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TRANSITION METAL CATALYZED *META*-C–H FUNCTIONALIZATION OF AROMATIC COMPOUNDS

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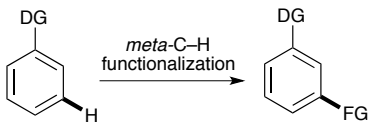
ABSTRACT: Direct functionalization of C–H bonds represents a powerful strategy for the synthesis of complex organic compounds due to its inherent efficiency. Among various approaches, transition metal catalyzed direct activation of unreactive C–H bonds is particularly effective for this purpose. However, the development of practical methods for transition metal catalyzed direct C–H functionalization has been challenging. Apart from identifying reaction conditions that allow activation of the relatively unreactive C–H bonds, these reactions also need to be selective, allowing one C–H bond to be differentiated from the rest of the ubiquitous C–H bonds of the compound. Whereas directing group guided, transition metal catalyzed *ortho*-C–H functionalization of aromatic compounds has seen significant growth in the past decades, methods for *meta*-C–H functionalization of arenes also have emerged. This review summarizes approaches for directing group guided, transition metal catalyzed *meta*-C–H functionalization of aromatic compounds. Some steric controlled, transition metal catalyzed formal *meta*-C–H functionalization reactions without coordinating directing groups are also discussed.

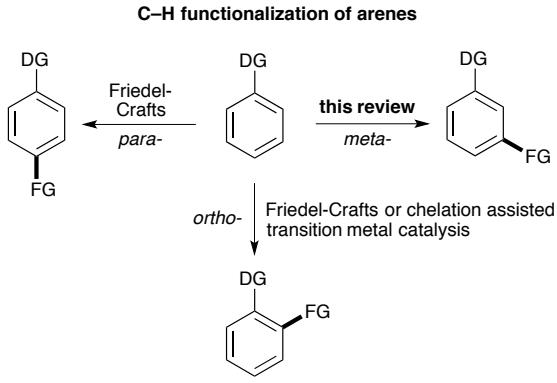


INTRODUCTION: Developing new organic synthesis techniques to meet the increasing

demand of fine chemicals for sustainable growth of the society is an important goal of organic chemistry. In this regard, chemists have been motivated to invent new methods to effectively synthesize small molecules for new pharmaceuticals, agrochemicals, and advanced materials. Organic chemistry has evolved from its infancy into a powerful science that propelled the development of many other scientific fields by enabling unprecedented access of complex organic compounds *via* chemical synthesis. Traditionally, much of the methods for organic synthesis have been based on manipulation of existing functional groups of primary feedstock provided by Nature or obtained from the petro-industry. Thus, the recent development of direct C–H functionalization is particularly notable as it allows direct conversion of the ubiquitous C–H bonds into C–C and C–X bonds without functional group manipulations,[1] thus allowing access of functionalized organic compounds with unprecedented efficiency.

Notwithstanding the tremendous development of C–H functionalization in the past decades and its major impact on the way of organic synthesis, many challenges exist. Apart from identifying reaction conditions that would allow activation of the relatively unreactive C–H bonds without homo-coupling of substrates, these reactions also need to be regioselective, allowing one C–H bond to be differentiated from the rest of the ubiquitous C–H bonds. In the past decades, the development of regioselective C–H functionalization has been closely associated with elucidating the inherent reactivity of C–H bonds and exploiting approaches to override such reactivity. These developments have been quite successful with aromatic compounds. Particularly, chelation-assisted C(sp^2)–H activation has evolved into a powerful tool for *ortho*-C–H functionalization of aromatic compounds,[2] which traditionally relied on the classical electrophilic Friedel-Crafts C–H acylation/alkylation of electron-rich or electron-neutral substrates.[3] On the

other hand, *meta*-selective C–H functionalization of arenes remains a significant challenge and in many cases still requires inefficient multi-step manipulations. Since aromatic compounds are ubiquitous in biomedically relevant agents and in advanced materials, synthetic methods that allow direct *meta*-C–H functionalization of arenes are highly desirable. In the past few years, innovative solutions to this elusive problem started to emerge. This review highlights these advances and showcase the state-of-the-art of transition metal catalyzed *meta*-C–H functionalization of aromatic compounds, and hopefully facilitates/encourages further development of this challenging but important research area.

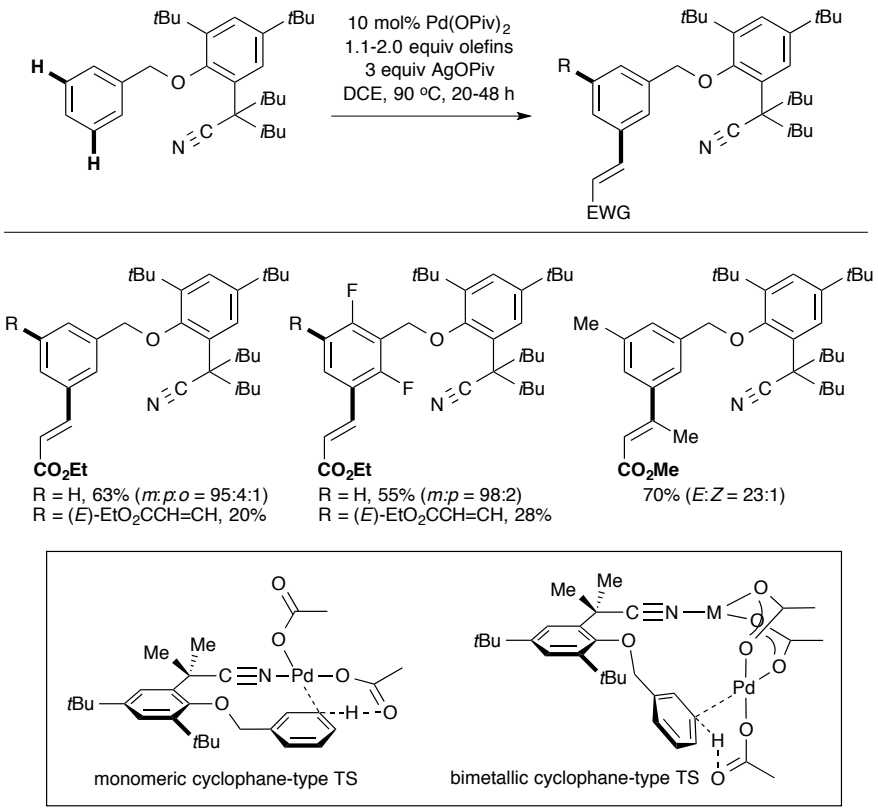


***Meta*-C–H functionalization under the direction of nitrile-containing templates:** Coordinating functional groups have been frequently used as directing groups in transition metal catalyzed C–H functionalization reactions. It is generally believed that these functional groups coordinate with and bring transition metals into proximity of C–H bonds to enable regioselective cyclometallation, such as by concerted metallation/deprotonation (CMD),[4] and allow subsequent transformations of the C–H bonds, often irrespective of the substitution pattern and electronic nature of the substrates. This strategy has seen enormous success in *ortho*-C–H functionalization of arenes by formation of five- and six-membered metallacycle intermediates. However, a

similar chelation-assisted *meta*-C–H functionalization would be challenging due to the difficulty in forming the energetically and conformationally demanding cyclophane-like macrocyclic metallacycle intermediates. Recently, in a series of publications, Yu and co-workers described an innovative approach to address this challenge using designed templates with nitrile as the coordinating group. Incorporated in elaborately engineered spacing groups for conformational pre-organization, these linear nitrile groups weakly coordinate with transition metals in an extended "end on" mode,[5] allowing the cyclophane-type transition states for *meta*-C–H activation.

In the initial report, toluene derivatives conjugated with such a nitrile-containing template via a benzyl ether linkage were reacted with electron-deficient olefins in the presence of $Pd(OPiv)_2$ and AgOPiv (Scheme 1).[6] The C–H olefination products were obtained with excellent *meta*-selectivity. This directing group could be readily removed by Pd/C-mediated hydrogenolysis, with concomitant reduction of the alkene, to give the *meta*-alkylated toluene as the product (not shown). Bis-*meta*-C–H olefination occurred when both of the *meta*- positions are available. Remarkably, the olefination reaction also occurred with *ortho*,*ortho*-disubstituted arenes, demonstrating the excellent *meta*-directing effect of the directing group. The reaction is compatible with both electron-donating and electron-withdrawing substituents of the arene for coupling with electron-deficient olefins such as acrylates, ethyl vinyl ketone, diethyl vinyl phosphonate, *etc*. The unique reactivity of the system also was demonstrated in the *meta*-C–H olefination using di- and tri-substituted electron-deficient olefins, which typically are unreactive in chelation-assisted *ortho*-C–H olefination by transition metal catalysis. The extensively engineered aryl spacing group was reported to be essential for the directing effect. It was hypothesized that the geometric constraint imposed by the aryl spacing group, the steric

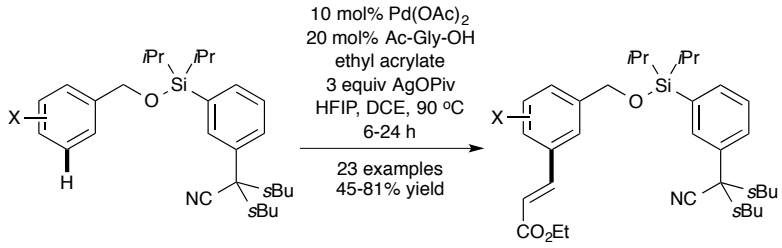
interactions of the benzyl ether linkage and the adjacent *t*Bu, and the Thorp-Ingold effect by the two isobutyl groups α- to the nitrile collectively distort the template toward a cyclophane-like conformation, and enable Pd(II)-mediated *meta*-C–H activation. Interestingly, a recent density functional theory study suggested a bimetallic (i.e. Pd-Pd or Pd-Ag) cyclophane-type transition state of the reaction (see inset of Scheme 1). Its slightly larger macrocyclic metallacyclophane allows some of the ring strains of the monomeric transition state to be relieved.[7]



Scheme 1. Pd-catalyzed *meta*-C–H olefination using a nitrile end-on template

Inspired by Yu's report, Tan and co-workers developed a silicon-tethered *meta*-directing group using the nitrile-containing template (Scheme 2).[8] A di-substituted phenyl group was also used as part of the spacing group to join the nitrile fragment and the silicon

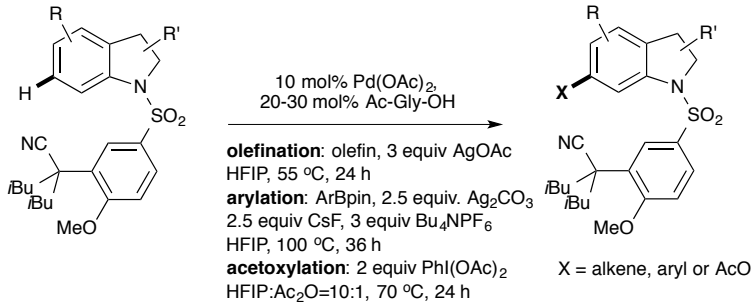
tether. Interestingly, 1,3- instead of 1,2-disubstitution of the phenyl of the spacing group was found to be optimal for the *meta*-directing effect, likely due to the larger size of the silicon atom along with elongated Si–C and Si–O bonds require greater separation of the nitrile and the silicon. This directing group could be tethered to primary and secondary alcohols under standard silyl protection/deprotection conditions. A catalytic system of $Pd(OAc)_2$/*N*-acyl glycine, along with silver acetate and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in dichloroethane allowed *meta*-C–H olefination with electron-deficient olefins containing ester, amide, ketone, and sulfone groups. The reaction was reported to be compatible with all the aromatic substitution patterns that had been tested. Whereas formation of bis-olefination products could not be avoided, the reactions proceeded with high *meta*-selectivity (up to *meta*:*others*=98:2) regardless of the substrate's electronic nature.



Scheme 2. Pd-catalyzed *meta*-C–H olefination using a silicon-tethered directing group

Recently, a similar *meta*-directing group featuring a sulfonamide linkage also has been developed by Yu, Movassaghi, and co-workers (Scheme 3).[9] In addition to serving as a covalent linker, the electron-withdrawing sulfonamide group also contributes by tampering the electron-rich indoline ring system of its intrinsic *ortho*-/*para*- reactivity toward electrophilic reactions. This *meta*-directing group was reported to be effective for

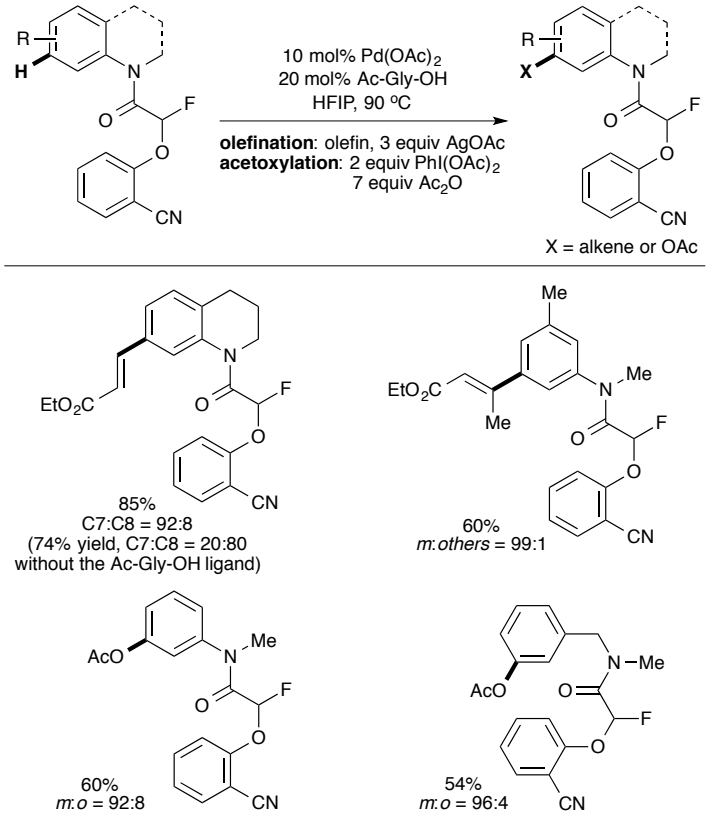
the C–H functionalization with a number of groups under the catalysis of $Pd(OAc)_2$ and *N*–acetyl glycine, the latter of which proposed to switch the C–H activation from an electrophilic palladation process to a concerted metallation/deprotonation (CMD) pathway.[10] Using excess of AgOAc as the oxidant, the C–H olefination of indolines with electron-deficient olefins occurred with excellent *meta*-selectivity and good yield. *meta*-C–H arylation of indolines was similarly carried out using arylboronic acid pinacol esters in the presence of excess of Ag_2CO_3, CsF, and Bu_4NPF_6. Similarly, this directing group proved to be effective for *meta*-acetoxylation of indolines with (diacetoxyiodo)benzene in the presence of acetic anhydride. In this case, substantial amounts of *para*-acetoxylated indolines (~10%) were also obtained, likely due to competing electrophilic palladation at the electron-rich C5 position.



Scheme 3. Pd-catalyzed *meta*-C–H functionalization of indolines

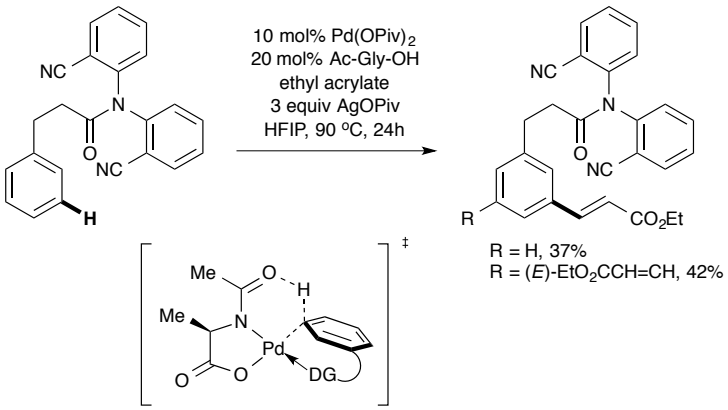
Substitution of organic compounds by fluorine, the most electron-negative element in the periodic table, often has a significant effect over molecular conformation.[11] This effect likely contributed to the observation that, as shown in Scheme 4, the fluorinated directing group gave significantly improved yield and better *meta*-selectivity than the similar but non-fluorinated groups in Pd(II)-catalyzed C–H olefination of tetrahydroquinolines.[12] Indeed, as revealed by the nuclear Overhauser effect (nOe) and X-ray crystallography study, the conformation of the fluorinated directing group was significantly different from

its non-fluorinated analog in that the carbonyl groups oriented in opposite directions. The use of *N*-acetyl glycine as a ligand also is crucial to the selectivity and efficiency of the reaction. It was hypothesized that ligation of *N*-acetyl glycine and the metal center led to a bulkier and more electron-rich catalyst for regioselective reaction at the less sterically hindered and more electron poor C7 position. This catalytic system also could be used with other anilide-type substrates, such as benzoxazines, benzylamines, 2-phenylpyrrolidines and 2-phenylpiperdines for *meta*-C–H olefination with mono-, di-, and tri-substituted electron deficient olefins. The utility of this directing group was further demonstrated in Pd(II)-catalyzed *meta*-C–H acetoxylation using $PhI(OAc)_2$, which proceeded *via* a Pd(II)/Pd(IV) redox cycle. Remarkably, this directing group is effective for *meta*-C–H acetoxylation of benzylamines where the C–H groups are 11 bonds away.



Scheme 4. A fluorinated *meta*-directing group for C–H functionalization

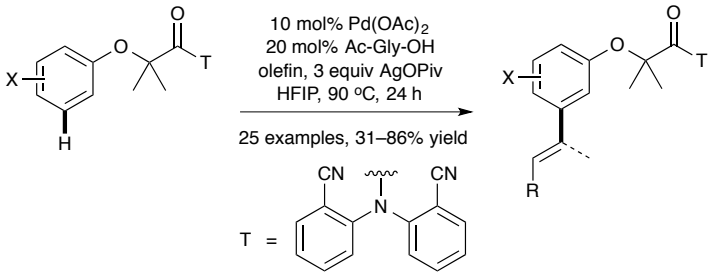
Diphenylamines incorporating the nitrile group have been demonstrated to be excellent directing groups as well for *meta*-C-H activation of arenes. Conjugated to hydrocinnamic acids *via* an amide linkage, these groups allowed $Pd(OAc)_2$-catalyzed *meta*-C–H mono- and di-olefination of arenes with ethyl acrylate (Scheme 5).[6] *N*-Acetyl glycine was found to be an essential ligand for good yield and selectivity.[13] The rigid and symmetrical planar structure of diphenylamines reduced the conformational flexibility of the substrates and presumably allowed "end on" coordination of nitrile and Pd(II) to bring the latter into close proximity of *meta*-C–H bonds. The effect of *N*-acetyl glycine was rationalized using a mechanism in which the amino acid functioned both as a dianionic bidentate ligand and an internal base for concerted metallation/deprotonation of C–H bonds (see inset of Scheme 5). Internal deprotonation by the more basic *N*-acyl carbonyl instead of the carboxylate (when in the absence of *N*-acetyl glycine) contributed to the improved reaction efficiency.[14]



Scheme 5. *meta*-C–H olefination of hydrocinnamic acids

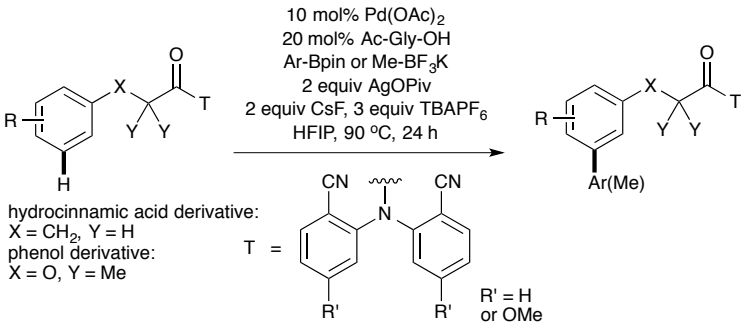
Such a diphenylamine also was used as a directing group for *meta*-C–H functionalization of phenols, overriding the strong *ortho*-/*para*-directing effect of the electron-donating

phenoxyl group. As shown in Scheme 6, phenol-diphenylamine conjugates, prepared by coupling the diphenylamine and phenol *via* an acetic acid linker, underwent Pd(II)-catalyzed C–H olefination with electron-deficient olefins to give mono- and di-olefination products with excellent *meta*- selectivity.[15] The reactions are compatible with both electron-donating and electron-withdrawing substituents on the aryls for coupling with electron-deficient mono- and di-substituted olefins. High selectivity of mono-olefination was obtained when *ortho*-substituted substrates were used. Basic hydrolysis of the amide linkage followed by reaction of the resulting α-aryloxy acetic acid with diphenylphosphoryl azide (DPPA) gave the *meta*-olefinated phenol products (not shown).



Scheme 6. *meta*-C–H olefination of phenols

The utility of these groups was further demonstrated in the *meta*-C–H arylation of hydrocinnamic acids and phenols with aryl boronic esters to give substituted biaryls (Scheme 7).[16] These reactions employed a catalytic system of $Pd(OAc)_2$ and *N*-acetyl glycine, with Ag_2CO_3 as the stoichiometric oxidant. CsF and $TBAPF_6$ were reported to be important additives for high yield. These reaction conditions also are effective for *m*eta-C–H methylation when $MeBF_3K$ instead of aryl boronic ester was used.



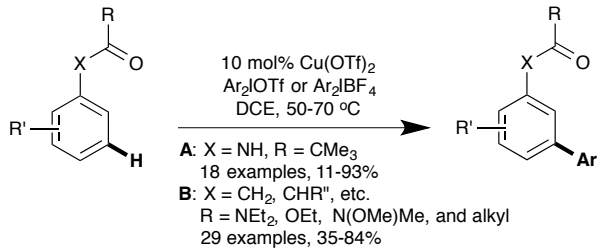
Scheme 7. *meta*-C–H arylation of hydrocinnamic acids and phenols

Cu-catalyzed *meta*-C–H arylation of arenes

The amido group has been a classical *ortho*/*para*- directing group for electrophilic substitution of arenes. It also has been frequently employed as a powerful *ortho*-directing group for transition metal catalyzed C–H activation of arenes *via* chelation-assisted cyclometallation. Thus, it was quite unexpected when Phipps and Gaunt discovered that the amido group would direct *meta*-C–H arylation of arenes with Ar_2IOTf under the catalysis of $Cu(OTf)_2$ (Scheme 8, condition **A**),[17] an electrophilic arylation reaction system previously used by the same group for C3-arylation of indoles.[18] Whereas benzamides and pivanilides were reported to be the most effective directing groups for the reaction, the carbamate and urea groups also allowed the *meta*-selective reaction to occur with moderate efficiency. Except for strongly electron-donating *ortho*-/*para*-directing groups (such as methoxyl) which may override the *meta*-directing effect, the amido group was tolerant of a wide range of substitutions of the anilide arene even though more electron-donating substituents tend to give better yields. Diaryliodonium salts with variously substituted arenes also are compatible with the reaction. Bis-*meta*-arylation products were obtained when both of the *meta*- positions are available.

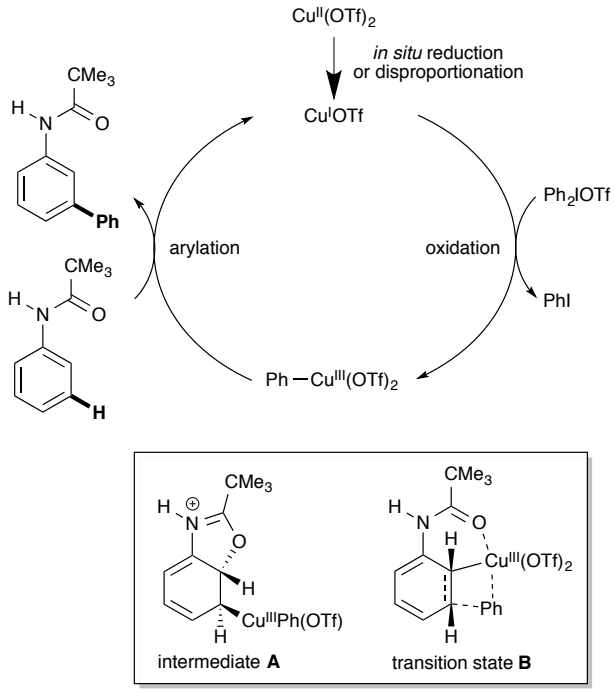
Subsequent studies by the same group showed that other α-aryl carbonyl compounds,

such as amides, esters, and ketones, also underwent the Cu-catalyzed *meta*-C–H arylation reactions (Scheme 8, condition **B**).[19] These reactions were reported to be compatible with diversely substituted aryl groups on both the diaryliodonium salts and the α-aryl carbonyl compounds.



Scheme 8. Cu-catalyzed *meta*-C-H arylation of arenes

These reactions appear to occur through an electrophilic arylation process.[20] However, the origin of the *meta*-selectivity is yet to be understood. In their initial report,[17] Gaunt and Phipps proposed a Cu(I)/Cu(III) catalytic cycle in which formation of intermediate **A** *via* dearomatizing anti-oxycupration by the acetamide carbonyl and a Cu(III)-aryl species to be responsible for the *meta*-selectivity (Scheme 9). Reductive elimination of **A** followed by rearomatization would give the *meta*-C–H arylation product. However, questions were raised about such a mechanism, which requires energy costly dearomatization, electrophilic cupration at the less electron-rich *meta*-position, and nucleophilic *O*–attack at the relatively electron-rich *ortho*-position.[21] Density functional theory study of the reaction by Wu, Li, and co-workers suggested a pathway of initial electrophilic attack of Cu(III) at the *ortho*-position, followed by a Heck-like four membered transition state **B** to effect *meta*-arylation. Further experimental and theoretical studies are necessary to elucidate the mechanism of the reaction.

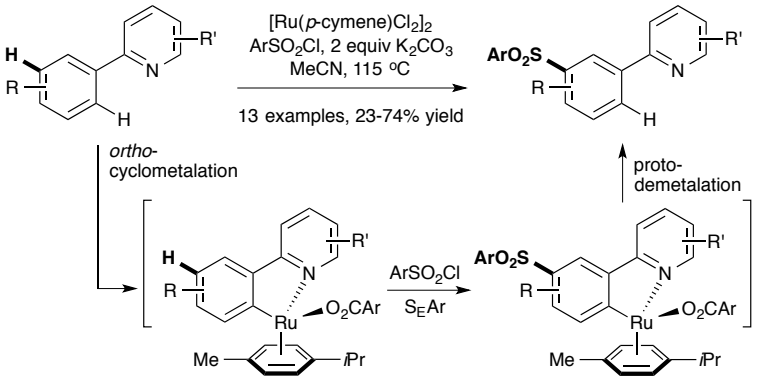


Scheme 9. Proposed Cu(I)/Cu(III)-catalytic cycles for *meta*-C–H arylation

Metallation-dictated *meta*-C–H functionalization

2-Phenylpyridine has been commonly used in transition metal catalyzed *ortho*-C–H functionalization because of its facile chelation-assisted cyclometallation reaction allowing for subsequent C–C or C–X bond formation to occur with relative ease. However, only the *meta*-sulfonation product was formed between 2-phenylpyridine and toluenesulfonyl chloride in the presence of various Ru sources (Scheme 10),[22,23] even though the *ortho*-product was exclusively formed using the same substrates but under Pd(II) catalysis.[24] In order to rationalize this unusual regioselectivity, Frost and co-workers proposed that the chelation-assisted cyclometallation by Ru catalysts did occur to give the metallacyclo intermediate. Instead of further reaction at the relatively stable Ru-C_{aryl} σ-bond, the strong *ortho*/*para*-directing effect of the Ru^{II} center by σ-activation led to electrophilic sulfonylation *para*- to the Ru-C_{aryl} bond.[25] The final product was

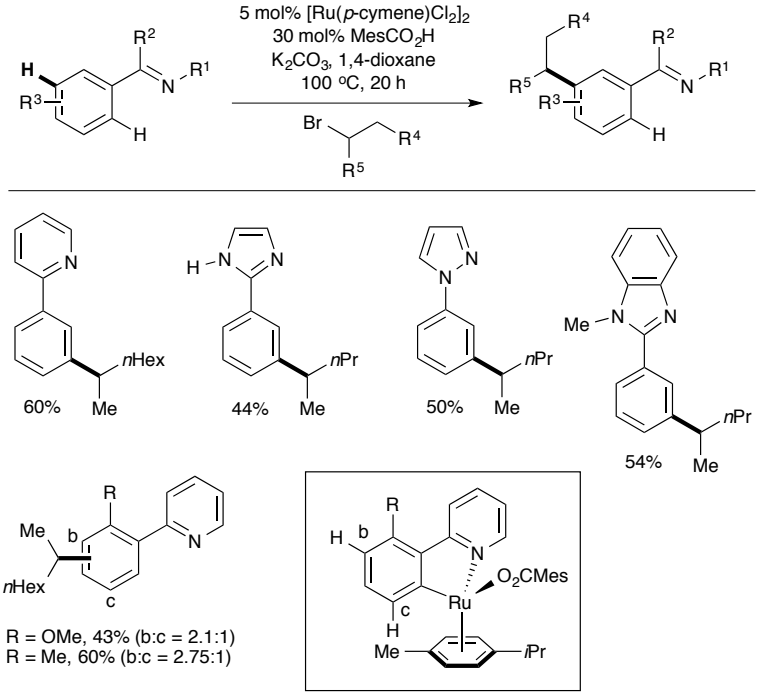
obtained after proto-demetallation. The *ortho*-position was less accessible due to the sterics surrounding the metal center. This hypothesis was supported by the observation that 2-(*m*-tolyl)pyridine failed to react with toluenesulfonyl chloride under the conditions. Since the chelation-assisted cyclometallation of 2-(*m*-tolyl)pyridine would occur at the more accessible *ortho*-C–H bond, the methyl group of the *m*-tolyl would be *para*- to the newly formed Ru-C_{aryl} bond, blocking the electrophilic sulfonylation reaction (not shown).



Scheme 10. Ru-catalyzed *meta*-sulfonylation of 2-phenylpyridines

Transition metal catalyzed C–C bond formation with secondary alkyl halides has been challenging because of the difficulty of oxidative addition at the relatively hindered and electron-rich secondary C–X bond, and the tendency of the alkyl-metal intermediates to undergo β-hydride elimination. However, consistent with the proposed S_EAr-type reaction mechanism, secondary alkyl halides have been reported to be effective alkylating reagents for *meta*-C–H alkylation of 2-phenylpyridines and pyrazolyl-, imidazolyl-, and benzimidazolyl-substituted arenes under the catalysis of $[RuCl_2(p\text{-cymene})]_2$/2,4,6-trimethylbenzoic acid ($MesCO_2H$) (Scheme 11).[26] When an enantiomerically enriched secondary alkyl halide was used as the substrate, its stereochemical information was lost during the reaction. *meta*-Substitution of the arene substrates led to significantly

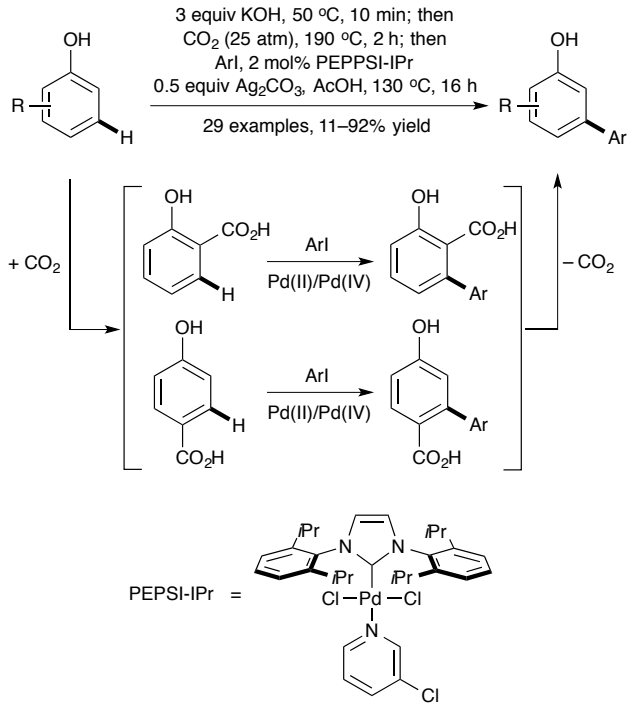
reduced yield, which is in parallel with the low reactivity of 2-(*m*-tolyl)pyridine toward sulfonylation by Ru-catalysis (*vide supra*). The alkylation of *ortho*-substituted arenes with 2-bromooctane led to mixtures of 1,2,3- and 1,2,5-trisubstituted arenes favoring the more congested 1,2,3-isomer. While counter intuitive, this observation could be readily explained using the proposed S_EAr-type reaction mechanism because the initially formed ruthenocycle (see inset in Scheme 11) would favor electrophilic alkylation *para*- to the Ru-C_{aryl} bond to give the more congested 1,2,3-trisubstituted arenes. Formation of the 1,2,5-trisubstituted isomers by electrophilic alkylation *ortho*- to the Ru-C_{aryl} bond is less favored due to steric shielding by the bulky Ru-*p*-cymene complex. Interestingly, only the *ortho*-alkylation product was formed when *n*-hexyl bromide were used (not shown). This observation was rationalized using the varying sterics and electrophilicities between primary and secondary alkyl halides.[27]



Scheme 11. Ru-catalyzed *meta*-alkylation of 2-phenylpyridines with secondary alkyl halides

***meta*-C–H functionalization *via* a traceless directing group relay strategy**

The weakly coordinating carboxyl group is an excellent directing group for *ortho*-cyclometallation of arenes in a wide range of transformations.[28] Using a CO_2-based traceless directing group strategy,[29] Larrosa and co-workers exploited the *ortho*-directing effect of a temporarily introduced carboxyl group for formal *meta*-C–H arylation of phenols.[30] This one-pot procedure started with carboxylating the phenol with KOH under 25 atm of CO_2 at 190 ^oC, followed by treating the reaction crude with iodoarenes, PEPPSI-IPr, Ag_2CO_3, and AcOH at 130 ^oC for 16 h (Scheme 12). Under these reaction conditions, C–H arylation of the hydroxylbenzoic acid intermediates occurred *ortho*- to the temporarily introduced carboxyl group *via* a Pd(II)/Pd(IV) catalytic cycle, which was followed by spontaneous proto-decarboxylation to give *meta*-arylated phenols. The procedure was reported to be completely *meta*-selective and gave mono-arylation products only. Interestingly, mechanistic studies showed that both the *ortho*- and *para*-hydroxylbenzoic acid intermediates were formed initially. However, since both of these isomers underwent carboxyl-directed C–H arylation *meta*- to the hydroxyl group, the two isomeric intermediates were converged to the same *meta*-arylated phenol product after proto-decarboxylation. This one-pot procedure is compatible with a wide range of substrates except for *ortho*-substituted aryl iodides or *para*-substituted phenols, both of which would cause significant steric encumbrance for Pd-catalyzed C-C bond formation. In principle, this one-pot procedure is applicable to other one-pot *meta*-C–H functionalization processes as well.



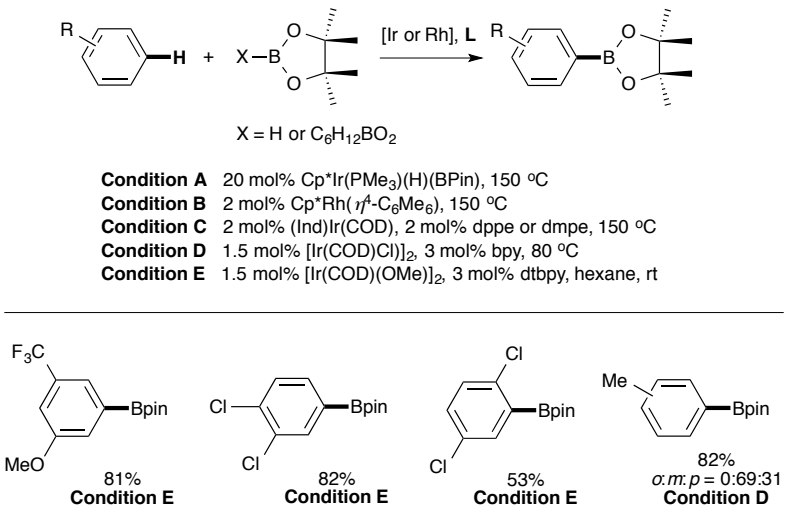
Scheme 12. *meta*-C–H arylation of phenols using a traceless carboxyl directing group relay strategy

Steric controlled formal *meta*-C–H functionalization

Sterics has been a universal factor that affects the kinetics and thermodynamics of chemical reactions. In the absence of dominating electronic factors, sterics may have a major influence over the course of reactions. Cases of transition metal catalyzed C–H functionalization of arenes without directing groups (including those under steric control) have been summarized in an excellent review by Glorius recently.[31] Thus, only a few examples that highlight the key features of steric controlled formal *meta*-C–H functionalization of arenes are covered in this section.

The C–H borylation of arenes is a powerful approach for preparation of arylborons,

which are versatile reagents for a wide range of transformations.[32] Whereas numerous transition metals are capable of catalyzing this transformation, iridium complexes have emerged as among the most efficient. For example, Smith, Maleczka, and co-workers demonstrated catalytic C–H borylation of arenes with pinacolborane (HBPin) using Cp*Ir(PMe_3)(H)(BPin) or Cp*Rh(η^4-C_6Me_6) as the catalyst (Scheme 13, **A** and **B**).[33] The same group also showed that more active catalysts could be obtained combining (Ind)Ir(COD) (Ind = η^5-C_9H_7, COD=1,5-cyclooctadiene) and a phosphine ligand, such as trimethylphosphine, 1,2-bis(dimethylphosphino)ethane (dmpe), or 1,2-bis(diphenylphosphino)ethane (dppe) (Scheme 13, **C**).[34] Concurrent with this study, Ishiyama, Miyaura, Hartwig, and co-workers developed the [Ir(COD)Cl]$_2$/2,2'-bipyridine (bpy) system as an exceptionally active catalyst for C–H borylation of arenes with bis(pinacolato)diboron (pin_2B_2, pin=$Me_4C_2O_2$) at 80 ^oC (Scheme 13, **D**).[35] Both boryl groups of the diboron participated in the reaction. Pinacolborane was also a viable boron source for the reaction. Continued optimization efforts also led to discovery of the combination of [Ir(COD)(OMe)]$_2$ and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy), which allowed the reaction to be carried out with remarkably high turnover numbers (Scheme 13, **E**).[36] In addition, this catalytic system allowed the reaction at room temperature in non-polar solvents (such as hexane) and excess of arene substrates were no longer necessary. This reaction has been reported to be compatible with a wide range of functional groups, such as halides (Cl, Br, and I), alkoxides, esters, nitriles, etc.

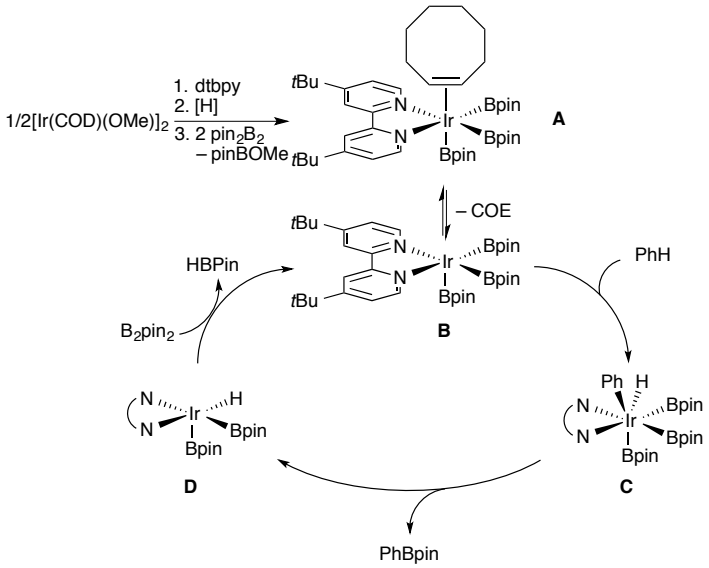


Scheme 13. Steric-controlled aryl C–H borylation

Despite the differences of the catalytic systems, these reactions share a common feature that the regioselectivity being mostly under steric control. Thus, 1,2- and 1,3-disubstituted arenes undergo Ir-catalyzed C–H borylation to give 1,2,4- and 1,3,5-trisubstuted arenes, respectively, with the boryl group introduced at the least hindered site, formally *meta*- to at least one of the substituents (Scheme 13). On the other hand, statistical mixtures of *meta*- and *para*-borylation products were formed when mono-substituted arenes were used. 1,4-Disubstituted arenes often give lower yield for the reaction, presumably a result of steric congestion at the transition state.

Mechanistic study of the Ishiyama-Miyaura-Hartwig system showed that the COD ligand was reduced to cyclooctene (COE) and the Ir(I)–dtbpy pre-catalyst underwent oxidative addition with B_2pin_2 to give Ir(III) trisboryl complex **A** and **B**, with the latter the likely catalytic species (Scheme 14).[35a,37] Oxidative addition (or σ–bond metathesis) of **B** by benzene gave Ir(V) complex **C**, which underwent reductive elimination to form **D** and concomitantly the C–H borylation product. Further reaction of **D** and B_2pin_2 regenerated **B** and completed the catalytic cycle. A similar Ir(III)/Ir(V) catalytic cycle was proposed by

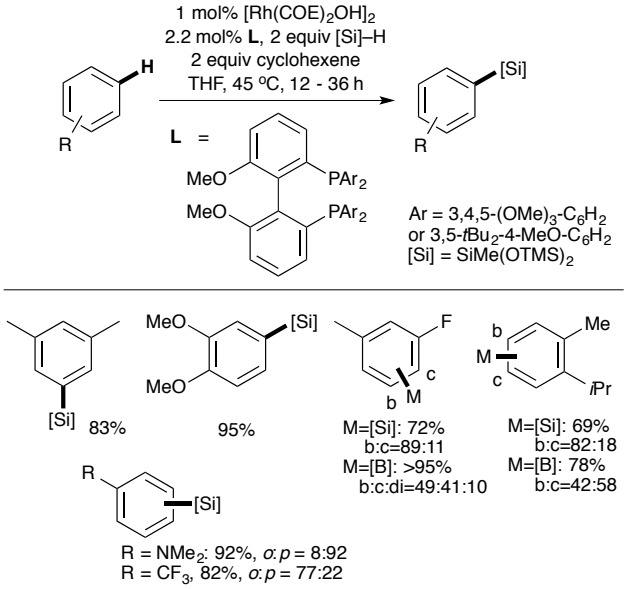
Smith and co-workers to account for the activity of their Ir(I)-phosphine catalytic system.[34] The superior activity of Ir(I)-dtbpy has been attributed to its increased solubility and that the *tert*-butyl group protected the ligand itself from being borylated. The methoxyl group of the iridium source (i.e. $[Ir(COD)(OMe)]_2$) also may have contributed to the increased reactivity by facilitating formation of the reactive (boryl)iridium complex.[36a]



Scheme 14. A proposed mechanism for Ir(I)/dtbpy-catalyzed aryl C–H borylation

Recently, a rhodium-catalyzed C–H silylation of arenes has been reported by Hartwig and Cheng.[38] Using cyclohexene as a scavenger of hydrogen, a catalytic system of $[Rh(COE)_2OH]_2$/2,2'-biphenylphosphines was found to be particularly effective for C–H silylation of arenes with $HSiMe(OTMS)_2$ to afford arylsilanes in good yields without using excess of reagents (Scheme 15). These reactions proceed under steric-control, with regioselectivities parallel those of the iridium catalyzed C–H borylation of arenes, but are more sensitive to the size of the remote functional groups. For example, the Rh-catalyzed C–H silylation of 3-fluorotoluene occurred with a selectivity of 89:11, favoring the mutual *meta*- site, but the Ir-catalyzed C–H borylation of the same substrate has

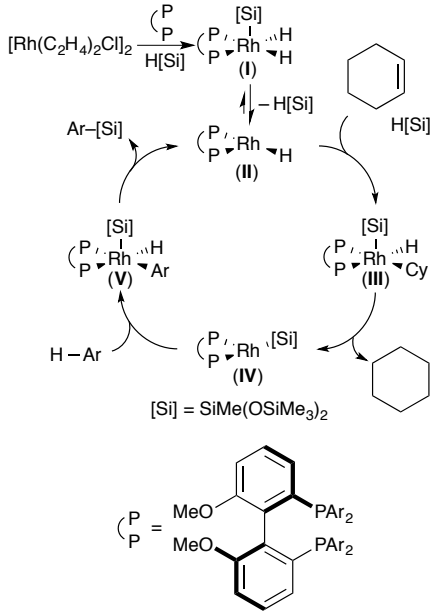
been unselective. Further, the Rh-catalyzed C–H-silylation of *o*-cymene afforded products with a selectivity of 82:18, favoring reaction *para*- to the larger of the two substituents. In contrast, a ratio of 42:58 was observed for Ir-catalyzed C–H borylation of the same substrate. This remarkable sensitivity to steric factors had been attributed to the bulky size of the ligand and the silicon reagent, and the use of rhodium. The silylation of *mono*-substituted arenes are less selective, allowing the electronic effects of the substituents manifest themselves in some cases to give silylation products preferentially at the more electron-rich site. For example, the silylation of *N*,*N*-dimethylaminobenzene occurred predominantly at the more electron-rich *para*-site while the silylation of trifluoromethylbenzene occurred preferentially at the less electron-poor *meta*-position.



Scheme 15. Rh-catalyzed C–H silylation of arenes

Detailed experimental and computational studies suggested a catalytic cycle as shown in Scheme 16,[39] with distorted square-based pyramidal silylrhodium dihydride complex **I**

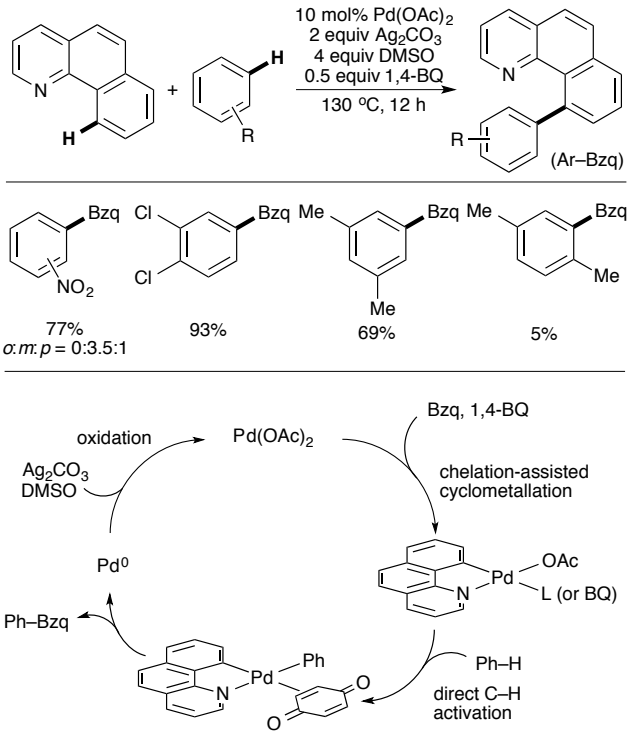
(isolated in crystalline form) as the resting state of the catalyst, but in equilibration with **II**. Oxidative addition of silane and hydrogen transfer to cyclohexene converted **II** to bisphosphine-ligated Rh(I) silyl intermediate **IV**. The cleavage of aryl C–H bond occurred by oxidative addition of **IV** to give **V**, which underwent reductive elimination to form the arylsilane and regenerated **II**.



Scheme 16. A proposed mechanism for Rh-catalyzed C–H silylation of arenes

Other transition metals also have been used for steric-controlled formal *meta*-C–H activation of arenes, but only a few examples are shown here. In 2007, Sanford and Hull reported an interesting Pd-catalyzed oxidative C–H cross coupling of coordinating benzo[*h*]quinoline (Bzq) (or 2-arylpyridine, 1-arylpyrazole, 2-arylpyrimidine, 8-methylquinoline, etc.) with non-coordinating arenes in the presence of Ag_2CO_3, 1,4-benzoquinone (BQ), and DMSO (Scheme 17).[40] The reaction proceeded with excellent chemoselectivity despite the potential of competing homo-dimerization of substrates. The proposed reaction pathway included: (i) chelation-assisted cyclometallation of Bzq

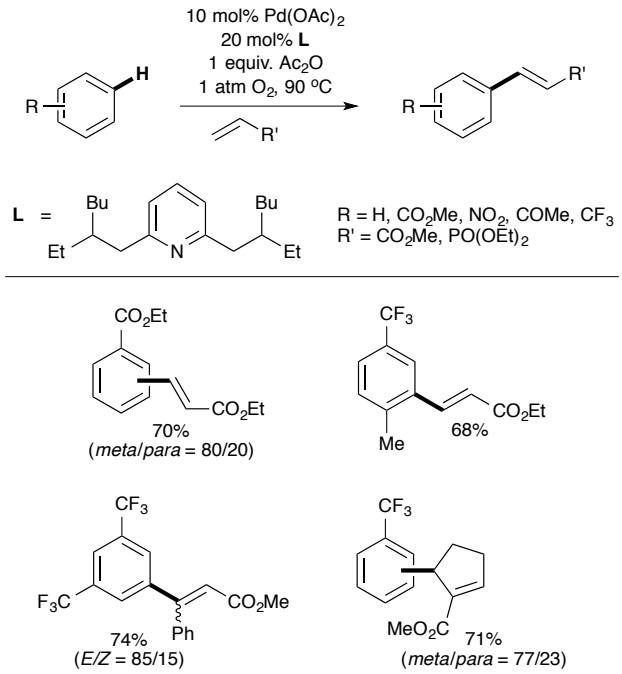
with Pd(II), (ii) 1,4-BQ coordinate with cyclometallated Pd(II), promoting direct C–H activation of the non-coordinating arene, (iv) reductive elimination to afford the cross coupling product and Pd(0), (v) re-oxidation of Pd(0) by Ag_2CO_3. The C–H activation of non-coordinating arenes proceeded under steric control. The reaction of Bzq and mono-substituted arenes gave mixtures of mostly *meta*- and *para*- coupling products, but regioselective cross coupling was observed with symmetrical 1,2- and 1,3-disubstituted arenes which coupled with Bzq at their most accessible sites. Arenes with both electron-withdrawing and electron-donating functional groups had been reported to be compatible with the reaction. However, the cross coupling using 1,4-disubstitution of benzene led to lower yield, possibly due to the steric interference of the substituents.



Scheme 17. Regioselective C–H cross coupling of benzo[*h*]quinoline and arenes

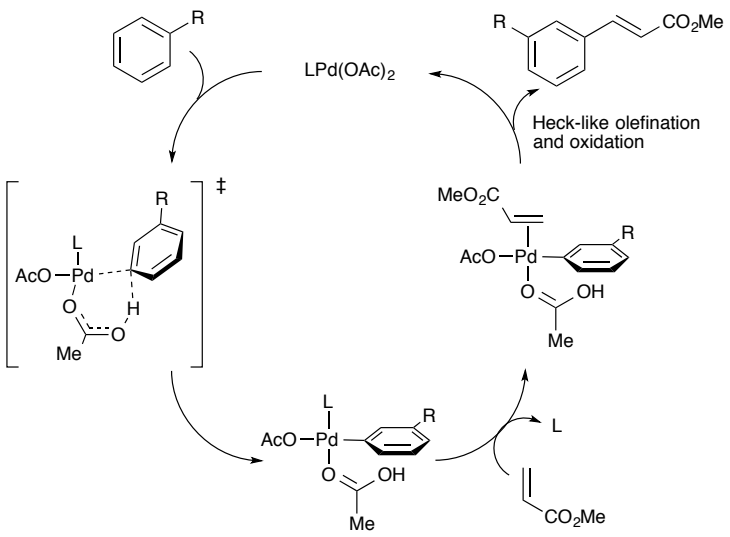
Electron-rich arenes are typically used for Pd(II)-catalyzed oxidative Heck-type coupling

with olefins.[41] In 2009, Yu and co-workers described the first example of Pd(II)-catalyzed C–H olefination of highly electron-deficient arenes (Scheme 18).[42] Their initial studies using simple 2,6-disubstituted pyridines as the ancillary ligand had been unsuccessful. Hypothesizing that facile dissociation of one of the two pyridyl ligands from the bis-coordinating complex of Pd(II) would be necessary for the reaction, it was proposed that 2,6-disubstituted pyridines with minimal steric hindrance immediately surrounding the pyridyl nitrogen, but with hindrance on ligand side chains would be desirable. These ligands would allow effective Pd–N coordination but disfavor bis-coordination of Pd with two pyridyl ligands. After extensive optimization, 2,6-bis(2-ethylhexyl)pyridine was found to be a suitable ligand for Pd(II)-catalyzed olefination of electron-deficient arenes. The reactions were carried out with excess arenes using 1 atm of O_2 as the stoichiometric oxidant and Ac_2O as an additive to accelerate catalyst turnover. The olefination of mono-substituted arenes gave mixtures of *meta*- and *para*- isomeric products in approximately 4:1 ratio, with no *ortho*-olefination product observed. Only the C5-olefination product was generated from 1,3-disubstituted arenes. Unsymmetric 1,4-disubstituted arenes underwent olefination *meta*- to the electron-withdrawing group. Di- and tri-substituted electron-deficient olefins have been reported to be compatible with the reaction as well.



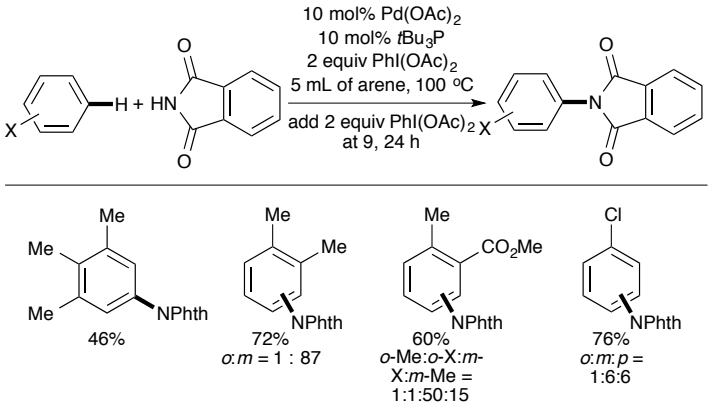
Scheme 18. Pd-catalyzed C–H olefination of electron-deficient arenes

Theoretical study of the reaction by Zhang and co-workers supported a reaction mechanism shown in Scheme 20.[43] It featured direct C–H activation by Pd(II) via concerted metallation/deprotonation (CMD), followed by ligand exchange to give a Pd(II)-olefin complex, which underwent a Heck-like coupling to form the product. The moderate *meta*- selectivity with mono-substituted arenes has been attributed to a minor electronic effect while the steric effect was responsible for the lack of *ortho*-olefination product.



Scheme 19. A proposed mechanism for Pd(II)-catalyzed C–H olefination

Hartwig and co-workers recently described a steric controlled, Pd-catalyzed C–H amination of arenes with phthalimide using $PhI(OAc)_2$ as the oxidant.[44] High throughput methods were used to explore variables that may affect the reaction. The optimized reaction conditions consist of portionwise addition of $PhI(OAc)_2$ to arenes in the presence of 10 mol% $Pd(OAc)_2$ (Scheme 20). Slightly higher yields and selectivities were observed in some cases when tBu$_3$P was used as an ancillary ligand. The reaction was compatible with both electron-rich and electron-poor arenes. Monosubstituted arenes form amination products mostly as mixtures of *meta*- and *para*- isomers. High regioselectivity was observed for amination of di- and tri-substituted arenes when the substituents mutually reinforce their steric control.



Scheme 20. Pd-catalyzed C–H amination of arenes

CONCLUSION

Direct C–H functionalization is making a dramatic impact on the way of organic synthesis. Compared with traditional approaches, transition metal catalyzed C–H functionalization allows access of C–C and C–X bonds from the ubiquitous C–H bonds with unprecedented efficiency. However, in order to be synthetically useful, these reactions also have to proceed in a regioselective manner, allowing selective activation of one C–H bond over the rest of the C–H bonds in the molecule. Chelation assisted C–H activation has evolved into a powerful approach for transition metal catalyzed *ortho*-C–H functionalization of aromatic compounds. However, *meta*-selective C–H functionalization remained a significant challenge. Recently, synthetic methods that allow *meta*-selective C–H functionalization have started to emerge. These methods include Pd-catalyzed *meta*-C–H functionalization of arenes using nitrile-containing directing groups, Cu-catalyzed *meta*-C–H arylation of amidoarenes or α-aryl carbonyl compounds, metallation-directed *meta*-C–H sulfonylation and secondary alkylation of arenes by Ru-catalysis, a CO_2-based traceless directing group relay strategy for *meta*-C–H functionalization of phenols, and steric controlled formal *meta*-C–H functionalization

catalyzed by various transition metals. Notwithstanding these major advances, significant challenges remain. For example, (a) whereas the nitrile-containing groups provided an excellent solution for directed *meta*-C–H functionalization, alternative *meta*-directing groups, especially those with higher atom economy, are desirable; (b) methods for *meta*-C–H activation via alternative reaction pathways have to be developed to meet the demand of functionalizing diverse aromatic systems; (c) further studies are necessary to understand the mechanism of *meta*-C–H activation processes and exploit their potential. Despite these challenges, further advances that empower synthetic chemists with efficient tools for *meta*-C–H functionalization are expected.[45]

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REFERENCES

1 For some reviews: (a) A. D. Ryabov, *Synthesis* **1985**, 233. (b) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (c) C. G. Hartung, V. Snieckus, In *Modern Arene Chemistry*; D. Astruc, Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 330−367. (d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174. (f) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013. (g) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417. (h) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (i) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074. (j) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624. (k) T. W. Lyons, M. S.

Sanford, *Chem. Rev.* **2010**, *110*, 1147. (l) T. Satoh, M. Miura, *Synthesis* **2010**, 3395. (m) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315. (n) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740. (o) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885. (p) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788. (q) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31. (r) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (s) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879. (t) J. Wencel-Delord, F. Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (u) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281.

2 (a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726 and ref 4k. For recent accounts on site-selective C–H activation, see: (b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936. (c) T. Brückel, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826. (d) G. B. Shul'pin, *Org. Biomol. Chem.* **2010**, *8*, 4217.

3 (a) C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877**, *32*, 725. (b) C. Friedel, J. M. Crafts, *Bull. Soc. Chim. France* **1877**, *27*, 530.

4 (a) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507. (b) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118. (c) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315.

5 H. Schwarz, *Acc. Chem. Res.* **1989**, *22*, 282.

6 (a) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518. For a comment, see: (b) T. Truong, O. Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 11677.

7 Y.-F. Yang, G.-J. Cheng, P. Liu, D. Leow, T.-Y. Sun, P. Chen, X. Zhang, J.-Q. Yu, Y.-D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 344.

8 S. Lee, H. Lee, K. L. Tan, *J. Am. Chem. Soc.* **2013**, *135*, 18778.

9 G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Yang, M. Movassaghi, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 10807.

10 G.-J. Cheng, Y.-F. Yang, P. Liu, P. Chen, T.-Y. Sun, G. Li, X. Zhang, K. N. Houk, J.-Q. Yu, Y.-D. Wu, *J. Am. Chem. Soc.* **2014**, *136*, 894.

11 (a) S. Paul, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Organometallics* **2010**, *29*, 4424. (b) J. W. Banks, A. S. Batsanov, J. A. K. Howard, D. O'Hagan, H. S. Rzepa, S. Martin-Santamaria, *J. Chem. Soc. Perkin Trans. 2* **1999**, 2409.

12 R.-Y. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215.

13 (a) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315. (b) K. M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, *78*, 8927.

14 G.-J. Cheng, Y.-F. Yang, P. Liu, P. Chen, T.-Y. Sun, G. Li, X. Zhang, K. N. Houk, J.-Q. Yu, Y.-D. Wu, *J. Am. Chem. Soc.* **2014**, *136*, 894.

15 H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 7567.

16 L. Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056.

17 (a) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593. For a comment, see: (b) R. E. Maleczka Jr., *Science* **2009**, *323*, 1572.

18 R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172.

19 H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 643. In this paper, the authors also raised the possibility of a "metal-free" process for *meta*-selective arylation as 3,3-dimethyl-1-(*o*-tolyl)butan-2-one and *o*-methylpivanilide were reported to be *meta*-arylated in the absence of copper, albeit at a higher temperature (80 ^{o}C instead of 70 ^{o}C). However, subsequent studies by Wu, Li, and co-workers (ref 21) showed that the reaction using *o*-methylpivanilide gave the *meta*-arylation product in very low yield when it was carried out under argon using carefully purified reagents and reaction apparatus. A somewhat higher yield was observed when the reaction was carried out in the air. It is not clear what caused the discrepancy of these reports.

20 (a) A. Casitas, X. Ribas, *Chem. Sci*. **2013**, *4*, 2301. (b) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177.

21 B. Chen, X.-L. Hou, Y.-X. Li, Y.-D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668.

22 (a) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298. (b) W. R. Reynolds, P. M. Liu, G. Kociok-Köhn, C. G. Frost, *Synlett* **2013**, *24*, 2687.

23 For a comment, see: F. Juliá-Hernández, M. Simonetti, I. Larrosa, *Angew. Chem. Int. Ed.* **2013**, *52*, 11458.

24 (a) X. Zhao, E. Dimitrijević, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466. (b) X. Zhao, V. M. Dong, *Angew. Chem. Int. Ed.* **2011**, *50*, 932.

25 M. Gagliardo, D. J. M. Snelders, P. A. Chase, R. J. M. Klein Gebbink, G. P. M. von Klink, G. van Koten, *Angew. Chem. Int. Ed.* **2007**, *46*, 8558.

26 N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877.

27 H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66.

28 For a review, see: K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, 45, 788.

29 For a review, see: G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.

30 (a) J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc*. **2014**, *136*, 4109. For related tandem carboxyl-directed C-H functionalization/decarboxylation, see: (b) S. Mochida, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 5776. (c) J. Cornella, M. Righi, I. Larrosa, *Angew. Chem. Int. Ed.* **2011**, *50*, 9429.

31 N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236.

32 (a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890. (b) J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992.

33 (a) C. N. Iverson, M. R. Smith III, *J. Am. Chem. Soc*. **1999**, *121*, 7696. (b) J.-Y. Cho, C. N. Iverson, M. R. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 12868.

34 J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka Jr., M. R. Smith III, *Science* **2002**, *295*, 305.

35 (a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc*. **2002**, *124*, 390. (b) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864.

36 (a) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056. (b) T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyaura, *Chem. Commun*. **2003**, 2924.

37 T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263.

38 (a) C. Cheng, J. F. Hartwig, *Science* **2014**, *343*, 853. For a comment, see: (b) M. Tobisu, N. Chatani, *Science* **2014**, *343*, 850.

39 C. Cheng, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 12064.

40 K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc*. **2007**, *129*, 11904.

41 (a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119. (b) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992. (c) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476. (d) M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem. Int. Ed.* **2003**, *42*, 3512.

42 Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072.

43 S. Zhang, L. Shi, Y. Ding, *J. Am. Chem. Soc.* **2011**, *133*, 20218.

44 R. Shrestha, P. Mukherjii, Y. Tan, Z. C. Litman, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 8480.

45 For a recent highlight, see: J. Schranck, A. Tlili, M. Beller *Angew. Chem. Int. Ed.* **2014**, *53*, 9426.