Pd-catalyzed oxidative coupling with organometallic reagents *via* C–H activation

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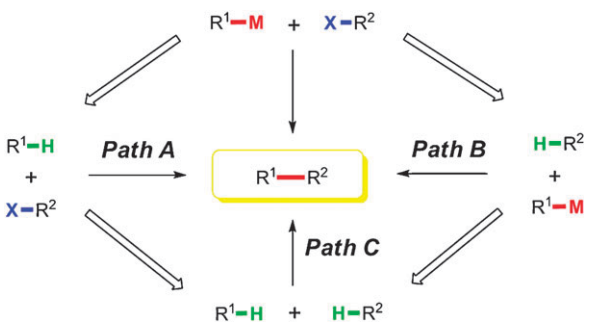
Direct selective palladium catalyzed C–H functionalization has become a highly attractive strategy in organic synthesis and represents a highly desirable goal. Compared with cross-coupling reactions of C–H bonds with aryl or alkyl halides/pseudohalides, the strategy of cross-coupling reactions of C–H bonds with organometallic reagents is of great significance and obvious advantages. This feature article provides a comprehensive summary of recent advances and an intensive analysis on Pd-catalyzed C–H activation and oxidative coupling with various organometallic reagents.

Introduction

Green and sustainable chemistry has attracted much attention and chemists have developed many novel synthetic methods to avoid the use of toxic chemicals and shorten synthetic routes. The C–H bond is the most common chemical bond in organic compounds and can be transformed into other functional groups through direct or indirect processes.[1] Undoubtedly, direct and selective C–H functionalization has become a highly attractive strategy to approach green, clean and efficient transformations.[2]

In the past several decades, transition metal catalyzed cross-coupling reactions have been well developed and widely applied in organic synthesis, which provides useful methods to construct complicated scaffolds.[3] For example, Suzuki–Miyaura coupling,[4] Stille coupling,[5] Kumada coupling,[6] Hiyama coupling,[7] and Negishi coupling,[8] have been well studied as powerful methods in the toolbox of organic chemists. It is well known that traditional cross-coupling involves two kinds of fully functionalized starting materials, including organic halides and organometallic reagents. Taking the place of either C–X or C–M or both with C–H is an ideal design to make cross-coupling more efficient and cleaner (Scheme 1).

In the past two decades, many research groups have reported the intermolecular and intramolecular cross-coupling reactions involving direct C–H activation with organic halides/pseudohalides as coupling partners.[9] Mechanistically, these processes were initiated by oxidative addition of organic halides/pseudohalides to Pd(0) species, followed by the



Scheme 1 Introduction of C–H bond activation into cross-couplings.

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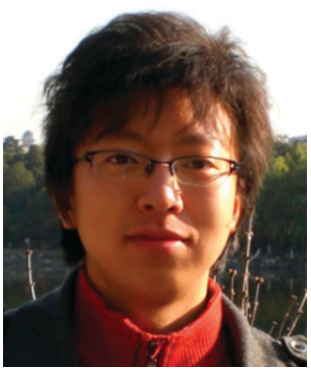
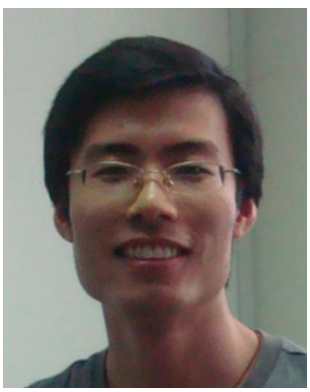


Chang-Liang Sun

Chang-Liang Sun was born in Jilin, China, in 1983. He received his BSc in chemistry from Jilin University in 2006. In September 2006, he joined the Shi group at Peking University in the College of Chemistry and Molecular Engineering. His current research interests include Ni-catalyzed activation of C–O bonds and transition metal catalyzed activation of carbon dioxide.



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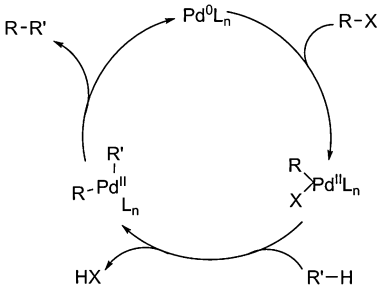
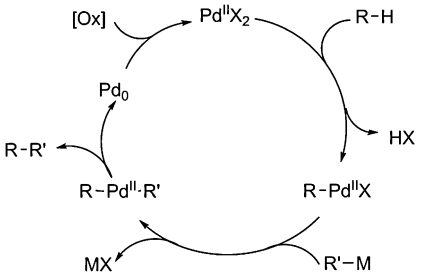
Bi-Jie Li was born in Hubei, China, in 1985. He received his BSc from Peking University in 2007. He is currently a second-year graduate student in the Shi group at Peking University in the College of Chemistry and Molecular Engineering. His current research interests focus on transition metal catalyzed sp^3 C–H bond activation.



Scheme 2 General mechanism of cross-couplings of C–H bonds with organic halides/pseudohalides.



Scheme 3 General mechanism of cross-couplings of C–H bonds with organometallic reagents.

electrophilic attack of the generated Pd(II) species to alkyl/aryl groups. Finally, deprotonation and reductive elimination took place and Pd(0) species were regenerated to complete the catalytic cycle (Scheme 2). Different parameters, such as bases, phosphine ligands, high-polarity solvents and high temperature were necessary to facilitate these transformations. More recently, cross-couplings directly starting from two C–H bonds have also been reported,[10] which showed the potential to approach the most efficient way to construct C–C bonds starting from simple arenes, although the selectivity and conditions might not reach practical levels as of now.

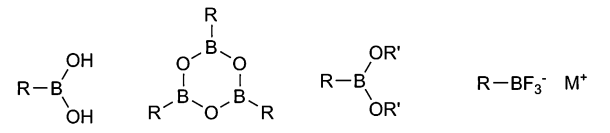
Compared with the remarkable processes of Pd(0)-catalyzed cross-coupling reactions of C–H bonds with aryl or alkyl halides/pseudohalides and their equivalents, the strategy of Pd(II)-catalyzed cross-coupling reactions of C–H bonds with organometallic reagents has only recently received more attention. Undoubtedly, such transformations involve different pathways and remain a challenge. Direct C–H functionalizations with different organometallic reagents *via* Pd catalysis has recently been developed extensively by our group amongst others.

In the proposed catalytic cycle, the electrophilic substitution toward aliphatic or aromatic systems with/without directing groups by Pd(II) species, initiates the transformation and generates aryl Pd(II) species. Subsequently, the alkyl or aryl Pd species are generated by transmetalation between organometallic reagents and the aryl Pd(II) precursor. Followed by reductive elimination to produce the desired product, the Pd(0) species are generated, which are reoxidized to Pd(II) species to complete the catalytic cycle (Scheme 3). Therefore, appropriate oxidants are necessary and acidic conditions would promote these processes. Thus, such a process is defined as an oxidative cross-coupling.

Mechanistically, neither ligands nor bases are needed, which makes the resulting system less toxic and pollutive. However, there are still several challenges: (1) the homo-coupling of organometallic reagents caused by Pd(II) species or oxidants in the system; (2) the incompatibility of reaction conditions between C–H activation and transmetalation; (3) the stability of organometallic reagents under the electrophilic C–H activation. Among the typical organometallic reagents, Grignard reagents (organomagnesium reagents), organolithium, organoaluminium and organozinc reagents are of high reactivity and low stability. As a result, they can hardly survive in the C–H activation process and thus are rarely introduced into such kinds of cross-couplings. Considering their intrinsic nature and wide applications in organic synthesis, organoboron, organosilicon and organotin reagents are ideal choices as coupling partners in these transformations.

Organoboron reagents as the coupling partners

Organoboron reagents, especially boronic acids, have been widely applied in organic synthesis as a particularly attractive class of reagents due to their availability, stability, nontoxicity and ease of handling. Suzuki–Miyaura coupling has become a powerful tool to construct complicated C–C scaffolds. Other analogs of boronic acids, such as cyclic boroxines, corresponding boronic esters and trifluoroborate salts, also showed great reactivities in many transformations (Scheme 4). Traditionally, organoboron reagents could be easily prepared by hydroboration or exchange with organometallic reagents. With the recent development of direct borylation of aryl and alkyl C–H bonds, organoboron reagents could be obtained in a more efficient and atom-economic way.[11]



Scheme 4 Various forms of organoboron reagents.

Zhang-Jie Shi

Zhang-Jie Shi was born in Anhui, China, in 1974. He obtained his BSc at East China Normal University in 1996, and PhD in the Shanghai Institute of Organic Chemistry (SIOC), CAS in 2001. After his postdoctoral studies at Harvard University and the University of Chicago, he joined the chemistry faculty of Peking University in 2004, where he was promoted to a full Professor in 2008.

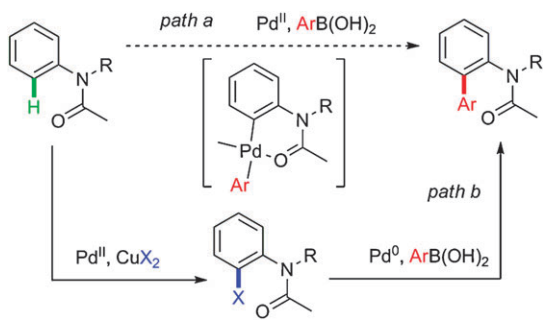
C–C bonds can be constructed by direct C–H activation using various methods.[12] However, processes to form C–C bonds starting from C–H bonds by Suzuki–Miyaura type coupling are rarely reported. Murai and Sames originally reported direct arylation of sp^3 and sp^2 C–H bonds directed by a heterocyclic group *via* Ru catalysis with aromatic boronic esters.[13] Our goal is to introduce the simplest and most common boronic acids into such direct arylations to develop more useful and efficient methodologies. In this field, Yu's group has been prominent, reporting Pd-catalyzed alkylation and arylation of sp^2 and sp^3 C–H bonds with boronic esters and boroxines with different directing groups.[14] Up to now, the application of directing groups is still the best means to tune the reactivity and control the regioselectivity.

Ortho-arylation of acetanilides

As our design, we first tried direct arylation of acetanilides, which showed high reactivity in various transformations.[15] The palladacycle obtained by electrophilic substitution (Scheme 5, path a) was proposed as a key intermediate, which is identical to that generated from oxidative addition with the corresponding halide and Pd(0) species (Scheme 5, path b). Such an intermediate may undergo transmetalation and subsequent reductive elimination to form the C–C bond. However, significant challenges remain: (1) after the catalytic cycles, Pd(0) species different from the initiated Pd(II) are obtained; (2) acidic conditions enhance electrophilicity of Pd(II) species, while most Suzuki–Miyaura couplings proceed under basic conditions. Thus, the proposed key point for this design is the choice of an appropriate base and oxidant.

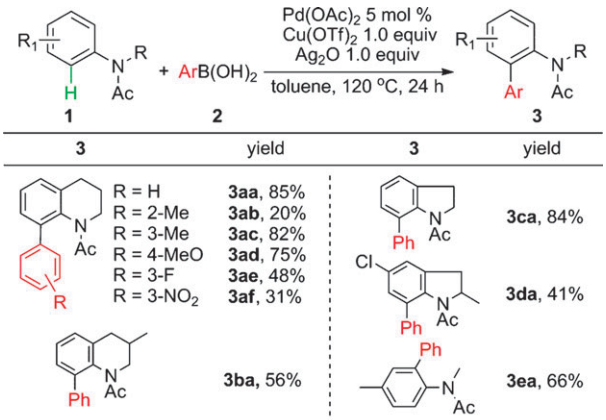
The substrate **1a** was chosen as a model substrate due to its high reactivity towards direct arylation with phenylboronic acid. After screening, we finally obtained the optimized reaction conditions (Table 1) and then different aromatic boronic acids were subjected. We observed that different substituents on the aromatic rings of the boronic acids were compatible with such arylation though electron-withdrawing groups decreased the yields (**3ae**, **3af**). The position of the substituents showed significant influence on yields and *meta* or *para* substituents provided the best yields (**3ac**, **3ad**). When *ortho*-substituted boronic acids (for example, *o*-tolylboronic acid) were used, the coupling reactions did not work well due to steric hindrance (**3ab**).

Various *N*-alkyl acetanilide derivatives were investigated (Table 1). *N*-Acetyl-2,3-dihydroindole and its derivatives were



Scheme 5 Design of a Suzuki–Miyaura coupling *via* C–H activation.

Table 1 Suzuki–Miyaura coupling of acetanilides with various boronic acids **2**[a]



[a] All the reactions were carried out with **1** (0.2 mmol) and arylboronic and **2** (0.4 mmol).

also good substrates for this transformation (**3ca**, **3da**). Notably, the relatively stable chloride group can survive for further functionalization (**3da**).

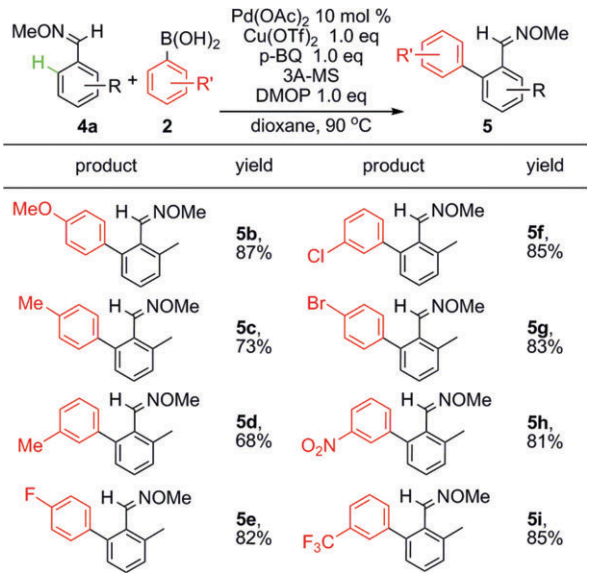
As already mentioned, this coupling is initiated by electrophilic attack of a Pd(II) center to the aromatic ring with the assistance of the acetamino group, followed by transmetalation and reductive elimination to produce the desired product. The other possibility is transmetalation of the boronic acid with Pd(II) salts to form initially an arylated Pd(II) species,[16] which may attack the aromatic ring in an electrophilic manner to form a diaryl palladium species, which then would undergo reductive elimination to give the final product.

Ortho-arylation of *O*-methyl oximes and their subsequential transformations

Due to the synthetic variety of C=X (X = O, N) groups,[17] investigation of the *ortho* arylation of aryl aldehydes and their derivatives using arylboronic acids is of great importance. Since the *O*-methyl oximyl group has been applied for *ortho* acetoxylation and amination of sp^2 C–H as well as sp^3 C–H bonds, it was further considered as an efficient directing group for direct arylation. The challenge for this arylation is to avoid the direct addition of arylboronic acids to the C=X group in the presence of Pd(II) species, which has been well studied by Lu and others.[18]

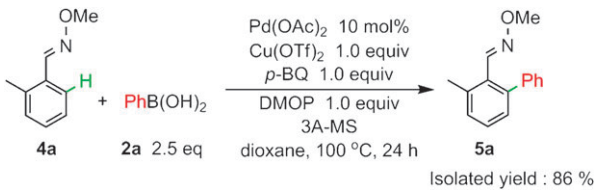
In fact, when the *ortho*-arylation of *O*-methyl (*E*)-2-methylbenzaldoxime **4a** with phenylboronic acid **2a** was tested in the presence of $Pd(OAc)_2$ and $Cu(OTf)_2$, annulated product 9*H*-fluoren-9-one and other byproducts were also observed in a low efficiency process. However, the addition to C=X (X = O or N) was suppressed under these conditions and the *in situ* generated acid was proposed to make the system complicated. Thus, further efforts was made to control the reaction at different stages by addition of bases or acids.[19] After many trials we found that 2,6-dimethoxypyridine (DMOP) is the most efficient base to improve the yield of

Table 2 Arylation of benzaldoximes *via* Pd-catalyzed C–H activation[a,b]



[a] All the reactions were carried out in 0.2 mmol scale. [b] Isolated yields.

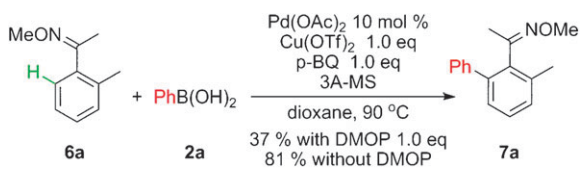
direct arylation (eqn (1)), which may arise from its appropriate steric hindrance and basicity.



(1)

Various boronic acids are suitable for this *ortho* arylation. (Table 2). The electronic properties of aromatic substituents did not significantly affect this transformation. Arylboronic acids bearing both electron-donating groups, such as MeO and Me (**5b**, **5c**, **5d**), and electron-withdrawing groups, such as NO_2 and CF_3, worked well as aryl sources (**5h**, **5i**). Notably, C–Br and C–Cl can be presented as a functional group on boronic acid for further functionalization (**5f**, **5g**).

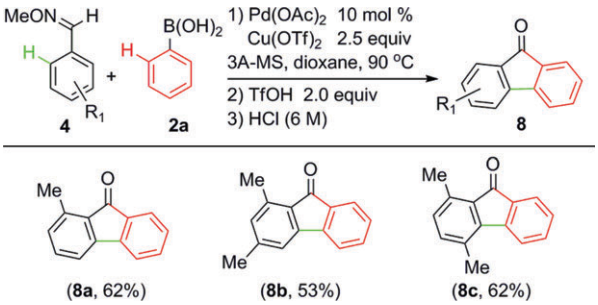
Unfortunately, such conditions of direct *ortho* arylation of aldoximes can not be directly applied into the similar arylation of aryl ketoximes, which resulted in an incomplete conversion, arising from its relatively high steric hindrance (eqn (2)). Thus, the additional base was removed to promote the efficiency. As designed, the *ortho* arylated product **7a** was obtained in 81% yield in the absence of DMOP (eqn (2)).



(2)

9*H*-fluoren-9-one and its derivatives are common scaffolds existing in many natural products and synthetic drugs[20] as well as intermediates in materials chemistry,[21] and much attention

Table 3 Cascade reaction to produce polysubstituted 9*H*-fluoren-9-ones **8** *via* Pd-catalyzed C–H activation[a,b]



[a] All the reactions were carried out in 0.2 mmol scale. [b] Isolated yields.

has been directed to this unique scaffold. After further screening, **8a** was isolated in 62% yield by sequentially adding TfOH and HCl in one pot (Table 3). Through this process, polysubstituted 9*H*-fluoren-9-ones **8a–8c** were obtained in one pot in moderate to good yields. Although the yields are not high, such a one-pot transformation provided a straightforward method to construct such scaffolds. It is important to note that, almost at the same time, Cheng and Daugulis reported similar strategies to achieve this goal by using aryl halides.[22]

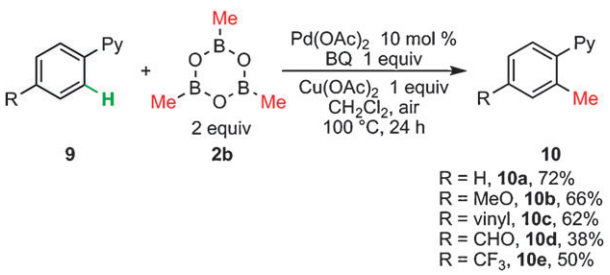
Ortho-arylation directed by pyridinyl group

Yu and co-workers first reported Pd-catalyzed direct methylation of sp^2 and sp^3 C–H bonds with methylboroxine by using pyridine (Py) as a directing group.[14a] Screening of coupling partners and reaction conditions indicated that the combination of $Pd(OAc)_2$, methylboroxine, $Cu(OAc)_2$ and benzoquinone provided an excellent efficiency and the desired product **10a** was obtained in 72% yield (Scheme 6). Functional groups attached to aryl rings, such as MeO, vinyl, CHO and CF_3, were tolerated (**10b–10e**), though electron-withdrawing groups obviously decreased the yields (**10d**, **10e**).

Importantly, this strategy can be applied in the direct functionalization of sp^3 C–H bonds. With methylboroxine as the methyl source, methylation was also achieved with the direction of the pyridinyl group, by running the reaction in acetic acid/O_2 (1 atm) rather than CH_2Cl_2/air (Table 4). Ether, alcohol and ester groups (entries 5–7) are compatible with this reaction. The methylation of the secondary sp^3 C–H bond was also possible (entry 8), albeit in lower yield.

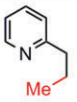
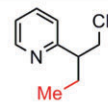
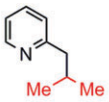
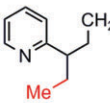
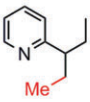
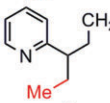
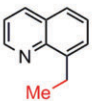
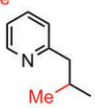
Ortho alkylation and arylation of carboxylic acids

Very recently, Yu and co-workers further reported the first example of Pd-catalyzed β-C–H activation of simple aromatic



Scheme 6 Methylation of sp^2 C–H bonds with methylboroxine.[a]

Table 4 Methylation of sp^3 C–H bonds with methylboroxine (Scheme 6)[a]

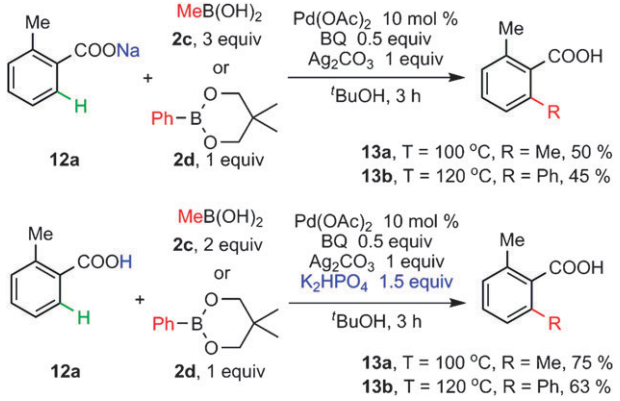
entry	product	yield	entry	product	yield
1		**11a**, 79 %	5		**11e**, 50 %
2		**11b**, 11 %	6		**11f**, 51 %
3		**11c**, 70 %	7		**11g**, 70 %
4		**11d**, 80 %	8		**11h**, 22 %

[a] 10 mol% $Pd(OAc)_2$, 2 equiv. of BQ, 2 equiv. of $Cu(OAc)_2$, 2 equiv. of **2b** and 100 °C, 24 h, HOAc, O_2.

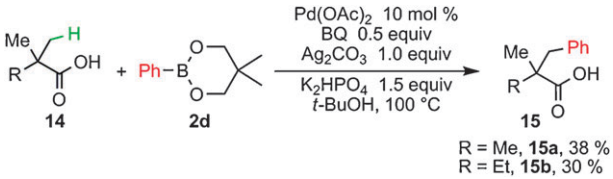
acids. A promising protocol was established for direct alkylation and arylation of sp^2 of carboxylic acids by using boronic acids and their derivatives (Scheme 7).[14b] Use of a suitable base highly improved the efficiency, according to the mechanism of the Suzuki–Miyaura coupling reaction. In their cases, K_2HPO_4 increased the yields of **13b** and **13c** to 75 and 63%, respectively (Scheme 7). Since the presence of K_2HPO_4 led to the *in situ* formation of potassium carboxylate, benzoic acids could be used instead of sodium carboxylates as substrates to facilitate this transformation.

The couplings of β-C–H bonds in aliphatic acids with **2d** were also attempted. The potassium carboxylate of **14** generated *in situ* using K_2HPO_4 afforded **13a** in 38% isolated yield (Scheme 8). This is the first example of arylation of an sp^3 C–H bond in the Suzuki–Miyaura cross-coupling manner.

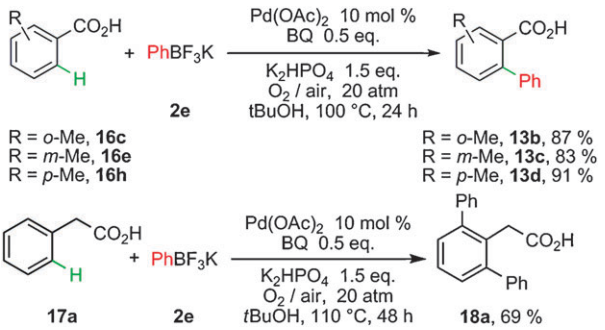
Moreover, Yu and co-workers disclosed a new catalytic system for C–H activation/C–C coupling. In this system, the scope of substrates was greatly extended by using aryltrifluoroborate salts as the coupling partners.[23] The use of 1 atm of O_2 or air led to the desired products in 60–70% yields after 72 h.



Scheme 7 Yu's protocol of C–H methylation and phenylation using boronic acids or esters.



Scheme 8 β-Arylation of aliphatic acids using $PhB(OR)_2$.



Scheme 9 Coupling of arylacetic acids with potassium aryltrifluoroborates.

However, the use of 20 atm of air or O_2 could shorten the reaction time and improve the yields (Scheme 9). This system could be expanded to the coupling of phenyl acetic acid with $PhBF_3K$, giving the diarylated product **18a** in 69% yield.

β-Arylation and alkylation of *O*-methyl hydroxamic acids

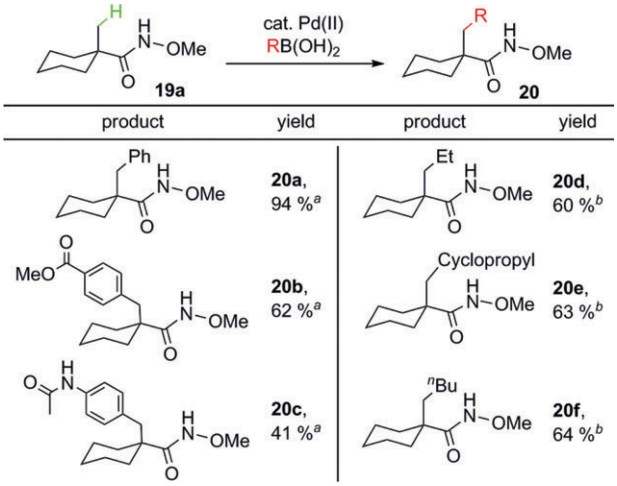
Very recently, Yu and co-workers further developed the first protocol for the coupling of sp^3 C–H bonds of *O*-methyl hydroxamic acids with both sp^2 and sp^3 boronic acids.[24] Since the CONHOMe group can be readily converted to esters and amides, or reduced to alkane fragments, this reaction is likely to find broad synthetic utility. It is noteworthy that the use of 2,2,5,5-tetramethyltetrahydrofuran as the solvent allows the coupling of sp^3 C–H bonds with alkylboronic acids. This solvent might serve as a sterically bulky ligand to prevent homo-coupling and β-hydride elimination from the alkyl fragments of the sp^3 boronic acids. Some typical products are shown in Table 5.

Direct arylation of electron-rich arenes and heterocycles

Although the cross-coupling between C–H bonds and organoboronic acids and their derivatives has advanced Suzuki–Miyaura coupling, the relatively low yields, the requirement of a directing group, and the complicated reaction conditions made them less attractive for real applications. Our efforts were made to develop new methods of Pd(II)-catalyzed cross-couplings between general C–H bonds and arylboronic acids.[25]

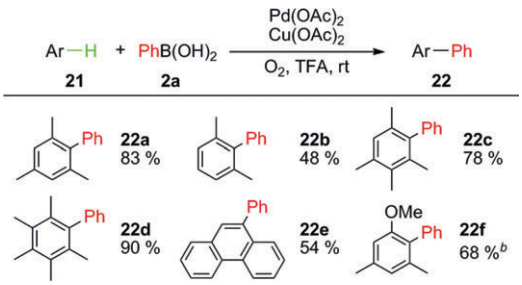
We tested the direct arylation of mesitylene (**21a**) with phenylboronic acid (**2a**) under various conditions. Finally we found that such transformation could progress under relatively strong acidic conditions in the presence of $Cu(OAc)_2$ as a co-catalyst and O_2 as a terminal oxidant. However, the substrate scope of the arenes is quite narrow. In general, electron-rich arenes bearing methyl substitutents showed good reactivities and the corresponding phenylated products **22**

Table 5 β-Arylation and alkylation of *O*-methyl hydroxamic acids



[a] Conditions A: **19a** (0.5 mmol), arylboronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), Ag_2O (1 mmol), BQ (0.25 mmol), K_2CO_3 (1 mmol), *t*-BuOH (3 mL), 70 °C, 18 h. [b] Conditions B: **19a** (0.5 mmol), alkylboronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), Ag_2O (1 mmol), K_2CO_3 (1 mmol), BQ (0.25 mmol), 2,2,5,5-tetramethylTHF (3 mL, inhibitor free, anhydrous), 70 °C, 18 h.

Table 6 Pd(II)-catalyzed direct coupling of electron-rich arenes with phenylboronic acid[a]

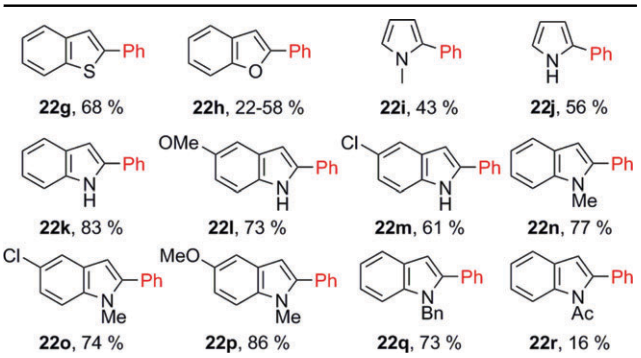


[a] **21a–21f** (1.0 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (5.0 mol%), $Cu(OAc)_2$ (1.0 equiv.) in TFA under 1 atm of O_2. [b] The ratio of arylation at the *ortho* and *para* positions was determined to be 2 : 1 by GC.

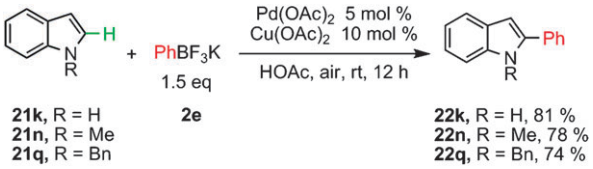
were obtained in good yields (Table 6). Electron-rich polyarenes and methoxy substituent were also beneficial for this transformation.

This system is perfectly suitable for direct arylation of electron-rich heteroaromatic systems, even under simpler conditions (Table 7). 2,3-Benzothiophene (**21g**) and 2,3-benzofuran (**21h**) were suitable substrates and the corresponding phenylated products at the 2-position were obtained in excellent regioselectivities. Moreover, *N*-heterocycles, such as pyrroles **21i**, **21j** and indoles **21k–21r**, were only monophenylated. No protection was required for the arylation of pyrrole **21j** and indoles **21k–21m**. The relatively low yields arose from the instability of substrates and products under acidic conditions. More functionalized indole derivatives (**21n–21q**) could be arylated at the 2-position with high efficiency, excellent selectivity, and good yields. Substrates **21m** and **21o** showed that C–Cl bonds were tolerated. *N*-Acetyl protection (**21r**) significantly diminished the yield, due to the decrease of electron density.

Table 7 Pd(II)-catalyzed direct coupling of heterocycles with phenylboronic acid[a]



[a] Reaction conditions: **22g–22r**, **2a** (1.5–2.0 equiv.), $Pd(OAc)_2$ (5.0 mol%) in AcOH at room temperature under 1 atm of O_2.



Scheme 10 Pd-catalyzed direct arylation of indoles with potassium phenyltrifluoroborate.

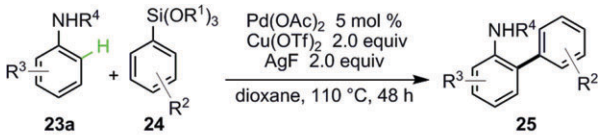
Later on, Zhang and co-workers also developed mild conditions to achieve $Pd(OAc)_2$-catalyzed regioselective cross-coupling between indoles and potassium aryltrifluoroborates in the presence of a catalytic amount of $Cu(OAc)_2$ in acetic acid at room temperature (Scheme 10).[26]

In summary, employing aryl/alkyl boronic acids and their derivatives as reagents, novel methods to construct C–C bonds *via* Pd(II)-catalyzed Suzuki–Miyaura type reactions have been developed starting from aryl C–H bonds, as well as aliphatic C–H bonds, with/without directing groups. Acetanilides, *O*-methyl oximes, pyridines, carboxylic acids, *O*-methyl hydroxamic acids and (hetero)arenes were successfully subjected to such transformations. Our studies also resulted in the direct arylation of common electron-rich arenes. The milder reaction conditions enabled these transformations to tolerate different functional groups very well. Further extension of substrate scope and application of such methods are still pictured in near future.

Organosilicon reagents as the coupling partners

Other than organoboron reagents, organosilicon reagents are another class of important organometallic reagents and are widely applied in organic synthesis. The Pd-catalyzed Hiyama coupling reaction is one of the most important examples using organosilicon reagents as coupling partners. Compared with other organometallic reagents, organosilicon reagents possess the lowest reactivity and a better tolerance of functional groups. The C–Si bonds are of only slight polarity due to the slightly higher electronegativity of carbon over silicon. In previous studies, fluorides were frequently used as additives to activate C–Si bonds by formation of the five- or six-coordinated silicates and facilitate the transmetalation of

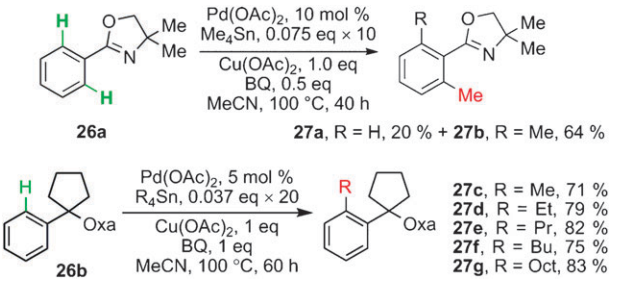
Table 8 Arylation with organosilane reagents *via* C–H activation[a]



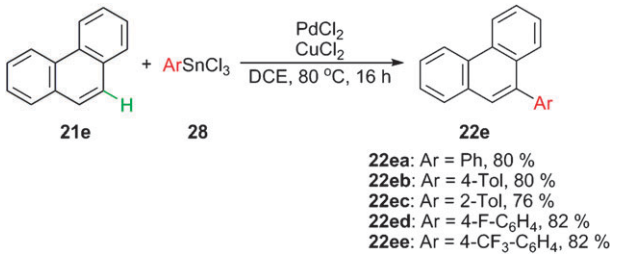
23a 24 25

entry	R^1	R^2	R^3	R^4	yield [b]
1	Me	H	H	Ac	**25a**, 74 %
2	Et	H	H	Ac	**25a**, 74 %
3	Et	4-OMe	H	Ac	**25b**, 71 %
4	Et	4-Me	H	Ac	**25c**, 62 %
5	Et	4-F	H	Ac	**25d**, 63 %
6	Et	4-Cl	H	Ac	**25e**, 61 %
7	Et	3-OMe	H	Ac	**25f**, 52 %
8	Me	H	4-OMe	Ac	**25g**, 68 %
9	Me	H	4-OAc	Ac	**25h**, 66 %
10	Me	H	4-OBz	Ac	**25i**, 64 %
11	Me	H	4-Me	Ac	**25j**, 71 %
12	Me	H	2-OMe	Ac	**25k**, 80 %
13	Me	H	H	$Ph(CH_2)_3$	**25l**, 46 %
14	Me	H	H	Bz	**25m**, 38 %
15	Me	H	H	Boc	**25n**, 0 %
16	Me	H	H	Me	**25o**, 0 %

[a] All the reactions were carried out in 0.2 mmol scale. [b] Isolated yields.



Scheme 11 Catalytic methylation of aryl C–H bonds using organotin reagents.



Scheme 12 Arylation of phenanthrene using aryltin trichlorides.

organosilicon reagents. Those facts made the cross-coupling between general arenes and organosilicon reagents more challenging. Our studies resulted in a unique case up to the present.[27]

In our research, Hiyama type coupling between acetanilide **38a** and trimethoxy(phenyl)silane **39a** could be promoted by AgF, which might play dual roles as both co-oxidant and fluoride source. In fact, the best oxidant for this transformation is $Cu(OTf)_2$ and the desired product was afforded in excellent yield (Table 8, entry 1).

Different trialkyloxy(aryl)silanes exhibited excellent reactivities in this transformation, regardless of electron-withdrawing groups or electron-donating groups on the phenyl rings of the phenylsilanes (Table 8, entries 2–7). C–Cl on phenylsilane survived, providing a great chance for further functionalization (entry 6). Under this condition, different acetanilides were also studied, with broad functional group compatibility (**40g–40k**). The effect of different groups on the N atom were also studied; $Ph(CH_2)_3$ and Bz groups led to relatively lower yields (**40l** and **40m**) while Boc and methyl groups were not effective at all in this process (**40n** and **40o**).

Organotin reagents as the coupling partners

Stille coupling using organotin reagents have been widely investigated, though usually only one of the four groups on tin was transferred, leaving the other three as spectators.[28] Due to their relatively high tolerance of functional groups, moderate reactivities and mild reaction conditions, organotin compounds were frequently used in total synthesis. However, the toxicity of organotin reagents is a considerable drawback which limits their applications.

Stille type cross-coupling starting from C–H activation was earlier studied than other cross-couplings. In 2005, Yu and co-workers discovered the first protocol for Pd(II)-catalyzed alkylations of aryl C–H bonds with a variety of primary-alkyl tin regents using a combination of directed C–H activation and batchwise addition of the organotin reagents. They found that catalytic alkylation of **26a** can be achieved by using 1 equiv. of $Cu(OAc)_2$ and 0.5 equiv. of benzoquinone in MeCN under air to afford mainly the dialkylated product **27b** directed by the oxazolinyl (Oxa) group (Scheme 11). A variety of primary alkyl tin reagents were tested under these new conditions, and the alkylated products were obtained in good yields (Scheme 11).[29] The addition of tin reagents in batches was necessary to avoid homo-coupling of tin reagents, but resulted in longer reaction time.

Very recently, Inoue and co-workers reported a direct Pd-catalyzed C–H bond arylation of simple arenes with aryltin reagents in the presence of $CuCl_2$, which was proved to be an activator for the Pd catalyst as well as an oxidant (Scheme 12). The use of aryltin trichloride not only diminished the toxicity of reagents, but also improved the atom-economy of carbon atoms. Moreover, the absence of the directing group highly expanded the substrate scope.[30]

Conclusions

In this feature article, we have summarized recent advances on Pd-catalyzed direct C–H functionalization *via* oxidative-couplings with organometallic reagents. Concerning the substrates, acetanilides, *O*-alkyl oximes, aryl and alkyl carboxylic acids, 2-aryl or alkyl pyridines, 2-aryl or alkyl oxazolines, *O*-methyl hydroxamic acids, and even common electron-rich (hetero)arenes without directing groups have been successfully introduced into these transformations. Some of the cross-coupling products could be further transformed into other useful scaffolds and compounds by condition-controlled cascade reactions. Concerning the oxidants, $Cu(OAc)_2$ was the most efficient in the system of palladium

catalysis and Ag(I) salts, *p*-BQ were also used frequently. The use of oxidants containing heavy metals depreciated these methods to some extent. In some cases, even O_2 or air could react as terminal oxidants, which provided a potential opportunity of developing more efficient and greener transformations.

In another aspect, the organometallic reagents involved were mainly organoboron, organosilicon and organotin reagents due to the consonance of their reactivities and stabilities. Moreover, the reactions using other organometallic reagents with higher reactivities, such as Grignard reagents and organozinc reagents, remain as a substantial challenge in this field. Importantly, recent developments *via* Fe catalysis by Nakamura and co-workers showed great potential in this area.[31]

Summarizing, Pd-catalyzed C–H activation and cross-coupling with organometallic reagents presents a new strategy in the field of cross-coupling reactions. Undoubtedly, these reactions have great prospects of applications in organic syntheses and industrial processes. In spite of their great significance and obvious advantages, there are still many problems to be solved, such as the relatively narrow substrate scope and the harsh and complicated reaction conditions. The clear understanding of the catalytic pathway is still elusive. We are striving in further developments to make these transformations more promising and practical.

Acknowledgements

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