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Conference paper

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Beyond C–H and C–O activation: the evolution of components in cross-coupling reactions[1]

Abstract: C–H and C–O bonds are two of the most abundant chemical bonds in nature. Direct application of C–H and C–O bonds to take place of C–X bonds in cross coupling reactions exhibited numerous advantages since the pre-activation and the emission of harmful wastes can be avoided. In this synopsis, a variety of novel transformations related to cross coupling reactions based on direct C–H and C–O activation are described.

Keywords: catalysis; C–C bond formation; cross-coupling reactions; green chemistry; inert bond activation; OMCOS-17.

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Palladium-catalyzed cross-coupling reaction is one of the most powerful methods to construct new C–C bond. Like a delicate "tool", it allows chemists to synthesize or modify complicated molecules efficiently. Due to its importance to organic synthesis, it became the topic of the Nobel Prize of Chemistry in 2010 [1]. However, organic halides, the commonly used coupling partners, bring several problems along with the great success of cross-coupling reactions. Stoichiometric amount of halide wastes, which are quite harmful to our environment, are generated from the reaction system as byproducts. Furthermore, organic halides are prepared from the raw materials such as hydrocarbons with tedious and dangerous processes to some extents. Thus, it is more expensive and not straightforward to choose organic halides as the coupling partners to form the C–C bond with rather low atom- and step-economy.

Due to the drawbacks of traditional cross-coupling reactions, the exploration of new approaches for C–C bond formation has attracted much attention during the past decades. The C–H and C–O bond are two of the most abundant chemical bonds in nature and widely spread among the fundamental materials for energy and chemistry. For example, coal, petroleum and natural gas are made up of hydrocarbons. Biomass, a kind of renewable energy source, contains a lot of C–O bonds. Compared with organic halides, direct transformation of hydrocarbons or *O*-containing compounds exhibits much better atom- and step-economy. More importantly, the byproducts of their reactions are carboxylic acid derivatives, alcohols or even water in theory, which are much more environment-friendly than the halides (Fig. 1). The direct transformation of inert C–H and C–O bond not only brings a revolution to the traditional methods based on active functional groups, but also helps to alleviate the crises in energy and environment. Therefore, it fulfills the requirement of green chemistry and sustainable development for human's society. This synopsis summarizes our efforts on transition metal-catalyzed C–H and C–O bond functionalization.

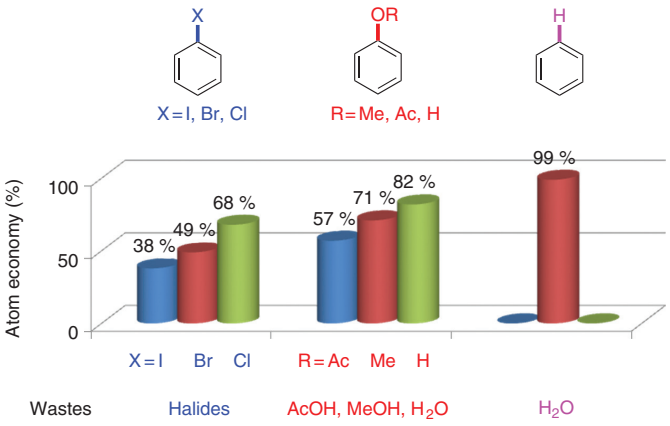


Fig. 1 The comparison of atom economy and corresponding waste among the halides, *O*-containing compounds and arenes.

C–O electrophiles in transition metal-catalyzed cross-coupling reactions

Even at the early stage of cross-coupling reactions, chemists have started to extent the scope of *O*-containing electrophiles to replace the organic halides. High reactive compounds such as triflates [2], sulfonates [3], phosphonates [4] and allyl carboxylates/carbonates [5] were used during the development of catalytic systems. However, other more readily available *O*-containing compounds, including ether, alcohols, phenols and non-activated carbonyl derivatives are rarely reported as electrophiles, which faces two major challenges: one is the relatively high bond dissociation energy (BDE) of such compounds, which makes the cleavage of C–O bond quite difficult. The other is the selectivity between the two groups linking to the oxygen atom and other C–O bonds in the same compound (Fig. 2) [6]. Inspired by the pioneering works of Wenkert [7], Milstein [8] and others [9], we initiated our study of C–O bond activation by using Ni catalysts.

Cross-coupling between organometallic reagents and carboxylates electrophiles

Though we had achieved the Kumada coupling between Grignard reagents and aryl or benzyl ethers [10], the poor functional group tolerance limited their application in synthesis. For this reason, we turned to the Suzuki–Miyaura coupling with easily available carboxylates as the electrophiles.

As shown in Fig. 2, acyl C–O bond is more active than phenyl C–O bond. However, an early report of Yamamoto revealed the clue that Ni(0) could cleave both C–O bonds of phenyl acetate under different conditions since the oxidative addition of acyl C–O bond to Ni(0) was reversible [11]. If the transmetalation could be enhanced, the balance of this reaction would move towards the desired product *via* phenyl C–O bond cleavage. After the optimization, we finally found 2-napthol acetate derivatives showed good reactivity in the presence of $NiCl_2(PCy_3)_2$ and K_3PO_4 in dioxane at 110 °C. The amount of H_2O was crucial for this reaction.

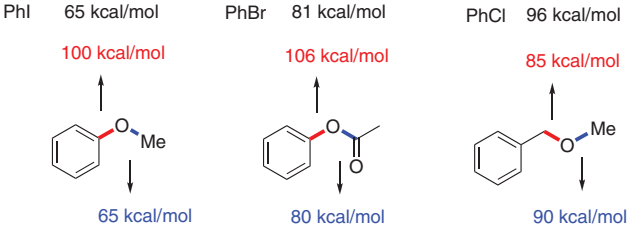
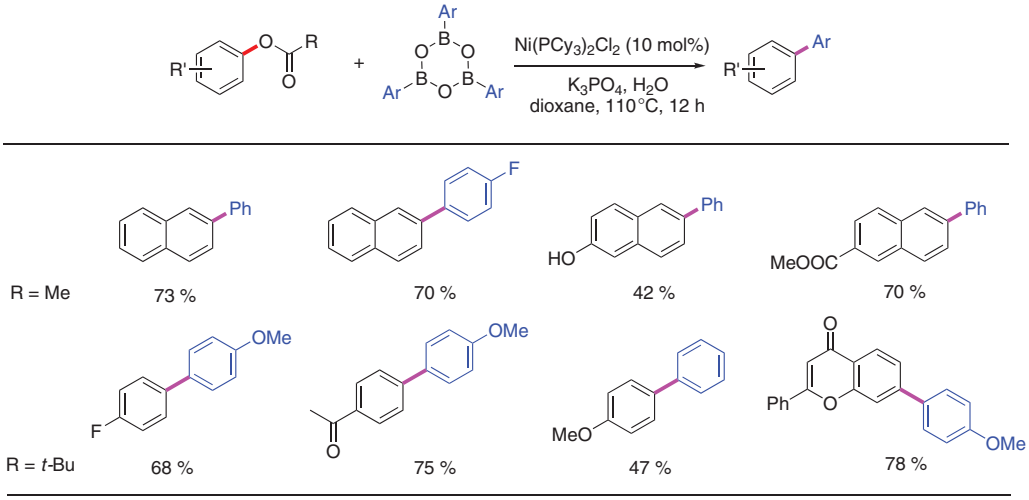


Fig. 2 Bond dissociation energy (BDE) values of C–X and C–O bonds.

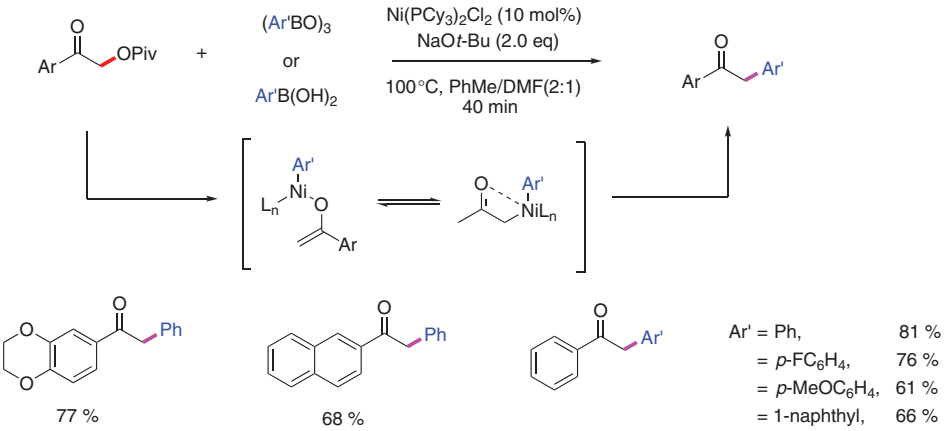
We thought this critical requirement may arise from the balance between promoting the reactivity of boron reagents and suppressing the hydrolysis of the substrates. Functional groups, such as ketones, esters, –OMe and –F were all compatible. Free phenols were also tolerated albeit in a lower yield. However, phenyl acetate decomposed under the same condition. When the corresponding pivalate was installed instead of acetate, the cross-coupling could proceed quite smoothly (Scheme 1) [12]. We proposed that the active Ni(0) species was generated by *in situ* reduction of Ni(II) pre-catalyst. It underwent oxidative addition with aryl carboxylates to cleave aryl C–O bond. The following transmetalation from arylboroxine and reductive elimination gave the desired coupling products, along with the regeneration of Ni(0) species.

With this strategy, we also achieved Suzuki–Miyaura coupling *via* sp^2 C–O bond activation of alkenyl carboxylates and carbamates [13, 14]. Meanwhile, Garg and Snieckus have made a lot of contribution in the same field [15].

Though much progress have been made in sp^2 C–O bond activation, relatively, the research in sp^3 C–O bond still lags behind. Other than the active allyl/benzyl ethers and esters [5, 10], the sp^3 C–O bond in alkyl ether was activated by Rh catalyst in Dong's work [16]. More recently, we developed the first example of α-pivaloxyl ketone arylation with phenyl boronic acids by Ni-catalyzed sp^3 C–O activation (Scheme 2) [17]. During the optimization, we found that bases, solvents and even the reaction time all had important effects on the reaction. Examination of different leaving groups of 2-hydroxyacetophenones showed only pivaloyl and phenyl group gave reliable results. Various *O*-containing groups and C–F bond were compatible. The



Scheme 1 Suzuki–Miyaura reaction of aryl carboxylates with arylboroxines.



Scheme 2 Suzuki–Miyaura reaction by sp^3 C–O activation in α-pivaloxyl ketones.

thermodynamically more stable C-arylated product was the dominant product though the equilibrium between alkyl and enolate Ni(II) intermediates existed.

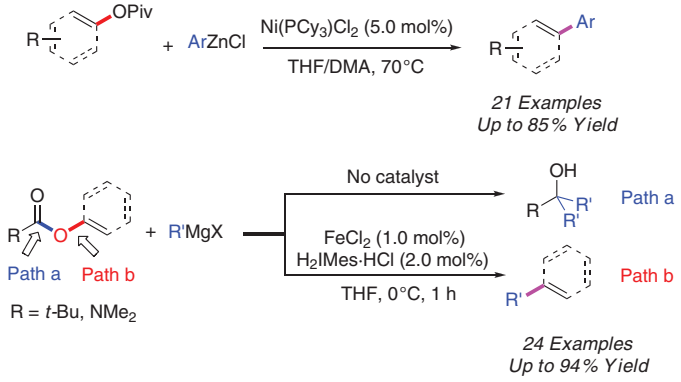
Due to the low reactivity of boronic reagents, high temperature and catalyst loading are always required. Thus, we further explored the coupling of aryl zinc reagents with aryl or alkenyl carboxylates under milder conditions. The steric hindrance of ester group had much effect on the stability of substrates, and the pivalates were proved to be proper coupling partners (Scheme 3) [18]. We also demonstrated the Negishi-type coupling of alkenyl acetates with a similar catalytic system [13].

Besides the success of cross-coupling with organoboron and organozinc reagents, we managed to develop the first Fe-catalyzed Kumada coupling of alkenyl pivalates and aryl carbamates with alkyl Grignard reagents, which favored nucleophilic attack to the carbonyl group in traditional transformations (Scheme 3) [19]. With a combination of $FeCl_2$ and NHC ligand, the catalytic system exhibited high efficiency with only 1 % catalyst loading in 1 h at 0 °C. Alkene, ether and even carbonyl group were tolerated well. Notably, we also found the β-H of the Grignard reagent was essential for the transformation. This work provides an alternative Fe catalytic system for C–O bond activation other than the commonly used Ni systems.

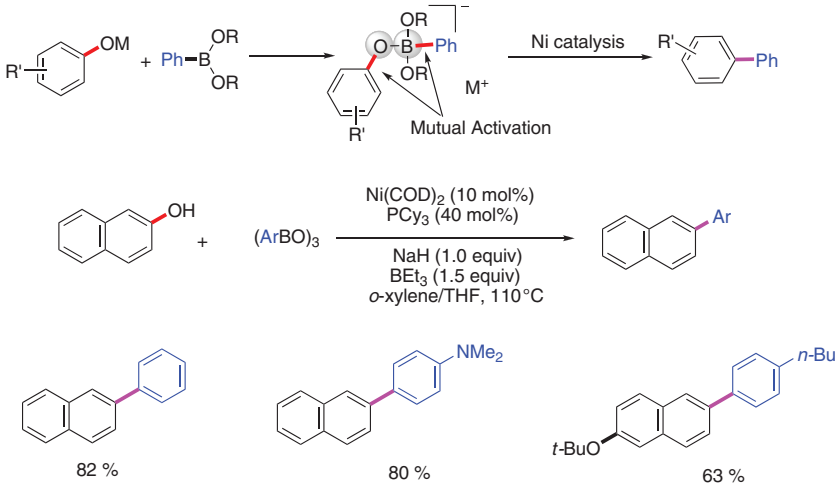
Phenols as electrophiles

Undoubtedly, the direct application of phenols in cross-coupling reactions is a far more ideal process, which avoids the introduction of extra protecting group to improve the atom- and step-economy. However, due to the poor leaving ability of hydroxyl group, the reactivity of phenol is much lower than its protected derivatives. It becomes worse that the transformation of phenolates in the basic condition of cross-coupling reaction can enhance the bond energy of aryl C–O bond. Finally, the phenolic anion with good coordination ability could bind to the catalyst that inhibited the C–O bond cleavage. Since the early observation reported by Wenkert [7b], little progress has been made in this challenging area [20].

The phenol C–O bond can be activated by the introduction of various protecting groups [21]. Meanwhile, the generation of borate can also facilitate the transmetalation step [22]. Noticed both the two clues, we hypothesized that the Lewis acidic three-coordinated organoboron reagent and the basic phenolate could react with each other to generate the borate intermediate, which could realize the activation of both aryl C–O bond and the C–B bond of organoboron reagent at the same time. So we called this strategy as the "mutual activation" (Scheme 4) [23]. To test whether such a novel strategy was effective in phenol C–O bond activation, we made much effort on the condition screening. The combination of $[Ni(cod)_2]$, PCy_3, NaH in *o*-xylene/THF mixed solvent at 110 °C was selected as the optimal condition. The addition of mild Lewis acid BEt_3 gave a supervising promotion of this reaction. The ^{11}B NMR study showed that the BEt_3 could interact with the borate. It provided a C–O and C–B bond double activation through a Lewis acid assisted Lewis acid effect (LA/LA) pathway [24]. The selective cleavage of hydroxyl C–O bond over the C–OR bond was also observed. Naphthols with various functional groups gave moderate to excellent yields, while phenol derivative poorly



Scheme 3 Negishi and Kumada reactions of aryl/alkenyl carboxylates.



Scheme 4 Cleavage of sp^2 C–O bond in naphtholates by mutual activation with organoboron reagents.

converted to the desired product. Both the length of C–O and C–B bond in the borate intermediate were longer than the ones in corresponding starting materials, which indicated that the mutual activation was reasonable in this reaction system (Fig. 3).

In a similar case, we were also pleased to find that the magnesium cation could activate the C–O bond in magnesium naphtholates. The crystal structure of $[2\text{-NaphOMgBr(THF)}_2]_2$ indicated that the naphtholate C–O bond length kept as the same as that in 2-naphthol. According to this information, we explored the Kumada coupling of magnesium 2-naphtholates [25]. Very recently, we have extended the application of this strategy to the activation of benzyl alcohols' sp^3 C–O bonds [26]. Benzyl alcohols coupled smoothly with aryl, benzyl and methyl Grignard reagents. When alkyl Grignard reagents were used instead, the reduction of hydroxyl group to methyl group was surprisingly observed in Fe, Co or Ni catalysis. Mechanistic investigation indicated that the benzylic hydroxyl group firstly underwent magnesiation to form the benzyl Grignard reagent *in situ*, then protonated by EtOH in the work-up protocol (Scheme 5). The benzyl Grignard reagent intermediate offered the potential for further diversity to other functionalities.

Pd-catalyzed oxidative coupling reactions of aromatic C–H bonds

Since direct C–H bond functionalization can minimize the pre-activation of the substrates and alleviate the waste pollution, the use of C–H bond to replace the C–halogen bond in cross-coupling reactions is a wise

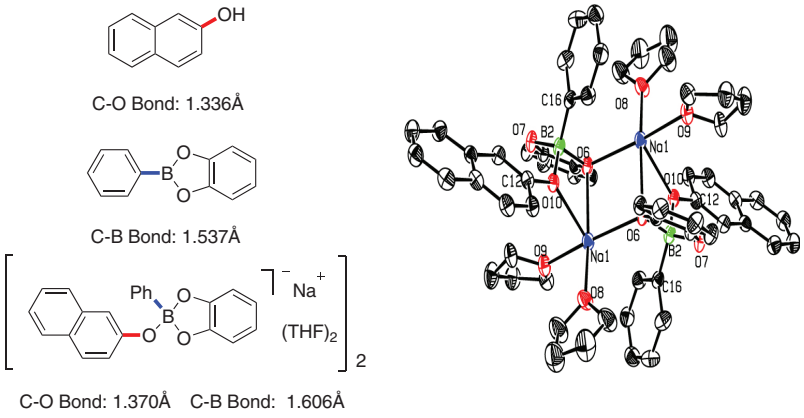
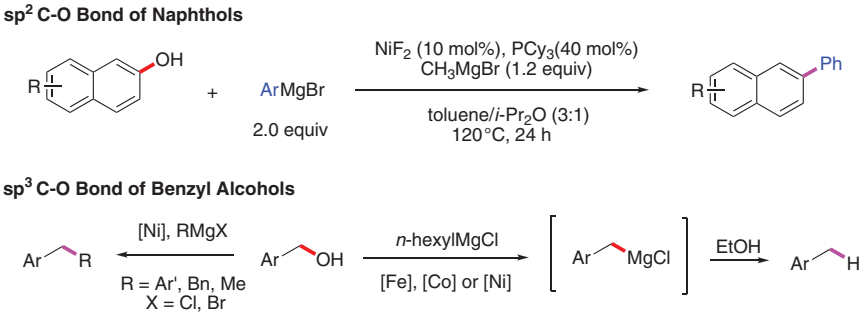


Fig. 3 The length of C–O, C–B bond in the borate crystal, 2-naphthol and boronic ester.



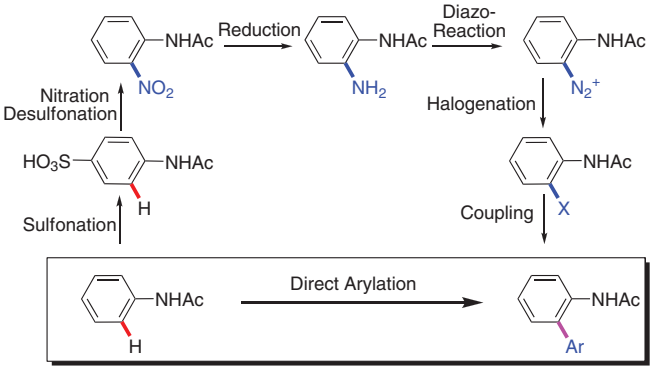
Scheme 5 Magnesium cation-promoted sp^2 and sp^3C–O bond activation.

choice. Despite the difficulties such as high bond dissociation energy, poor coordination ability to metal catalysts and the hard selectivity control of C–H bond, chemists have developed numerous methods to functionalize the C–H bond since 1960s [27]. Unlike the C–halogen and C–O bond, C–H bond has nucleophilic carbon center. When it reacts with nucleophiles, the addition of extra oxidant is required to neutralize the electrons. This transformation is termed as "oxidative coupling" of C–H bonds with nucleophiles. In recent years, this type of coupling has become a very popular approach to carbon–carbon or carbon–heteroatom bond formation [28].

Oxidative coupling of arenes with organometallic reagents

The transformation from aromatic C–H bond to biaryl compounds is quite tedious based on active functional groups by traditional methods. These reactions often require harsh conditions, and produce a lot of harmful wastes. Compared with the above route, direct C–H arylation with organometallic reagents shows its great superiority of atom- and step-economy (Scheme 6). The pioneering work reported by Oi illustrated the feasibility of oxidative coupling of C–H bond with organotin reagents [29]. Compared with organotin reagents, the organosilicon reagents were much less toxic and more available. To date, the Hiyama cross-coupling has been widely investigated [30], while the report of oxidative coupling with organosilicon reagent as the nucleophiles is quite rare. Herein, we demonstrate the first example of C–H arylation with arylsilanes in 2007 [31].

Initially, we chose acetanilide as the substrate. The electron-donating acetamido directing group could not only enhance the electron density of aromatic ring to facilitate the electrophilic palladation step, but also offer the opportunity for further functionalization of the products. In our optimized condition, $Cu(OTf)_2$ was the suitable oxidant to reoxidize Pd(0) back to Pd(II). AgF might play the dual role as the co-oxidant and the fluoride source to facilitate the transmetalation of the organosilicon reagents. Both trimethoxyl- and triethoxyl-arylsilanes were proper coupling partners, while phenyl silanol was not efficient enough. Several kinds

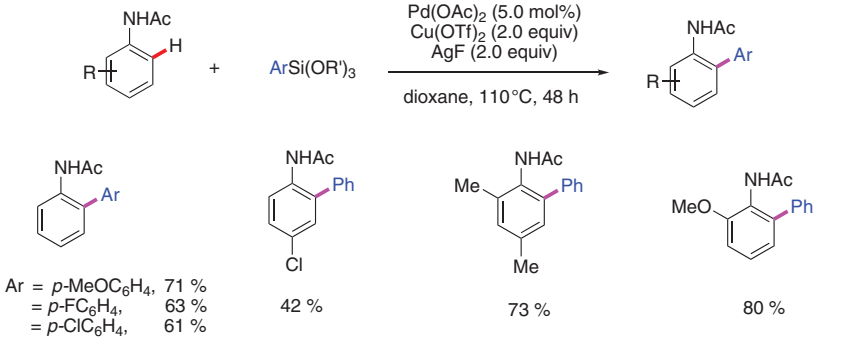


Scheme 6 Direct arylation vs. traditional synthetic pathway.

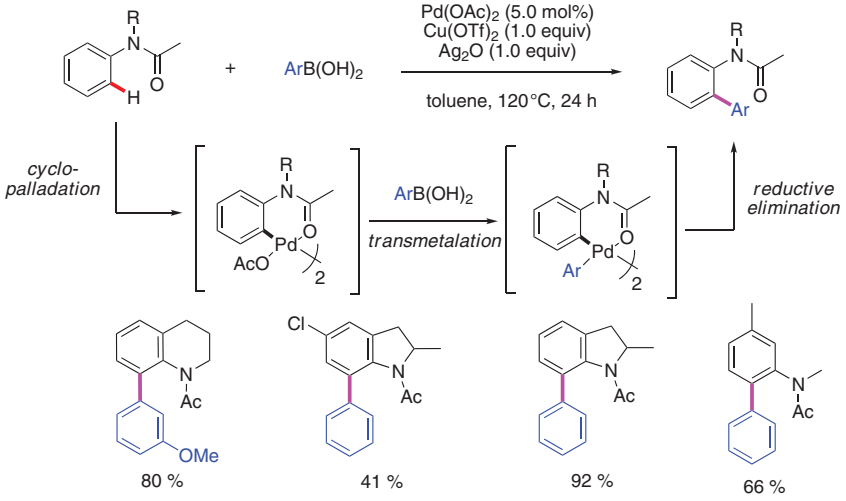
of directing groups were also tested. However, only benzoyl- and formyl-protected aniline gave relatively low yield other than acetanilide. Various functional groups, including halogen atoms, ethers and esters were tolerated (Scheme 7). We proposed that a palladacycle complex was the key intermediate involved in this reaction, which was similar to the observation in our previous work of oxidative C–H halogenations [32] and others' reports [33]. Later on, Loh and Miura also described their discovery in C–H arylation with organosilicon reagents in enamides and heterocycles [34, 35].

The organoboron reagent is another kind of nucleophile most widely used in cross-coupling reactions [36]. After the first catalytic example about the oxidative coupling of aromatic ketones and arylboronates by Kakiuchi [37], Sames and Yu also made their progress in sp^2 and sp^3 C–H oxidative coupling with aryl and alkyl organoboron reagents [38, 39]. On the base of our previous work, we developed the first acetamido group-directed oxidative coupling of *N*-alkyl acetanilides and arylboronic acids [40]. The combination of $Cu(OTf)_2$ and Ag_2O could tune the contradictory requirements of acidity for the electrophilic cyclopalladation and the transmetalation of boronic acids. Different *N*-protected acetamido directing groups were compatible in this reaction. Preliminary mechanistic study indicated that a palladacycle intermediate was generated prior to the transmetalation step (Scheme 8).

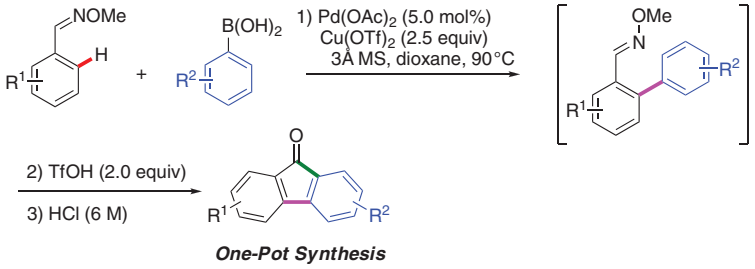
Then we further investigated C–H oxidative coupling with arylboronic acids in different substrates. We managed to realize the *ortho* arylation of *O*-methyl oximes. More interestingly, we also developed the cascade arylation/annulation to form 9*H*-fluoren-9-one derivatives in one pot (Scheme 9) [41]. Furthermore, the C2-selective arylation of free indole and other heterocycles was also achieved in acidic conditions at room temperature at the first time. Notably, the good reactivity and selectivity of some simple arenes showed the value of this chemistry in synthesis (Scheme 10) [42].



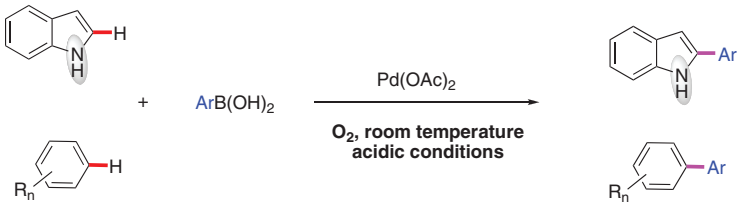
Scheme 7 Oxidative coupling of arenes with arylsilanes.



Scheme 8 Oxidative coupling of arenes with arylboronic acids.



Scheme 9 Cascade *ortho*-arylation/annulation to synthesize fluorenones from aryl oximes.

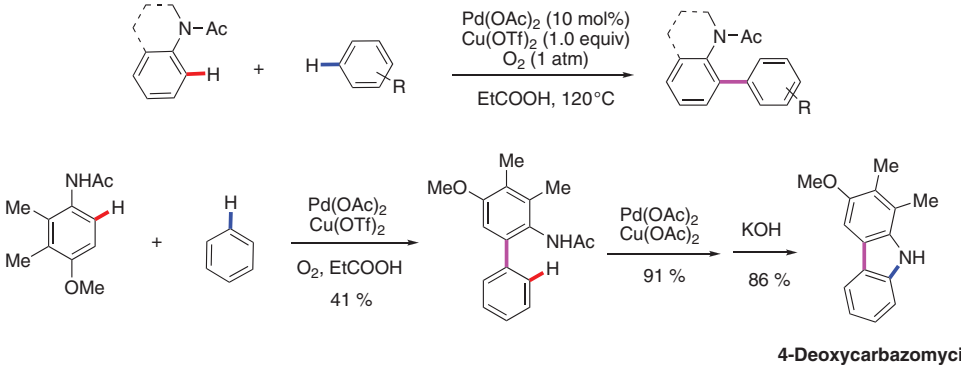


Scheme 10 Pd-catalyzed oxidative arylation of indoles and simple arenes.

Pd(II)-catalyzed cross dehydrogenative arylation

Obviously, C–H bond itself is a nucleophile superior to others for its abundance in nature and free of pre-activation. In contrast to the well-developed Pd-catalyzed homo-coupling of arenes [28a], the cross-coupling of two arene substrates faces the difficulties of controlling chemo- and regio- selectivity of two arene partners. Only limited examples have been reported previous or meanwhile to our work [43]. To solve the problems, we planned to use directing groups to improve the chemo- and regio- selectivity in the cross dehydrogenative arylation (CDA). *N*-acetyl-1,2,3,4-tetrahydroquinoline derivatives were chosen as the substrates. The optimal conditions consisted of $Pd(OAc)_2$, $Cu(OTf)_2$, propanoic acid and O_2 atmosphere. Single isomer was obtained when *o*-xylene was used as the coupling partner. The high regioselectivity was controlled by the directing group in the first C–H activation as well as steric effects in the second C–H activation. Further study indicated that free N–H could also be arylated, which provided the approach to the carbazole derivatives by cascade reaction [44]. Finally, 4-deoxycarbozomycin B was successfully synthesized with this methodology (Scheme 11) [45].

This area has developed quite rapidly in the next several years [28]. Most of the cases focus on the utilization of various directing groups or special substrates (for example, heteroarenes and polyfluoroarenes) to enhance the reactivity and selectivity of C–H bond [46, 47]. But in our mind, it's more attractive to use simple arenes to synthesize valuable compounds directly, which could dramatically broaden the substrate



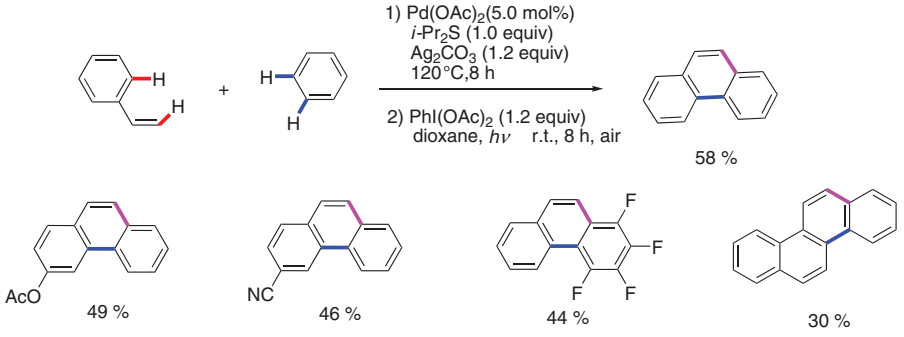
Scheme 11 Pd(II)-catalyzed cross dehydrogenative arylation and its application in the synthesis of 4-deoxycarbazomycin B.

scope of the oxidative coupling between C–H bonds. Thus we pay our attention to the synthesis of polycyclic aromatic hydrocarbons (PAHs), which are the fundamental frameworks of graphenes. Even for the simplest polycyclic molecule phenanthrene, the traditional synthesis pathway is rather complicated and lots of harmful reagents are employed [48]. In our original design, we planned to realize the straightforward synthesis of phenanthrenes from styrenes and arenes by dual oxidative coupling of alkene and aryl C–H bonds. Firstly, we successfully optimized Pd-catalyzed Heck-type oxidative coupling between benzene and styrene. However, the *trans*-stilbene obtained in the first step didn't fulfill the requirement of the second dehydrogenative annulation in configuration. Therefore, we conducted a photo-promoted oxidative annulation in the presence of $PhI(OAc)_2$ to convert the *trans*-stilbene to phenanthrene in good yields. When we carried out these two steps in semi-one-pot fashion, a variety of functionalized fused aromatic rings were obtained in moderate yields directly from styrene and benzene derivatives through this effective and practical protocol (Scheme 12) [49].

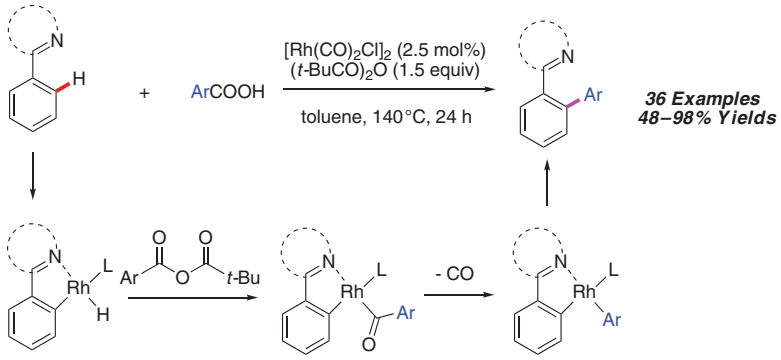
Redox-economic cross-coupling of carboxylic acids with aromatic C–H bonds

The oxidant is the essential element in the oxidative coupling. It can maintain the catalytic cycle by reoxidizing the low-valent metal generated from reductive elimination to active species. However, at recent stage, clean oxidants such as O_2 and H_2O_2 are not universal for all the cases. High cost and toxic oxidants, especially the late transition metals, play the predominant role in oxidative couplings, which brings a stoichiometric amount of waste. Besides the C–H activation initiated by the electrophilic metalation of high-valent metals, an alternative strategy is the C–H bond oxidative addition to low-valent metal center, thus also generates the organometallic complex for the following transformation [50]. In this pathway, C–H bond acts as the "oxidant" for the coupling and avoids the use of additional oxidants, which achieves the goal of redox-economy.

Carboxylic acids are considered as important coupling partners for its availability, stability and non-toxicity. In previous studies, the direct decarboxylative coupling of carboxylic acids and arenes required the participation of oxidants [51]. When we turned to the low-valent metal catalytic system, we discovered the first example of cross-coupling between aryl carboxylic acids and arenes without the use of extra oxidants [52]. The result of optimization indicated $[Rh(CO)_2Cl]_2$ exhibited the best catalytic activity in the presence of $(t\text{-BuCO})_2O$. This reaction had very broad substrate scope: various functionalities were tolerated well and different *N*-containing groups could serve as efficient directing groups. In mechanistic study, we detected the generation of CO other than CO_2 by GC-MS, which implied a different pathway from typical decarboxylative couplings. We suggested that a Rh(III)-hydride species was firstly formed *via* C–H bond oxidative addition to Rh(I) catalyst. Then it was converted to the acyl Rh(III) intermediate after reacting with the mixed anhydride generated from the carboxylic acid and pivalic anhydride. The following decarbonylation and reductive elimination led to the final product (Scheme 13).



Scheme 12 Straightforward synthesis of polycyclic aromatic hydrocarbons (pahs) from styrenes and arenes.



Scheme 13 Cross-coupling of carboxylic acids with aromatic C–H bonds directed by *N*-containing groups.

Conclusion and outlook

As shown above, nowadays, cross-coupling by C–H and C–O activation instead of involving organic halides represents the trend of the development in methodology. A lot of exciting breakthroughs have been achieved in the past decades. However, several challenges such as harsh condition, limited substrate scope and the utilization of high cost and toxic noble metals still remain. In our opinion, efforts in future will mainly focus on three aspects. Firstly, we should solve the old problems in the known transformations. Our groups has developed methods to replace the noble transition metal catalysts with normal transition metals [53], or even organo-catalysis system in C–H arylation [54, 55]. Secondly, more efficient catalytic systems which can facilitate the transformation on sp^3 carbon center are required. Finally, novel types of transformations should be explored. For example, the C–H nucleophilic addition to polar double bonds would be a good choice to replace the use of moisture-sensitive Grignard and lithium reagents in the future [56]. And the coupling between C–H and C–O bond, as described by the leading discovery of Itami [57] and Yi [58], is a meaningful combination of ideal nucleophile and electrophile for organic synthesis.

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