CHAPTER 9

SUZUKI–MIYAURA CROSS-COUPLING

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Organic Reactions, Vol. 100, Edited by Scott E. Denmark et al.

INTRODUCTION

In 1979, Akira Suzuki and Norio Miyaura introduced the coupling reaction of organoboron species and organo(pseudo)halides mediated by a palladium catalyst (Scheme 1).[1,2] This reaction has evolved to become a very important method for carbon–carbon bond formation in organic chemistry. Suzuki–Miyaura is often the cross-coupling reaction of choice because it employs relatively non-toxic and stable organoboron species as the source of nucleophilic carbon (R^2), proceeds under comparatively mild reaction conditions, displays extensive functional group compatibility, and generally affords high yields of cross-coupled product R^1–R^2.

$$X\text{–}R^1 \;+\; R^2\text{–}BY_2 \xrightarrow[\text{base, solvent/water}]{\text{palladium}} R^1\text{–}R^2$$

Scheme 1

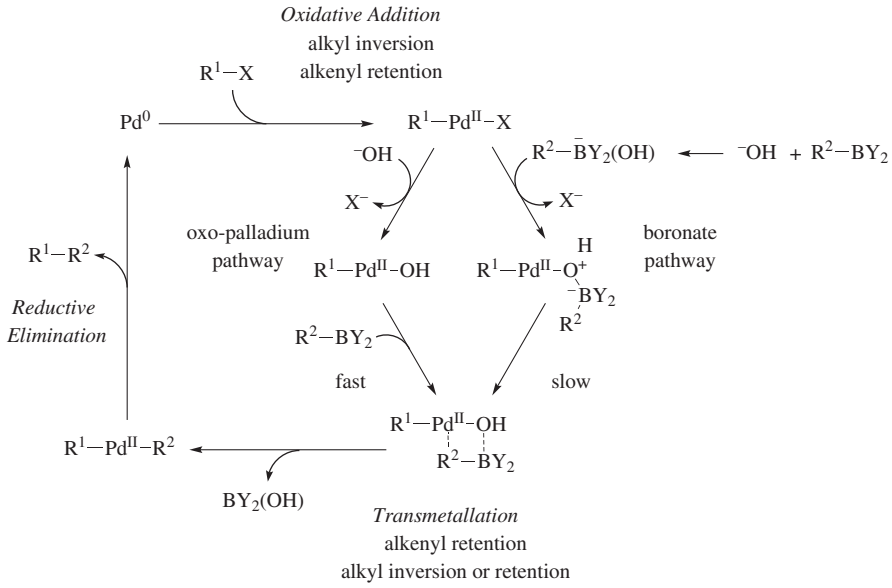
Since the discovery that palladium can catalyze this coupling, much research has focused on finding alternative, more earth-abundant, metal catalysts. There are now many examples of Suzuki–Miyaura cross-couplings that utilize nickel,[3−9] iron,[6,9−14] or copper[15−19] as the catalyst. Similarly, a wide variety of leaving groups on the electrophilic carbon (R^1) have been found to undergo successful cross-couplings; these groups include carbonates,[20] carbamates,[8,20] sulfamates,[20,21] sulfones,[22] sulfonyl chlorides,[23] esters,[24] amides,[3] nitriles,[25] and ammonium salts.[26,27] This chapter will focus on the cross-couplings of organoboron reagents with organo(pseudo)halides by palladium catalysts.

A number of reviews of the Suzuki–Miyaura cross-coupling reaction have been published, focusing on the historical aspects,[28,29] the organoboron coupling partner,[30−32] the organo(pseudo)halide coupling partner,[33] catalysts,[34,35] and ligands.[36] General overviews of the subject are also available.[37−42]

MECHANISM AND STEREOCHEMISTRY

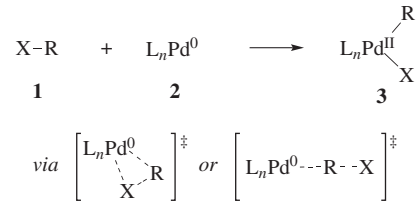
Mechanism

The Suzuki–Miyaura cross-coupling reaction entails three main steps: (i) oxidative addition, (ii) transmetalation, and (iii) reductive elimination (Scheme 2).



Scheme 2

The first step in the catalytic cycle involves addition of electrophilic coupling partner **1** to palladium(0) complex **2** by oxidative addition, generating palladium(II) species **3** (Scheme 3). The reaction proceeds from coordinatively unsaturated palladium complex **2** and is accelerated by electron-rich ligands. The transition structure typically involves a bis-ligated palladium complex ($n = 2$), although when bulky ligands (such as tri-*tert*-butylphosphine or tri(2-tolyl)phosphine) are employed, a mono-ligated, 12-electron complex ($n = 1$) may be required.[43]

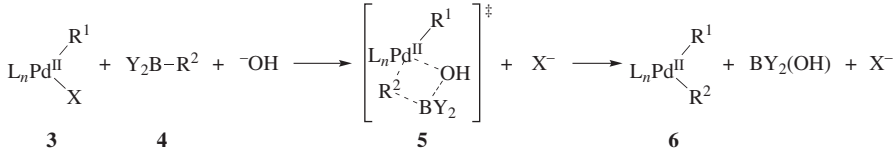


Scheme 3

The relative reactivity of X in the electrophilic coupling partner (compound **1**) usually follows the trend I > OTf > Br ≫ Cl, although sometimes this order can

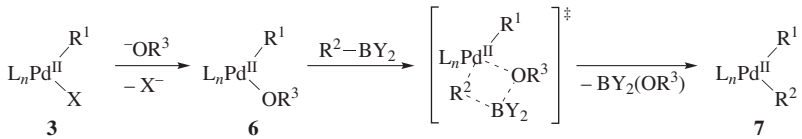
be different, depending on the ligand on palladium.[44–46] When X = Cl, this oxidative addition step is often rate-determining. For a specific X group, electron-poor R groups undergo oxidative addition faster than electron-rich R groups. The addition of unactivated organochloride reagents to palladium(0) requires strongly electron-donating ligands (e.g., tri-*tert*-butylphosphine, tricyclohexylphosphine, or $ArPCy_2$) on the metal.

Transmetalation between organoboron reagent **4** and palladium(II) complex **3** generates diorganopalladium complex **6** (Scheme 4). This step can occur by two pathways: the oxo-palladium pathway or the boronate pathway, with the relative flux dependent on the reaction components, ligands, and conditions. Both pathways involve an intermediate containing a palladium–oxygen–boron linkage, the exact nature of which depends on the specific reaction conditions.[47,48] In most cases, transmetalation proceeds with retention of configuration on the organoboron reagent and may involve a transition structure such as complex **5**.[49] For the set of examples in which the rate has been directly measured (L = triphenylphosphine; X = Cl, Br, I), the oxo-palladium pathway is many orders of magnitude faster than the boronate pathway.[50,51]



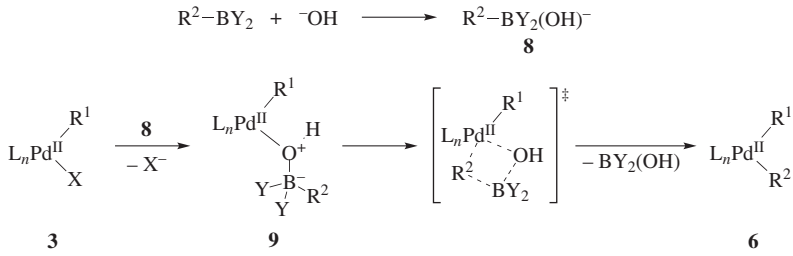
Scheme 4

The oxo-palladium transmetalation pathway (Scheme 5) relies on a substitution of the (pseudo)halide at the palladium(II) center by a hydroxide or alkoxide anion. The resulting oxo-palladium moiety helps guide the organoboron reagent to the palladium and then undergoes σ-bond metathesis with the organoboron reagent to generate diorganopalladium complex **7**. The oxo-palladium pathway, involving palladium alkoxide or hydroxide **6**, was proposed on the basis of observations made during couplings that employed alkenylboron and alkynylboron reagents. Specifically, Suzuki and Miyaura found that anionic, tetraalkylboron reagents gave poor yields in coupling reactions in the absence of alkoxide or hydroxide bases.[52] Subsequent studies, both theoretical and experimental, identify the oxo-palladium pathway as the most common route to the pre-transmetalation intermediate.[50,53–56]



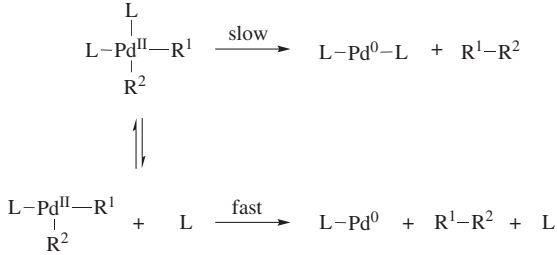
Scheme 5

The boronate pathway for assembly of the pre-transmetalation intermediate (Scheme 6) occurs when the organoboron reagent reacts with the hydroxide directly, generating boronate anion **8**. This anion then displaces the X ligand on palladium to form boronate palladium complex **9**, which undergoes a σ-bond metathesis to afford diorganopalladium complex **6**. This mechanism dominates during couplings of especially Lewis basic organoboron coupling partners, as demonstrated in a kinetic study reported by Soderquist.[53]



Scheme 6

Reductive elimination (Scheme 7) completes the catalytic cycle, forming the new carbon–carbon bond and releasing the palladium(0) complex to restart the cycle. Although the reductive elimination can occur from a tetracoordinate *cis*-palladium complex, it is faster from the corresponding tricoordinate *cis*-complex. Sterically bulky ligands accelerate the reductive elimination step by promoting ligand dissociation.[57–60]

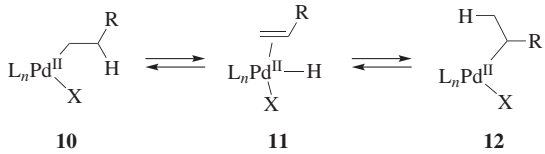


Scheme 7

Stereochemical and Constitutional Considerations

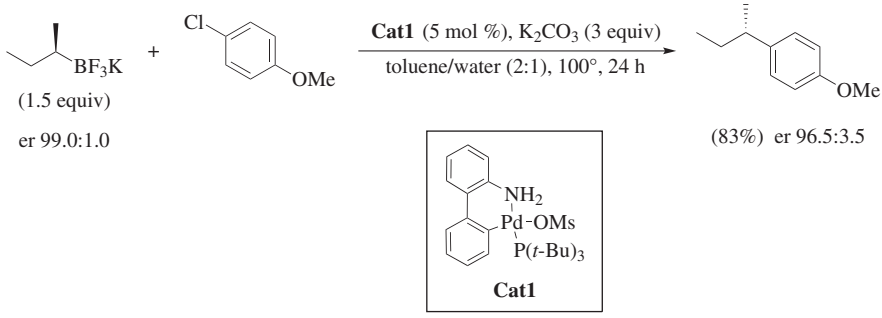
Cross-couplings of alkyl and alkenyl groups allow for stereoselective and site-selective Suzuki–Miyaura reactions. These reactions are particularly useful in drug and natural product syntheses. The oxidative addition of alkyl(pseudo)halides proceeds with inversion of configuration,[61] whereas (pseudo)haloalkenes proceed with retention of olefin geometry. Aryl halides oxidatively add to palladium(0) complexes by a mechanism related to the S_NAr reaction.[62]

Electrophiles with β-hydrogen atoms (e.g., complex **10**) can undergo β-hydride elimination after oxidative addition; this unproductive side reaction forms η^2-alkene–palladium hydride complex **11** (Scheme 8).[61] The process is reversible and results in isomerization of the alkyl group derived from the electrophile, producing isomeric complex **12**. Although bulky ligands can reduce or prevent the undesired β-hydride elimination in some cases, effective examples of the Suzuki–Miyaura coupling of alkyl electrophiles remain rather rare.



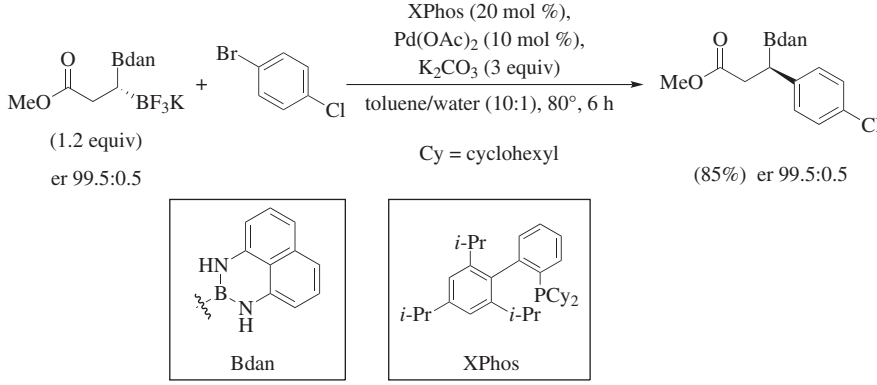
Scheme 8

Non-functionalized primary alkylboron species retain configurational identity, as determined by deuterium labeling, through transmetalation.[49,53] Cyclopropyl[63] and benzylboronates[61,64] behave analogously, but secondary alkyl organoboron species that do not contain any coordinating functionality predominantly undergo inversion of configuration (Scheme 9).[65]



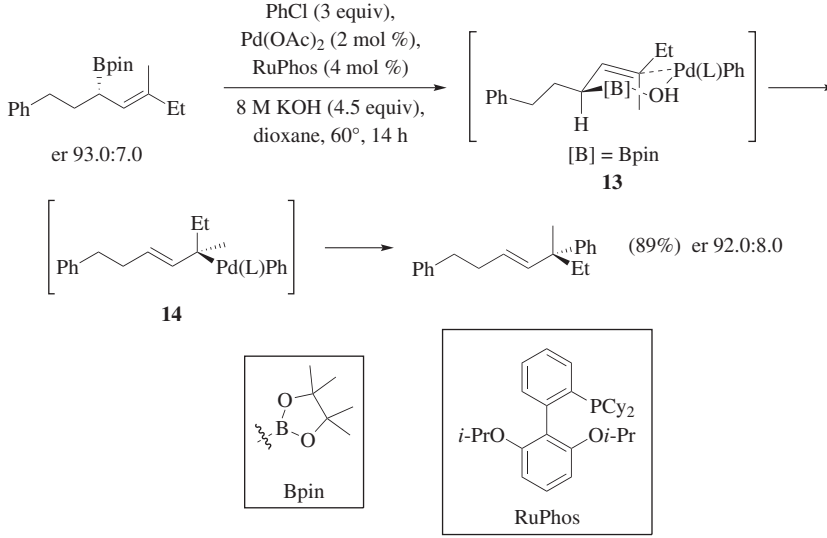
Scheme 9

Primary alkylboron species in which the alkyl chain is functionalized undergo transmetalation with inversion of configuration in some cases (e.g., an amide[66] or 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl (Bpin)[67] at the α-position, or an ester at the β-position (Scheme 10)[68]) and with retention in others (e.g., 2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborin-2-yl (Bdan)[69] or a benzyl ether[64,70] at the α-position). The presence of competing Lewis acids (e.g., indium(III) isopropoxide) can modulate these effects, allowing a switch from inversion to retention when there is an amide at the α-position.[71] Secondary alkyl organoboron species that contain an amide at the β-position undergo inversion.[68,72,73] In some cases, the functional group may coordinate intramolecularly to the boron to activate it for transmetalation, thus bypassing the requirement for a palladium–oxygen–boron linkage.[65,66,71,72]



Scheme 10

Under standard Suzuki–Miyaura cross-coupling conditions, allylic boronate esters afford products resulting from substitution at either the α-carbon (the site of the boron group) or the γ-carbon (the alkene terminus remote from boron);[74] Scheme 11 depicts a reaction that occurs selectively at the γ-position.[75] The site selectivity is temperature-dependent, possibly reflecting changes in the relative rates of reductive elimination versus isomerization via a π-allyl species.[76] Use of the RuPhos ligand leads to high γ-selectivity, irrespective of the allylic substitution pattern. This selectivity does not arise from thermodynamic equilibration via the π-allyl species, but instead from selective *syn*-S_E2' transmetalation (via transition structure **13**), followed by rapid reductive elimination from the resulting σ-allyl



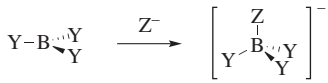
Scheme 11

palladium intermediate (structure **14**), all without significant isomerization.[75,77] High α-selectivity can be achieved by the use of an *N*-heterocyclic ligand which favors a *syn*-S_E2 transmetalation pathway, again followed by rapid reductive elimination.[77]

SCOPE AND LIMITATIONS

An extensive and diverse range of organoboron reagents are utilized in the Suzuki–Miyaura coupling, with each class offering certain advantages. This diversity allows for many interesting variants on the standard coupling reaction.

Trigonal planar, sp^2-hybridized organoboron compounds have an empty p-orbital perpendicular to the trigonal plane. The relatively unpolarized carbon–boron bonds are not significantly nucleophilic, but they can react in neutral form to generate the pre-transmetalation intermediate by the oxo-pathway (Scheme 5). To increase the nucleophilicity, organoboron compounds can form ate complexes with a coordinating ligand, typically an anion (e.g., hydroxide, alkoxide, or fluoride) (Scheme 12), thus facilitating access to the pre-transmetalation intermediate by the boronate pathway (Scheme 6).



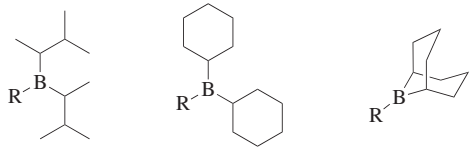
Scheme 12

Both the neutral organoboron reagent and its corresponding boronate complex can undergo protodeboronation. This process can be a major side reaction in Suzuki–Miyaura cross-coupling reactions, but it is not always undesirable. For example, this reaction can be used to purge unreacted boronic acid from a product waste stream. Aqueous protodeboronation can be acid- or base-catalyzed, but also occurs under neutral conditions.[73,78,79] The rate of protodeboronation ranges over many orders of magnitude, with the mechanism depending on the identity of the organoboron substrate and the conditions used for the coupling; pH, water concentration, organic cosolvent or bi-phase, and concentrations of other metal ions (e.g., copper, zinc) can all affect the reaction. Other side reactions involving the organoboron reagent include oxidation,[80] palladium-catalyzed homocoupling,[81] and disproportionation.[79]

Organoboron Substrates

Organoboranes. Examples of Suzuki–Miyaura cross-coupling reactions involving an organoborane are almost exclusively reserved to alkylboranes and alkenylboranes, because these compounds can be readily prepared by the hydroboration of alkenes and alkynes, respectively.

Organoboranes require anion activation for efficient coupling. A problematic side reaction is the competing transfer of one of the 'spectator' alkyl ligands to the palladium instead of the desired transmetalation of the R group. The use of secondary alkyl ligands such as disiamylborane **15**, dicyclohexylborane **16**, or 9-borabicyclo[3.3.1]nonane **17** (Figure 1) can help to minimize this undesired side reaction.

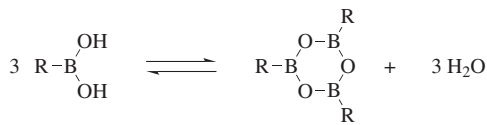


15 **16** **17**

Figure 1. Commonly used organoboranes.

Boronic Acids. These reagents remain the most widely applied organoboron species in Suzuki–Miyaura cross-coupling reactions.[82] They benefit from wide commercial availability, stability, and a tendency for crystallinity, which makes them convenient to handle. Boronic acids generally require activation with a coordinating anion before they can transmetalate to palladium.

Under dehydrating conditions, including simple dissolution in organic media, boronic acids **18** can form the corresponding boroxines **19** (Scheme 13). Although boroxines are in equilibrium with the boronic acid, the ratio of boronic acid to boroxine in the pure material can be hard to determine using standard analytical techniques. Therefore, when a precise amount of organoboron substrate is required, the use of a boronic acid may be impractical.

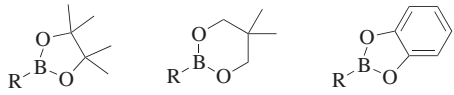


18 **19**

Scheme 13

Boronic Esters. The most common examples of this class of reagent are the pinacol, neopentyl, and catechol esters (compounds **20**–**22**, respectively; Figure 2). These reagents tend to generate fewer side products than the corresponding boronic acids,[83,84] and in many cases can be purified by either column chromatography or distillation. However, they are also commonly perceived as being less active coupling partners. Like boronic acids, boronic esters typically require anion activation during coupling,[85] and they may require hydrolysis to the boronic acid prior to coupling. In the presence of water, an equilibrium is established between the boronic ester and corresponding boronic acid, and although a water-free boronic ester coupling

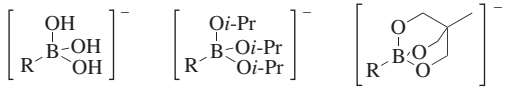
has been described,[86] the possibility that traces of water induce the Suzuki–Miyaura coupling cannot be excluded.



20 **21** **22**

Figure 2. Commonly used boronic esters.

Boronates. The most common examples of boronates are the trihydroxy, triisopropyl, and cyclic triol 'ate' species (compounds **23**–**25**, respectively; Figure 3), which are often formed as the corresponding lithium salts. Additional anions, such as hydroxide, alkoxide, or fluoride are not usually required for these complexes to undergo Suzuki–Miyaura coupling. Trialkoxyboronates, e.g., boronates **24** and **25**, are generally viewed as being more resistant to protodeboronation than the corresponding boronic acid/trihydroxyboronate **23**, although very few studies have specifically examined this side reaction.[87]



23 **24** **25**

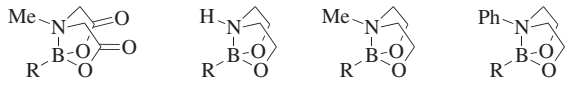
Figure 3. Commonly used boronates.

Trifluoroborates. Trifluoroborates are typically employed as their potassium salts (compound **26**; Figure 4), which are generally very stable, crystalline, non-hygroscopic solids. Cesium[88] and tetraalkylammonium[89] salts are also known. The easy preparation,[90,91] purification, and characterization of trifluoroborate salts makes them attractive reagents for Suzuki–Miyaura coupling.[88,92] The reagents require partial or complete acid-catalyzed hydrolysis to the boronic acid prior to coupling.[93] By careful tuning of the hydrolysis conditions to effect slow release of the active coupling species, the extent of side product formation can be reduced as compared to the direct coupling of the corresponding boronic acid.[94] The fluoride liberated by the hydrolysis can have beneficial effects on the coupling, but can also cause corrosion of glass reaction vessels.[81]

26

Figure 4. Trifluoroborate structure.

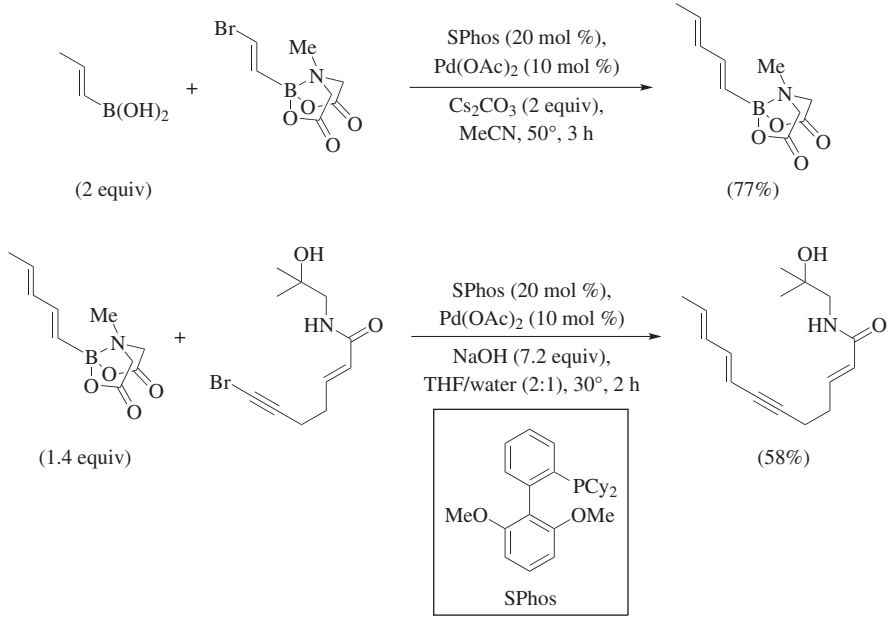
***N*-Coordinated Boronates.** These reagents provide a protected form of boronic ester, in which a nitrogen atom forms a dative bond to the boron. Common ligands are *N*-methyliminodiacetic acid (MIDA), diethanolamine, *N*-methyldiethanolamine, and *N*-phenyldiethanolamine (compounds **27**–**30**; Figure 5), with MIDA being most frequently used. MIDA boronates are stable to air, to numerous synthetic conditions employed for chemical modifications to R, and to column chromatography.[95]



27 **28** **29** **30**

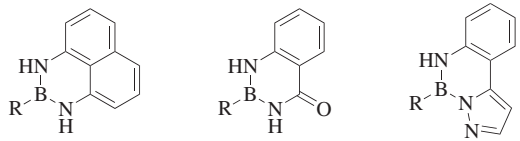
Figure 5. Commonly used *N*-coordinated boronates.

Before participating in a cross-coupling reaction, MIDA boronates require hydrolysis; the hydrolysis can be conducted beforehand, or effected in situ in rapid or slow-release modes.[96,97] As with trifluoroborates, slow release of the boronic acid can reduce side reactions. Because the MIDA boronate is inert to transmetalation, iterative Suzuki–Miyaura cross-couplings are possible in which a boronic acid is selectively coupled in the presence of a MIDA boronate,[98] and the MIDA boronate in the resulting product can subsequently be deprotected, forming a new boronic acid coupling partner (Scheme 14).[99]



Scheme 14

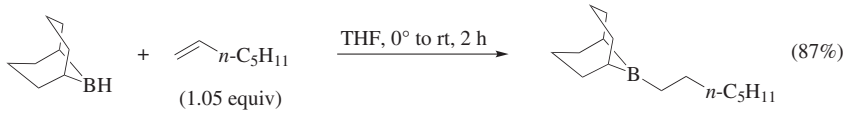
Boronamides. These reagents provide a protected form of boronic acid, in which a diamine ligand participates in two covalent nitrogen–boron bonds. Commonly employed ligands are 1,8-diaminonaphthyl (dan), anthranilamide, and 2-(pyrazol-5-yl)aniline (compounds **31**–**33**; Figure 6), with dan being the most stable to hydrolysis. These derivatives display high stability toward aqueous basic cross-coupling reaction conditions and are thus often employed in iterative cross-coupling sequences. Boronamides are hydrolyzed to the corresponding boronic acid in acidic aqueous media.



31 **32** **33**

Figure 6. Commonly used boronamides.

Alkylboron Reagents. Alkylboron reagents can be synthesized by a predictable, anti-Markovnikov hydroboration of an alkene (Scheme 15).[100] Many procedures have been developed to perform this reaction enantioselectively.[101,102]

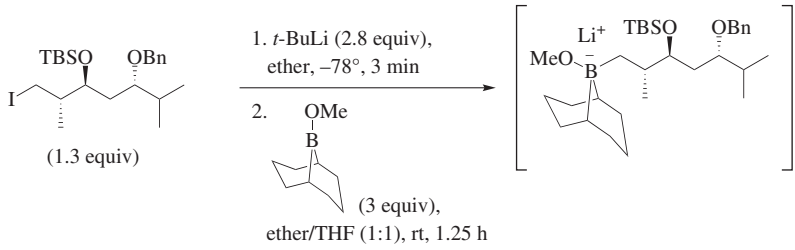


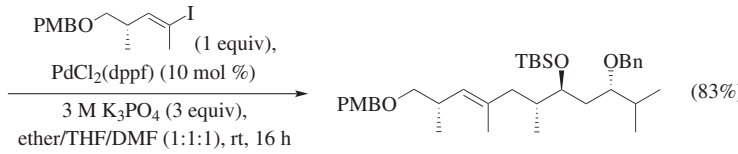
Scheme 15

The Markovnikov hydroboration product can also be formed with high selectivity using copper,[69,103–110] rhodium,[111,103,106,112–116] and other catalysts.[117] A few examples of C–H activation exist for the synthesis of alkylboron reagents from alkanes.[118–120] Alkylboronate reagents can be efficiently prepared by reaction of an R_2B–alkoxy species with an alkyllithium reagent (Scheme 16).[121]

Alkylboron coupling partners require careful treatment in *B*-alkyl Suzuki–Miyaura cross-coupling reactions because of the propensity of alkylpalladium species to undergo β-hydride elimination. Specially designed ligands are sometimes required for efficient reactions.[122]

Alkenylboron Reagents. Alkenylboron reagents can be prepared by the hydroboration of alkynes.[123] Many examples proceed with high site selectivity, often using catalytic methods. Alkenylboronic acids can be prepared from alkenylhalides by a sequence involving lithium–halogen or magnesium–halogen exchange, quenching with trimethyl- or triisopropylborate, and hydrolysis.[124] Borylation can be used to generate 1,2-diborylated alkene products.[117,125–127] Miyaura borylation—the



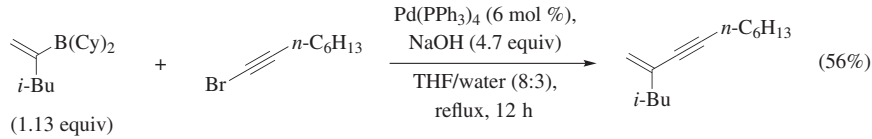


dppf = 1,1'-ferrocenediyl-bis(diphenylphosphine)

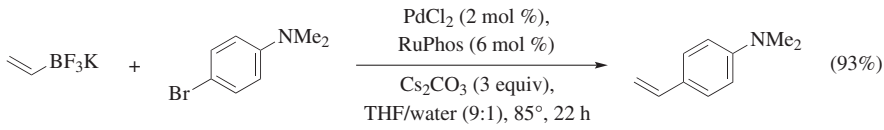
Scheme 16

palladium-catalyzed cross-coupling of an organo(pseudo)halide with a diboron reagent ($X_2B–BY_2$)—is a common method for the preparation of alkenylboron reagents.[128] Alkenylboron compounds have also been generated by C–H activation of alkenes.[118,119,129]

Alkenylboron compounds generally transmetalate and couple efficiently (Schemes 17 and 18),[130,131] although special bases (e.g., thallium alkoxides, thallium carbonates,[132] or silver oxide[133]) are sometimes employed; the mechanistic origins of the beneficial effects of such bases have not been elucidated.



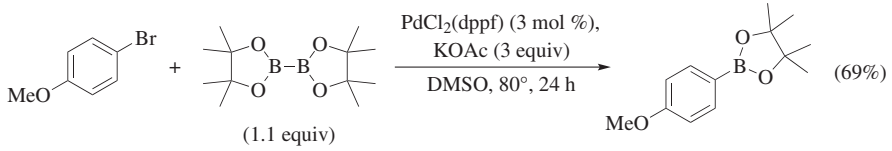
Scheme 17



Scheme 18

Arylboron Reagents. Arylboron reagents are commonly prepared from the corresponding aryl(pseudo)halides by catalytic methods,[134] especially Miyaura borylation[128] (Scheme 19),[128] or from aryl halides by lithium– or magnesium–halogen exchange followed by reaction with trimethyl- or triisopropylborate. Readily

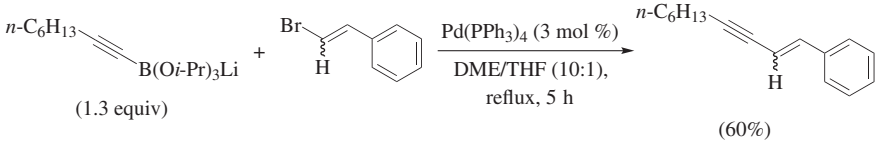
available, unfunctionalized arenes can subjected to C–H activation to prepare these compounds.[118−120,129,135]



Scheme 19

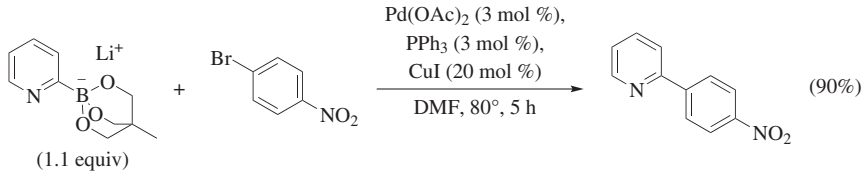
Alkynylboron Reagents. Alkynylboron reagents are prepared by deprotonation of a terminal alkyne followed by reaction of the alkynyl anion with an appropriate source of boron, usually trimethyl- or triisopropylborate. The alkynylboronate can then be used to prepare a range of boron derivatives, including trifluoroborates, pinacol esters, MIDA reagents, and boronamides, as described above. In addition, catalysts can be used to facilitate the dehydrogenative coupling of a terminal alkyne and borane.[118,119,136−138]

Alkynylboron compounds (and the corresponding ate salts) generally transmetalate cleanly and couple effectively (Scheme 20).[139]

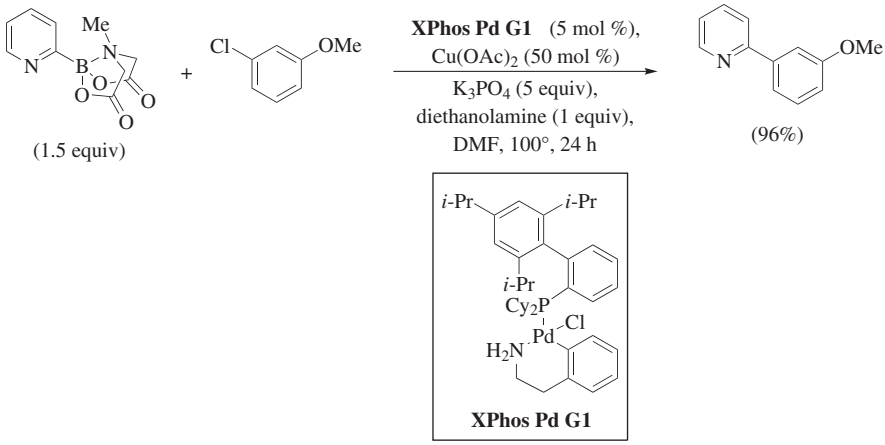


Scheme 20

Heteroarylboron Reagents. Heteroarylboron reagents are prepared in a manner similar to that for arylboron reagents, but they can be challenging to purify and to couple. Some specific classes of heterocyclic boron reagents are highly prone to protodeboronation,[79] which hinders their use in Suzuki–Miyaura coupling reactions. For example, the 2-pyridyl group is particularly problematic. However, heterocyclic boron reagents can often be coupled efficiently either by using protected boron reagents, such as a cyclic triolate (Scheme 21),[140] or by generating the reactive species under slow-release conditions from a MIDA boronate (Scheme 22).[141]



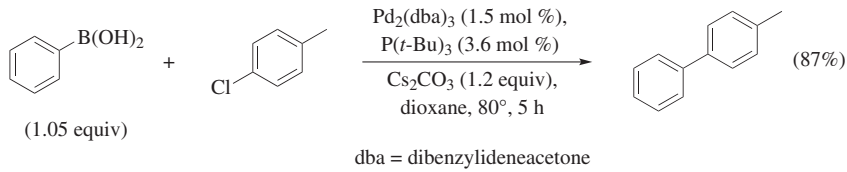
Scheme 21



Scheme 22

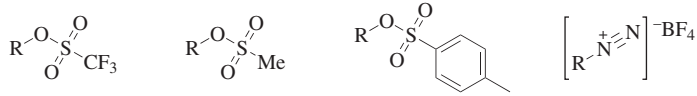
Organo(pseudo)halide Substrates

Organo(pseudo)halides serve as the electrophilic coupling partners in Suzuki–Miyaura coupling reactions. Many variants exist for the organo(pseudo)halide. Side reactions of the organo(pseudo)halide include homocoupling or protodehalogenation (reduction). Organoiodides and organobromides are used extensively in Suzuki–Miyaura cross-coupling reactions owing to their ease of coupling in many catalyst/ligand systems. The commercial availability of bromides generally makes them the organohalide of choice. On large scale, bromide waste from the cross-coupling is readily recycled, often by oxidation to bromine using chlorine gas.[142] Organochlorides were originally found to be unreactive under classical Suzuki–Miyaura cross-coupling conditions. Electron-rich ligands (such as trialkylphosphines or *N*-heterocyclic carbenes), however, facilitate the oxidative addition step of organochlorides, making these electrophiles feasible coupling partners (Scheme 23).[143]



Scheme 23

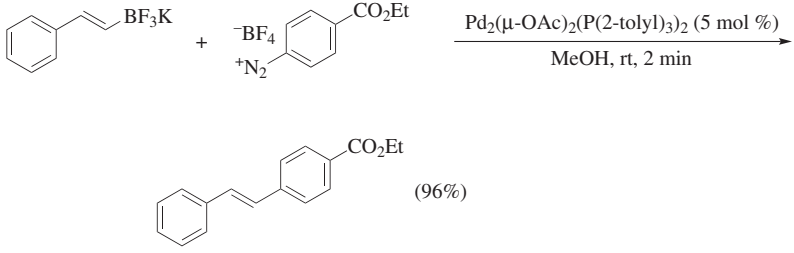
Organopseudohalide electrophiles include triflates, mesylates, tosylates, and diazonium salts (substrates **34**–**37**, respectively; Figure 7). These electrophiles are of particular use in total synthesis because they can be generated from functional groups that are compatible with Suzuki–Miyaura cross-coupling reactions, opening up the possibility for sequential couplings on a single substrate.



34 **35** **36** **37**

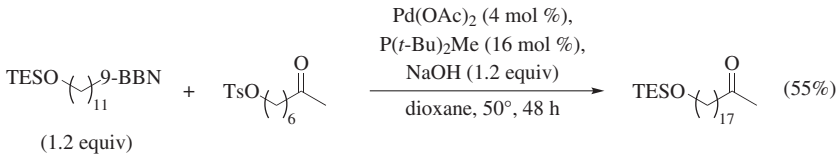
Figure 7. Commonly used organopseudohalides.

Utilizing organopseudohalides allows for the synthesis of complex organic frameworks from a more diverse set of starting materials than would be possible with simple halide leaving groups. Sequential, metal-catalyzed coupling reactions are possible because pseudohalide leaving groups are often synthesized from common functional groups (e.g., alcohols and amines), which are generally stable to Suzuki–Miyaura cross-coupling conditions. Diazonium salts are particularly reactive, giving high yields in short reaction times at relatively low temperatures (Scheme 24).[144]



Scheme 24

Alkynyl, alkenyl, aryl, and heteroaryl electrophiles have few general limitations for coupling. In contrast, alkyl electrophiles are challenging because they frequently undergo β-hydride elimination after oxidative addition. Bulky ligands can significantly reduce this side reaction (Scheme 25),[61] but examples are still uncommon.



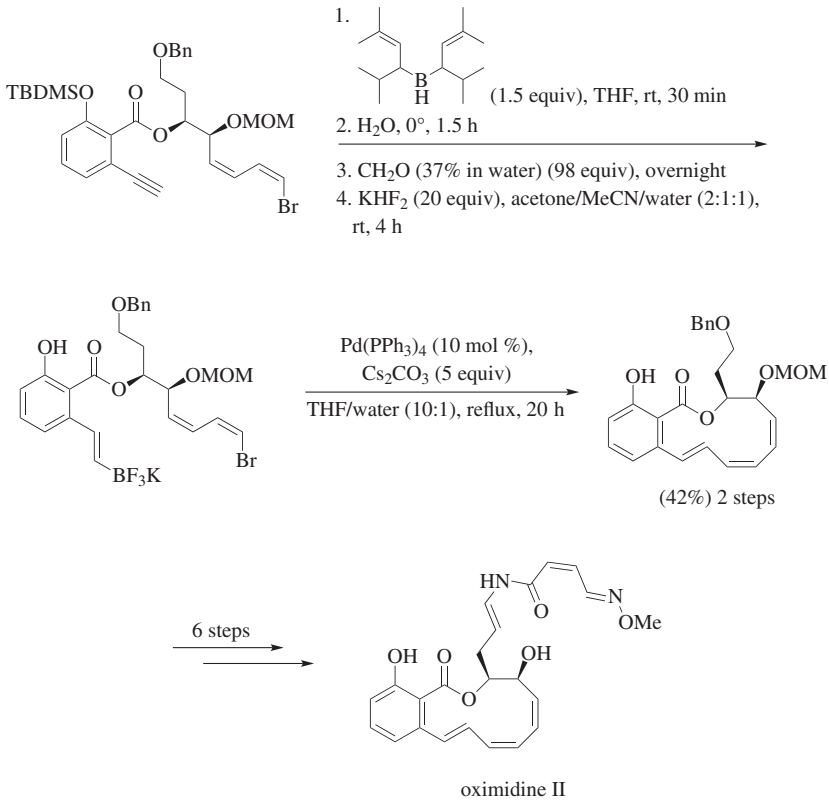
Scheme 25

APPLICATIONS TO SYNTHESIS

The diversity and predictability of the Suzuki–Miyaura cross-coupling reaction, as outlined above, lends itself to the preparation of biologically active compounds, to the total synthesis of natural products, and to the industrial-scale production of agrochemicals and pharmaceuticals. Some selected examples are described below.

Oximidine II

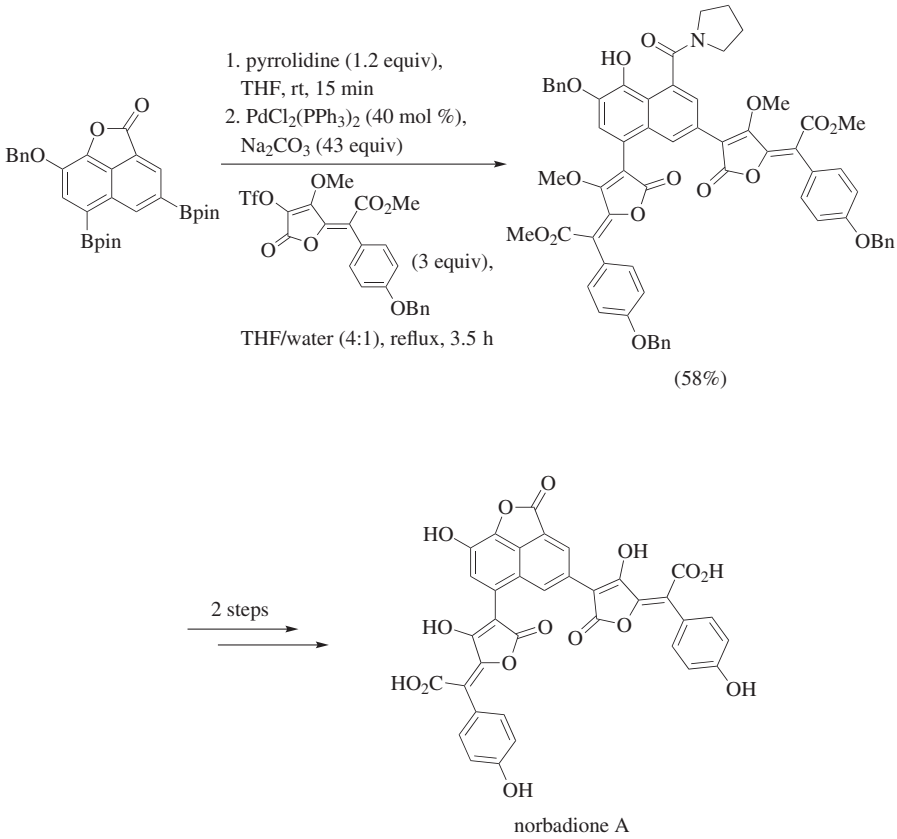
First isolated in 1999 from *pseudomonas* sp., oximidine II shows promise as an antitumor macrolide owing to its nanomolar cytotoxicity in mutant rat fibroblasts.[145] A macrocyclization utilizing a Suzuki–Miyaura cross-coupling of a potassium alkenyltrifluoroborate salt with an alkenylbromide assembles the twelve-membered ring in the core structure of oximidine II (Scheme 26).[146] The remainder of the synthesis follows a previously reported route.[147]



Scheme 26

Norbadione A

The pigment norbadione A was first isolated in 1984 from the *Xerocomus badius* mushroom.[148] Norbadione A has been prepared by a convergent synthesis, in which a bis-boronic ester—pre-activated by lactone ring-opening—participates in a cross-coupling reaction with two equivalents of a triflate electrophile to construct the core structure. The desired product is obtained in two additional steps (Scheme 27).[149]



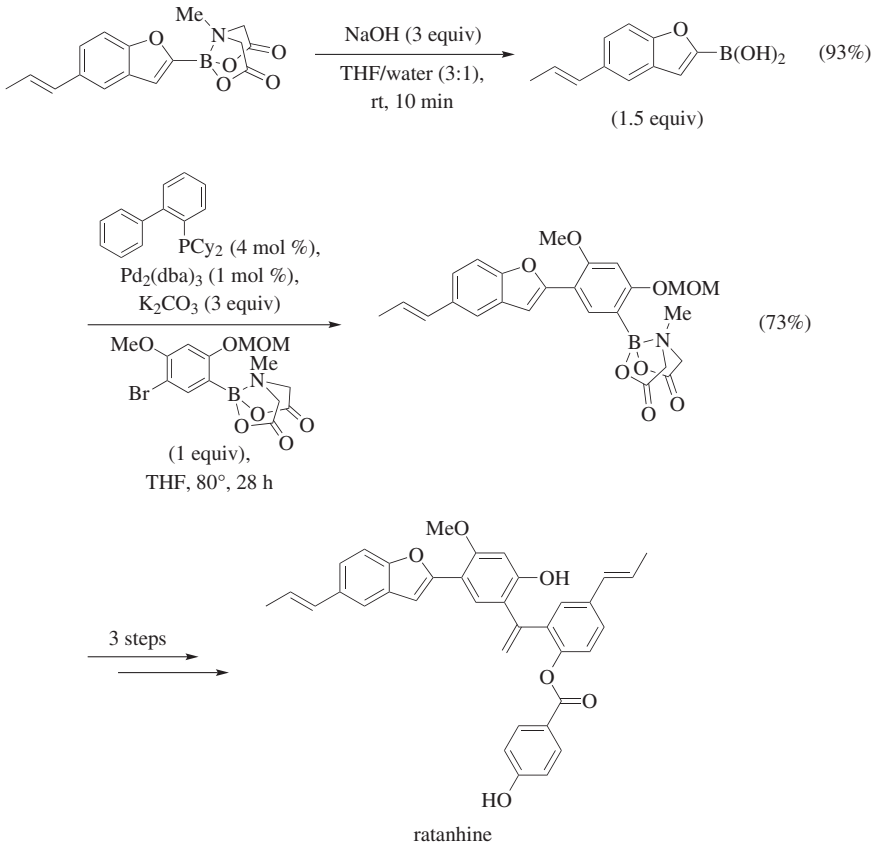
Scheme 27

Ratanhine

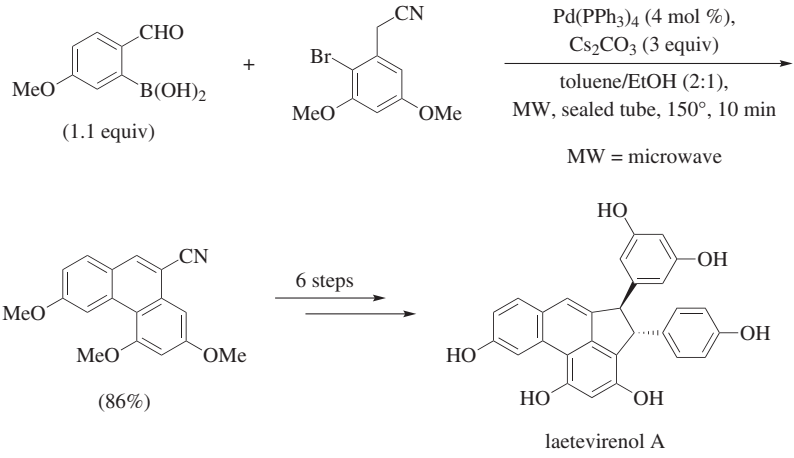
Ratanhine is a potent anti-inflammatory compound found in the root extract of *Krameria lappacea*.[150] A modular synthesis for ratanhine utilizes a MIDA boronate, which allows the selective cross-coupling of a boronic acid in the presence of the protected boron species. The MIDA group is then hydrolyzed to facilitate a sequential Suzuki–Miyaura cross-coupling reaction to afford ratanhine in three further steps (Scheme 28).[98]

Laetevirenhol A

Laetevirenhol A is a strong antioxidant isolated from *Parthenocissus laetevirens* in 2008.[151] This compound can be prepared by a route that involves a Suzuki–Miyaura cross-coupling of a hindered arylbromide performed in tandem with an aldol condensation, under microwave conditions, to assemble the key phenanthrene core. Further elaboration generates laetevirenol A (Scheme 29).[152]



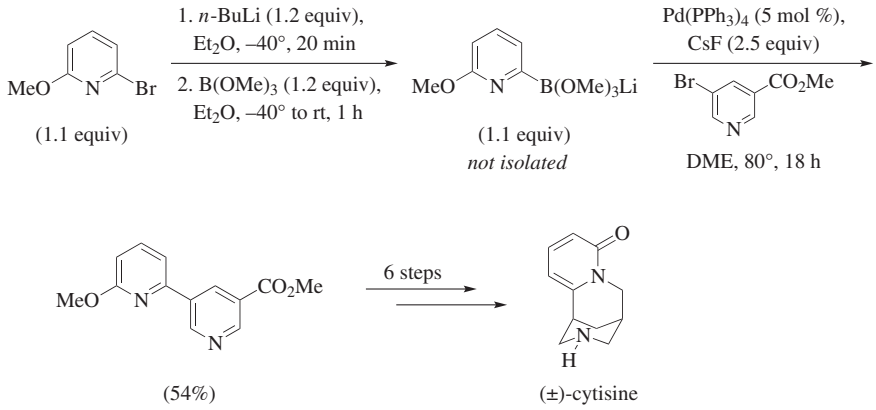
Scheme 28



Scheme 29

(±)-Cytisine

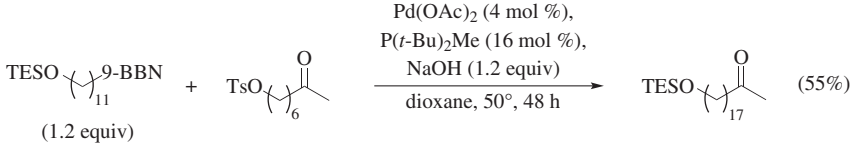
Used historically as an aid to quit smoking, cytisine is found in many plant varieties and has a physiological effect similar to that of nicotine.[153] An expedient synthesis of the bipyridine precursor to (±)-cytisine utilizes two pyridyl bromides.[154] The unstable 2-pyridylboron reagent is introduced to the reaction as the trimethylboronate salt, reducing the extent of protodeboronation. A further five steps (involving reduction and generation of a fused bicycle) affords (±)-cytisine (Scheme 30).



Scheme 30

19-(Triethylsiloxy)nonadecan-2-one

This synthesis of a long-chain ketone highlights a rare example of an alkyl–alkyl Suzuki–Miyaura cross-coupling (Scheme 31).[61]

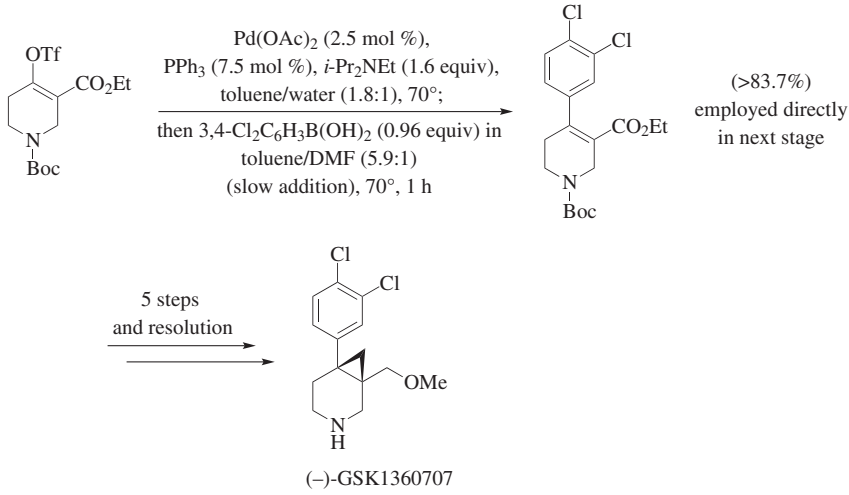


Scheme 31

(–)-GSK1360707

(–)-GSK1360707 is an arylated piperidine that is a potent reuptake inhibitor of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine, and it was developed for the treatment of depression (Scheme 32). The route employed for scale-up provided >10 kg material for clinical trials and involves a Suzuki–Miyaura coupling as the second step in an overall seven-step synthesis, which includes a chiral-column chromatographic resolution. An in situ generated alkenyl triflate undergoes

an efficient coupling with 3,4-dichlorophenyl boronic acid at 70°. Slow addition of a substoichiometric quantity of a solution of the boronic acid to the reaction vessel substantially reduces the extent of boronic acid homocoupling: the 3,3′,4,4′-tetracholorbiphenyl byproduct was present in the product solution at <30 ppm.[155]



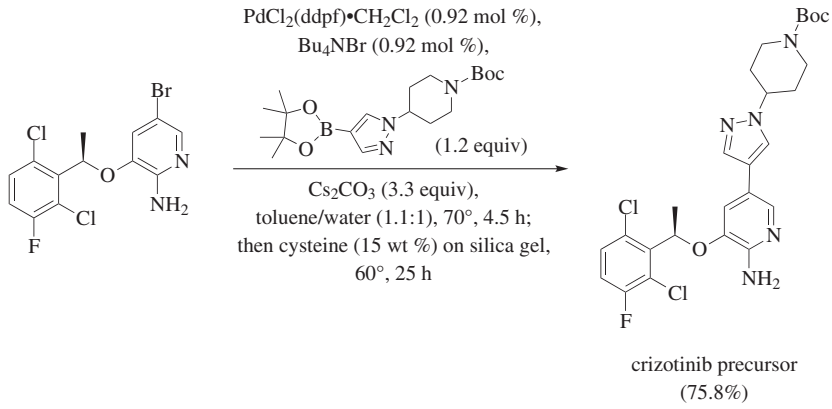
Scheme 32

Crizotinib

Crizotinib is used as treatment for specific forms of lung cancer, and it functions by blocking anaplastic lymphoma kinase in cancer cells that have an overactive version of the enzyme.[156] Large quantities (>100 kg) of crizotinib were required for Phase III clinical trials and were produced by a route that employed a Suzuki–Miyaura cross-coupling as the penultimate step in the synthesis.[157] Significant optimizations of the coupling, notably changing solvent from 1,2-dimethoxyethane to toluene, using a phase-transfer catalyst (tetrabutylammonium bromide), and reducing the catalyst concentration to 0.92 mol %, results in a process that enables the preparation of >50 kilograms of crizotinib per run. A 3-bromopyridyl electrophile is coupled with a *B*-(3-pyrazolyl)pinacolboronate to generate the pyrazolylpyridine core; the coupling is selective for the bromide over the two chlorides (Scheme 33).[157] Palladium residues are purged by stirring the crude reaction mixture with cysteine (15 wt % on silica). Deprotection of the *N*-piperidyl moiety by acidic hydrolysis of the *N*-Boc group affords crizotinib.

COMPARISON WITH OTHER METHODS

The Suzuki–Miyaura cross-coupling reaction is a powerful and versatile tool for forming carbon–carbon bonds. One major advantage of the Suzuki–Miyaura cross-coupling reaction over related methods is that many boronic acids are commercially



crizotinib precursor
(75.8%)

Scheme 33

available. Indeed, the utility of the Suzuki–Miyaura cross-coupling reaction has itself led to a major expansion of the range of boronic acids that are commercially available. Other metal-catalyzed cross-couplings are comparable in scope, although each has its own individual benefits and drawbacks.

Negishi Reaction

The Negishi reaction involves the cross-coupling of organozinc reagents with organo(pseudo)halides, generally utilizing a palladium or nickel catalyst.[158,159] Although the reaction is often avoided because of the air and water sensitivity of most organozinc reagents, the high reactivity does provide the benefit of short reaction times, and this cross-coupling is especially useful for $C(sp^2)$–$C(sp^3)$ bond formations. A protocol has been developed to overcome the issue of air sensitivity for aromatic and heteroaromatic organozinc reagents.[160,161]

Migita–Stille–Kosugi Reaction

This robust reaction involves a palladium- or nickel-catalyzed cross-coupling of an organotin reagent with an organo(pseudo)halide.[162,163] The transmetalation of organotin compounds to the catalytic metal center is frequently viewed as one of the most efficient examples in cross-coupling. However, the considerable toxicity of organotin compounds,[164] both in the substrate and in the reaction waste stream, causes challenges associated with their handling and purification,[165] thus limiting the applications of this reaction.

Kumada–Tamao–Corriu Reaction

This reaction employs the original organometallic donor, an organomagnesium species, in a palladium- or nickel-catalyzed cross-coupling with an organo(pseudo)halide partner.[166] Similar to the Negishi cross-coupling reaction,

the Kumada–Tamao–Corriu cross-coupling is rarely employed owing to the high reactivity of organomagnesium reagents with water or with functional groups in the reaction partners (for example, carbonyl groups cannot be present). Analogously, highly efficient couplings that employ in situ generated organolithium species have also been developed.[167]

Hiyama–Denmark Reaction

The Hiyama–Denmark reaction employs organosilanes, and in particular silanols, with organo(pseudo)halide coupling partners, generally with a palladium or nickel catalyst.[168,169] Organosilanes are very stable and convenient to handle, but the process has not yet been widely adopted, despite numerous advantages over other palladium-catalyzed methods for carbon–carbon bond formation.[170]

Mizoroki–Heck Reaction

This well-known cross-coupling reaction does not require an organometallic donor and entails the palladium- or nickel-catalyzed cross-coupling of alkene nucleophiles with organo(pseudo)halide electrophiles.[171] Although limited to alkenyl nucleophiles, the Mizoroki–Heck reaction avoids the necessity of an organometallic reagent and the associated issues of functional-group compatibility, making the Mizoroki–Heck reaction a cheap and expedient method for generating functionalized alkenes.

Sonogashira Reaction

Like the Mizoroki–Heck reaction, the Sonogashira reaction does not involve an organometallic donor, although one is generated in situ. The reaction involves a dual copper/palladium-catalyzed coupling of alkynes with organo(pseudo)halides.[172] Although limited to terminal alkynes as the nucleophilic coupling partner, the reaction is often favored over other cross-coupling reactions when substituted alkynes are required, or when the final product is accessible by selective reduction of the alkyne to an alkenyl or alkyl moiety. Variants of the reaction catalyzed only by palladium are also known.[173]

Oxidative Direct Arylation

This reaction class involves the coupling of an arene with an arylmetal, aryl(pseudo)halide, or arene by C–H activation.[174] This process is catalyzed by a variety of transition metals in the presence of a stoichiometric oxidant.[175,176] Site selectivity is a major issue, but it can often be controlled by directing groups or by the native selectivity of the various C–H bonds towards the metal catalyst center. The ability to use unfunctionalized arenes makes the process attractive, but the conditions are generally harsher than those used in other cross-coupling reactions.

EXPERIMENTAL CONDITIONS

Preparation of Organoboron Precursors

Hydroboration of Alkynes/Alkenes. Hydroboration requires a boron hydride reagent that can add to an alkyne or alkene. A common reagent is 9-BBN;[177] the steric bulk substantially increases the anti-Markovnikov selectivity relative to that obtained with simple primary borane reagents. The resulting 9-alkyl/alkenyl-BBN reagents are generally used in situ.

Lithium/Magnesium–Halogen Exchange. Organoboron substrates can be prepared from the corresponding organohalides by lithium/magnesium–halogen exchange. The resulting organolithium or organomagnesium compound is then treated with an electrophilic boron reagent, such as triisopropyl borate.[178] This approach has lower functional-group compatibility compared to other methods owing to the formation of the organolithium or organomagnesium species.

Miyaura Borylation. Organohalides and diboron compounds can be used to prepare organoboron reagents under mild conditions. The Miyaura borylation is palladium- or nickel-catalyzed and often employs bis(pinacolato)diboron as the borylating agent.

Direct C–H Borylation. Rhenium, ruthenium, rhodium, palladium, and iridium have been used to catalyze the borylation of C–H bonds.[179] This type of reaction allows for expedient and economic generation of organoboron reagents.

Suzuki–Miyaura Coupling

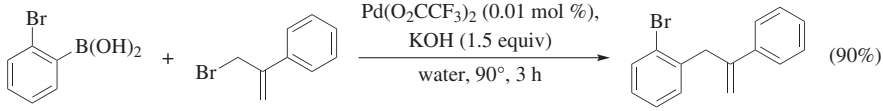
Organoboron Reagents. Organoboron reagents can be divided into three categories: (i) *active* organoboron reagents that can couple directly without the use of any additives, such as trialkoxyboronates; (ii) *inactive* organoboron reagents that require activation (e.g., by hydroxide, alkoxide, or fluoride) in order to couple, such as organoboranes (e.g., compound **15**), boronic acids **18**, or boronate esters (e.g., compound **20**); or (iii) *protected* organoboron reagents that are inert to coupling conditions and require hydrolysis or partial hydrolysis prior to application, such as trifluoroborates **26**, boronamides (e.g., compound **31**), and *N*-coordinated boronates (e.g., compound **27**).

Organo(pseudo)halides. Organoiodides, bromides, and pseudohalides generally undergo smooth oxidative addition to Pd(0). Organochlorides often require the use of electron-rich ligands on the palladium catalyst to facilitate the oxidative addition step.

Solvents. A mixture of solvents is often used for the coupling of inactive and protected organoboron reagents. Typical mixtures consist of THF, dioxane, or toluene mixed with water or an alcohol. The water/alcohol is used to help solubilize the base or fluoride source and, in conjunction with the base, to form the corresponding hydroxide or alkoxide anion that is required to activate either the palladium catalyst or the boron reagent for coupling. Water is also employed as a cosolvent to facilitate slow release of the reactive boron species. Addition of a surfactant enables micellar catalysis in water.[180] Active organoboron reagents generally use anhydrous organic solvents.

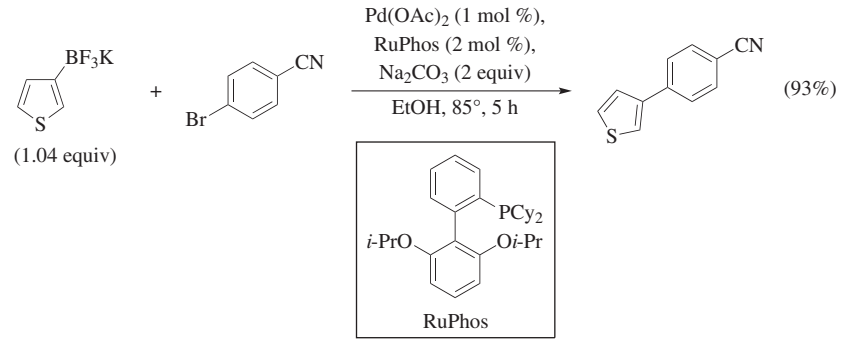
Additives. The alkali metal salts of hydroxide or carbonate are often used as bases, but hydroxide additives may be incompatible with functional groups present in the substrates. Inorganic fluoride salts can also be used as the base/activator; they are particularly mild and are preferred for couplings in total synthesis. Cesium and potassium are the most common cations, the former being generally more soluble in organic solvent mixtures.

EXPERIMENTAL PROCEDURES

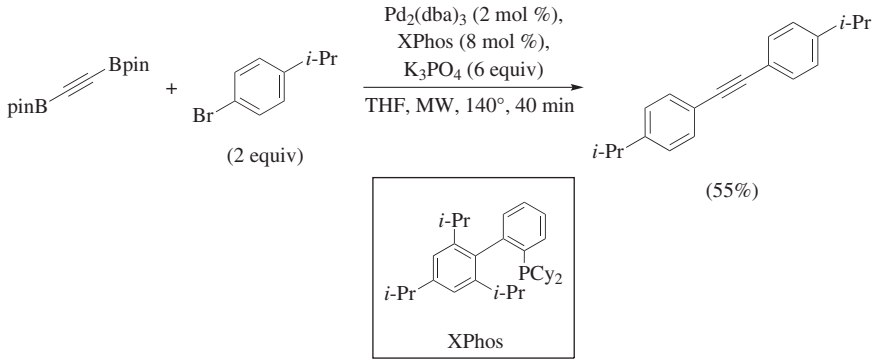


(1.2 equiv)

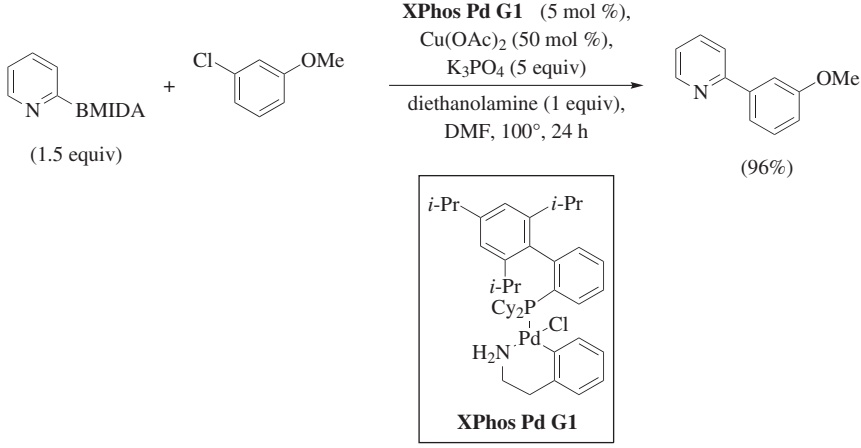
3-(2-Bromophenyl)-2-phenyl-1-propene [Coupling of an Aryl Boronic Acid with an Allylic Bromide].[181] A mixture of (3-bromoprop-1-en-2-yl)benzene (197 mg, 1.0 mmol), 2-bromophenylboronic acid (241 mg, 1.20 mmol, 1.2 equiv), KOH (84 mg, 1.5 mmol, 1.5 equiv), and palladium trifluoroacetate (0.033 mg, 0.0001 mmol, 0.01 mol %) in water (3.0 mL) in a round-bottomed flask was stirred and heated at 90° for 3 h. The flask was removed from the oil bath and cooled to rt. Water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/hexane) to provide the title compound as a colorless oil (246 mg, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 2H), 4.92 (s, 1H), 5.58 (s, 1H), 7.13 (m, 1H), 7.28 (m, 3H), 7.39 (m, 2H), 7.54 (d, J = 7.96 Hz, 2H), 7.63 (d, J = 7.96 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 41.4, 114.7, 125.2, 126.0, 127.4, 127.7, 128.0, 128.4, 131.0, 132.8, 139.0, 140.7, 145.5; HRMS–ESI (m/z): $[M + H]^+$ calcd for $C_{15}H_{14}Br$, 273.0273; found, 273.0268.



4-(Thiophen-3-yl)benzonitrile [Coupling of a Heterocyclic Trifluoroborate Salt with an Aryl Bromide].[182] A Biotage microwave vial was charged with $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 1 mol %) [sic], RuPhos (14 mg, 0.03 mmol, 2 mol %) [sic], 4-bromobenzonitrile (46 mg, 0.25 mmol), potassium thiophen-3-yltrifluoroborate (49 mg, 0.26 mmol, 1.04 equiv), and Na_2CO_3 (53 mg, 0.5 mmol, 2 equiv). The vial was sealed with a cap lined with a disposable Teflon septum, evacuated, and purged with nitrogen. The evacuation–nitrogen purge sequence was performed three times. Ethanol (1.4 mL) was added by syringe, and the mixture was stirred and heated at 85° for 5 h. The reaction mixture was allowed to cool to rt and then was filtered through a thin pad of silica gel (EtOAc/MeOH, 3:1). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (hexane/EtOAc, 7:1) to yield the pure product as an off-white solid (43.07 mg, 93%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (m, 1H), 7.43 (m, 1H), 7.56 (m, 1H), 7.65–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 110.6, 119.0, 122.7, 126.0, 127.0, 127.2, 132.8, 140.1, 140.5; HRMS–CI (*m*/*z*): M^+ calcd for $C_{11}H_7NS$, 185.0294; found, 185.0299.

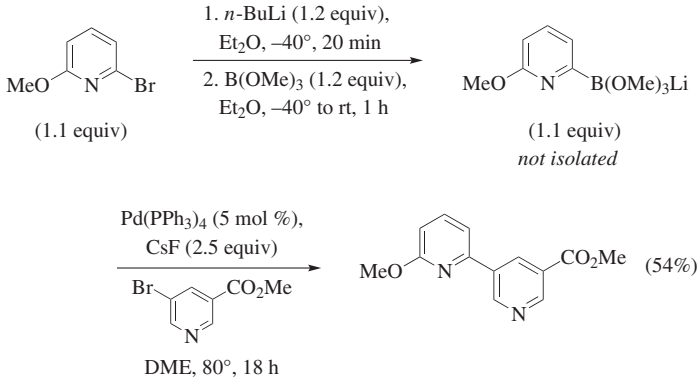


1,1′-(1,2-Ethynediyl)bis(4-isopropylbenzene) [Coupling of an Alkynyl Boronic Ester with an Aryl Bromide].[183] 2,2′-(1,2-Ethynediyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (100 mg, 0.36 mmol), 4-bromoisopropylbenzene (109 μL, 0.72 mmol, 2 equiv), $Pd_2(dba)_3$ (7 mg, 0.0072 mmol, 2 mol %), XPhos (21 mg, 8 mol %), and K_3PO_4 (458 mg, 2.16 mmol, 6 equiv) were dissolved in THF (3 mL) and the solution was heated to 140° in a microwave reactor for 40 min. The reaction mixture was cooled to rt, poured into water (50 mL), and extracted with chloroform (1 × 10 mL). The organic layer was washed with water (40 mL) and brine (2 × 40 mL). The aqueous fractions were combined and extracted with chloroform (10 mL); the organic extract was washed again with brine (2 × 40 mL). The combined organic fractions were dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 20:1) to afford the title compound (52 mg, 55%): mp 186° (dec); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, J = 6.9 Hz, 12H), 2.92 (sept, J = 6.9 Hz, 2H), 7.21 (d, J = 8.0 Hz, 4H), 7.46 (d, J = 7.9 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 34.1, 88.9, 120.9, 126.5, 131.6, 149.1; HRMS–EI (m/z): M^+ calcd for $C_{20}H_{22}$, 262.1722; found, 262.1721. Anal. Calcd for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 90.73; H, 8.54.



2-(3-Methoxyphenyl)pyridine [Coupling of an *N*-Coordinated Boronate with an Aryl Chloride].[141] Under air, 3-chloroanisole (125 μL, 1.02 mmol), XPhos Pd G1 methyl *tert*-butyl ether adduct (37 mg, 0.05 mmol, 5 mol %), and 2-pyridyl MIDA boronate (356 mg, 1.52 mmol, 1.5 equiv) were added to a flame-dried 40-mL I-CHEM vial equipped with a PTFE-coated stir bar. The vial was sealed with a septum cap and back-filled with argon. To the vial were added DMF (8 mL) and diethanolamine (96 μL, 1.0 mmol, 1 equiv) by syringe. The vial was brought into a glove box, and K_3PO_4 (1.061 g, 5.0 mmol, 5 equiv) and $Cu(OAc)_2$ (91 mg, 0.5 mmol, 50 mol %) were added. The vial was sealed with a septum cap and removed from

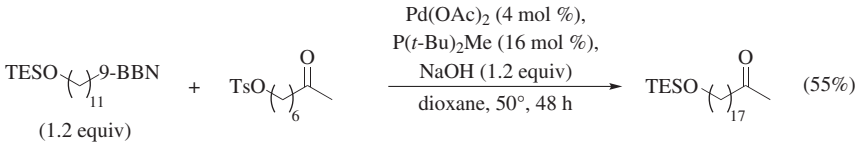
the glove box. The reaction mixture was stirred at 100° for 24 h and then cooled to 23° over 0.5 h. To the vial was added 2 M HCl (10 mL), and the resulting solution was shaken. To the vial was then added 2 M NaOH (10 mL), and the resulting solution was shaken and poured into a 100-mL separatory funnel, using Et_2O (~20 mL) to aid in the transfer. The biphasic mixture was shaken, and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 × 10 mL). The organic fractions were combined, washed with brine (10 mL), and dried over Na_2SO_4. The solution was then filtered and concentrated in vacuo. The resulting residue was adsorbed onto Celite and subjected to Florisil column chromatography (hexanes/EtOAc, 95:5 to 80:20) to afford the title compound as a yellow oil (182 mg, 96%): R_f 0.3 (hexanes/EtOAc, 80:20); ^{1}H NMR (acetone-d_6, 500 MHz) δ 3.87 (s, 3H), 6.99 (ddd, J = 0.5, 2.5, 7.5 Hz, 1H), 7.31 (ddd, J = 1.0, 5.0, 7.5 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.66 (dt, J = 1.5, 8.0 Hz, 1H), 7.71 (t, J = 2.0 Hz, 1H), 7.84 (td, J = 2.0, 7.5 Hz, 1H), 7.92 (dt, J = 1.0, 8.0 Hz, 1H), 8.65 (d, J = 5.5 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 55.5, 112.8, 115.4, 119.7, 121.0, 123.2, 130.4, 137.6, 141.6, 150.3, 157.3, 161.0; HRMS–ESI (m/z): $[M + H]^+$ calcd for $C_{12}H_{12}NO$, 186.0919; found, 186.0920.



Methyl 6-Methoxy-2,3′-bipyridine-5′-carboxylate [Coupling of a Lithium Aryltrimethoxyboronate with an Aryl Bromide].[154] To a dry, 50-mL, round-bottomed flask was added a solution of *n*-BuLi in hexanes (2.5 M, 3.10 mL, 7.8 mmol, 1.2 equiv), and the vessel was cooled to –40°. A solution of 2-bromo-6-methoxypyridine (1.33 g, 7.1 mmol, 1.1 equiv) in anhydrous ether (10 mL), precooled to –40° in a jacketed addition funnel above the reaction, was slowly added into the reaction flask. The resulting mixture was stirred at –40° for 20 min. The orange reaction mixture was treated dropwise with trimethoxyborane (0.881 mL, 7.8 mmol, 1.2 equiv). The reaction mixture became rose-colored, and the temperature increased slightly during addition. The reaction solution was stirred at –40° for 30 min and then was allowed to warm to rt over 30 min, at which point it was

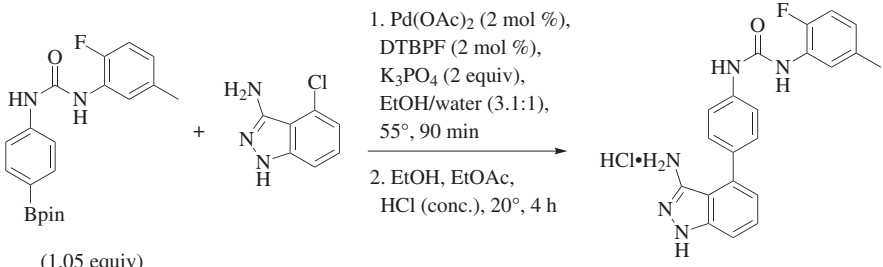
transferred to a round-bottomed flask using a small amount of CH_2Cl_2 to aid the transfer. Volatile liquids were evaporated in vacuo to afford a foam.

A second flask was charged with methyl 5-bromonicotinate (1.39 g, 6.4 mmol), $Pd(PPh_3)_4$ (372 mg, 0.32 mmol, 5 mol %), and dry DME (7 mL). The mixture was stirred for 15 min and then added to the crude borate residue, followed by additional DME (18 mL). The reaction mixture was treated with CsF (2.43 g, 16 mmol, 2.5 equiv), and a reflux condenser was attached to the flask. The reaction mixture was heated at reflux for 18 h. The reaction mixture was then partitioned between EtOAc (220 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2×60 mL) and then with saturated brine solution (90 mL). The solution was dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in the minimum amount of hot EtOAc and cooled to ambient temperature. The solution was treated with hexanes, whereupon crystal formation occurred. The solid was purified by silica gel column chromatography (hexane/EtOAc, 85:15) to afford the title compound (0.85 g, 54%) as a solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 3H), 4.04 (s, 3H), 6.77 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.68 (dd, J = 7.3, 8.3 Hz, 1H), 8.87 (s, 1H), 9.21 (s, 1H), 9.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.5, 53.4, 110.8, 113.1, 125.8, 134.3, 134.7, 139.3, 150.4, 150.8, 151.7, 164.0, 165.7; HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{12}N_2O_3$, 245.0926; found, 245.0917.



19-(Triethylsiloxy)nonadecan-2-one [Coupling of an Alkyl 9-Borabicyclo (3.3.1)nonane with an Alkyl Tosylate].[61] In air, $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 4 mol %), NaOH (48 mg, 1.2 mmol, 1.2 equiv), and 8-tosyloctan-2-one (299 mg, 1.0 mmol) were added to a Schlenk tube equipped with a magnetic stir bar. The vessel was evacuated and filled with argon (three cycles). Di-*tert*-butylmethylphosphine (32 μL, 0.16 mmol, 16 mol %), and 9-(1-triethylsilyloxyundecane)-9-borabicyclo[3.3.1] nonane (0.17 M solution in dioxane, 1.2 mmol, 1.2 equiv) were added sequentially by syringe. The resulting mixture was stirred vigorously at 50° for 48 h, during which time a fine white precipitate formed. The thick, heterogeneous reaction mixture was then diluted with Et_2O and filtered through silica gel with copious washings (Et_2O or EtOAc). The resulting solution was concentrated, and the residue was purified by silica gel column chromatography (hexanes/EtOAc, 97:3) to provide the title compound as a colorless liquid (219 mg, 53%): IR (thin film) 2926, 2854, 2876, 1721 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.73 (q, J = 7.7 Hz, 6H), 1.14 (t, J = 7.7 Hz, 9H), 1.21–1.74 (m, 30H), 1.76 (s, 3H), 2.04 (t, J = 7.4 Hz, 2H), 3.69 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 5.6, 7.8, 24.7, 27.0, 29.9, 30.2, 30.51, 30.54, 30.58, 30.71, 30.72, 30.76 (three coincident resonances), 30.78 (three

coincident resonances), 34.0, 43.9, 63.5, 206.4; HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{53}O_2Si$, 413.3809; found, 413.3810.



DTBPF = 1,1'-bis(di-*tert*-butylphosphino)ferrocene

Linifanib [Large-Scale Coupling of an Aryl Boronic Ester with an Aryl Chloride].[184] 4-Chloro-1*H*-indazol-3-amine (21.6 kg, 129 mol), 1-(2-fluoro-5-methylphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (50.0 kg, 135 mol, 1.05 equiv), and K_3PO_4 (54.7 kg, 260 mol, 2 equiv) were suspended in water (165 kg) and ethanol (345 kg) that had been purged of oxygen (<100 ppm, Alpha-Omega Oxygen Analyzer, series 3000) by bubbling nitrogen through the mixture before addition to the solids. The catalyst solution was prepared by first purging ethanol (55 kg) to <10 ppm oxygen by bubbling with nitrogen, then adding the ethanol to a combination of $Pd(OAc)_2$ (580 g, 2.6 mol, 2 mol %) and 1,1′-bis(di-*tert*-butylphosphino)ferrocene (1.22 kg, 2.6 mol, 2 mol %) and heating the mixture to 55° for 45 min. The catalyst was then transferred to the suspension of reactants, and the reaction mixture was heated to 55° for 1.5 h. After cooling to 20°, EtOAc (1100 kg) and 20% NH_4Cl in water (170 kg) were added to the reaction solution. The mixture was stirred for 30 min, allowed to settle for an additional 30 min, and then the bottom layer was discarded. The organic layer was washed with 20% NH_4Cl in water (410 kg) by mixing the layers for 30 min and allowing them to settle for 30 min, after which point the lower layers were discarded. The organic layer was then washed water (270 kg) according to the same procedure. The organic layer then was distilled under reduced pressure (5–10 mm Hg) to ~600 L. The distillation was continued, and the solvent level maintained at 600 L with continuous addition of toluene (820 kg), during which time the product crystallized. After cooling the product slurry to 20°, the product was collected by filtration, washed with toluene (2 × 260 kg) and dried under a flow of nitrogen for 1 h. The product wet cake was suspended in EtOAc (1380 kg) and EtOH (300 kg), and then conc HCl (102 kg) was added. After stirring at 20° for 4 h, the product HCl salt was collected by filtration, washed with EtOAc (2 × 100 kg), and dried under vacuum at 50° for 16 h to afford the HCl salt of the title compound (49.0 kg, 92%) as a white solid.

The HCl salt of the title compound was suspended in EtOAc (1200 kg) and EtOH (525 kg), and then was washed with a solution of $Na_2HPO_4 \bullet 7H_2O$ (46 kg) in water

(1335 kg) and a solution of NaH_2PO_4 (23 kg) in water (490 kg). The resulting solution of free base was filtered through a 0.5-μm in-line filter and then was treated with Filterol GR (41 kg) for 4 h. After filtration, the solution was treated with Acticarbone CPL carbon (9 kg) for 4 h and then filtered again. The resulting solution was distilled under reduced pressure (5–10 Torr) to ∼1300 L. The distillation was continued, and the solvent level was maintained at 1300 L with continuous addition of EtOH (2720 kg). Additional EtOH (560 kg) was added to the resulting suspension, and the mixture was heated to 50° to dissolve the bulk of the material. The solution then was cooled to 20°, and the crystallization was completed by the addition of water (1280 kg). The product was collected by filtration, washed with water (2 × 200 kg), and dried under vacuum at 70° for 4 h to afford 40.9 kg of title compound (84% overall yield) as a white solid: mp 209–211°; IR (KBr) 3241, 1689, 1607, 1548, 1316, 1228, 794 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 4.35 (s, 2H), 6.70–6.86 (m, 2H), 7.07 (dd, J = 8.4, 11.3 Hz, 1H), 7.26 (d, J = 3.7 Hz, 2H), 7.36–7.46 (m, 2H), 7.60 (d, J = 8.5 Hz, 2H), 8.00 (dd, J = 2.0, 7.9 Hz, 1H), 8.53 (d, J = 2.5 Hz, 1H), 9.20 (s, 1H), 11.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 108.3, 110.2, 114.2 (d, J = 18.8 Hz), 117.7, 118.8, 120.7, 122.4 (d, J = 7.3 Hz), 126.0, 126.6 (d, J = 10.2 Hz), 129.0, 132.5, 133.1 (d, J = 3.4 Hz), 135.0, 138.6, 141.7, 147.7, 149.8 (d, J = 237.0 Hz), 151.7; LRMS–ESI (m/z): $[M + H]^+$ 376.0. Anal. Calcd for $C_{21}H_{18}FN_5O \bullet 0.25C_2H_6O$: C, 66.74; H, 5.08; N, 18.10. Found: C, 66.60; H, 4.83; N, 18.31.

TABULAR SURVEY

The table entries include examples from the literature up through October 2017. The tables are organized by the structure of the transferable group attached to boron as the primary rubric, with the structure of the electrophile as the secondary rubric. Each rubric follows the order of presentation in the manuscript: alkyl, alkenyl, aryl, alkynyl, heterocyclic. Alkylboron reagents are presented in Tables 1–3, alkenylboron reagents in Tables 4–6, arylboron reagents in Tables 7–10, alkynylboron reagents in Tables 11 and 12, and heterocyclic boron reagents in Tables 13 and 14. Table 15 contains reactions of organoboron compounds with benzylic, allylic and propargylic electrophiles.

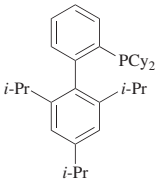
Within each table, entries are ordered by carbon count of the organoboron reagent. Not included in the carbon count are those carbons that are attached to the transferrable group through heteroatoms, and those in the non-transferrable groups on boron.

In reactions wherein the (*E*)/(*Z*) ratios of starting materials and/or products are not shown, the isomer depicted is predominant or the ratio is unreported in the original literature.

The following abbreviations, excluding those found in "*The Journal of Organic Chemistry* Standard Abbreviations and Acronyms" are used in the text and the Tables.

Ad	adamantyl
Bdan	2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborin-2-yl
Bpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl
$B(sia)_2$	bis(1,2-dimethylpropyl)boranyl
Cy	cyclohexyl
dba	dibenzylideneacetone
MIDA	*N*-methyliminodiacetic acid
MW	microwave
TES	triethylsilyl
Tol	tolyl, methylphenyl

CHART 1. LIGANDS USED IN TABLES



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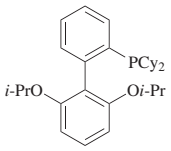

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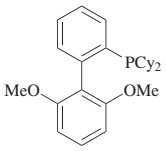

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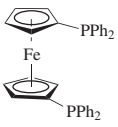

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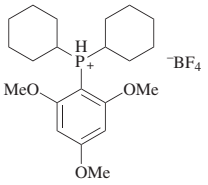
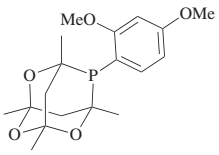


LB-Phos•HBF$_4$



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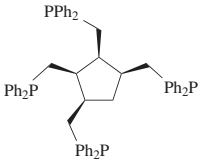

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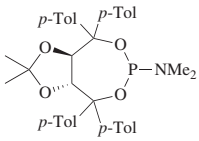

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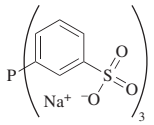

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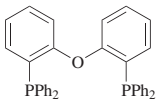

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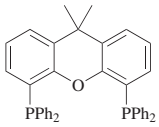

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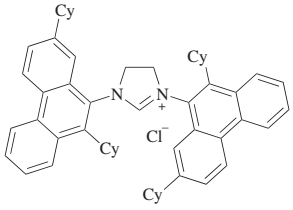

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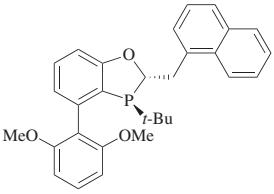

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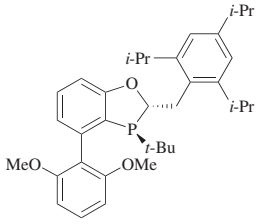
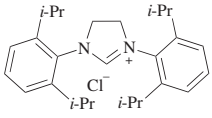


HandaPhos



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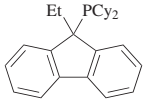

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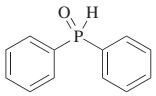

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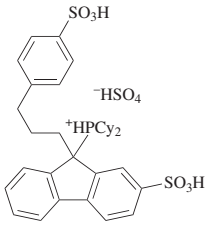

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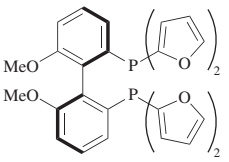

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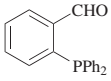
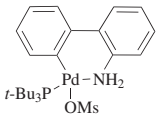
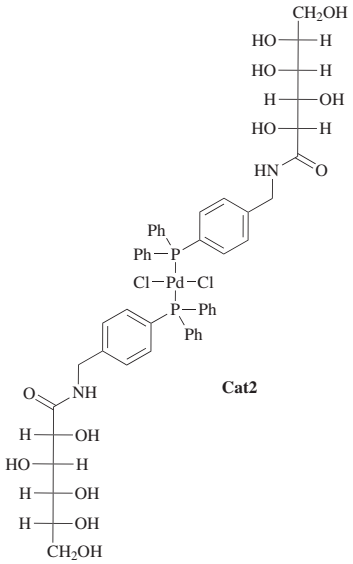


L10

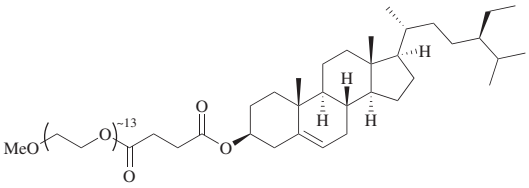
CHART 2. CATALYSTS USED IN TABLES



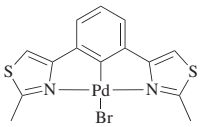
Cat1



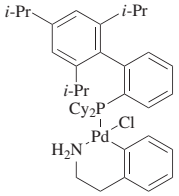
Cat2



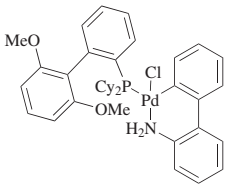
Nok



Cat3



XPhos Pd G1



SPhos Pd G2

TABLE 1. CROSS-COUPLINGS OF ALKYLBORON REAGENTS WITH ALKYL ELECTROPHILES

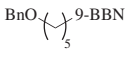
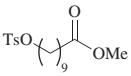
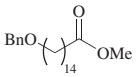
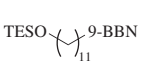
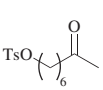
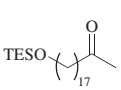
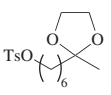
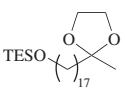
Alkylboron Reagent	Alkyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_5				
 1.2 eq		$Pd(OAc)_2$ (4 mol %), $P(t\text{-}Bu)_2Me$ (16 mol %), NaOH (1.2 eq), dioxane, 50°, 48 h	 (60)	61
C_6				
$n\text{-}C_6H_{13}$—9-BBN 1.2 eq		$Pd(OAc)_2$ (4 mol %), **L1** (5 mol %), $K_3PO_4 \bullet H_2O$ (1.2 eq), THF, rt, 24 h	$n\text{-}C_{12}H_{25}$—CN (62)	185
1.2 eq	Br—$n\text{-}C_{12}H_{25}$	$Pd(OAc)_2$ (4 mol %), **L1** (5 mol %), $K_3PO_4 \bullet H_2O$ (1.2 eq), THF, rt, 24 h	$n\text{-}C_{18}H_{38}$ (93)	185
$n\text{-}C_6H_{13}$—$B(OH)_2$ 1.5 eq	Br—$n\text{-}C_{12}H_{25}$	$Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me$ (10 mol %), KO*t*-Bu (3 eq), *t*-amyl alcohol, rt, 24 h	$n\text{-}C_{18}H_{38}$ (66)	186
C_{11}				
 1.2 eq		$Pd(OAc)_2$ (4 mol %), $P(t\text{-}Bu)_2Me$ (16 mol %), NaOH (1.2 eq), dioxane, 50°, 48 h	 (55)	61
1.2 eq		$Pd(OAc)_2$ (4 mol %), $P(t\text{-}Bu)_2Me$ (16 mol %), NaOH (1.2 eq), dioxane, 50°, 46 h	 (67)	61

TABLE 2. CROSS-COUPLINGS OF ALKYLBORON REAGENTS WITH ALKENYL ELECTROPHILES

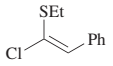
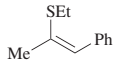
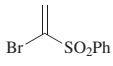
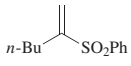
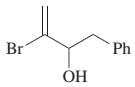
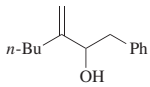
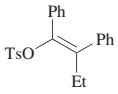
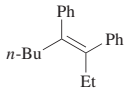
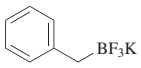
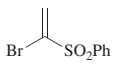
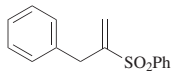
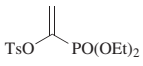
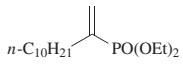
Alkylboron Reagent	Alkenyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_1				
$Me-B(OH)_2$ 1.3 eq		$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (1.5 eq), THF, 40°, 5 h	 (66)	187
C_4				
n-Bu—BF_3K 1.5 eq		$Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), Cs_2CO_3 (2 eq), toluene/water (4:1), 50°, 15 h	 (71)	188
n-Bu—$B(OH)_2$ 1.5 eq		$Pd(OAc)_2$ (5 mol %), LB-Phos•HBF_4 (5 mol %), K_2CO_3 (4.5 eq), toluene, 110°, 5.7 h	 (80)	189
1.1 eq	 $(E)/(Z)$ = 100:0	$Pd(OAc)_2$ (1 mol %), RuPhos (2 mol %), K_3PO_4•H_2O (1.5 eq), toluene/water (3:1), 70°, 24 h	 (98) $(E)/(Z)$ = 99:1	122
C_7				
 1.5 eq		$Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), Cs_2CO_3 (2 eq), toluene/water (4:1), 50°, 15 h	 (60)	188
C_{10}				
n-$C_{10}H_{21}$—BF_3K 2 eq		$Pd(OAc)_2$ (7 mol %), SPhos (15 mol %), Cs_2CO_3 (2.5 eq), toluene/water (4:1), 60°, 20 h	 (99)	190

TABLE 3. CROSS-COUPLINGS OF ALKYLBORON REAGENTS WITH ARYL ELECTROPHILES

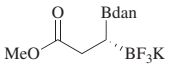
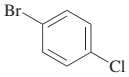
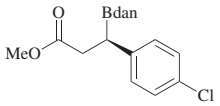
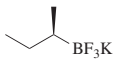
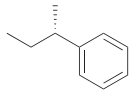
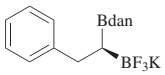
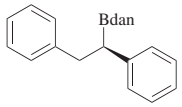
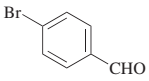
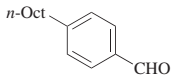
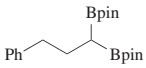
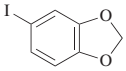
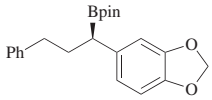
Alkylboron Reagent	Aryl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_2				
BEt_3 0.4 eq		$Pd(OAc)_2$ (2.5 mol %), (*n*-Bu)Ad_2P (5 mol %), K_3PO_4 (2 eq), toluene/water (10:1), 100°	 (90)	191
C_3				
 er 99.5:0.5 1.2 eq		$Pd(OAc)_2$ (10 mol %), XPhos (20 mol %), K_2CO_3 (3 eq), toluene/water (10:1), 80°, 6 h	 (85) er 99.5:0.5	68
C_4				
 er 99.0:1.0 1.5 eq		**Cat1** (10 mol %), K_2CO_3 (3 eq), toluene/water (2:1), 100°, 24 h	 (93) er 98.0:2.0	65
C_8				
 er 97.0:3.0 1.5 eq		$Pd(OAc)_2$ (10 mol %), XPhos (20 mol %), K_2CO_3 (3 eq), toluene/water (10:1), 80°, 6 h	 (15) er 90.5:9.5	69
n-Oct—$B(OH)_2$ 2 eq		**L2**[$PdCl(C_3H_5)$] (0.01 mol %), K_2CO_3 (2 eq), xylene, 130°, 20 h	 (74)	192
C_9				
 1.1 eq		$Pd(OAc)_2$ (5 mol %), **L3** (10 mol %), KOH (15 eq), dioxane/water (1:1), rt, 12 h	 (88) er 92.0:8.0	67

TABLE 4. CROSS-COUPLINGS OF ALKENYLBORON REAGENTS WITH ALKENYL ELECTROPHILES

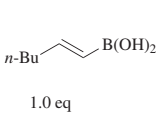
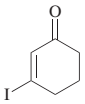
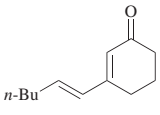
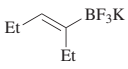
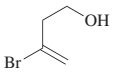
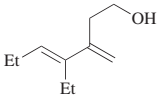
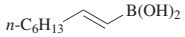
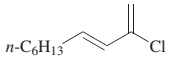
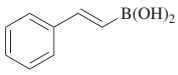
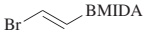
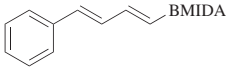
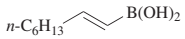
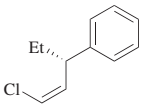
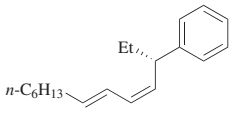
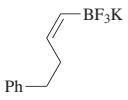
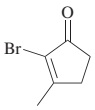
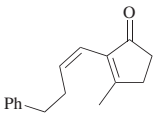
Alkenylboron Reagent	Alkenyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_6				
 1.0 eq		$Pd(OAc)_2$ (2.5 mol %), TPPTS (5 mol %), *i*-Pr_2NH (2.5 eq), MeCN/water (3:1), rt	 (95)	193
 1.1 eq		$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (3 eq), THF/water (10:1), 70°, 2 h	 (66)	194
C_8				
	 4 eq	$Pd_2(dba)_3$ (0.5 mol %), XPhos (2 mol %), K_3PO_4 (2 eq), toluene, 100°, 4 h	 (92)	195
 1.5 eq		$Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), KF (2 eq), toluene, rt, 24 h	 (92)	196
 1.5 eq	 pure (*Z*) isomer er 98.0:2.0	$Pd_2(dba)_3$ (5 mol %), XPhos (10 mol %), CsF (3 eq), dioxane, 100°, 16 h	 (*Z*)/(*E*) > 99:1 er 98.0:2.0 (77)	197
C_{10}				
 1.1 eq		$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (3 eq), THF/water (10:1), 70°, 12 h	 (95)	194

TABLE 5. CROSS-COUPLINGS OF ALKENYLBORON REAGENTS WITH ARYL ELECTROPHILES

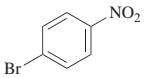
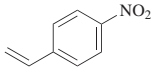
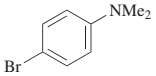
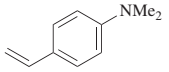
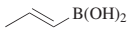
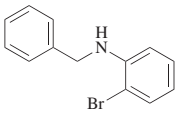
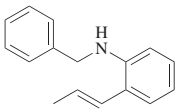
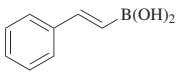
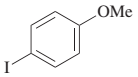
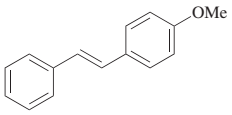
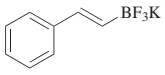
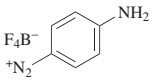
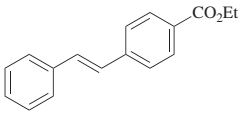
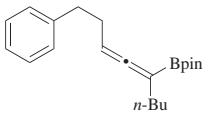
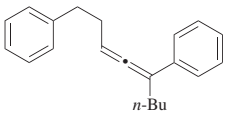
Alkenylboron Reagent	Aryl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_2				
 1.1 eq		5% Pd/C (2 mol %), $NaOAc•3H_2O$ (3 eq), NMP, 100°, 24 h	 (78)	198
1.05 eq		$PdCl_2$ (2 mol %), RuPhos (6 mol %), Cs_2CO_3 (3 eq), THF/water (9:1), 85°, 22 h	 (93)	131
C_3				
 1.25 eq		$Pd(PPh_3)_4$ (5 mol %), Na_2CO_3 (1 eq), DME/water (4:1), reflux, 20 h	 (92)	199
C_8				
 1.5 eq		**Cat3** (0.001 mol %), K_2CO_3 (3 eq), dioxane, 80°, 8 h	 (92)	200
 1.2 eq		$Pd_2(OAc)_2(P(2\text{-}Tol)_3)_2$ (5 mol %), MeOH, 20°, 2 min	 (96)	144
C_{15}				
		$PdCl_2(PPh_3)_2$ (5 mol %), CuCl (2 mol %), Na_2CO_3 (2 eq), MeOH/toluene (4:1), rt, 16 h	 (18)	201

TABLE 6. CROSS-COUPLINGS OF ALKENYLBORON REAGENTS WITH ALKYNYL ELECTROPHILES

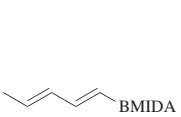
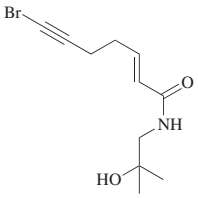
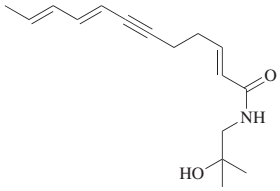
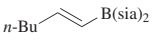
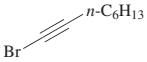
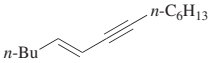
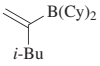
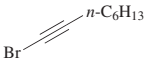
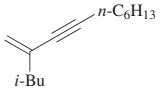
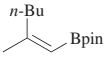
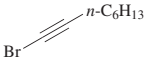
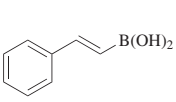
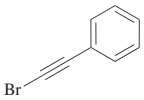
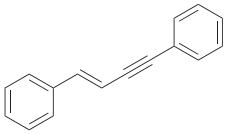
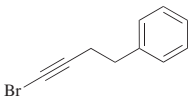
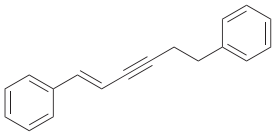
Alkenylboron Reagent	Alkynyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_5  1.4 eq		$Pd(OAc)_2$ (10 mol %), SPhos (20 mol %), NaOH (7.2 eq), THF/water (2:1), 30°, 2 h	 (54)	99
C_6  1.1 eq		$Pd(PPh_3)_4$ (1 mol %), NaOMe (2.2 eq), benzene/methanol (2:1), 80°, 2 h	 (100)	1
 1.13 eq		$Pd(PPh_3)_4$ (6 mol %), NaOH (4.7 eq), THF/water (8:3), reflux, 12 h	 (56)	130
C_7  1.2 eq		$PdCl_2$(DPEPhos) (1 mol %), (n-Bu)$_4$NF (2 eq), THF, 60°, 12 h	 (93)	202
C_8  1.2 eq		$Pd(dba)_2$ (0.1 mol %), Cs_2CO_3 (2 eq), MeOH, rt, 12 h	 (67)	203
 1.5 eq		$Pd(PPh_3)_4$ (5 mol %), KOH (6 eq), dioxane/water (5:1), 90°, 14 h	 (84)	204

TABLE 7. CROSS-COUPLINGS OF ARYLBORON REAGENTS WITH ALKYL ELECTROPHILES

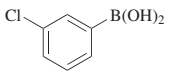
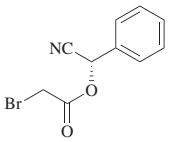
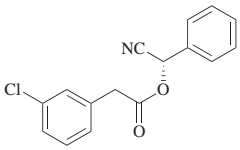
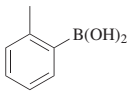
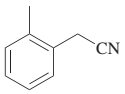
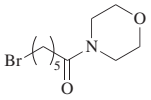
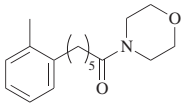
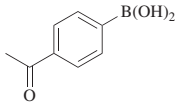
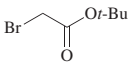
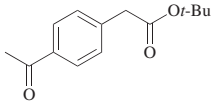
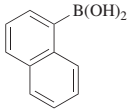
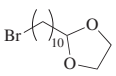
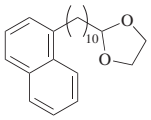
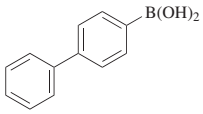
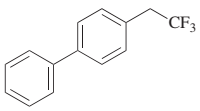
Arylboron Reagent	Alkyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_6				
 1.5 eq		$Pd(OAc)_2$ (3 mol %), $P(2\text{-Tol})_3$ (9 mol %), KF (3 eq), toluene, 60°, 1.5 h	 (73) er 99.5:0.5	205
C_7				
 1.5 eq		$Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %), Na_2CO_3 (1.5 eq), dioxane/water (10:1), 60°, 12 h	 (89)	206
1.5 eq		$Pd(OAc)_2$ (5 mol %), $(t\text{-Bu})_2MePH^+ BF_4^-$ (10 mol %), KO*t*-Bu (3 eq), *t*-amyl alcohol, rt, 24 h	 (76)	186
C_8				
 1.3 eq		$Pd(OAc)_2$ (3 mol %), $P(2\text{-Tol})_3$ (10 mol %), K_2CO_3 (5.4 eq), THF/water (145:1), rt, 18 h	 (76)	207
C_{10}				
 1.5 eq		$Pd(OAc)_2$ (5 mol %), $P(t\text{-Bu})_2Me$ (10 mol %), KO*t*-Bu (3 eq), *t*-amyl alcohol, rt, 24 h	 (97)	186
C_{12}				
	 2 eq	$Pd_2(dba)_3$ (5 mol %), XantPhos (17 mol %), Cs_2CO_3 (4 eq), dioxane/water (31:1), 80°, 12 h	 (81)	208

TABLE 8. CROSS-COUPLINGS OF ARYLBORON REAGENTS WITH ALKENYL ELECTROPHILES

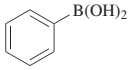
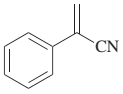
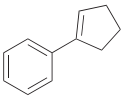
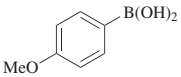
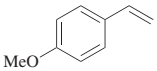
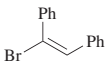
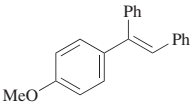
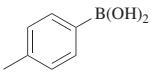
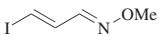
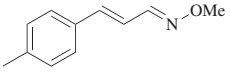
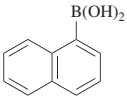
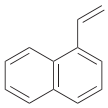
Arylboron Reagent	Alkenyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_6				
	 2 eq	$Pd_2Cl_2(allyl)_2$ (1 mol %), **L2** (2 mol %), K_2CO_3 (2 eq), xylene, 100°, 20 h	 (79)	209
1.2 eq		$Pd(OAc)_2$ (2 mol %), **L4** (4 mol %), KF (1.5 eq), 18-crown-6 (1.5 eq), THF, 50°, 16 h	 (87)	210
 1.5 eq	 Generated from 1,2-dibromoethane and KOH in situ	$Pd(OAc)_2$ (4 mol %), PPh_3 (8 mol %), KOH (3 eq), MeOH/THF (1:1), sealed tube, 100°, 1 h	 (87)	211
1.2 eq		$Pd(OAc)_2$ (0.5 mol %), PPh_3 (1 mol %), KOH (2 eq), MeOH/THF (1:1), 25°, 1 h	 (98)	212
C_7				
	 2 eq	$Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (2 eq), dioxane, 60°, 10 h	 (59)	213
C_{10}				
 1.5 eq	 Generated from 1,2-dibromoethane and KOH in situ	$Pd(OAc)_2$ (2 mol %), PPh_3 (4 mol %), KOH (3 eq), MeOH/THF (1:1), 100°, 1 h	 (87)	209

TABLE 9. CROSS-COUPLINGS OF ARYLBORON REAGENTS WITH ARYL ELECTROPHILES

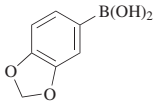
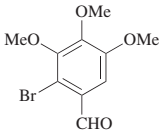
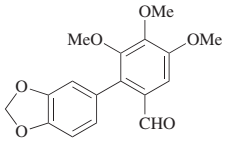
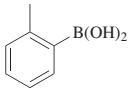
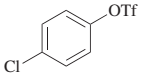
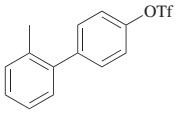
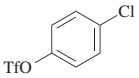
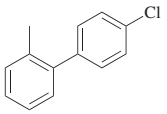
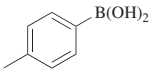
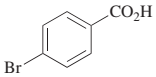
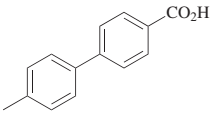
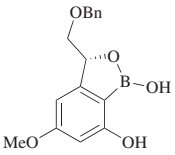
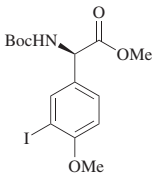
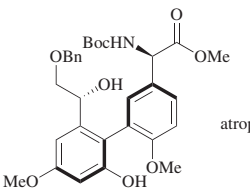
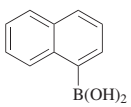
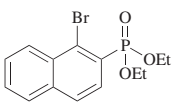
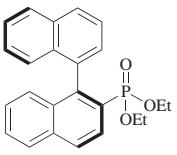
Arylboron Reagent	Aryl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_6				
		$PdCl_2(PPh_3)_2$ (4 mol %), KF (2 eq), toluene/water (10:1)	 (79)	214
C_7				
 1.0 eq		$Pd_2(dba)_3$ (1.5 mol %), P(*t*-Bu)$_3$ (3 mol %), KF (3 eq), THF, rt, 24 h	 (95)	46
1.0 eq		$Pd(OAc)_2$ (3 mol %), PCy_3 (6 mol %), KF (3 eq), THF, rt, 48 h	 (87)	46
 1.3 eq		**Cat2** (0.1 mol %), K_3PO_4 (2 eq), water, 80°, 30 min	 (99)	215
C_8				
		$Pd(PPh_3)_4$ (20 mol %), Na_2CO_3 (1.2 eq), toluene/MeOH/water (20:2:1), 90°, 4 h	 (84) atropisomer dr 67:33	216
C_{10}				
 2 eq		$Pd(OAc)_2$ (5 mol %), **L5** (6 mol %), K_3PO_4 (3 eq), THF, rt, 12 h	 (88) er 95.0:5.0	217

TABLE 10. CROSS-COUPLINGS OF ARYLBORON REAGENTS WITH ALKYNYL ELECTROPHILES

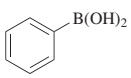
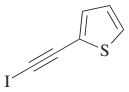
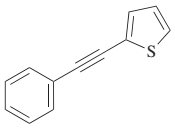
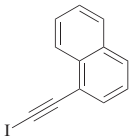
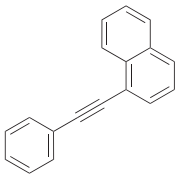
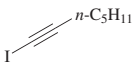
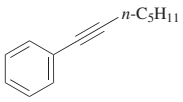
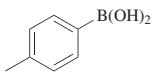
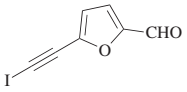
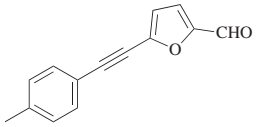
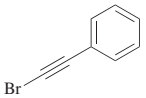
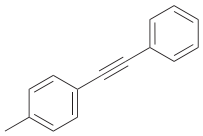
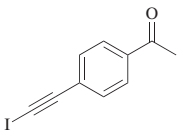
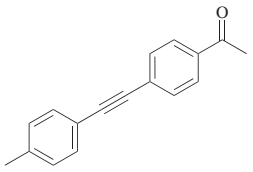
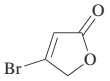
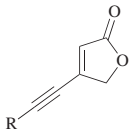
Arylboron Reagent	Alkynyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_6				
 1.2 eq		$Pd(dba)_2$ (0.1 mol %), Cs_2CO_3 (2 eq), MeOH, rt, 12 h	 (95)	203
1.2 eq		$Pd(dba)_2$ (0.1 mol %), Cs_2CO_3 (2 eq), MeOH, rt, 12 h	 (74)	203
1.2 eq		$Pd(dba)_2$ (0.1 mol %), Cs_2CO_3 (2 eq), MeOH, rt, 12 h	 (68)	203
C_7				
 1.5 eq		$PdCl_2$ (1 mol %), K_2CO_3 (2 eq), MeOH/toluene/water (3:3:1), 80°, 8 h	 (86)	218
1.2 eq		$Pd(dba)_2$ (0.1 mol %), Cs_2CO_3 (2 eq), MeOH, rt, 12 h	 (91)	203
1.5 eq		$PdCl_2$ (1 mol %), K_2CO_3 (2 eq), MeOH/toluene/water (3:3:1), 80°, 8 h	 (92)	218

TABLE 11. CROSS-COUPLINGS OF ALKYNYLBORON REAGENTS WITH ALKENYL ELECTROPHILES

Alkynylboron Reagent	Alkenyl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_{2-9} 		$Pd(dppf)Cl_2•CH_2Cl_2$ (5 mol %), THF, rt		219

R	Time (h)	
$(Me)_3Si$	4	(71)
$Cl(CH_2)_3$	3	(89)
t-Bu	3	(95)
isopropenyl	3	(88)
n-Bu	4	(95)
1-cyclohexenyl	5	(80)
Ph	6	(91)
$4\text{-}MeC_6H_4$	6	(87)

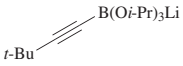
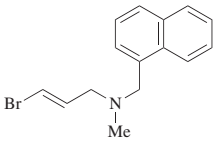
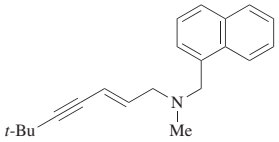
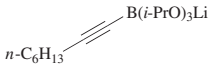
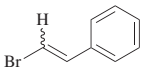
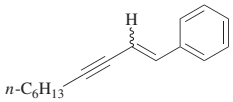
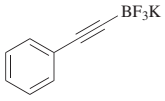
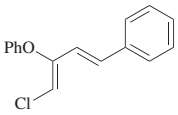
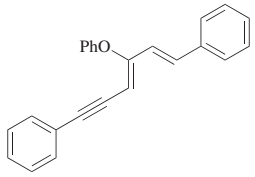
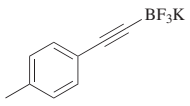
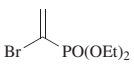
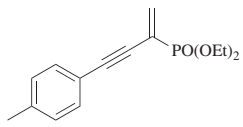
C_6  2.0 eq		$Pd(PPh_3)_4$ (5 mol %), CuI (5 mol %), DMF, 60°, 36 h		(98)	220
C_8  1.36 eq Generated in situ from the corresponding alkynyl lithium reagent		$Pd(PPh_3)_4$ (1 mol %), DME/THF (10:1), 80°, 5 h		(60)	139
 1.5 eq		$Pd_2(dba)_3$ (2.5 mol %), DPEPhos (5 mol %), CsF (3 eq), Cs_2CO_3 (3 eq), THF, 65°, 12 h		(20)	221
C_9  1.5 eq		$Pd_2(dba)_3$ (5 mol %), SPhos (20 mol %), Cs_2CO_3 (2 eq), toluene/water 4:1, 50°, 10 h		(82)	222

TABLE 12. CROSS-COUPLINGS OF ALKYNYLBORON REAGENTS WITH ARYL ELECTROPHILES

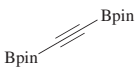
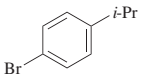
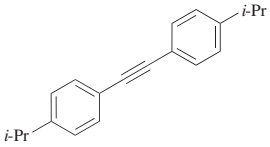
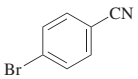
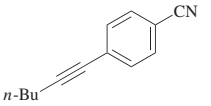
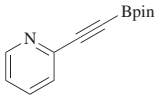
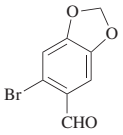
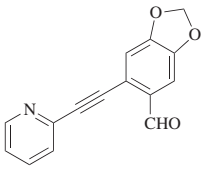
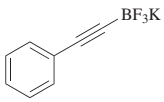
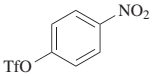
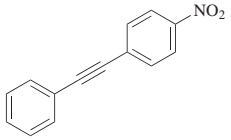
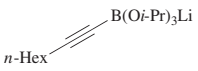
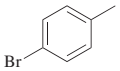
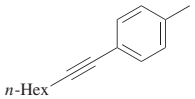
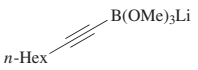
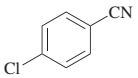
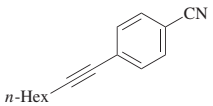
Alkynylboron Reagent	Aryl Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_2				
	 2 eq	$Pd_2(dba)_3$ (2 mol %), XPhos (8 mol %), K_3PO_4 (6 eq), THF, MW, 140°, 40 min	 (55)	183
C_6				
 1.0 eq		$Pd(dppf)Cl_2•CH_2Cl_2$ (9 mol %), Cs_2CO_3 (3 eq), THF/water (20:1), reflux, 12 h	 (98)	223
C_7				
 1.2 eq		$Pd(OAc)_2$ (0.1 mol %), HandaPhos (0.102 mol %), Et_3N (2 eq), Nok (2 wt %) in water, 25°, 28 h	 (83)	224
C_8				
 1.1 eq		$PdCl_2(dppf)•CH_2Cl_2$ (5 mol %), $(i\text{-Pr})_2NEt$ (3 eq), *i*-PrOH/water (2:1), MW, 100°, 15 min	 (96)	225
 1.36 eq		$Pd(PPh_3)_4$ (3 mol %), DME/THF (10:1), 80°, 5 h	 (98)	139
 1.3 eq		$Pd_2(dba)_3$ (3 mol %), SIPr•HCl (6 mol %), CsF (1 eq), DME/dioxane (1:1), reflux, 3 h	 (94)	226

TABLE 13. CROSS-COUPLINGS OF HETEROCYCLIC BORON REAGENTS

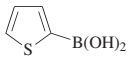
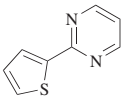
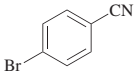
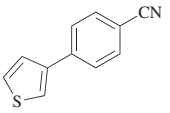
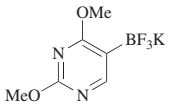
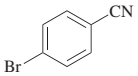
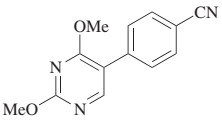
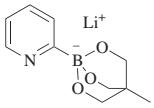
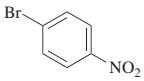
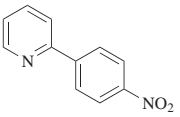
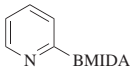
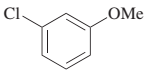
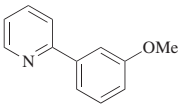
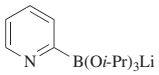
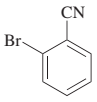
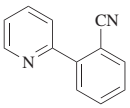
Heterocyclic Boron Reagent	Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_4				
 1.5 eq		Na_2PdCl_4 (0.5 mol %), **L6** (1 mol %), K_2CO_3 (2 eq), *n*-BuOH, 100°, 14 h	 (89)	227
 1.04 eq		$Pd(OAc)_2$ (1 mol %), RuPhos (2 mol %), Na_2CO_3 (2 eq), EtOH, 85°, 5 h	 (93)	182
 1.04 eq		$Pd(OAc)_2$ (3 mol %), RuPhos (6 mol %), Na_2CO_3 (2 eq), EtOH, 85°, 12 h	 (88)	182
C_5				
 1.1 eq		$Pd(OAc)_2$ (3 mol %), PPh_3 (3 mol %), CuI (20 mol %), DMF, 80°	 (90)	140
 1.5 eq		**XPhos Pd G1** (5 mol %), $Cu(OAc)_2$ (50 mol %), K_3PO_4 (5 eq), diethanolamine (1 eq), DMF, 100°, 24 h	 (96)	141
 1.5 eq		$Pd_2(dba)_3$ (1 mol %), **L7** (6 mol %), KF (3 eq), dioxane, 110°, 20 h	 (90)	228

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TABLE 14. CROSS-COUPLINGS OF HETEROCYLIC ELECTROPHILES

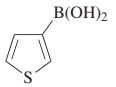
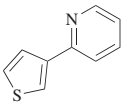
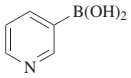
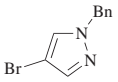
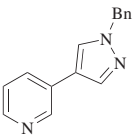
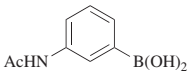
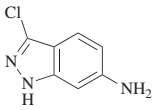
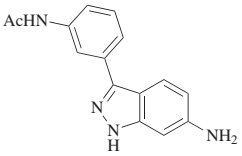
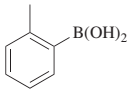
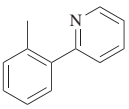
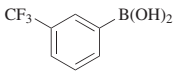
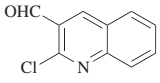
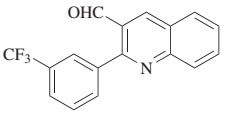
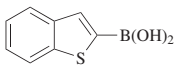
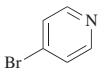
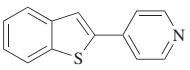
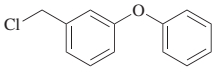
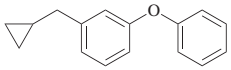
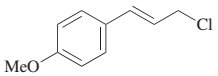
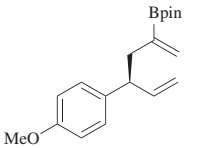
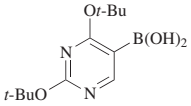
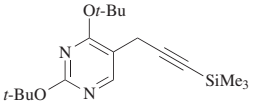
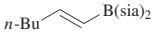
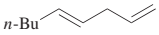
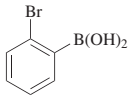
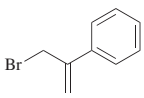
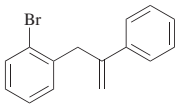
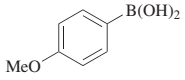
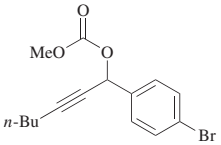
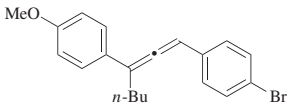
Organoboron Reagent	Heterocyclic Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_4  2 eq		$Pd_2Cl_2(allyl)_2$ (0.1 mol %), **L2** (0.2 mol %), K_2CO_3 (2 eq), xylenes, 130°, 20 h	 (90)	229
C_5  1.1 eq		$Pd_2(dba)_3$ (1 mol %), PCy_3 (2.4 mol %), K_3PO_4 (1.7 eq), dioxane/water (2:1), 100°, 18 h	 (73)	230
C_6  2 eq		**SPhos Pd G2** (2 mol %), K_3PO_4 (2 eq), dioxane/water (4:1), 100°, 15 h	 (90)	231
C_7  1.1 eq		$Pd_2(dba)_3$ (0.5 mol %), $P(t\text{-}Bu)_3$ (1 mol %), KF (3.3 eq), THF, rt, 24 h	 (97)	46
 1.2 eq		Na_2PdCl_4 (0.005 mol %), **L8** (0.01 mol %), K_2CO_3 (2 eq), *n*-BuOH/water (3:1), 100°, 12 h	 (95)	232
C_8  2 eq		$Pd_2Cl_2(allyl)_2$ (1 mol %), **L2** (2 mol %), K_2CO_3 (2 eq), xylenes, 130°, 20 h	 (90)	229

TABLE 15. CROSS-COUPLINGS OF ORGANOBORON REAGENTS WITH BENZYLIC, ALLYLIC, AND PROPARGYLIC ELECTROPHILES

Organoboron Reagent	Electrophile	Conditions	Product(s) and Yield(s) (%)	Refs.
Please refer to the charts preceding the tables for ligand and catalyst structures.				
C_3				
 1.75 eq		$Pd_2(dba)_3$ (5 mol %), RuPhos (10 mol %), K_2CO_3 (2 eq), toluene/water (19:1), sealed tube, 120°, 3 h	 (77)	233
 1.2 eq		$Pd_2Cl_2(allyl)_2$ (2.5 mol %), **L9** (5 mol %), CsF (10 eq), THF, 23°, 20 h	 (79) er 99.0:1.0	234
C_4				
 1.0 eq		$Pd(PPh_3)_4$ (2.5 mol %), $NaHCO_3$ (2.5 eq), DME/water (4:3), reflux, 4 h	 (32)	235
C_6				
	 1.2 eq	$Pd(PPh_3)_4$ (3 mol %), **L3** (2 mol %), NaOH (2 eq), benzene/water (3:1), reflux, 2 h	 (87)	236
 1.2 eq		$Pd(O_2CCF_3)_2$ (0.01 mol %), KOH (1.5 eq), water, 90°, 3 h	 (90)	181
 1.5 eq		$Pd_2(dba)_3$•$CHCl_3$ (2 mol %), **L10** (8 mol %), dioxane, 30°, 12 h	 (87)	237

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