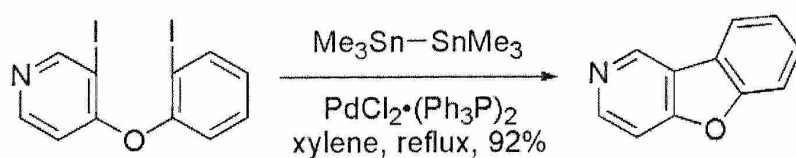




Palladium in Heterocyclic Chemistry

A Guide for the Synthetic Chemistry
2nd edition



JIE JACK LI AND GORDON W. GRIBBLE

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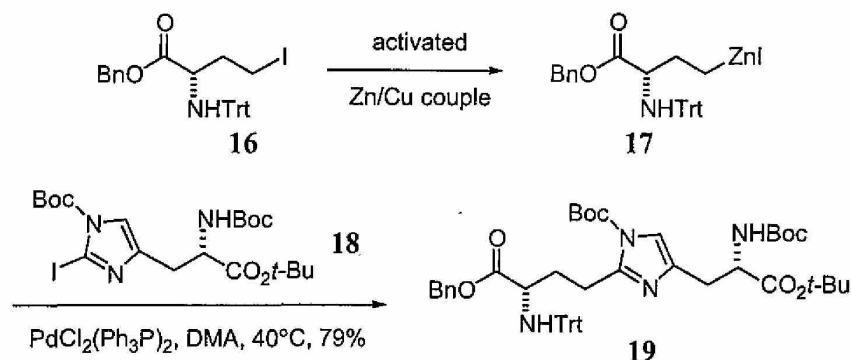
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The high functional group tolerance of these transformations is nicely illustrated by the coupling shown below. Evans and Bach prepared organozinc reagent **17** that contains both ester and amide functional groups via quantitative metalation of iodide **16** with activated Zn/Cu couple. Treatment of 2-iodoimidazole **18** with three equivalents of **17** in the presence of catalytic $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ provided adduct **19** in 79% yield [21].



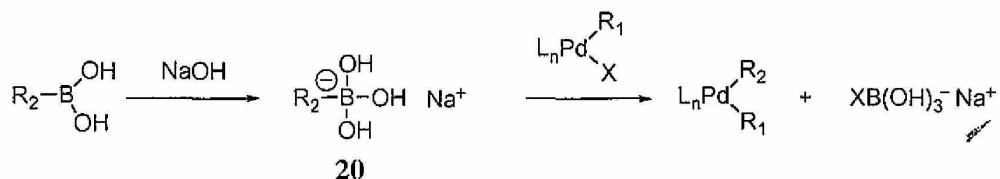
The successful Negishi coupling between *alkylzinc reagent* **17** and 2-iodoimidazole **18** also illustrates that primary aliphatic alkyl groups can be effectively cross-coupled using this method. Although competing β -hydride elimination of the intermediate (aryl)(alkyl)Pd(II) complex can lead to side products (typically the aryl halide is reduced and the alkyl nucleophile is oxidized to an olefin), there are many examples of Negishi couplings of alkylzinc reagents that indicate C–C bond-forming reductive elimination supercedes β -hydride elimination side reactions [16]. Cross-coupling of alkyl organometallics can also be achieved using Suzuki or Stille reactions (described below).

1.2.2. The Suzuki coupling

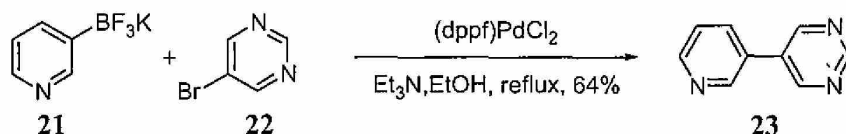
The Suzuki reaction is one of the most frequently employed Pd-catalyzed C–C bond-forming reactions, and involves the cross-coupling of organoboron reagents with organohalides (or triflates) [22]. This transformation has two significant advantages over related Stille couplings of organostannanes (see below). First of all, organoboron reagents have very low toxicity, especially compared to aryl(trialkyl)tin derivatives. In addition, the boron-containing side products of these transformations are usually easily removed through a simple alkali workup, whereas the trialkyltin halide byproducts of Stille coupling reactions are much more difficult to remove. For these reasons, Suzuki coupling is a more attractive choice than Stille coupling for syntheses conducted on a large scale.

The main limitations of using organoboronic acids in cross-coupling chemistry are three-fold. These compounds are quite reactive towards many nucleophiles and oxidants, which prohibits installation of the boronic acid functional group early in a synthetic sequence. Moreover, purification of boronic acids is often problematic. Finally, since the C–B bond is relatively nonpolar, transmetalation of an organoboron reagent to Pd(II) will not occur without coordination of an anionic base or a fluoride ion to the boron atom to afford a four-coordinate “ate”-complex (e.g. **20** shown below). This requirement poses some limitations with respect to transformations of base- or fluoride-sensitive substrates, although these

limitations are usually not insurmountable obstacles and problems can frequently be solved with a judicious choice of reaction conditions.

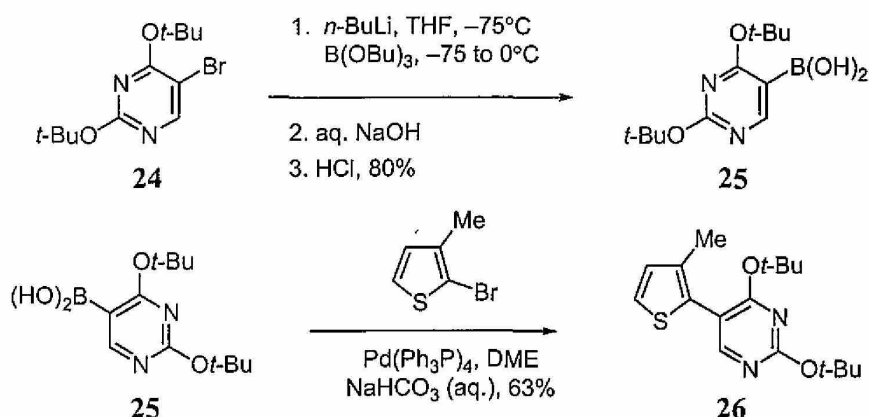


Recently, there has been considerable progress in the development of new organoboron reagents for cross-coupling chemistry that overcome some of the limitations described above. Most notably, Molander has described the use of air- and moisture-stable alkyl, aryl, and vinyl potassium trifluoroborate salts in Suzuki coupling reactions [23]. For example, the cross-coupling of **21** with **22** afforded biaryl **23** in 64% yield. These salts are easier to purify and handle than the analogous boronic acid derivatives, and they have proven to be stable to epoxidation reactions that allow for the preparation and cross-coupling of functionalized organoboron derivatives [24]. Although there are considerably fewer known heteroarylboron reagents than the related heteroarylstannanes, a growing number of these compounds are appearing in the literature.

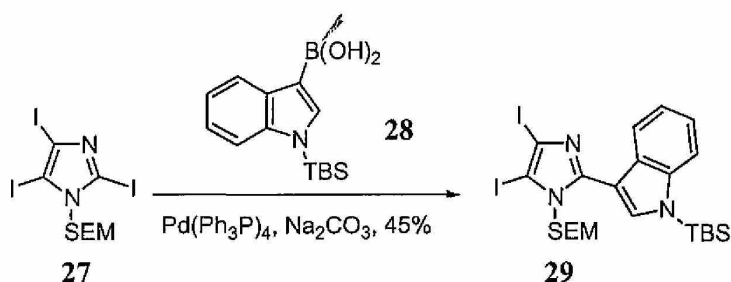


As each of the ensuing chapters will entail, pyrrolyl-, indolyl-, pyridinyl-, pyrimidinyl-, thienyl-, pyrazinyl-, and furylboron reagents have been documented, although those derived from thiazoles, oxazoles, and imidazoles have yet to be described in the primary literature. The most popular methods for synthesizing heteroarylboron reagents include: (a) halogen-metal exchange of a heteroaryl halide followed by treatment with a borate; and (b) direct metalation of a heteroarene followed by quenching with a trialkylborate [25]. As a representative example, the conversion of bromopyrimidine **24** to the corresponding boronic acid (**25**) followed by subsequent Suzuki coupling is described below.

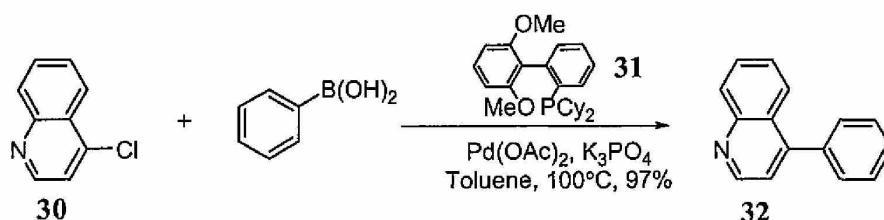
The preparation of 5-pyrimidineboronic acid is not trivial because the requisite lithiopyrimidine is prone to react with another substrate molecule by undergoing addition to the azomethine carbon [26]. However, the analogous transformation of 2,4-di-*tert*-butoxy-5-bromopyrimidine (**24**) can be effected in good yield. The halogen-metal exchange can be conducted at -75°C , and the nucleophilic attack of the corresponding organolithium species on the azomethine carbon of a second molecule is retarded due to steric hindrance [26]. The organolithium reagent generated upon lithium-halogen exchange is then treated with tri-*n*-butylborate, followed by basic hydrolysis and acidification to afford 2,4-di-*t*-butoxy-5-pyrimidineboronic acid (**25**). The Suzuki coupling of boronic acid **25** with a variety of heteroaryl halides was conducted to prepare 5-substituted heteroarylpyrimidines such as **26**, which were then hydrolyzed to 5-substituted uracils for investigation of potential antiviral properties [27].



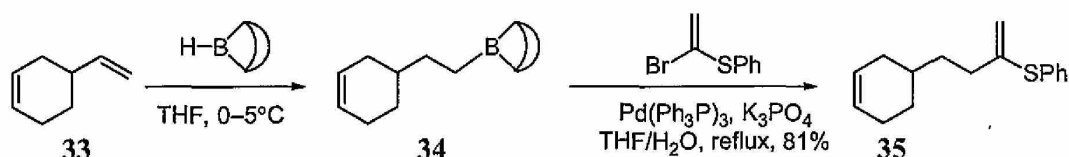
Recognizing the distinct difference in reactivity for each site of *N*-protected 2,4,5-triiodoimidazole **27**, Ohta's group executed the regioselective arylation of this substrate [28]. As shown below, coupling of **27** with one equivalent of 3-indolylboronic acid **28** provided imidazolylindole **29**; the Suzuki reaction occurred regioselectively at C(2) of the imidazole ring. Product **29** was subsequently employed in the total synthesis of nor-topsentin C.



In recent years, a number of groups have been involved in the development of new, highly active catalysts for Suzuki coupling reactions [29]. For example, the groups of Buchwald and Fu have developed catalysts for the coupling of aryl chlorides with arylboronic acids [30]. With many catalysts (e.g. $\text{Pd}(\text{PPh}_3)_4$), chlorobenzene is very unreactive because the oxidative addition of aryl chlorides to $\text{Pd}(0)$ is slow (relative to analogous oxidative additions of aryl iodides, bromides, and triflates). However, in the presence of sterically hindered, electron-rich phosphine ligands (e.g. $\text{P}(t\text{-Bu})_3$ or 2-dicyclohexylphosphinobiphenyl derivatives), enhanced reactivity is acquired presumably because the oxidative addition of an aryl chloride is more facile with a more electron-rich palladium complex. Extensions of these methods to Suzuki couplings using inexpensive heteroaryl chlorides have also been described [23, 31]. For example, the $\text{Pd}(\text{OAc})_2/\mathbf{31}$ catalyzed Suzuki coupling of phenylboronic acid with 4-chloroquinoline (**30**) provided **32** in 97% yield [31]. This methodology should be amenable to large-scale synthesis as the required ligands are now commercially available, the transformations can be effected with low catalyst loadings, and the organic chlorides are less expensive and more readily available than other organic halides.



As in the Negishi reaction, various *alkylboron reagents* have also been successfully coupled with electrophilic partners [32]. For example, Suzuki *et al.* coupled 1-bromo-1-phenylthioethene with 9-[2-(3-cyclohexenyl)ethyl]-9-BBN (34), prepared by a simple addition of 9-borabicyclo[3.3.1]nonane (9-BBN) to 4-vinyl-1-cyclohexene (33), to furnish 4-(3-cyclohexenyl)-2-phenylthio-1-butene (35) in good yield [33].



1.2.3. The Stille coupling

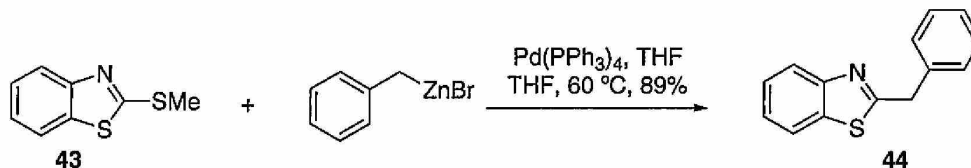
The Stille reaction is the Pd-catalyzed cross-coupling between an organostannane and an electrophile to form a new C–C single bond [34]. It is regarded as the most versatile method in Pd-catalyzed cross-coupling reactions with organometallic reagents for two reasons. First, the organostannanes are readily prepared, purified, and stored. Second, the Stille conditions tolerate a wide variety of functional groups. In contrast to the Suzuki, Kumada, and Heck reactions that are run under basic conditions, the Stille reactions are usually run under neutral conditions. The pitfall of the Stille reaction is the toxicity of stannanes, which makes this process unsuitable for large-scale synthesis.

Stille coupling reactions of organic triflates are often facilitated by added LiCl when conducted in THF solvent. Presumably the chloride anion replaces the triflate ligand on palladium following oxidative addition, which leads to increased stability of the Pd(Ar)(X) species [35]; this additive may also assist in the transmetalation step. However, LiCl is not needed when the Stille reactions are carried out in polar solvents like NMP [36].

Many Stille coupling reactions are improved by the use of added Cu(I) co-catalysts [37]. Farina and Liebeskind postulated that Cu(I) performs dual roles in these transformations [34d, 38]. In ethereal solvents, Cu(I) acts as a phosphine ligand scavenger to facilitate formation of the coordinatively unsaturated Pd(II) intermediate needed to effect transmetalation. In addition, Cu(I) may also react with the organostannane to form a more reactive organocopper reagent in highly polar solvents such as NMP in the presence of soft ligands (e.g. AsPh₃).

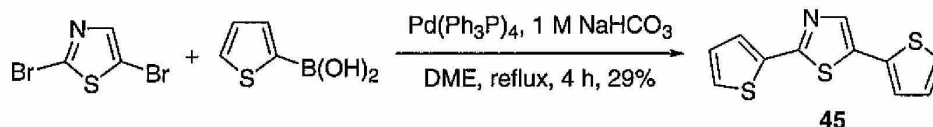
Heteroarylstannanes are more prevalent than their heteroarylboron counterparts. As the following chapters will entail, all of the heteroarylstannanes are known with the one exception of quinoxalines bearing tin at the C(2) or C(3) positions. The exception could be simply a result of lack of necessity—as this aromatic group could be installed through cross-coupling of the available quinoxaliny halides.

Besides halothiazoles, thiomethyl groups have also found utility as leaving groups in the Negishi coupling reaction of thiazoles [26]. For instance, reaction of **43** with benzylzinc bromide under the normal Negishi conditions resulted in **44**.

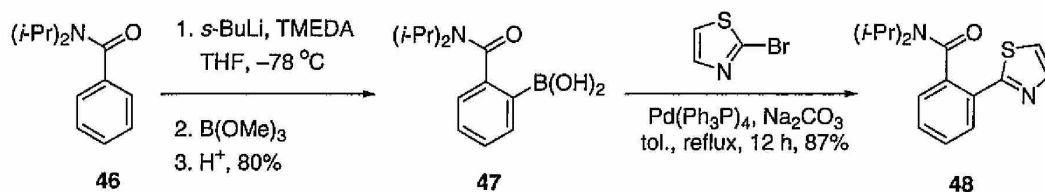


7.2.2. Suzuki coupling

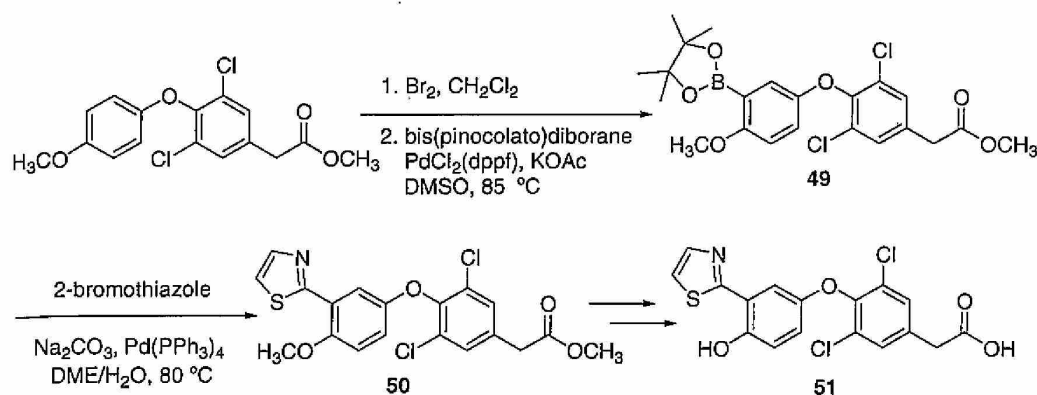
The synthesis of thiazole boronic acids is quite complicated. In fact, attempts to prepare 2-thiazoleboronic acid were unsuccessful [27]. As a consequence, the Suzuki reaction involving thiazoles is only possible when the thiazole component serves as the electrophilic coupling partner. Halothiazoles have shown the greatest utility in this regard. For instance, 2,5-di-(2-thienyl)thiazole (**45**) was prepared by the union of 2,5-dibromothiazole and easily accessible 2-thiopheneboronic acid [27]. Unfortunately, the yield was poor and analogous reactions of 2,5-dibromothiazole with 3-thiopheneboronic acid and 2-selenopheneboronic acid both failed.



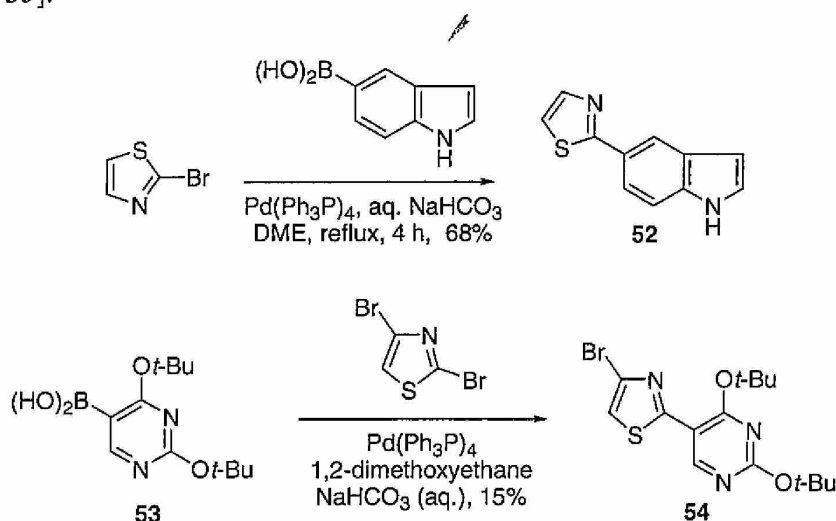
Snieckus *et al.* enlisted a combination of directed *ortho*-lithiation and Suzuki coupling to assemble some unsymmetrical heterobiaryls [28]. Carboxamidophenylboronic acid **47** was derived from sequential metalation of amide **46** and treatment with B(OMe)_3 followed by acidic workup. Hetero cross-coupling of **47** with 2-bromothiazole occurred smoothly to furnish phenylthiazole **48**. Similarly, a hetero cross-coupling between 2-bromothiazole and 3-formyl-4-methoxyphenylboronic acid produced a heterobiaryl as an intermediate of an orally bioavailable NK_1 receptor antagonist [29].



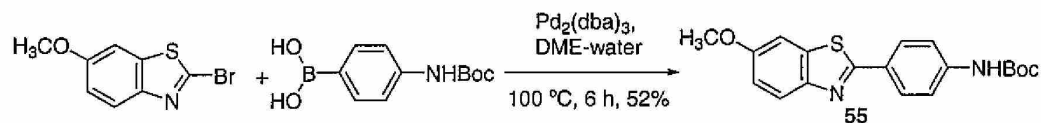
An alternate strategy was utilized in the synthesis of a potential thyroid receptor ligand [30]. Electrophilic bromination was followed by the Miyaura boronic ester synthesis to yield **49** [31]. Suzuki coupling between **49** and 2-bromothiazole was then accomplished to provide **50**, a precursor to the derivative **51**. Unfortunately, the presence of the thiazole at C(3), in **51** resulted in a decrease in binding affinity and selectivity as compared to the lead compound.



In addition to arylthiazoles, heteroarylthiazoles also have been synthesized using halothiazoles and heteroarylboronic acids. Suzuki coupling of 2-bromothiazole and 5-indolylboronic acid led to 5-substituted indole **52** [32]. The Suzuki coupling of 2,4-dibromothiazole with 2,4-di-*t*-butoxy-5-pyrimidineboronic acid (**53**) resulted in selective heteroarylation at the 2-position to give pyrimidylthiazole **54** although the yield was low [33–35].

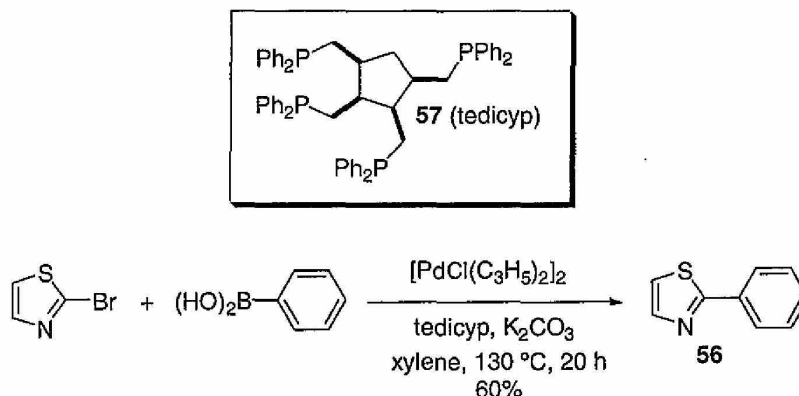


2-Bromobenzothiazole has also been used as the electrophile in the Suzuki coupling reactions with a variety of structurally diverse boronic acids [36]. Among these examples, derivative **55**, a positron emission tomography (PET) probe precursor was produced for the *in vivo* imaging of Alzheimer's disease.

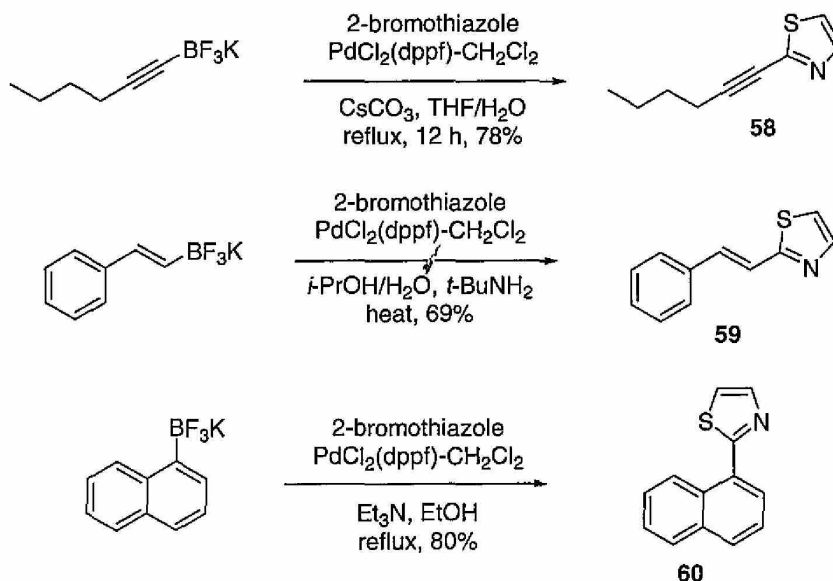


Laurenti and Santelli have recently introduced the tetrakisphosphine ligand (Tedicyp) **57** for use in palladium coupling reactions [37]. The catalyst formed from the combination of **57** and $[\text{PdCl}(\text{C}_3\text{H}_5)_2]$ has been shown to be remarkably efficient for allylic substitution and Heck vinylation reactions [38]. Additionally, efficient yields have been achieved

in the Suzuki coupling reaction between arylboronic acids and other heteroaryl bromides [39]. Specifically, the coupling reaction between 2-bromothiazole and benzeneboronic acid to produce **56** was achieved using a substrate/catalyst ratio of 10,000:1.



Molander has published a series of papers demonstrating the utility of potassium alkyl, alkenyl-, alkynyl-, and aryltrifluoroborates in palladium coupling reactions. The crystallinity and air-stability of these trifluoroborate salts make the use of these an interesting alternative to the use of boronic acids or esters. Good yields have been obtained in several related palladium coupling processes, which are most easily classified as Suzuki couplings. The broad applicability of this process is demonstrated by the production of **58** [40], **59** [41], and **60** [42].

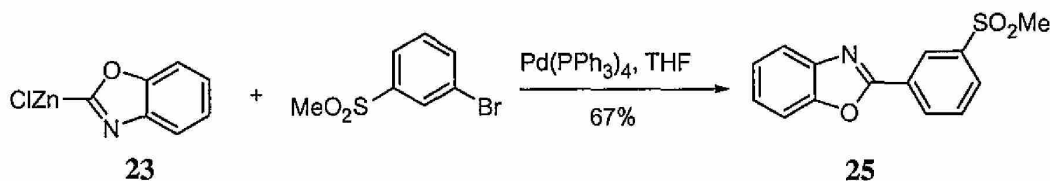


7.2.3. Stille coupling

7.2.3.1. Synthesis of stannylthiazoles

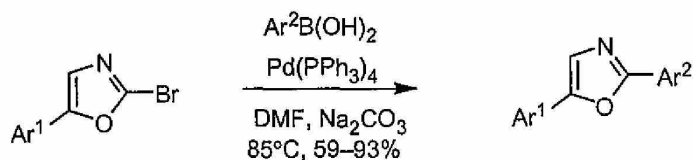
Two frequently used methods for preparing stannylthiazoles involve either direct metalation or halogen-metal exchange followed by treatment with alkyltin chloride. Dondoni

An improved and scalable method for 2-arylbenzoxazole **25** was reported by Reeder *et al.* via the Negishi reaction of **23** with aryl bromides [27].

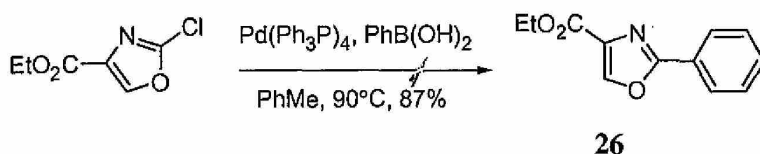


8.3.2. Suzuki coupling

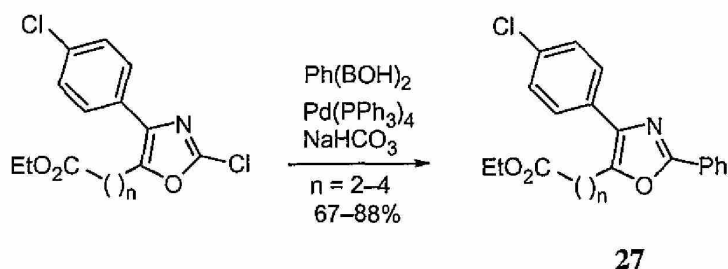
The Suzuki reaction represents the Pd-catalyzed cross-coupling reaction between organoboron reagents and aryl and heteroaryl halides. Vachal and Toth have developed a versatile approach to the synthesis of 2,5-diaryloxazoles using a Suzuki coupling [33]. Thus, 2,5-diaryloxazoles were prepared from 2-bromo-5-aryloxazole and electron rich and electron deficient boronic acids [33].



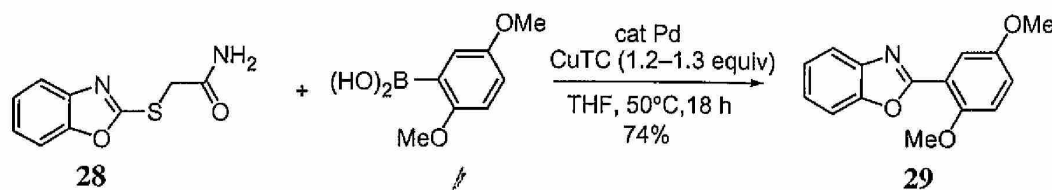
The readily available ethyl 2-chlorooxazole-4-carboxylate proved to be a versatile scaffold for the synthesis of 2,4-disubstituted oxazoles and 2,4,5-trisubstituted oxazoles. 2,4-Disubstituted oxazole **26** was prepared from 2-chlorooxazole-4-ethylcarboxylate *via* the Suzuki coupling with phenylboronic acid [26]. The carboxylic functionality at C(4) of **26** could then be exploited by a variety of synthetic transformations.



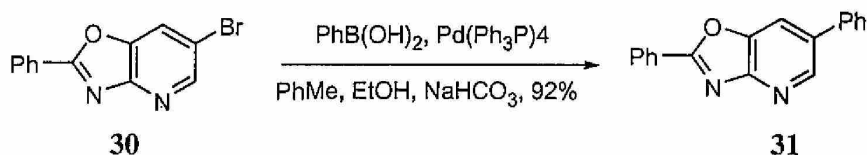
Maekawa *et al.* reported that a series of ω -oxazolylalkanoic acid derivatives as antidiabetic agents, promoting the glucose-dependent secretion of insulin. ω -(5-Oxazolyl)alkanoates **27**, the key intermediates for the synthesis of target compounds, were prepared *via* Suzuki coupling of substituted 2-chlorooxazole with phenylboronic acid [34].



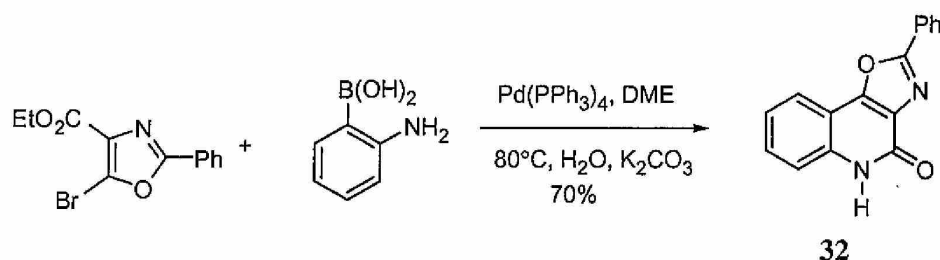
A Pd-catalyzed base-free coupling of arylboronic acids with π -deficient heteroaromatic thioethers was mediated by copper(I) thiophene-2-carboxylate CuTC [35]. Benzoxazole with a thioglycolamide pendant (**28**) was coupled with arylboronic acid in the presence of $\text{Pd}_2(\text{dba})_3/\text{tris}(2\text{-furyl})\text{phosphine}$ (TFP) to give 2-arylbenzoxazole **29**. The modifiable leaving group of this system suggested possible applications ranging from solid support-based reagents to pendant substrate recognition [35].



Attempts to prepare oxazolyboronic acids have failed probably due to the equilibrium between the cyclic and acyclic valence bond tautomers of the lithiooxazoles. A somewhat relevant Suzuki coupling involved the Pd-catalyzed cross-coupling of 6-bromo-2-phenyloxazolo[4,5-*b*]pyridine (**30**) with phenylboronic acid to provide 6-phenyl-2-phenyloxazolo[4,5-*b*]pyridine (**31**) [36].

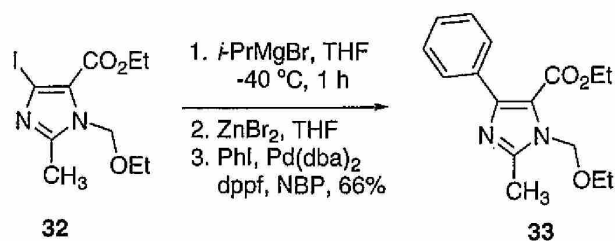


A series of 2-aryloxazoloquinolones **32** having high affinity for the GABA receptor were prepared *via* a Pd-catalyzed intramolecular diaryl coupling of ethyl 5-bromo-2-phenyl-oxazole-4-carboxylate with 2-aminophenylboronic acid followed by cyclization [37]. This one-pot intramolecular Suzuki reaction was followed by cyclization to afford a tricyclic compound **32**.

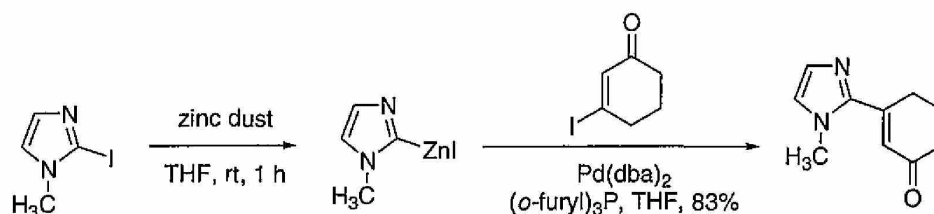


8.3.3. Suzuki–Miyaura coupling

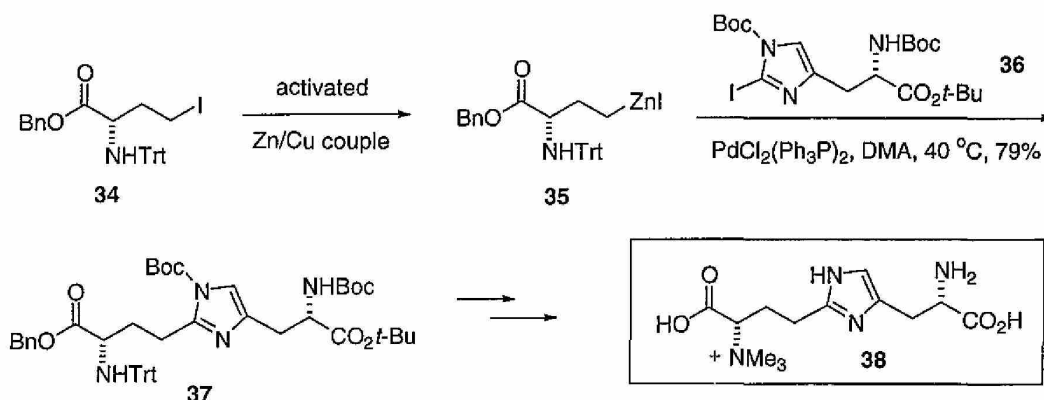
Application of the resin “capture-release” methodology to macrocyclization *via* an intramolecular Suzuki–Miyaura coupling was reported recently [38]. Aryl boronic acid was trapped by an ammonium hydroxide-form Dowex® Ion Exchanger resin (D-OH^-), leading to polymer-ionically bound borates **33**, which further cyclized into macroheterocycles **34** under the Suzuki–Miyaura coupling conditions [38].



Third, direct oxidative addition of organohalides to Zn(0) offers another synthetic strategy of preparing imidazol-2-ylzinc reagents. This method is advantageous over the usual transmetalations using organolithium or Grignard reagents because of the better tolerance of functional groups. Treating 1-methyl-2-iodoimidazole with readily available zinc dust, the Knochel group produced the expected imidazol-2-zinc iodide [25]. The subsequent Negishi reaction was carried out with vinyl-, aryl-, and heteroaryl halides.



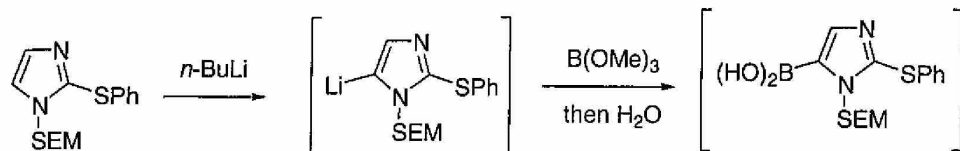
In addition to its use as the nucleophile in the Negishi reaction, imidazolyl iodides have found some usage as electrophiles under these conditions. Evans and Bach prepared organozinc reagent **35** from quantitative metalation of iodide **34** by using an activated Zn/Cu couple in the presence of an ester functionality. Treating 2-iodoimidazole **36** with three equivalents of **35** in the presence of $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ afforded adduct **37**, which was then transformed into diphthine (**38**) in five additional steps [26].



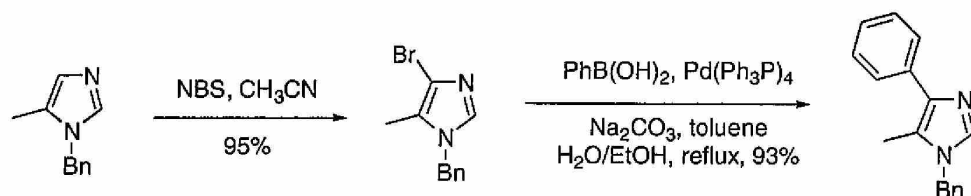
9.3.2. Suzuki coupling

Imidazolylboronic acids are not well-known. 5-Imidazolylboronic acid was prepared *in situ* by Ohta's group using selective lithiation at C(5) from 1,2-protected imidazole.

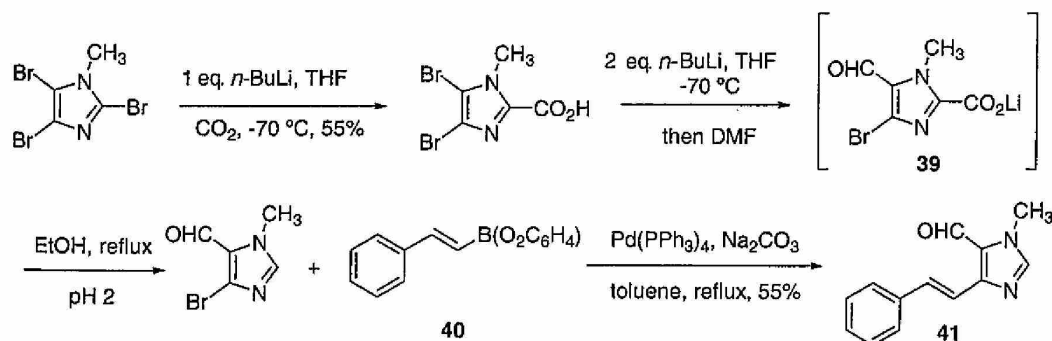
However, the subsequent Suzuki coupling with 3-bromoindole gave the expected indolylimidazole in only 7% yield [27]. This observation indicated that more investigation into imidazolylboronic acids is necessary to better understand their synthesis and behavior.



Nonetheless, to make imidazole-containing molecules, haloimidazoles may serve as electrophilic coupling partners for the Suzuki reaction. As described in Section 9.1, regioselective bromination at the C(4) position could be achieved for a 1,5-dialkylimidazole using NBS in CH_3CN . The Suzuki coupling of 1-benzyl-4-bromo-5-methylimidazole with phenylboronic acid assembled the unsymmetrical heterobiaryl in 93% yield, whereas the corresponding Stille reaction with phenyltrimethyltin proceeded in only moderate yield (51%) [10].

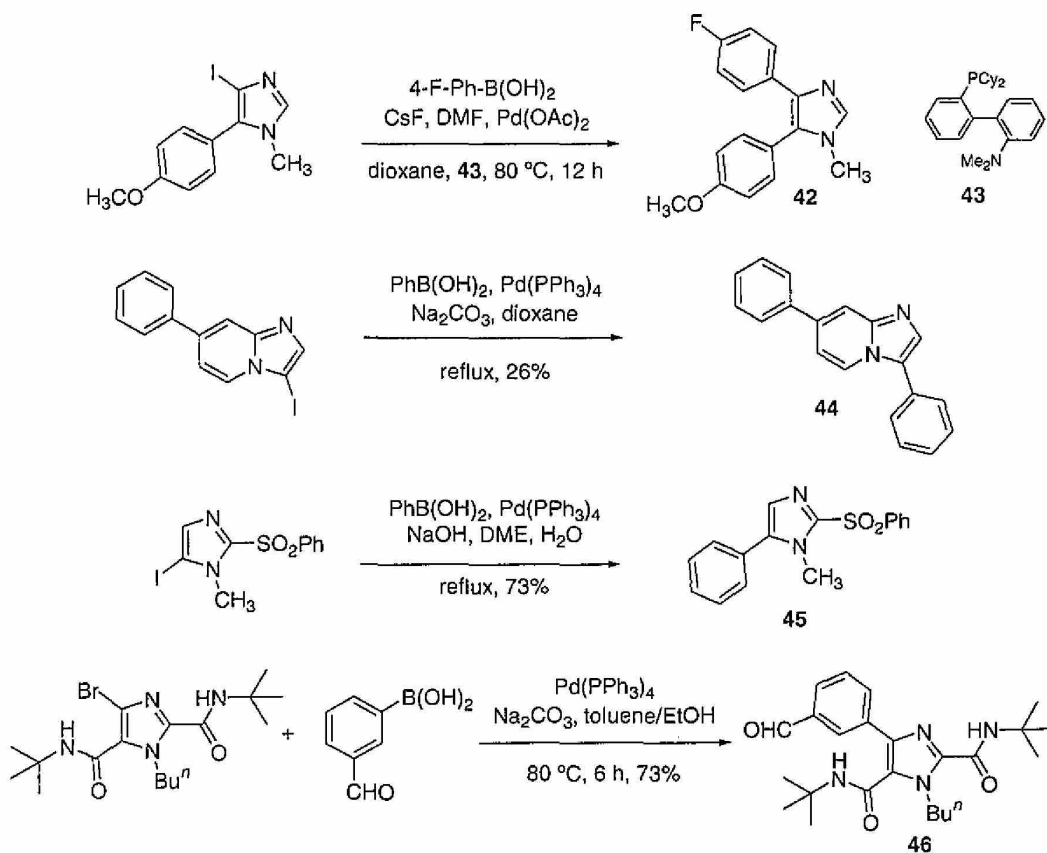


In similar studies, the 4,5-disubstituted-1-methyl imidazole **41** has been prepared. In an effort to synthesize molecules with this substitution pattern, Shapiro and Gomz-Lor utilized a carboxylate at C(2) to serve as a blocking group [28]. As shown below, regioselective halogen-metal exchange allowed for the introduction of the carboxylate at C(2). A second halogen-metal exchange at C(5), resulted in formylation with DMF to give **39**. Finally, the blocking carboxylate group could be removed under strongly acidic conditions. The 4,5-disubstituted imidazole **41** was thus produced in high yield upon coupling with boronate ester **40**.

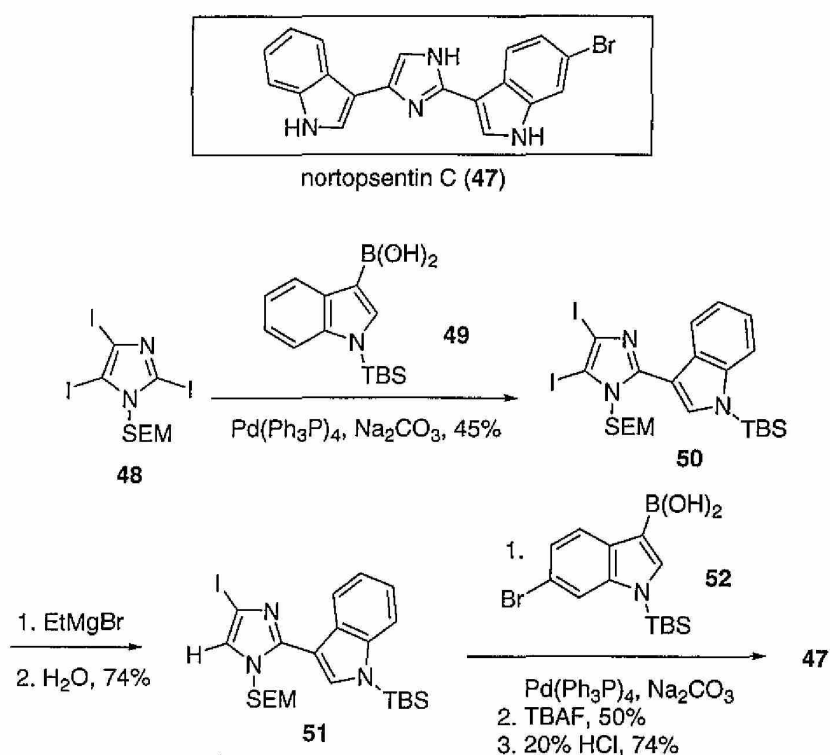


There have been several similar investigations involving the use of imidazolyl halides as the electrophile in the Suzuki reaction. Predominantly, these reactions have been

utilized for synthesis in search of biologically active compounds containing the imidazole nucleus. The synthesis of **42** [23], **44** [29], **45** [30], and **46** [31] serve as examples in this regard.



Perhaps, the most elegant demonstration of the Suzuki coupling in imidazole synthesis comes from efforts for the synthesis of the natural product nortopsentin C. Nortopsentin C (**47**), along with nortopsentins A and B, was isolated from the marine sponge *Spongosorites ruetzleri*. They all possess a characteristic 2,4-bisindolylimidazole skeleton and exhibit cytotoxic and antifungal activities. Successive and regioselective diarylation *via* Suzuki coupling reactions using halogenated imidazole to make nortopsentins have been disclosed in the total synthesis of **47** by Ohta's group [32, 33]. The *N*-protected 2,4,5-triiodoimidazole (**48**) was coupled with one equivalent of the 3-indolylboronic acid **49** to install indolylimidazole **50**. The Suzuki reaction occurred regioselectively at C(2) of the imidazole ring. Subsequently, a regioselective halogen-metal exchange reaction took place predominantly at C(5) to access **51**. A second Suzuki coupling reaction at C(4) of **51** with 6-bromo-3-indolylboronic acid **52** resulted in the assembly of the entire skeleton. Two consecutive deprotection reactions removed all three silyl groups to deliver the natural product (**47**). This synthesis elegantly exemplifies the chemoselectivity of the Suzuki reaction between an arylbromide and an aryl iodide. The desired regioselectivity was achieved *via* manipulation of the substrate functionalities.



9.3.3. Stille coupling

In contrast to the scarcity of precedents in the imidazolylboronic acids, abundant reports exist on imidazolylstannanes. In the Stille reaction, the imidazole nucleus may serve as either the nucleophile as an imidazolylstannane or the electrophile as an imidazole halide. One advantage of the Stille reaction is that it often tolerates delicate functionalities in both partners.

One method for preparing imidazolylstannanes is direct metalation followed by treatment with R_3SnCl [34]. 1-Methyl-2-tributylstannylimidazole, derived in such manner, was coupled with 3-bromobenzylphosphonate to furnish heterobiaryl phosphonate 54 [35]. Under the same reaction conditions, 4-bromobenzylphosphonate led to the adduct in 69% yield, whereas only 24% yield was obtained for 2-bromobenzylphosphonate. The low yield encountered for the *ortho* derivative may be attributed to the steric factors to which the Stille reaction has been reported to be sensitive [36]. Heterobiaryl phosphonates such as 54 are not only substrates for the Wadsworth–Horner–Emmons reaction, but also bioisosteric analogs of the carboxylic acid group.

