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# Aryl-aryl cross-couplings that avoid the preparation of haloaromatics

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*Advances in the development of cross-coupling protocols that avoid haloaromatics are reviewed. Most of the reports that are discussed appeared in the literature within the past 2 years and describe either alternatives to halogenated electrophiles or halogen-free preparations of the organometallic partners. However, while this review is not limited to cross-couplings that are entirely free of haloaromatics, coverage of the topic is largely restricted to reactions affording new aryl-aryl, aryl-heteroaryl and heteroaryl-heteroaryl carbon-carbon bonds during the cross-coupling event.*

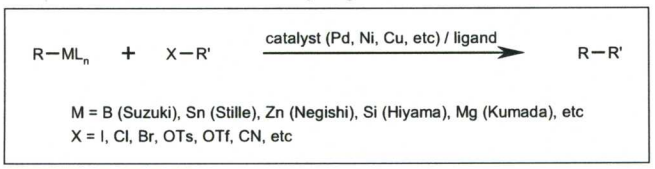
***Keywords*** Arenes, catalysis, C-H activation, cross-couplings, haloaromatics, heteroarenes, *ortho*-metallation

## Introduction

Transition metal-catalyzed cross-coupling reactions are a mainstay of organic synthesis. Although the scope of such reactions has greatly expanded over the last several years, cross-couplings traditionally involve the union of an $sp^2$ organometallic with an $sp^2$ electrophile to form an $sp^2$-$sp^2$ carbon-carbon bond via σ-bond construction (Scheme 1) [1]. These reactions tend to be selective, functional group tolerant and scalable. Owing in part to such features, cross-couplings have been embraced by the pharmaceutical, agrochemical and materials industries. Indeed, the Suzuki variant [2] of these cross-coupling reactions is the third most common C-C bond forming reaction that is used in the preparation of drug candidates [3].

Haloaromatics (Ar-X, where X = I, Br or Cl) are used as electrophiles in cross-coupling reactions with aryl organometallics, where the metal includes B, Sn, Zn, Si and In. These aryl organometallics are often derived from the corresponding haloaromatics. This reliance on haloaromatics in the preparation of both electrophilic and nucleophilic cross-coupling partners can be problematic. The preparation of certain haloaromatics can be laborious, particularly when substitution patterns do not conform to the rules of electrophilic aromatic substitution chemistry. Even when the associated chemistry is straightforward, the environmental and/or regulatory factors associated with haloaromatics must still be managed [4]. Because of such drawbacks, chemists have sought to invent cross-coupling protocols that avoid haloaromatics.

**Scheme 1. Traditional cross-coupling reactions.**



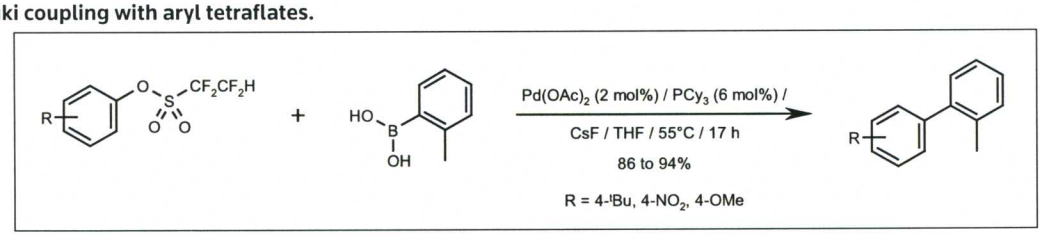

## Alternatives to halogenated electrophiles

### *Triflates*

Aryl triflates have long been recognized as alternatives to aryl halides in cross-coupling reactions [5]. These compounds can be readily prepared from the corresponding phenols and exhibit reactivity comparable to those of aryl chlorides and bromides. The labile nature of trifluoromethanesulfonates has led to the introduction of more robust fluoroalkanesulfonates, including nonaflates [6] and, more recently, tetraflates (Scheme 2) [7].

New and expanded applications of fluoroalkanesulfonates continue to emerge, including new Suzuki [8-13], Stille [14] and Hiyama [15,16] coupling examples. Lastly,

**Scheme 2. Suzuki coupling with aryl tetraflates.**




**Cy** cyclohexyl, **THF** tetrahydrofuran.

methodology for the arylation of heterocycles based on C-H activation, originally developed for use with aryl halides [17] (*vide infra*), has recently been extended to aryl triflates [18].

## *Tosylates*

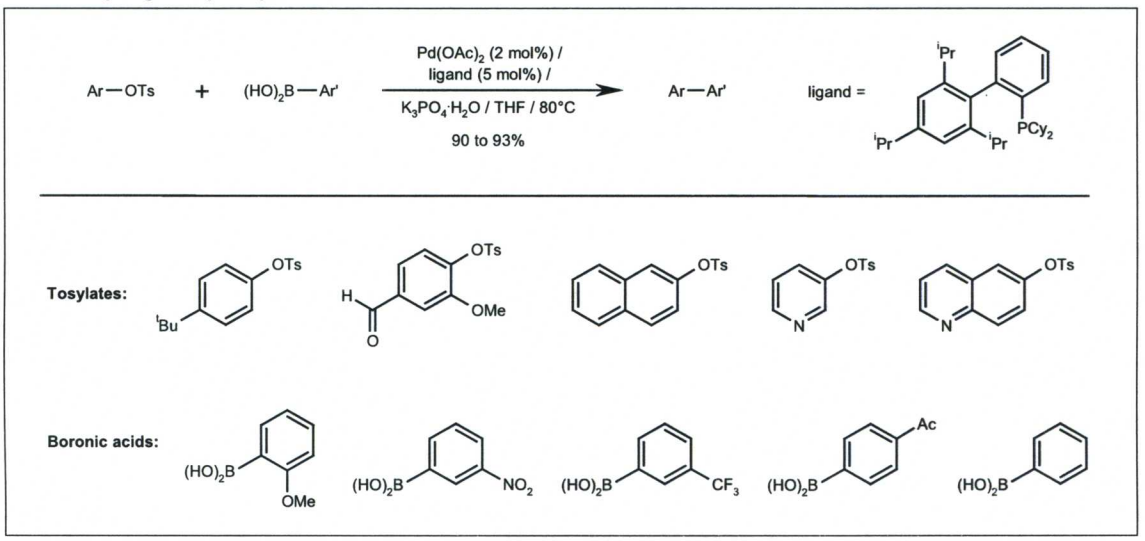
Aryl tosylates are attractive alternatives to both aryl halides and aryl triflates: they are relatively cheap, easy to prepare, thermally stable and less prone to hydrolysis than the analogous triflates [19]. They are also less reactive than aromatic chlorides. Despite the lower reactivity of aryl tosylates, Buchwald and co-workers succeeded in cross-coupling these compounds with arylboronic acids (Scheme 3) [20].

Tosylates are increasingly being used in new cross-coupling methods [21]. For example, when used in combination with Ru-catalyzed aromatic C-H activation (*vide infra*), aryl tosylates afforded monoarylated products that were unattainable from the related aryl halides (Scheme 4) [22,23]. In addition to tosylates, aryl mesylates can also be used in aryl-aryl cross-couplings [24].

## *Methoxy groups*

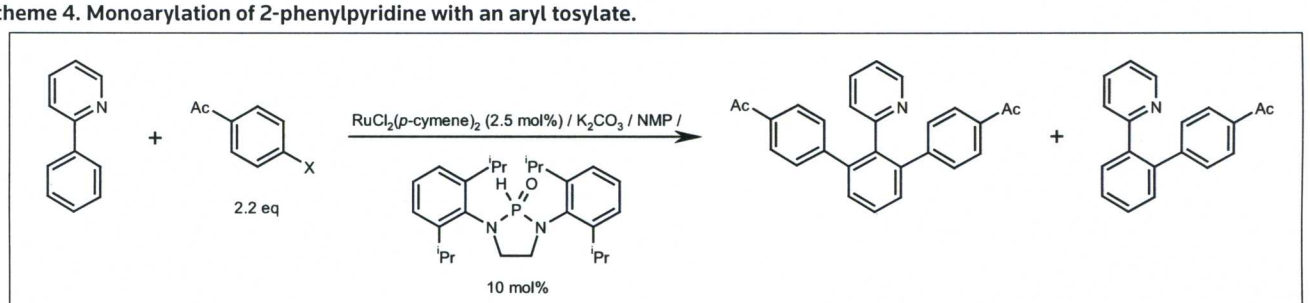
Aryl methyl ethers were first used as electrophiles in Kumada cross-couplings [25,26]. For Suzuki reactions, oxidative addition is routinely facilitated by a nearby directing group [27]; however, Tobisu *et al* have reported a nickel-catalyzed Suzuki coupling that involves

**Scheme 3. Suzuki coupling of aryl tosylates.**




**Cy** cyclohexyl, **THF** tetrahydrofuran.

**Scheme 4. Monoarylation of 2-phenylpyridine with an aryl tosylate.**




| X | T (°C) | t (h) | di (%) | mono (%) |
|---|---|---|---|---|
| Cl | 105 | 24 | 91 | 7 |
| Cl | 120 | 1 | 56 | 38 |
| OTs | 120 | 24 | < 1 | 78 |

**NMP** *N*-methylpyrrolidinone.

non-directed oxidative addition into an aryl C-OMe bond (Scheme 5) [28]. Currently, this methodology only appears to work with substrates possessing two or more fused aromatic rings or a conjugating substituent: these features are assumed to compensate for a presumed temporary loss of aromaticity accompanying the oxidative addition.

## Thioethers

Suzuki couplings with *S*-tolyl- (Scheme 6), *S*-Me- and α-thioacetamide-substituted heterocycles were reported by Liebeskind and Srogl [29], and Guillaumet and co-workers [30]. The sulfur-containing heterocycles were easy to prepare and were robust. Moreover, they proved to be superior to the corresponding halides.

## Cyanides

Numerous examples of Ni-catalyzed cross-coupling reactions involving aryl cyanides as the substrates for oxidative addition have been reported by Miller and co-workers [31-34]. In these reactions, the nucleophiles were always modified Grignard reagents, which were themselves prepared from halides. For additional information regarding the development of this exciting class of substrates, including mechanistic details, the reader is directed to an excellent review recently authored by Tobisu and Chatani [35].

## Aryldiazonium salts

Aryldiazonium salts have been successfully used in cross-coupling reactions, where they tend to be more reactive than the corresponding halides [36]. While the use of these substrates as coupling partners has been reviewed [37], some advances in this chemistry deserve to be highlighted. Specifically, a new generation of thiourea ligands, which were purposely developed for the cross-coupling of aryldiazonium substrates, allows reactions to proceed under aerobic conditions and at room temperature [38]. Under these conditions, cross-couplings of aryldiazoniums and arylboronic acids leave chlorides, bromides and iodides untouched (Scheme 7).

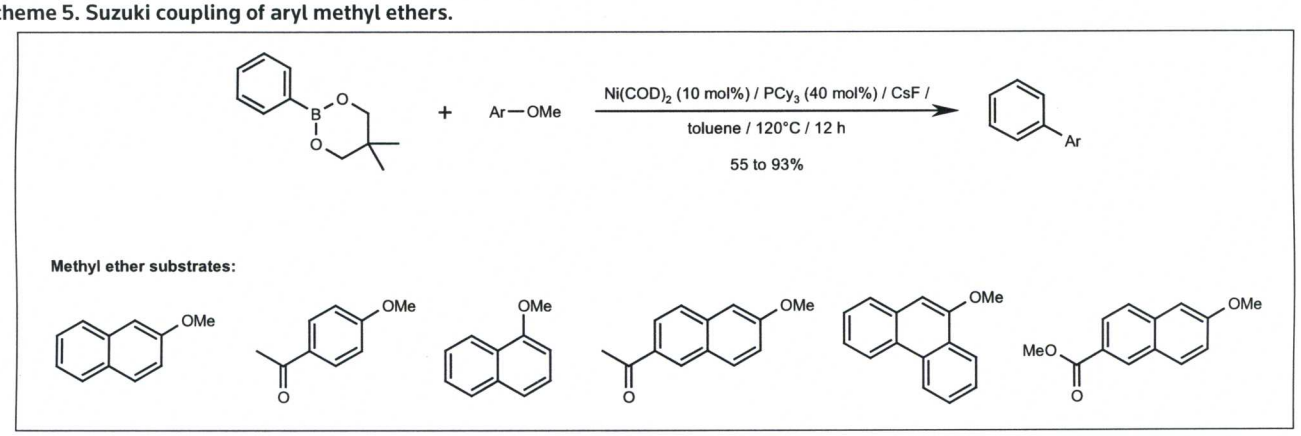
## Aryltriazenes and aryltrimethylammonium salts

Although aryldiazonium salts are attractive alternatives to haloaromatics, they are traditionally prepared under harsh conditions and are prone to decompose upon storage. To alleviate these problems, the reactions of aryltriazenes [39] and aryltrimethylammonium salts [40] have been explored. Aryltrimethylammonium salts are readily accessible from the corresponding dimethylamines and methyl trifluoromethanesulfonate. Blakey and MacMillan have effectively cross-coupled aryltrimethylammonium salts irrespective of the electron density around either cross-coupling partner (Scheme 8) [40]. Somewhat surprisingly, this chemistry has not yet been widely adopted by the synthetic community.

## Amines

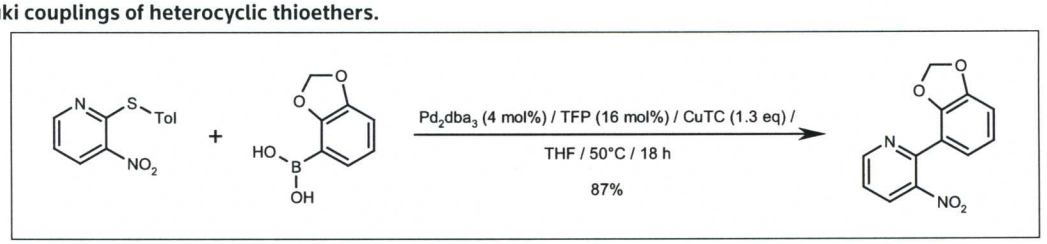
Ten years after the previous example of a transition metal oxidative addition into an aniline C-N bond was reported [41], Chatani and co-workers cross-coupled

**Scheme 5. Suzuki coupling of aryl methyl ethers.**



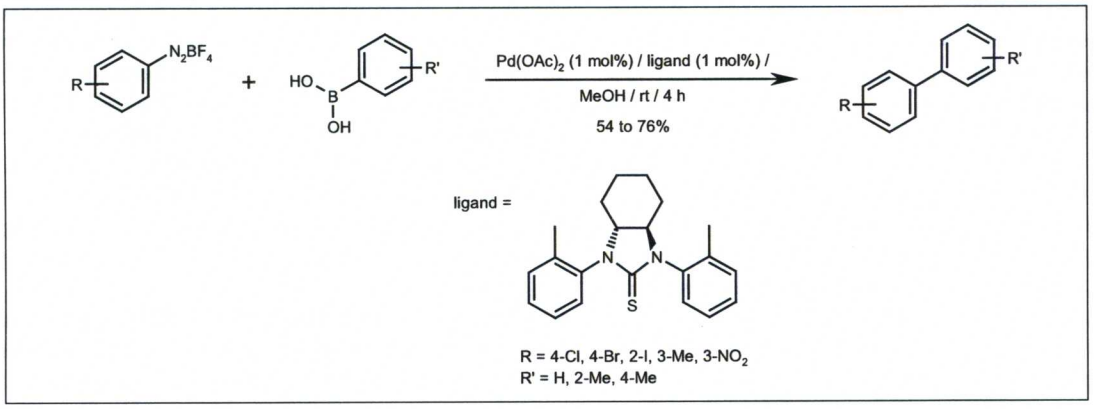

**COD** 1,5-cyclooctadiene, **Cy** cyclohexyl.

**Scheme 6. Suzuki couplings of heterocyclic thioethers.**

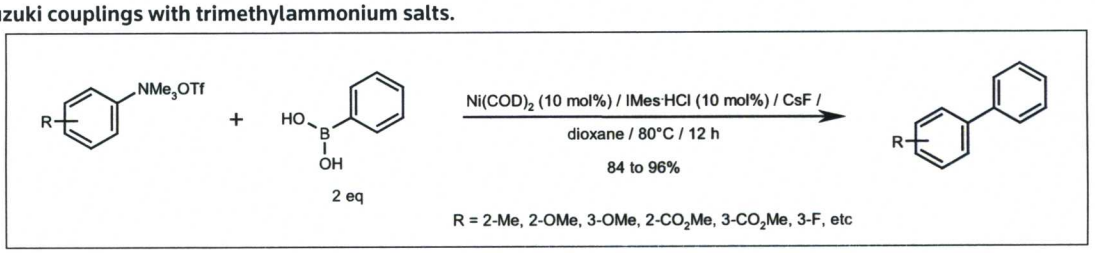



**CuTC** copper(I) thiophenecarboxylate, **dba** dibenzylideneacetone, **TFP** tri-(2-furyl)-phosphine, **Tol** tolyl, **THF** tetrahydrofuran.

**Scheme 7. Suzuki couplings of aryldiazonium salts in the presence of halosubstituents.**

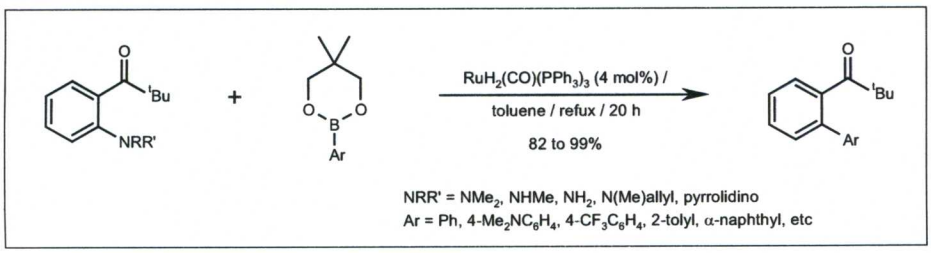



**Scheme 8. Suzuki couplings with trimethylammonium salts.**

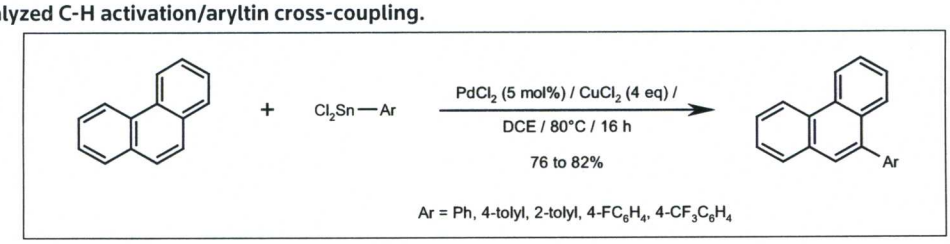



**COD** 1,5-cyclooctadiene, **IMes** 1,3-dimesitylimidazol-2-ylidene.

**Scheme 9. Directing group-assisted Suzuki coupling of aromatic amines.**




**Scheme 10. Pd-catalyzed C-H activation/aryltin cross-coupling.**




**DCE** dichloroethane.

unfunctionalized aromatic amines with arylboronates [42]. Reaction at the C-N bond is promoted by a neighboring carbonyl group. In order to avoid competitive C-H activation [43] and to achieve selective coupling at only the amino-bearing carbon, a second 1,2-substituent or increased steric bulk (eg, a $^t$Bu group) about the carbonyl is required. Incorporation of these structural restrictions enabled the reaction of a variety of electron-rich and electron-poor arylboronic esters, heteroaryls and even alkenyl- and alkylboronates to afford the cross-coupled products in excellent yields. The reactions also appeared to be independent of the exact nature of the NRR' group (Scheme 9).

## *C-H activation*

C-H activation has been used to afford intermediates that play the role of the electrophile in cross-couplings with organometallics [44]. For example, Inoue and co-workers recently reported the cross-coupling of symmetric arenes with aryltins (Scheme 10) [45].

Heteroarenes can also be arylated in this manner, but the regiocontrol of the reaction depends on the nature of the heteroaromatic [17,46]. For example, in the Suzuki coupling reported by Shi and co-workers, indoles are selectively arylated at C(2) (Scheme 11) [47].

Regioselectivity can also be achieved by the assistance of directing groups [44,48]. Among such examples [49,50], the chemistry of Shi and co-workers is particularly interesting [51]. Using an acetamide as a directing group, aryl-Pd(II) bonds can be selectively generated and reacted with boronic acids [52] or trialkoxyarylsilanes [53] in a similar manner to that reported in 2003 by Kakiuchi *et al* [43]. A valuable feature of this chemistry is its compatibility with other possible directing groups (eg, acetate, benzoate), as well as with halides. A variety of substituted acetanilides have proved to be useful in this methodology (Scheme 12). The same concept was later extended to 'two-fold' C-H activations (*vide infra*).

## Alternatives to haloaromatics as precursors to the organometallic cross-coupling partners

As previously discussed, the nucleophilic halves of many cross-coupling reactions are built from haloaromatics. As with the search for electrophilic alternatives to haloaromatics, the progress of research into avoiding haloaromatics during the synthesis of various organometallic coupling partners has been rapid.

### *Ortho-metallation*

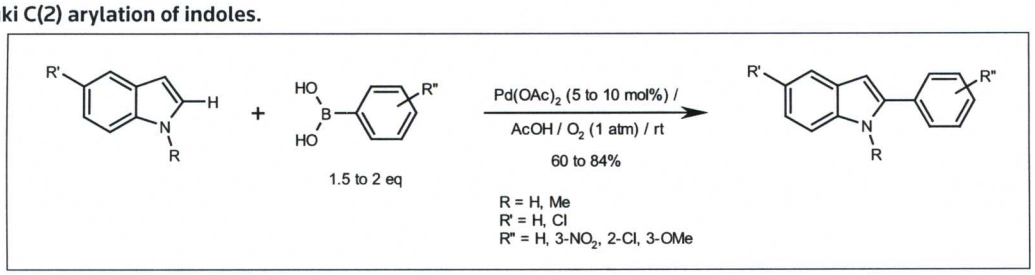
The organometallic reagents that are used in most cross-coupling protocols can be generated via transmetallation of the corresponding aryllithium or Grignard species. While these compounds are often formed from the corresponding aryl halides, the presence of correctly positioned and functionalized substituents can allow for the ready deprotonation of *ortho* C-H bonds. Such *ortho*-metallations can be facilitated by a variety of directed metallation groups, which range from amides to sulfides [54]. Contemporary versions of these reactions have been the foundation of some new cross-coupling protocols [55].

Snieckus and co-workers established the one-pot directed *ortho*-borylation Suzuki cross-coupling of pyridines bearing a diethyl amide, a diethyl carbamate, a chloride or a fluoride directing group (Scheme 13) [56]. The boronic ester that is generated undergoes Suzuki cross-coupling with a variety of aryl bromides. Similar *ortho*-borylation reactions have been reported for other pyridine derivatives [57], pyridazines [58] and pyrazoles [59]. All of the borylated products were demonstrated to be suitable coupling partners in Suzuki cross-coupling reactions.

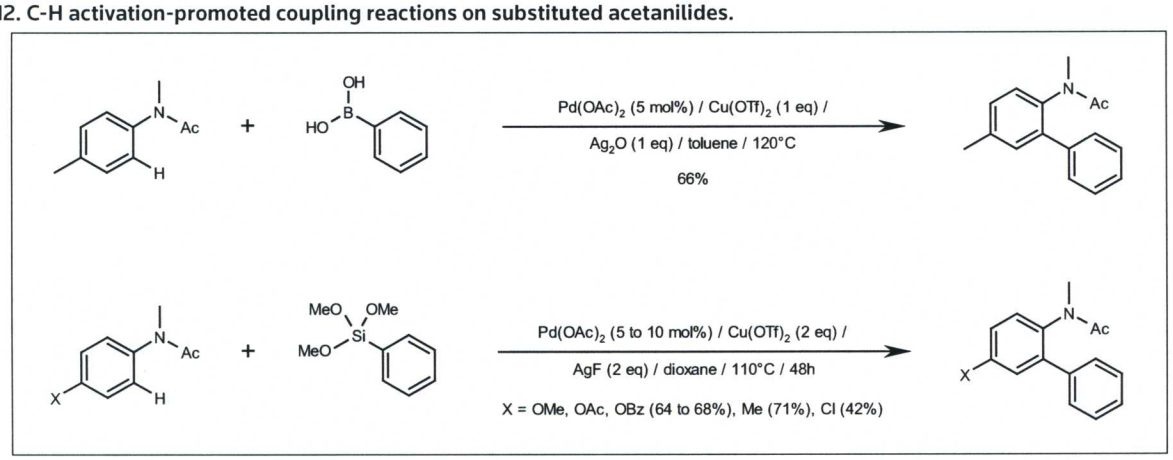
### Organozinc compounds

Directed deprotonation/zincation can generate nucleophiles that participate in Negishi cross-coupling reactions. Toward this end, Knochel and co-workers recently developed a new class of magnesium amides that are complexed with lithium chloride: (2,2,6,6-tetramethylpiperidine)$_2$Mg·2LiCl

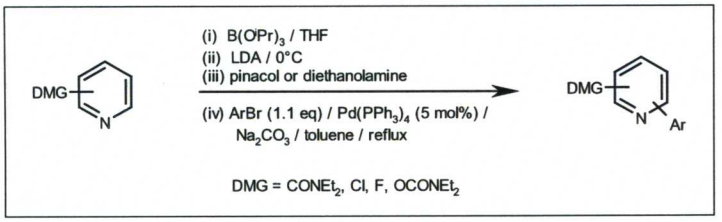
**Scheme 11. Suzuki C(2) arylation of indoles.**




**Scheme 12. C-H activation-promoted coupling reactions on substituted acetanilides.**

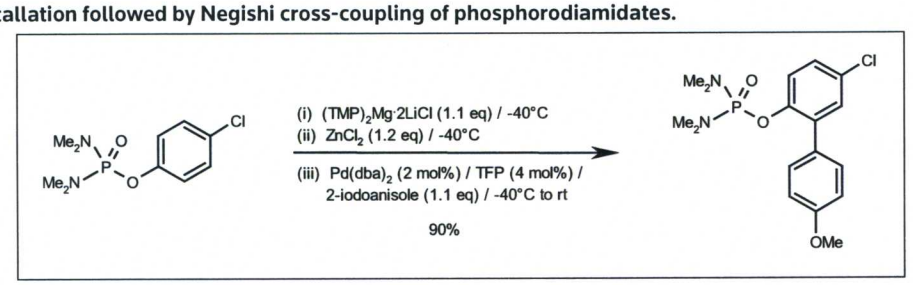


**Scheme 13. Directed *ortho*-borylation/Suzuki cross-coupling of pyridines.**



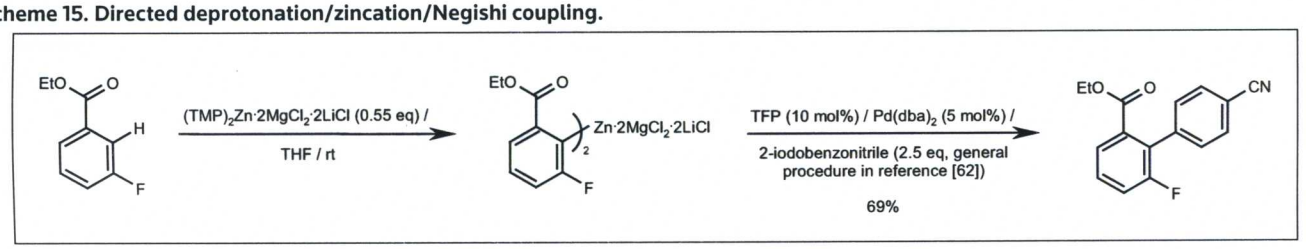

**DMG** directed metallation group, **LDA** lithium diisopropylamide, **THF** tetrahydrofuran.

**Scheme 14. *Ortho*-metallation followed by Negishi cross-coupling of phosphorodiamidates.**



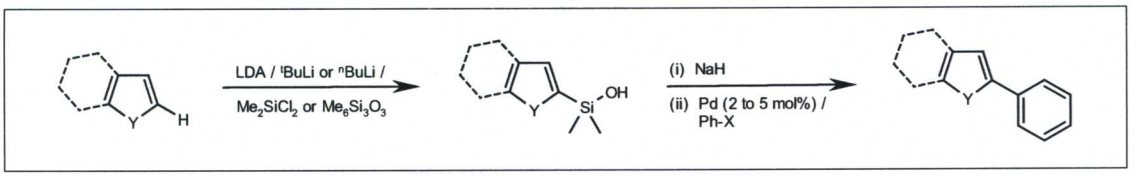

**dba** dibenzylideneacetone, **TFP** tri-(2-furyl)-phosphine, **TMP** 2,2,6,6-tetramethylpiperidine.

**Scheme 15. Directed deprotonation/zincation/Negishi coupling.**




**dba** dibenzylideneacetone, **TFP** tri-(2-furyl)-phosphine, **THF** tetrahydrofuran, **TMP** 2,2,6,6-tetramethylpiperidine.

**Scheme 16. Generation and cross-coupling of five-membered heterocyclic silanols.**




**LDA** lithium diisopropylamide.

[$(TMP)_2Mg{\cdot}2LiCl$] *ortho*-metallates benzoic esters, benzonitrile, pyridine derivatives [60] and functionalized arylphosphorodiamidates [61]. Transmetallation with $ZnCl_2$ gave the corresponding arylzinc species, which underwent Pd-catalyzed Negishi cross-couplings with aryl iodides (Scheme 14). Usefully, removal of the arylphosphoramide group leaves 1,3- or 1,4-substituted biaryls.

Wunderlich and Knochel have also incorporated zinc into the lithium magnesiate: $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ can selectively deprotonate a variety of substituted arenes and heteroarenes [62]. Aldehydes, nitro groups, esters, fluorides, chlorides and bromides are tolerant of the reaction conditions. The resulting organozinc species are able to participate in Pd-catalyzed Negishi couplings (Scheme 15).

In a similar approach, Mongin and co-workers used a mixture of $ZnCl_2{\cdot}$tetramethylethylenediamine (TMEDA) and LiTMP to functionalize benzofuran and benzothiophene [63]. As with the Knochel chemistry, the zinc species that was formed *in situ* could be directly cross-coupled.

## Arylsilanes

Furans, thiophenes, *N*-protected pyrroles and indoles can all be deprotonated at their 2-position. Quenching the anions with $Me_2SiCl_2$ or $Me_6Si_3O_3$ gives the silanols in moderate to

good yields (Scheme 16) [64]. Deprotonation of the silanols with NaH quantitatively generates the silanolates. These silanolates are relatively easy to handle, can be stored for several weeks at room temperature and cross-couple with aryl halides under fluoride-free conditions.

## Arylstannanes

Thiazoles also undergo ready deprotonation at the 2-position. Recently, Zambon *et al* demonstrated that they could affect a metallotropic rearrangement that shifts the metal to the 5-position by tuning the reaction conditions [65]. Trapping of the anion afforded 5-trimethylsilylthiazole or 5-trimethylstannylthiazole, two compounds that are traditionally synthesized via metal-halogen exchange. Stille coupling of 5-trimethylstannylthiazole proceeded in 67% yield (Scheme 17).

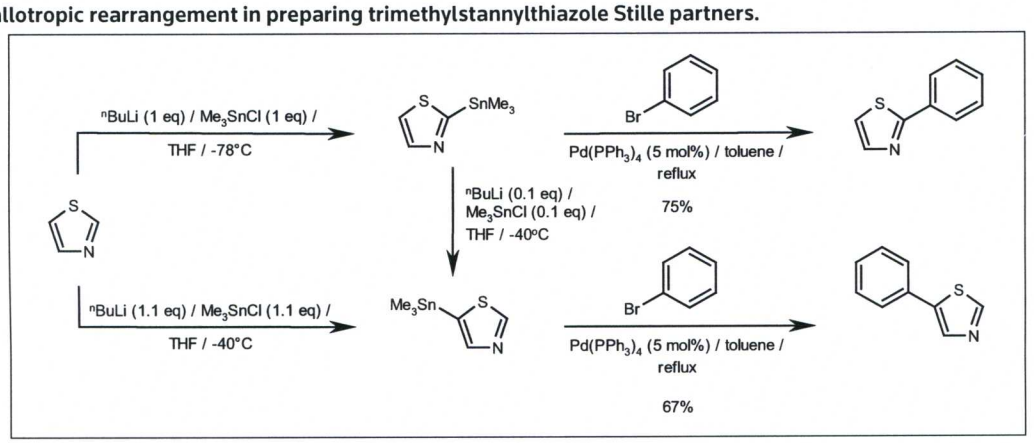
## Arylindium compounds

Organoindium compounds are new and highly atom-economical cross-coupling partners: Sarandeses and co-workers observed all three groups on the indium transfer during cross-coupling reactions [66]. To date, $aryl_3In$ compounds have mostly been derived from aryl halides following conversion to the Grignard or the lithium species. However, a procedure was described in 2007 where the *ortho*-lithiations of anisole, phenylcarbamate, fluorobenzene, *N*-Boc indole and 2-methoxypyridine were followed by the *in situ* generation of the triarylindiums. These compounds could then be cross-coupled with a range of electrophiles using palladium catalysis (Scheme 18) [67].

## *Generation from triflates*

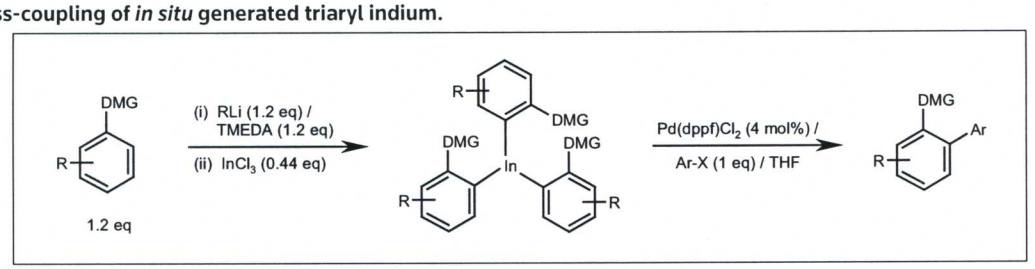
Just as triflates can act like haloaromatics in the C-C bond-forming reactions that were reviewed previously, these same compounds can substitute for haloaromatics in the transition metal-mediated routes to various compounds including organosilanes [68], stannanes [69] and organoboranes [70]. Included among the more recent advances in the use of triflates is the rhodium-catalyzed generation of arylsiloxanes that was developed by Murata *et al* (Scheme 19) [71].

**Scheme 17. Metallotropic rearrangement in preparing trimethylstannylthiazole Stille partners.**



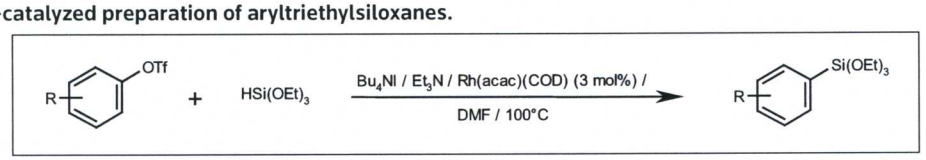

**THF** tetrahydrofuran.

**Scheme 18. Cross-coupling of *in situ* generated triaryl indium.**




**dppf** 1,1'-bis(diphenylphosphino)ferrocene, **DMG** directed metallation group, **THF** tetrahydrofuran, **TMEDA** tetramethylethylenediamine.

**Scheme 19. Rhodium-catalyzed preparation of aryltriethylsiloxanes.**




**acac** acetylacetone, **COD** 1,5-cyclooctadiene, **DMF** *N*,*N*-dimethylformamide.

## *C-H activation*

Synthetic chemists have long sought catalytic C-H activation/functionalizations that allow for a direct aryl-H to aryl-M transformation without recourse to strong bases or neighboring groups. Such methods are now becoming available and represent significant advances toward the goal of eliminating the need for haloaromatics in the preparation of organometallics.

## Arylboronic esters

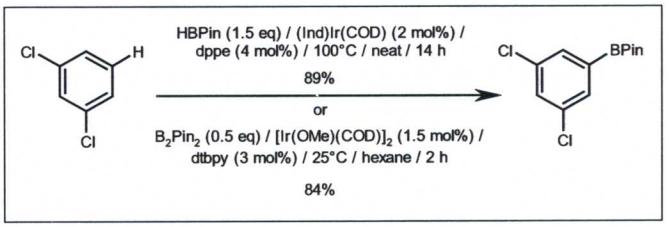
In 1999, Iverson and Smith were the first to describe a metal-catalyzed (iridium) thermal catalytic C-H activation of benzene [72]. Continued development [73,74] led to the identification of catalytic $\eta^5$-indenyl-iridium-1,5-cyclooctadiene (Ind)Ir(COD) and pinacolborane (HBPin) in combination with a bisphosphine ligand (1,2-bis(dimethylphosphino)ethane [dmpe] or 1,2-bis(diphenylphosphino)ethane [dppe]) at 100 to 150°C as a general method for the direct borylation of benzenes (Scheme 20) [75]. Shortly thereafter, Ishiyama and co-workers reported similar success with 1.5 mol% $[Ir(OMe)(COD)]_2$ and bis(pinacolato)diboron ($B_2Pin_2$) plus a 4,4'-di-*tert*-butylbipyridine (dtbpy) ligand, but with the benefit of being able to operate at room temperature [76,77]. Importantly, (Ind)Ir(COD) and $[Ir(OMe)(COD)]_2$ are commercially available, as is $[Ir(Cl)(COD)]_2$, which, while not as active, has the advantage of being relatively robust and economical. The Ir loadings have also decreased by an order of magnitude or more as the experimental protocols and substrate scope have become better defined [78,79].

In addition to obviating the need for haloaromatics, these C-H activation/borylations display interesting chemo- and regioselectivity. Although protic functionality (eg, alcohols, carboxylic acids) and substituent groups that are capable of undergoing hydroboration (eg, alkenes, aldehydes) can be problematic, esters, nitriles, carbamates, ethers, chlorides, bromides and iodides are well tolerated. Furthermore, while electron-poor arenes react faster than electron-rich arenes, it is the steric environment imposed by these substituents that mainly dictates the regiochemical outcome of the reaction. As a consequence, 1,3-disubstituted arenes borylate at the *meta*-position even when the substituents are *ortho/para* directing. This feature allows access to arylboronic esters and their derivatives that are not easily accessible by traditional approaches.

The disadvantage of this sterically driven selectivity is that monosubstituted arenes and differently 1,2-disubstituted arenes tend to give mixtures. With differently 1,4-disubstituted arenes, selectivity during the borylation step can be realized if the steric differentiation between the two groups is large. High selectivity is mostly observed with 1,4-substituted fluorobenzenes and benzonitriles [80]. Borylations of 4-substituted benzonitriles can be directed *ortho* to *meta*-directors and *meta* to *ortho/para*-directors (Scheme 21).

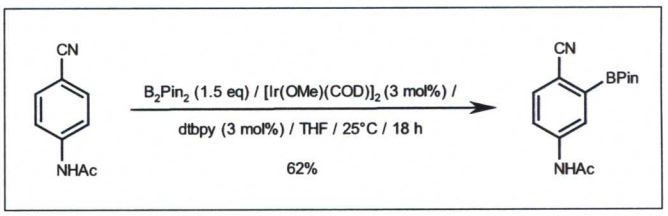
The placement of boron *ortho* to a substituent when unhindered *meta* or *para* positions are available remains a challenge. Recently, Boebel and Hartwig offered a creative

**Scheme 20. Iridium-catalyzed borylation of 1,3-dichlorobenzene.**



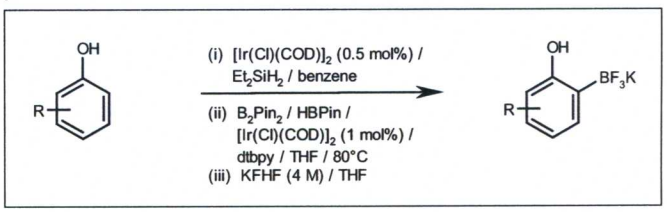

**COD** 1,5-cyclooctadiene, **dppe** 1,2-bis(diphenylphosphino)ethane, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Ind** $\eta^5$-indenyl, **Pin** pinacol.

**Scheme 21. Iridium-catalyzed borylation of 1,4-substituted benzonitriles.**




**COD** 1,5-cyclooctadiene, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Pin** pinacol, **THF** tetrahydrofuran.

**Scheme 22. Iridium-catalyzed silylation/*ortho*-borylation of phenols.**

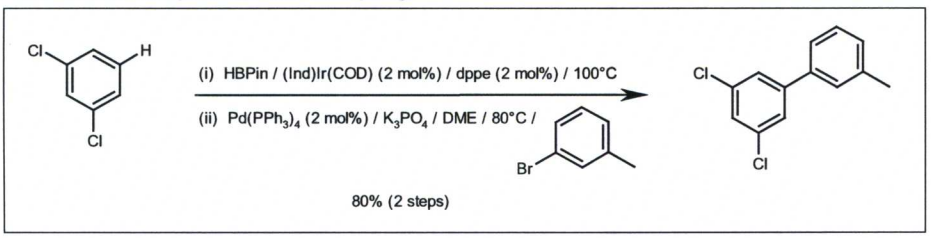



**COD** 1,5-cyclooctadiene, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Pin** pinacol, **THF** tetrahydrofuran.

solution to this problem [81]. Recognizing that the Ir catalyst rapidly inserts into a Si-H bond, the authors positioned such silanes at a benzylic carbon or on a phenol oxygen. Once in place, these silanes guide borylation to the *ortho* position. KFHF removes the silane with concomitant conversion of the boronic ester to the fluoroborate salt that can be used for cross-coupling reactions (Scheme 22). This strategy requires the existence of a suitable attachment point for the silane; nonetheless, this approach is clearly worth advancing.

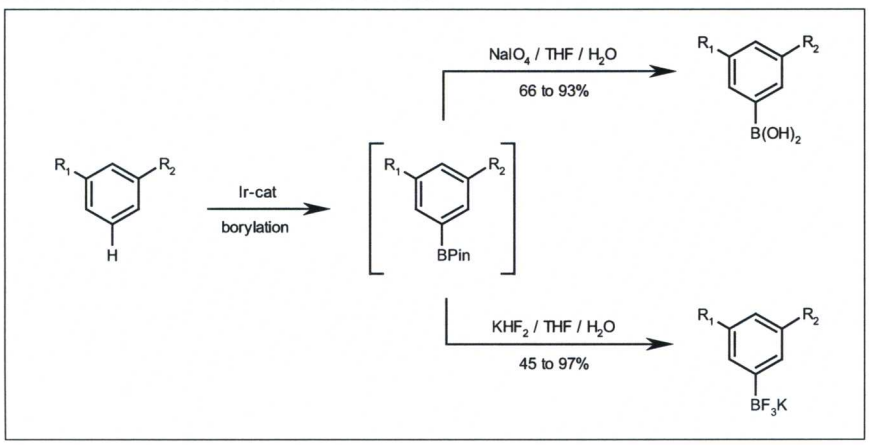
Because catalytic borylations are mild and inherently clean (hydrogen gas is produced as the only stoichiometric byproduct), one-pot C-H activation/borylation/Suzuki sequences affording biaryls and a polyphenylene have proved to be fairly straightforward. This was first demonstrated by Maleczka, Smith and co-workers in 2002 (Scheme 23) [75]. In 2008, Miyaura and co-workers published a full account of their own research on such sequences and also described a new and practical synthesis of pinacolborane [82].

**Scheme 23. One-pot C-H activation/borylation/Suzuki coupling.**



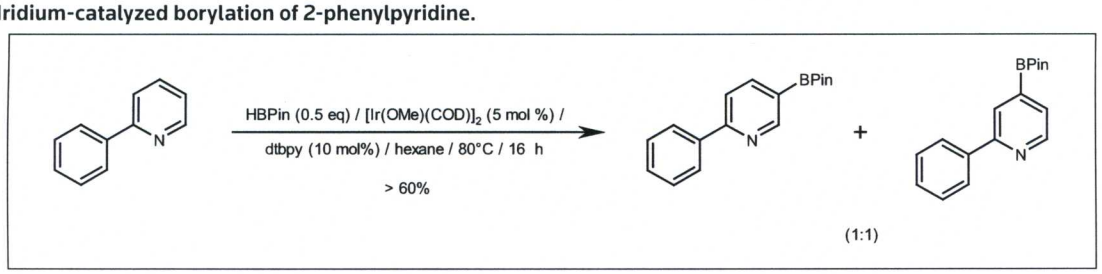

**COD** 1,5-cyclooctadiene, **DME** dimethoxyethane, **dppe** 1,2-bis(diphenylphosphino)ethane, **Ind** $\eta^5$-indenyl, **Pin** pinacol.

**Scheme 24. One-pot generation of boronic acids and trifluoroborates.**




**Pin** pinacol, **THF** tetrahydrofuran.

**Scheme 25. Iridium-catalyzed borylation of 2-phenylpyridine.**



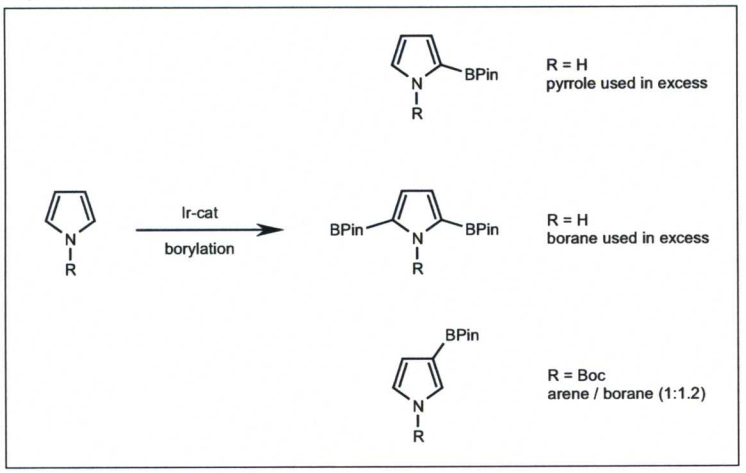

**COD** 1,5-cyclooctadiene, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Pin** pinacol.

Catalytic borylations have also been combined with other *in situ* chemical events [83-85]. For example, Hartwig and co-workers have established two-step one-pot syntheses of the more reactive arylboronic acids and aryl trifluoroborate salts (Scheme 24) [86].

Many heteroarenes respond well to Ir-catalyzed borylation conditions [87-89]; however, each class of heterocycles and often molecules within a heterocyclic class can exhibit very different reactivities and selectivities. In general, heteroarenes react faster than benzenes. This was clearly demonstrated by Marder and co-workers who showed that 2-phenylpyridine exclusively borylated on the pyridine ring (Scheme 25) [90]. This result complements the C-H activation chemistry of Kalyani and Sanford, who demonstrated that pyridine nitrogens direct Pd(II)-catalyzed activation of adjacent phenyl rings [91].

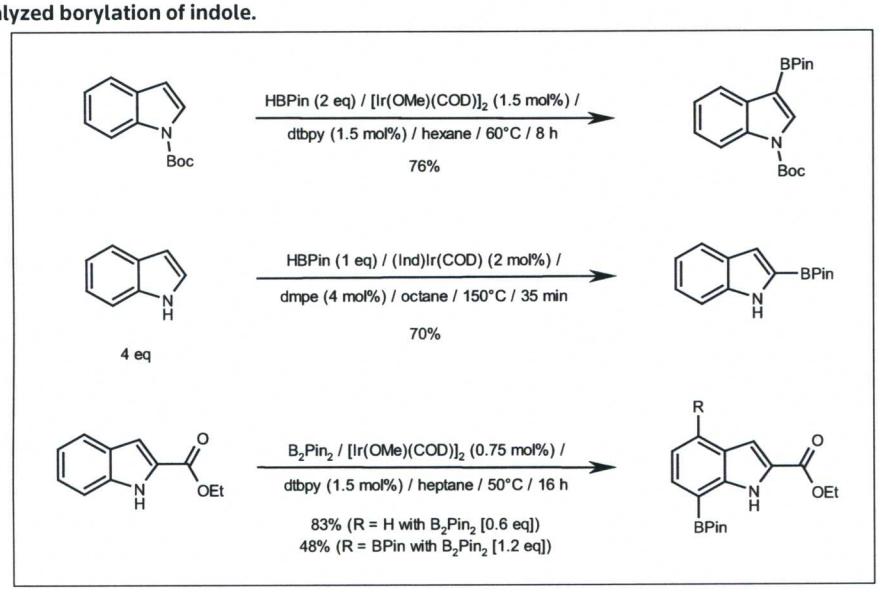
The research of Marder and co-workers also illustrates how the heteroatom can play a role in the regiochemical outcome of these reactions. For example, pyridines are reluctant to borylate at the 2- or 6-positions [87-90], which leads to the failure of pyrazine to borylate to any appreciable extent [89]. In contrast, pyrroles and other five-membered heterocycles prefer to borylate at the 2- and 5-positions, provided there are no other steric constraints (Scheme 26). For example, pyrrole borylates at the 2-position when used in excess or the 2,5-diborylated pyrrole is produced if it is the borylating agent that is in excess. In contrast, *N*-substituted pyrroles borylate preferentialy, if not exclusively, at the 3-position [87,92].

**Scheme 26. Iridium-catalyzed borylation of pyrrole.**




**Pin** pinacol.

**Scheme 27. Iridium-catalyzed borylation of indole.**




**Boc** *tert*-butyloxycarbonyl, **COD** 1,5-cyclooctadiene, **dmpe** 1,2-bis(dimethylphosphino)ethane, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Ind** $\eta^5$-indenyl, **Pin** pinacol.

Similarly, *N*-Boc-indole borylates at the 3-position, while unprotected indole borylates initially at the 2-position (Scheme 27) [87-89]. If the 2-position of indole is blocked then borylation will occur at the 7-position, indicating a heteroatom directing effect that is rarely observed with substituted arenes [93,94]. Interestingly, bisborylation of 2-substituted indoles affords 4,7-bisborylated analogs [94].

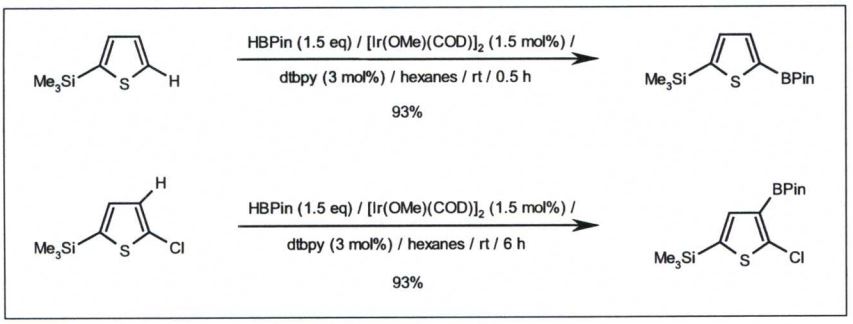
Iridium-catalyzed borylation of thiophenes occurs within minutes at the 2- and 5-positions [87,89,94,95] with an increase in chemoselectivity (eg, the ketone in 2-acylthiophene survives) and the ability to borylate adjacent to other substituents. For example, the catalytic borylation of 5-chloro-2-trimethylsilylthiophene affords the 4-borylated product in 93% yield after 6 h (Scheme 28) [95].

Furans [87], benzofurans [87-89], benzothiophenes [87-89], quinolines [87] and porphyrins [96] have also been borylated using Ir-catalysis. Usefully, many of these heterocyclic borylations have been followed by *in situ* Suzuki cross-couplings. These include 7-borylated indoles, 2- and 3-borylated thiophenes [95] and 3-substituted pyrroles (Scheme 29) [92].

## Arylsilanes

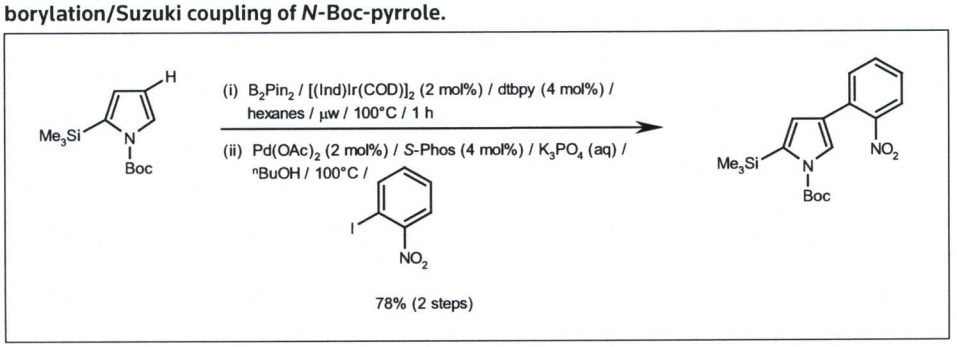
In addition to boronic esters, silyl moieties have also been placed on arenes via catalytic C-H functionalization. As with the C-H activation/borylations, the chemo- and regioselectivity of C-H activation/silylations are high and regiochemistry is primarily controlled by steric effects. Miyaura and co-workers demonstrated that fluorosilanes could be incorporated into disubstituted arenes in the

**Scheme 28. Borylation of substituted thiophenes.**



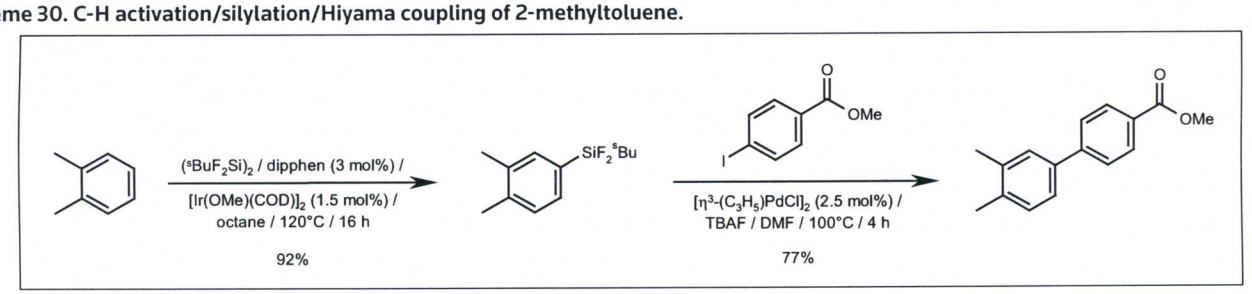

**COD** 1,5-cyclooctadiene, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Ind** $\eta^5$-indenyl, **Pin** pinacol.

**Scheme 29. One-pot borylation/Suzuki coupling of *N*-Boc-pyrrole.**




**Boc** *tert*-butyloxycarbonyl, **COD** 1,5-cyclooctadiene, **dtbpy** 4,4'-di-*tert*-butyl-2,2'-bipyridine, **Ind** $\eta^5$-indenyl, **Pin** pinacol, **S-phos** 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl.

**Scheme 30. C-H activation/silylation/Hiyama coupling of 2-methyltoluene.**




**COD** 1,5-cyclooctadiene, **dipphen** 2,9-diisopropyl-1,10-phenanthroline, **DMF** *N*,*N*-dimethylformamide, **TBAF** tetra-*n*-butylammonium fluoride.

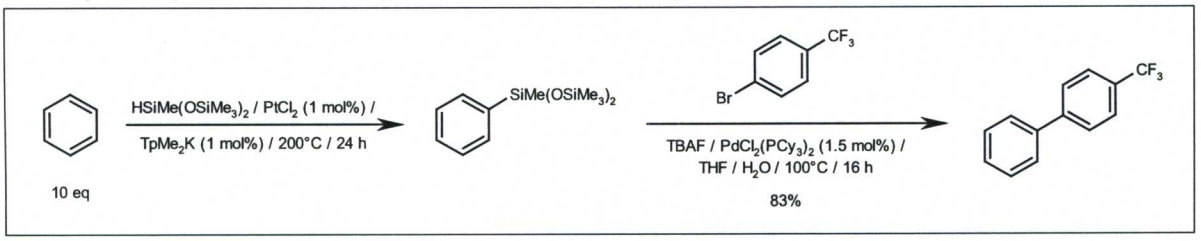
presence of $[Ir(OMe)(COD)]_2$. The resultant arylfluorosilanes couple readily with aryl iodides (Scheme 30) [97]. Unfortunately, a 10:1 excess of arene to $(^sBuF_2Si)_2$ must be used to obtain high yields. However, this ratio is an improvement over the 60 equivalents previously used in silylations with $(^tBuF_2Si)_2$ [98]. Thiophene, furan, pyrrole, indole and benzofuran have also been silylated using this method [99].

Other metals such as rhodium [100], ruthenium [101-103] and platinum [104-106] have been used to functionalize arenes with trialkylsilane. Given the relatively low reactivity of tetraorganosilanes toward Hiyama cross-couplings, Murata *et al* explored a catalytic route to arylsiloxanes [107]. Toward this end, the platinum-catalyzed reaction of 1,1,1,3,5,5,5-heptamethyltrisiloxane and potassium hydrotris(3,5-dimethylpyrazolyl)boronate ($TpMe_2K$) with arenes at high temperature afforded $ArSiMe(OSiMe_3)_2$ compounds [107]. The authors demonstrated the viability of a one-pot C-H silylation/Hiyama cross-coupling that proceeded in good yield (Scheme 31). The chemo- and regioselectivity of the reaction sequence was comparable to previously discussed arene C-H activations, but the arenes were again used in 10-fold excess.

## Cross-couplings via catalytic C-H activation in the presence of traditional electrophiles

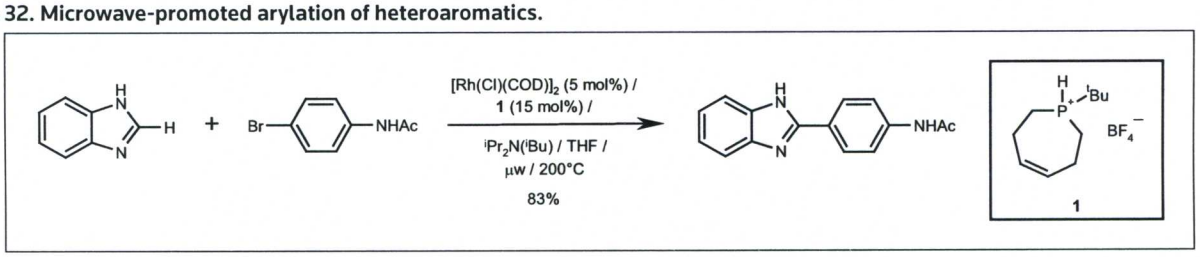
Certain heteroatom-directed catalytic C-H arene and heteroarene functionalizations take place in the presence of an electrophile. This allows for a subsequent *in situ*

**Scheme 31. One-pot catalytic C-H activation/silylation/Hiyama cross-coupling.**



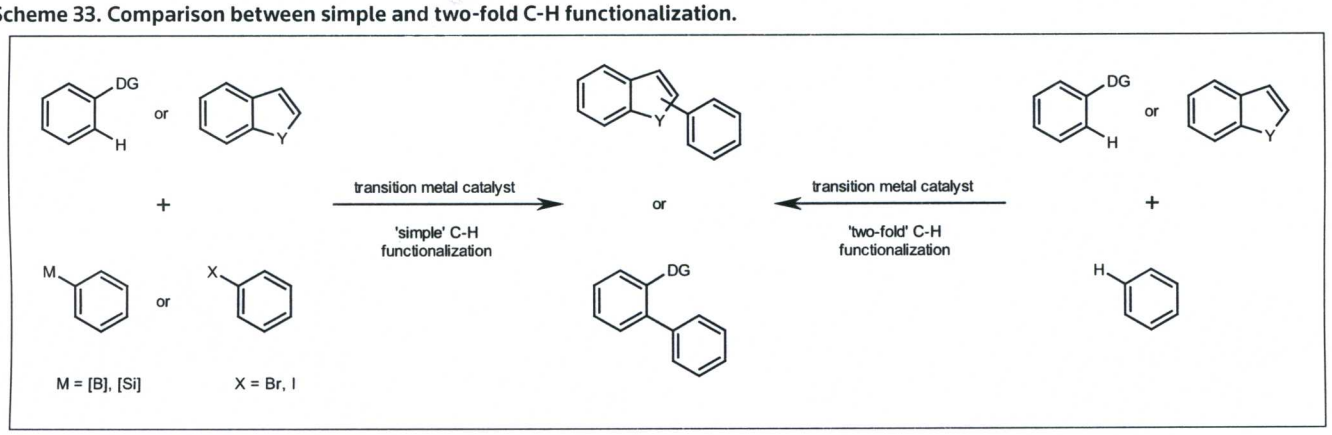

**Cy** cyclohexyl, **TBAF** tetra-*n*-butylammonium fluoride, **THF** tetrahydrofuran, **$TpMe_2K$** potassium hydrotris(3,5-dimethylpyrazolyl)boronate.

**Scheme 32. Microwave-promoted arylation of heteroaromatics.**




**COD** 1,5-cyclooctadiene, **THF** tetrahydrofuran.

**Scheme 33. Comparison between simple and two-fold C-H functionalization.**




**DG** directing group.

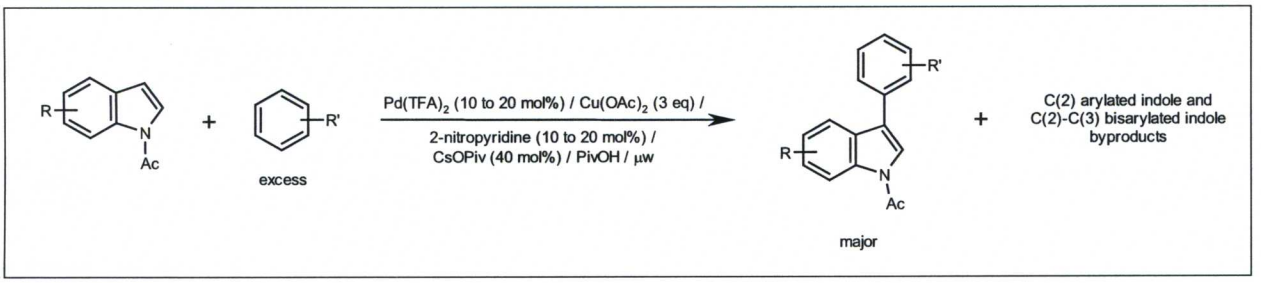
aryl-aryl cross-coupling reaction, thereby bypassing the formation of more traditional cross-coupling organometalics. In 2007 and 2008, such catalytic arylations were the subject of several excellent reviews [17,44,46,108]. Catalytic arylation studies of appropriately functionalized arenes [23,109,110] and heteroarenes [111-114] continue. These include the microwave-promoted, aryl-aryl cross-coupling of heteroaromatics and aryl bromides using a rhodium catalyst and an *in situ*-generated phosphine ligand that was developed by Ellman and co-workers in 2008 (Scheme 32) [115]. Usefully, both $[Rh(Cl)(COD)]_2$ and the (*Z*)-1-*tert*-butyl-2,3,6,7-tetrahydrophosphepinium-$BF_4$ salt (**1**) used in this microwave-promoted cross coupling are air stable and thus a dry box is not needed for this chemistry.

## Two-fold C-H activation

An exceptional advance in the use of C-H activation in cross-couplings has been the development of reactions based on a double C-H functionalization [51]. This methodology is based on the ability of a substrate, specifically a heterocycle [116,117] or an arene possessing a directing group [118-120], to undergo C-H activation and then react with another unfunctionalized aromatic via another C-H activation. Such a sequence would afford cross-coupled products without involving a halide, pseudohalide or organometallic group in the reaction process (Scheme 33).

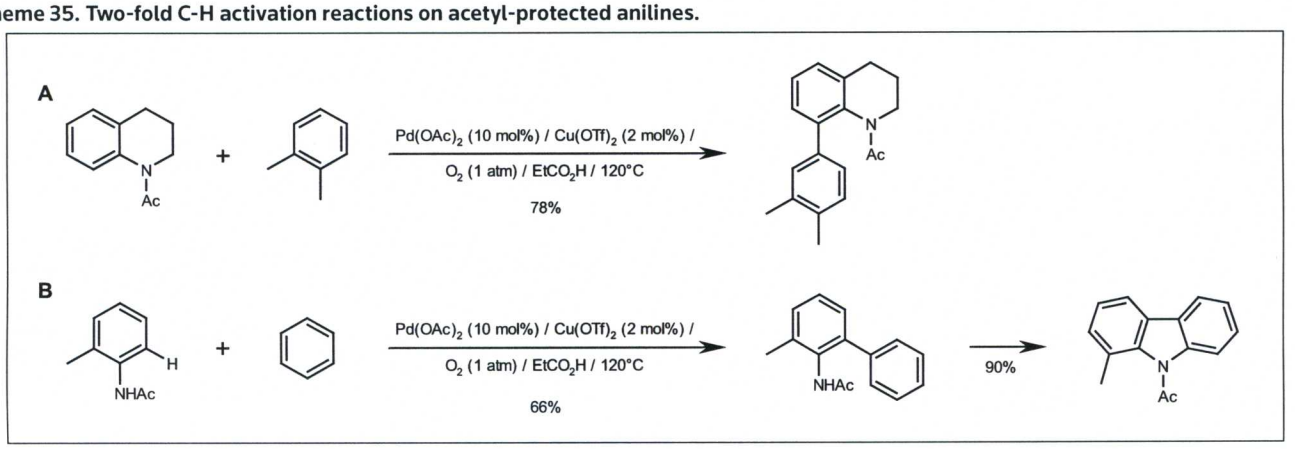
Inherent difficulties in this chemistry are regiocontrol and the need to avoid homocoupling, although related methods have been employed to specifically effect the formation of homocoupling products [121,122]. Stuart and Fagnou solved the homocoupling problem by the cross-coupling of indoles and unactivated arenes (Scheme 34) [116]. While the substrate was limited to symmetric arenes (eg, benzene, 4-methoxyanisole, 4-difluorobenzene, 4-xylene), no homocoupled products were observed and

**Scheme 34. Direct arylation of indoles.**

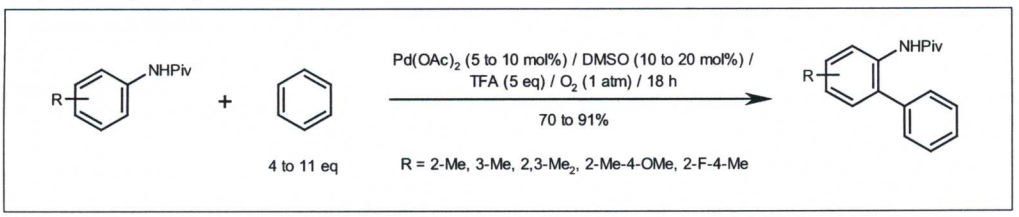



**Piv** pivaloyl, **TFA** trifluoroacetic acid.

**Scheme 35. Two-fold C-H activation reactions on acetyl-protected anilines.**




**Scheme 36. Direct arylation of pivaloyl-protected anilines.**




**DMSO** dimethylsulfoxide, **Piv** pivaloyl, **TFA** trifluoroacetic acid.

C(3) arylation was favored over C(2) arylation or diarylated products. Interestingly, the publication of this result nearly coincided with the demonstration by DeBoef and co-workers [117] that a similar arylation of indoles and benzofurans with benzene, anisol or 4-xylene favored coupling at the C(2) position of the heteocycles.

In another recent example, Shi and co-workers used an acetamide as the director in a two-fold Pd(II)-catalyzed C-H activation/cross-coupling reaction (Scheme 35A and 35B) [118]. Again, the arene that couples to the acetamide must be symmetric to avoid regiochemical mixtures. If non-symmetric arenes are desired, the same Pd(II)-catalyzed C-H activation can be used in combination with arylboronic acids and trialkoxylarylsilanes (*vide supra*) [51]. Furthermore, the scope of this two-fold method remains restricted to *N*-acetyl-1,2,3,4-tetrahydroquinolines; however, simple acetanilides have been elegantly employed in the formation of carbazoles. Finally, the current two-fold chemistry is limited by the need for approximately 10 to 30 equivalents of the arene.

Buchwald and co-workers reported that the use of a pivaloyl-protected amine improves the generality of this chemistry (Scheme 36) [119]. The bulk of the substituent allows for selective monoarylation even in the absence of a blocking *ortho* substituent and this change also allowed for lower arene stoichiometry (4 to 11 equivalents).

## Summary

Over the past several years many alternatives to haloaromatics in cross-couplings have emerged. Compounds such as tosylates, nitriles and methyl ethers are joining triflates as commonly used cross-coupling electrophiles. C-H activation and new advances in directed metallations have similarly decreased the reliance on

haloaromatics for the preparation of organometallic reactants. While still in the early stages of development, a variety of new catalytic C-H activation/cross-coupling protocols that bypass the need to prepare traditional cross-coupling partners have recently been reported and may represent the advent of truly green methods for the construction of aryl-aryl bonds.

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•• of outstanding interest
• of special interest

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