

# Palladium-Catalyzed Cross-Coupling Reactions of Organoboronic Acids with Organic Electrophiles

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The palladium-catalyzed cross-coupling reactions of organoboronic acids with organic electrophiles are summarized. Because this mild, versatile reaction is tolerant of a wide variety of functional groups on either coupling partner, is regiospecific and stereospecific, and gives high yields of product, it is ideal for use in the synthesis of various functionalized biaryls. Many such biaryls, after, or even without, further modification of the functional groups, can undergo ring closure to tricyclic and polycyclic compounds.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

With the rapid development of palladium-catalyzed cross-couplings of organometallics (Mg, Li, Cu, Zn, Zr, Al, Sn and B) with organic electrophiles to form carbon-carbon bonds during the last two decades, synthetic chemists today have many more options which are available for consideration. Among these possibilities, many organometallic reagents will not tolerate sensitive functionalities which may be imperative for the total synthetic sequences. For instance, lithium, Grignard and copper reagents will not tolerate various sensitive functional groups on either coupling partner. In addition, some of the organometallic reagents are air or moisture sensitive, are highly toxic or arduous to prepare, and few can be purified and stored.

Arene- and alkene-boronic acids are one of few organometallic classes which tolerate a wide range of functional groups. Also, most arene- and alkene-boronic acids are inert to air, resistant to heat, and can be recrystallized from water or alcohol. In addition, organoboronic acids are economically available and environmentally less toxic than most organometallics.

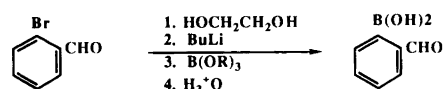
The electronegativity of boron is about 2.0, which is relatively close to the value of 2.5 for carbon, and is higher than the electronegativities of lithium and magnesium, as well as of essentially all transition metals, which range from 0.86 to 1.75. Owing to the smaller difference in electronegativities between boron and carbon, organoboron reagents generally do not react with organic halides, carbonyl functions and some active hydrogen compounds. It is this small difference in electronegativity that creates

the wide functional group compatibility of organoboron reagents.

The palladium-catalyzed cross-coupling reaction of organotin reagents with electrophiles<sup>1</sup> is also a versatile process which tolerates a wide variety of functional groups. Organotin reagents can be coupled with a wider spectrum of electrophiles such as acid halides, benzyl halides, vinyl and aryl halides, even saturated organic halides and some derivatives of alcohols. However, organoboronic acid reagents have advantages over tin reagents in terms of reduced toxicity and process cost.

## 1. Preparation of organoboronic acids

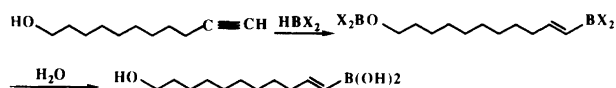
Organoboronic acids have been readily prepared by well-established methods such as partial oxidation of the corresponding triorganoboranes,<sup>2</sup> and halogenation of triorganoboranes followed by hydrolysis of the resulting halides to give the acids.<sup>3</sup> By far the most widely used method for areneboronic acids, however, is reaction of Grignard or lithium reagents with boron halides or borates.<sup>4</sup> When the halide from which the Grignard or lithium reagent is derived has a functional group sensitive to Grignard reagent, a protection-deprotection procedure is required. This method has been used for the preparation of 2-formylbenzeneboronic acid in the separated yield of 57%<sup>5</sup> (Scheme 1).



Scheme 1.

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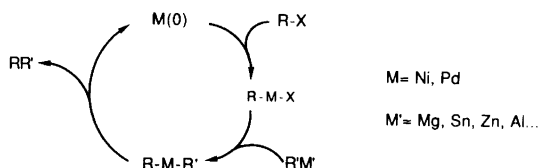
Alkeneboronic acids can be easily prepared by hydroboration of appropriate acetylenic precursors with catecholborane<sup>6</sup> (Scheme 2). Generally speaking, the vinylboronic acids are easier to purify than their catechol derivatives, and therefore the quality of the resulting boronic acids can be controlled.



Scheme 2.

## 2. Mechanism

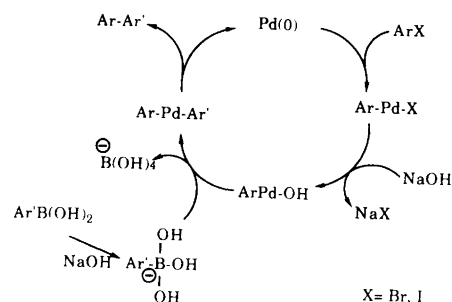
The general catalytic cycle for the cross-coupling of organometallics with organic halides catalyzed by transition metals [usually nickel(0) or palladium(0) species], shown in Scheme 3, is widely accepted.<sup>7</sup> These coupling reactions involve the oxidative addition of organic halides to the palladium(0) complex to form organopalladium halides (R-M-X). This step is followed by transmetalation with main-group organometallics (R'M') to provide the diorganopalladium complex (R-M-R'), which can undergo a reductive elimination, leading to carbon-carbon bond formation and regenerating the catalyst.



Scheme 3.

Similarly, Suzuki has suggested a catalytic cycle for the cross-coupling of organoboranes with organic halides.<sup>8</sup> The crucial difference between organoborane cross-coupling cycle and the general catalytic cycle is that, in the former, the oxidative addition is followed by the metathetical displacement of the halide ion from R-Pd-X by a basic species to give an organopalladium alkoxide (R-Pd-OR) or organopalladium hydroxide (R-Pd-OH), depending on the base used. These organopalladium alkoxides and organopalladium hydroxides are believed to be more reactive than the organopalladium halide (*vide infra*). Since boronic acids are chemically quite similar to organoboranes, the mechanism of the cross-coupling of boronic acids with organic halides may be similar to that for organoboranes suggested by Suzuki (Scheme 4).

The mechanisms of the oxidative addition and reductive elimination sequences have been intensively studied, and are reasonably well understood.<sup>9,10</sup> However, much less is known about the transmetalation reaction. Stille has inferred that the transmetalation reaction takes place by an electrophilic substitution mechanism, with the organopalladium halide acting as the electrophile.<sup>1</sup>



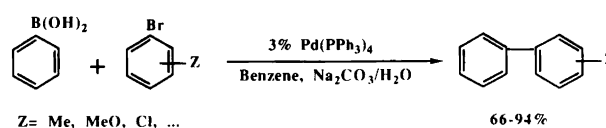
Scheme 4.

As shown in Scheme 4, two equivalents of base are required in this catalytic cycle. One equivalent is utilized in the formation of boronate, which is consistent with the fact that boronic acids act as acids in the Lewis sense, with the formation of a tetravalent boron atom.<sup>11,12</sup> The anionic nature of the organic group in organoboronic acids is expected to be enhanced by the formation of an organoboronate.<sup>13</sup> The second equivalent of base is consumed in the metathetical displacement to form organopalladium hydroxide. Obviously, the organopalladium hydroxide should be more reactive than the organopalladium halide, since the Pd-O bond is more polar than the Pd-Br bond, owing to the greater electronegativity of oxygen relative to bromine (the palladium is the positive end and the oxygen is the negative end of the dipole). As result, the electrophilicity of the organopalladium hydroxide is stronger than that of the organopalladium bromide, and the electrophilic transmetalation reaction is facilitated. Thus, the transmetalation reaction is favored by the formation of both the arylboronate and the organopalladium hydroxide.

This catalytic cycle clearly explains the failure of attempts<sup>14</sup> to couple organoboronic acids in the absence of base. It also implies the possibility of selectively coupling organometallics bearing boron and other metal functionalities such as tin functional groups with electrophiles, since it is known that the tin coupling reaction does not require the presence of base.

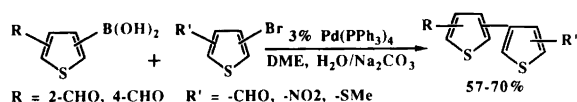
## 3. Aryl-aryl coupling

In 1981, Suzuki and his co-workers first reported that benzeneboronic acid could be coupled with aryl halides, catalyzed by palladium phosphine complex and in the presence of sodium carbonate<sup>14</sup> (Scheme 5). This cross-coupling reaction, referred to as the Suzuki reaction, is catalyzed by 3% tetrakis(triphenylphosphine)palladium(0), with benzene or toluene as the solvent, and requires 2 equivalents of aqueous sodium carbonate solution.



Scheme 5.

Shortly after the Suzuki's discovery, Gronowitz *et al.* carried out an extensive exploration of this coupling reaction in order to extend it to the synthesis of various biaryls, heterobiaryls, teraryls and condensed ring systems. They found that although the electron-rich areneboronic acids are prone to be deboronated under Suzuki coupling conditions, such deboronations could be suppressed by using glycol dimethyl ether (DME) as the solvent<sup>15-17</sup> (Scheme 6). This modification has been labelled the Gronowitz coupling process.



Scheme 6.

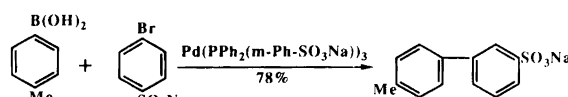
Since the first report of this coupling reaction, a number of functionalized biaryls and heterobiaryls have been prepared by this regiospecific coupling reaction. Table 1 lists some representative biaryls; more examples can be found in the references cited.

As shown in Table 1, a wide variety of areneboronic acids (such as benzene, thiophene, furan, selenophene, pyrimidine, pyridine and indoleboronic acids) have been regiospecifically coupled to various halides (such as phenyl, thienyl, pyridyl, pyrimidyl, furanyl, thiazolyl, quinolyl and pyrazolyl halides). The tabulated examples also show that this cross-coupling reaction tolerates

various functional groups including hydroxy and carboxy groups on either coupling partner.

The most frequently employed halides in boronic coupling reactions are aryl bromides, but the reactivity of halides shows the order of Ar-I > Ar-Br > Ar-Cl. Except for a few electron-deficient heteroaryl chlorides, aryl chlorides are usually not reactive enough to participate in the cross-coupling. A recent paper from Mitchell and Wallbank showed that nitrogen-containing electron-deficient heteroaryl chlorides could be coupled with areneboronic acid to give biaryls in good yields, by using [1,4-bis(diphenylphosphine)butane]palladium(II) chloride [Pd(dppb)Cl<sub>2</sub>] as the catalyst.<sup>18</sup>

The most often used catalyst in this boronic acid coupling is tetrakis(triphenylphosphine)palladium(0). However, other palladium catalysts have been employed with success, such as Pd(dppb)Cl<sub>2</sub>,<sup>18</sup> Pd(OAc)<sub>2</sub>,<sup>19</sup> PdCl<sub>2</sub>,<sup>20</sup> Pd(dppf)(OAc)<sub>2</sub><sup>21</sup> and Pd[PPh<sub>2</sub>(*m*-C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>M)]<sub>3</sub>.<sup>22</sup> Recently, Casalnuovo and Calabrese reported<sup>22</sup> that the water-soluble Pd(0) complex Pd[PPh<sub>2</sub>(*m*-PhSO<sub>3</sub>M)]<sub>3</sub> (M = Na, K) catalyzed the cross-coupling of highly lipophobic sodium *p*-bromobenzenesulfonate with *p*-methylbenzenboronic acid to give the coupling product in the yield of 78%, compared with a yield of 36% catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> (Scheme 7).



Scheme 7.

Table 1. Synthesis of biaryls.

No.	Ar-X	Ar'B(OH) <sub>2</sub>	Ar-Ar'	Yield(%)	Ref.
1	<i>o</i> -MePh-Br	Phenyl	<i>o</i> -MePh-Ph	94 <sup>a</sup>	14
2	<i>o</i> -MeOPh-Br	Phenyl	<i>o</i> -MeOPh-Ph	99	14
3	<i>p</i> -ClPh-Br	Phenyl	<i>p</i> -ClPh-Ph	89	14
4	<i>p</i> -MeO <sub>2</sub> CPh-Br	Phenyl	<i>p</i> -MeO <sub>2</sub> CPh-Ph	94	14
5	2-SMe,3-Br,thiophene	3-Thienyl	2-SMe-3,3'-Bithienyl	55	15
6	2-NO <sub>2</sub> ,3-Br,thiophene	3-Thienyl	2-NO <sub>2</sub> -3,3'-Bithienyl	63	15
7	2-CHO,3-Br,thiophene	3-Thienyl	2-CHO-3,3'-Bithienyl	67	15
8	2-Br,3-I,thiophene	3-Thienyl	2-Br-3,3'-Bithienyl	57	15
9	2-CHO,3-Br,thiophene	2-CHO,3-thienyl	2,2'-Di-CHO-3,3'-bithienyl	70	16
10	Br-pyridyl	Thienyl	Thienylpyridines <sup>b</sup>	57-74	17
11	5-Br-pyrimidine	3-Thienyl	5-(3-Thienyl)pyrimidine	72	28
12	5-Br-Pyrimidine	3-Selenienyl	5-(3-Selenienyl)pyrimidine	57	28
13	3-Br-thiophene	5-Pyrimidyl	5-(3-Thienyl)pyrimidine	69	28
14	2-NO <sub>2</sub> Ph-Br	2-CHO,3-furan	3-(2'-NO <sub>2</sub> Ph)-2-CHO-furan	85	27
15	4-FPh-Br	5-Indole	5-(4'-F-Ph)indole	75	29
16	2-Cl-pyrimidine	5-Indole	5-(2-Pyrimidyl)indole	52	29
17	2-Br-furan	5-Indole	5-(2-Furyl)indole	82	29
18	2-Br-thiazole	5-Indole	5-(2-Thiazolyl)indole	68	29
19	3-Br-quinoline	Phenyl	3-Phenylquinoline	93	30
20	Br-ph	<i>o</i> - <i>tert</i> -butylsulfonylPh	<i>o</i> - <i>tert</i> -Butylsulfonyl-Ph-Ph	78	31
21	1-CN,2-F,4-Br-Ph	<i>p</i> -MeO-phenyl	4-MeO,4'-CN,3'-F-Ph-Ph	88	32
22	2-MeO <sub>2</sub> C,3-NH <sub>2</sub> ,6-Br-pyrazine	Phenyl	2-MeO <sub>2</sub> C,3-NH <sub>2</sub> ,6-phenyl pyrazine	60	21
23	<i>p</i> -IPh-OH	Phenyl	<i>p</i> -HO-Ph-Ph	70-95	19,20
24	<i>p</i> -BrPhCH <sub>2</sub> COOH	<i>p</i> -Me-Ph	<i>p</i> -HO <sub>2</sub> CCH <sub>2</sub> - <i>p</i> '-Me-Ph-Ph	71	22
25	2-Cl,3-NO <sub>2</sub> -pyridine	4-Pyridyl	2-(4-Pyridyl)-3-NO <sub>2</sub> -pyridine	75	18
26	1,3,5-tri-Br-Ph	Phenyl	3,5-Di-Br-Ph-Ph	67	33

<sup>a</sup> GLC Yield. <sup>b</sup> All six isomeric thienylpyridines.

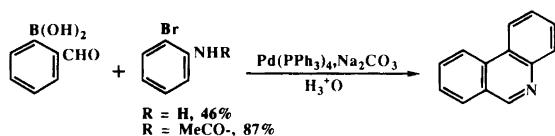
In contrast with the cross-coupling reactions of tin or zinc reagents which do not require the presence of base, the boronic acid coupling reaction does require the base. The best results are achieved with the use of a relatively weak base. Although sodium carbonate is a most frequently used, other bases are also effective. For instance, sodium hydrogencarbonate,<sup>16,23</sup> triethylamine<sup>21,24</sup> and thallium hydroxide<sup>25,26</sup> have been applied for particular purposes. By using triethylamine as the base and DMF as the solvent, Thompson and co-workers<sup>21</sup> first reported the use of a non-aqueous system consisting of triethylamine in DMF for boronic acid coupling. This non-aqueous system has proved to be suitable for the synthesis of furoquinoline.<sup>27</sup>

As mentioned in the introduction, the cross-coupling of areneboronic acids with aryl halides is ideal for use in the synthesis of unsymmetrical and functionalized biaryls which are very useful intermediates for condensed ring systems. The synthesis of some functionalized unsymmetrical biaryls will be described in a separate chapter of condensed ring systems, because of the interest in such compounds as important intermediates in the total synthesis of tricyclic and polycyclic ring systems.

#### 4. Synthesis of condensed ring systems

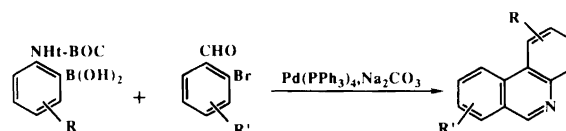
One of the main methods of synthesizing tricyclic aromatics is the cyclization of *ortho*-monofunctional or *ortho*, *ortho'*-difunctional biaryls. Accordingly, the development of versatile synthesis for functionalized biaryls provides a convenient route for the construction of tricyclic aromatics. Since the cross-coupling of areneboronic acid with aryl halide tolerates almost all kinds of functionality on either coupling partner, suitably substituted areneboronic acid and aryl halide partners can be chosen so that the biaryl formed in the coupling process will undergo spontaneous ring closure to tricyclic or polycyclic aromatic compounds. Thus a one-pot construction of condensed ring systems can be effected.

**4.1. Phenanthridines.** In 1986, Gronowitz and his co-workers<sup>5,34</sup> first reported that the palladium-catalyzed cross-coupling reaction of areneboronic acids with aryl bromides could be used in the one-pot construction of various tricyclic heteroaromatics. For example, phenanthridine could be generated in one pot and in a good yield from readily available *o*-formylbenzeneboronic acid and *o*-bromoaniline (Scheme 8). Mechanistically, the aryl halide acts as an electrophile in the oxidative addition step in the catalytic cycle, therefore, the coupling of *o*-formylbenzeneboronic acid with 2-acetamidobromobenzene gave a higher yield than with 2-bromoaniline, as illustrated in Scheme 8.



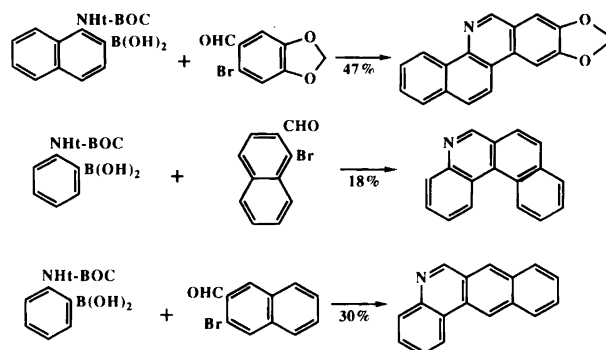
Scheme 8.

Alternatively, phenanthridine was constructed by this cross-coupling reaction in a reverse manner reported by Siddiqui and Snieckus<sup>35</sup> (Scheme 9), that is, the benzeneboronic acid bearing an *o*-amino precursor instead of an *o*-formyl group was coupled with *o*-formylbromobenzene to give phenanthridine. In this methodology, the *o*-*tert*-butoxycarbonylamino benzeneboronic acid was easily obtained by an innovative connection of directed *ortho*-metallation and boronation.



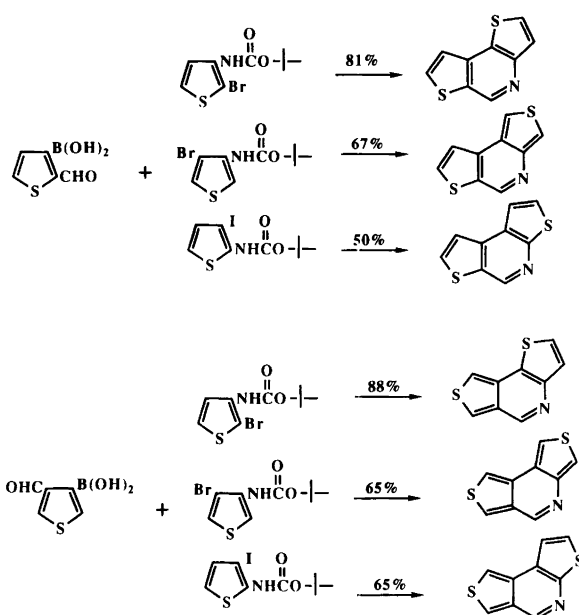
Scheme 9.

**4.2. Benzophenanthridines.** As an extension and generalization of the one-pot construction of the phenanthridine skeleton, several benzophenanthridines were prepared<sup>35,36</sup> (Scheme 10) by the method mentioned above. These preparations demonstrated the versatility of this method for the preparation of diverse benzophenanthridines. Previously tedious and inefficient classical methods were required for the preparation of these azo aromatics.



Scheme 10.

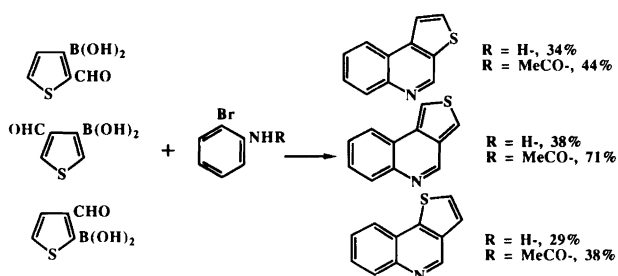
**4.3. Dithieno[b,d]pyridine.** There are nine structurally possible isomers of angular dithienopyridines. Three of them have been previously prepared via the Curtius rearrangement of dithienylcarbonyl azide to give the corresponding dithienopyridones, which were then transformed into the parent dithienopyridines by the reduction with  $\text{LiAlH}_4\text{-AlCl}_3$ .<sup>37</sup> By using the boronic coupling method, six of them were obtained in good to excellent yields in one-pot processes<sup>38</sup> (Scheme 11). In these preparations, *o*-halothiényl carbamates were chosen as the halide coupling partners, since the corresponding *o*-bromoaminothiophenes were unknown and simple aminothiophenes are known to be very unstable. The halothiényl carbamates were easily obtained by the reaction of the corresponding carboxylic acid with diphenylphosphorazidate and *tert*-butyl alcohol in the presence of triethylamine.



Scheme 11.

Attempts to couple 3-formyl-2-thiopheneboronic acid with the three carbamates required to prepare the three missing isomers failed, owing to the rapid deboronation of 3-formyl-2-thiopheneboronic acid. However, by using the corresponding organotin reagent as the organometallic coupling partner, the three missing isomers could be obtained in modest yields.<sup>39,40</sup>

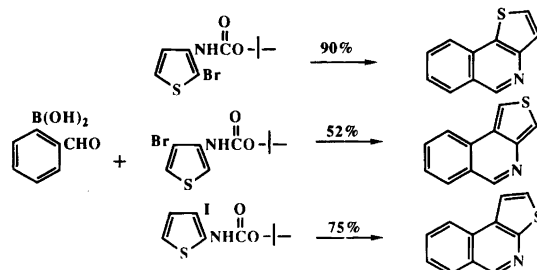
**4.4. Thieno[*c*]quinolines.** Although a great deal of work has already gone into the making derivatives of thieno[*c*]quinolines because of their usefulness as antipyretic, analgesic and antiinflammatory agents, the three parent isomers of thieno[*c*]quinolines were, until recently, unknown. The cross-coupling of three isomeric *o*-formylthiophene boronic acids with 2-bromoaniline or 2-bromoacetanilide led to the first synthesis of these three parent compounds in modest yields<sup>5</sup> (Scheme 12).



Scheme 12.

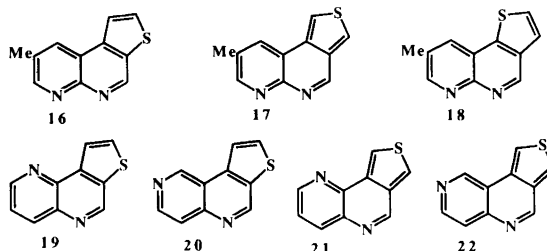
**4.5. Thieno[*c*]isoquinolines.** Similarly, all three possible isomers of thieno[*c*]isoquinoline could be prepared by this one-pot construction of angular tricyclic heteroaromatics<sup>23</sup> (Scheme 13). Previous literature methods for the construction of the thieno[*c*]isoquinoline skeleton were based on the condensation of

functionalized isoquinolines with  $\alpha$ -bromo keto compounds. The disadvantage of these methods is that the functionalized isoquinolines are not available and require several steps to prepare.



Scheme 13.

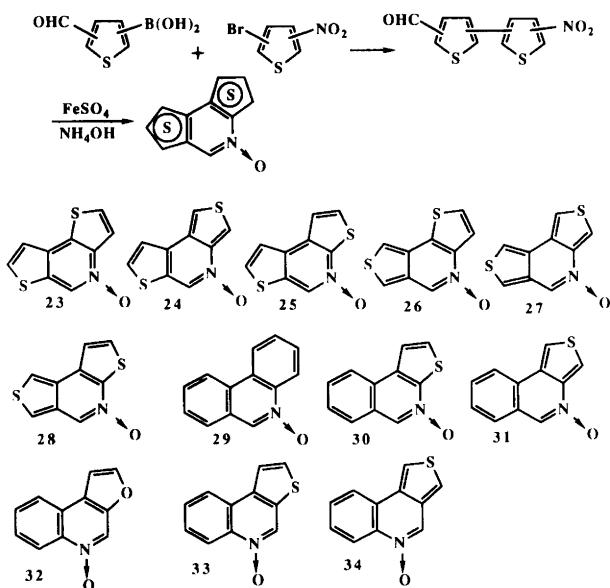
**4.6. Thieno[*c*]naphthyridines.** An extension and generalization of this versatile one-pot construction of nitrogen-containing angular tricyclic aromatics led to the preparation of diverse thieno[*c*]naphthyridines (compounds **16–17**,<sup>5</sup> **19–22**<sup>41</sup>) in modest to good yields (Scheme 14). The chemistry of thieno-fused naphthyridines is almost completely unknown; this simple preparation opens the possibility for extensive studies of these interesting systems.



Scheme 14.

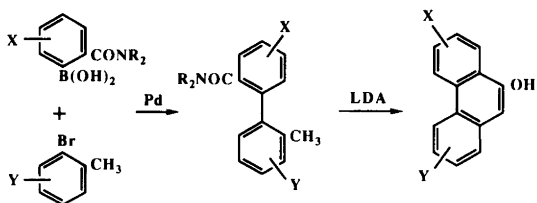
In sections 4.1 to 4.6, one-pot constructions of phenanthridine and its analogs are described. In the following sections (4.7–4.9), the preparation of functionalized biaryls wherein the functional groups of which are modified in a stepwise manner will be summarized.

**4.7. Phenanthridine *N*-oxide and its analogs.** In 1984, Gronowitz's research group synthesized six *o,o'*-formylnitrobithienyls,<sup>42</sup> in the hope that the reduction of the nitro group to an amino group would simultaneously lead to dehydration between the formyl and the amino groups, and therefore lead to ring-closure to the corresponding dithienopyridines. However, the reduction of *o,o'*-formylnitrobithienyls with ferrous sulfate and aqueous ammonia gave dithienopyridine *N*-oxides (compounds **23–28**),<sup>42</sup> instead of the parent compounds. Apparently, the closure of the hydroxylamine intermediates to form aromatic rings occurred faster than the further reduction to the amines. Additional tricyclic *N*-oxides (compounds **29–31**, **33**, **34**,<sup>43</sup> compound **32**<sup>27</sup>) were similarly prepared, demonstrating the generality of this synthesis.



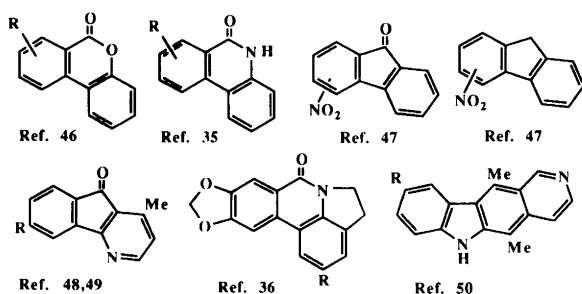
Scheme 15.

**4.8. Phenanthrenes.** A general and efficient method for the synthesis of phenanthrenes has been described<sup>44</sup> (Scheme 16) based on the ring closure of *o,o'*-dialkylcarbamoyl biphenyls prepared by the benzeneboronic acid coupling reaction. A variety of substituted phenanthrene derivatives have been prepared using this method. Furthermore, the presence of a 9-hydroxy group allows further modification and transformation of the derived phenanthrenes. For example, the 9-hydroxy group can be readily transformed into a triflate which is a good leaving group in various palladium-catalyzed cross-coupling reactions.<sup>1,45</sup>



Scheme 16.

**4.9. Other ring systems.** A number of additional tricyclic ring systems have been prepared by methodology based



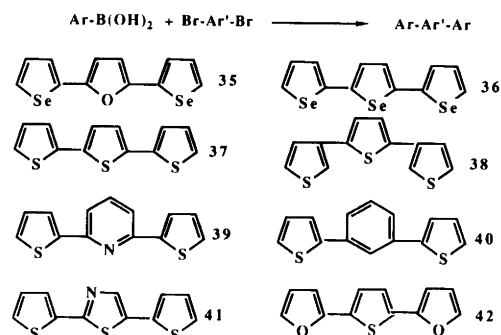
Scheme 17.

on the ring closure of functionalized biaryls derived from cross-coupling reactions of areneboronic acids with aryl halides. Scheme 17 provides representative structures of these condensed ring systems, together with the literature citations.

## 5. Multiple aryl coupling

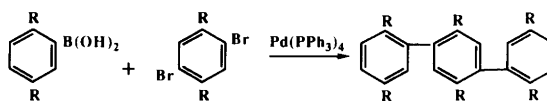
Teraryl and polyaryl compounds have provided important targets for chemists for many years. This interest stems from the expectation that such compounds may show biological properties such as photo-enhanced activity against fungi, nematodes, insect larvae, algae and human erythrocytes. In addition, teraryls are also of interest as monomers for the preparation of conducting polymers. Teraryls have been successfully used as key intermediates in the synthesis of macromolecules as ion-selective chromogenic ionophores.

**5.1. One-pot multiple coupling.** A number of teraryl and polyaryls have been prepared in one-pot via the palladium-catalyzed cross-coupling reactions of areneboronic acid with dihaloarenes. Recently, Gronowitz and his co-workers reported that diversely electron-rich mixed heteroteraryls could be readily prepared by the reaction of 2 equivalents of areneboronic acid with dibromoarenes (compounds **35**, **36**,<sup>51</sup> **37–42**<sup>52</sup>) (Scheme 18). Such electron-rich heteroteraryls could be polymerized to give candidates for conducting organic polymers.



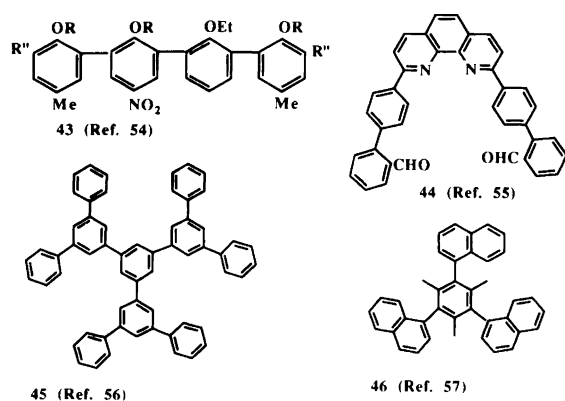
Scheme 18.

Similarly, two-fold aryl-aryl coupling between *o,p*-dialkylbenzeneboronic acid could be accomplished with 1,4-dibromobenzene to give the desired teraryl in one pot<sup>53</sup> (Scheme 19). This synthesis has proved more effective than the coupling of monobromo Grignard reagents with dibromobenzene derivatives, for which HPLC analysis indicated an oligomeric mixture. This alkylated terphenyl could be easily polymerized to give soluble poly(*para*-phenylene)s.



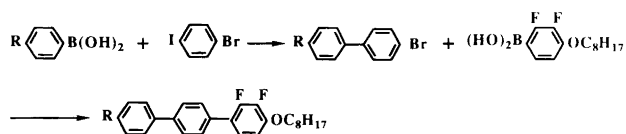
Scheme 19.

Together with the corresponding literature citations, the structures of several very interesting polyaryls synthesized by this methodology are listed in Scheme 20. Compound **43** is a key intermediate for the total synthesis of ion-selective chromogenic ionophores useful for colorimetric assays of body and other fluids.<sup>54</sup> The formyl groups in compound **44** were converted into bromomethyl groups, which were then reacted with an aza-crown ether to form a macrobicyclic hard and soft ligand.<sup>55</sup>



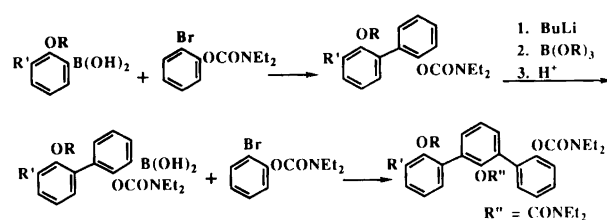
Scheme 20.

**5.2. An iterative coupling.** An iterative cross-coupling of areneboronic acid with dihaloarenes will give the corresponding teraryl or polyaryl. The advantage of this iterative tactic over the one-pot method is that various unsymmetrical teraryls could be obtained. Because an iodo group on an arene ring is more reactive than a bromo group in this palladium-catalyzed reaction, an iterative cross-coupling of *p*-bromo(iodo)benzene with different benzeneboronic acids could give unsymmetrical terphenyls. In a search for better low-melting liquid crystals, Gray and his co-workers reported the synthesis of a number of teraryls via the strategy shown in Scheme 21.<sup>58,59</sup>



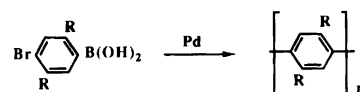
Scheme 21.

In 1987, Snieckus and his co-workers<sup>60,61</sup> developed an iterative *ortho* metallation transition-metal-catalyzed cross-coupling strategy to construct terphenyls and quaterphenyls. As shown in Scheme 22, the areneboronic acid was first coupled with the bromobenzene bearing an *ortho*-directing group to give the intermediate, which was then *ortho*-metallated and boronated to generate the arylboronic acid intermediate. In turn the boronic acid was coupled with the second aryl halide to give the teraryls. When the starting areneboronic acid is a biphenyl boronic acid, the final product is a quaterphenyl.



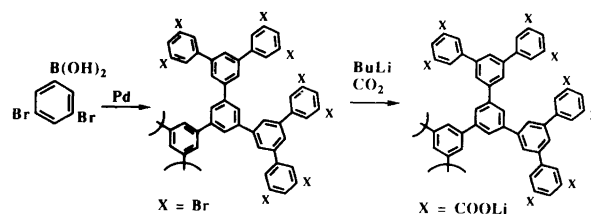
Scheme 22.

**5.3. Polymerization.** Recently, Reahn *et al.*<sup>62,63</sup> reported a palladium-catalyzed polymerization of benzene derivatives bearing both bromo and boronic acid functional groups. This polymerization was used for the synthesis of linear alkyl-substituted poly(*para*-phenylene) (PPP) derivatives and the degree of polymerization achieved ranged between 30 and 50 (Scheme 23).



Scheme 23.

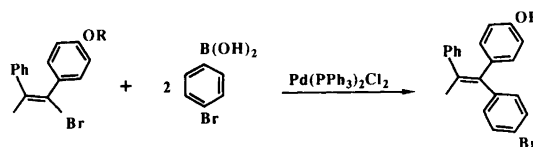
Kim and Webster<sup>64</sup> reported that 3,5-dibromobenzenboronic acid could be polymerized to give the branched polyphenylene. The residue bromo groups in the polyphenylene were then transformed into water-soluble lithium carboxylates via the metal-halogen exchange reaction and followed by the reaction with carbon dioxide (Scheme 24).



Scheme 24.

## 6. Aryl-vinyl coupling

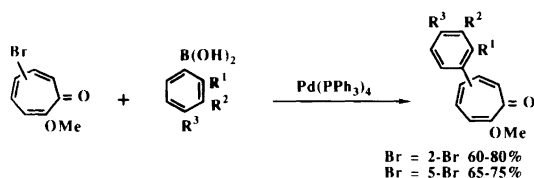
Highly stereoselective arylation of vinyl halides via the cross-coupling reaction of an areneboronic acid with vinyl halides has been reported. McCague *et al.*<sup>65</sup> showed that tomaxifen analogs could be prepared by this aryl vinyl coupling method. The use of areneboronic acid as the organometallic reagent partner has an advantage over other organometallic reagents (Zn, Mg, Sn) in terms of regioselectivity (Scheme 25). It is interesting to



Scheme 25.

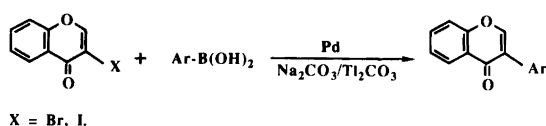
note that the possible intermolecular self-coupling of *p*-bromobenzeneboronic acid has not proved to be a significant by-reaction in this case, since the desired cross-coupling product was obtained in a separated yield of 56%.

In a search for a better synthetic approach to tropone derivatives, which may be useful as immunomodulators, Suri and his co-workers<sup>66,67</sup> developed an efficient synthesis of various arylated tropone derivatives via the aryl-vinyl coupling method (Scheme 26).



Scheme 26.

Owing to their wide distribution in nature and their physiological activities, isoflavonoids have attracted a great deal of effort towards their synthesis. A new synthesis of isoflavone derivatives by means of this boronic acid coupling reaction was reported by Suzuki *et al.*<sup>68,69</sup> (Scheme 27). They found that the aqueous conditions are not suitable for benzeneboronic acids with electron-withdrawing substituents which accelerate the rate of protonolysis, or those with two *ortho* substituents which retard the transmetalation step in the mechanism of the cross-coupling reaction. For these boronic acids, an alternative procedure, using the esters of boronic acids and thallium carbonate as the base, gave very high yields of the desired products.

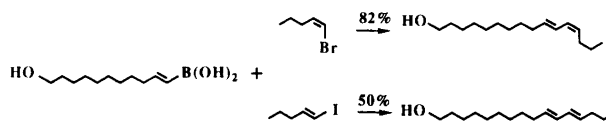


Scheme 27.

## 7. Vinyl-vinyl coupling

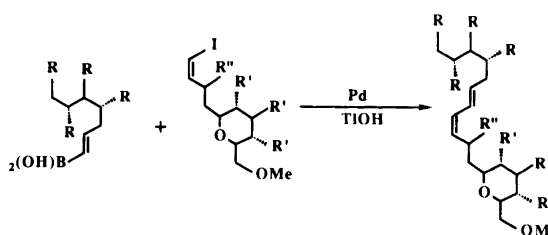
Although numerous methods for the preparation of conjugated dienes utilizing organoaluminum, borane, copper and magnesium reagents have appeared, the search for more efficient and stereospecific approaches is still a very active field in synthetic organic chemistry. In 1983, Suginome and Suzuki<sup>6</sup> reported that various conjugated dienes could be prepared by the palladium-catalyzed cross-coupling reaction of alkeneboronic acids and vinyl halides. Owing to the ready availability, stability and the compatibility of various functionalities on either coupling partner, this alkeneboronic acid coupling reaction provides a new promising methodology for the synthesis of various conjugated dienes. A well-known pheromone bombykol and its geometrical isomer have been prepared

by this method using sodium ethoxide as the base<sup>6</sup> (Scheme 28).



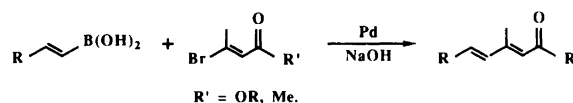
Scheme 28.

Kishi *et al.*<sup>25</sup> reported that the reaction rate of this coupling could be greatly accelerated by using TlOH or  $\text{Ag}_2\text{O}$  as the base, both of which form water insoluble salts instead of NaX. Under the TlOH conditions, the coupling could be achieved even at 0°C, allowing its application to substrates with fragile functional groups as well as large molecular weights. A number of biologically interesting and structurally complicated diene compounds has been synthesized based on the cross-coupling of vinylboronic acids and halides using TlOH as the base.<sup>25,26,70</sup> For instance, the complete carbon backbone of the marine natural product palytoxin was constructed by this method in the excellent yield of 94% (Scheme 29).



Scheme 29.

A stereospecific synthesis of dienic esters and ketones has been also developed based on this vinyl-vinyl coupling in the presence of Pd catalyst and sodium hydroxide.<sup>71</sup> As in aryl-aryl coupling, this vinyl-vinyl cross-coupling reaction of alkeneboronic acids tolerates ester and keto groups, as shown in Scheme 30.

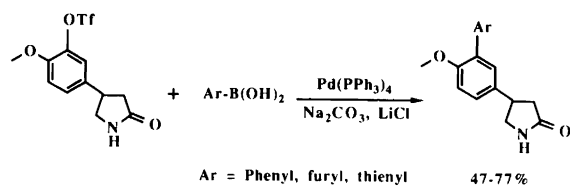


Scheme 30.

## 8. Triflate as electrophile

Recently, Huth<sup>72</sup> and Snieckus<sup>45</sup> found that areneboronic acids could be coupled with triflates catalyzed by palladium complexes in the presence of base. Thus, various analogs of the clinical antidepressant Risperidone have been synthesized by this method (Scheme 31). Yields could be increased by the addition of two equivalents of lithium chloride.<sup>72</sup> On the other hand, a number of biaryls have been obtained by this coupling in good to excellent yield without the addition of lithium chloride.<sup>45</sup> This is a remarkable contrast with organotin-triflate





Scheme 31.

coupling reactions which require the addition of lithium chloride to the reaction mixture for satisfactory yields to be obtained.

Snieckus *et al.*<sup>45</sup> also reported that the relative reactivities of aryl halides and triflate in the coupling reaction are in the order of I, Br > OTf. The discovery that areneboronic acids can be coupled with aryl triflates should be very valuable, since aryl triflates can be easily obtained from phenols.

## 9. Conclusions

Organoboronic acids provide versatile, conveniently prepared reagents for the palladium(0)-catalyzed cross-coupling of aryl and vinyl halides and triflates. The compatibility of organoboronic acids with a wide variety of functional groups allows them to be coupled with many electrophiles that are not compatible with the organometallic reagents commonly employed in cross-coupling reactions. This property has been exploited for the one-pot as well as the stepwise generation of polycyclic ring systems. It also permits the preparation of functionalized polyaryl and dienyl compounds. These reagents also possess the advantage of shelf-life stability and comparatively low toxicity.

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