for cross-coupling reactions.[396] An interesting consideration is that this group can act as a "phase tag" for the easy extraction of the reaction products.[397]

There are also recent examples of the use of the *ipso*-substitution reaction, such as the *ipso*-iodination, applied to 2-(trimethylsilyl)pyridines for the synthesis of biologically active products.[398] In addition, silylated pyridines can be used for the generation of pyridynes in the presence of a fluoride source and when a suitable leaving group is at the vicinal carbon.[399] Furthermore, bipyridyl silylated montmorillonite has been used as an anchored ligand for ruthenium in the oxidation reaction of aromatic alkenes.[400]

4-Methoxy-3-(triisopropylsilyl)pyridine (**287**) has been transformed into the chiral 1-acylpyridinium salt **288** by reaction with the chloroformate derived from (+)-*trans*-2-(α-cumyl)cyclohexanol (TCC), reacting afterward with organometallics such as pentenylmagnesium bromide to give the diastereomerically enriched dihydropyridone **289**, after hydrolysis (Scheme 78).[401] This methodology using this pyridinium salt[402] (and others[403]) has found profuse applications for the synthesis of natural products. In addition, 3-(trimethylsilyl)pyridin-2-yl triflate was converted into 2,3-pyridyne by reaction with cesium flouride and was trapped with furans.[404]

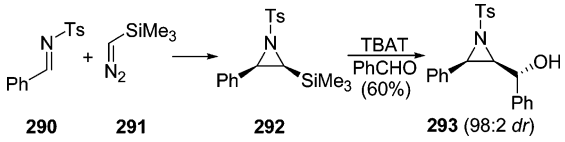
Scheme 78



5.1.3. Nonaromatic Heterocycles

Silylated aziridines can be transformed into aziridinyl anions by treatment with a fluoride source. Thus, (trimethylsilyl)diazomethane (**291**) adds directly to *N*-sulfonylimines, such as **290**, to afford the corresponding silylaziridine **292** with 95:5 *cis*-stereoselectivity.[405,406] When these kinds of silylaziridines react with a flouride source such as triphenyltrifluorosilicate (TBAT), an azirinidyl anion is formed, being able to react with electrophiles such as benzaldehyde, affording the corresponding alcohol **293** with retention of the preliminary *cis*-configuration and also with high diastereoselectivity at the newly created stereocenter (Scheme 79).[406] In addition, epoxysilanes,[407,408] can be transformed into oxiranyl anions by treatment with fluoride as mentioned previously, examples being the generation of an

Scheme 79

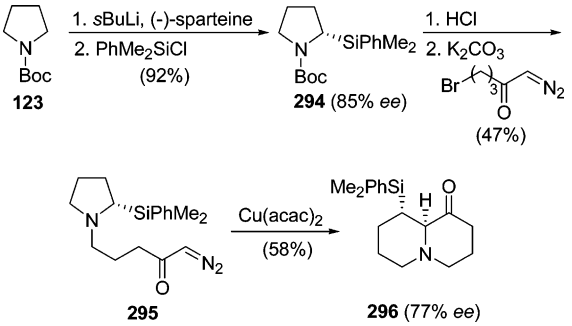


oxiranyl anion from a (trimethylsilyl)epoxylactone and tetra-*n*-butylammonium fluoride (TBAF) and its reaction with aldehydes,[409] or the recent TBAF-mediated generation of an amide carbonyl-stabilized oxiranyl anion.[410]

4-(Trimethylsilyl)azetidin-2-ones have been transformed into 4-fluoroazetidin-2-ones by anodic oxidation in the presence of triethylamine−hydrogen fluoride complex.[411] In addition, silylated oxygen-containing four-membered heterocycles such as 4-silylated β-lactones have been obtained by cyclization between an acylsilane and ynolates[412] or metalated cyclopropyl thiol esters.[413] Moreover, silylthietanes have been obtained by photoinduced cycloadditions of silylated thioketones with electron-deficient olefins.[414]

The silyl group of 2-silylpyrrolidines such as compound **294** [asymmetrically introduced to *N*-Boc-pyrrolidine (**123**) according to the organolithium/sparteine-silylation methodology (see above)] can act as a stereochemical control element in a carbenoid addition to the ring nitrogen in the alkylated intermediate **295**. Subsequent Stevens [1,2]-shift of the corresponding ammonium ylide gives the quinolizidine **296** as a single diastereoisomer (Scheme 80).[415]

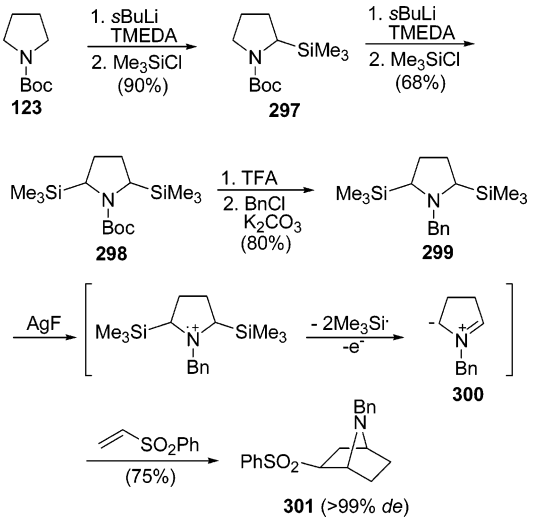
Scheme 80



In addition, 3,4-substituted pyrrolidines bearing a 2-silyl group have been diastereomerically obtained from 3,4-disubstituted pyrrolidines using the former asymmetric lithiation−silylation sequence.[25] Moreover, *N*-Boc-protected 2-(trimethylsilyl)pyrrolidine has been deprotonated with *sec*-butyllithium and reacted with trimethylsilyl chloride to give the corresponding disilylated pyrrolidine, which can be electrochemically oxidized, affording a 2-silylpyrrolidinium ion able to react with nucleophiles such as allyltrimethylsilane or homoallylmagnesium bromide.[416] Furthermore, the dimethylphenylsilyl group has also recently been introduced at the α-position of a pyrrolidine using a mesylate substitution reaction with the corresponding silyl cuprate, in the construction of functionalized peptidomimetics.[417]

N-Boc-protected 2,5-bis(trimethylsilyl)pyrrolidine (**298**) has been prepared from the corresponding *N*-Boc-pyrrolidine (**123**) by sequential double α-lithi-

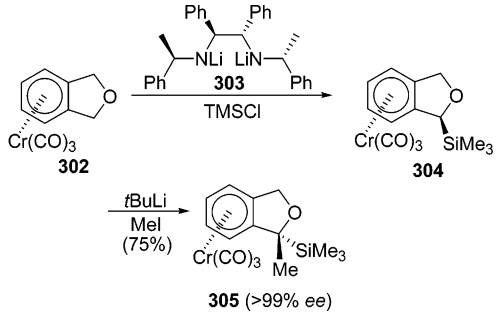
Scheme 81

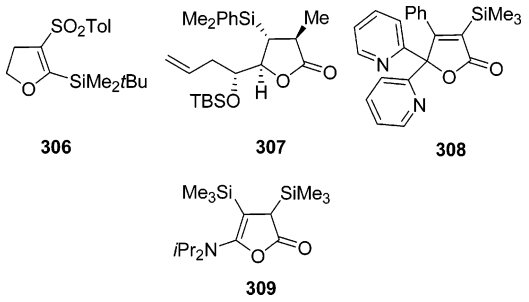


ation−silylation via the monosilylated intermediate **297** (Scheme 81). This 2,5-bis(trimethylsilyl)pyrrolidine **298** can be benzylated to compound **299**, which is a precursor of nonstabilized azomethine ylide **300** in a process initiated by a one-electron oxidation either by photoinduced electron transfer (PET) processes or by using silver(I) fluoride as a one-electron oxidant (Scheme 81). The ylide **300** can react in a [3 + 2]-cycloaddition fashion with dipolarophiles[418] such as phenyl vinyl sulfone to give the corresponding adduct **301**.[418c] This strategy has been used for the synthesis of epibatidine and analogues,[418b,c] as well as for the preparation of azatricycloalkanes after intramolecular cycloaddition.[419] On the other hand, the same methodology has also been employed starting from *N*-Boc-protected piperidine[418,419] or azepane.[418b,c]

Silylated oxolanes are prepared generally by the lithiation−silylation sequence,[408] although methods, such as a rhodium-catalyzed 1,3-dipolar cycloaddition using a cobalt-containing silylated carbonyl ylide, have been reported.[420] A recent example of the application of the lithium−silicon methodology is the deprotonation of prochiral phthalan-derived chromium complex **302**, which takes place using the chiral lithium amide **303** in the presence of trimethylsilyl chloride at −100 °C. Further deprotonation of the silyl complex **304** and quenching with an electrophile gives complex **305** in >99% ee (Scheme 82).[421] This compound can be desilylated using tetra-*n*-butylammonium fluoride (TBAF), furnishing pure *endo*-diastereomer after protonation. A recent example of the application of a silylated oxolane can be found in the synthesis of the opioid (+)-bractazonine,[422] or the synthesis of a part of the antibiotic lactonamycin.[423] In addition, isobenzofurans have been generated from silylated lactols.[424] Recently, 5-silylated 2,3-dihydrofurans such as **306** have been prepared from alkynyliodonium salts,[425] and their 4-silylated counterparts from allenylsilanes, in a reaction catalyzed by a scandium complex, being used in Friedel−Crafts acylations.[426] Moreover, 4-silylated γ-lactones, such as **307**, can be prepared by conjugate addition of lithium bis(dimethylphenylsilyl)cuprate to 5*H*-furan-2-ones,[427] whereas some 3-silylated 5*H*-furan-2-ones, such as **308**, have been obtained by ruthenium-catalyzed [2 + 2 + 1]-cyclocoupling of di-2-pyridyl ketone, (trimethylsilyl)acetylenes, and carbon monoxide,[428] and 6-aminated bis(trimethylsilyl)-3*H*-furan-2-ones such as **309** by amination of bis(trimethylsilyl)-1,2-bisketene with secondary amines.[429]

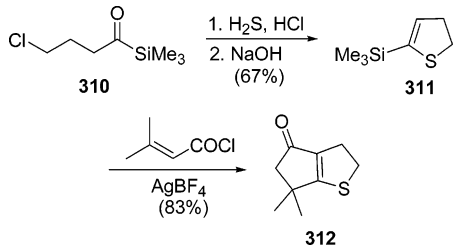
Scheme 82





The 3-silylated 2,3-dihydrothiophene **311** has been obtained from the γ-chloroacyltrimethylsilane **310** by treatment with hydrogen sulfide and hydrogen chloride (Scheme 83), a methodology which has been applied to the preparation of up to 14-membered cycles.[430] These cyclic vinyl sulfides can be applied to the synthesis of thioannulated cyclopentenones via the Nazarov cyclization, after treatment with 3,3-dimethylacryloyl chloride in the presence of silver tetrafluoroborate, affording compound **312**.[430b]

Scheme 83

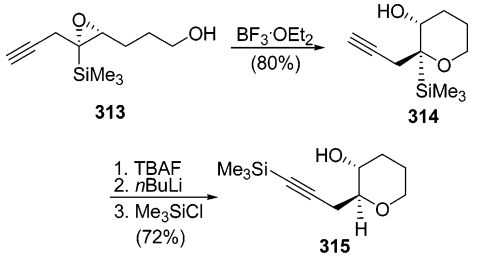


α-Silylated piperidine and tetrahydroquinoline derivatives have been transformed into the corresponding α-cyanoamines by electrochemical cyanation.[431] In addition, 3-silylated 2,3-dihydro-1*H*-pyridin-4-ones have been obtained by addition of organometallic compounds to 3-silyl-4-methoxyacylpyridinium salts, being interesting intermediates in the asymmetric synthesis of natural products (see above).[401−403]

α-Silylated tetrahydropyrans, prepared by the usual lithium−silicon transmetalation,[408] have been used as a source of alkoxycarbenium ions via anodic oxidation, reacting further with carbon nucleophiles such as allylic silanes.[432] Furthermore, the chiral

epoxysilane **313** has been recently cyclized to give the silylated tetrahydropyran **314**, which, after fluoride-promoted desilylation and acetylene silylation, gives the tetrahydropyran **315** (Scheme 84), in a strategy

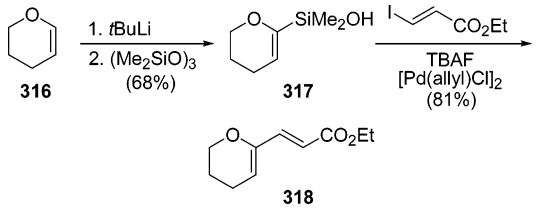
Scheme 84



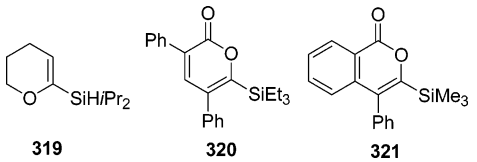
for the synthesis of naturally frequent *trans*-fused ("ladder") polyethers.[433] On the other hand, the conjugate addition of silyl cuprates to monosaccharide-derived 2,3-dihydro-4*H*-pyran-4-ones allows the synthesis of silyl glycosides which can be used for the sila-Baeyer−Villiger oxidation or as precursors of *C*-glycosides.[434]

6-Silylated 3,4-dihydro-2*H*-pyrans can be obtained by intramolecular cyclization of haloacylsilanes after heating in a polar solvent, a methodology also applied to 5-silylated 2,3-dihydrofurans.[435] In addition, the dihydropyran-derived silanol **317** can be prepared by lithiation of dihydropyran (**316**) followed by addition of hexamethylcyclotrisiloxane, being suitable for palladium-catalyzed cross-coupling reactions with either aryl iodides or ethyl (*E*)-3-iodoacrylate to give in the last case compound **318**, if a fluoride source is present (Scheme 85).[436] A dihydropyran-derived silyl hydride

Scheme 85

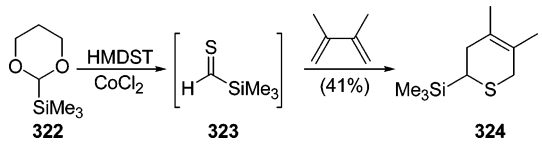


(**319**) has also been prepared following a similar methodology.[436] Moreover, 6-silylated pyran-2-ones such as compound **320** and 3-silylisocoumarins such as heterocycle **321** have been obtained via palladium-catalyzed annulation of silylalkynes,[437] a methodology which has also been used for the preparation of 5-silylpyran-2-ones by means of nickel catalysis.[438]

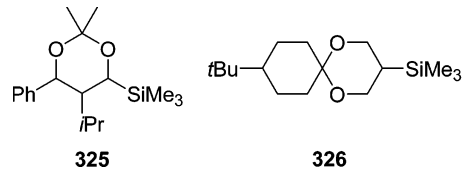


2-Silylated 1,3-dioxanes, such as compound **322**, have been prepared from the corresponding 2-silyl-1,3-dithianes[208] by treatment with mercury(II) chloride/mercury(II) oxide in ethylene glycol.[439] Subsequent exposure of this acetal to hexamethyldisilathiane (HMDST) and cobalt(II) chloride led to the thioformylsilane intermediate **323**, which can be

Scheme 86



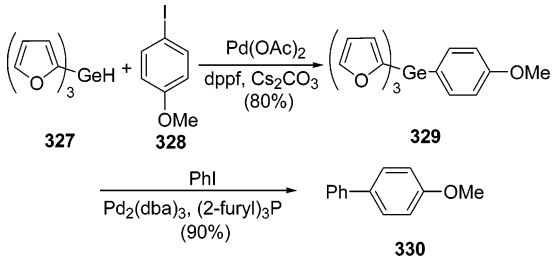
trapped with 2,3-dimethylbutadiene to give the adduct **324** (Scheme 86).[439] Using this type of cycloaddition, but employing cyclopentadiene and trimethylsilyl phenyl thioketone as a dienophile, the resulting adduct has been protodesilylated to give 2-thiabicyclo[2.2.1]hept-5-ene.[440] In addition, 4-silylated 1,1-dimethyl-1,3-dioxanes such as **325** have been obtained by acetalization of the corresponding diols obtained after reduction of products obtained from the diastereoselective aldol condensation of acylsilane silyl enol ethers with acetals.[441] Moreover, 5-(trimethylsilyl)-1,3-dioxanes such as compound **326**, obtained by acetalization of ketones using 2-(trimethylsilyl)-1,3-propanediol, have been used as carbonyl protecting groups, susceptible to unmasking using lithium tetrafluoroborate.[442]



5.2. Germanium Heterocycles

Tri(2-furyl)germane[443] has found recent interesting uses in palladium-catalyzed reactions, bridging the existing gap between group 4-derived arylsilanes and arylstannanes in cross-coupling chemistry. Thus, tri(2-furyl)germane (**327**) can be transformed into an aryltrifurylgermane such as compound **329** by palladium(0)-promoted coupling with an aryl halide such as compound **328**. Subsequent cross-coupling reaction between aryltrifurylgermane **329** and iodobenzene allows the preparation of the diaryl compound **330** (Scheme 87).[444] Tri(2-furyl)germane has also been

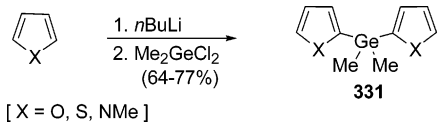
Scheme 87



used in Et_3B-induced hydrogermylation of alkenes and silyl enol ethers,[445] or alkynes and dienes in water,[446] as well as in the synthesis of acylgermanes by palladium(0)-catalyzed reaction with alkynes in the presence of carbon monoxide.[447] In addition, tri(2-furyl)germane has been employed for nucleophilic addition to aldehydes and α,β-unsaturated carbonyl compounds in the presence of a catalytic amount of a base.[448]

The reaction of lithiated heterocycles such as furan, thiophene or *N*-methylpyrrole with Me_2GeCl_2 gives Me_2Ge-bridged dimers **331** (Scheme 88). Subsequent

Scheme 88



n-butyllithium-promoted deprotonation at 5- and 5′-positions and further reaction with Me_2GeCl_2 gave rise to linear oligomers, except in the case of the pyrrole derivative, which afforded a macrocyclic tetramer.[449] In addition, a germanium-based linker of the type $GeMe_2Cl$ has been used for anchoring lithiated silylthiophenes, in an strategy designed for the solid-phase synthesis of oligothiophenes via Suzuki cross-couplings, using an orthogonal Si/Ge protection due to the susceptibility of a α-silyl but not a α-germyl substituted thiophene toward *ipso*-protodemetalation.[450]

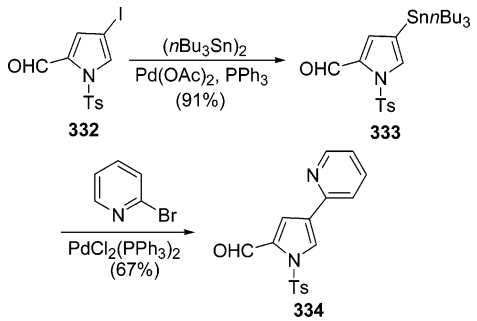
5.3. Tin-Heterocycles

In general, heterocyclic stannanes have been obtained by reaction of their corresponding heterocyclic organolithiums with a chlorostannane or in some cases by transmetalation. These metalated heterocycles have found application mainly in palladium-catalyzed cross-coupling reactions (the so-called Stille−Migita coupling),[451] although the above-mentioned heteroarylboron and heteroarylsilicon *ipso*-substitution also take place here.

5.3.1. Aromatic Five-Membered Rings

The general method for the preparation of stannylpyrroles is the reaction of the corresponding *N*-protected heteroaryllithium (see above) with a chlorostannane. However, other methods producing stannylated pyrroles with a free N−H moiety based on cyclization reactions have been reported.[452] In addition, *N*-protected 3-stannylpyrroles such as compound **333** have been prepared by a palladium-catalyzed reaction between the corresponding pyrrole **332** and a bis(trialkylstannane), as shown in Scheme 89,[453] which also illustrates the subsequent synthesis

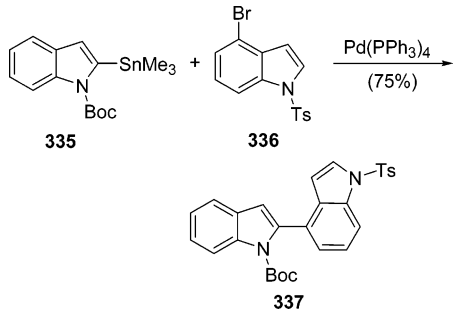
Scheme 89



of formylpyrrole **334** from compound **333**, the most common application of these stannylated heterocycles.[454] Other reactions such as *ipso*-substitutions have been reported.[455]

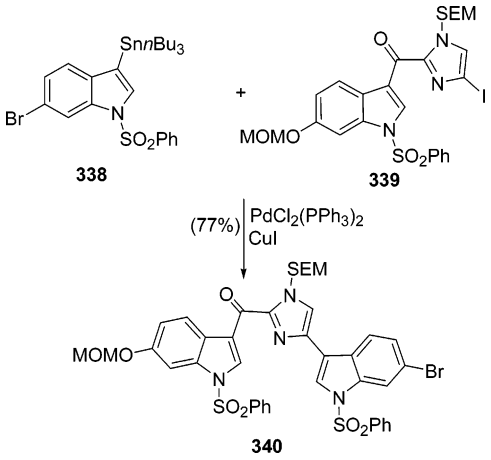
2-Stannylated indoles are prepared usually by direct deprotonation of the corresponding *N*-protected indole and further treatment with a trialkylstannyl chloride, whereas their 3-stannylated counterparts can be prepared by halogenation of the corresponding *N*-protected indole followed by lithiation and reaction with trialkylstannyl chloride, or even by the palladium(0)-catalyzed coupling between a 3-halogenated indole and a bis(trialkylstannane). These tin derivatives have been used, for instance, in *ipso*-substitution reactions,[456] but their main interest usually is in palladium-catalyzed Stille cross-coupling reactions,[457] even in the solid phase,[458] a methodology which has been often employed in natural product synthesis. For instance, in a key step for the synthesis of the slime mold alkaloid arcyriacyanin A, the 2-(trimethylstannyl)indole **335** is coupled with the brominated indole **336** under palladium(0)-mediated catalysis to give bis(indole) **337** (Scheme 90).[459]

Scheme 90



Examples of the use of 3-trialkylstannylated indoles in Stille couplings can be found in the total synthesis of or approaches to dragmacidin D,[460] penems,[461] diazonamide A,[462] staurosporine,[463] nevirapine derivatives,[464] the marine cytotoxic agents grossularides-1 and -2,[465] *dl*-cypridina luciferin analogues,[466] or the marine alkaloids topsentin, deoxytopsentin, and bromotopsentin. A key step in the synthesis of the latter one is shown in Scheme 91, where (tri-*n*-

Scheme 91

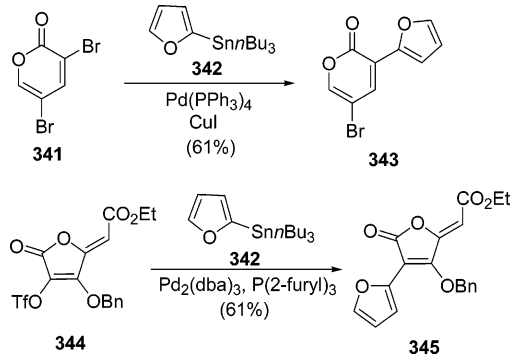


butylstannyl)indole **338** couples with the imidazoloindole **339** to give compound **340**.[467] In addition, stannylindoles have been coupled to propiolates,[468] and stannylated 7-azaindoles have also been em-

ployed in Stille reactions,[469] a method used for the preparation of 7-azaolivacine analogues.[470]

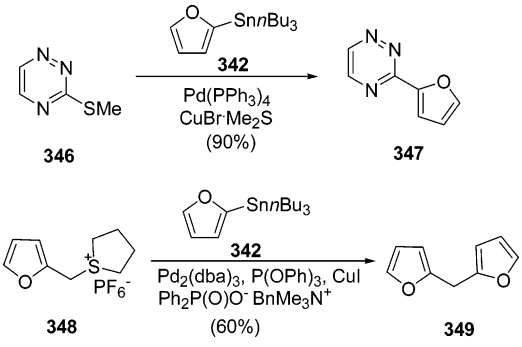
Furan-derived organostannanes have been obtained mainly from the corresponding organolithiums as in the case of pyrroles (see above), their use being dedicated mainly to palladium-catalyzed Stille cross-coupling reactions. Thus, many examples of the use of furanylstannanes in palladium-catalyzed cross-coupling reactions have been reported in the last several years, generally using different halides as coupling counterparts[454e,471] as shown in the regioselective Stille coupling of 3,5-dibromo-2-pyrone (**341**) with 2-(tri-*n*-butylstannyl)furan (**342**) under copper cocatalysis, affording pyrone **343** (Scheme 92).[471r]

Scheme 92



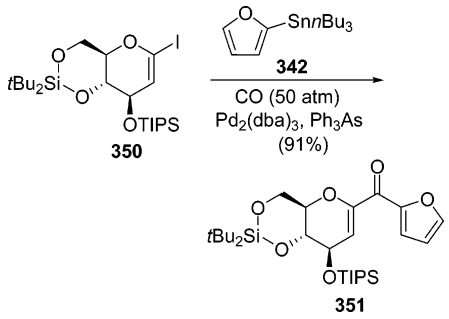
This Stille coupling has also been performed with the halide,[472] or even the palladium catalyst,[473] anchored to a solid phase. Furthermore, the reaction has been carried out under microwave irradiation,[474] and recently in supercritical carbon dioxide.[475] The cross-coupling reaction using stannylated furans has also been carried out using triflates as counterparts[476] [an example being the synthesis of the alkylidenetetronic ester **345** from triflate **344** (Scheme 92)[476c]], triflones,[477] phosphates,[478] iodanes,[479] and acid chlorides.[480] In addition, thioethers have also been used as coupling partners under copper(I)-promoted palladium catalysis,[481] as in the case of the (methylsulfanyl)triazine **346** shown in Scheme 93,[481b] and

Scheme 93



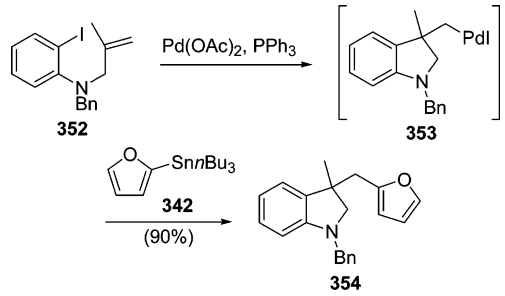
even sulfonium salts such as the hexafluorophosphate **348**, finally affording the adducts **347** and **349**, respectively,[482] in the last case the presence of an nBu_3Sn scavenger, such as $Ph_2P(O)O^-BnMe_3N^+$, being necessary. Furthermore, palladium-catalyzed homocoupling of heteroarylstannanes have also been reported,[483] together with carbonylative Stille couplings, as is the case for the reaction shown in Scheme 94 where the iodoglucal **350** has been used to give compound **351**.[484]

Scheme 94



Different palladium-catalyzed tandem cyclization−anion capture processes have been reported using 2-furyl- and 2-thienyltins,[485] an example being the synthesis of furanylindoline **354** from the amine **352** through palladated species **353** (Scheme 95).[485b]

Scheme 95



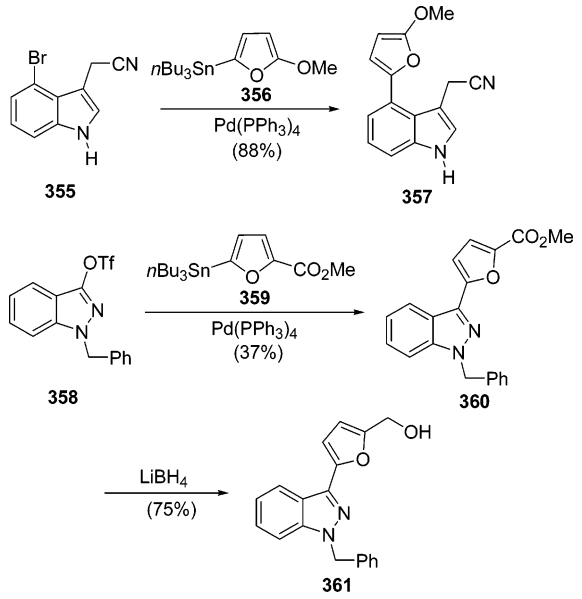
Acyclic propargyl carbonates have also been used in cascade reactions toward the synthesis of diheteroarylated dienes[486] and heteroaryl-substituted azabicyclohexanes.[487]

There are also recent examples of the use of cross-couplings using stannylfurans or -thiophenes under copper,[488] nickel,[489] and manganese[488a,e,490] catalysis, as well as homocouplings using copper.[491] In addition, the stannyl group can also be used for the introduction of electrophiles onto the furan aromatic ring,[492] as well as interchanged with lithium, as shown in the generation and use of 3-lithiofuran in recent total syntheses of (+)- and (−)-saudin[493] and sphydrofuran.[494] Moreover, stannanes such as 2-furyltributylstannane have been used as nucleophile species in reactions such as the regioselective opening of 5-*O*-benzyl-1,2:3,4-di-*O*-isopropylidene-D-psicofuranose mediated by trimethylsilyl triflate.[495]

Examples of the use of heteroarylstannanes such as furylstannanes in Stille couplings toward natural or pharmacological products synthesis are frequent, as in the preparation of different GABA-A active ligands,[496] PET tracers,[497] penems,[498] and the antitumor agents epothilones (in this case many other heteroarylstannanes also being used[49]), and in the preparation of inhibitors of gyrase B[500] and phosphotyrosine mimetics.[501] In addition, other examples are furostifolide,[502] precursors of neurotoxins such as lophotoxin[503,504] and pukalide,[504] diarylfuran antimicrobials,[505] and the *Ergot* alkaloids rugulosavines

A and B, a key step in their preparation being the synthesis of indolylfuran **357** via palladium-catalyzed coupling of (tri-*n*-butylstannyl)furan **356** with the bromoindole **355** (Scheme 96).[506] Other recent ex-

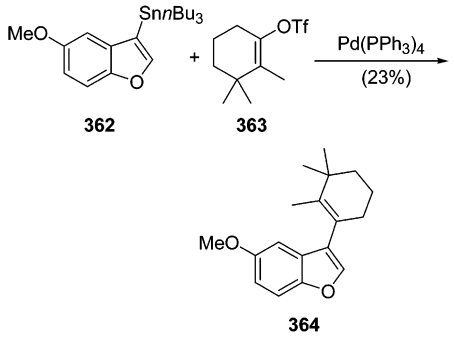
Scheme 96



amples are the use of stannylfurans, together with stannylthiophenes, in the synthesis of antimycobacterial purines,[507] the preparation of some model insect antifeedants,[508] and the synthesis of the antiinflamatory drug YC-1 (**361**), this last compound obtained by Stille coupling between the furyltrimethylstannane **359** [prepared by palladium-catalyzed coupling of the corresponding bromofuran with $(Me_3Sn)_2$] and the indazole **358**, followed by reduction of the intermediate derivative **360** (Scheme 96).[509]

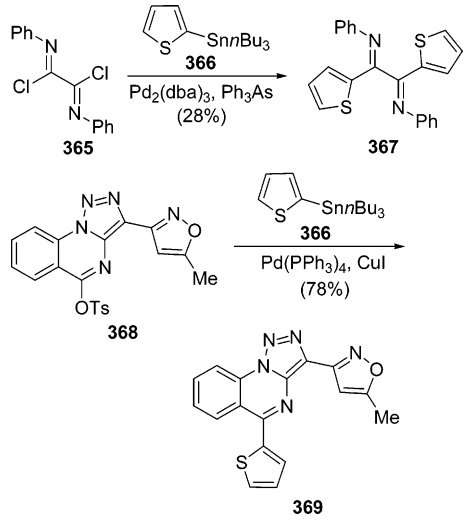
Stannylated benzofurans have also been employed in Stille couplings for natural product syntheses, a recent example being the palladium-catalyzed coupling between the tin derivative **362** (prepared from the corresponding heteroaryllithium) and the triflate **363** to give benzofuran **364**, in strategies and studies toward the total synthesis of the sponge metabolite frondosin B (Scheme 97).[510]

Scheme 97



The Stille cross-coupling reaction has frequently been employed using thienylstannanes, as counterparts of furylstannanes, and organic halides in many transformations, examples being the synthesis of heteroarylindoles,[511a] pyridyl-2-hydroxythiophenes,[511b] 5-substituted pyrimidines with antiviral activity,[512] heteroarylpyridazines,[513] indolizidines,[514] endothelin antagonists,[515] rubrolide M congeners,[516] and heterobiaryl carboxylic acids through solid-supported synthesis.[517] In addition, 2-halovinyl ethers have been used as coupling counterparts,[518] together with bis(imidoyl chlorides) such as compound **365** to afford the coupling product **367** after coupling with stannane **366** (Scheme 98).[519] Moreover, triflates have

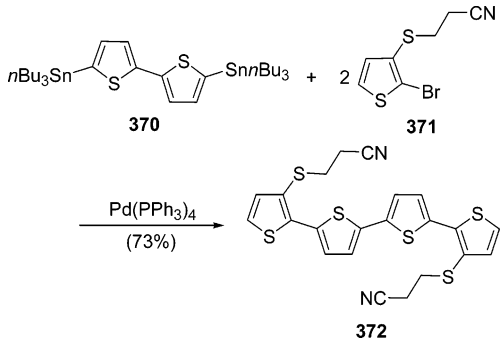
Scheme 98



also been used as coupling partners of thienylstannanes, examples being the synthesis of heteroarylated spiranes[520] and diheteroarylmaleic anhydrides.[521] Tosylates such as compound **368** have also been used, as illustrated in the synthesis of the triazoloquinazoline **369**, obtained in studies toward selective ligands for the benzodiazepine binding site of GABA-A receptors (Scheme 98).[522]

Electronically and optically interesting poly(thiophenes) have been frequently prepared from 2-stannylated thiophenes using the Stille coupling, recent examples in the literature being numerous,[523] as in the case shown in Scheme 99, where bis(tri-*n*-butyl-

Scheme 99

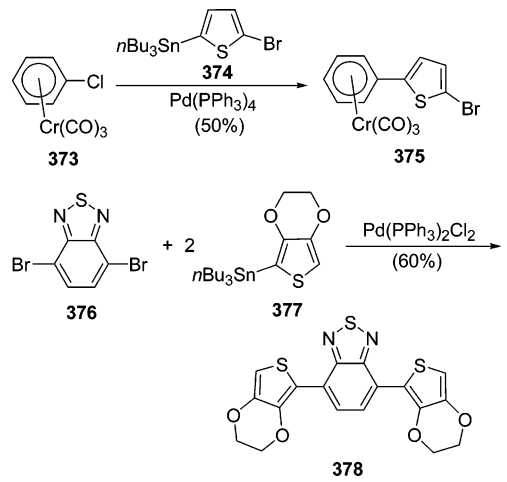


stannyl)bithiophene **370**, prepared as usual by deprotonation of the corresponding bithiophene and treatment with tri-*n*-butylstannyl chloride, is coupled to the 2-bromothiophene **371** to give quaterthiophene **372**.[523d]

Other optically interesting systems containing heteroaromatics such as the thiophene moiety have been prepared using the Stille coupling, so the chromium

complex **375** (obtained by coupling complex **373** and stannylated bromothiophene **374**), an intermediate in the synthesis of organochromium/organoiron dipoles[524] (Scheme 100), or the benzothiadiazole **378**

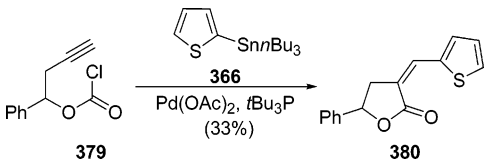
Scheme 100



(prepared by coupling of dibromo derivative **376** and stannane **377**), which is interesting for the design of photoluminiscent materials for light-emmiting diodes,[525] is prepared (Scheme 100). In addition, other systems, such as diheteroarylquinones,[526] diarylbenzodiazines,[527] dithienothiophenes,[528] and bioluminiscent coelenterazine analogues,[529] have been obtained using stannylated thiophenes. There are also applications in the synthesis of macromolecules, mainly for molecular recognition, such as thiaheterohelicenes,[530] spirosilanes,[531] thiophene-containing porphyrins,[532] phthalocyanines,[533] or calixarenes,[534] and thiophene analogues of oligophenylenes.[535] Furthermore, examples of the synthesis of mixed thiophene/furan oligomers have also been reported.[536]

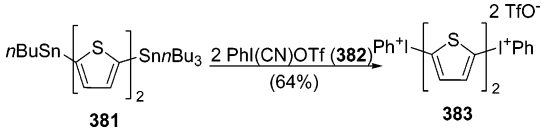
The palladium-catalyzed cyclization−anion capture process, shown previously with furylstannanes, has also been performed with alkynylchloroformates such as compound **379** and 2-(tri-*n*-butylstannyl)thiophene (**366**) for the synthesis of the substituted α-methylene-γ-butyrolactone **380** (Scheme 101).[537]

Scheme 101



Heteroaryliodonium salts derived from thiophenes, such as thienyl(phenyl)iodonium triflate **383**, have been obtained by treatment of the corresponding thienylstannane **381** with the iodonium transfer reagent **382** (Scheme 102),[538] related iodonium salts

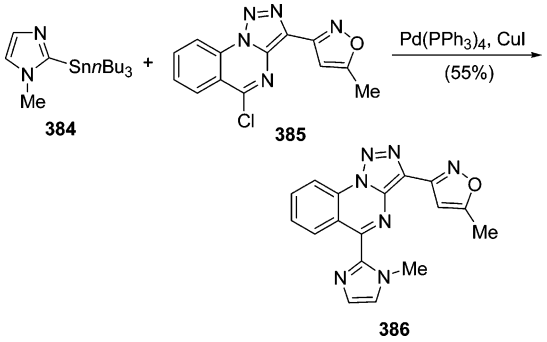
Scheme 102



being employed in heteroaromatic fluorination reactions.[539]

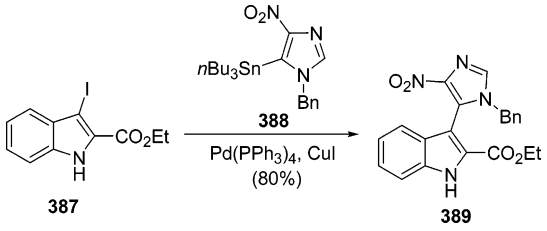
Stannylated 1,3-azoles have been prepared following the usual lithiation−stannylation sequence, being dedicated mainly to palladium-catalyzed Stille cross-couplings. Examples using *N*-protected imidazolylstannanes can be found in the coupling between 2-(tri-*n*-butylstannyl)-*N*-methylimidazole (**384**) and the imino chloride **385**, affording compound **386** (Scheme 103)[540] or phosphonates,[541] and the coupling

Scheme 103



between the nitro-substituted 4-stannylimidazole **388** [prepared from the corresponding 4-iodide by palladium-catalyzed coupling with $(Bu_3Sn)_2$] and the iodoindole **387** to give the derivative **389** (Scheme 104).[542] Other examples of Stille couplings using

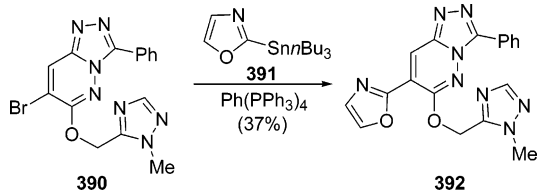
Scheme 104



2-substituted 5-stannylimidazoles[543] are applicable to the synthesis of cytotoxic agents grossuralines-1 and -2[544] or an imidazolyl isomer of the alkaloid didemnimide C.[545a] 5-Stannylimidazoles have also been prepared by a 2,5-dilithiation, followed by a double stannylation and a 2-hydrodestannylation sequence.[545b] In addition, the stannyl group on imidazoles has also been employed for *ipso*-iodination reactions, as in the synthesis of inhibitors of phosphodiesterase PDE4.[546]

2-Oxazolylstannanes can be obtained by lithiation and stannylation without ring opening although with some difficulties,[547] being used in Stille couplings as in the case shown in Scheme 105, where 2-(tri-*n*-butylstannyl)oxazole (**391**) reacts with the bromide **390,** affording compound **392**, in a synthesis of some

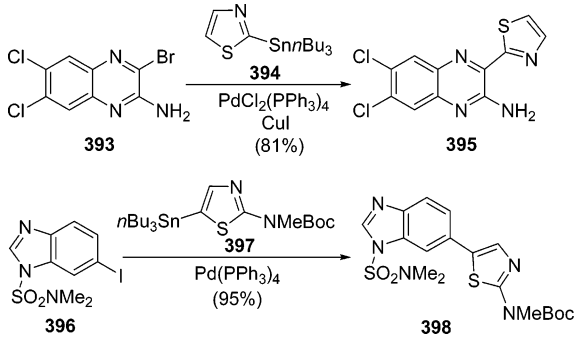
Scheme 105



ligands for the benzodiazepine binding site of GABA-A receptors,[548] triflates having also been used as coupling counterparts.[549] In addition, examples of the use of 2-substituted 5-(tri-*n*-butylstannyl)-[550] or 2,5-disubstituted 4-(tri-*n*-butylstannyl)oxazole[551] are also described.

An example of the use of 2-stannylthiazoles in palladium-catalyzed cross-couplings is the reaction between (tri-*n*-butylstannyl)thiazole **394** and the bromoquinoxalinylamine **393** to give compound **395** (Scheme 106).[471j] There are also examples of cou-

Scheme 106



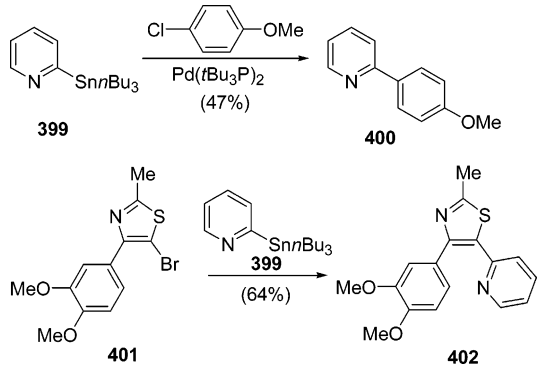
plings between this tin reagent and triflates[478b,501] or bromoquinolizinium salts,[471i] as well as its use in palladium-catalyzed tandem cyclization−anion capture processes.[485b] 5-Stannylated thiazoles (prepared from the corresponding thiazolyllithium after direct lithiation when a substituent is at C-2) such as the tin derivative **397** have been recently employed in Stille cross-coupling reactions to iodoindoles[511] or iodobenzimidazoles, such as compound **396** shown in Scheme 106, to give the thiazolyl-substituted compound **398**.[552] In adddition, 4-stannylated thiazoles have usually been obtained by a sequential halogen−lithium−tin interchange,[553a] although after lithiation of 4-bromo-2-stannylthiazoles to give the 4-stannylated heterocycles rearrangements have been observed.[553b] Palladium-catalyzed reaction using 4-(trialkylstannyl)thiazoles has been used, for instance, in the total synthesis of the antitumor agent epothilone E and analogues.[449,554]

5-Stannylated *N*-substituted pyrazoles are usually prepared by a direct lithiation−stannylation sequence, being used in Stille couplings,[555] whereas examples using 4-stannylpyrazoles, prepared by the bromine−lithium−tin interchange, can be found in the synthesis of either inhibitors of acyl-CoA[556] or substituted quinolizinium salts.[471i] In addition, 4-(tri-*n*-butylstannyl)pyrazoles have been prepared by a 1,3-dipolar cycloaddition reaction of bis(tri-*n*-butylstannyl)acetylene with nitrile oxides,[557] whereas 4-stannylated pyrazoles and isoxazoles have recently been synthesized from 4-haloazoles by stannylcupration.[381]

5.3.2. Aromatic Six-Membered Rings

Stannylpyridines have usually been prepared by the reaction of the corresponding pyridyllithium (see above) with a halostannane or stannyl triflate, their use being dedicated almost exclusively to the palladium-catalyzed Stille coupling reaction. Thus, 2-(tri-alkylstannyl)pyridines have been used in Stille cross-coupling reactions with chloroarenes,[558] bromoarenes,[471i,541,559] iodoarenes,[560] bromopyridinium cations,[454e] haloheteroaryls,[457c,471r,561] 8-bromopurines,[562] and aryl or vinyl triflates.[478b,501,563] As an example, Scheme 107 shows the recent rather difficult Stille

Scheme 107



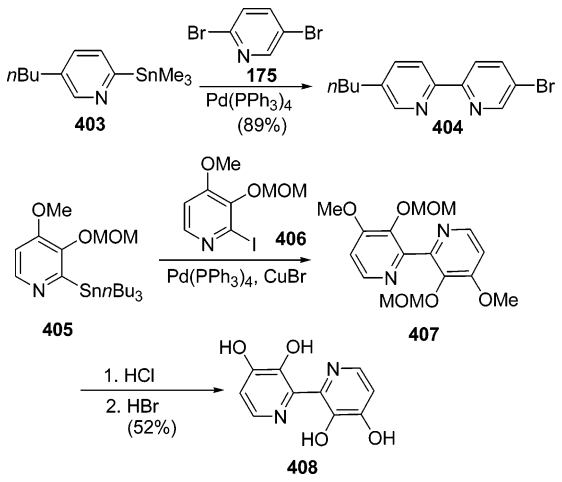
cross-coupling reaction between a chlorinated arene and 2-(tri-*n*-butylstannyl)pyridine (**399**) to give compound **400**,[558] as well as the coupling between bromothiazole **401** and the same stannylated compound, affording thiazole derivative **402**.[561c] In addition, 2-stannylpyridines have been used in diarylation reactions with alkynes[564] and homocoupling reactions,[483,565] also achieved under copper and manganese catalysis,[488f] similarly to some cross-coupling reactions.[488a]

The Stille cross-coupling reaction using 2-(trialkylstannyl)pyridines has been used in the synthesis of pharmacologically interesting compounds, for example, inhibitors of gyrase B,[500] β-lactamase,[566] or topoisomerase I,[567] analogues of the antibiotic streptonigrin,[568] functionalized benzodiazepinediones,[569] the antibiotic dimethyl sulfomycinnamate,[570] and modified HIV-1 protease inhibitors.[571]

2-(Trialkylstannyl)pyridines have been profusely used in Stille cross-coupling reactions for the synthesis of bipyridines, poly(bipyridines), and terpyridines, which have found widespread use as building blocks in the assembly of new supramolecular structures that have been employed in polymer and dendrimer chemistry,[572a,b,573] using the known efficient metal−pyridine coordination,[572b−f] also showing novel photo- or electrochemical or catalytic properties.[574] An example of the synthesis of a simple bromobipyridine (**404**) is shown in Scheme 108, for the Stille cross-coupling reaction between 2-(trimethylstannyl)pyridine **403** and 2,5-dibromopyridine (**175**),[575] or the reaction between the (tri-*n*-butylstannyl)pyridine **405** and the iodopyridine **406**, which gives rise to the bipyridine mushroom toxin orelline **408**, after deprotection of the corresponding adduct **407** (Scheme 108).[576] Many other examples of the synthesis of bipyridines[112b,577] and oligo(pyridines)[578] using the Stille reaction with 2-stannylated pyridines have also been reported.

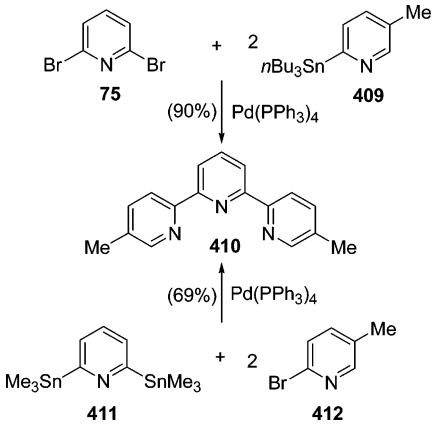
Among these oligo(pyridines), 2-2,2′:6,2′-terpyridines have been extensively studied as complexing agents for a wide range of transition-metal ions, achieving an impressive array of properties with

Scheme 108



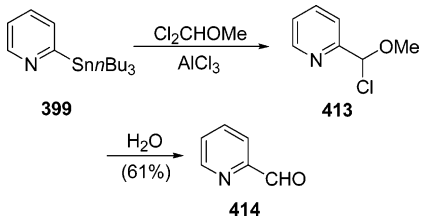
electronic and biochemical applications.[579] The synthesis of terpyridines has been achieved in many cases via the coupling between a 2-(trialkylstannyl)-pyridine and a 2,6-dihalopyridine, subsequent halogen−lithium−tin interchange, and further cross-coupling with another molecule of 2-halopyridine.[579] For symmetrically substituted terpyridines such as compound **410**, other possible methodologies involve the coupling between two monostannylated pyridines, such as compound **409**, and a 2,6-dihalopyridine such as compound **75**, or via the coupling between a 2,6-distannylated pyridine, such as compound **411**, which can be prepared by reaction of sodium trimethylstannylide with 2,6-dichloro- or 2,6-dibromopyridine, and a 2-halopyridine, such as compound **412** (Scheme 109).[580] Examples of the synthesis of terpyridines and related systems using 2-trialkylstannylated pyridines and all these methodologies are numerous.[581]

Scheme 109



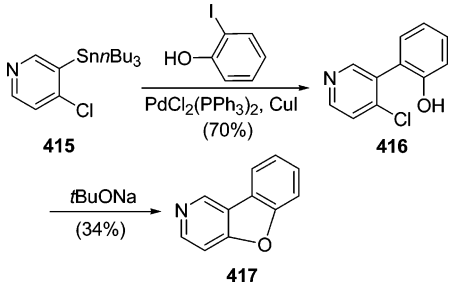
Different dinucleating ligands combining phenol and pyridine moieties have been prepared by palladium-catalyzed cross-coupling reactions using 2-(tri-*n*-butylstannyl)pyridine (**399**).[582] There are also examples of the use of stannylated pyridines in electrophilic aromatic substitutions since the C−Sn bond in the pyridine can be cleaved by electrophiles more easily than the C−H bond. Thus, **399** reacts with dichloromethoxymethane in the presence of a Lewis acid to give, after hydrolysis of the chloroether intermediate **413**, the corresponding aldehyde **414** (Scheme 110).[583]

Scheme 110



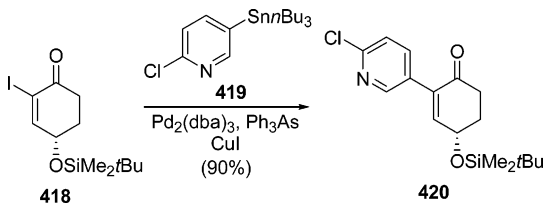
3-(Trialkylstannyl)pyridines have been used in palladium-catalyzed Stille cross-coupling reactions with haloarenes[560,584] such as *o*-iodophenol, which couples with 4-chloro-3-(tri-*n*-butylstannyl)pyridine (**415**) (prepared by *ortho*-lithiation of 4-chloropyridine using LDA) to give pyridinylphenol **416**, a precursor of benzo[4,5]furo[3,2-*c*]pyridine (**417**) after basic treatment (Scheme 111).[585] In addition, examples of Stille cross-couplings between 3-pyridylstannanes and haloarenes on a solid support[471g] and haloazoles[561b,c] can be found, as well as their use in the synthesis of fusaric acid[586] or 5-substituted 7-azaindoles.[587] Furthermore, 2-stannylated pyridine *N*-oxides and *N*-methylpyridinium salts, as well as the corresponding derivatives from quinolines and isoquinolines, have also been used in Stille cross-coupling reactions.[588]

Scheme 111



Examples of the use of 3-stannylated pyridines in the synthesis of pharmacologically interesting compounds can be found in the Stille reaction of chloropyridylstannane **419** with the α-acylvinyl cation equivalent[276b] α-iodoenone **418**, affording the adduct **420**, which is a key intermediate in the synthesis of epibatidine (Scheme 112).[589] A similar approach using this stannane has also been used by other groups.[590] In addition, examples of the use of 3-(tri-*n*-butylstannyl)pyridine in Stille reactions are the syntheses of nicotine[591] and ephothilone E[499,554a] analogues, inhibitors of topoisomerase I,[567] HIV-1 protease,[571] farnesyltransferase,[592] or phosphodi-

Scheme 112

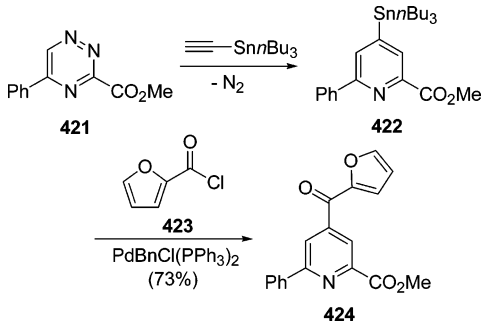


esterase type 4D,[593] and antistaphylococcal agents.[594] Moreover, differently substituted 3-stannylated pyridines have been used in the synthesis of cytisine,[595] and some cyclooxygenase-2 inhibitors[596] or duocarmycin pharmacophores.[597]

Although not as frequently as 2-stannylated pyridines, their 3-stannyl counterparts have also been used for metal−pyridine coordination systems,[598] such as subphthalocyanine cages,[599] fullerene receptors,[600] or coordination nanotubes,[601] and also in the substitution of 2,2′:6,6-terpyridines[581j] as well as the synthesis of planar polymers.[578c]

4-(Trialkylstannyl)pyridines have been prepared by the usual transmetalation methodology, although they can also be obtained from 1,2,4-triazines after inverse demand Diels−Alder reaction with ethynyltributyltin followed by molecular nitrogen extrusion.[602] An example of this methodology is shown in Scheme 113, where the 4-stannylpyridine **422** is

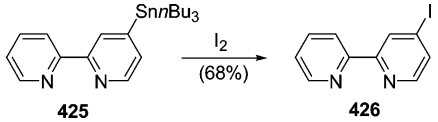
Scheme 113



obtained from triazine **421** and used in Stille cross-couplings with heteroaryl bromides and acid chlorides such as compound **423** to give the corresponding pyridyl ketone **424**.[602a] Examples of the Stille reaction between 4-stannylated pyridines and heteroaromatic thioethers,[481b] aryl halides,[603] bromopyridines[604] and aryl triflates,[605] as well as the Stille reaction on 4-stannylated pyridyl cations,[454e] have been reported.

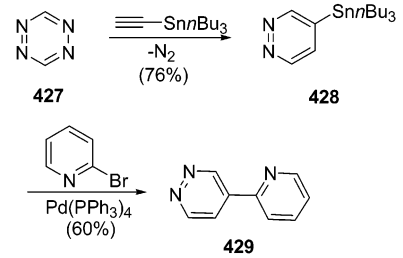
4-Pyridylstannanes have been used for the synthesis of pharmacologically interesting compounds using the Stille reaction, for example, in strategies toward the streptonigrin CD moiety[605] or the synthesis of cyclin-dependent kinase (Cdk4) inhibitors,[606] antibacterial agents,[607] or the cytotoxic marine alkaloid amphimedine.[608] In addition, examples of the use of the Stille coupling for the generation of molecular structures through metal-directed self-assembly[609] or poly(4-pyridyl)-substituted aromatics[610] are described. There are also examples of the use of the easy *ipso*-substitution on 4-stannylpyridines using electrophilic reagents, such as halogens, allowing introduction of the electrophilic group under mild reaction conditions and regiospecifically.[602a,611] Thus, stannylated bipyridine **425** reacts with iodine to give the iodinated bipyridine **426** (Scheme 114).[611]

Scheme 114



Similarly to 4-(tri-*n*-butylstannyl)pyridines (Scheme 113), the corresponding stannylated pyridazines have also been prepared, apart from the typical transmetalation, via cycloaddition of 1,2,4,5-tetrazine (**427**) to ethynyltributyltin followed by molecular nitrogen extrusion.[612] The final metalated pyridazine **428** has been used in Stille couplings with aryl and heteroaryl halides[612] such as 2-bromopyridine to give the corresponding adduct **429** (Scheme 115),[612a] or for tin−

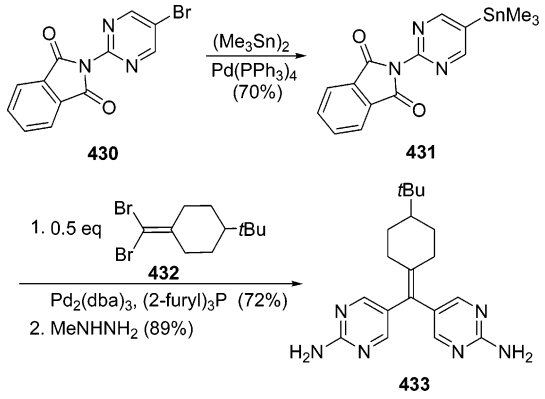
Scheme 115



lithium transmetalations[612a] or *ipso*-substitutions.[612b] The same cycloaddition but employing bis(tri-*n*-butylstannyl)acetylene has been used for the preparation of distannylated pyridazines.[612a] This methodology has also been used for the synthesis of the corresponding silyl- and germyl-substituted pyridazines.[612a]

Pyrimidinylstannanes have been obtained using the lithium−tin exchange or, as in the case of 5-bromophthalimidopyrimidine (**430**), the palladium(0)-catalyzed stannylation using hexamethylditin (Scheme 116).[613] Further double Stille reaction between com-

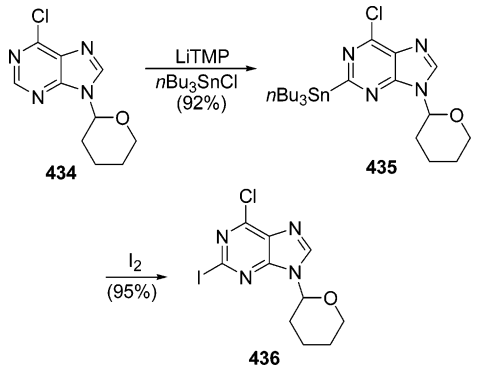
Scheme 116



pound **431** and a geminal vinylic dibromide such as **432** afforded the bis(aminopyrimidine) adduct **433** after cleavage of the phthalimido group with methylhydrazine (Scheme 116).[613a] This and other related aminopyrimidines have been employed in molecular recognition chemistry.[613] As additional examples, other 5-stannylpyrimidines have been used in Stille reactions for the preparation of ligands in guest-controlling assemblies,[598a] heterobiaryl phosphonates,[541] or anatoxin-a analogues,[496] whereas 4-(trimethylstannyl)pyrimidines have been used in a recent synthesis of the marine metabolite deoxyvariolin B,[614] or supramolecular assemblies.[615]

2-(Tri-*n*-butylstannyl)purines such as compound **435** can be prepared by LiTMP-induced 2-lithiation followed by stannylation of compound **434** (Scheme

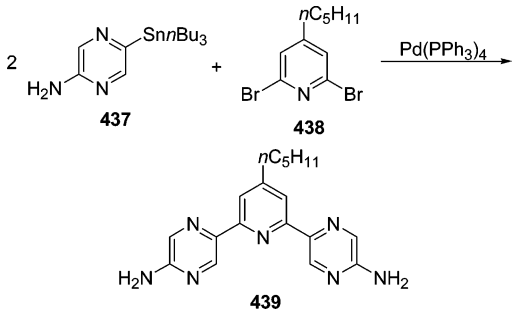
Scheme 117



117), being able to be used for electrophilic *ipso*-halogenation such as the iodination shown in Scheme 117 to give the iodopurine **436** in a step for the preparation of cyclin-dependent kinase (CDK) inhibitors.[616a] In addition they have been used for Stille couplings in combinatorial chemistry libraries,[616b] or for the synthesis of 2-substituted adenosines.[617]

There are also recent examples of the use of (trialkylstannyl)pyrazines in Stille reactions, such as the case shown in Scheme 118, where (trimethyl-

Scheme 118



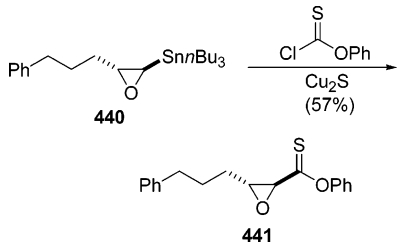
stannyl)pyrazine **437** (prepared from the corresponding bromo derivative by palladium-catalyzed stannylation using hexamethylditin) cross-couples to dibromopyridine **438** to give terpyridine-related compound **439**, suitable for metal complexation in supramolecular assemblies.[615] In addition, (tri-*n*-butylstannyl)pyrazines have been used for the preparation of anatoxin-a analogues[496] and pyrazine polymers.[618]

5.3.3. Nonaromatic Heterocycles

Stannylated epoxides can be prepared by epoxidation of the corresponding vinylstannanes, obtained by tri-*n*-butylstannyl cupration from alkenes or allenes,[619] and can be employed in stereoselective cross-coupling reactions mediated by copper(I) sulfide,[620] as shown in Scheme 119 for the synthesis of the thioester **441** starting from stannylated epoxide **440**.

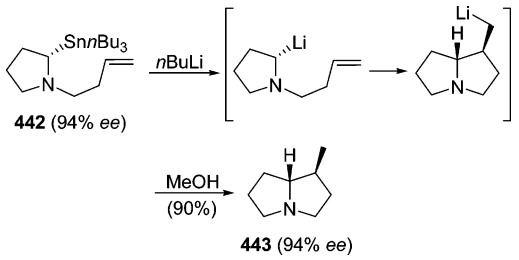
2-Stannylated pyrrolidines are prepared by alkyllithium-mediated deprotonation of *N*-substituted pyrrolidines followed by quenching with a trialkylstannyl halide, although other methods based on amine−BF_3 complexes have been reported,[621] their principal use being the generation of the corresponding organolithiums by the rapid tin−lithium exchange.[166c] A recent example of the use of this

Scheme 119



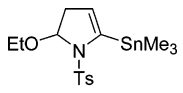
transmetalation technique is the lithiation of the enantiomerically enriched stannane **442**, which gave rise to the pyrrolizidine alkaloid (+)-pseudoheliotridane **443** after intramolecular carbolithiation and quenching with methanol (Scheme 120).[622] In addi-

Scheme 120



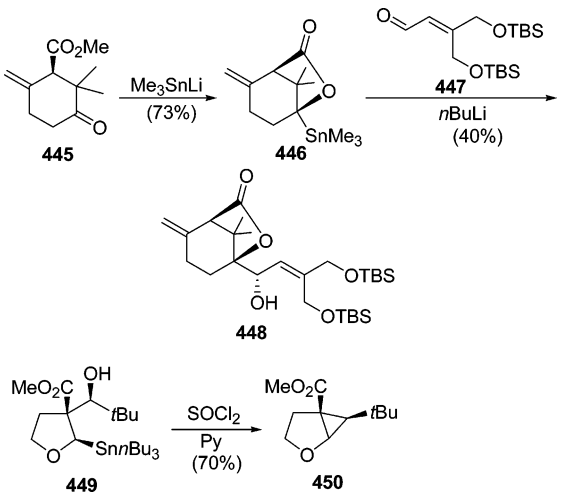
tion, using racemic mixtures of 2-stannylpyrrolidines and a tin−lithium exchange in the presence of chiral diamines or amino alcohols, dynamic resolution takes place, allowing the enantioselective synthesis of 2-substituted pyrrolidines.[623]

N-Protected 5-stannylated 2,3-dihydro-1*H*-pyrroles, such as compound **444**, have been prepared by palladium-catalyzed cross-coupling of the corresponding enol triflates with hexamethyldistannane.[624] The same procedure has been used for the prepararation of (trimethylstannyl)maleimides, starting from the corresponding bromo derivatives.[625]



2-(Trialkylstannyl)tetrahydrofurans have been obtained by reaction of a trialkylstannyllithium with α-chlorotetrahydrofurans,[626] but other unsubstituted 2-stannylated oxolanes have also been prepared by reductive lithiation of phenylthioxolanes using lithium 4,4′-di-*tert*-butylbiphenylide and quenching with tri-*n*-butylstannyl chloride.[627] The obtained 2-stannyloxolanes have been used for tin−lithium exchange processes.[627] Related to this use is the synthesis of the (trimethylstannyl)lactone **446** (obtained by addition of lithium trimethylstannylide to the ketone **445**), which has been used for tin−lithium transmetalation and addition to aldehydes, such as compound **447**, giving alcohol **448**, useful for the syntheses of taxoids (Scheme 121).[628] In addition, other uses for stannylated oxolanes, such as the cyclization of the oxolanyl alcohol **449** to give the 2-oxabicyclo-[3.1.0]hexane **450** (Scheme 121), have been reported.[629] The starting alcohol **449** can be diastereoselectively obtained by addition of the enolate of the

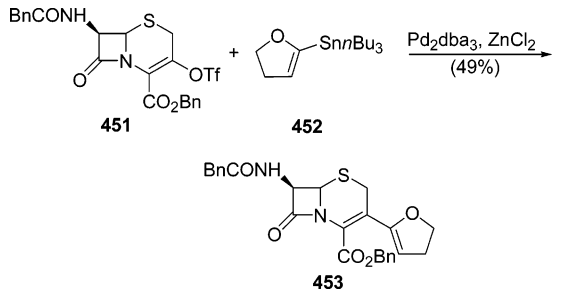
Scheme 121



corresponding 3-oxiranyl ester to pivalaldehyde, the tri-*n*-butylstannyl group acting as a stereocontrol element.[630] In addition, *γ*-butyrolactones can be obtained by ozonolysis of 2-(tri-*n*-butylstannyl)-oxolanes.[631]

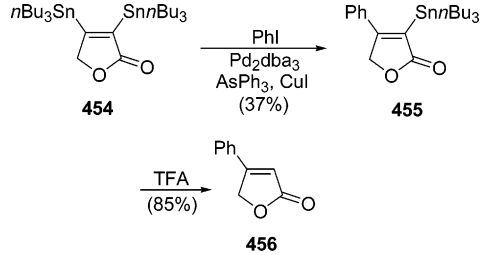
5-Stannylated 2,3-dihydrofuran **452**, prepared by the α-lithiation−stannylation sequence, has been used in a Stille cross-coupling reaction with vinyl triflates such as the cephalosporin derivative **451** to give the corresponding adduct **453** (Scheme 122).[632a]

Scheme 122

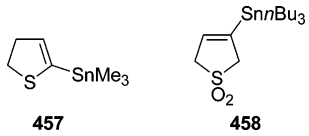


In addition, this stannylated moiety has been used in copper-promoted homocouplings.[632b] Furthermore, 3- and 4-(tri-*n*-butylstannyl)furan-2(5*H*)-ones have been used for introducing the furanone moiety by means of palladium-catalyzed cross-coupling reactions,[633] a recent example being the regioselective Stille coupling reaction between the bisstannylated furanone **454** and iodobenzene to afford the monostannylated furanone **455**, which gives 4-substituted furanone **456** after *ipso*-destannylation (Scheme 123).[633e]

Scheme 123

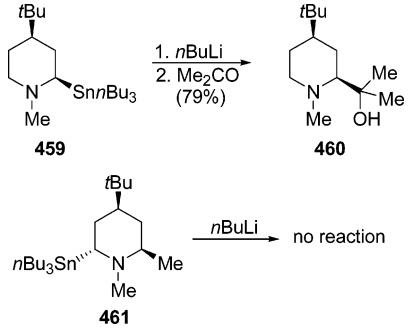


5-Stannylated 2,3-dihydrothiophenes such as compound **457** can be prepared from the corresponding vinyl triflates via a palladium-catalyzed cross-coupling reaction using hexamethylditin.[198] However, higher yields of the tri-*n*-butylstannyl counterparts have been obtained by treating the same triflate with the high-order cuprate (*n*Bu$_3$Sn)*n*BuCuLi$_2$CN,[198] although other methods such as the α-lithiation of tetramethylene sulfoxide with LDA followed by addition of tri-*n*-butylstannyl chloride, in a tin-mediated Pummerer-type reaction, have been reported.[634] In addition, 3-(tri-*n*-butylstannyl)sulfolene (**458**) has been used in Stille couplings[635] and in an *ipso*-iodination reaction.[636]



α-Stannylated *N*-substituted piperidines have been obtained, as in the case of pyrrolidines, following the usual α-lithiation−stannylation sequence, conformational studies showing unexpected small energy differences between conformers, in which the tin atom is equatorial or axial, attributed to conformational distortions.[637] Further studies performed on the tin−lithium exchange reaction using 2-(tri-*n*-butylstannyl)-*N*-methylpiperidine **459**, conformationally locked by a 4-*tert*-butyl substituent, revealed that if the tin moiety is equatorial, transmetalation occurs smoothly, reacting with carbonyl electrophiles such as acetone to give stereoselectively compound **460**, whereas alkyl halides seem to undergo an SET reaction, affording nonselective alkylation products (Scheme 124).[638] However, an axially oriented tin

Scheme 124

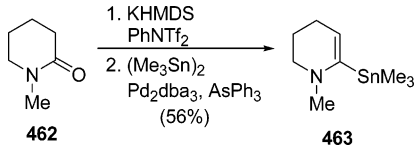


derivative, as in the case of compound **461**, failed to transmetalate, suggesting that a synclinal relationship between the nitrogen lone pair and the carbon−tin bond is required for the transmetalation to occur (Scheme 124).[638]

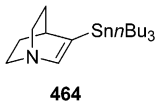
1,2,3,4-Tetrahydroisoquinolines *N*-amidated with gulonic acid have been 1-stannylated by the lithium−tin sequence, these compounds being able to suffer a tin−lithium exchange, allowing diastereoselective 1-alkylations.[639]

6-Stannylated 1,2,3,4-tetrahydropyridines such as compound **463** have been prepared from the corresponding enol triflate (obtained in this case from the corresponding lactam **462**) by palladium(0)-catalyzed

Scheme 125



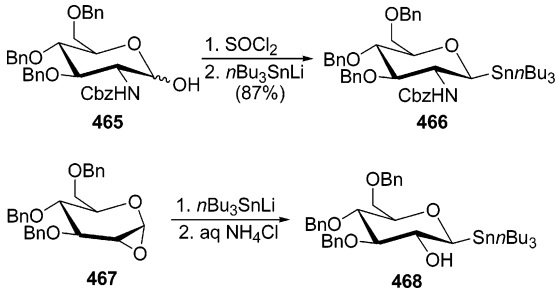
cross-coupling using hexamethylditin (Scheme 125), and have been used for the generation of the corresponding organolithium by tin−lithium transmetalation.[640] In addition, 3-(tri-*n*-butylstannyl)-1-azabicyclo[2.2.2]oct-2-ene (**464**) has been cross-coupled



with bromofurans for the synthesis of antimuscarinic derivatives,[641] or with acetylenes for the preparation of *Cinchona* alkaloid derivatives.[642] Moreover, 3-iodinated pyridin-2-ones have been stannylated at the 3-position using hexamethylditin under palladium catalysis, being employed in Stille couplings for the preparation of (−)-cytisine analogues.[643]

The anomeric position of tetrahydropyrans has been stannylated frequently in sugar chemistry to achieve tin−lithium transmetalation with alkyllithiums and subsequent reaction with electrophiles.[203,644] These α-stannylated derivatives have been usually prepared by a substitution reaction on a chlorotetrahydropyran derivative obtained from a pyranose, such as compound **465**, using lithium tri-*n*-butylstannylide to give in this case the stannyltetrahydropyran **466**,[644c] or by ring opening of an epoxide, such as **467**, using the same nucleophile to afford the corresponding sugar derivative **468**[203c] (Scheme 126). In addition, lithium trialkylstannylides

Scheme 126

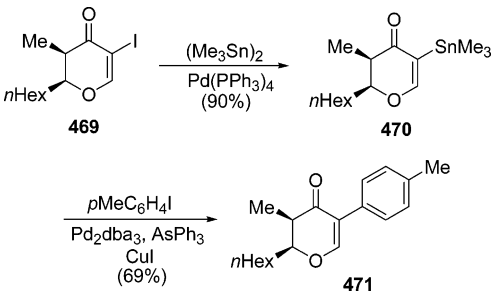


reacted in a Michael addition fashion with monosaccharide-derived 2,3-dihydro-4*H*-pyran-4-ones to give stannyl glycosides.[355]

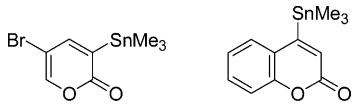
(5,6-Dihydro-4*H*-pyran-2-yl)trialkylstannanes can be prepared by α-lithiation of dihydropyrans and further reaction with trialkylstannyl halides,[166c,195b,645] although other syntheses from δ-lactones or α-sulfonyltetrahydropyrans[646] or even via tungsten pentacarbonyl-promoted alkynol endocyclization[647] have been employed, their use being dedicated principally to a subsequent tin−lithium transmetalation[166c,195b,645] or a palladium-catalyzed Stille cross-coupling reaction.[648] In addition, examples of carbonylative Stille cross-coupling reactions,[649] and copper(I)-promoted[650] or palladium(II)-mediated[651] homocouplings, have been reported.

Trimethylstannylated dihydropyran-4-one **470**, prepared from the iodide **469** by palladium-catalyzed coupling with hexamethylditin, undergoes Stille cross-coupling with *p*-methyliodobenzene to give the 5-substituted dihydropyran-4-one **471** (Scheme 127).[652]

Scheme 127

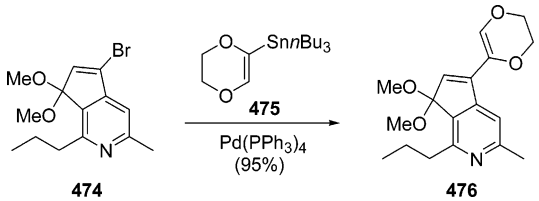


This Stille coupling has also been performed employing stannylated pyran-2-ones[653] and coumarins,[654] such as **472** and **473**, respectively. In addition, electrophilic displacement of the tri-*n*-butyltin substituent by halogens has been carried out on 4- and 5-stannylated pyran-2-ones.[655] Moreover, 3,4-dihydro-2*H*-thiopyrans can be stannylated at the 6-position by the usual lithiation−stannylation sequence.[656]



5-(Tri-*n*-butylstannyl)-2,3-dihydro-1,4-dioxine (**475**), prepared from the corresponding organolithium, has been used in palladium-catalyzed Stille cross-couplings, an example being its reaction with the vinylic bromide **474** to give compound **476**, an intermediate in the total synthesis of the rubrolone aglycon (Scheme 128).[657] In addition, stannane **475**

Scheme 128



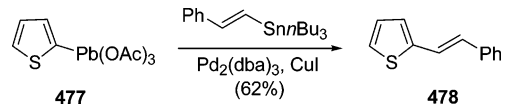
has been used, for example, in a Stille coupling for the synthesis of the AB taxane ring system,[658] whereas related stannylated benzo[1,4]dioxines have also been used for cross-coupling reactions.[471j,478c,659]

5.4. Lead Heterocycles

Not many examples can be found of the use of heterocyclic lead compounds applicable to organic synthesis. Thienyllead triacetate (**477**), prepared by direct plumbylation of thiophene using lead tetraacetate,[660] has been cross-coupled with (*E*)-(tri-*n*-

butyl)-β-styrylstannane under palladium catalysis in the presence of copper(I) iodide to give the corresponding thiophene **478** (Scheme 129).[661]

Scheme 129

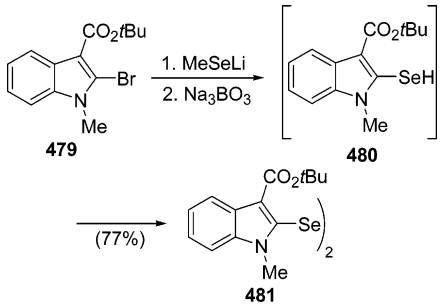


6. Group 5 Metal-Containing Heterocycles

6.1. Selenium Heterocycles

Selenylated heteroaromatics are usually prepared by reaction of the corresponding heteroaryllithiums with a selenylating agent.[662] Thus, treatment of *N*-substituted pyrrole, furan, or thiophene with *n*-butyllithium followed by addition of selenium metal and final hydrolysis affords the corresponding selenols, which are rather unstable.[663] However, if the quenching is performed using trimethylsilyl chloride instead of an acid, the obtained (trimethylsilyl)seleno derivative is stable and can give rise to the selenol upon treatment with acid. This methodology has been applied to *N*-methylpyrrole, its 2-selenol derivative being the most unstable.[663,664] Selenols or selenolates can give bisseleno compounds after oxidative treatment,[665,666] as shown in Scheme 130, where a 2-bromo-

Scheme 130

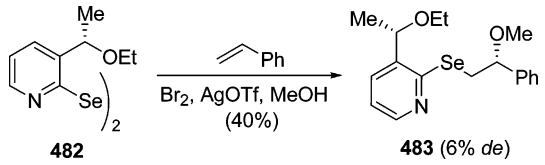


indole such as compound **479** reacts with lithium methylselenide, affording the tyrosine kinase inhibitor bis(selenoindole) compound **481**, after oxidation of the selenol intermediate **480**.[667]

Thiophene-derived bis(organoselenium) compounds have been cleaved using, for instance, bromine, affording thiophenylselanyl bromides, which have been used as electrophilic selenylation agents,[668] or with iodobenzene diacetate for the synthesis of oligo(seleno-2,5-thienylenes).[666] In addition, 2-(phenylselanyl)thiophenes have been prepared by lithiation and reaction with diphenyl diselenide and used in radical cycloadditions.[669] There are also reports on the synthesis of (phenylselanyl)pyrroles[670,671] or isoxazoles[671] using different cyclization reactions.

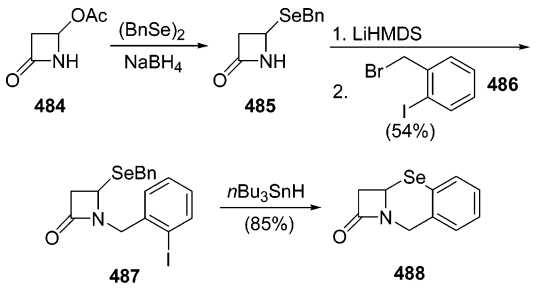
The pyridine-derived chiral diselenide **482** has been employed in the asymmetric addition to styrene in methanol, in the presence of bromine for cleavage of the diselenide bridge, affording the selenoether **483** although only in 6% de (Scheme 131).[672] In addition, a chiral 2-pyridinyl-derived camphorselenide has been transformed into a hydroxyselenoxide, which has been employed as a chiral protonating agent.[673]

Scheme 131

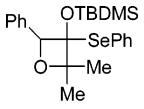


4-(Benzylselanyl)azetidinone (**485**) has been recently prepared by the reaction of sodium benzylselenoate (obtained by reduction of dibenzyl diselenide) with 4-acetoxyazetidinone (**484**) (Scheme 132). Subsequent treatment of compound **485** with

Scheme 132



lithium hexamethyldisilazide (LiHMDS), followed by reaction with an activated electrophile such as the benzyl bromide **486**, affords compound **487**, which cyclizes under radical conditions to give the selenocephem **488**.[674] In addition, other 4-selanylazetidinones, prepared by α-methoxyacetyl chloride-induced cyclization of a three-component compound (generated from diphenyl diselenide, electron-deficient alkynes, and isocyanides), can act as precurors of the carbapenen framework.[675] Moreover, 3-(phenylselanyl)-3-siloxyoxetanes such as **489**, useful in radical chemistry, have recently been prepared by a Paternò−Büchi reaction of silyl *O,Se*-ketene acetals with aromatic aldehydes.[676]

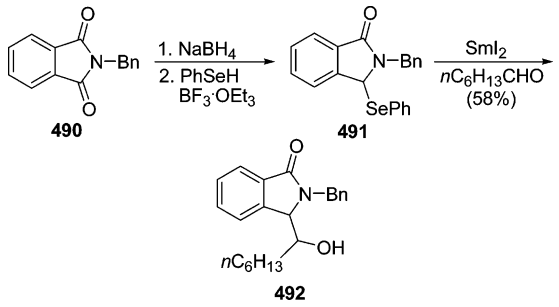


489

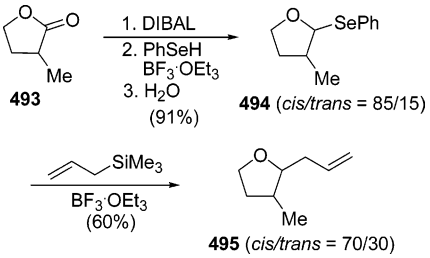
The introduction of a selanyl group on a pyrrolidine ring, usually by deprotonation and reaction with a phenylselanyl halide, is generally intended for further oxidation and elimination to introduce an insaturation in the system. Examples of this synthetic use can be seen in approaches to α-allokainoids,[677] and in the synthesis of spirotryprostine B[678] or (+)-dibromophakellstatin.[679] In addition, there are reports on the use of selanyl substituents for radical chemistry, as shown in Scheme 133 for the samarium(II) iodide-promoted reaction between the selanylated lactam **491** (prepared by monoreduction of phthalimide **490** and Lewis-acid-promoted reaction with phenylselanol) and *n*-heptanal, giving alcohol **492**.[680]

2-(Phenylselanyl)tetrahydrofurans such as compound **494** have recently been synthesized from γ-lactones, such as compound **493**, by successive teatment with diisobutylaluminum hydride (DIBAL), selenophenol, and boron trifluoride, followed by aque-

Scheme 133



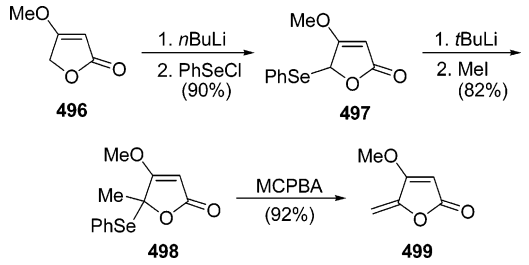
Scheme 134



ous workup (Scheme 134).[681] The obtained 2-(phenylselanyl)tetrahydrofuran **494** can be used for a α-allylation by treatment with allyltrimethylsilane in the presence of boron trifuoride, giving compound **495**.[682] This method of 2-selanylation of tetrahydrofurans through a lactol intermediate or a related 2-alkoxy- or 2-acetoxytetrahydrofuran has been profusely used for subsequent radicalary deselanylation with application in nucleoside synthesis,[683] for radical cyclizations in the synthesis of glycosyllactones and amino acids[684] such as (+)-furanomycin,[685] for oxidation−elimination processes,[686] for the formation of selenium-stabilized carbanions, or in selenium−lithium exchange.[687] In addition, tris(phenylselanyl)-borane has also been used for phenylselanylation of a bicyclic 2-methoxytetrahydrofuran, in a photoinduced cyclization for the preparation of functionalized diquinanes.[688] Moreover, the combination of iodosobenzene diacetate, sodium azide, and diphenyl diselenide has also been used for the α-selanylation of tetrahydrofuran.[689] Furthermore, dimethyl (phenylselanyl)malonate has been used in a radical addition to a oxabicycloheptenone to give a selanylated bicyclic tetrahydrofuran, which has been used as a starting material for the synthesis of *epi*-thromboxanes,[690] as well as nephromopsinic[691,692] and phaseolinic and dihydropertusaric[692] acids.

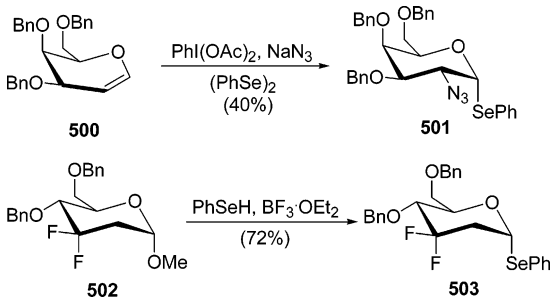
4-(Phenylselanyl)-2,3-dihydrofurans have been obtained by addition of phenylselanyl chloride to 2,3-dihydrofurans, followed by base-induced chloride elimination, the obtained selanylated compounds being used in the synthesis of spiroketopiperazines.[693] In addition, a 3-phenylselanyl group in 5*H*-furan-2-one has been used as an easily removable protective group for the 3-position, which allows specific functionalization at the 5-position via aldol reactions.[694] Moreover, the phenylselanyl group has been used as an alkene creator in a recent synthesis of 5-alkylidene-5*H*-furan-2-ones. Thus, 4-methoxy-5*H*-furan-2-one (**496**) can be selanylated at the 5-position to give the selanylated derivative **497**, which can be 5-deprotonated and reacts with alkyl halides such as methyl iodide to give derivative **498**, which can be transformed into the 5-methylidene derivative **499** (Scheme 135), a compound being used in a synthesis of the antibiotic tetrodecamycin.[695]

Scheme 135



α-(Phenylselanyl)tetrahydropyrans have been prepared using iodosobenzene diacetate, sodium azide, and diphenyl diselenide, a procedure which has also been used with 1,4-dioxane.[689] The anomeric carbon in glycosides can be selanylated using this method starting from dihydropyrans,[696] such as compound **500**, affording the selanyl azide **501** (Scheme 136),[696a]

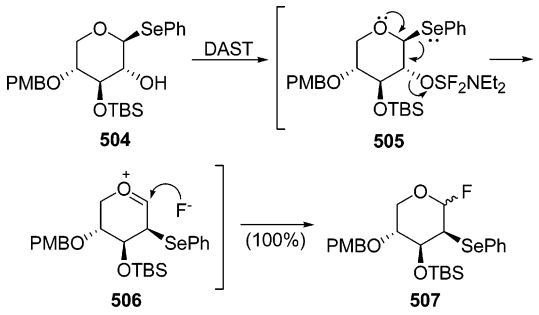
Scheme 136



as well as using phenylselanol and a Lewis acid[697] starting from *C*-glycoside derivatives, such as compound **502**, to give the selanyl compound **503** (Scheme 136),[697b] or by nucleophilic substitution on α-halopyranosides using sodium phenylselenolate.[698] Phenylselanylated glycosides have been shown to be versatile glycosyl donors after activation using dicollidine perchlorate (IDCP) or NIS,[699] or even with the combination 1-benzenesulfinylpiperidine (BSP)/2,4,6-tri-*tert*-butylpyrimidine (TTBP)/triflic anhydride[700] or 2,6-di-*tert*-butylpyridine/methyl triflate[701] or others,[702] methodologies which have been applied to oligosaccharide chemistry. In addition, selanylglycosides have been activated to achieve glycosyl cations using photoinduced electron transfer,[703] and also have been used for radical couplings.[704] Glycosyl diselenides have been recently prepared using tetraethylammonium tetraselenotungstate as a selenium transfer reagent.[705]

α-Selanylated tetrahydropyrans, such as compound **504**, experience 1,2-migration of the phenylselanyl group in the presence of diethylaminosulfur trifluoride (DAST) with subsequent installation of a fluoride group at C-1 in compound **507** (Scheme 137).[706] The reaction probably takes place via the intermediate **505**, which would give rise to a oxocarbenium ion **506**, rather than to an alternative episelenenium ion according to the loss of stereoselectivity in the creation of the carbon−fluorine bond. This methodol-

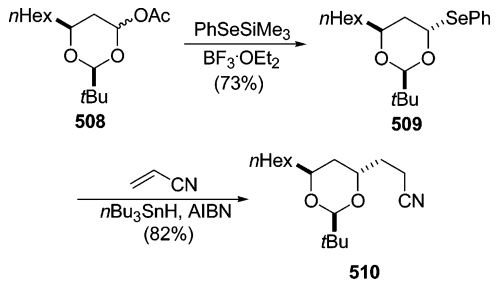
Scheme 137



ogy has been used for the synthesis of everninomicin 13,384-1.[707] In addition, 6-(phenylselanyl)-3,4-dihydro-(2*H*)-pyrans can be obtained via lithiation followed by reaction with diphenyl diselenide.[317]

4-Selanylated 1,3-dioxanes, such as compound **509**, can be prepared by reaction of the corresponding 4-acetoxy-1,3-dioxane **508** with boron trifluoride in the presence of $PhSeSiMe_3$, being employed in radical conjugate addition to acrylonitrile to give the corresponding adduct **510** (Scheme 138),[708] whereas their

Scheme 138

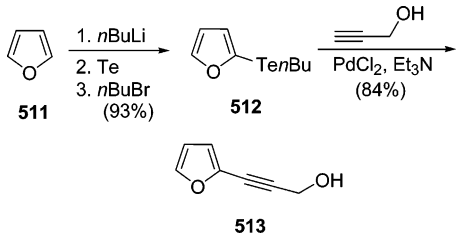


5-selanylated counterparts have been prepared by acetalization of the diols obtained after cross-aldol reaction between benzaldehyde and *β*-(phenylselanyl)enoxysilanes followed by ketone reduction.[709] In addition, 1,4-dioxane has been selanylated using the combination of iodosobenzene diacetate, sodium azide, and diphenyl diselenide.[689]

6.2. Tellurium Heterocycles

Heteroaryltellurium compounds have been obtained mainly by treatment of heteroaryllithiums with elemental tellurium.[662a,710] The further reaction of the formed highly nucleophilic heteroaryltellurolate anion with an alkyl bromide has allowed the preparation of tellurium compounds such as 2-(*n*-butyltelluro)furan (**512**), prepared from furan (**511**) by the former methodology, which has been used in palladium(II) chloride-catalyzed cross-coupling reactions with acetylenes (the so-called Sonogashira−Hagihara reaction) such as propargyl alcohol to give acetylenic furan derivatives such as the product **513**, which show anti-inflamatory activity (Scheme 139).[711] This methodology has also been applied to (*n*-butyltelluro)thiophenes[712a] and 2,5-bis(*n*-butyltelluro)-thiophene.[712b] Lithium thienyltellurolate has also been employed in vinylic substitution reactions, as has been shown recently with enol phosphates.[713] Furthermore, tellurides have been employed for the

Scheme 139

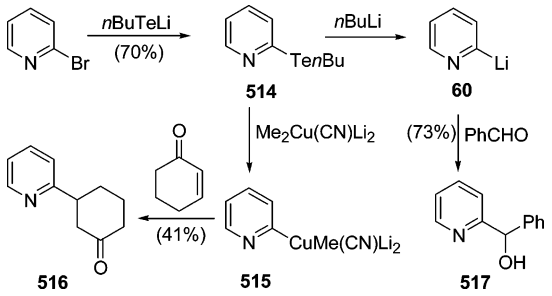


preparation of highly sensitive heteroaryllithiums via the rapid tellurium−lithium exchange reaction.[162]

Organotellurolate anions have also been obtained by reduction with a hydride of the corresponding ditellurolides, prepared by oxidation of lithium tellurolates.[662a,710] In this way, and using sodium borohydride, sodium thiophenetellurolate has been prepared, which has been used, for example, in epoxide ring-opening reactions with applications in radical cyclizations[714] or in the ring opening of 1,3-propanesultone for the preparation of water-soluble tellurides with thiol peroxidase and antioxidant activities.[715] Moreover, diaryl tellurides undergo tellurium−zinc exchange in the presence of a catalytic amount of $Ni(acac)_2$, a reaction which has also been performed employing the corresponding thiophene-derived tellurides.[716] In addition, vinylic tellurides have been prepared by reaction of vinyl Grignard reagents with aryltellurenyl halides, such as 2-thienyltellurenyl bromide, which is generated by treatment of the corresponding ditellurolide with bromine.[717]

Pyridyltellurium derivatives can be prepared from halopyridines by nucleophilic aromatic substitution reaction using lithium butanetellurolate.[718,719] An example of the use of this methodology is the preparation of the telluride **514** from 2-bromopyridine, the corresponding tellurium derivative being suitable for a rapid tellurium−lithium exchange to afford intermediate **60**, or transmetalation with lithium dimethylcyanocuprate, affording the organocuprate **515**, giving alcohol and ketone derivatives **517** and **516**, respectively, after reaction of the transmetalated species with the corresponding electrophiles (Scheme 140).[718] The pyridyl telluride **514** can also be treated

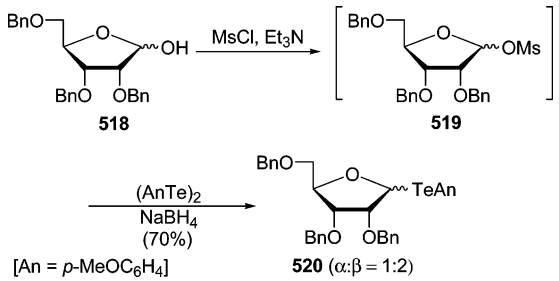
Scheme 140



with zincates such as Me_3ZnLi, giving rise to tellurium−zinc exchange followed by addition reaction to benzaldehyde.[719]

The reaction of the mesylated compound **519**, obtained from protected D-ribofuranose **518**, with sodium *p*-anisyl telluride (generated by reduction of the corresponding ditelluride) gave the corresponding

Scheme 141



ribofuranosyl *p*-anisyl telluride **520** (Scheme 141), which can react in different ways. Thus, it affords the corresponding anomeric radical in the presence of a radical initiator such as triethylboron and reacts with electron-poor aromatics such as pyridinium cations. Moreover, furanosyl telluride **519** generates the corresponding anomeric cation in the presence of a Lewis acid and reacts with electron-rich aromatics, whereas it suffers tellurium−lithium transmetalation in the presence of an alkyllithium and can react with electrophiles.[720]

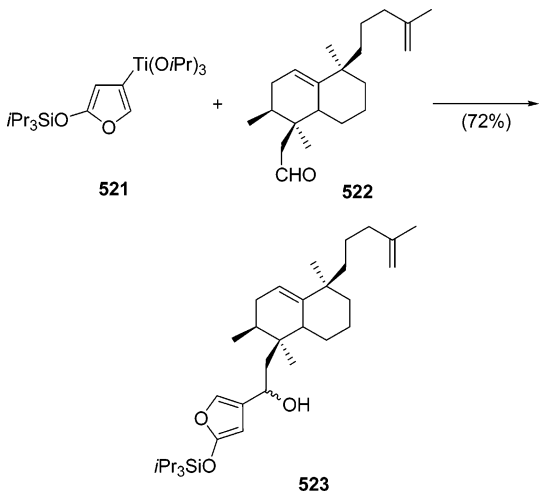
1-Aryl telluroglycosides can be obtained by reaction of bromoglycosides with sodium aryltellurolates,[721] being employed for photochemically and thermally generated radical formation in carbohydrate chemistry.[722] In addition, *O*-glycosides have been obtained from telluroglycosides and alcohols via oxycarbenium ions by anodic oxidation[723] or, similarly to selenoglycosides (see above), by an NIS-promoted reaction.[724] Moreover, glycosyl fluorides have been prepared from phenyl telluroglycosides by reaction with DAST in the presence of halonium ion activators.[725]

7. Transition-Metal-Containing Heterocycles

7.1. Titanium Heterocycles

Although rarely used, heteroaryltitanium compounds have proved to have good reactivity and high chemoselectivity, especially when the substrates are rather sensitive to other more basic nucleophiles. A recent example of their use is the (silyloxyfuranyl)-titanium reagent **521** [prepared by bromine−lithium exchange of the corresponding silyloxyfuran followed by transmetalation using $TiCl(OiPr)_3$],[726] which has been used in an addition reaction to the aldehyde **522**, affording alcohols **523**, used in a total synthesis of the sesquiterpenoid (+)-dysidiolide (Scheme 142).[727] Another example is the reaction between *N*-benzylindole-2,3-dicarboxylic anhydride and (3-bromo-4-pyridyl)titanium triisopropoxide, with regioselective anhydride ring opening.[728]

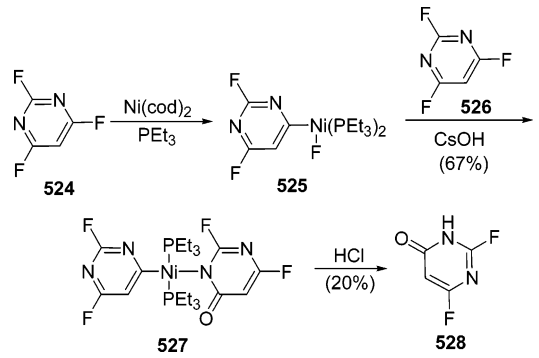
Scheme 142



7.2. Nickel Heterocycles

Examples of heterocyclic nickel compounds with application in organic synthesis but not forming part of a catalytic cycle are very rare, an example being the nickel-assisted C−F bond activation in 2,4,6-trifluoropyrimidine. Thus, treatment of $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) with triethylphosphane and 2,4,6-trifluoropyrimidine (**524**) gives the nickel derivative **525**, which, if treated with an excess of trifuoropyrimidine in the presence of cesium hydroxide, gives rise to the regioselective formation of the metalated compound **527**, which affords difluoropyrimidinone **528** after hydrolysis, although in low yield (Scheme 143).[729]

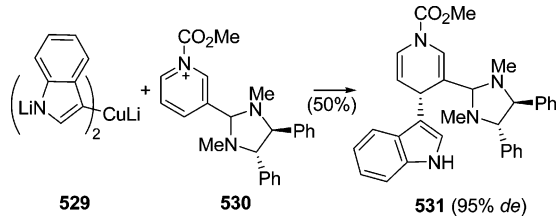
Scheme 143



7.3. Copper Heterocycles

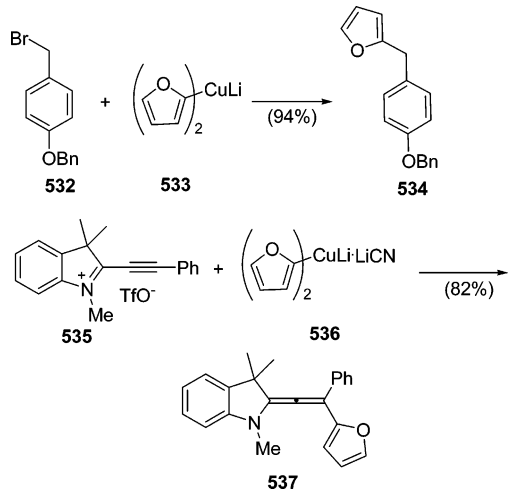
Heteroarylcopper reagents of the type Het_2CuLi have been prepared, like other low-order organocuprates, from 2 equiv of a lithium heteroaromatic and a copper(I) salt, CuX (usually X = I, Br).[730] High-order cuprates $R_2CuCNLi_2$, usually prepared in the same way but using CuCN, are normally more reactive than their low-order counterparts, only one of the two R groups being generally transferred.[730] An example of the use of benzo-condensed five-membered heteroaromatic-derived low-order cuprates can be found in the indolylcopper reagent **529**, which has been added to the chiral *N*-acylpyridinium salt **530** to give the corresponding dihydropyridine **531** (Scheme 144).[731]

Scheme 144



Low-order furylcuprates such as (2-furyl)$_2$CuLi (**533**) have been used, for example, in the substitution reaction with the benzylic bromide **532**, affording the corresponding compound **534**, which, after reductive benzyl ether cleavage, can be anchored to the Merrifield resin for solid-phase Diels−Alder reactions (Scheme 145).[732] They have also been used in S_N2'

Scheme 145

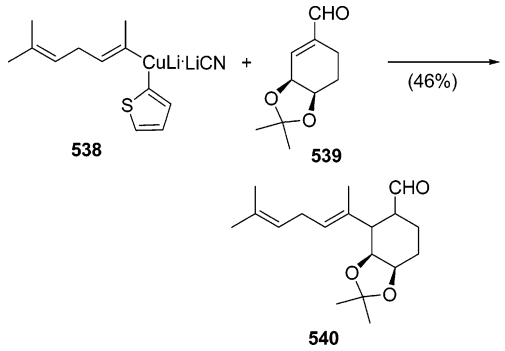


reactions on chiral carbonates[733] and, together with indole-, thiophene-, and benzo[*c*]thiophene-derived cuprates, in the opening of chiral tosylated aziridines,[734] whereas 2-furylcopper has been employed in an addition reaction to acetylenic triflones.[735] Moreover, high-order furylcuprates, such as compound **536**, have been used in additions to indolium triflates, such as **535**, affording in this case aminoallene **537**, which can be thermally isomerized to indolobenzazepines (Scheme 145).[736] They have also been employed in nucleophilic opening of epoxides.[737]

Thiophene derivatives, such as lithium di(3-thienyl)cuprate, have been used, for example, in substitution reactions to 3-chloro-1,4-oxathiane,[229] whereas 2-thienylcuprates [obtained by mixing 2-thienylmagnesium bromide, $CuBr_2$, and LiBr (1:1:2)] are used in substitution reactions with oxalyl chloride,[738] monoesters of dicarboxylic acid chlorides,[739] or α-acetoxy carboxylic acid chlorides.[740]

Mixed high-order cyanocuprates of the type R(2-thienyl)CuCNLi$_2$[741] bearing a nontransferable 2-thienyl ligand not only are very reactive, but also show high thermal stability and high selectivity. These thienylcuprates can be prepared by reaction of commercial (2-thienyl)CuCNLi (obtained from 2-thienyllithium and CuCN) with the corresponding organolithium or -magnesium, although in other cases even vinylic tellurides have been employed.[742] Recent examples of the use of this thiophene-derived cuprate reagent can be seen in substitution reactions[743] applied to the synthesis of brevetoxin B[744] or jasmonoids,[745] in the opening of epoxides for the synthesis of *syn*-1,2-diols,[746] and to the synthesis of the fungal metabolite fumagillol,[747] the sponge metabolite (−)-mycalolide,[748] or different sphingosines.[749] In addition, they have been used in Michael additions,[750] as in the example shown in Scheme 146, where the cuprate **538** adds to the chiral aldehyde **539** to give

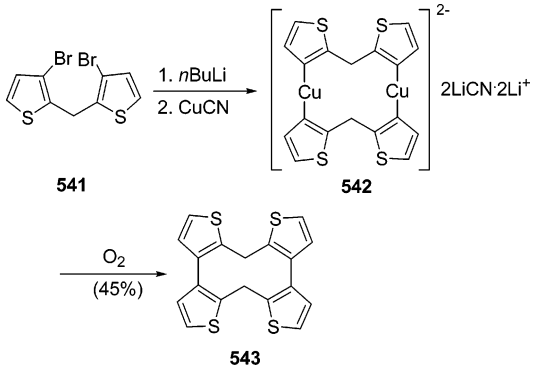
Scheme 146



compound **540**, which is an intermediate in another synthesis of fumagillol.[751] Michael additions to prostaglandin analogues[752] and additions to *N*-acyldihydropyridones as in the synthesis of (−)-slaframine[753] or 1-deoxynojirimycin,[754] as well as couplings to tosylates under palladium catalysis, have been reported.[755]

The reaction of (2-thienyl)CuCNLi with lithium amides such as lithium methylphenylamide promoted by oxygen has allowed the electrophilic amination of thiophene at the 2-position.[756] This type of coupling promoted by oxygen using cuprates has also been applied to the preparation of 10-membered ring cyclophanes, as shown in Scheme 147, for the prepa-

Scheme 147

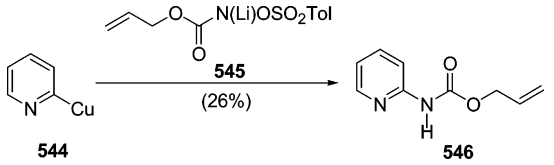


ration of the cuprate **542** from compound **541**, followed by oxidative coupling to cyclophane **543**.[757] In addition, (2-thienyl)$_2$CuCNLi$_2$ has been used in electrophilic amination reactions by treatment with *N*-alkylhydroxylamines[758] and in additions to the iminic function of 1-aza-1,3-butadienes.[759]

There are also examples of the use of high-order organocuprates from 1,3-azoles such as *N*-substituted imidazoles or thiazoles as nucleophiles in substitution and epoxide ring-opening[737,760] reactions.

The 2-pyridylcopper reagent **544**, prepared by transmetalation of 2-pyridyllithium with copper(I) bromide, is able to react with lithium allyl-*N*-lithio-*N*-(tosyloxy)carbamate (**545**) to give the amination product **546** (Scheme 148).[761] In addition, 3-pyridyl-derived low-order cuprates have been employed in asymmetric S_N2' reactions with chiral carbonates,[733] whereas high-order 2-pyridyl-derived cuprates have been used in electrophilic amination reactions,[758] and epoxide ring-opening processes.[737]

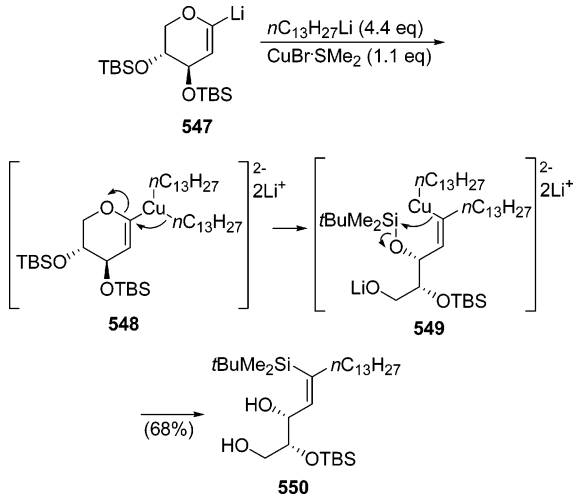
Scheme 148



The treatment of 2-lithiated *N*-Boc-pyrrolidine or -piperidine with a copper salt such as copper(I) cyanide with or without 2 equiv of lithium chloride gives the corresponding pyrrolidinylcopper reagents, which can be used for conjugated Michael additions to electrophilic olefins.[762] From these studies, the strong influence of factors such as the quality of the *sec*-butyllithium employed in the lithiation step in the final result can be observed.[762b]

A cuprate generated from 2-lithiotetrahydrofuran has been used in a vinylic substitution reaction of a triflate on a cephalosporin derivative, although a mixture of the desired compound and isomerization and ring-opening products was obtained.[632a] In addition, a glucosylcopper(I) reagent has been added to cationic molybdenum complexes in an approach to the synthesis of *C*-glycosides.[763] Moreover, the higher order cuprate **548** derived from the α-lithiated xylal **547** (obtained by tin−lithium exchange) suffers 1,2-metal rearrangement to give the alkenyl cuprate **549**, which undergoes a selective intramolecular oxygen−carbon silyl transfer, affording compound **550**, an intermediate in the synthesis of D-*erythro*-sphingosine and D-*erythro*-ceramide (Scheme 149).[764]

Scheme 149



7.4. Zinc Heterocycles

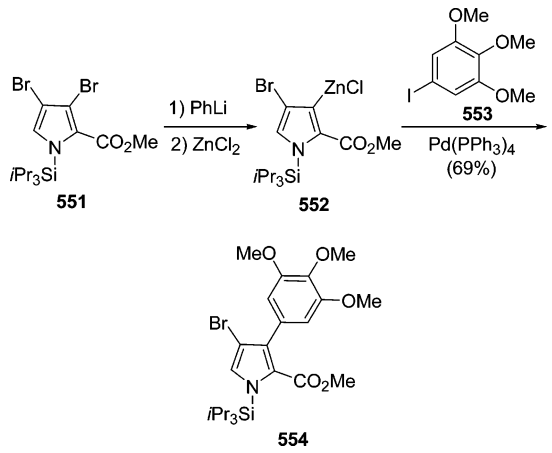
Organozincs are a useful class of organometallics due to their tolerance of numerous functional groups.[765,766] The heterocyclic zinc derivatives are generally prepared by exchange reactions of the corresponding organolithiums or -magnesiums with zinc halides, being stable at higher temperatures than their precursors.[765] Other methods for their preparation employ zinc dust,[765,766,767a] active Rieke zinc,[765,766] or even electrochemical methods.[767b]

Heteroarylzincs have been used particularly in palladium-catalyzed cross-coupling reactions with unsaturated halides (the so-called Negishi coupling),[768] being an alternative to boronic derivatives (Suzuki reaction), aryltin derivatives (Stille reaction), or silicon derivatives (Hiyama reaction) because many functionalities are tolerated as well, mild reaction conditions also generally being employed.

7.4.1. Aromatic Five-Membered Rings

An example of palladium-catalyzed coupling reactions involving pyrrolylzincs is shown in Scheme 150,

Scheme 150



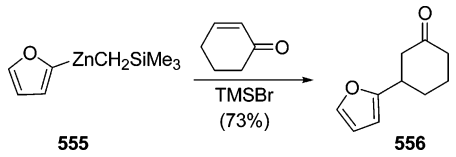
where the dibrominated *N*-protected pyrrole **551** is monolithiated and reacts with zinc dichloride, affording the corresponding organozinc **552**, which is cross-coupled with the aryl iodide **553** to give compound **554**, which can be transmetalated and coupled again to give an intermediate in the synthesis of marine alkaloids lamellarins.[769a] In addition, 2-pyrrolylzincs, as well as other heteroarylzincs, have been coupled with 6-halopurines to get interesting nucleosides and nucleotides,[769b−d] some of them showing significant cytostatic activity.[769d] Moreover, indolylzincs have also been used in palladium-catalyzed Negishi cross-couplings.[770]

Examples of the use of furylzincs as nucleophiles in addition reactions to aldehydes can be found in the asymmetric synthesis of 1-deoxy-8,8a-di-*epi*-castanospermine[771] and cyclic hydropyran oligolides.[772] In addition, 2-furylzinc chloride has been used in substitution reactions with PBr_2-substituted phosphinines.[773]

Mixed dialkyl- or diarylzincs such as compound **555**, prepared by treatment of 2-lithiofuran with (trimethylsilyl)methylzinc iodide, bears one nontransferable (trimethylsilyl)methyl group, which avoids the wasting of one transferable group. These mixed diorganozincs can be used in conjugate Michael additions with exclusive 1,4-regioselectivity,[774] as shown in the addition of reagent **555** to cyclohexenone, affording the corresponding ketone **556** (Scheme 151),[774cc] a reaction which has also been performed using the corresponding thiophene and *N*-methylpyrrole derivatives,[774c] as well as their benzocondensed counterparts.[774a]

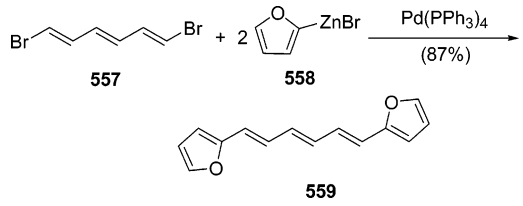
Furylzincs have also been used in different Negishi coupling reactions, for example, to aryl halides,[775] β-iodo-β,γ-enones,[776] tosyloxymethylenefuranones,[777]

Scheme 151



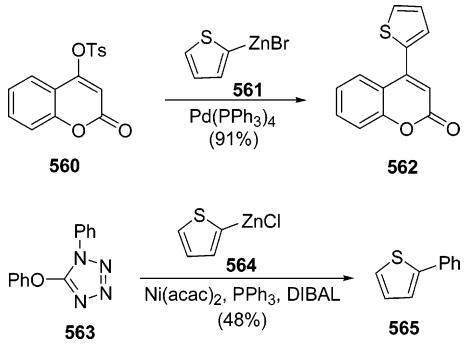
or dibromotrienes[778] such as compound **557**, which reacts with 2-furylzinc bromide (**558**) under palladium(0) catalysis to give the triene **559** (Scheme 152),[778b] a reaction which has also been carried out with 2-thienylzinc bromide.[778b]

Scheme 152



Thienylzincs have been recently prepared, apart from the usual methods, by activation of the corresponding thienyl bromides by low-valent cobalt species arising from the reduction of cobalt halide by zinc dust.[779] Thienylzincs have been used as nucleophiles, for example, in addition to carbonyl compounds,[220] substitution reactions with chlorostannane resins,[780a] or additions to 1,2-dihydropyrans,[780b] but mainly in palladium-catalyzed homocoupling[781] or cross-coupling reactions, for example, to aryl iodides and bromides,[535,782] even in perfluorinated solvents[783] or ionic liquids,[784] polymer-bound bromo aryl compounds,[785] 5-bromo-2,4-dienals,[786] tosyloxymethylenefuranones,[777] and 4-tosylcoumarins, such as compound **560**, which couples with 2-thienylzinc bromide (**561**) to give the expected coumarin derivative **562**, in studies toward combinatorial libraries (Scheme 153).[787] In addition, nickel(0) has been used as a

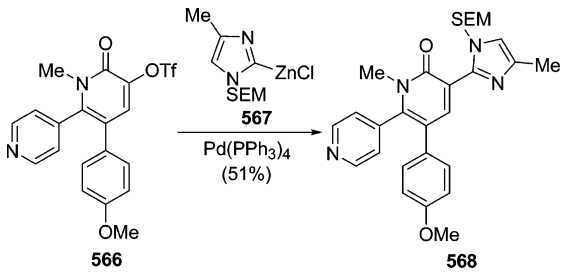
Scheme 153



catalyst in reactions involving cross-couplings between thienylzincs and thienyl bromides for the preparation of polythiophenes,[788] 4-diethylphosphonoxycoumarins,[789] benzylsulfonium salts,[790] and heteroaromatic ethers derived from phenols such as 1-phenyl-5-phenyloxy-1*H*-tetrazole (**563**), which couples with 2-thienylzinc chloride (**564**) to give 2-phenylthiophene (**565**) (Scheme 153).[791]

2-Zincated 1,3-azoles, prepared by a simple direct lithiation−zincation sequence, have been used mainly in palladium-catalyzed Negishi cross-couplings, as in the reaction of the triflate **566** with the *N*-silylated imidazolylzinc chloride **567** to afford compound **568** (Scheme 154), in studies toward the synthesis of

Scheme 154

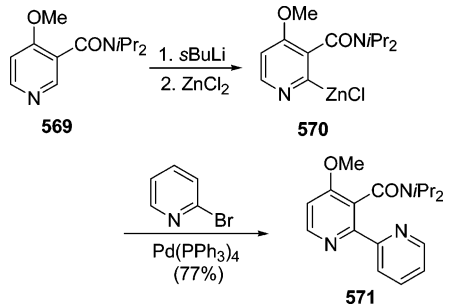


potentially interesting anxiolytics.[549] Imidazol-4-ylzinc chloride has also been used in the synthesis of α_2 adrenoceptor agonists,[247] whereas oxazol-2-ylzinc[792] and thiazol-2-ylzinc[793] derivatives have also been employed in Negishi cross-couplings. Moreover, copper-catalyzed cross-coupling reactions have also been performed using *N*-methylimidazol-2-ylzinc iodide.[794] In addition, thiazol-4-ylzinc bromide has also been used in additions to nitrones.[100] Furthermore, a recent example of the use of a pyrazolylzinc chloride, prepared by C-5-lithiation and transmetalation, for a Negishi cross-coupling, has been reported.[522]

7.4.2. Aromatic Six-Membered Rings

Pyridylzincs have been obtained generally from the corresponding halopyridines by a lithium−zinc transmetalation, although deprotonative zincation of bromopyridines using aminozincates,[795a] and even a direct insertion of zinc into perfluoropyridines in the presence of metal salts, has been reported.[795b] As usual, pyridylzincs have been used mainly in the Negishi cross-coupling reaction.[301,796] Other recent examples are the Negishi reaction between 2-pyridylzinc bromide and bromooxazoles[797] or thiazoles.[798] An example of these processes is the generation of the 2-pyridylzinc chloride **570** (obtained by lithiation of the corresponding pyridine **569** via DoM reaction followed by transmetalation), which is cross-coupled with 2-bromopyridine to give the bipyridine **571** (Scheme 155), a starting material in the synthesis

Scheme 155

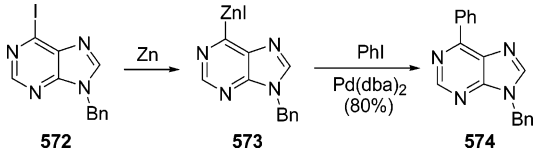


of the bipyridinic antibiotic caerulomycin.[799] In addition, 6-bromo-2-pyridylzinc chloride has been used in palladium-catalyzed cross-couplings, and the

remaining bromide can be transformed into another zinc derivative and cross-coupled again to give heteroarotinoids.[800] Furthermore, epibatidine analogues have been obtained using the Negishi methodology with pyridylzincs,[801] as well as steroidal inhibitors of the human cytochrome $P450_{17\alpha}$.[802]

Organozincs derived from diazines have been obtained from lithiated diazines, and reacted in cross-coupling reaction with haloaryls, the use of sonication lowering reaction times and improving yields.[803] However, 6-iodopurine derivatives readily insert zinc dust at room or higher temperature, affording zincated nucleic acid base derivatives which undergo Negishi reaction with aryl iodides, as shown in Scheme 156 for the zincation of the purine **572**

Scheme 156



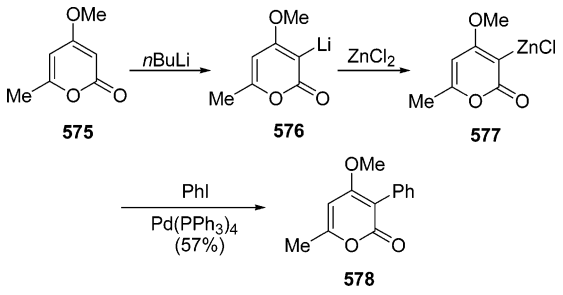
572 **573** **574**

followed by palladium-catalyzed cross-coupling reaction between the corresponding zincated derivative **573** and iodobenzene to give finally the coupled adduct **574**.[804]

7.4.3. Nonaromatic Heterocycles

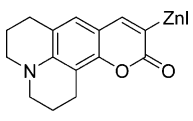
2-Azetidinylzinc species have been prepared from the corresponding iodides by direct zinc metal insertion, and undergo palladium-catalyzed cross-coupling reactions.[805] In addition, 3-substituted 2*H*-pyran-2-ones have been prepared according to the example outlined in Scheme 157. Thus, 2*H*-pyran-2-one **575**

Scheme 157



575 **576** **577** **578**

can be lithiated at C-3, giving the intermediate **576**, which can be transmetalated to the organozinc derivative **577**, experiencing further palladium-catalyzed Suzuki cross-coupling reaction to give the corresponding substituted pyranone **578**,[806] a coupling also employed with 5-zincated pyran-2-ones and pyridin-2-ones.[807] Recently, a 3-cumarinylzinc iodide **(579)** has been employed as a nuclophile in the reaction with a chlorodiarylphosphane, affording a fluorogenic dye.[808]

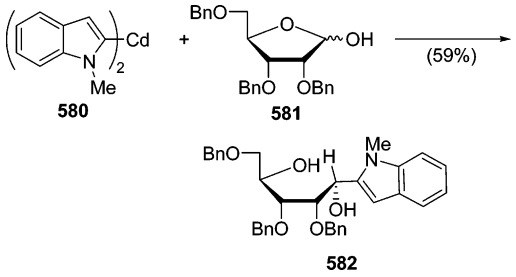


579

7.5. Cadmium Heterocycles

Cadmium-derived heterocycles can be prepared by reaction of the corresponding Grignard reagents with cadmium(II) chloride. Thus, heteroaryls bearing cadmium metal at the 2-position such as thiophene, benzo[*c*]thiophene, *N*-methylindole, and pyridine have been employed in additions to riboses, usually with good stereoselectivity, as shown in Scheme 158 for the addition of (2-indolyl)cadmium **580** to furanose **581** to give the expected addition compound **582**.[220]

Scheme 158

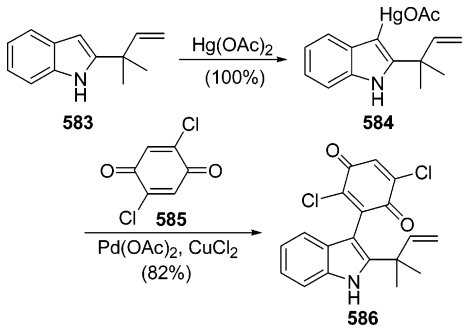


580 **581** **582**

7.6. Mercury Heterocycles

Electron-rich heteroaromatics can be mercuriated by reaction with a mercury(II) salt. The obtained organometallics can be used, for example, in halodemercuriation or palladium-promoted coupling reactions.[809a] Thus, indole **583** has been mercuriated to give compound **584** using mercury(II) acetate and coupled to dichloroquinone **585** under palladium catalysis to give the corresponding indole **586**, used in studies toward the synthesis of insulin mimetic demethylasterriquinones (Scheme 159).[809b] Other

Scheme 159

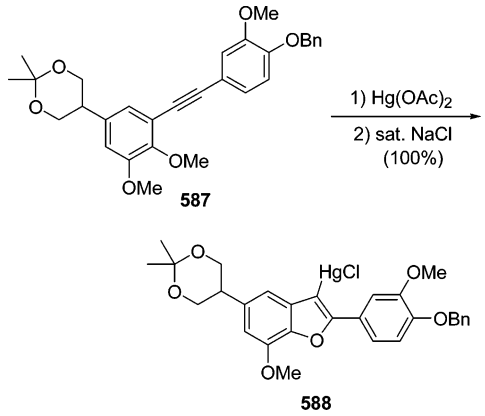


583 **584** **585** **586**

examples of the use of indole-derived organomercurials in palladium-promoted couplings involve approaches to the ergot alkaloid skeleton,[810] or intramolecular cyclizations for the synthesis of (+)-austamide and relative compounds.[811] The mercury metal can also be interchanged by other metals such as boron for subsequent Suzuki couplings (as shown recently in a total synthesis of dragmacidin D[270a]) or even aluminum.[320]

Mercuriated benzofurans have been obtained by mercury(II) acetate-promoted cyclization of alkynes such as compound **587** followed by quenching with sodium chloride, affording the chloromercurial **588** (Scheme 160).[812] The mercury in compound **588** can be reduced with sodium borohydride to the corresponding benzofuran in a methodology which has

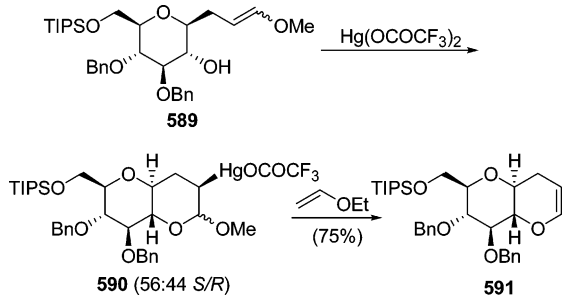
Scheme 160



been applied to the synthesis of different neolignans.[812] In addition, the mercuriation of the thiophene ring, which usually takes place easily and with high selectivity at the 2-position, probably due to coordination to the sulfur atom,[813] affords heteroarylmercury systems, which have been recently used in palladium-catalyzed homocouplings for the synthesis of bridged oligothiophenes,[814] or in iododemercuriation reactions for subsequent Suzuki couplings.[815] Furthermore, polychlorinated thiophene mercurials have also been reported.[816]

Generally, mercury-derived nonaromatic heterocycles arise as intermediates in carbon−carbon double bond addition processes. Examples can be seen in the synthesis of 3-deoxy-D-*lyxo*-2-heptusolaric acid derivatives,[817] or in methodologies for the preparation of fused cyclic polyethers, as shown in Scheme 161, where the pyran **589** is treated with mercury(II) trifluoroacetate to give a α-mercurial acetal intermediate **590**, which can be converted to the dihydropyran **591** by treatment with ethyl vinyl ether.[818]

Scheme 161

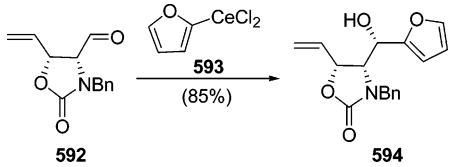


8. Lanthanide-Metal-Containing Heterocycles

8.1. Cerium Heterocycles

Heteroarylceriums have been obtained by reaction of heteroaryllithiums with cerium trichloride. The reported examples of the use of this very soft nucleophiles deals mainly with additions to carbonyl compounds. Thus, 2-furanylcerium dichoride (**593**) has been diastereoselectively added to the oxazolinocarbaldehyde **592** to give *syn*-alcohol **594** (Scheme 162).[819] There are also examples of the use of other heteroarylceriums from thiophene and *N*-methylindole in stereoselective coupling with riboses.[220]

Scheme 162



9. Conclusions

In this review we have shown the impressive amount of synthetic uses that have been found for metalated heterocycles in the last several years. Starting from lithiated heterocycles, not only important for themselves, but also being considered as the main entrance to almost all the other metalated systems, the introduction of a heterocyclic moiety in a synthetic path involving these types of metal-derived compounds is usually direct and efficient. Since techniques for lithiation in practically any position of heteroaromatics are now well stablished via direct deprotonation, halogen exchange, or directed *ortho*-metalation, the entrance to many metalated systems seems wide open. However, the use of chiral lithium bases for achieving highly asymmetric transformations will surely deserve special attention and further development in the future. In addition, techniques for the use of low-cost metals such as sodium or potassium in heterocyclic metalations should be interesting for development, as well as more research on the field of organometallics bearing different functionalities. The different palladium-catalyzed cross-coupling reactions deserve special mention. Taking a glance at the number of recent publications using, for instance, boron- or tin-derived heterocyclic systems using these transition-metal-assisted transformations, the synthetic importance of these metalated heterocycles can be easily seen. Particularly, cross-coupling reactions involving boron-containing heterocycles will probably be more used in the future than their tin-derived counterparts, especially in large-scale transformations for environmental reasons. Moreover, less exploited cross-couplings using the also environmentally friendly silylated heterocycles should experience further development. No doubt that metalated heterocycles will continue to be indispensable tools in organic synthesis in the future, as they are in the present.

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