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Transition Metal-Catalyzed C-H Bond Functionalizations by the Use of Diverse Directing Groups

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Abstract:

Transition metal-catalyzed direct functionalization of C-H bond is one of the key emerging strategies that is currently attracting tremendous effort with the aim to provide alternative environmentally friendly and efficient ways for the construction of C-C and C-hetero bonds. In particular, the strategy involving regioselective C-H activation assisted by various functional groups shows the high potential, and significant achievements have been made in both the development of novel reactions and the mechanistic study. In this review, we attempt to give an overview for the development of utilizing the functionalities as directing groups. The discussion is directed towards the use of different functional groups as directing groups for the construction of C-C and C-hetero bonds via C-H activation by using various transition metal catalysts. The synthetic applications and mechanistic features of these transformations will be discussed, and the review is organized on the basis of the type of directing groups and then the type of bond being formed or the catalyst.

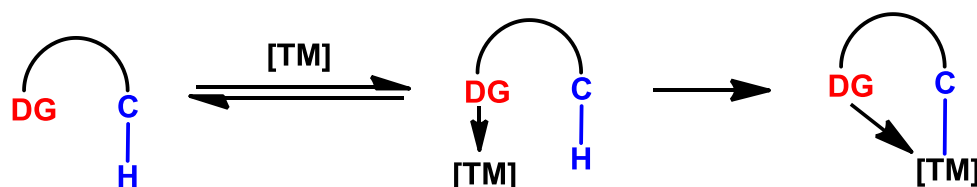
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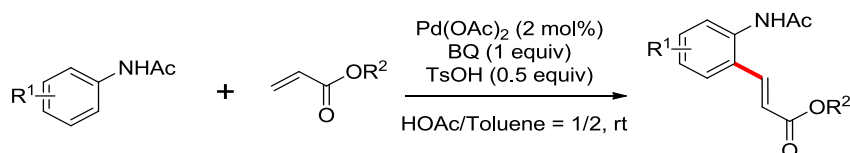
1 Introduction

Direct C-H bond functionalization has emerged as a powerful tool in organic synthesis by providing original disconnections of complex molecules from simple starting materials and improving the overall efficiency of the desired transformation, and thus radically transforms the ways for chemists to approach a synthetic challenge. Recent decades have witnessed the development of transition-metal catalysis through the activation of C-H bond by metal insertion, which has resulted in many pioneering discoveries.¹ While the idea of using C-H bonds as starting points for chemical synthesis has become prevalent, with a survey of the development in this area, the sufficient reactivity for the cleavage of the strong C-H bond and the control of site selectivity are two main challenges. In this regard, functional group-assisted C-H bond cleavage shows great promise. Site selectivity can be controlled by the close proximity of C-H bond to the reactive metal centre and the prerequisite substrate-catalyst interactions is significantly promoted through coordination of heteroatom with transition metal catalysts (Scheme 1). Consequently, coordination of transition metals with directing groups is usually considered as a fundamental step involved in these catalytic C-H bond functionalization processes.



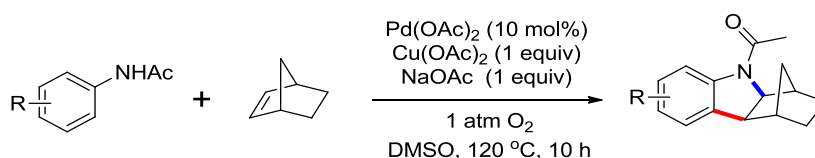
Scheme 1 Site selectivity controlled by transition metal catalyzed C-H activation.

Despite the fact that many examples of stoichiometric C-H bond cleavage by various metals were discovered, the development of a catalytic method as a key step towards a synthetically useful process was not realized until the pioneering work of Lewis and Murai. As early as 1986, Lewis and coworker observed the regioselective mono- and di-*ortho*-alkylations of phenol with ethylene using an *ortho*-metalated ruthenium phosphite complex.^{2a} In 1993, an efficient *ortho*-selective alkylation of aromatic ketones with olefins in the presence of a ruthenium catalyst was reported by Murai and co-workers.^{2b} The high efficiency and site selectivity in this transformation was attributed to the easier insertion of ruthenium into the *ortho*-C(sp²)-H bond after the coordination of ruthenium with ketone to



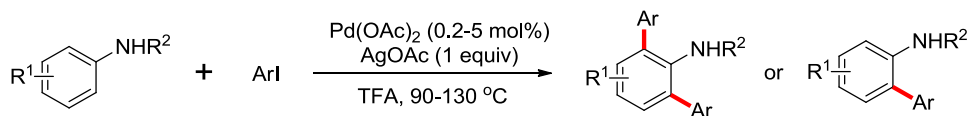
Scheme 2 Selective Pd-catalyzed oxidative coupling of anilides with olefins.

Leeuwen and co-workers demonstrated the *ortho*-olefination of anilides with acrylates by the palladium-catalyzed oxidative coupling reaction at room temperature in 2002 (Scheme 2).⁴ Compared with the direct olefination of arenes reported by Fujiwara and others, the high *ortho*-selectivity was observed. It was believed that this was the first example by the use of anilide as the directing group for the C-H functionalization, and many relevant works about *ortho*-olefination of anilides were reported in the following years.⁵



Scheme 3 Pd-catalyzed C-H activation/oxidative cyclization of acetanilide.

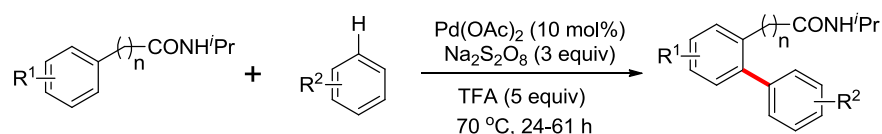
While much success was achieved in this selective olefination with acrylates, a significant challenge was represented for aliphatic olefins due to the β -hydrogen elimination. Advance in this respect was recently accomplished by Jiang who showed that palladium-catalyzed transformation of anilides with norbornenes took place to give an array of functionalized indolines (Scheme 3).⁶ Notably, β -hydride elimination was almost halted due to the strained structure of norbornenes and an oxidative cyclization could be achieved to give the indolines.



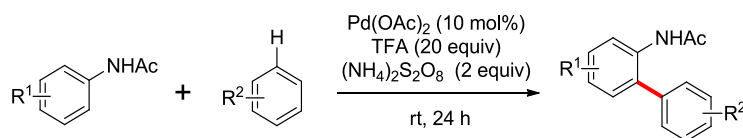
Scheme 4 *ortho*-Arylation of anilide by using of C-H activation.

(Scheme 5a).^{8b} The electrophilic attack of a Pd(II) species into the aromatic ring with the assistance of the acetamino group may initiate the coupling reaction. The subsequent transmetalation and reductive elimination produced the arylated product (Scheme 6, Path a). Another possibility was the first formation of arylated Pd(II) species by transmetalation of the boronic acid with Pd(II) salts, followed by an electrophilic attack of Pd(II) to the aromatic ring to form a diaryl palladium species, which underwent reductive elimination to give the arylation product (Scheme 6, Path b). Shi and co-workers also for the first time applied for the arylsilanes as coupling partners to approach the direct arylation to construct biaryls through this oxidative coupling strategy (Scheme 5b).^{8c}

The direct hydrogenative arylation of acetanilides with another molecular of arenes through double C-H activation strategy was described by Shi and co-workers (Scheme 5c).^{8d} A remarkable feature of this reaction was the use of arenes as the coupling substrates rather than aryl halides or metallic aromatics, which allowed the efficient biaryl synthesis via dual C-H coupling with high regioselectivity. However, it was necessary to use the arenes in excess (often as solvent) in order to obtain higher yields in this reaction. Further study by Buchwald and co-workers indicated that the arylation of anilides with arenes could occur by the use of 4-11 equiv of the arene substrates in TFA and metal-containing cocatalyst was not required under an oxygen atmosphere (Scheme 7).⁹



Scheme 8 Pd-catalyzed *ortho*-arylation with simple arenes.

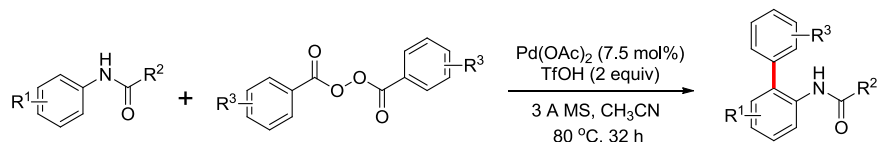


Scheme 9 *ortho*-Arylation of anilides at room temperature.

A notable advance of above transformations was achieved by Dong and co-workers by the use of sodium persulfate ($\text{Na}_2\text{S}_2\text{O}_8$) as the oxidant (Scheme 8).¹⁰ In their reaction, the scope of the coupling partners could be extended to phenylacetamides and benzamides, and an intramolecular cross-coupling for preparing lactams was also described. The relevant

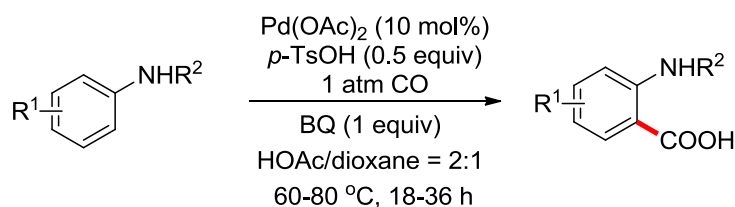
trifluoroacetate-bridged bimetallic Pd complexes derived from anilides were prepared and their stoichiometric reactivity was investigated.

More recently, this arylation was achieved at ambient temperature using highly electrophilic cationic palladium ($\text{Pd}[\text{TFA}]^+$) as catalyst by You and co-workers (Scheme 9).¹¹ In addition, the *ortho*-acetoxylation of anilides with acetate acid was developed by the same group under similar conditions.



Scheme 10 Palladium-catalyzed decarboxylative *ortho*-arylation of *N*-substituted anilides.

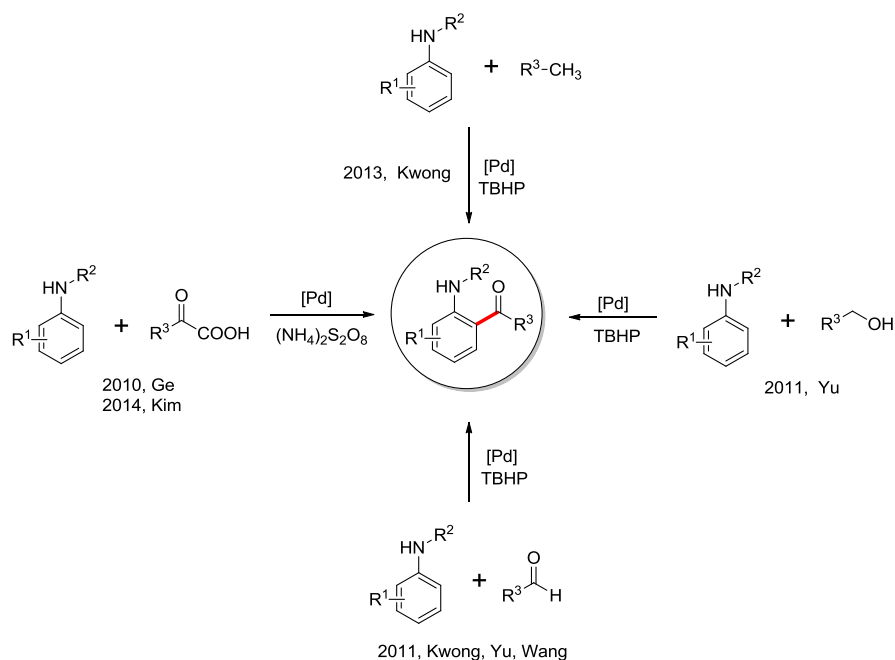
The Pd-catalyzed decarboxylative *ortho*-arylation of amides using aryl acylperoxides as arylation agents was reported by Wang and co-workers (Scheme 10).¹² With the release of CO_2 , a variety of *ortho*-arylated anilide compounds could be prepared. When *N*-methoxyarylamides were used as the substrates under the reaction conditions, the cyclization reaction occurred after the decarboxylative arylation to give various phenanthridinones in moderate to good yields.



Scheme 11 Pd(II)-catalyzed C-H *ortho*-carboxylation.

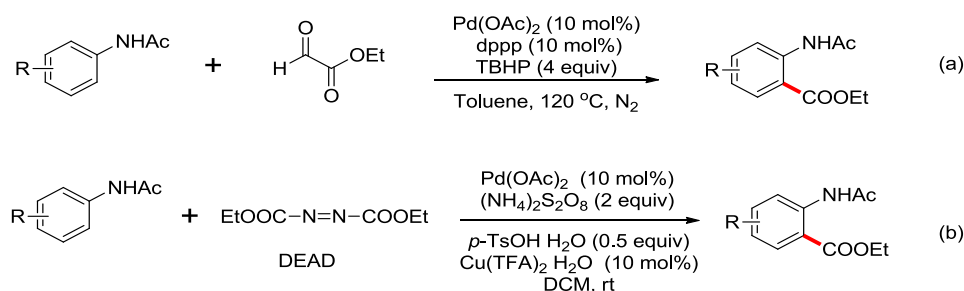
The palladium-catalyzed *ortho*-carboxylation of anilides with carbon monoxide was demonstrated in 2010 by Yu and co-workers (Scheme 11).¹³ Since carbon monoxide may impede the C-H activation process and reduce Pd(II) to Pd(0), highly electrophilic cationic Pd(II) species and relatively acidic conditions were required. The author adopted *p*-TsOH as additive and HOAc as cosolvent to carry out the reaction smoothly. Besides the preparation of the useful anthranilic acids, the mechanistic insights of the reaction were also explored in detail by the authors. The strong evidence for the key intermediates from a mixture of anhydride and benzoxazinone were displayed and the reaction mechanism was well elucidated. This methodology afforded a rapid and convenient route to assembly of diverse biologically

active benzoxazinone and quinazolinone derivatives from simple anilides.



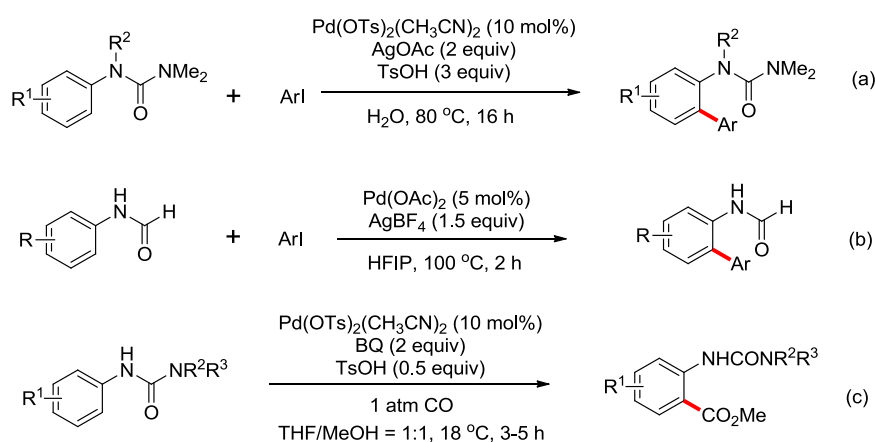
Scheme 12 Palladium-catalyzed oxidative C-H bond acylation of acetanilides.

The Pd-catalyzed decarboxylative *ortho*-acylation of anilides with α -oxocarboxylic acids was described by Ge and co-workers in 2010 (Scheme 12).¹⁴ The reaction was conducted at room temperature and *ortho*-acylated anilides were afforded in good to excellent yields after the release of a molecule of CO₂. This protocol also exhibited good feasibility and compatibility with both aryl and aliphatic α -oxocarboxylic acids. The method could be extended to prepare the corresponding C7-acylated indolines.¹⁵ Later, commercially available aromatic and aliphatic aldehydes were employed as the acylation reagents by the groups of Li, Kwong, Wang and Yu, respectively, which allowed the formation of *ortho*-acylated anilides easier.¹⁶ More than 2 equiv TBHP was required for these transformations. Benzylic alcohols and toluene were found to be the good substrates for the *ortho*-acylation of anilides under the similar reaction conditions by the use of more TBHP.¹⁷



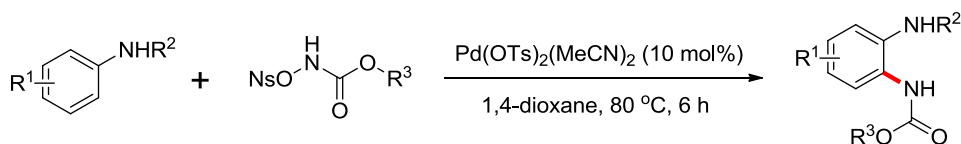
Scheme 13 Palladium-catalyzed *ortho*-C-H ethoxycarboxylation of anilides.

In 2012, Tan and co-workers successfully developed the palladium-catalyzed *ortho*-esterification of anilides by the use of glyoxylates (Scheme 13a).¹⁸ A bidentate phosphine ligand dppp was found to be beneficial for the reaction. The exploration of using a readily available agent azodicarboxylate (DEAD) as the esterification reagent was reported by You's group (Scheme 13b).¹⁹ The reaction could be carried out under ambient temperature with $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as oxidant, allowing the facile synthesis of anthranilic acid derivatives. According to the controlled experiments, a Pd(II)/Pd(IV) catalytic cycle may be involved in the ethoxycarboxylation process via a radical pathway.



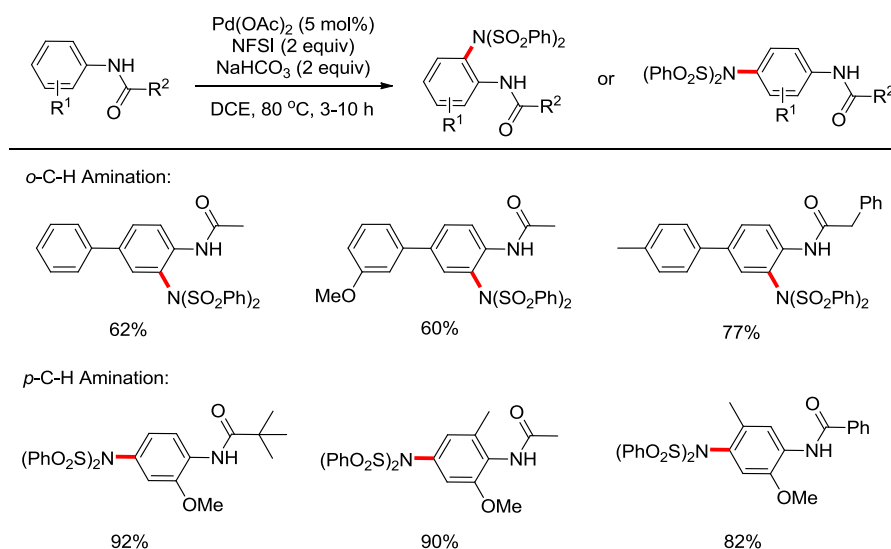
Scheme 14 *ortho*-C-H activation reactions directed by urea and formamide.

Based on amide-assisted C-H activation of anilides, a range of urea, formamide, guanidine and carbamate controlled *ortho*-olefination and -arylation of arenes were established.²⁰ For example, the palladium-catalyzed *ortho*-olefination of aryl ureas with acrylates^{20b-c} and *ortho*-arylations of aryl ureas with aryl iodides (Scheme 14a) or other arylation agents^{20d-f} have been developed. In a related study, Xu and Huang group developed a palladium-catalyzed *ortho*-arylation of formanilides (Scheme 14b), in which formamide was used as a directing group^{20g}. The obtained biarylformanilide products could be easily converted to the relevant biarylisocyanides or *N*-heterocycles. Recently, Lloyd-Jones and Booker-Milburn group reported a urea directed palladium-catalyzed carbonylation at room temperature in CO (1 atmosphere) to afford biologically and synthetically important anthranilic acid derivatives and heterocycles (Scheme 14c).^{20a} $[\text{Pd}(\text{OTs})_2(\text{MeCN})_2]$ was chosen as an efficient precatalyst and presented the exclusive activating effect of the urea substrates.



Scheme 15 Pd-catalyzed intermolecular *ortho*-C-H amidation of anilides.

A palladium catalyzed intermolecular *ortho*-C-H amidation of anilides using *N*-nosyloxycarbamates as nitrogen source for the synthesis of diverse 2-aminoanilines was developed by Yu and co-workers in 2010 (Scheme 15).²¹ This reaction exhibited good regioselectivity and functional group tolerance, and could proceed under relatively mild and simple reaction conditions. The *N*-nosyloxycarbamates were supposed to produce nitrene to insert into the cyclopalladated complex via a metal-nitrene pathway. A Pd(IV) or a dimeric Pd(III) complex were also possibly involved in the reaction process.

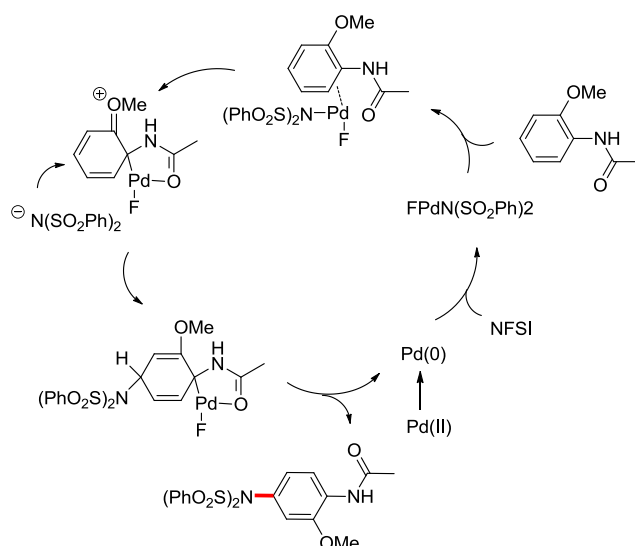


Scheme 16 Palladium-catalyzed C-H aminations of anilides with NFSI.

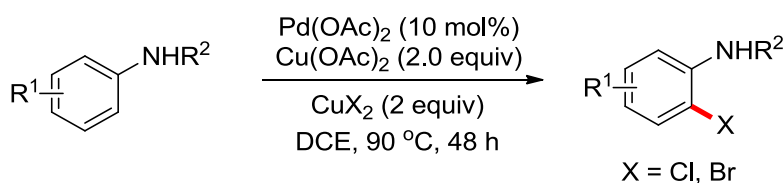
The direct construction of *ortho*-C-N bond of anilides was explored by Zhang and co-workers in 2011 by using *N*-fluorobenzenesulfonimide (NFSI) as nitrogen source (Scheme 16).²² NFSI is a popular oxidant and can also be used as the fluorine reagent. Surprisingly, NFSI showed excellent reactivity as a nitrogen source in their experiments and the *ortho* C-H amination products generated with high regioselectivity by the palladium catalysis. Interestingly, an active $\text{FPdN}(\text{SO}_2\text{Ph})_2$ species was supposed to undergo the electrophilic palladation with the assistant of amide group, leading to the formation of a dearomatized spiro-cyclopalladium intermediate. The key intermediate could be captured by $\text{N}(\text{SO}_2\text{Ph})_2$ anion via nucleophilic amination followed by hydride elimination to afford *ortho*-amination

products. It was reasonable that when 2-OMe-substituted anilides were used as the substrates under the optimal conditions, the *para*-amination products were obtained in high yields. An important observation by Zhang was that the addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) had little effect on the reaction, implicating that a radical process was not involved in the reaction pathway.

The proposed mechanism of this remarkable transformation involved initial oxidative addition of the NFSI to a palladium(0) species, followed by the electrophilic palladation resulting the dearomatized spiro-palladacycle intermediate. Thereafter, an amination reaction took place, and subsequent hydrogen elimination yielded the amination product (Scheme 17).

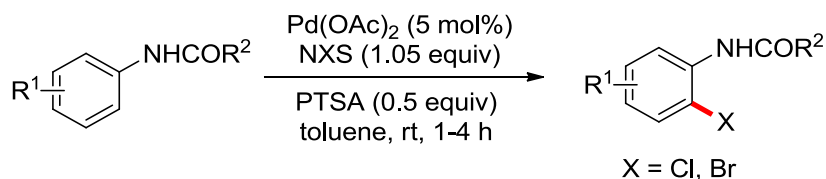


Scheme 17 The proposed mechanism.



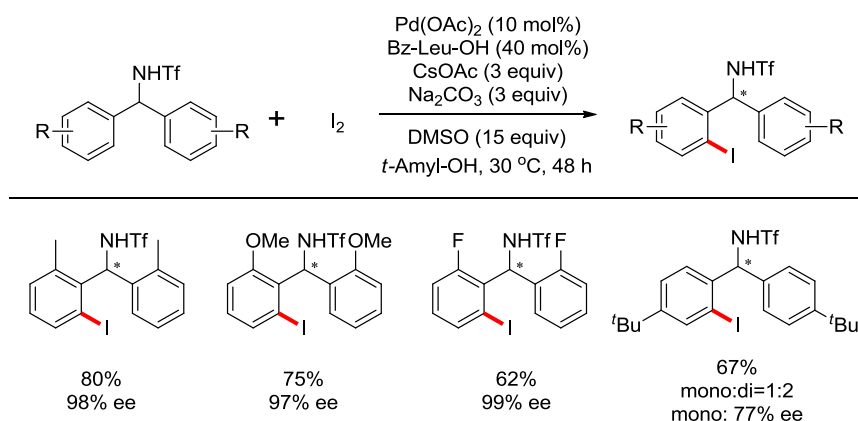
Scheme 18 Pd-catalyzed highly selective halogenation of substituted acetanilides.

Pioneering research of the formation of C-X bond using amide as directing group was described by Shi and co-workers in 2006 (Scheme 18).²³ The halogenation reaction proceeded regioselectively as a result of the chelation effect of amide directing group with CuCl₂ or CuBr₂ as halide sources. A cyclopalladation complex of acetanilide was prepared and was presumably involved in the reaction as the key intermediate through a Pd(II)/Pd(IV) or Pd(II)/Pd(0) mechanism.



Scheme 19 Pd-catalyzed mild C-H halogenation of anilides.

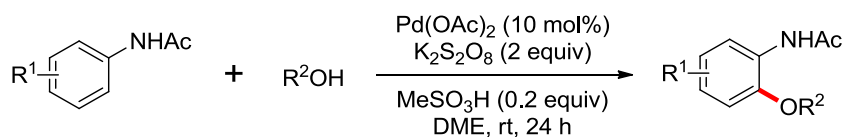
An advance was achieved by Bedford and co-workers using *p*-toluenesulfonic acid (PTSA) as the crucial additive (Scheme 19).²⁴ Thus, the Pd-catalyzed *ortho*-halogenation smoothly took place at room temperature in air within 1-4 hours with *N*-halosuccinimide (NXS) as the halide sources. The formation of *para*-bromination by-product through electrophilic pathway was suppressed under their reaction conditions although the electrophilic bromination was the major product in the presence of PTSA without palladium catalyst.



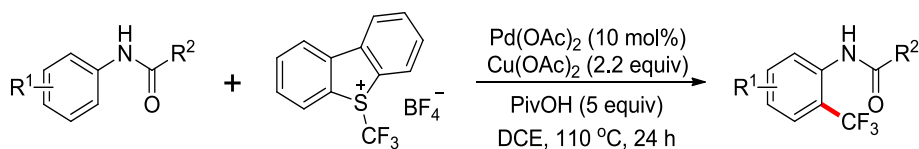
Scheme 20 Pd-catalyzed enantioselective C-H iodination.

The more challenge *ortho*-iodination was reported by Yu and co-workers recently using cheaper and milder molecular I_2 as the sole oxidant (Scheme 20).²⁵ Notably, a wide range of heterocycles that were previously incompatible with directed C-H activation showed excellent reactivity to give the corresponding iodinated heterocycles in good yields. Since the product separation of this catalytic system was much simpler, they successfully developed the first enantioselective C-H iodination reaction to synthesize a variety of chiral diarylmethylamines using a mono-*N*-benzoyl-protected amino acid as chiral ligand by the employment of trifluoromethanesulfonyl-protected diarylmethylamines as the substrates and readily available molecular iodine as the sole oxidant.²⁶ In this reaction, the choice of suitable base and additive had a significant influence on both the yield and enantioselectivity. The useful

iodination reaction could also be extended to gram-scale reaction under mild reaction conditions with the slight decrease of enantioselectivity.



Scheme 21 Pd-catalyzed directed *ortho*-alkoxylation of anilides.



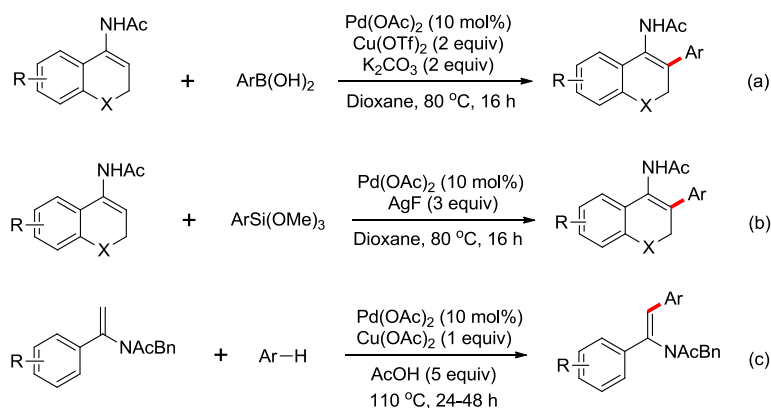
Scheme 22 Palladium-catalyzed trifluoromethylation of aromatic C-H bond.

Palladium-catalyzed directed *ortho*-alkoxylation of anilides with primary and secondary alcohols was developed by Wang and co-workers (Scheme 21).²⁷ In their study of the palladium-catalyzed *ortho*-alkoxylation of *N*-methoxybenzamides, poor yield was obtained for the methoxylation of acetanilide.²⁸ After extensive optimization of the reaction conditions, the addition of catalytic methanesulfonic acid (MSA) was found to have significant effect on the reaction efficiency and a wide variety of aryl alkyl ethers could be synthesized in moderate to excellent yields at room temperature in the presence of 20 mol% MSA.

The palladium-catalyzed *ortho*-trifluoromethylation of anilides using Umemoto's reagent as trifluoromethyl source was described recently by Shi and co-workers (Scheme 22).²⁹ The reaction exhibited broad substrate scope and high reactivity and efficiency. A series of control experiments for mechanism research indicated that the C-H cleavage was involved in the rate-determining step at the catalytic process. Furthermore, a palladacycle complex was synthesized and successfully used as catalyst in the reaction, and the stoichiometric reaction from the palladacycle complex could also afford the desired product. All of the relevant studies provided the solid evidence of the reaction mechanism. In addition, various *ortho*-trifluoromethyl anilide products could be easily transformed into different patterns of active molecules through existing methods.

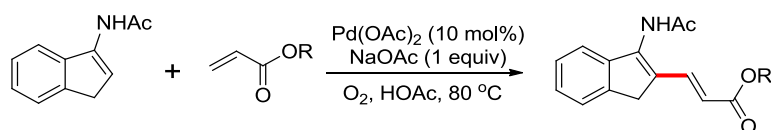
Enamides are the important synthetic intermediates and the stable enamine surrogates that have been widely used in both academic and industry. Due to the special electron-donating property of nitrogen atom, the enamides are quite rarely used as coupling

partners. The simple extension of catalytic systems to C(sp²)-H bond activation of enamides is also proved to be difficult.



Scheme 23 Pd-catalyzed directed arylation of enamides.

In 2009, Loh and co-workers developed the first palladium-catalyzed direct coupling of cyclic enamides with aryl boronic acids to generate various cyclic enamides derivatives in moderate to good yields (Scheme 23a).^{30a} A six-membered palladacycle with the metal coordinated to the acetamino group was supposed to be the key intermediate for the C-H activation. By using of the same strategy, they developed a palladium-catalyzed arylation of cyclic enamides with Hiyama organosilanes in the presence of 3 equiv AgF (Scheme 23b).^{30b} Both of these procedures required the aryl-metal species as the coupling partners. Recently, this group constituted a significant improvement by using the simple unactivated arenes as the coupling partner (Scheme 23c).^{30c} Absolute stereocontrol of the double bond to form highly substituted enamides with perfect *Z* selectivity was achieved in their transformation.



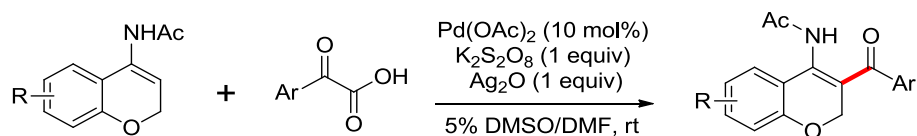
Scheme 24 The Heck type coupling of enamides with acrylates.



Scheme 25 Palladium-catalyzed direct alkylation of *N*-vinylacetamides.

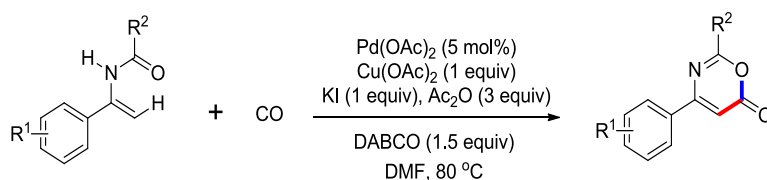
The Fujiwara oxidative olefination of enamides with acrylates and acrylonitrile was reported by Loh and co-workers using ambient oxygen as sole oxidant with excellent regioselectivity (Scheme 24).³¹ A key six-membered cyclic vinylpalladium complex was

isolated and characterized by ^1H NMR spectroscopy and single crystal X-ray analysis, which was propounded to be the intermediate during the olefination reaction of enamides. Good functional group tolerance and excellent regioselectivities were the notable features of the reaction. Very recently, a palladium catalyzed direct ethynylation reaction between *N*-vinylacetamides and (bromoethynyl)triisopropylsilanes was reported by the same group (Scheme 25).³² A wide range of conjugated enyne products were obtained in moderate to good yields. In order to obtain the high reactivity, a mixture solvent of DCM and DMSO was necessary, and DMSO was supposed to act as a weak ligand to stabilize the palladium catalyst via coordination. A Pd(II)/Pd(IV) pathway was proposed for the reaction.

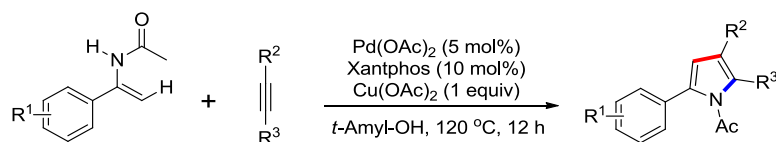


Scheme 26 Palladium-catalyzed acylation of enamides.

The palladium-catalyzed acylation of enamides using α -oxocarboxylic acids as decarboxylative acylation agent was demonstrated by Duan and Guo in 2012 (Scheme 26).³³ This elegant method provided an efficient route for the preparation of various acylated enamides from readily available α -oxocarboxylic acids under mild reaction conditions.



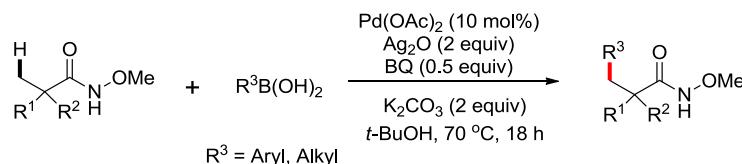
Scheme 27 Palladium-catalyzed carbonylation of enamides.



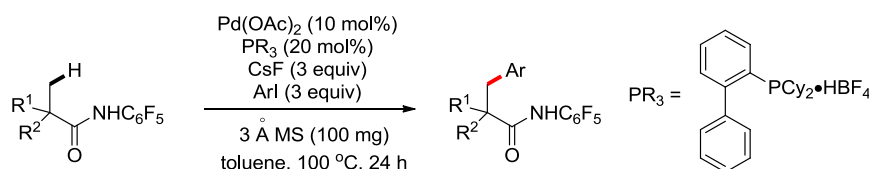
Scheme 28 Pd-catalyzed synthesis of substituted pyrroles.

The palladium-catalyzed synthesis of heterocycles from enamides was investigated by Guan and co-workers (Scheme 27).³⁴ They discovered that 1,3-oxazin-6-ones could be generated by the palladium-catalyzed carbonylation of enamides with CO (1 atm). The use of KI and DABCO in the reaction remarkably increased the efficiency of the reaction. It was a convenient and environmentally friendly method for the preparation of this important

six-membered heterocycles. More recently, they described an oxidative annulation reaction between enamides and alkynes by palladium catalysis to give highly substituted pyrroles via the C(sp²)-H bond activation (Scheme 28).³⁵ In this case, the phosphine ligand (Xantphos) could significantly improve the conversion of the reaction. Various functional groups could be tolerated, and the poly-substituted pyrroles, which were not easy to be prepared by other methods, could be produced in high yields.

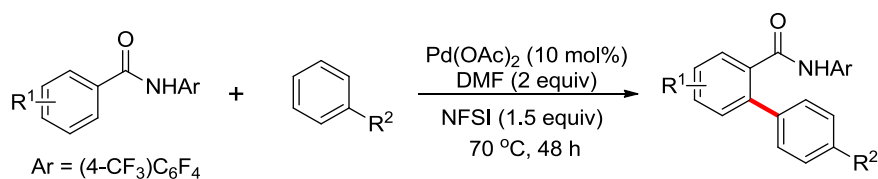


Scheme 29 β -Arylation or alkylation of *O*-methyl hydroxamic acids.

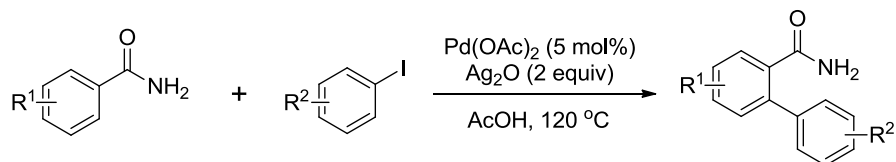


Scheme 30 Pd(0)/PR₃-catalyzed intermolecular arylation of sp³ C-H bonds.

The first palladium catalyzed functionalization of a C(sp³)-H bond with aryl and alkyl boronic acids by the use of CONHOMe as a directing group was reported by Yu and co-workers in 2008 (Scheme 29).³⁶ The reaction employed air as stoichiometric oxidant to replace the expensive silver salts and the CONHOMe group can be easily transformed into some other useful functional groups. The potential utility of this elegant protocol was broad and could be extended to afford some biological active molecules. Shortly after, the same group developed a novel Pd(0)/PR₃-catalyzed intermolecular arylation of C(sp³)-H bonds directed by CONH-C₆F₅ group (Scheme 30).³⁷ Compared with the useful C(sp³)-H functionalizations using Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalysis reported by Yu,³⁸ this reaction employed Pd(0)/PR₃ as catalytic system. Buchwald's Cyclohexyl JohnPhos and CsF were utilized as ligand and base respectively to improve the reactivity of the reaction. This protocol provided an efficient approach to the arylation of carboxylic acids. To have a deeper understanding of the reactivity of Pd(0)/PR₃-catalyzed intermolecular arylation of sp³ C-H bonds, a further detailed mechanistic investigation of this reaction was demonstrated by the same group in 2013.³⁹

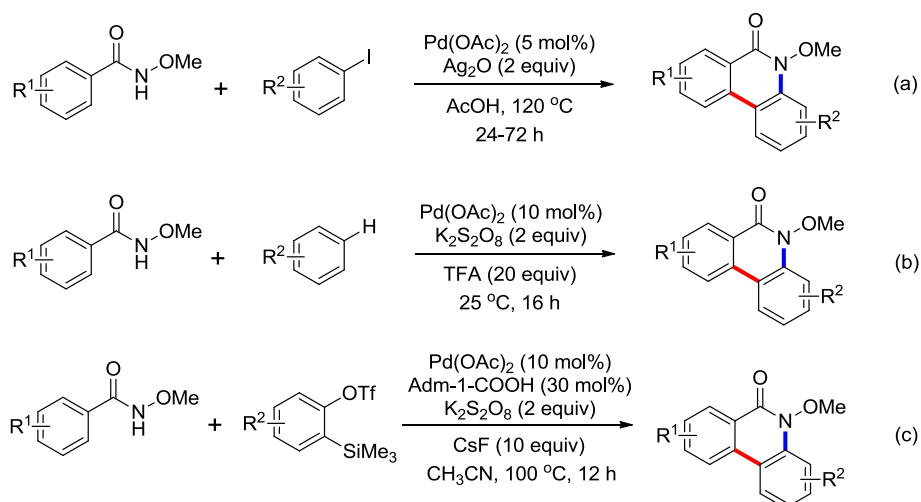


Scheme 31 Pd-catalyzed C(sp²)-H arylation using simple arenes as the arylating agents.



Scheme 32 *ortho*-Arylation of benzamides with simple amide as a directing group.

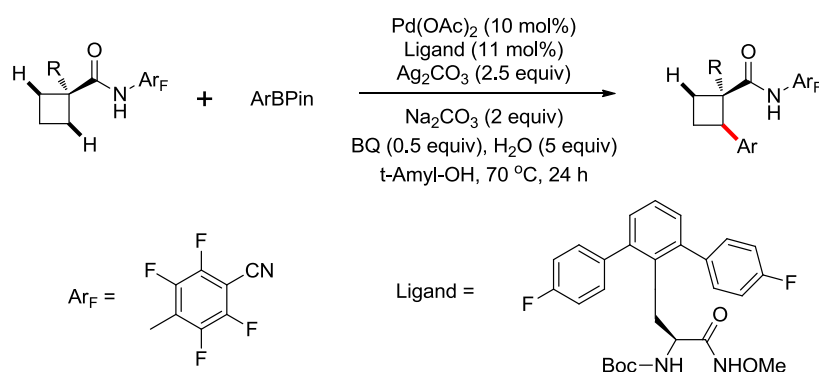
The Pd-catalyzed C(sp²)-H arylation directed by amides using simple arenes as the arylating agents was reported by Yu group in 2011 (Scheme 31).⁴⁰ The reaction featured the exceedingly high *para*-selectivity for the C-H/C-H coupling reactions. The F⁺ reagents were used as bystander oxidants for the high yield and regioselectivity, in which NFSI was the optimal one. The reaction pathway was supposed to be divided into two C-H activation processes. The first C-H activation step was a well-known procedure directed by acidic amide group and the second C-H activation step presumably underwent an electrophilic palladation mechanism based on the result of the KIE experiment. The elegant method provided alternative route for the synthesis of a series of synthetically useful biaryl products. In 2012, Wang and co-workers developed a palladium-catalyzed *ortho*-arylation of benzamides by aryl iodides with simple amide CONH₂ as a directing group (Scheme 32).⁴¹ It was the first time to use *N*-unsubstituted amide CONH₂ as a directing group. The acquired biphenyl-2-carboxamides products could be readily transformed to various biaryl derivatives.



Scheme 33 Oxidative cyclization of *N*-methoxybenzamides with different aryl sources.

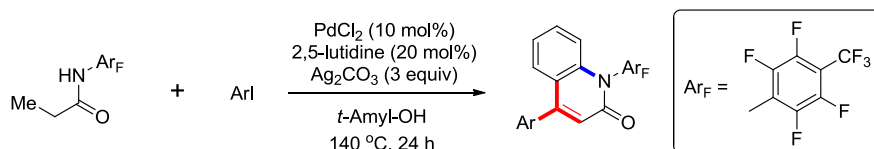
Phenanthridinones are regarded as the key units of important biologically active molecules and natural products. A one-pot cascade reaction to synthesize phenanthridinones through the palladium-catalyzed reaction of *N*-methoxybenzamides and aryl iodides was developed by Wang and co-workers in 2011 (Scheme 33a).⁴² The dual C-H activation included intermolecular C-C bond formation by directed arylation and intramolecular C-N bond formation in one pot. The Pd(II)-Pd(IV)-Pd(II) and Pd(II)-Pd(0)-Pd(II) catalytic cycles were proposed to be involved in the reaction system. Later, Cheng and co-workers reported a more convenient method to produce the phenanthridinones by palladium-catalyzed multiple C-H activation reactions of *N*-methoxybenzamides with simple arenes at ambient temperatures (Scheme 33b).⁴³ It was a great improvement of replacing aryl iodides with more readily available arenes. K₂S₂O₈ was used as oxidant and TFA was chosen to be an important additive to promote the reactivity of the reaction. This methodology was efficient and practical for the synthesis of diverse phenanthridinone derivatives. More recently, a palladium-catalyzed cyclization of benzamides with highly reactive benzyne to afford phenanthridinones in one pot was described by Jeganmohan and co-workers (Scheme 33c).^{44a} The sterically hindered 1-adamantanecarboxylic acid (Adm-1-COOH) acted as an effective additive and enhanced the reaction yields. The highly reactive benzyne was used as a π -component to insert into *ortho*-metalated five-membered palladacycle for the cyclization reaction. Almost at the same time, Xu and co-workers also reported a similar work of palladium-catalyzed oxidative annulation of arynes and cyclooctynes with benzamides for the

synthesis of phenanthridinones and isoquinolones in high efficiency.^{44b}

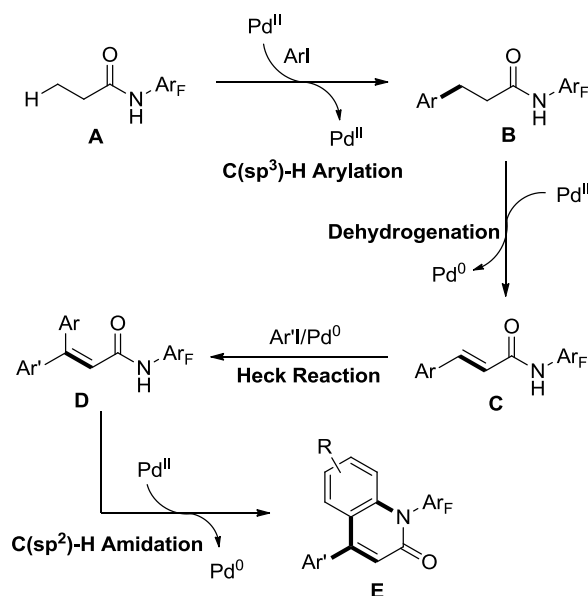


Scheme 34 Enantioselective C(sp³)-H arylation using achiral hydroxamic acid ligand.

Enantioselective functionalization of prochiral unactivated C-H bonds is of great significance and remains a great challenge. An enantioselective method for Pd(II)-catalyzed arylation of methylene β -C(sp³)-H bonds in cyclobutanecarboxylic acid derivatives using arylboron reagents as arylating agents was developed by Yu and co-workers recently (Scheme 34).⁴⁵ The chiral mono-*N*-protected α -amino-*O*-methylhydroxamic acid (MPAHA) ligands played the key role in achieving high yields and enantioselectivities of the reaction. As early as 2011, the same group had reported the first Pd(II)-catalyzed enantioselective C-H activation of cyclopropanes using a novel mono-*N*-protected amino acid as ligand.⁴⁶ These protocols provided new methods to enantioselectively construct a variety of biologically active cyclopropane and cyclobutanecarboxylic acid derivatives.

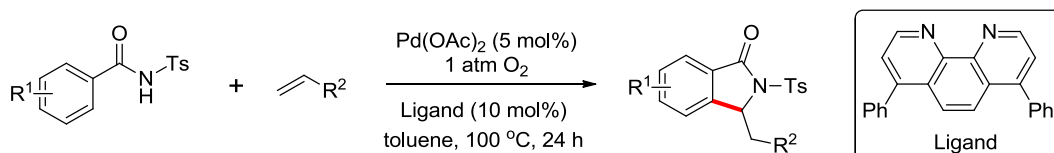


Scheme 35 One-pot synthesis of diverse 4-aryl-2-quinolinones.



Scheme 36 The plausible reaction mechanism.

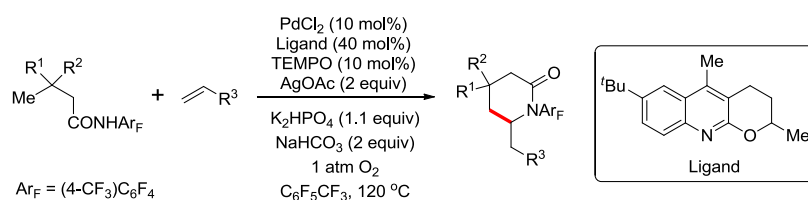
A ligand promoted triple sequential arylation of the β -C(sp³)-H bonds of propionamide followed by amidation to prepare diverse 4-aryl-2-quinolinones in one pot was developed by Yu and co-workers in 2014 (Scheme 35).⁴⁷ These cascade reactions contained C(sp³)-H arylation, dehydrogenation, Heck reaction and C(sp²)-H amidation. Similar to the previous studies of ligand-controlled β -arylation reactions of primary and secondary C(sp³)-H bonds by the same group,⁴⁸ the crucial role of a suitable ligand could not be ignored. 2,5-Lutidines was chosen as the effective ligand to promote the triple sequential C-H activation reactions and a stereospecific Heck reaction. The plausible mechanism was proposed: at first, hydrocinnamide **B** was afforded by the β -arylation of the primary C(sp³)-H bond, followed by the β -hydride elimination assisted by Pd insertion to give cinnamide intermediate **C**. Then the intermediate **C** underwent Heck coupling with a second aryl iodide to yield the arylated cinnamide intermediate **D**, which proceeded intramolecular amidation to provide the final product 4-aryl-2-quinolinone **E** (Scheme 36).



Scheme 37 *N*-Acylsulfonamide assisted synthesis of isoindolinones.

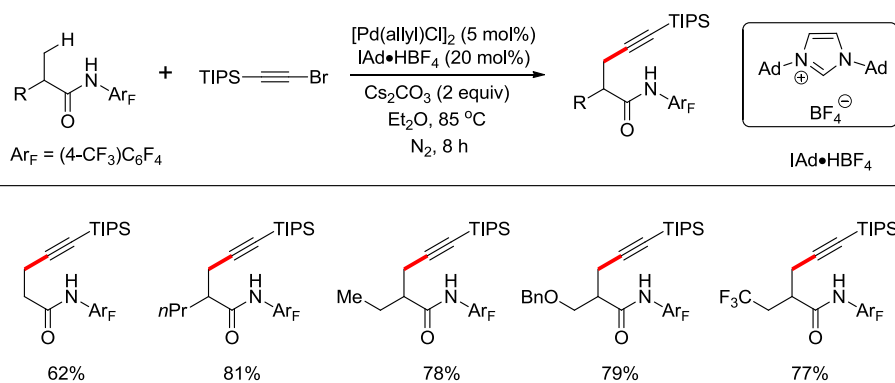
A Pd-catalyzed tandem C-H olefination/annulation sequence employed tosyl amide as a novel directing group to afford a wide range of isoindolinones was developed by Zhu and

co-workers in 2011 (Scheme 37).⁴⁹ Various aliphatic alkenes as well as conjugated alkenes were all compatible with this protocol. Bathophenanthroline was utilized as superior ligand to promote the reaction. Eco-friendly molecular oxygen functioned as the sole oxidant. The reaction was green and practical with the water as the only waste. In the same year, Booker-Milburn and Wang groups also reported the similar methodology for the synthesis of isoindolinones via Pd-catalyzed C-H activation of *N*-alkoxybenzamides respectively.⁵⁰ A series of the isoindolinone products were obtained by the use of these general cascade reactions. Furthermore, the substituted phthalimides could also be afforded by carbonylation with CO.



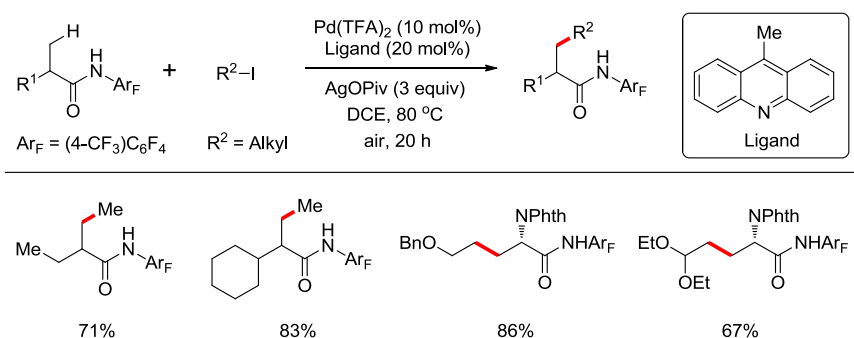
Scheme 38 Ligand-enabled γ -C-H olefination.

The development of C(sp³)-H olefination is more difficult and remains a challenge. Recently, Yu and co-workers established aquinoline-based ligand enabled γ -C-H olefination and carbonylation of aliphatic acids directed by a weakly coordinating amide directing group (Scheme 38).⁵¹ After detailed screening of different pyridine- and quinoline-based ligands, the developed quinoline-based ligand containing pyran structural motif was vital for the smooth transformation of γ -C-H to furnish a variety of highly functionalized all-carbon quaternary centers. Compared with the ligand-promoted β -C-H functionalizations of aliphatic acids developed by the same group,⁵² the γ -C-H activation of aliphatic acids had more challenges and greater synthetic significance.



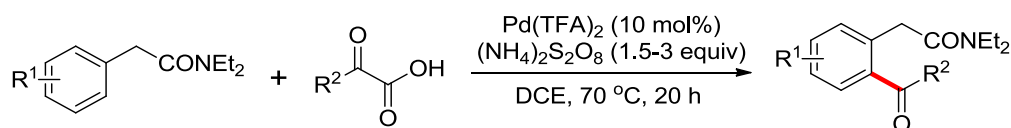
Scheme 39 β -Alkynylation of carboxylic acid amides.

Concerning the C(sp²)-H alkylation reactions, the alkylation of inert C(sp³)-H bonds is not easy to achieve. The first alkylation of β-C(sp³)-H bonds with alkynyl bromides using Pd(0)/N-heterocyclic carbene (NHC) and Pd(0)/phosphine (PR₃) catalysts was reported by Yu and co-workers in 2013 (Scheme 39).⁵³ Suitable ligands played remarkable influence on the reactivity of the reaction and a wide range of PR₃ and NHC ligands were screened for this reaction. PCy₃·HBF₄ and IAd·HBF₄ were optimal, respectively. Polar, strongly coordinating solvents gave no desired product. A variety of amides from commercially available carboxylic acids could be readily installed the alkynyl group at the β-position using this protocol.



Scheme 40 Ligand-promoted alkylation of C(sp³)-H bond.

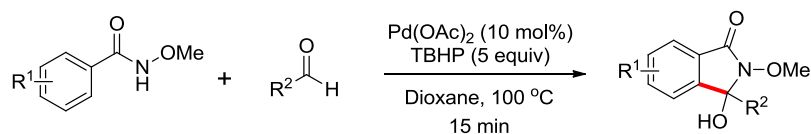
The C-H alkylation catalyzed by transition metal constitutes a useful alternative tool for C-C bond formation. Besides alkylborons, diverse alkylhalides were utilized as coupling partners in transition metal-catalyzed C-H alkylation for the past few years. A ligand-promoted Pd(II)-catalyzed C(sp³)-H and C(sp²)-H alkylation of simple amides utilizing alkyl iodides as alkylating agent was presented by Yu group in 2014 (Scheme 40).⁵⁴ Pyridine- or quinoline-based ligands were identified to have some positive effect on Pd-catalyzed C(sp³)-H functionalization.^{47-48, 51} As for oxidant, AgOPiv was more effective than Ag₂CO₃ to improve the yield of the reaction. A broad series of biologically active unnatural amino acids and geometrically controlled tri- and tetrasubstituted acrylic acids could be produced smoothly by this efficient alkylated methodology.



Scheme 41 Pd(II)-catalyzed decarboxylative acylation of phenylacetamides.

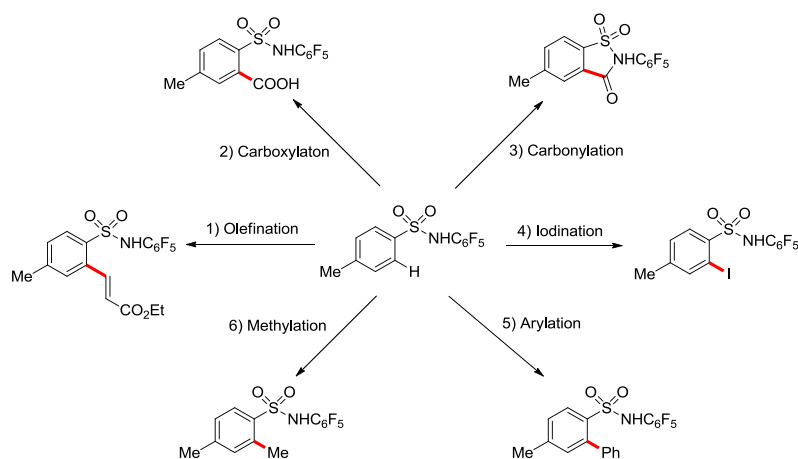
An efficient method for Pd-catalyzed oxidative decarboxylative acylation of

phenylacetamides with α -oxocarboxylic acids under mild conditions was developed by Kim and co-workers in 2013 (Scheme 41).⁵⁵ $(\text{NH}_4)_2\text{S}_2\text{O}_8$ was identified as superior oxidant and DCE was used as the optimal solvent. Under the reaction system, a wide range of bisacylated products of symmetrical phenylacetamides and monoacylated products of unsymmetrical phenylacetamides were successfully obtained, which could also be further transformed into various synthetically important 3-isochromanone derivatives via reduction and intramolecular cyclization process.



Scheme 42 Pd-catalyzed synthesis of hydroxyl isoindolones.

The first Pd-catalyzed C-H activation/annulation reaction for the convenient synthesis of hydroxyl isoindolones using *N*-OMe benzamide and benzaldehyde as the starting substrates was presented by Zhao and co-workers in 2013 (Scheme 42).⁵⁶ The readily available TBHP was the optimal oxidant for the reaction. Compared with Rh-catalyzed double-activation reactions for the synthesis of hydroxyl isoindolones reported by Kim and co-workers,⁵⁷ this reaction exhibited many notable features, such as short reaction times, wide substrate scope and high atom efficiency. The reaction mechanism was supposed to undergo a radical process after a series of control experiments were carried out.



Scheme 43 Pd-catalyzed diverse reactions directed by the sulfonamide functionality.

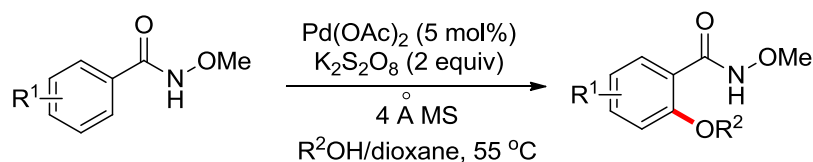
A diverse range of reactions directed by the sulfonamide functionality under different catalytic conditions were reported by Yu and co-workers in 2011 (Scheme 43).⁵⁸ After extensive screening and optimizations, a series of divergent *ortho*-C-H functionalization

processes, including olefination, carboxylation, carbonylation, iodination, arylation, and alkylation, were successfully achieved, providing straightforward route for the synthesis of various sulfonamide analogues.



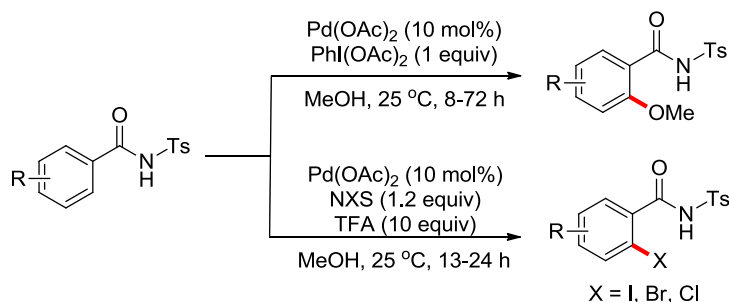
Scheme 44 Pd-catalyzed intermolecular C-H amination with alkylamines.

Besides the direct C-C bond construction from a C-H bond, the direct C-H amination is a significant issue in C-H functionalization. Yu and co-workers explored the palladium-catalyzed intermolecular C-H amination of *N*-aryl benzamides utilizing electrophilic *O*-benzoyl hydroxylamines as nitrogen sources. (Scheme 44).⁵⁹ The *O*-benzoyl hydroxylamines could also be *in situ* generated from secondary smines and benzoyl peroxide in one pot. This useful finding had the vital significance on the study of intermolecular C-H amination with alkylamines, providing a complementary route to synthesize diverse biologically active arylamines. As early as 2008, the same group reported a catalytic C-H lactamization reaction using a Pd(II) catalyst.⁶⁰ Various *N*-methoxyhydroxamic acids were used as substrates for the preparation of β -, γ -, and δ -lactams. A Pd(II)/Pd(IV) pathway was possibly involved in the catalytic C-H amination process.



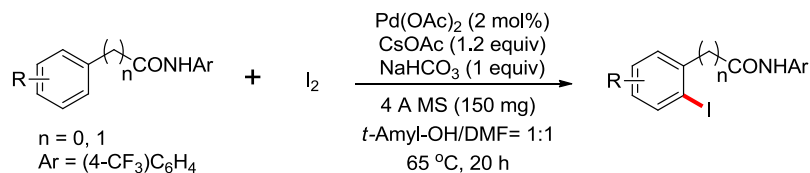
Scheme 45 Pd-catalyzed intermolecular C-O bond formation.

Wang and co-workers developed a Pd-catalyzed *ortho*-alkoxylation using *N*-methoxy amide group (CONHOMe) as *ortho*-directing group (Scheme 45).⁶¹ K₂S₂O₈ was superior for other oxidants and the molecular sieve was necessary for the high yield of the reaction. A Pd(II)/Pd(IV) pathway catalytic cycle was presumably involved in the reaction. A wide range of alkoxylation of *N*-methoxybenzamides could be furnished and further converted to various derivatives for the potential synthetic application.



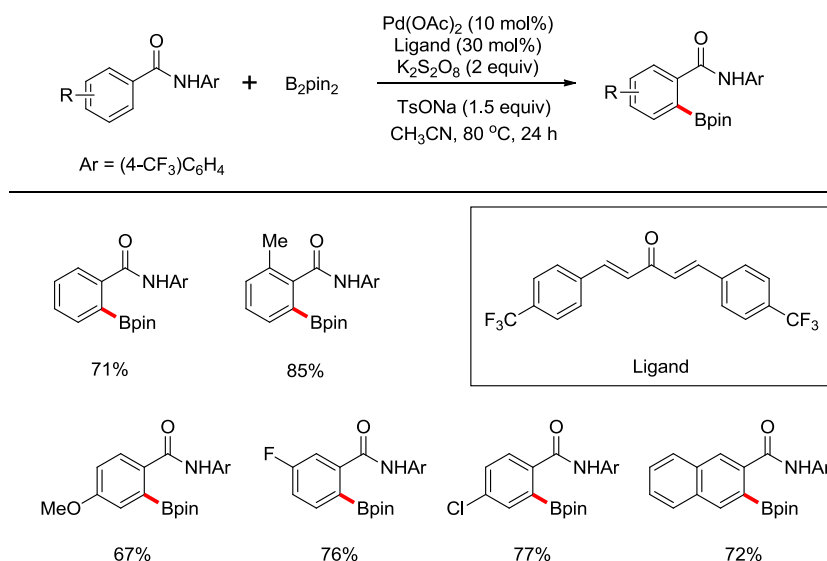
Scheme 46 Palladium(II)-catalyzed *ortho*-alkoxylation and halogenation of *N*-tosylbenzamides.

Under simple and mild conditions, Fabis and coworkers demonstrated a palladium-catalyzed *ortho*-C-H alkoxylation and halogenation of substituted arenes directed by *N*-tosylcarboxamide group (Scheme 46).⁶² MeOH and NXS acted as alkoxylation and halogenated sources, respectively. Under the efficient methodology, various *ortho*-alkoxylation and *ortho*-halogenations of *N*-tosylbenzamides were afforded in high yields, which could be further transformed into different valuable synthetic intermediates by some readily manipulations. A palladacycle was isolated and characterized by X-ray analysis to investigate the process of C-X and C-O bond formation



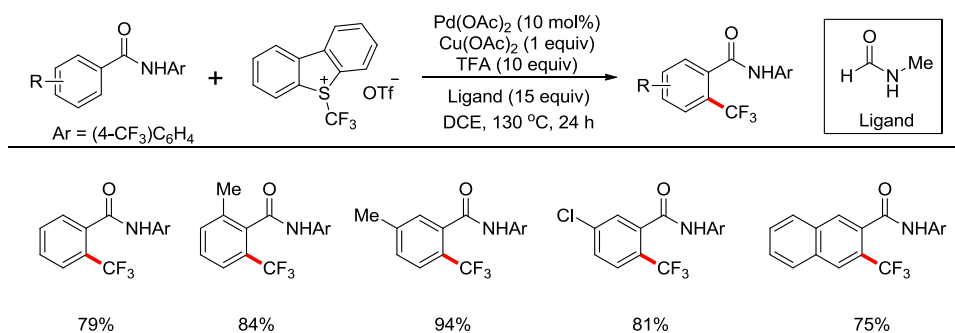
Scheme 47 Pd(II)-catalyzed C-H iodination using molecular I_2 as the sole oxidant.

Recently, Yu and co-workers reported a Pd(II)-catalyzed *ortho*-C-H iodination of various arenes as well as a wide range of heterocycles directed by a weakly coordinating amide auxiliary using cheaper and milder I_2 as the sole oxidant (Scheme 47).⁶³ CsOAc was identified as iodide scavenger and $NaHCO_3$ was used as coadditive to form the imidate structure by N-H deprotonation of the amide, which could dramatically improve the reactivity of the reaction. This convenient protocol exhibited wide substrate scope including various heterocycles that showed poor reactivity in many directed C-H activation reactions.



Scheme 48 Pd-catalyzed oxidative *ortho*-C-H borylation of arenes.

The first Pd-catalyzed *ortho*-C-H borylation with *N*-arylbenzamides and diboron reagent (B₂Pin₂) under oxidative conditions was developed by Yu and co-workers in 2012 (Scheme 48).⁶⁴ The usage of electron-deficient dba ligand was necessary for significantly improving the yield of the borylated product with excellent monoselectivity. The choice of suitable base was also essential for the good efficiency of the reaction and TsONa was the optimal one. This borylation reaction showed broad substrate scope and could be easily extended to the gram scale in moderate yield. Notably, the borylated products could also be transformed into a wide range of synthetically useful synthons in excellent yields.

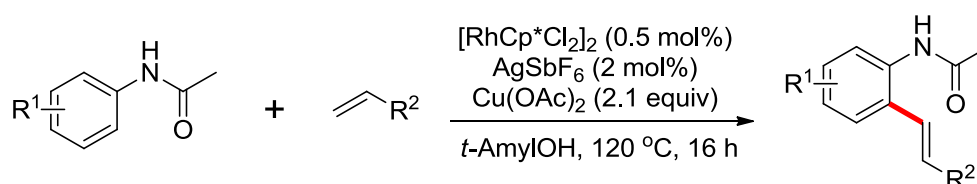


Scheme 49 Pd(II)-catalyzed *ortho* trifluoromethylation of arenes.

Trifluoromethylated arenes are important structural motifs and widely exist in diverse pharmaceuticals, agrochemicals and organic materials. Trifluoromethylation of aryl C-H bonds catalyzed by transition-metal has emerged as a powerful tool to construct C-CF₃ bond. A Pd(II)-catalyzed trifluoromethylation of a range of *N*-arylbenzamides using Umemoto's reagent as trifluoromethylating agent was developed by Yu and co-workers (Scheme 49).⁶⁵

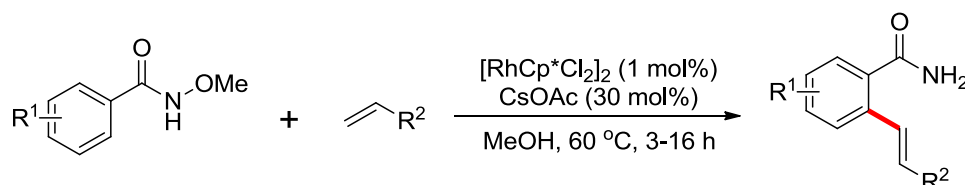
The ligand had a significant impact on this reaction and *N*-methylformamide was the best choice, which was identified as both ligand and base. Different potential coordination modes of acidic amides with palladium(II) catalyst were proposed, which might promote the reactivity of directing C-H activation. A wide array of biologically active trifluoromethylated products were delivered by this elegant strategy from readily available synthetically versatile arenes.

2.2 Rh catalyzed C-H functionalization



Scheme 50 Rh(III) catalyzed olefination and vinylation of unactivated acetanilides.

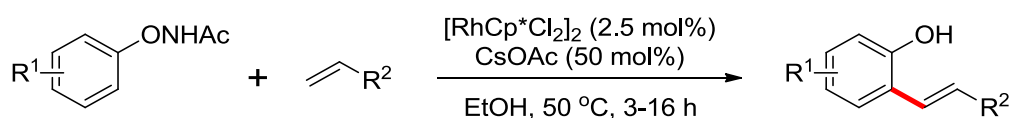
As a powerful catalyst, the widespread use of rhodium catalyst in C-H functionalizations has undergone drastic progress in recent years.^{1u, 3d, 66} In the catalyzed oxidative olefination of acetanilides or benzamides, Rh catalysts exhibited many notable features in contrast to common Pd catalysts, such as lower catalyst loadings, broad functional group tolerance and high reactivity of electron-neutral olefins. A Rh(III) catalyzed oxidative *ortho*-olefination and vinylation of various acetanilides derived from the corresponding anilines was demonstrated by Glorius and co-workers in 2010 (Scheme 50).⁶⁷ Both electron-withdrawing and electron-donating groups were compatible with the reaction and the yield was up to 98%. It is worthwhile to note that ethylene could also be involved in this reaction and a satisfactory yield of styrenes could be smoothly prepared, which were difficult to be accessed by other direct catalytic oxidative-Heck reactions. The produced olefins had synthetical versatility and could be applied to natural product total synthesis.



Scheme 51 Rh(III)-catalyzed directed C-H olefination.

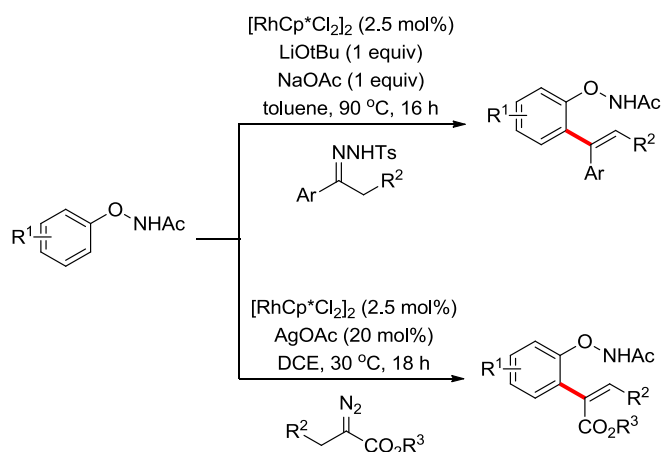
Later, an efficient Rh(III)-catalyzed C-H olefination reaction of *N*-methoxybenzamides under mild conditions was reported by the same group (Scheme 51).⁶⁸ It is important to note

that they exploited CONH(OMe) as directing group and N-O bond as internal oxidant, avoiding the addition of external oxidant. This reaction had more advantages than previous similar reports⁶⁹: mild reaction conditions, excellent regio- and mono-selectivity and broad substrate scope and high yields. In addition, when the -OMe group on the benzamide N was replaced with more accessibly Rh-chelated *O*-pivaloyl group, diverse tetrahydroisoquinolinone derivatives were afforded. This strategy provided a practical route to the olefination of benzamide derivatives and selective construction of valuable tetrahydroisoquinolinone products.



Scheme 52 Rhodium(III)-catalyzed C-H olefination.

By the similar strategy, Lu and Liu developed an efficient Rh(III) catalyzed C-H olefination reaction with *N*-phenoxyacetamides and alkenes to afford *ortho*-alkenyl phenols by the use of an oxidizing directing group in 2013 (Scheme 52).⁷⁰ The N-O bond was identified as internal oxidant to promote the olefination process and could be cleaved after the completion of the reaction. This reaction offered a convenient route for the synthesis of *ortho*-alkenyl phenols under mild conditions.

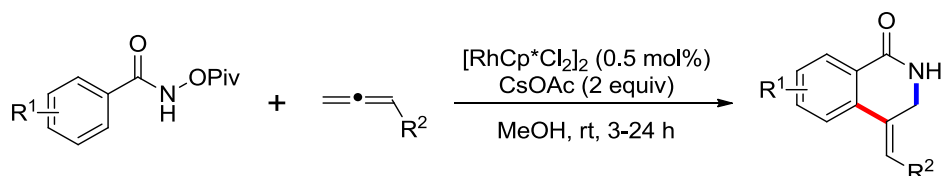


Scheme 53 Rhodium(III)-catalyzed *ortho*-alkenylation of *N*-Phenoxyacetamides.

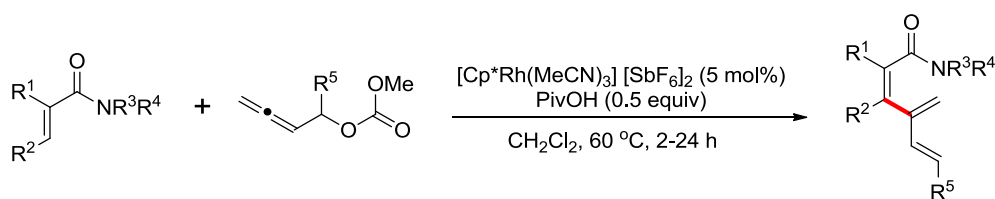
N-Tosylhydrazones were regarded as the precursors for the *in situ* generation of diazo substrates, which were extensively involved in the Rh(III)-catalyzed directed *ortho* C-H bond functionalization reactions.⁷¹ A Rh(III)-catalyzed *ortho*-alkenylation of *N*-phenoxyacetamides with *N*-tosylhydrazones or diazoesters via C-H activation was demonstrated by Wang and

co-workers in 2014 (Scheme 53).⁷² As a new type of coupling partners, *N*-tosylhydrazones were successfully applied in the chelation-assisted C-H functionalizations for the first time. The oxidizing directing group, which contained an N-O bond, was chosen to orient the *ortho*-alkenylated reaction. Under the mild reaction conditions, a wide range of *ortho*-alkenyl phenols were obtained in moderate to good yields. Rh(III)-carbene migratory insertion process was proposed to exist in the catalytic cycles.

Due to the poor electron density of the pyridyl ring and the strong coordination of the nitrogen atom, few examples of oxidative olefination of pyridines have been reported. A Rh(III)-catalyzed oxidative olefination of pyridines and quinolines using pivalamides at the *ortho*-position as the directing group was developed by Shi and co-workers in 2013.⁷³ Cu(OAc)₂ was supposed to be coordinated with the pyridine nitrogen to afford the high reactivity. This efficient protocol was successfully applied to synthesize pharmaceutically important molecules. After one year, the same group reported a rhodium(III)-catalyzed selective olefination of picolinamide derivatives with carboxamides as directing groups, providing a convenient method for the synthesis of diverse 3-alkenylpicolinamides.⁷⁴



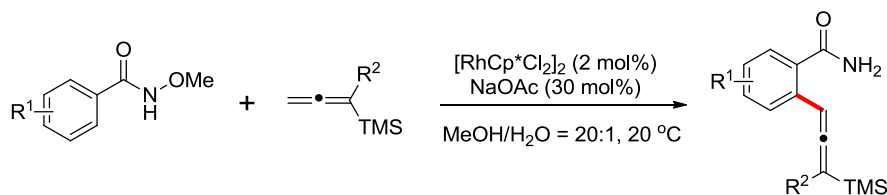
Scheme 54 Mild rhodium(III)-catalyzed C-H activation/annulation with allenes.



Scheme 55 Rhodium(III)-catalyzed alkenyl C-H activation with allenyl carbinol carbonate.

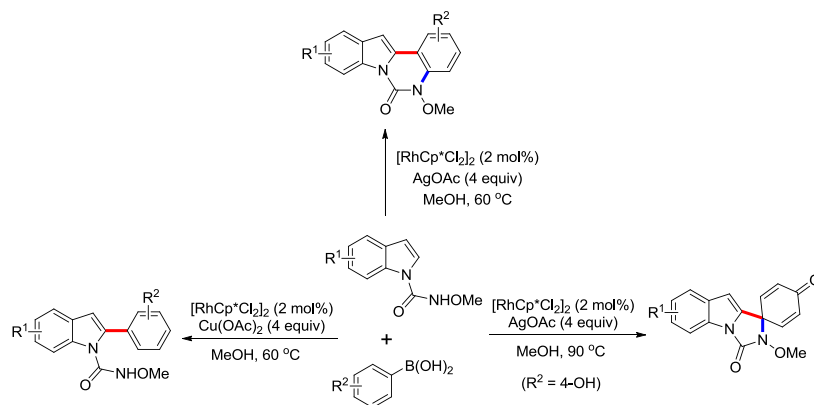
In contrast to alkenes and alkynes, the application of allenes as the coupling partners in Rh-catalyzed C-H functionalization transformation remains sparse. Recently, an efficient Rh(III)-catalyzed intermolecular annulation of *N*-pivaloyloxy benzamide derivatives with allenes for the rapid construction of biologically important 3,4-dihydroisoquinolin-1(2H)-ones was disclosed by Glorius and co-workers in 2012 (Scheme 54).⁷⁵ The deuteration experiments were conducted and the C-H bond cleavage was presumably involved in the rate-determining

step. The reaction might proceed in a concerted metalation/deprotonation (CMD) pathway and the steric interference had a distinct influence on the regioselectivity of the allenyls. Later, the same group reported a Rh(III)-catalyzed alkenyl coupling reaction directed by amide groups with allenyl carbinol carbonates to afford a variety of [3]dendralenes (Scheme 55).⁷⁶ This protocol provided an practical and straightforward way to access [3]dendralenes with diverse substitution patterns.



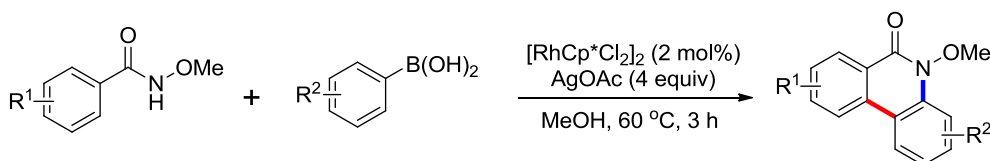
Scheme 56 Room-temperature synthesis of trisubstituted allenylsilanes.

The first example of Rh(III)-catalyzed *ortho* allenylation of *N*-methoxybenzamides with allenylsilanes to produce diverse poly-substituted allenylsilanes under very mild reaction conditions was developed by Ma and co-workers in 2013 (Scheme 56).⁷⁷ The reaction was supposed to undergo C-H bond cleavage, allene insertion and β -H elimination to give the final 2-(3-silylallenyl)benzamides products. The transformation showed many noteworthy advantages, such as ambient reaction temperature, insensitive to air and moisture, high efficiency and broad functional groups tolerance. The products could be further transformed into a wide range of useful corresponding derivatives and the presented protocol had a broad application potential from the view of synthesis. A rhodium-catalyzed coupling-cyclization reaction of 2,3-allenols with *N*-methoxybenzamides to synthesize various optically active 2,5-dihydrofurans via C-H functionalization was reported by the same group.⁷⁸ The tetramethylcyclopentadienyl anion was used as an effective ligand and highly efficient axial-to-central chirality transfer was observed in the process of the reaction.

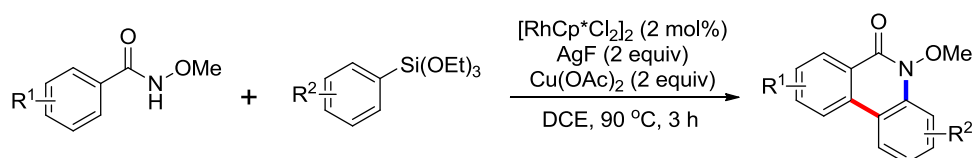


Scheme 57 Rh(III)-catalyzed selective coupling of indole derivatives and aryl boronic acids.

A Rh(III)-catalyzed selective coupling of *N*-methoxy-1*H*-indole-1-carboxamide and aryl boronic acids was described by Cui and co-workers recently (Scheme 57).⁷⁹ Through the switch of different reaction conditions or substitutions, three distinct reaction patterns of arylation, [4+2] cyclization, and [4+1] cyclization were achieved smoothly, producing divergent products. The C-H activation and electrophilic addition were proposed to be involved in the reaction pathway.



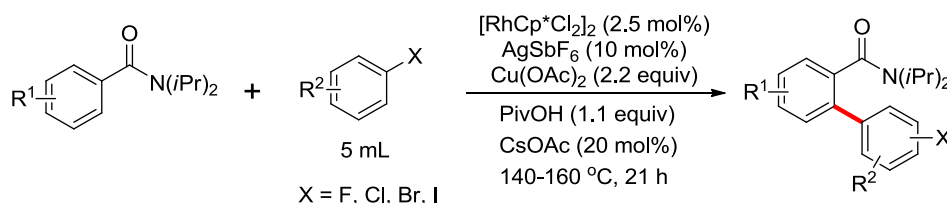
Scheme 58 The dual C-H activation of *N*-methoxybenzamides with aryl boronic acids.



Scheme 59 Rhodium-catalyzed annulation of *N*-methoxybenzamides with arylsilanes.

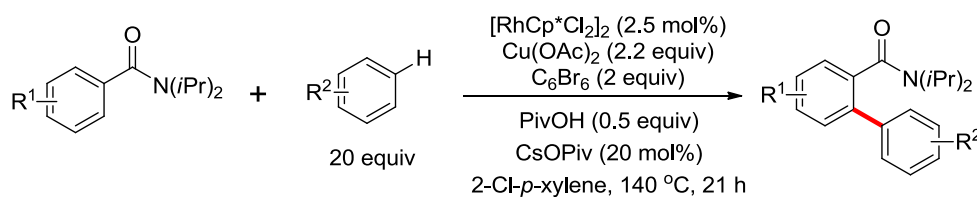
The Rh(III)-catalyzed dual C-H activation of *N*-methoxybenzamides with aryl boronic acids through one-pot C-C/C-N bond formation to provide various substituted phenanthridinones in good yields was developed by Cheng and co-workers in 2012 (Scheme 58).⁸⁰ Previous methods to synthesize phenanthridinones by the use of palladium catalysts have been reported by Wang⁴² and Cheng⁴³ in 2011. The presence of a silver salt was crucial to the reaction and 4 equivalents of Ag₂O were necessary for the highest yield of the product. High regioselectivity and efficiency of this catalytic reaction were achieved. Two years later, the same group reported a similar Rh(III)-catalyzed dual C-H bond activation and annulation reactions for the one-pot synthesis of substituted phenanthridinone derivatives using

aryltrioethoxysilanes in the place of aryl boronic acids (Scheme 59).⁸¹ AgF was used as the scavenger of organosilicon reagents.



Scheme 60 Rh(III)-catalyzed dehydrogenative aryl-aryl bond formation.

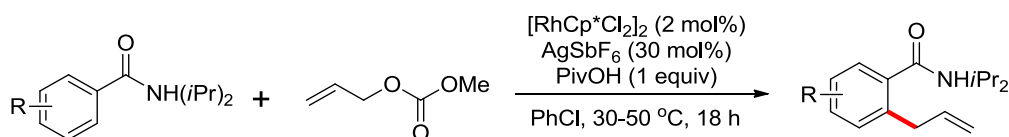
A unique Rh(III)-catalyzed selective dehydrogenative cross-coupling between benzamides and aryl halides (I, Br, Cl) to form biaryl products by means of double C-H activation was disclosed by Glorius and co-workers in 2012 (Scheme 60).⁸² Importantly, the halogen did not participate in the reaction and was survived under the reaction conditions. The combination of catalytic amount of CsOPiv (20 mol%) together with 1.1 equiv of PivOH inhibited the undesired homocoupling of aryl halides. The benzamide bearing a NiPr₂ group as the directing group could further improve the reactivity of cross-coupling reaction. Mechanistic investigations indicated that this catalytic system proceeded by two separate C-H activation steps on each coupling partner. At the same year, Glorius and co-workers extended the Rh(III)-catalyzed selective dehydrogenative cross-coupling into vinylic substrates bearing a directing group.⁸³ A wide range of synthetically valuable tri- and tetrasubstituted olefins were furnished in moderate yields.



Scheme 61 The cross-dehydrogenative coupling of simple arenes and heterocycles.

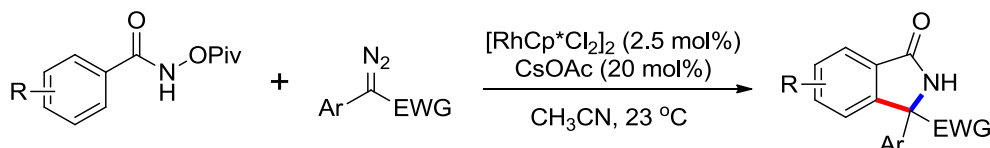
A novel Rh(III)-catalyzed dehydrogenative cross-coupling reaction of benzamide derivatives with simple arenes as arylating agents was demonstrated by Glorius and co-workers in the same year (Scheme 61).⁸⁴ The directed oxidative cross-dehydrogenative coupling (CDC) of two non-prefunctionalized arenes was achieved with the assistance of the directing group. Polybrominated benzenederivative (C₆Br₆) was chosen to be the optimal and inexpensive additive/cooxidant to promote the reaction. Pivalic acid (PivOH) and cesium pivalate (CsOPiv) had also some positive effects to improve the efficiency of the reaction.

Under the reaction conditions, a wide range of synthetically useful biaryl patterns were readily afforded in moderate to good yields.



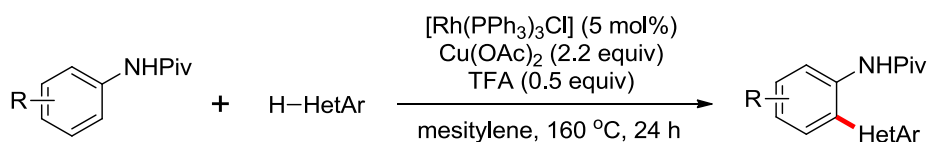
Scheme 62 Direct C-H allylation of arenes with allyl carbonates.

Allylarene is a kind of important scaffold in natural products and biologically active compounds. The methods for the direct C-H allylation of arenes have been rarely studied. In 2013, Glorius and co-workers reported a Rh(III)-catalyzed intermolecular direct C-H allylation reaction with readily available allyl carbonates as allyl source under mild reaction conditions (Scheme 62).^{85a} A slight excess of AgSbF₆ had some notable effects to facilitate the process of the allylation reaction. Some mechanistic investigations implied that the C-H bond cleavage was involved in the rate-limiting step and a concerted metalation–deprotonation (CMD) process was the key step. This reaction was an excellent alternative to the existing methods to access allylated aromatics. At the same year, a similar work of Rh(III)-catalyzed direct olefination of arenes using allyl acetate as olefinating agent via C-H activation was developed by Loh and co-workers.^{85b}



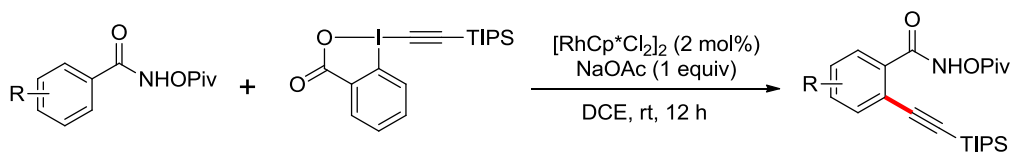
Scheme 63 A coupling of benzamides and donor/acceptor diazo compounds.

A Rh(III)-catalyzed coupling reaction/annulation of *O*-pivaloyl benzhydroxamic acids with donor/acceptor diazo compounds to give diverse isoindolones with a stereogenic carbon was demonstrated by Rovis and co-workers (Scheme 63).^{71b} Different with CO and isocyanides, diazo compounds were chosen as one-carbon components in the cyclization reaction. A broad range of benzhydroxamic acids and diazo compounds were compatible with the reaction conditions and various isoindolones were smoothly afforded. Especially, the isoindolones containing quaternary carbons with a trifluoromethyl group were successfully obtained using this elegant method.



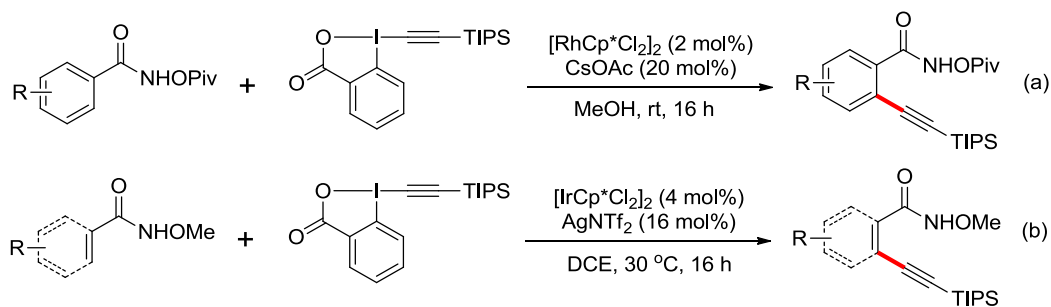
Scheme 64 The *ortho*-C-H heteroarylation of aromatic amines.

An unprecedented Wilkinson catalyst $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$ catalyzed highly regioselective cross-coupling of aromatic amines derivatives with various heteroarenes via dual C-H activations was reported by You and co-workers recently (Scheme 64).⁸⁶ The reaction overcame the intrinsic obstacles of the common C-H/C-H oxidative cross-coupling reactions: the poor regioselectivity and the requirement of a large excess of the arenes. A wide variety of important aryl-heteroaryl frameworks were rapidly constructed by the use of this efficient protocol, and some highly extended π -conjugated heteroacenes that had great air stability as organic semiconductors in electronic devices were synthesized. Compared with classical catalytic system of $[\text{RhCp}^*\text{Cl}_2]_2/\text{AgSbF}_6$, the current innovative catalyst system was much less expensive and had more potential to be applied to other C-H activation reactions.



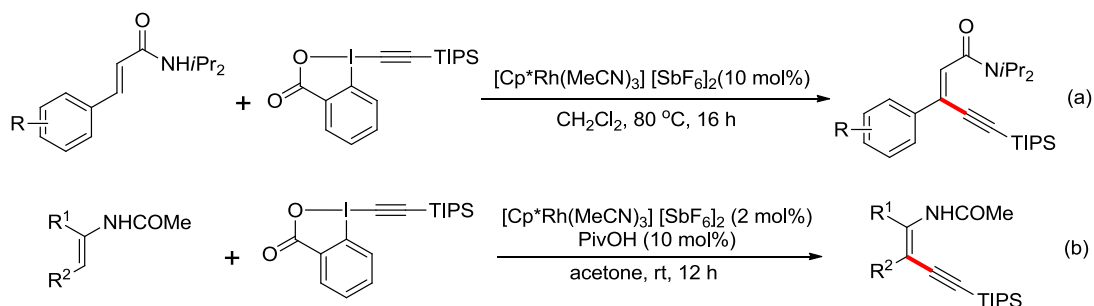
Scheme 65 Rhodium-catalyzed C-H alkylation of arenes.

Alkynes are important functional groups in organic synthesis because of their versatility to be readily converted into a lot of useful structural motifs. Besides the Sonogashira coupling reaction, the comparable C-H alkylation is another powerful and practical tool to construct alkyne compounds. The rhodium(III)-catalyzed *ortho*-C-H alkylation of electron-poor arenes bearing the amide directing group by taking advantage of the hypervalent iodine reagent as the alkyne source was discovered by Loh and co-workers (Scheme 65).⁸⁷ The reaction showed many notable features, such as mild reaction conditions, broad substrates scope and high efficiency and selectivity for monoalkynylation. This useful protocol could also have the applications for the further functionalization of natural products or related complex molecules. Shortly after, A Rh(III)-catalyzed C-H alkylation of acrylamide derivative employing Tosyl-imide as weakly coordinating directing group was demonstrated by the same group.⁸⁸



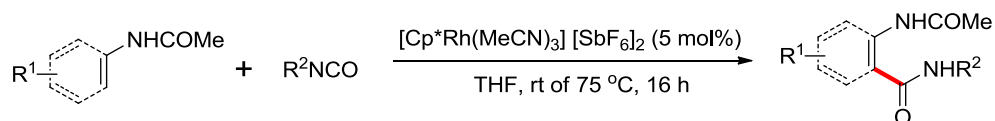
Scheme 66 Rh(III)- and Ir(III)-catalyzed C-H alkylation of arenes.

Using the hypervalent iodine-alkyne reagents, Li and co-workers also developed the chelation-assisted C-H alkylation of various (hetero)arenes (Scheme 66).⁸⁹ Both Rh(III) and Ir(III) catalysts could catalyze the transformation of alkylation, providing the complementary insights in C-H alkylation of different substrates. The reaction system was compatible with many directing groups, such as heterocycles, *N*-methoxy imines, azomethine imines, secondary carboxamides, azo compounds, *N*-nitrosoamines, and nitrones. The selectivity of mono- and dialkylation was controllable for the *N*-heterocyclic directing groups. Systematic mechanistic investigations were conducted and the Rh(III) alkynyl complex and Rh(III) vinyl complex were presumably identified as key intermediates in the reaction.



Scheme 67 Rhodium(III)-catalyzed olefinic C-H alkylation of enamides.

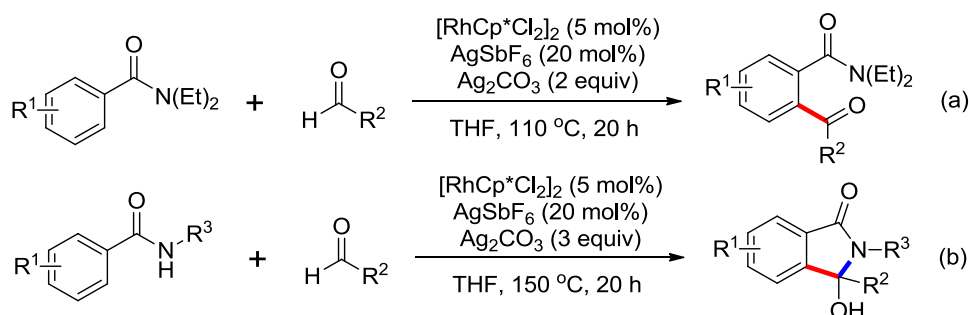
The Rh(III)-catalyzed direct alkylation of alkenes using hypervalent iodine-alkyne reagents was studied by Glorius group⁹⁰ and Loh group⁹¹ respectively (Scheme 67). In these transformations, the valuable building blocks of conjugated 1,3-enynes were generated.



Scheme 68 Rh(III)-catalyzed amidation of aryl and vinyl C-H bonds with isocyanates.

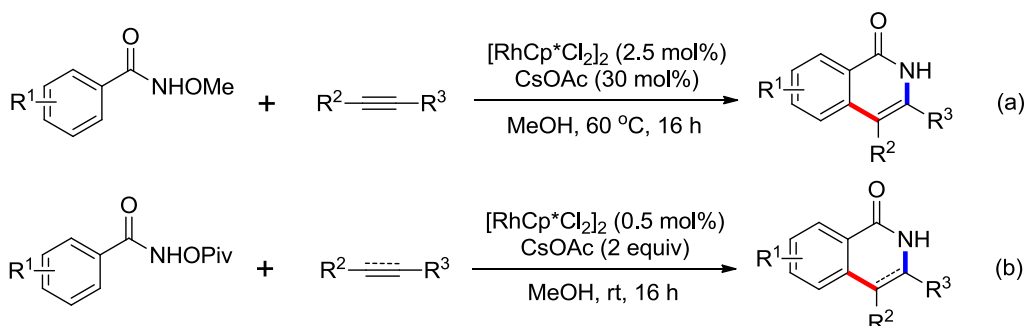
Ellman and co-workers presented the first example of Rh(III)-catalyzed coupling of

anilides and enamides with isocyanates to form *N*-acyl anthranilamides and enamine amides (Scheme 68).⁹² [Cp*Rh(MeCN)₃](SbF₆)₂ was identified as the efficient catalyst. Some kinetic examinations of the reaction were conducted to gain more insights into the reaction mechanism. An efficient method for Rh(III)-catalyzed oxidative carbonylation of aromatic amides via C-H/N-H activation to form a wide variety of phthalimides was described by Rovis group⁹³ and a rhodium-catalyzed annulation of *N*-benzoylsulfonamide with isocyanides through C-H activation to provide a straightforward approach to a wide range of 3-(imino)isoindolinones was developed by Zhu and co-workers.⁹⁴



Scheme 69 Rhodium-catalyzed oxidative *ortho*-acylation of benzamides with aldehydes.

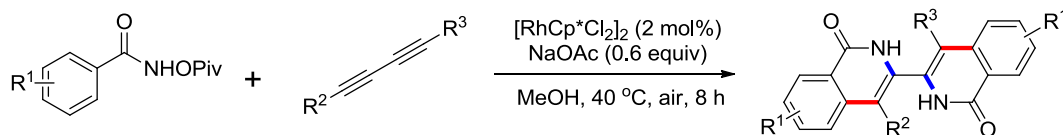
The rhodium-catalyzed regioselective acylation of benzamides via C-H bond activation using aldehydes as the acyl sources was reported by Kim and co-workers in 2011 (Scheme 69a).⁵⁵ Silver carbonate was the optimal oxidant of the reaction. A wide variety of benzamides and aldehydes were successful involved in the reaction and the relevant aryl ketones, which were crucial structural motifs in biologically active compounds and functional materials, could be afforded in moderate to good yields. Based on the above works, another different reaction pattern using the similar substrates was developed by Kim (Scheme 69b).⁹⁵ The rhodium-catalyzed oxidative acylation followed by an intramolecular cyclization took place, affording a range of 3-hydroxyisoindolin-1-one building blocks, which were ubiquitous structural motifs in synthetic and naturally occurring bioactive compounds. High temperature (150 °C) was necessary for the reaction. The relevant competition reaction was conducted to gain insight into the catalytic process and the insertion of aldehyde to a rhodacycle intermediate was presumably involved in the rate-limiting step of the transformation.



Scheme 72 Rhodium(III)-catalyzed heterocycle synthesis using an internal oxidant.

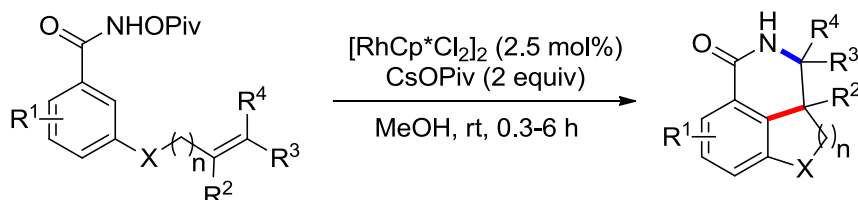
A conceptually new method to rhodium(III)-catalyzed isoquinolone synthesis from benzhydroxamic acid precursors in the absence of an external oxidant was demonstrated by Guimond and co-workers in 2010 (Scheme 72a).⁹⁹ The inner N-O bond was used as an internal oxidant, which had been successfully applied to the C-N bond formation by Hartwig.¹⁰⁰ The redox neutral isoquinolone synthesis proceeded under mild reaction conditions, was also insensitive to air and moisture with broad functional group tolerance. Shortly after, the same group developed a more reactive internal oxidant/directing group that could readily afford a wide variety of isoquinolones at room temperature with lower catalyst loadings (0.5 mol%) (Scheme 72b).¹⁰¹ It was a significant improvement of the previous work. The terminal alkynes and alkenes were compatible with the reaction conditions, expanding the substrate scope of the reaction and furnishing various monosubstituted isoquinolones and 3,4-dihydroisoquinolones in good yields. Extensive mechanistic investigations and DFT calculations were conducted, indicating that concerted metalation deprotonation (CMD) process was proposed to be the turnover limiting step and a stepwise C-N bond reductive elimination/N-O bond oxidative addition mechanism was suitable for the current reaction.

A rhodium(III)-catalyzed oxidative cycloaddition of benzamides and alkynes via C-H/N-H activation to form a series of isoquinolones in good yields was disclosed by Rovis and co-workers.¹⁰² $\text{Cu}(\text{OAc})_2$ was regarded as stoichiometric oxidant and AgSbF_6 was used to sequester the halides. Many competition experiments between different alkynes were carried out and the results revealed that more electron-rich alkynes were favored in the reaction but the regioselectivity of insertion was supposed to be largely dependent on steric factors.



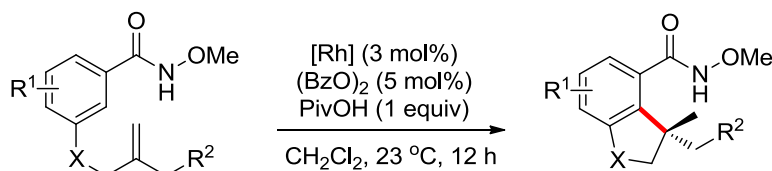
Scheme 73 The direct synthesis of diverse bisheterocycles by Rh(III) catalysis.

Based on the above pioneering works, a rhodium(III)-catalyzed versatile and flexible C-H activation/1,3-diyne general strategy for the rapid assembly of diverse polysubstituted bisheterocycles in high efficiency and selectivity was achieved by Glorius recently (Scheme 73).¹⁰³



Scheme 74 Rhodium(III)-catalyzed intramolecular amidoarylation.

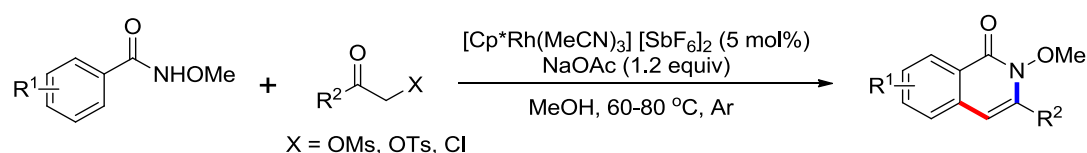
The rhodium(III)-catalyzed distinct reaction patterns of tethered olefin-containing benzamides directed by the amide group was developed by Rovis and co-workers (Scheme 74).¹⁰⁴ Intramolecular hydroarylation, amidoarylation, and dehydrogenative Heck-type reaction were achieved with different substrates. A wide variety of tethered alkenes could be involved in the reaction and the corresponding five- or six-membered biologically useful fused oligocyclic lactams products were produced in good to excellent yields. The diastereoselectivity of the amidoarylation product could be controlled by using of a substrate containing a pre-existing stereocenter. More recently, Glorius group reported the almost identical work through intramolecular redox-neutral cyclization process of a wide variety of tethered olefin-containing benzamides via C-H activation.¹⁰⁵ A rhodium(III)-catalyzed intramolecular amidoarylation of alkyne via a C-H activation pathway for the synthesis of 3,4-fused tricyclic indoles was independently reported by Xu^{106a} and Li^{106b}, further expanding the synthetic utility of intramolecular redox-neutral annulation reaction.



Scheme 75 Asymmetric hydroarylations of 1,1-disubstituted alkenes.

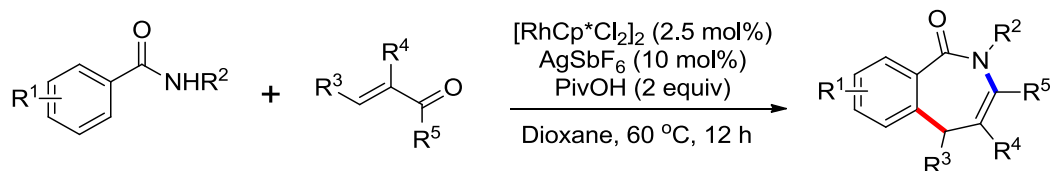
An enantioselective intramolecular rhodium(III)-catalyzed hydroarylation to afford functionalized dihydrobenzofurans that possessed a quaternary stereocenter directed by the CONHOMe group under mild conditions was demonstrated by Cramer and co-workers in

2014 (Scheme 75).¹⁰⁷ The existence of special chiral Cp ligand could significantly enhance the enantioselectivity of the hydroarylation of aryl hydroxamates. The scope of the enantioselective hydroarylation was broad and a wide range of substituents were tolerant. The *meta*-alkoxy group of the olefin side chain played the role of a secondary directing group for Rh-catalyzed reactions. Diverse dihydrofurans bearing methyl-substituted quaternary stereocenters were produced in moderate to good yields. As early as 2012, Rovis and Cramer independently reported a chiral rhodium complex catalyzed directed C-H bond functionalization for the synthesis of asymmetric tetrahydroisoquinolinone derivatives with high enantioselectivity.¹⁰⁸



Scheme 76 Redox-neutral rhodium(III)-catalyzed synthesis of *N*-heterocycles.

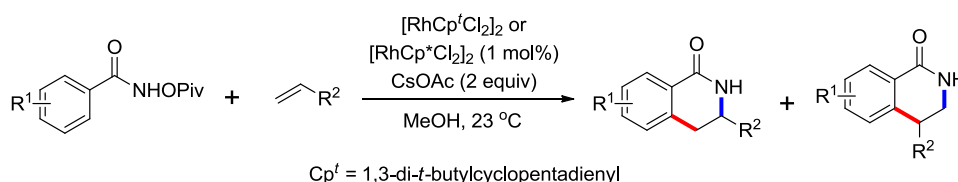
Since α -(pseudo)halo ketones are widely utilized as electrophiles in cross-coupling reactions, they could be applied in transition-metal-catalyzed C-H activation. More recently, the first example of using α -halo and pseudohalo ketones as C(sp³)-based electrophiles in Rh(III)-catalyzed C-H activation to synthesize diverse *N*-heterocycles under mild and redox-neutral reaction conditions was developed by Glorius and co-workers (Scheme 76).¹⁰⁹ In this reaction, α -(pseudo)halo ketones were identified as oxidized alkyne equivalents to undergo the Rh(III) catalyzed redox-neutral annulations. Various important *N*-heterocycles, such as 3-aryl- and 3-alkyl-substituted isoquinolones, 2-pyridones, 1, 2-benzothiazines, and 2-methylated indole could be obtained in moderate to excellent yields under the mild conditions.



Scheme 77 Cyclization of amides with α,β -unsaturated aldehydes and ketones.

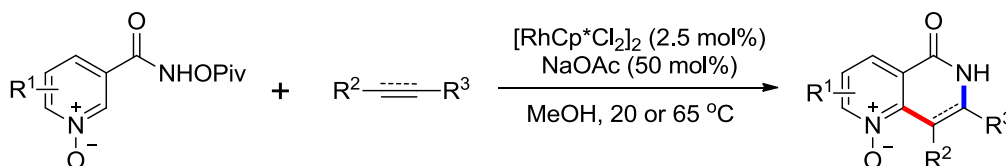
Azepine and its derivatives are important skeletal motifs in numerous natural products and synthetic compounds. Extensive attention has been paid to the development of effective methods towards these useful molecules. In 2013, Glorius and co-workers developed an

efficient methodology of rhodium(III)-catalyzed intermolecular annulations for the synthesis of azepine derivatives utilizing simple and readily available benzamides and α,β -unsaturated aldehydes or ketones as starting materials (Scheme 77).¹¹⁰ PivOH was the best additive to improve the reaction efficiency by releasing H₂O as the only waste. The scope of the substrates was broad and a wide range of azepine derivatives could be readily prepared in moderate to excellent yields. Some control experiments indicated that the catalytically active species [RhIII Cp*] was identified as a transition-metal catalyst and a Lewis acid catalyst was used for dehydration process simultaneously. The annulations procedure was presumably supposed to undergo C-H activation, cyclization and condensation steps.



Scheme 78 Rh(III)-catalyzed C-H activation for the synthesis of dihydroisoquinolones.

A rhodium(III)-catalyzed alkene migratory insertion in a range of benzhydroxamic acids for the synthesis of dihydroisoquinolones was reported by Rovis and co-workers in 2014 (Scheme 78).¹¹¹ The sterically bulky di-*tert*-butylcyclopentadienyl ligand (Cp^f) was used as an effective ligand to increase the regioselectivity of the reaction, because the classical Cp* ligand exhibited relatively low selectivity. Crystallographic results of the 5-membered RhCp^f metallacycle offered some evidence for the enhanced regioselectivity. Other transformations employing rhodium(III)-catalyzed C-H activation/annulation reactions of benzhydroxamic acids with different coupling partners were reported and the relevant *N*-heterocycles were afforded in various manners.¹¹²

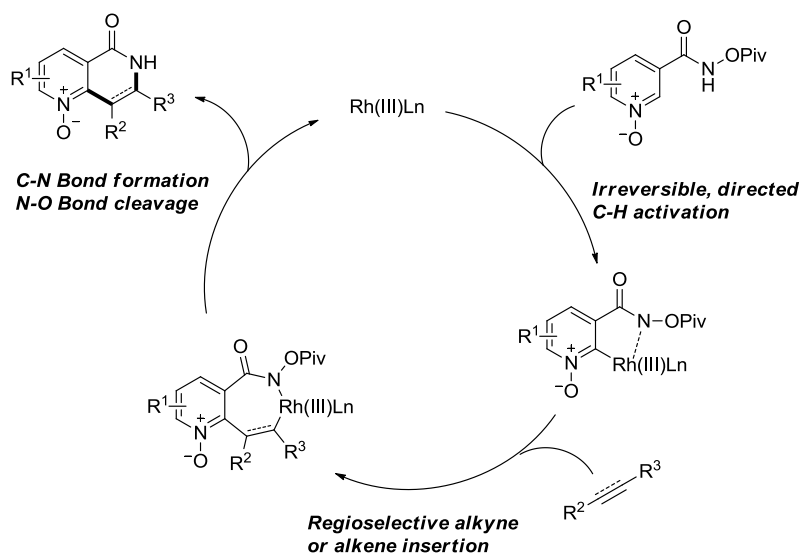


Scheme 79 Rh(III)-catalyzed regioselective synthesis of naphthyridinones.

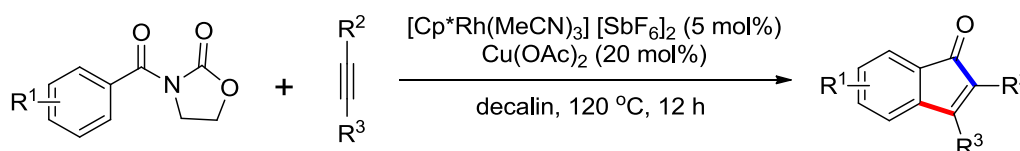
Rh(III)-catalyzed [4+2] annulations reactions of aromatic carboxamides with alkynes is a powerful and efficient route for the preparation of some fused nitrogen-containing heterocycles. However, application of this method to electron-deficient pyridine derivatives

has proved to be quite difficult. Poor selectivity and low reaction rates of pyridines constituted main challenges of relevant C-H functionalization reactions. A Rh(III)-catalyzed C-H activation/annulation of nicotinamide *N*-oxides with alkynes or alkenes to afford naphthyridinone *N*-oxide or dihydronaphthyridinone *N*-oxide products under mild conditions was demonstrated by Huckins and co-workers in 2013 (Scheme 79).¹¹³ The existence of *N*-oxide could increase the reaction rates and enhance the desired regioselectivity. Many marked features, such as low catalyst loadings, mild reaction conditions, good yields and regioselectivities were achieved.

The postulated mechanism was given based on the deuterated experiments (Scheme 80). Initially, a C-H cyclometallation at the 2-position of the pyridine *N*-oxide ring was proceeded to produce rhodium cycle complex, which underwent regioselective alkyne/alkene insertion into the Rh-C bond to afford seven-membered ring metalocycle. The subsequent reductive elimination gave the final naphthyridinone *N*-oxide product by using the N-O bond as internal oxidant to re-oxidize the Rh(I) to Rh(III).



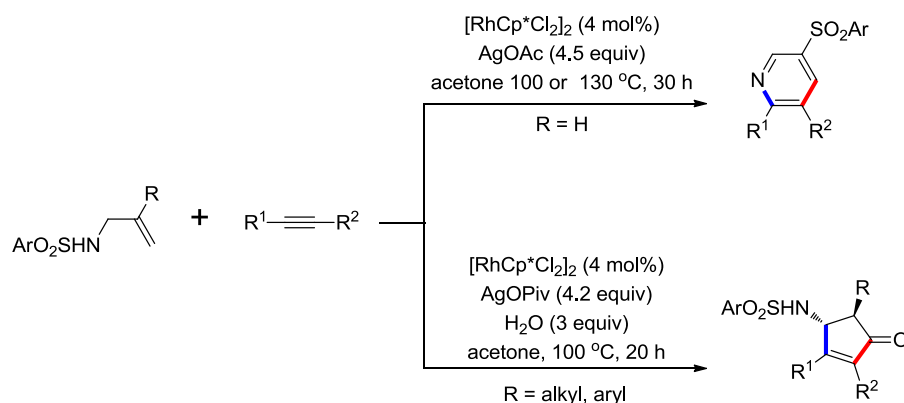
Scheme 80 The plausible mechanism.



Scheme 81 Rhodium/copper-catalyzed annulation of benzimidazole derivatives with internal alkynes.

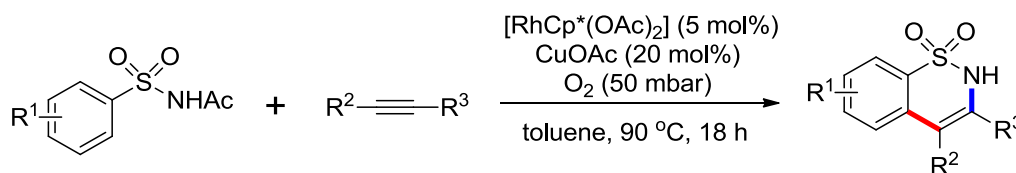
Shi and co-workers reported a rhodium(III)-catalyzed C-H activation/annulation of benzimidazole derivatives from abundant and essentially unfunctionalized benzoic acids with alkynes to

form diverse synthetically valuable indenones (Scheme 81).¹¹⁴ *N*-Acyloxazolidinone with proper directing ability and electrophilicity was identified as the optimal directing group and the highest yield was obtained. Decahydronaphthalene was the best solvent for the reaction. A wide range of functionalized indenone products were prepared from readily available benzimide derivatives under the redox neutral conditions. Later, Li and coworker reported a Rh(III)-catalyzed C-H functionalization of 1-benzoylpyrrolidine with propargyl alcohols for the synthesis of (4-benzylidene)isochroman-1-ones.¹¹⁵ Highly enantio-enriched lactones could be obtained by the use of optically pure propargyl alcohols as the starting materials.



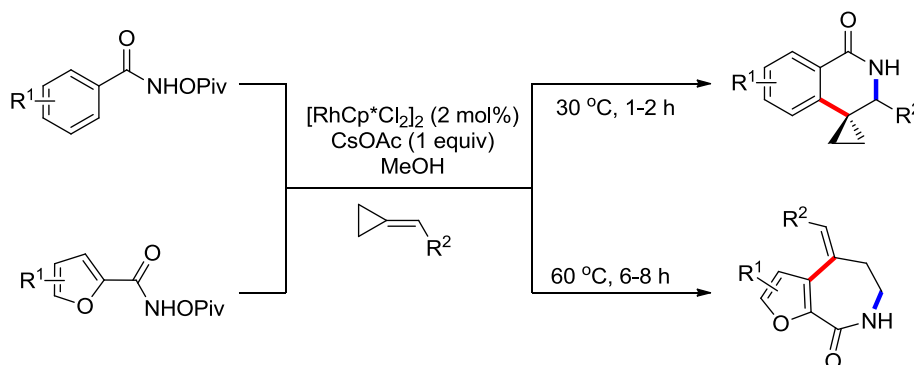
Scheme 82 Oxidative coupling of *N*-allyl arenesulfonamides with alkynes.

A rhodium(III)-catalyzed C-H activation for the efficient construction of pyridines and cyclopentenone rings from readily available *N*-allyl sulfonamides and alkynes using sulfonamides as effective directing groups was demonstrated by Li and co-workers in 2012 (Scheme 82).¹¹⁶ When *N*-allyl *p*-tolylsulfonamide was used as substrate, AgOAc (4.5 equiv) proved to be an ideal oxidant to support a twofold oxidation process, affording 3-sulfonylpyridine product in good yield. Several cross-over experiments evidenced the possible involvement of a formal oxidative intermolecular 1,3-shift process of the sulfonyl group. When introducing a methyl (blocking) group into the olefin unit to inhibit 1, 3-shift process of the sulfonyl group, the unexpected cyclopentenone products were generated. The corresponding ketone oxygen atom was likely come from the water. The reaction exhibited broad substrate scope and the high selectivity was determined by the allyl moiety of the sulfonamide.

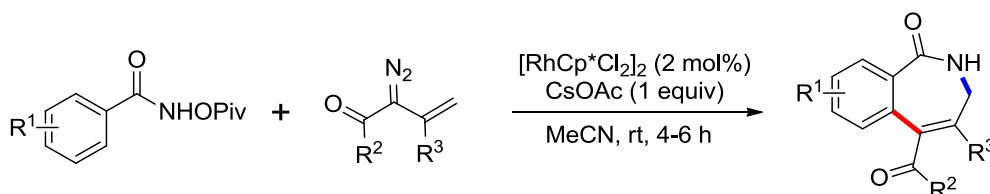


Scheme 83 Access to sultams by Rhodium(III)-catalyzed directed C-H activation.

A rhodium(III)-catalyzed oxidative C-H activation of simple and widely available sulfonamides and subsequent addition of internal alkynes for the convenient synthesis of the benzosultams was established by Cramer and co-workers (Scheme 83).¹¹⁷ The acylated sulfonamide was chosen as suitable directing group to construct a wide range of pharmaceutically important sulfonamides. Catalytic amounts of copper(I) acetate and molecular oxygen (50 mbar) as a terminal oxidant were beneficial for the high conversions and yields of the reaction. This reaction was a general and attractive method to access the synthetic and medicinal important aryl sultams. Furthermore, there are many other good examples of sulfonamide-assisted C-H activation in recent years¹¹⁸.



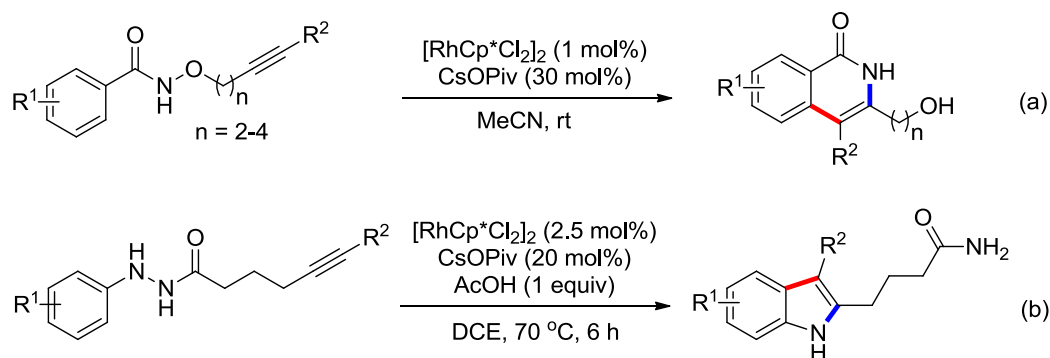
Scheme 84 The C-H activation/cycloaddition of benzamides and methylenecyclopropanes.



Scheme 85 The C-H activation/[4+3] cycloaddition of benzamides and vinylcarbenoids.

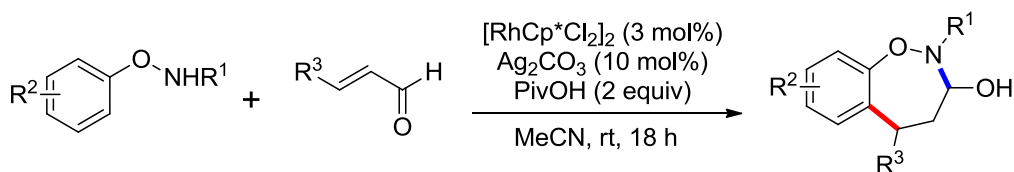
Cui and co-workers demonstrated a Rh(III)-catalyzed C-H activation/cycloaddition of benzamides and methylenecyclopropanes for the divergent synthesis of biologically valuable spiro dihydroisoquinolinones and furan-fused azepinones under mild conditions (Scheme 84).¹¹⁹ A carboxylate assisted C-H activation via a concerted metalation/deprotonation (CMD) pathway and MCPs mild insertion process were presumably involved in the reaction. For the

formation of azepinone, the fused electron-rich furan moiety could stabilize the metal intermediate and promote a cyclopropyl carbinyl-butenyl rearrangement via ring opening process to give azepinone product. They also investigated a Rh(III)-catalyzed C-H activation/[4+3] cycloaddition of benzamides with vinylcarbenoids, which could be utilized as suitable three-carbon coupling partners to give azepinones (Scheme 85).^{71e} CsOAc was regarded as the optimal additive and rendered the desired product in 95% yield. A wide variety of azepinones were formed in moderate to good yields by this general and versatile approach. It was the first example of utilization of vinylcarbenoids as three-carbon components in Rh(III)-catalyzed cycloaddition reactions.

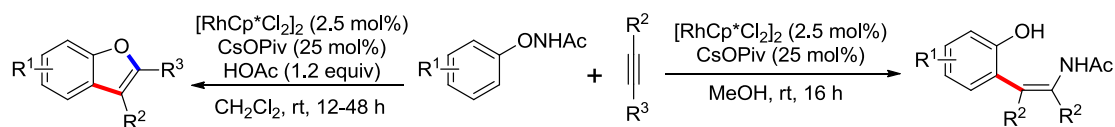


Scheme 86 Rhodium(III)-catalyzed intramolecular redox-neutral annulation.

An efficient rhodium(III)-catalyzed intramolecular annulation of alkyne tethered hydroxamic esters for the facile synthesis of hydroxyalkyl-substituted isoquinolone/2-pyridone derivatives was demonstrated by Park and co-workers (Scheme 86a).¹²⁰ This reaction showed reverse regioselectivity compared to the previous intermolecular version of rhodium-catalyzed C-H/N-O bond functionalization reactions. The reaction proceeded under mild reaction conditions and obviated the use of external oxidants. It was noteworthy that the total synthesis of some phenanthroindolizidine alkaloids was successfully accomplished by this method. After two years, Li and Zhou reported a similar Rh(III)-catalyzed intramolecular redox-neutral C-H activation/annulation of a tethered alkyne to afford 2-amidealkyl indoles with completely reversed regioselectivity (Scheme 86b).¹²¹ The strategy was also applied to the highly efficient formal total synthesis of goniomitine using Rh(III)-catalyzed C-H activation/annulation as a key step. A rhodium(III)-catalyzed intramolecular annulations to synthesize tricyclic isoquinoline derivatives in good yields was also developed by Gulías and co-workers in 2013.¹²²

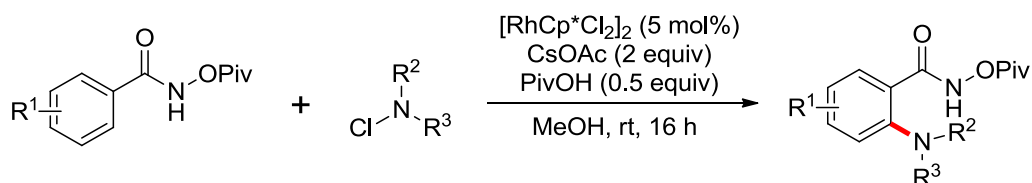


Scheme 87 Rhodium(III)-catalyzed C–H activation/annulation of *N*-phenoxyacetamides.



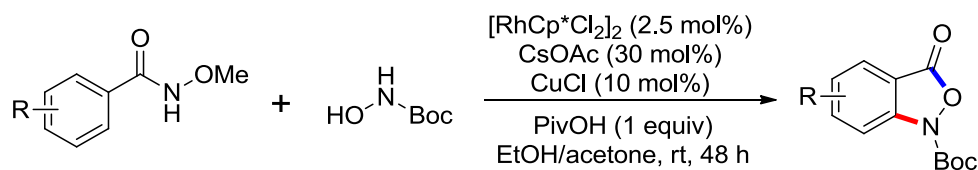
Scheme 88 Rhodium(III)-catalyzed redox-neutral coupling of *N*-phenoxyacetamides.

A Rh(III)-catalyzed intermolecular [4+3] annulation method for the rapid synthesis of 1,2-oxazepines from *N*-phenoxyacetamides and α , β -unsaturated aldehydes reported by Zhao and co-workers (Scheme 87).¹²³ This atom-economic protocol might involve C–H activation, alkene insertion, and intramolecular nucleophilic attack from a Rh amide to yield 1, 2-oxazepine products, which were readily transformed to biologically important chroman derivatives. Previously, Lu and Liu described a mild rhodium(III) catalyzed redox-neutral coupling of *N*-phenoxyacetamides and alkynes for the synthesis of *ortho*-hydroxyphenyl substituted enamides or benzofurans with high regioselectivity and yields (Scheme 88).¹²⁴



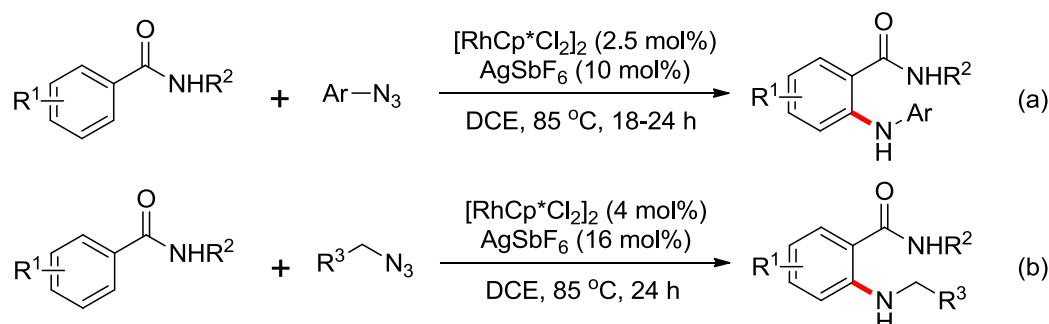
Scheme 89 Rh(III)-catalyzed direct C–H amination using *N*-chloroamines.

A rhodium(III)-catalyzed direct C–H amination of *N*-pivaloyloxy benzamides with *N*-chloroamines under mild conditions was achieved by Glorius and co-workers (Scheme 89).¹²⁵ The versatile *N*-pivaloyloxy amide and *N*-chloroalkylamines was used as the directing group and readily accessible nitrogen source. This novel method provided a complementary route to construct some important arylamine structures.



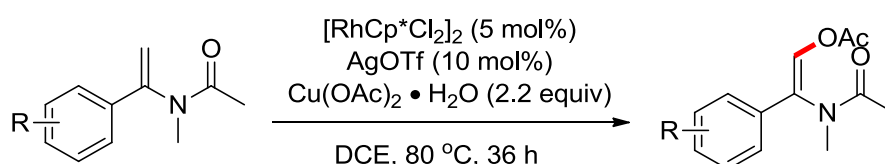
Scheme 90 Hydroxyamination of aryl C–H bonds with *N*-hydroxycarbamate.

Recently, Zhang and co-workers developed a novel aryl C-H bond hydroamination catalyzed by synergistic combination of rhodium and copper catalysis using commercially available *N*-Boc-hydroxylamine as nitrogen source (Scheme 90).¹²⁶ A wide variety of bioactive benzo[*c*]isoxazole derivatives were readily prepared by this efficient protocol. The electrophile nitrosocarbonyl compound was *in situ* generated by copper-catalyzed aerobic oxidation and used as coupling partner under mild reaction conditions.



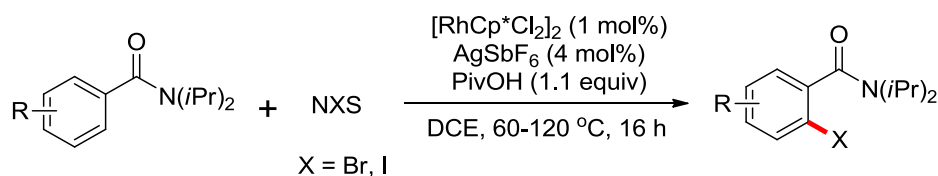
Scheme 91 Rhodium-catalyzed direct C-H amination of benzamides.

Chang and co-workers presented the first example of rhodium-catalyzed direct arene C-H amination of benzamides utilizing sulfonyl azides as the amine source to afford a range of diarylamines, which were widely existed in biologically active natural products (Scheme 91a).¹²⁷ The procedure did not require external oxidant and released N_2 as a single by-product, providing a practical and environmentally benign amination process. The elegant method was also readily extended to the amination of ketoximes with high reactivity and functional group tolerance, emphasizing the generality of this method. Later, they extended the scope of the rhodium-catalyzed direct amination reaction to various alkyl azides (Scheme 91b).¹²⁸ Both benzyl and aliphatic azides bearing a wide range of functional groups were identified as the nitrogen source and involved in the reaction to give synthetically more important and diverse *N*-alkylaniline products successfully. Besides amides, the reaction could also be extended to some substrates bearing weak coordinating groups such as aromatic ketones and aryl ketoximes. A plausible and rational amination pathway was also proposed based on the mechanistic studies.

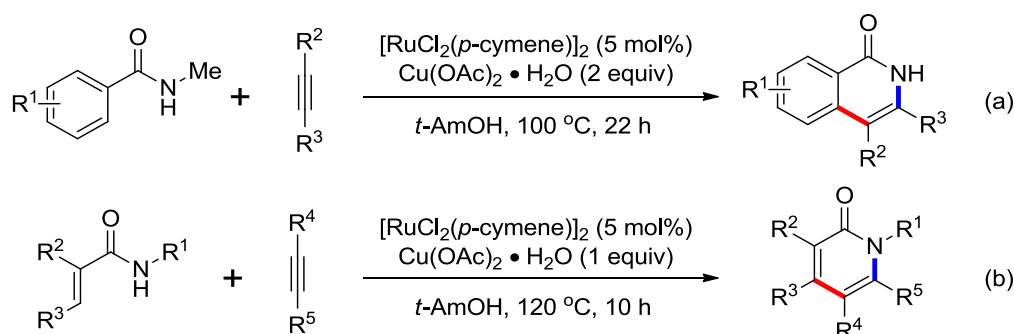


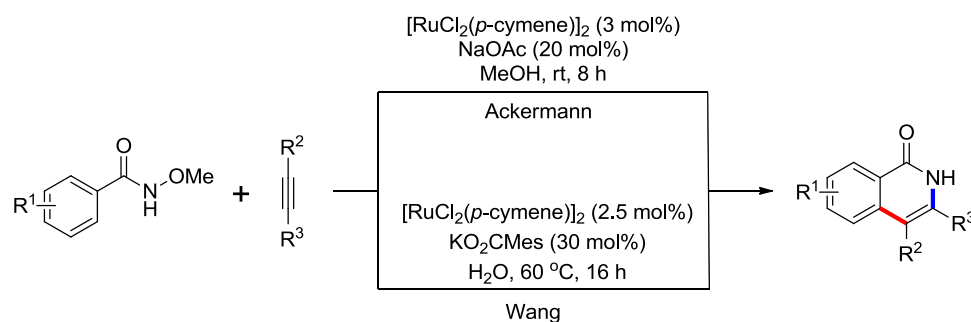
Scheme 92 Amide-assisted acetoxylation of vinyl C(sp²)-H bonds.

The first rhodium-catalyzed acetoxylation of an olefinic C(sp²)-H bond in enamides with high regio- and stereoselectivity to afford a variety of substituted vinyl acetates with absolute *Z*-configuration was accomplished by Zhang and co-workers recently (Scheme 92).¹²⁹ Cu(OAc)₂ was utilized as the oxidant and the source of acetate in the reaction. The isotope effect studies indicated that the step of carbometalation by abstracting the olefinic hydrogen was reversible and the C-H activation might not be involved in the rate-determining step.

**Scheme 93** [Rh(III)Cp*]-catalyzed *ortho*-bromination and iodination of arenes.

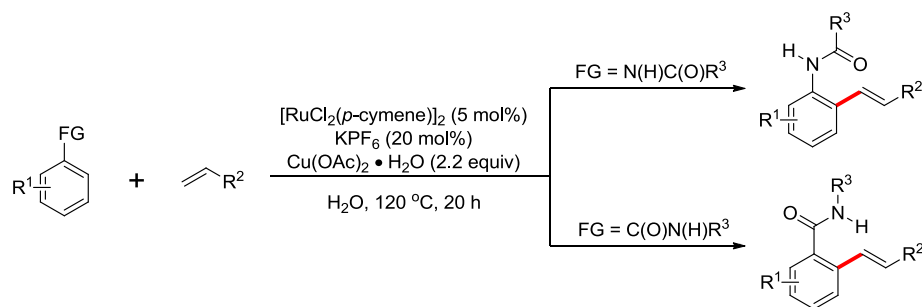
The first example of Rh(III)-catalyzed direct *ortho* bromination and iodination reaction of different aromatic compounds via C-H activation for the convenient synthesis of *ortho*-brominated and -iodinated aromatic products was reported by Glorius and co-workers in 2012 (Scheme 93).¹³⁰ This general and practical strategy was compatible with many different directing groups, offering new possibilities to prepare a wide range of aromatic halides. The Rh(III)-catalyzed halogenations reaction of vinylic C-H bonds was reported by the same group later, which provided a general and efficient approach to a variety of substituted haloacrylic acid derivatives.¹³¹

2.3 Ru catalyzed C-H functionalization**Scheme 94** Ruthenium-catalyzed synthesis of isoquinolones and 2-pyridones.



Scheme 95 Ruthenium-catalyzed redox-neutral synthesis of isoquinolones.

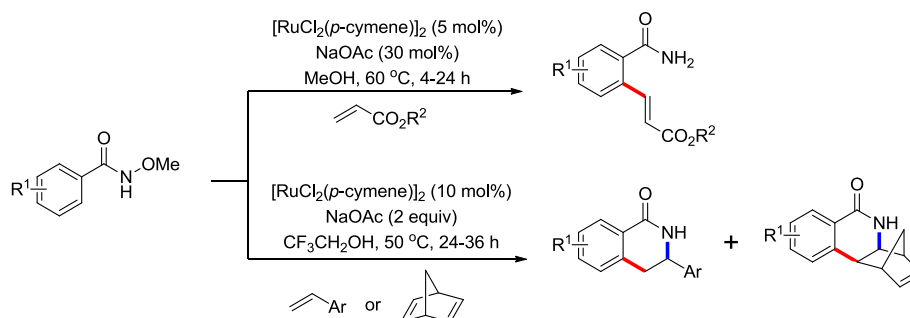
Compared with a lot of well-developed rhodium-catalyzed oxidative annulations to synthesize diverse heterocycles, the use of less-expensive ruthenium catalysts for oxidative annulations was far from studied at the same stage.^{1x} Due to its extraordinary reactivity and selectivity, the $[\text{RuCl}_2(p\text{-cymene})]_2$ complex has been used as a catalyst for diverse C-H bond functionalization reactions with high efficiency. The first ruthenium-catalyzed oxidative annulation reaction of alkynes with benzamides for the facile synthesis of a wide range of isoquinolones with broad scope was reported by Ackermann and co-workers (Scheme 94a).¹³² Detailed mechanistic investigations showed that a carboxylate assisted C-H bond metalation was the rate-limiting step, which was different from the rhodium-catalyzed isoquinolone synthesis.^{99, 101-102} They also investigated the ruthenium-catalyzed oxidative annulations of acrylamides and alkynes with stoichiometric amounts of external oxidants to synthesize 2-pyridones (Scheme 94b).¹³³ The ruthenium-catalyzed C-H functionalization under mild conditions to deliver a series of isoquinolone motifs was reported by Ackermann and Wang group respectively (Scheme 95).¹³⁴



Scheme 96 Ruthenium-catalyzed oxidative C-H alkenylations.

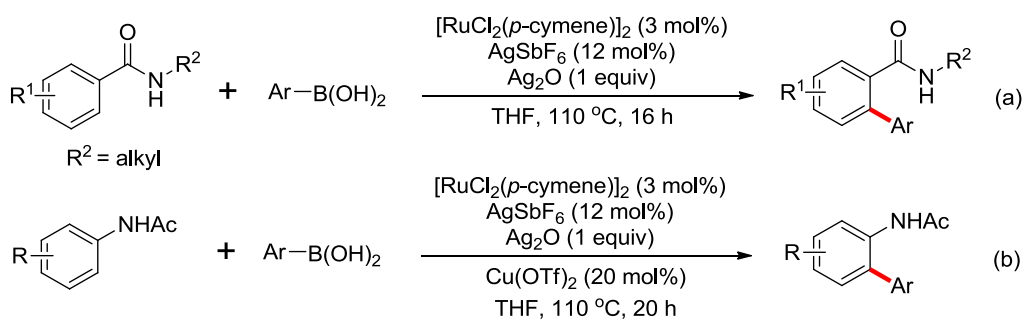
A ruthenium catalyzed cross-dehydrogenative alkenylations of various anilides and benzamides was reported by Ackermann and co-workers (Scheme 96).¹³⁵ A cationic ruthenium(II) complex was chosen as the optimal catalyst and water was used as a green

solvent. Detailed mechanistic studies provided the strong evidence for the different mechanisms of the two transformations. The cycloruthenation step in oxidative alkenylation of acetanilide was reversible, whereas an irreversible C-H bond metalation was involved in cross-dehydrogenative alkenylations of benzamides.

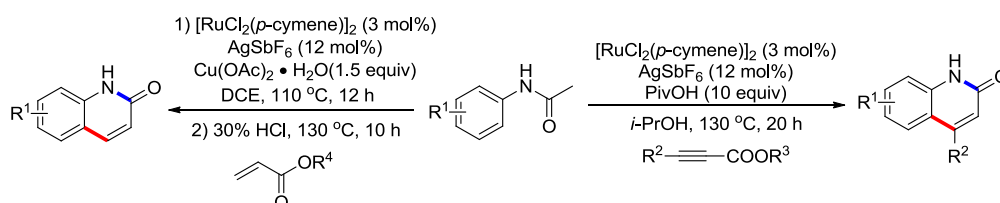


Scheme 97 Ruthenium-catalyzed oxidative C-H bond olefination.

The first ruthenium catalyzed oxidative C-H bond olefination of *N*-methoxybenzamides using CONH(OMe) group as an oxidizing directing group was developed by Wang and co-workers (Scheme 97).¹³⁶ With the variance of olefinic partners and solvents, two types of products were afforded in moderate to good yields. On the basis of the mechanistic studies, the reaction presumably proceeded by an intermolecular carboration of alkene via rate-determining C-H bond activation and followed by reductive elimination to form the desired products.



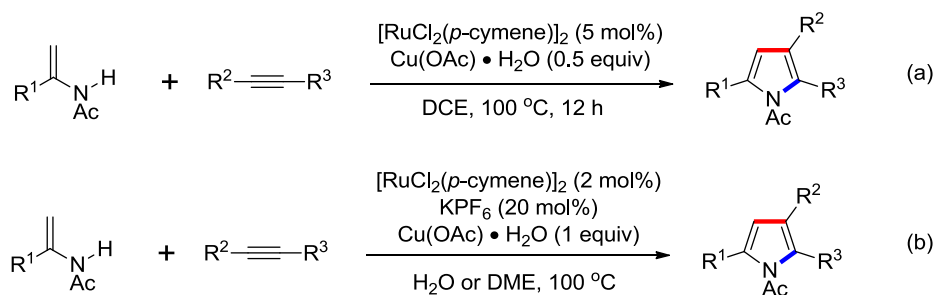
Scheme 98 Ruthenium-catalyzed *ortho*-arylation of benzamides and anilides.



Scheme 99 Ruthenium-catalyzed cyclization of anilides with propiolates or acrylates.

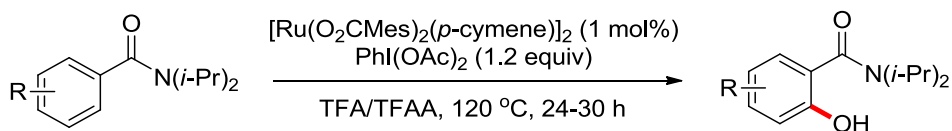
In 2012, Jeganmohan and co-workers reported a ruthenium-catalyzed *ortho*-arylation of *N*-alkyl benzamides with substituted aromatic boronic acids with high regioselectivity.

(Scheme 98a).¹³⁷ When substituted alkenylboronic acids were used as starting reactants, the corresponding *ortho*-alkenylation of *N*-alkyl benzamides was achieved successfully. The *ortho*-arylated *N*-alkyl benzamides were readily converted into fluorenones under current methodology. Later, the same group developed a ruthenium-catalyzed oxygen atom directed *ortho*-arylation of acetanilides with aromatic boronic acids (Scheme 98b).¹³⁸ It was noteworthy that diarylated products or *N*-arylated acetanilides were not observed under the reaction conditions. The obtained *ortho*-arylated *N*-substituted anilines were key synthetic intermediates for various organic transformations and could be further converted into biologically useful phenanthridine and carbazole derivatives. Shortly after, they demonstrated a Ru-catalyzed cyclization of anilides with propiolates or acrylates to deliver 2-quinolinones bearing diverse functional groups in good to excellent yields, extending the application of Ru-catalyzed C-H functionalization reactions (Scheme 99).¹³⁹

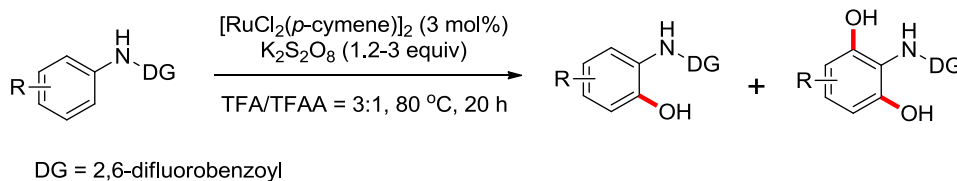


Scheme 100 Ruthenium-catalyzed pyrrole synthesis.

Wang and Liu respectively reported an efficient and regioselective ruthenium-catalyzed oxidative annulation of enamides with alkynes via the cleavage of C(sp²)-H/N-H bonds to afford a wide range of biological and pharmaceutical important pyrrole derivatives (Scheme 100a).^{140a} With the addition of AgSbF₆ and MeOH, some *N*-unsubstituted pyrroles could be smoothly obtained by Wang's work. The reaction developed by Liu could be carried out in the aqueous medium (Scheme 100b).^{140b}

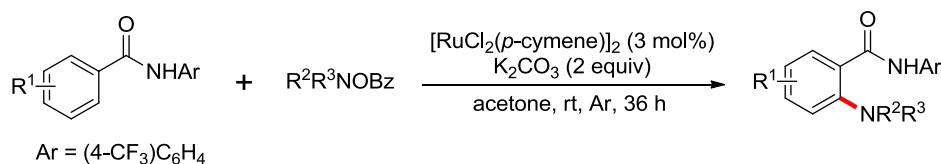


Scheme 101 Ru-catalyzed oxidative C(sp²)-H bond hydroxylation.



Scheme 102 Ru-catalyzed C-H mono- and dihydroxylation of anilides.

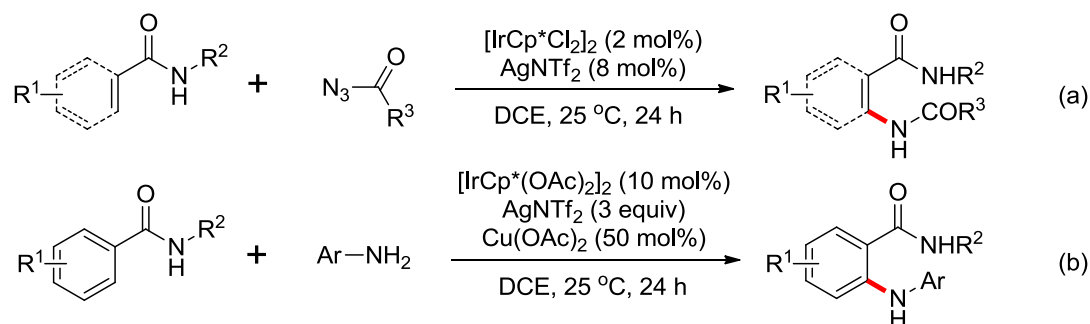
A ruthenium-catalyzed *ortho*-selective C-H bond hydroxylations on benzamides with $\text{PhI}(\text{OAc})_2$ as the terminal oxidant was disclosed by Ackermann and co-workers (Scheme 101).¹⁴¹ The reaction had some notable features, such as weakly coordinating benzamides as readily modifiable directing groups, a low catalyst loading, high efficiency, and regioselectivity. One year later, they developed a similar strategy of ruthenium-catalyzed site selective $\text{C}(\text{sp}^2)\text{-H}$ bond oxygenations on aryl Weinreb amides, which could be readily transformed into the corresponding ketones and aldehydes.¹⁴² Rao and co-worker reported the first Ru(II)-catalyzed C-H mono- and dihydroxylation of anilides for the synthesis of 2-aminophenols and heterocycles with a new directing group strategy (Scheme 102).¹⁴³ The 2,6-difluorobenzoyl group was chosen as a double-functional directing group, which could serve as not only a readily cleavable coordinating group but also a potential structural component for further complex molecule synthesis.



Scheme 103 Ru(II)-catalyzed *ortho*-C-H amination of arenes and heteroarenes.

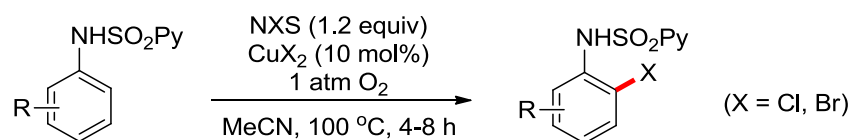
The Ru(II)-catalyzed *ortho*-C-H amination directed by a weakly coordinating amide group using electrophilic *O*-benzoyl hydroxylamines as N-source at room temperature was developed by Yu and Dai (Scheme 103).¹⁴⁴ The scope of this reaction for heteroarene substrates was substantially broader than Pd-catalyzed C-H amination reaction reported by the same group,⁵⁹ showing the excellent reactivity of the weakly coordinating directing group with Ru(II) catalysts.

2.4 Other metals (Ir, Cu, Co) catalyzed C-H functionalization

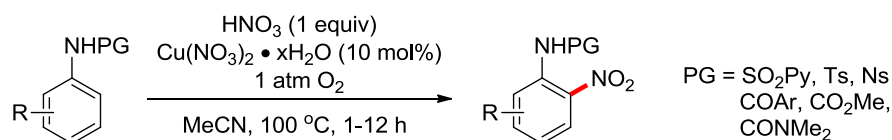


Scheme 104 Iridium-catalyzed C-H amination with acyl azides and anilines.

Chang and co-workers developed the iridium-catalyzed direct C-H amidation of arenes and alkenes using acyl azides as the nitrogen source under mild conditions (Scheme 104a).¹⁴⁵ The acyl azides were utilized as the nitrogen donor of an acyl amino group in the reaction to afford a broad range of amidated arenes and olefins with high functional group tolerance. An *in situ* generated cationic half-sandwich iridium complex was proposed to be involved in the reaction and used as an active catalyst. The amidation reaction featured the absence of external oxidants, molecular nitrogen as a single byproduct and wide substrate scope, enabling this environmentally benign method to be practical in organic synthesis and medicinal chemistry. An iridium-catalyzed direct C-H amination of benzamides by employing anilines as nitrogen sources at room temperature was reported by the same group (Scheme 104b).¹⁴⁶ For the first time, this transformation achieved the amination by the use of the simple and readily available anilines in the place of azides. A unique iridacyclic species was synthesized and unambiguously characterized, revealing that the Ir metal was coordinated to the carbonyl O atom rather than the amide nitrogen atom, which was different from the previously reported palladacycle complexes. It was the first example of Ir-catalyzed direct C-H amination of benzamides using simple aniline as coupling partners to construct a wide variety of synthetically and medically useful arylamine products.

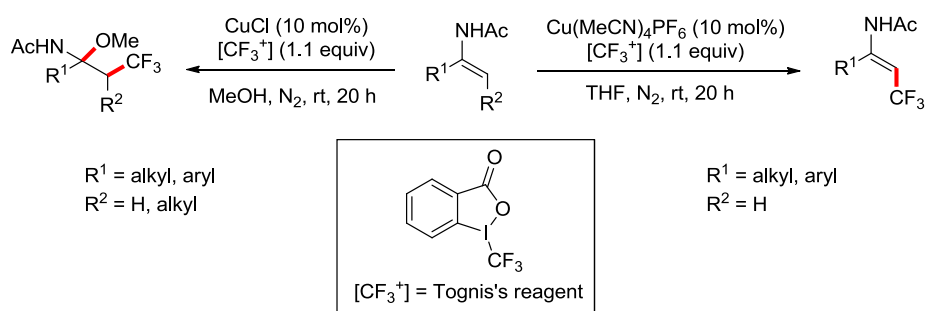


Scheme 105 Copper-catalyzed *ortho*-halogenation of protected anilines.

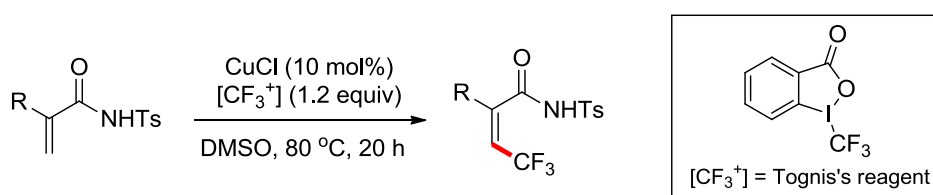


Scheme 106 Copper-catalyzed mild nitration of protected anilines.

A practical Cu-catalyzed direct *ortho*-halogenation of anilines employing a readily removable *N*-sulfonyl directing group under aerobic conditions was developed by Carretero and co-workers (Scheme 105).¹⁴⁷ *N*-halosuccinimides (NXS, X = Cl, Br) were identified as convenient X⁺ sources to participate in the reaction. Various halogenated anilines, which were versatile precursors for a lot of heterocyclic frameworks, could be produced by this efficient method. They disclosed a practical copper-catalyzed direct nitration of protected anilines employing nitric acid as the nitrating agent (Scheme 106).¹⁴⁸ This reaction had broad substrate scope in terms of *N*-protecting groups (sulfonamides, carbamates, amides, and ureas) and remarkable functional group tolerance. The dinitrated aniline derivatives were also prepared by using two equivalents of HNO₃. The final products could be regarded as valuable building blocks to some relevant nitrogenated architectures.

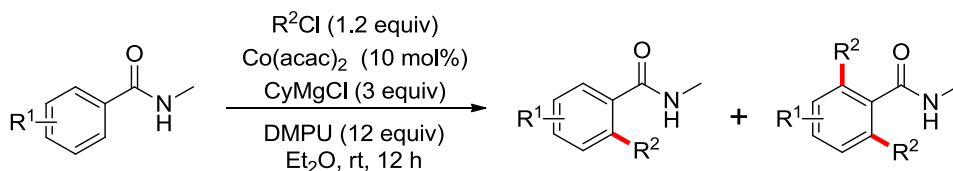
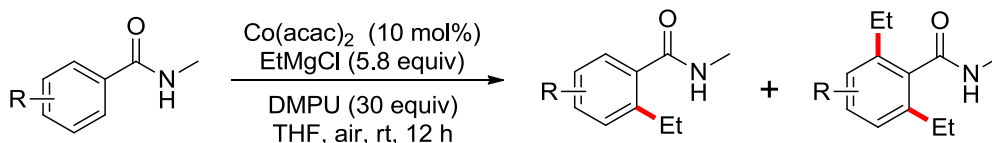
**Scheme 107** Copper-catalyzed olefinic trifluoromethylation of enamides.

The first example of copper-catalyzed C-H trifluoromethylation of enamides for the direct formation of olefinic C-CF₃ bonds at room temperature was reported by Loh and co-workers (Scheme 107).¹⁴⁹ The Togni's reagent was used as trifluoromethylation agent. The amido group introduced onto the olefin moiety had dual roles: stabilizing the putatively formed α -carbonium and inducing the subsequent proton elimination or a migration process during the reaction. The Lewis acidity of the copper catalyst was also beneficial for the reactivity of the transformation. The oxytrifluoromethylation of enamides was realized by slight modification of the reaction conditions.

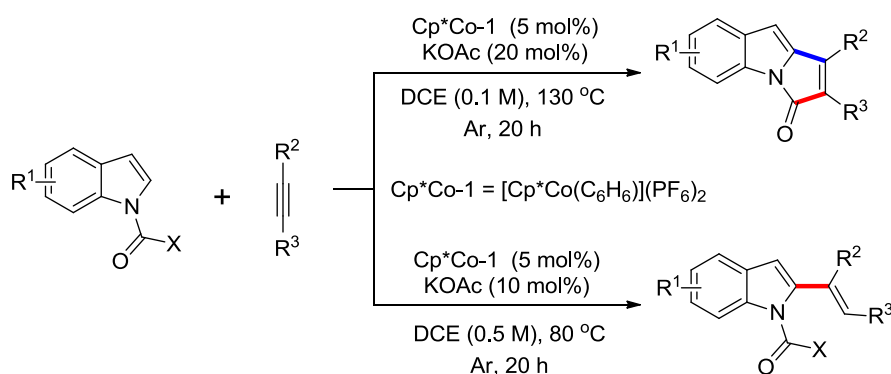


Scheme 108 Copper-catalyzed olefinic trifluoromethylation.

The copper-catalyzed C-H trifluoromethylation of electron-deficient alkenes was demonstrated by Loh and co-workers (Scheme 108).¹⁵⁰ Comparing with the electron-rich alkenes, the trifluoromethylation of electron-deficient alkenes had more challenges. The directing group was deemed to have a vital effect on the success of this C-CF₃ bond formation. Based on the sufficient results of a set of control experiments, the involvement of radical species was proposed in the catalytic process and olefinic C-H bond activation was not involved in the rate-determining step. This reaction tolerated various substituted acrylate derivatives and a broad range of synthetically useful functionalities.

**Scheme 109** Cobalt-catalyzed *ortho*-alkylation of secondary benzamide.**Scheme 110** Cobalt-catalyzed coupling of alkyl Grignard reagent with benzamide.

A cobalt-catalyzed coupling of a secondary benzamide with an alkyl chloride in the presence of cyclohexyl magnesium chloride (CyMgCl) at room temperature was developed by Nakamura and co-workers (Scheme 109).¹⁵¹ It was a rare example of using cobalt catalyst to introduce a saturated hydrocarbon group directly to benzamide substrates through C-H bond activation. An inexpensive ligand, 1, 3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), could remarkably promote the transformation through increasing the reactivity of alkyl cobalt species. Alkyl chlorides bearing a wide range of functional groups could readily take part in the reaction to give the desired products. Later, a cobalt-catalyzed coupling of alkyl Grignard reagent with benzamide and 2-phenylpyridine derivatives using atmospheric air as the sole oxidant under mild conditions was demonstrated by the same group (Scheme 110).¹⁵² The reaction mechanism might be different from the previously reported coupling with alkyl chlorides.

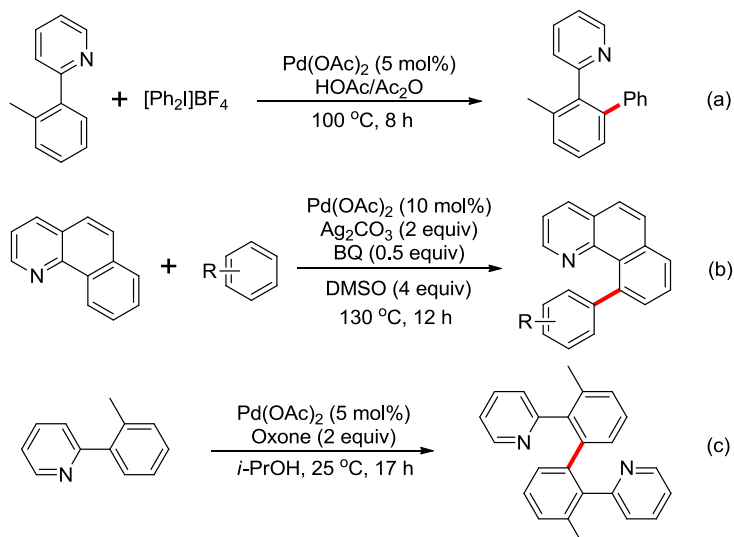


Scheme 111 Co-catalyzed C-H alkenylation of indoles and pyrroloindolones synthesis.

Recently, a Co(III)-catalyzed C2-selective C-H alkenylation/annulation cascade of *N*-carbamoyl indoles to afford diverse pyrroloindolones in one-pot was demonstrated by Kanai and co-workers (Scheme 111).¹⁵³ A cationic high valent Cp*Co(III) complex, [Cp*Co(III)(C₆H₆)](PF₆)₂, was utilized as effective catalyst due to the unique nucleophilic activity of the Co-C bond. The catalytic activity of the Cp*Co(III) complex in the reaction was significantly different from those of Cp*Rh(III) complexes. A wide range of C2-alkenylated indoles and pyrroloindolones were delivered by this method, showing the high functional tolerance. Detailed mechanistic studies on the catalytic process shed light on the reaction mechanism. The indolyl-Co species was produced by regioselective C-H metalation at the C2-position of indole via a concerted metalation-deprotonation mechanism with the aid of an acetate unit.

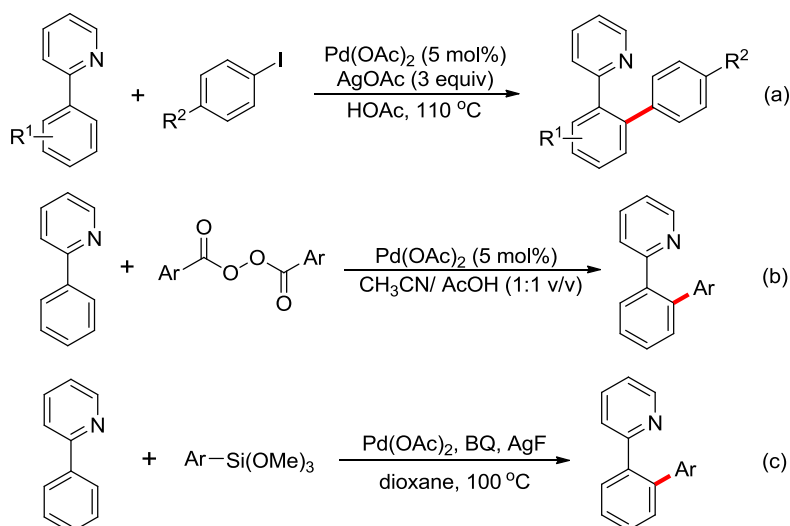
3 The C-H functionalization directed by nitrogen-containing unsaturated bond

3.1 The C-H functionalization directed by heterocycle



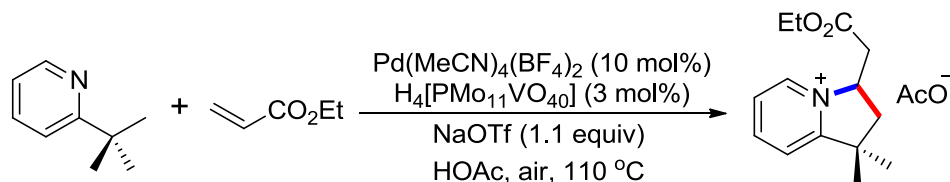
Scheme 112 Palladium-catalyzed C-H arylation of 2-arylpyridines and derivatives.

The first palladium-catalyzed heterocycle-directed arylation was demonstrated by Sanford and co-workers in 2005 (Scheme 112a).¹⁵⁴ The selective *ortho*-arylation of diverse arylpyridines, quinolines, pyrrolidinones, oxazolidinones, and benzodiazepines could be achieved via the Pd(II)/Pd(IV) catalytic cycle using diphenyliodonium salts as arylation reagents. However, a mixture of the analogous phenylated compound was obtained using the [Ph-I-Ar]BF₄ as the arylation reagent. Notably, the unsymmetrical mesityl/aryl-substituted iodonium reagents [Mes-I-Ar]BF₄ provided a single arylated product in good to excellent isolated yields. Importantly, detailed mechanistic studies supported a Pd(II)/Pd(IV) catalytic cycle that was different with the traditional Pd(0)/Pd(II) cycle. A related example of Pd-catalyzed oxidative cross-coupling of diverse L-C_{Ar}-H and Ar-H substrates was reported by the same group, in which the BQ could bind to the initially formed cyclometalated Pd(II) complex to promote the subsequent C-H activation of Ar-H (Scheme 112b).¹⁵⁵ They also studied the oxidative homocoupling coupling of two 2-arylpyridine derivatives (Scheme 112c).¹⁵⁶



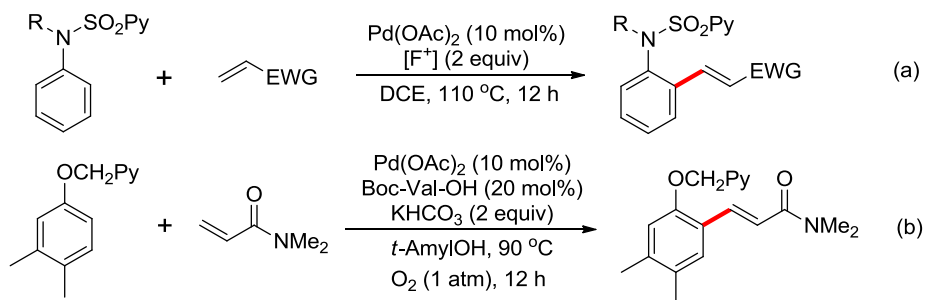
Scheme 113 Pd-catalyzed arylation of arenes using different arylation reagents.

Iodobenzenes were used as coupling reagents in the palladium-catalyzed arylation using pyridines or pyrazoles as directing groups by Daugulis and co-workers (Scheme 113a).¹⁵⁷ Notably, the transformation allowed the functionalization of not only aromatic but also benzylic and even unactivated sp³ C-H bonds. Longer reaction time was required when electron-poor iodides were used. Further attempts to use acyl peroxides and aryl trimethoxysilanes as arylation reagents in the palladium-catalyzed arylation of C-H bond of heteroarenes were studied by Yu¹⁵⁸ and Sun¹⁵⁹, respectively (Scheme 113b, c).



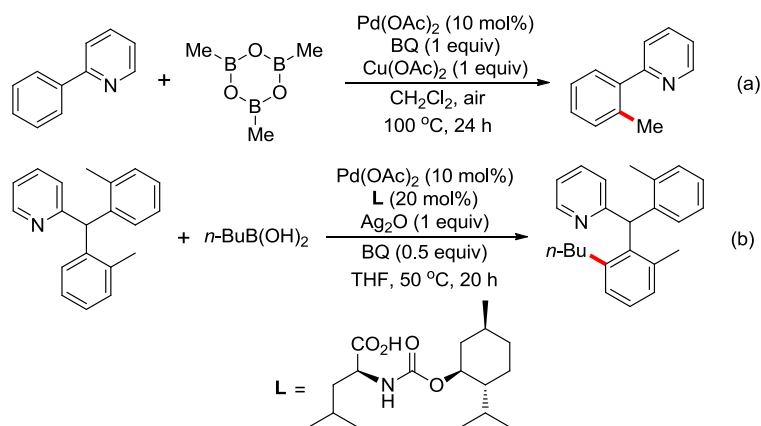
Scheme 114 Pd-catalyzed sp³ C-H olefination using pyridines as directing groups.

Pd-catalyzed pyridine-directed alkenylation of unactivated C(sp³)-H bonds was reported by Sanford and co-workers (Scheme 114).¹⁶⁰ The transformation underwent the initial C-H olefination and the subsequent intramolecular Michael addition to afford the 6,5-*N*-fused bicyclic cores. Notably, this reaction utilized air as the terminal oxidant and proceeded efficiently with various 2-alkylpyridines and α , β -unsaturated alkenes.



Scheme 115 Pd-catalyzed C(sp²)-H olefination using pyridines as directing groups.

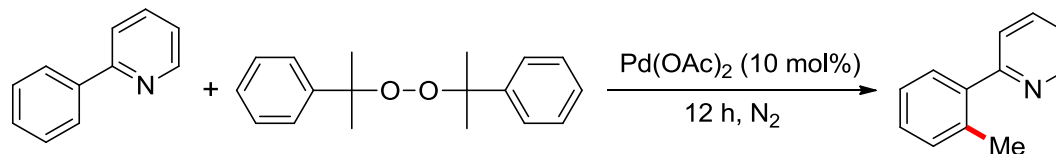
Meanwhile, palladium-catalyzed C-H olefination of arenes using pyridines as directing groups via remote coordination was developed. For example, Carretero and co-workers found that *N*-(2-pyridyl)sulfonyl anilines could serve as a removable directing group in the Pd-catalyzed oxidative olefination (Scheme 115a).¹⁶¹ Subsequently, You and Lan applied 2-pyridylmethyl ether as an efficient directing group to achieve the C-H alkenylation, in which a presumed seven-membered cyclopalladated intermediate was formed via the chelation-assisted *ortho* C-H cleavage (Scheme 115b).¹⁶² It was notable that the non-activated olefins such as styrene derivatives, *n*-decene could efficiently couple with the substrates to provide the products in good to excellent yields.



Scheme 116 Palladium-catalyzed C-H alkylation of 2-arylpyridines and derivatives.

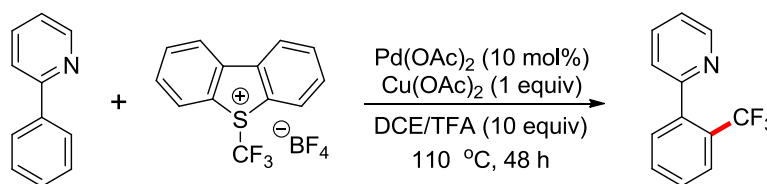
The first palladium-catalyzed alkylation of sp² and sp³ C-H bonds with methylboroxine and alkylboronic acids was demonstrated by Yu and co-workers in 2006 (Scheme 116 a).¹⁶³ The author supposed that benzoquinone played the key role in the C-H activation and reductive-elimination process. Cu(OAc)₂ was the oxidant to regenerate the Pd(II) in the catalytic cycle. Using the same strategy, they developed the asymmetric sp² C-H alkylation reaction of arenes with boronic acids as alkylating reagents (Scheme 116b).¹⁶⁴ The use of

monoprotected amino acids as chiral ligands allowed the success of the enantioselective C-H alkylation reaction.



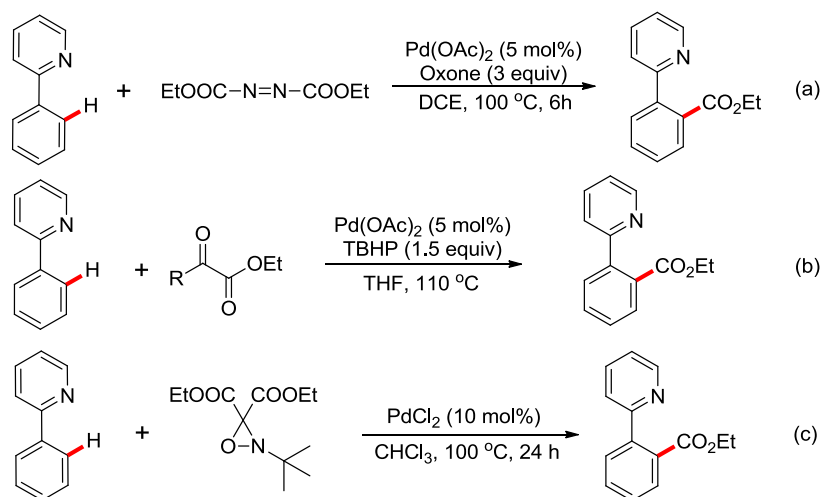
Scheme 117 Palladium-catalyzed methylation of aryl C-H bond by using peroxides.

A novel palladium-catalyzed methylation of aryl C-H bond with peroxides was achieved by Li in 2008 (Scheme 117).¹⁶⁵ The key methylpalladium intermediate was generated from dicumyl peroxide, which was used as both methylating reagents and hydrogen acceptor. The amount of the peroxide exerted an important influence on the products, in which 4 equiv of the peroxide was used to generate the dimethylation product as the single product.



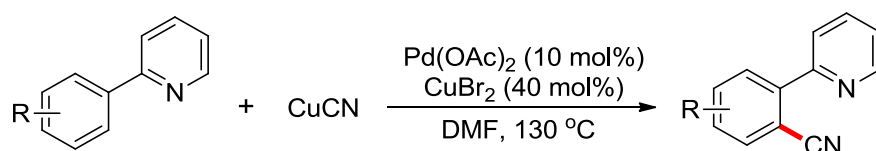
Scheme 118 Pd(II)-catalyzed *ortho*-trifluoromethylation of arenes.

Yu and co-workers demonstrated the first palladium-catalyzed trifluoromethylation of arenes with 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (Scheme 118).¹⁶⁶ The presence of copper(II) acetate significantly improved the yield, while other oxidants proved to be ineffective. The use of TFA was found to be indispensable for the success of this Ar-CF₃ bond-forming protocol. A wide range of substituents such as keto, ester, and nitro groups were compatible in the reaction.



Scheme 119 Palladium-catalyzed C-H ethoxycarbonylation of arenes.

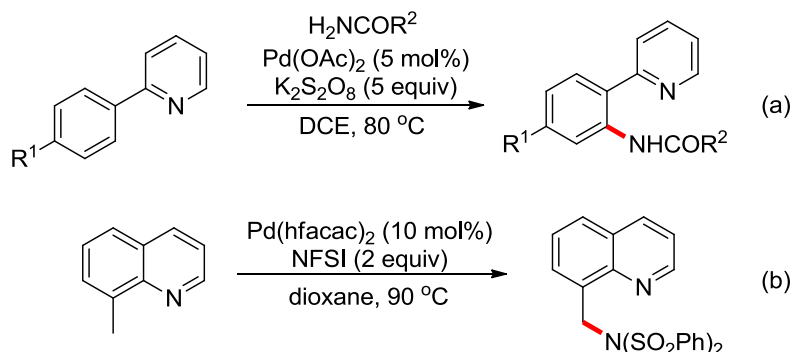
The palladium-catalyzed oxidative ethoxycarbonylation of aromatic C-H bond with diethyl azodicarboxylate (DEAD) was reported by Yu and co-workers (Scheme 119a).¹⁶⁷ The transformation was operated without the use of carbon monoxide and protection against air/moisture. The authors proposed that the ethoxyacyl radical, which was generated from thermal decomposition of DEAD, might undergo the insertion into Pd-C bond via formation of Pd(IV) species to afford the product. A related example of the palladium-catalyzed direct alkoxy carbonylation of aromatic C-H bonds with α -keto esters was achieved by Wang and co-workers (Scheme 119b).¹⁶⁸ The reactions of 2-arylpyridines, 2-arylquinolines, benzo[*h*]quinolines, 2-phenylpyrimidines, *N*-pyrimidinylpyrroles and *N*-pyrimidinylindoles with diverse benzoylformates proceeded smoothly to generate the desired alkoxy carbonylation products in good yields. Recently, oxaziridine was also found to be an excellent CO₂Et group donor by Shi and co-workers (Scheme 119c).¹⁶⁹ The key step of the ring opening mechanism of oxaziridnes involved the initial insertion of Pd(II) into the N-O bond of oxaziridine to generate the Pd(IV) species and the subsequent rearrangement by a shift of CO₂Et from the carbon to the Pd via a C-C bond cleavage process.



Scheme 120 Palladium-catalyzed C-H cyanation of arenes.

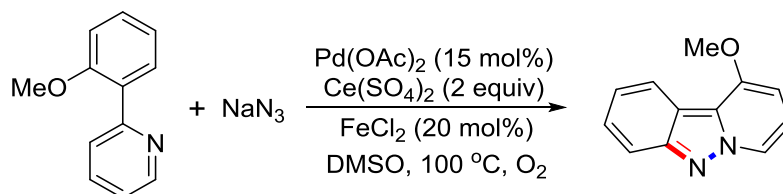
Palladium-catalyzed C-H cyanation of 2-phenylpyridine using CuCN as the cyanation source was demonstrated by Cheng and co-workers in 2009 (Scheme 120).¹⁷⁰ A ligand

exchange of CN^- after the initial cycle metalation of $\text{Pd}(\text{OAc})_2$ was involved in key step of the reaction. The procedure was successfully applied in the synthesis of *Menispermum dauricum* DC.



Scheme 121 Palladium-catalyzed C-H amidation of sp^2 or sp^3 C-H bonds.

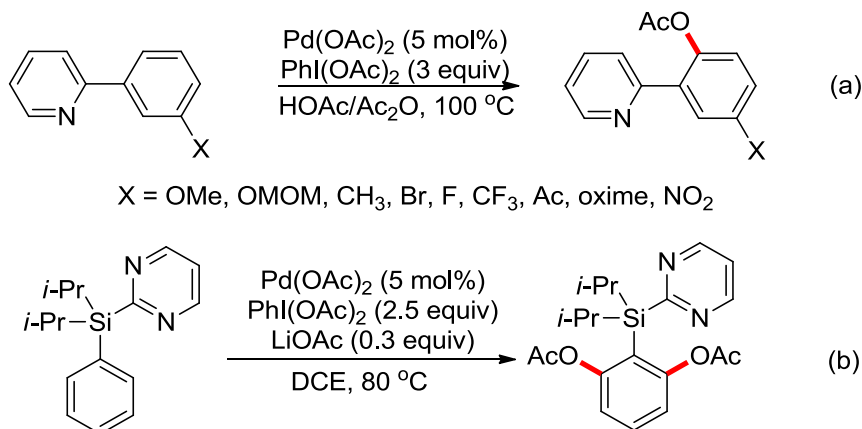
A pioneer work on the palladium-catalyzed C-H amidation of unactivated sp^2 and sp^3 C-H bonds was reported by Che and co-workers in 2006 (Scheme 121a).¹⁷¹ Various amides, including carbamates, acetamides, and sulfonamides were proven to be the effective amidation reagents to give the products in middle to high yields. Importantly, the catalytic amidation of unactivated $\text{C}(\text{sp}^3)\text{-H}$ bonds of 8-methylquinoline was achieved. The authors believed that the nitrene species, which were generated from oxidation of amides by $\text{K}_2\text{S}_2\text{O}_8$, were crucial to the mechanism. Other nitrogen sources, such as iodobenzene diacetate/bistosylimide, $\text{PhI}(\text{OAc})\text{NTs}_2$, and *N*-fluorobis(phenylsulfonyl)imide (NFSI) has been used to construct the C-N bond via the palladium-catalyzed C-H activation (Scheme 121b).¹⁷² The substrates bearing various substituents, such as methyl, bromine, fluorine and nitro, were tolerated to give the corresponding products in good to excellent yields.



Scheme 122 Pd-catalyzed tandem C-H azidation and N-N bond formation of arylpyridines.

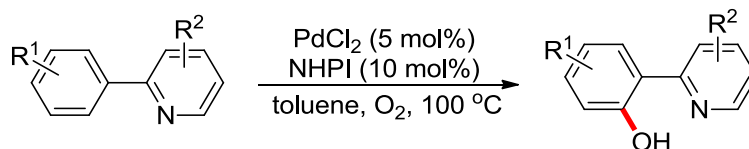
A palladium-catalyzed tandem C-H azidation and N-N bond formation of arylpyridines was developed by Jiao and co-workers (Scheme 122).¹⁷³ $\text{Ce}(\text{SO}_4)_2$ was used as an oxidant for the generation of $\text{Pd}(\text{IV})$ species and the yields of the products dramatically decreased when $\text{Ce}(\text{SO}_4)_2$ was replaced by other oxidants. It was interesting that FeCl_2 or O_2 could increase

the efficiency of this reaction. The method provided an alternatively concise approach for the construction of bioactively important pyrido[1,2-*b*]indazoles.



Scheme 123 Palladium-catalyzed C-H oxygenation using pyridine directing groups.

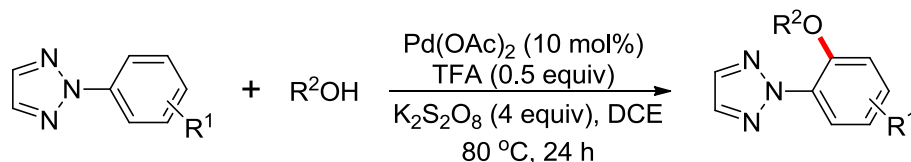
Sanford and co-workers reported a palladium-catalyzed acetoxylation of *meta*-substituted arene substrates using PhI(OAc)₂ (Scheme 123a).¹⁷⁴ The reactions showed good functional group tolerance with respect to the *meta*-substituent on the arenes. A silicon-tethered pyridine was subsequently developed as the directing group in the palladium-catalyzed C-H oxygenation of arenes by Gevorgyan and co-workers (Scheme 123b).¹⁷⁵ Compared with traditional heterocycle directing groups, the 2-pyrimidyldiisopropylsilyl (PyrDipSi) group owned the advantages of easy to be removed and transformed. A wide range of functional groups, such as methoxy, carbomethoxy, amide, and acetyl, could be tolerated. LiOAc was found to be crucial for the successful second C-H oxygenation, suggesting that the reaction went through a concerted metalation-deprotonation (CMD) pathway.



Scheme 124 PdCl₂ catalyzed sp²-H hydroxylation of 2-arylpyridine.

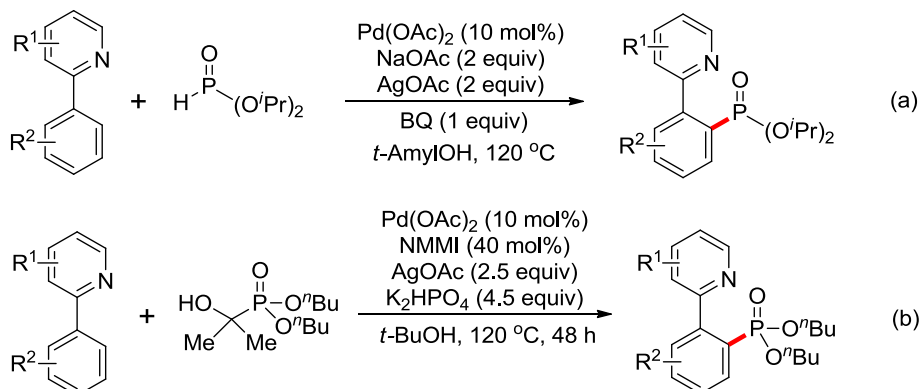
The PdCl₂ and *N*-hydroxyphthalimide co-catalyzed C-H hydroxylation of 2-arylpyridines was achieved in the presence of oxygen by Jiao and co-workers (Scheme 124).¹⁷⁶ The results of O¹⁸-labeling experiment indicated that the oxygen atom in the hydroxy group originated from the molecular oxygen. Hydroxyl radical was involved in the NHPI catalytic process in this transformation, which was demonstrated by EPR (electron paramagnetic resonance

spectroscopy) with DMPO (5,5-dimethyl-1-pyrroline noxide) as the radical trap reagent. This chemistry provided a green and practical method to synthesize a variety of substituted 2-(pyridin-2-yl)phenols.



Scheme 125 Palladium-catalyzed *ortho*-alkoxylation of 2-aryl-1,2,3-triazoles.

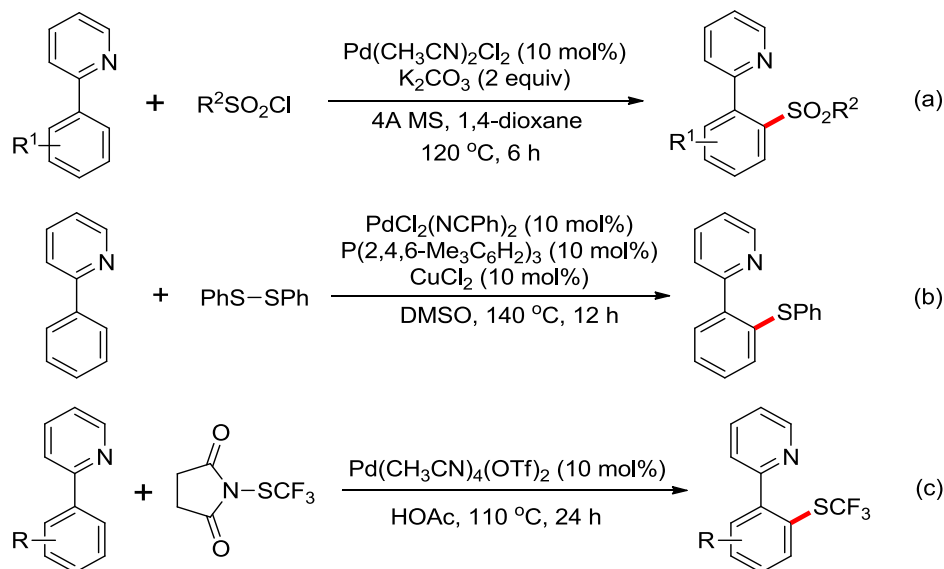
The palladium-catalyzed *ortho*-alkoxylation of 2-aryl-1,2,3-triazoles was developed by Kuang and co-workers (Scheme 125).¹⁷⁷ A Pd(IV) intermediate was supposed to be involved in the catalytic reaction, which was generated from the oxidation of Pd(II) by $K_2S_2O_8$. The subsequent ligand exchange and reductive elimination gave the final alkoxylation products and regenerated the palladium(II) catalyst. Functional groups such as halide, ester, ether, and ketone were tolerated under the oxidizing reaction conditions. Various primary alcohols, including EtOH, *n*-BuOH, and $HO(CH_2)_2OH$, were applied in this transformation to give the corresponding alkoxylation products.



Scheme 126 Palladium-catalyzed phosphorylation of 2-arylpyridines.

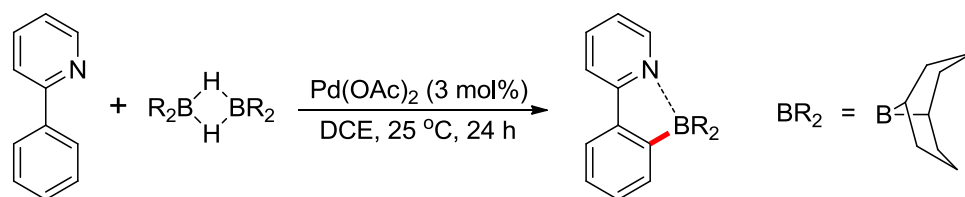
Yu and co-workers demonstrated the first palladium-catalyzed phosphorylation of arenes using H-phosphonates (Scheme 126a).¹⁷⁸ It should be noted that slow addition of H-phosphonate to the reaction with a syringe pump was essential to avoid the expeditious deactivation of the catalyst. The use of BQ was found to be necessary for the formation of the products, which promoted the reductive elimination in a similar manner to that observed in the coupling of C-H bonds with organometallic reagents. H-phosphonates bearing different substituents, such as Cl, F, CF_3 , CN and OMe, could couple with 2-arylpyridines smoothly to

give the products in moderate yields. Murakami and co-workers also described an analogous phosphonation reaction of 2-arylpyridines, in which α -hydroxyalkylphosphonate was used to generate the H-phosphonate *in situ* by treatment with a base in the reaction condition (Scheme 126b).¹⁷⁹



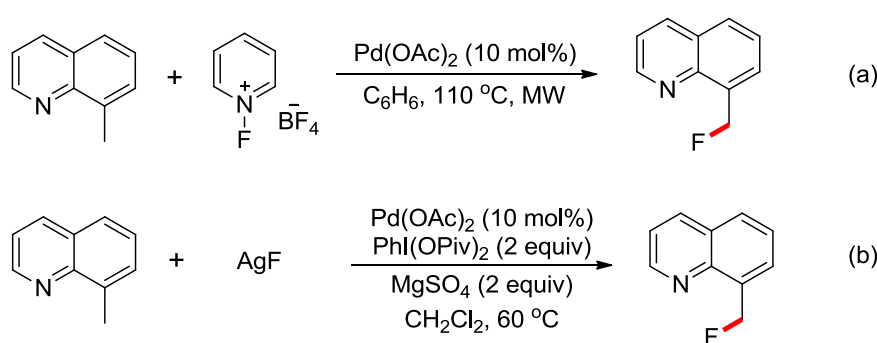
Scheme 127 The formation of C-S bond via Pd-catalyzed C-H activation

The construction of C-S bond via palladium-catalyzed C-H functionalization with arylsulfonyl chlorides was reported by Dong and co-workers (Scheme 127a).¹⁸⁰ When DMF was used as the solvent and CuCl_2 was applied as cocatalyst, the C-Cl bond could be constructed. The direct thiolation of aryl C-H bonds in arenes was also achieved using disulfides or thiols by Nishihara and co-workers (Scheme 127b).¹⁸¹ It was proposed that the phosphine ligands played a crucial role in the dissociation of the palladium dimer to form the active monomeric species. The reaction proceeded efficiently with just 0.6 equivalents of disulfides, indicating that the arenethiols were oxidized to regenerate the corresponding disulfides under the oxidative reaction conditions. Very recently, the monotrifluoromethylthiolation of arene C-H bonds was achieved using a structural analog of NCS under the Pd-catalyzed condition by Shen and co-workers (Scheme 127c).¹⁸²



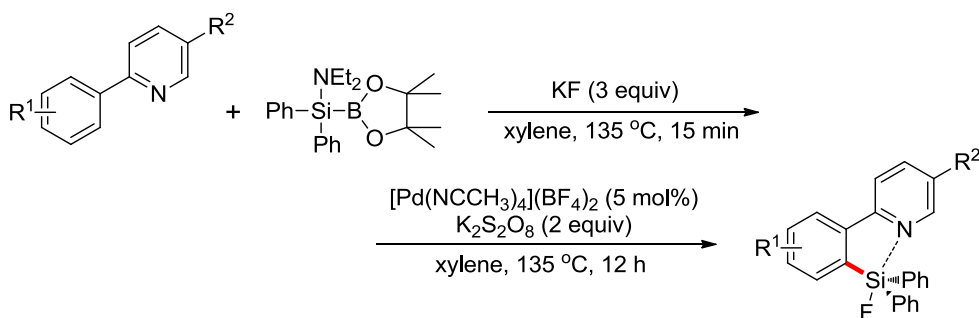
Scheme 128 Palladium-catalyzed C-H borylation of 2-phenylpyridine.

The first palladium-catalyzed regioselective borylation of 2-phenylpyridine derivatives was reported by Takai and co-workers (Scheme 128).¹⁸³ The Lewis acidity of the borane reagents influenced the reactivity of the reaction, and the pinacolborane as well as bis(pinacolate)diboron failed to afford the corresponding products. When 9-borabicyclo[3.3.1]nonane (9-BBN) was used, the reaction proceeded successfully even at room temperature. The interaction between Lewis basic nitrogen and Lewis acidic boron atoms was crucial to the high activity. It was interesting that the reaction proceeded even in the absence of the palladium catalyst at higher temperature.



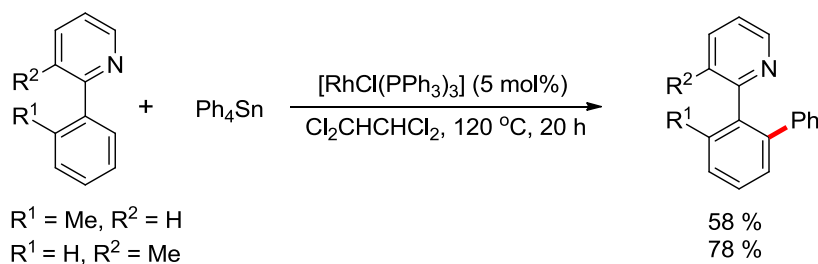
Scheme 129 Palladium-catalyzed fluorination of carbon-hydrogen bonds.

Pd-catalyzed formation of aromatic and benzylic C-F bonds using electrophilic fluorinating reagents was described by Sanford (Scheme 129a).¹⁸⁴ With the microwave irradiation, the *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate was used as a highly effective F⁺ source to give the fluorination products in the moderate yields. A diversity of functional groups, including aryl halides, nonenolizable ketones and esters, trifluoromethyl substituents, and methyl ethers, were tolerated in the reaction. The reaction might involve a Pd(II)/Pd(IV) process. They also investigated a palladium-catalyzed C-H fluorination of 8-methylquinoline derivatives using nucleophilic fluoride (Scheme 129b).¹⁸⁵ The major side product was the oxygenation product, and among the different hypervalent iodine reagents, PhI(OPiv)₂ led to the best ratio of the fluorination products/oxygenation products. However, the replacement of expensive AgF with CsF, RbF, NBu₄F, or KF under the optimized reaction conditions almost halted the reaction.



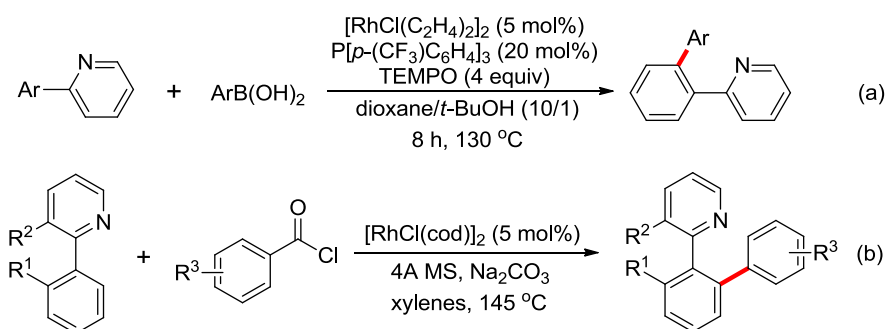
Scheme 130 Palladium-catalyzed C-H fluorosilylation of 2-phenylpyridines.

Kanai and co-workers reported a new palladium-catalyzed C-H fluorosilylation of 2-phenylpyridines (Scheme 130).¹⁸⁶ Treatment of 2-phenylpyridines with amino(1,3,2-dioxaborolan-2-yl)diphenylsilane produced fluorosilylated 2-phenylpyridines in good to excellent yields by palladium catalysis. The pyridyl group acted as both a directing group to promote C-H fluorosilylation before the reaction and a component of the silafluorene equivalents in the products. This fluorosilylation reaction presented high functional-group tolerance and proceeded in good to excellent yields, even on gram scale.



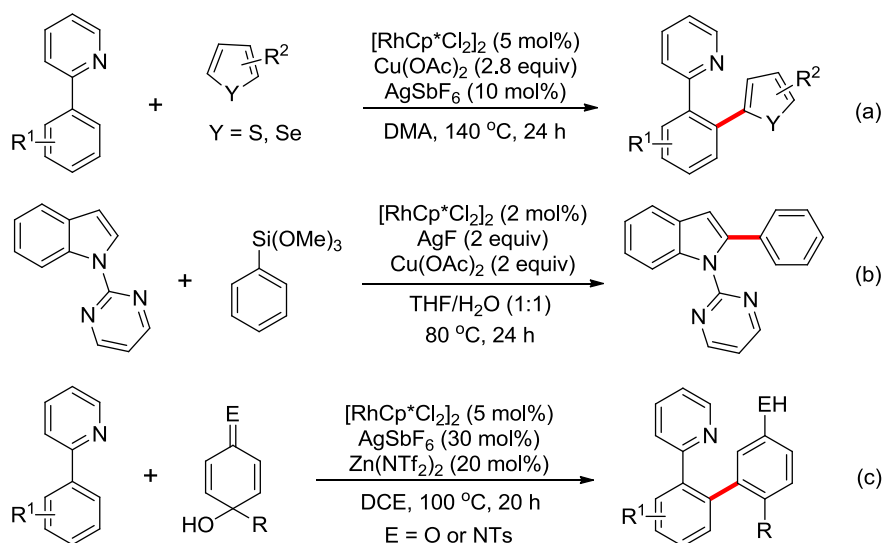
Scheme 131 Rhodium-catalyzed arylation of 2-arylpyridines with arylstannanes.

The rhodium-catalyzed direct *ortho*-arylation of 2-arylpyridines with arylstannanes represented the first effective catalytic cross-coupling of an aryl C-H bond with aryl metal compounds to give biaryls (Scheme 131).¹⁸⁷ The pyridyl group was proposed to direct the transition metal-catalyzed C-H bond cleavage of an aromatic ring. In general, the reaction gave both mono- and di- arylated products. The selective generation of mono-arylated products could be achieved with *ortho*- or *meta*-substituted substrates.



Scheme 132 Rhodium-catalyzed C-H arylation of arenes with different arylation reagents.

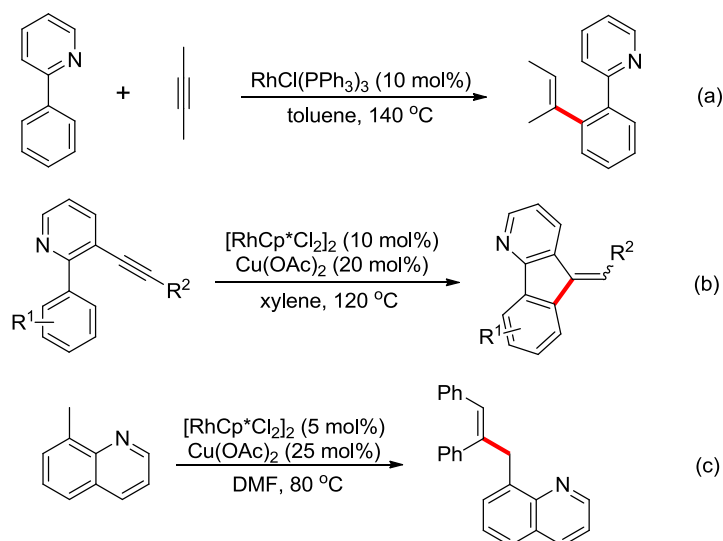
A rhodium-catalyzed pyridine directed arylation of arenes with less toxic arylboronic acids was reported by Studer (Scheme 132a).¹⁸⁸ The commercially available 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) was used as the oxidant and the phosphine ligand played the crucial role to the reactivity. Later on, a rhodium-catalyzed arylation of arenes with aryl chlorides as the non-organometallic coupling partners was developed by Yu and co-workers (Scheme 132b).¹⁸⁹ A decarbonylation process took place under the reaction conditions, and an increase of rhodium catalyst loading to 10 mol% could provide the double arylated compound as the major products.



Scheme 133 The synthesis of π -conjugated organic molecules via C-H activation.

A rhodium-catalyzed pyridyl-directed intermolecular formation of $C(sp^2)$ - $C(sp^2)$ bonds via double C-H bond cleavage was reported by Kambe and co-workers (Scheme 133a).¹⁹⁰ In this transformation, the $C(sp^2)$ -H bond of the electron-rich heterocycles such as thiophene and selenophene directly coupled with the arenes to give the biaryl heterocyclic derivatives in moderate to high yields. More recently, an efficient rhodium(III)-catalyzed C-H bond

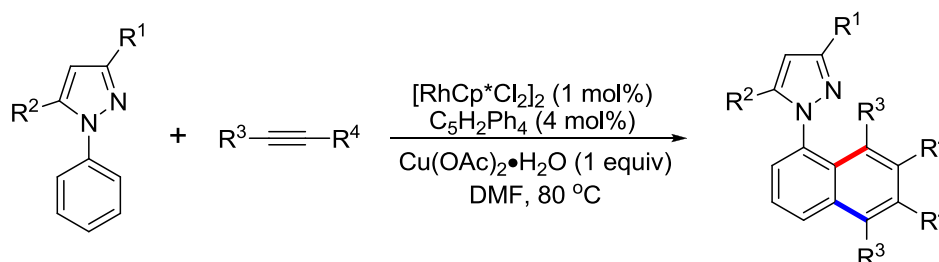
arylation of (hetero)arenes with organosilanes was developed by Loh and co-workers (Scheme 133b).¹⁹¹ This reaction could take place at relatively lower temperature in aqueous media and a variety of functional groups were well tolerated. A Rhodium(III)-catalyzed arylation of arenes bearing a directing group using 4-hydroxycyclohexa-2,5-dienones as the arylating reagents for the synthesis of 3-arylated phenols was disclosed by Li and co-workers (Scheme 133c).¹⁹² The rearomatization process was identified to be the driving force of the reaction.



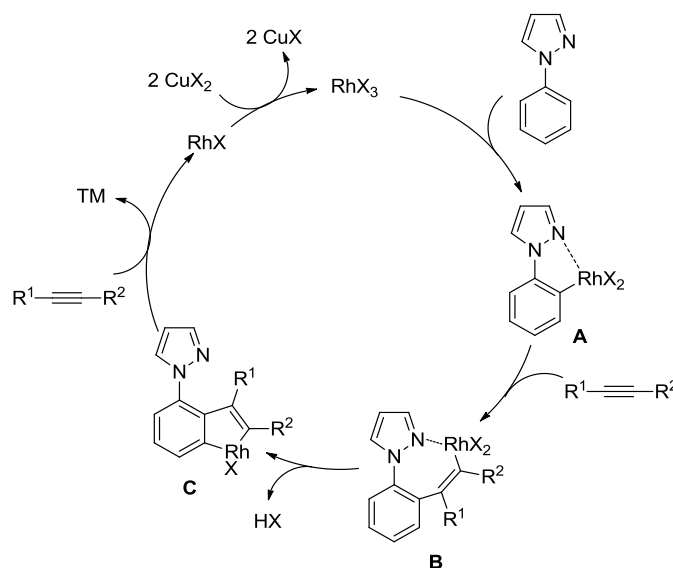
Scheme 134 Rhodium-catalyzed alkenylation of C(sp²)/C(sp³)-H bonds.

The rhodium-catalyzed C-H alkenylation of 2-phenylpyridine was reported by Lim and Kang, in which PPh₃ was indispensable to keep the activity of Rh(I) catalyst (Scheme 134a).¹⁹³ Unsymmetric alkynes with a single bulky substituent, such as 1-(trimethylsilyl)-1-propyne, showed high regioselectivity and favored the mono-alkenylated product. The primarily polymeric materials were generated when terminal alkynes were used, while regioisomeric mixtures were obtained by the use of unsymmetric alkyne, such as 2-hexyne. Recently, the Rh(III)-catalyzed intramolecular olefination of 3-alkynyl-2-arylpyridines to afford 4-azafluorene compounds was reported by Shibata, in which a nitrogen-containing multi-cyclic skeleton could be realized through the pyridine-directed C-H bond activation (Scheme 134b).¹⁹⁴ The more challenging rhodium-catalyzed C(sp³)-H olefination of 8-methylquinoline with alkynes was demonstrated by Wang and co-workers (Scheme 134c).¹⁹⁵ A five-membered rhodacycle has been

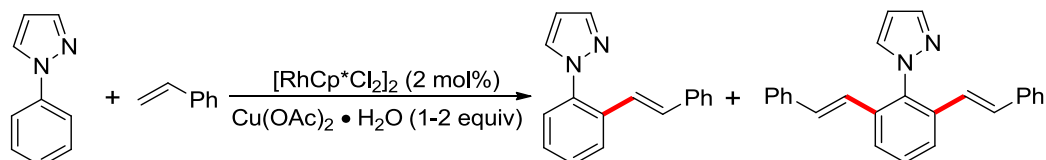
structurally characterized, thus revealing the key intermediate in the C-H activation step.



Scheme 135 The synthesis of fluorescent naphthyl- and anthrylazoles via C-H activation.



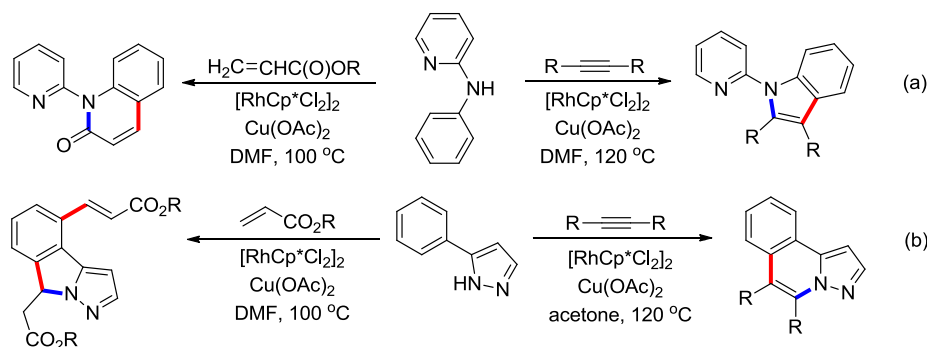
Scheme 136 The plausible mechanism.



Scheme 137 Rhodium-catalyzed mono- and divinylations of 1-phenylpyrazoles.

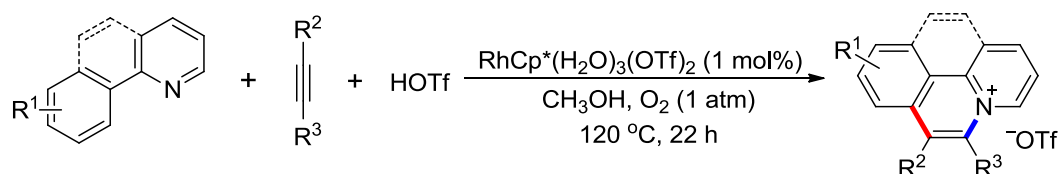
A novel Rh(III)-catalyzed heterocycle-assisted arylation was developed by Miura in 2008, in which polyarylated naphthyl- and anthrylazole derivatives could be provided by the direct coupling of phenylazoles with internal alkynes (Scheme 135).¹⁹⁶ The reaction involved the cleavage of multiple C-H bonds and the fluorescent properties of the products were studied. The coordination of the nitrogen atom in the 2-position of **1a** to a Rh(III) species formed the rhodacycle intermediate **A**, which inserted into the triple bond of alkyne to give the intermediate **B**. The second C-H activation of intermediate **B** generated the intermediate **C**, which underwent the second insertion to the alkyne. The subsequent reductive elimination gave the product and liberated the Rh(I). Cu(OAc)₂ was required as the external oxidant to

regenerate the Rh(III) catalyst (Scheme 136). Later on, they investigated the selective Rh(III)-catalyzed alkenylation of 1-phenylpyrazoles, in which the installation of two different vinyl groups was possible by a simple one-pot strategy (Scheme 137).¹⁹⁷ A Rh(III)-catalyzed cascade C-H activation of pyridines via oxidative annulation of functionalized pyridines with two alkyne molecules for the synthesis of diverse quinolines was demonstrated by Li and co-workers in 2011.¹⁹⁸



Scheme 138 Rh(III)-catalyzed oxidative coupling of arenes with alkynes and alkenes.

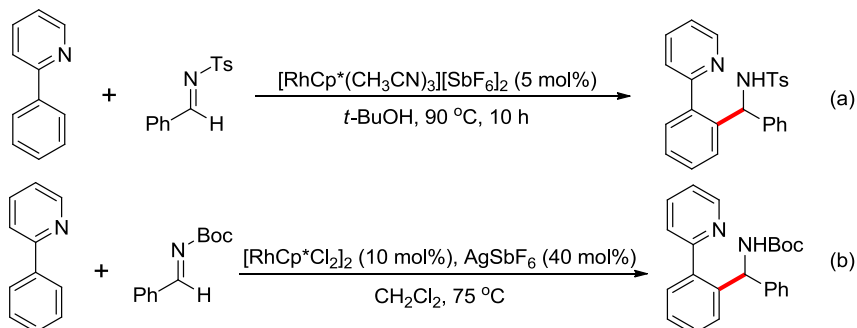
The Rh(III)-catalyzed indole synthesis from *N*-aryl-2-aminopyridines with alkenes was reported by Li and co-workers (Scheme 138a).¹⁹⁹ The authors proposed that the *N*-aryl-2-aminopyridines went through the initial olefination and the subsequent intramolecular annulation afforded the indole derivatives. The corresponding quinolone products could also be afforded using acrylates as coupling reagents. After this work, they applied the strategy in the synthesis of pyrazole derivatives (Scheme 138b).²⁰⁰



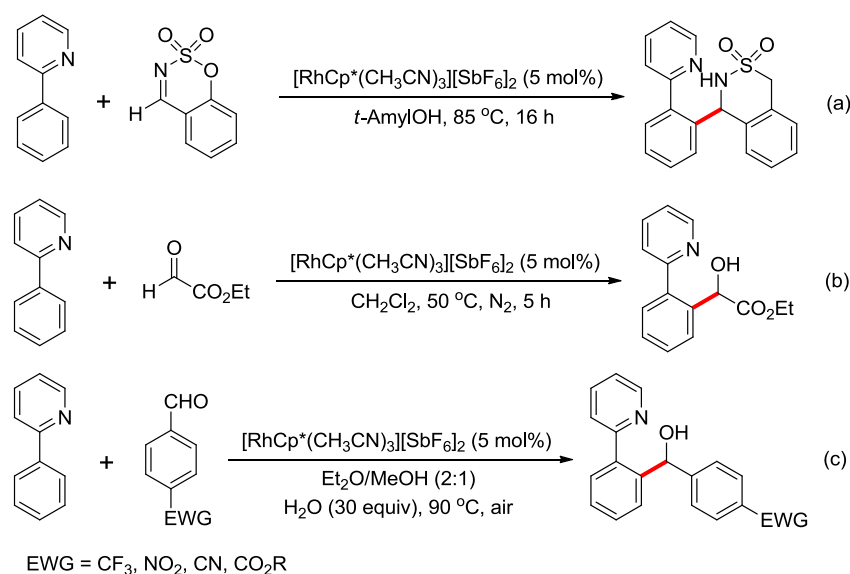
Scheme 139 An efficient Rh/O₂ catalytic system for oxidative C-H activation/annulations.

To overcome the drawbacks of the use of stoichiometric metal oxidants in the Rh(III)-catalyzed C-H activation reaction, an efficient Rh/O₂ catalytic system for the synthesis of isoquinolinium salts from arenes and alkynes was developed by Huang (Scheme 139).²⁰¹ The symmetrical diarylalkynes containing various electron rich or deficient functional groups reacted smoothly to give the corresponding products in moderate to high yields, while the unsymmetrical alkynes gave a mixture of isomers in a moderate ratio.

Stoichiometric reaction of the cyclometalated rhodium complexes provided strong evidence of facile oxidation of Rh(I) to Rh(III) by molecular oxygen facilitated by the additive acid. By using the same catalytic system, they achieved the synthesis of 2-vinylindoles.²⁰²



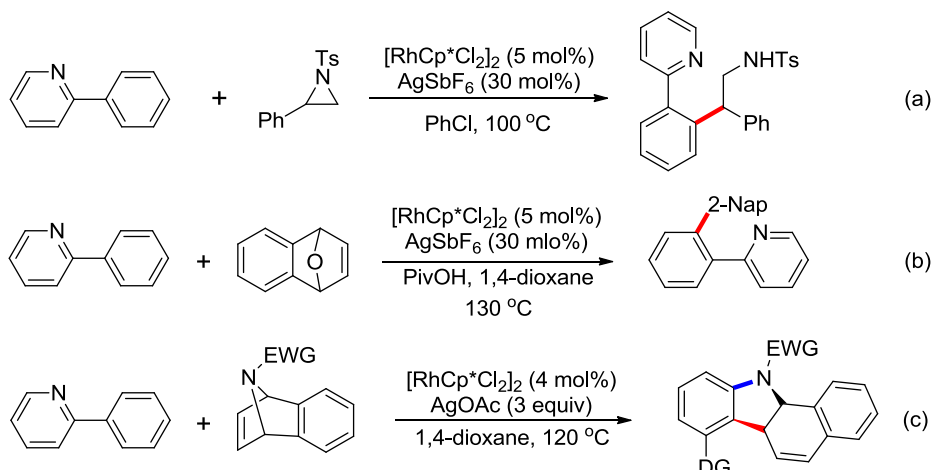
Scheme 140 Rhodium-catalyzed C-H addition to *N*-Ts-imines or Boc-imines.



Scheme 141 Rhodium-catalyzed C-H addition to sulfimides or aldehydes.

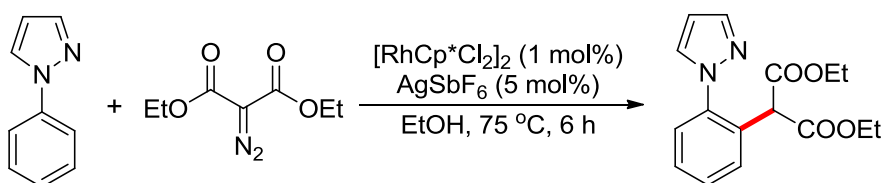
Another dream reaction based on the C-H activation is the nucleophilic addition reaction toward C=X motifs.^{1y} The rhodium(III)-catalyzed pyridine-directed C-H addition to *N*-Ts-imines or Boc-imines was reported for the first time by Shi group^{203a} and Ellman's group^{203b} in 2011, simultaneously (Scheme 140). These reactions showed excellent functional group compatibility. Shi and co-workers also systematically studied the mechanism by isolating the key intermediates and kinetic studies to clearly support the C-H activation pathway.²⁰⁴ Bergman and co-workers proposed that the arylation reaction was initiated by the electrophilic deprotonation of phenyl C-H bond of 2-phenylpyridine to form an Ar-Rh(III) intermediate. The subsequent coordination of the *N*-Boc-imine would promote the imine

addition, and the protonolysis regenerated the catalyst. By the use of $[\text{RhCp}^*(\text{CH}_3\text{CN})_3][\text{SbF}_6]_2$ as the pre-activated catalyst, the pyridine-directed C-H addition to other polar multiple bonds (Scheme 141a),^{205a} ethyl glyoxylate (Scheme 141b),^{205b} and aryl aldehydes (Scheme 141c)^{205c} was achieved recently. With the same strategy, alkenyl C-H could also nucleophilic addition to the C=X bonds under mild condition.^{205d}



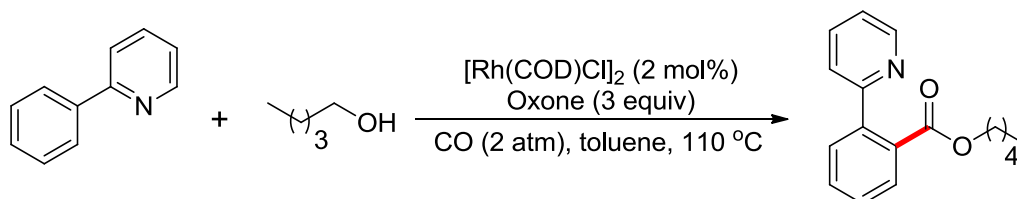
Scheme 142 Rh(III)-catalyzed coupling of arenes with ring-opening reagents.

The rhodium-catalyzed ring-opening of aziridenes was applied in the pyridine-directed alkylation by Li and co-workers (Scheme 142a).^{206a} Both electron-donating and electron-withdrawing substituents at the *meta* and *para* position of the phenyl group were tolerated to afford the corresponding β -branched amines. The chelation of the pyridine and the sulfonamide N atoms with Rh atom furnished a rather rare eight-membered ring, which was further stabilized by fusing with a four-membered ring. They demonstrated that the 7-azabenzonorbornadienes or 7-azabenzonorbornadienes could be used as coupling reagents in the Rh(III)-catalyzed C-H functionalization of (hetero)arenes, in which dihydrocarbazoles and dehydrative naphthylation products could be afforded, respectively (Scheme 142b, c).^{206b} Li also reported other Rh(III)-catalyzed C-H functionalization reactions using pyridine as directing group to construct C-C bonds through varying the type of the reaction substrates.^{206c-d}

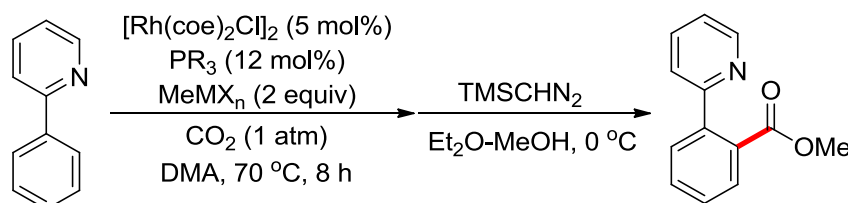


Scheme 143 Rh (III)-catalyzed azacycle-directed alkylation of arenes.

The rhodium(III)-catalyzed C-C coupling of diazomalonates with arenes was reported by Li and co-workers (Scheme 143).^{71c} Several directing groups, such as pyrazole, pyrimidine and oxazole, were proved effective in the alkylation of (hetero)aromatics with good functional group compatibility. The carbenoid C-H coupling mechanism was proposed by the authors, and the isolation of the key intermediate supported the proposed pathway.

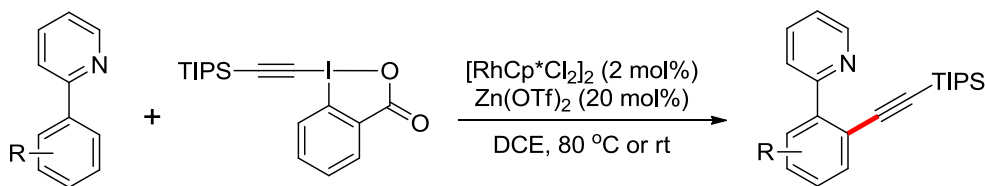
**Scheme 144** Rhodium-catalyzed direct oxidative carbonylation of aromatic C-H bond.

The first rhodium-catalyzed direct oxidative carbonylation of aromatic C-H bond with CO and alcohols was reported by Zhang and co-workers (Scheme 144).²⁰⁷ The reaction showed high regioselectivity and good functional group tolerance, but the yields of carbonylation products were highly influenced by the steric hindrance and boiling point of the alcohol used.

**Scheme 145** Rh(I)-catalyzed direct carboxylation of arenes with CO₂.

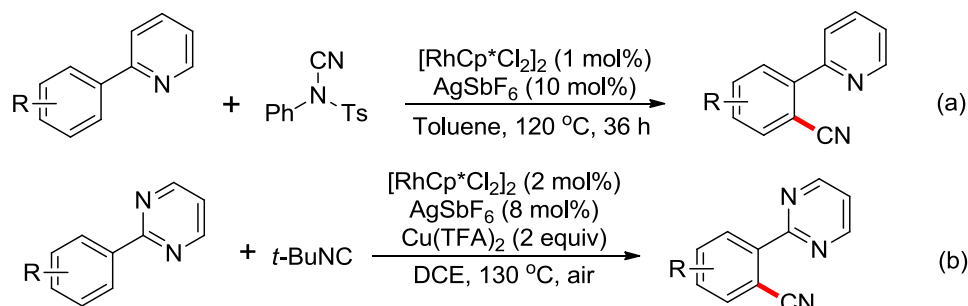
The use of non-toxic CO₂ as the carbon source to construct the C-C bond in the Rh-catalyzed acylation of arenes was investigated by Iwasawa (Scheme 145).²⁰⁸ Various substituted and functionalized 2-arylpyridines and 1-arylpyrazoles underwent the carboxylation in the presence of the rhodium catalyst and a stoichiometric methylating reagent, AlMe₂(OMe), to give carboxylated products in good yields. Methylrhodium(I) species was proposed to be the key intermediate, which underwent C-H activation to afford rhodium(III). The subsequent reductive elimination of methane gave the

nucleophilic rhodium(I). This approach had a promising application in the field of carbon dioxide fixation.



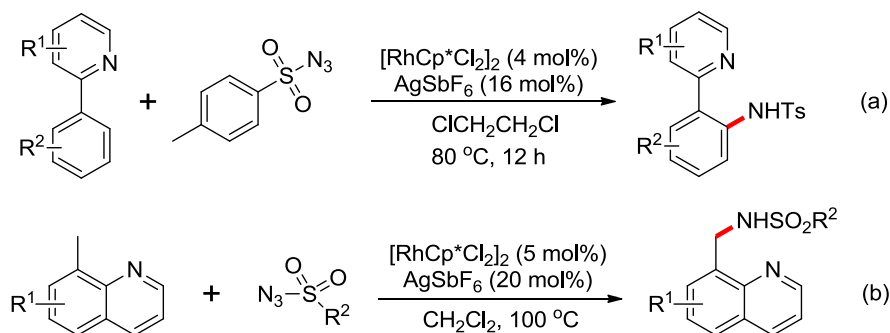
Scheme 146 Rh(III)-catalyzed C-H alkylation of arenes.

Alkynes as fundamental building blocks are widely used in synthetic chemistry and material science. Recently, alkynylated hypervalent iodines was developed as a versatile and powerful alkynylating reagent, which was applied in the rhodium-catalyzed C-H alkylation of arenes by Li and co-workers (Scheme 146).⁸⁹ The high yield of the product was attributed to the use of $\text{Zn}(\text{OTf})_2$, which might play a dual role in both activating the catalyst by reversible chloride abstraction and activating the alkyne substrate. A rhodium(III) alkynyl complex and a Rh(III) vinyl complex was established as key intermediates.



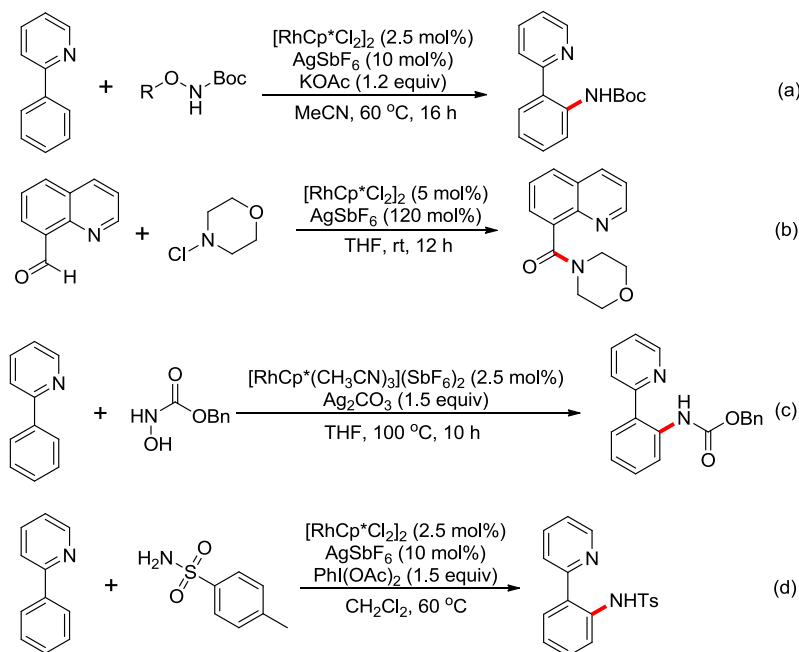
Scheme 147 Rhodium-catalyzed C-H cyanation of arenes.

Anbarasan and co-workers reported a rhodium catalyzed cyanation of arenes using *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as an environmentally benign electrophilic cyanating reagent (Scheme 147a).²⁰⁹ The authors proposed that the key step was the transformation of the aryl motif to the nitrile carbon atom from the cyanating reagent after the initial rhodium-catalyzed C-H activation. More recently, Xu and co-workers reported the rhodium-catalyzed C-H bond cyanation of arenes with *tert*-butyl isocyanide, in which the additive $\text{Cu}(\text{TFA})_2$ was used as an oxidant to regenerate the Rh(III) catalyst (Scheme 147b).²¹⁰



Scheme 148 Rhodium-catalyzed C-H amidation of $\text{C}(\text{sp}^2)/\text{C}(\text{sp}^3)$ -H bond.

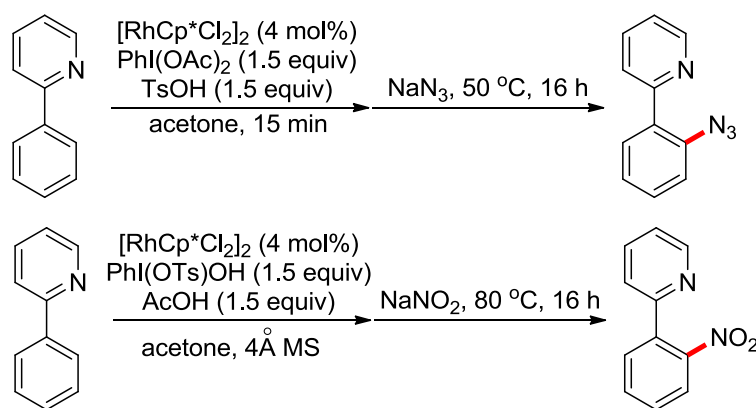
The pioneering work of rhodium-catalyzed intermolecular amidation of arenes with sulfonylazides via chelation-assisted C-H bond activation has been reported by Chang and co-workers (Scheme 148a).²¹¹ The amidation required no external oxidants and released N_2 as the single byproduct, thus offering an environmentally benign C-N arylation procedure that can be readily scaled-up. The more challenging rhodium-catalyzed $\text{C}(\text{sp}^3)$ -H amidation with azides was achieved by Wang and co-workers (Scheme 148b).²¹² The key step was a $\text{C}(\text{sp}^3)$ -H activation process to afford a five-membered rhodacyclic intermediate, which was partially supported by the isolation and the subsequent characterization of the intermediates.



Scheme 149 The construction of C-N bond with different nitrogen sources.

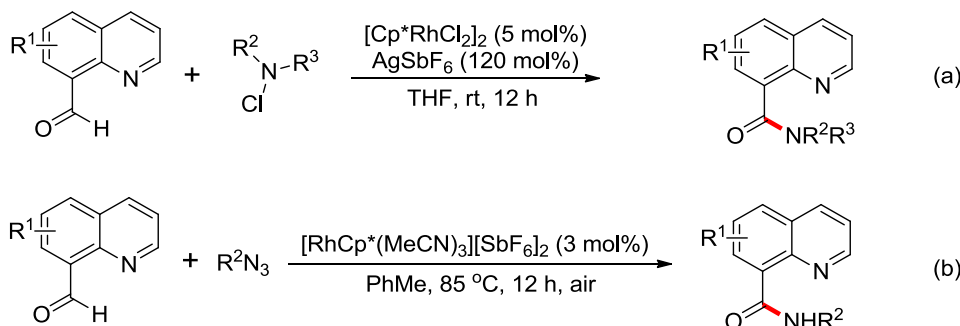
Other electrophilic nitrogen sources, such as hydroxylamines (Scheme 149a),²¹³ chloroamines (Scheme 149b)²¹⁴ were also used in the C-H bond activation to construct the C-N bond. The 2,4,6-trichlorobenzoyl groups as substituents on the N-atom gave the

amidation product in excellent yields under the redox-neutral reaction conditions. When *N*-hydroxycarbamates were used as coupling reagents, Ag_2CO_3 was found to be the ideal oxidant for the reaction (Scheme 149c).²¹⁵ Su and co-workers reported a rhodium-catalyzed intermolecular *N*-chelating-directed aromatic C-H amidation with amides (Scheme 149d).^{216a} A wide range of substituents of 2-arylpyridines, such as aldehydes and bromide groups were tolerated. The success was attributed to the additive $\text{PhI}(\text{OAc})_2$, which may serve as an oxidant to regenerate Rh(III) intermediate, or react with sulfonamide to afford the nitrene precursor. A Rh(III)-catalyzed C-H amidation of arenes bearing different chelating groups using readily available *N*-arenesulfonated imides as efficient amidating reagents was reported by Wan, Li and co-workers.^{216b}



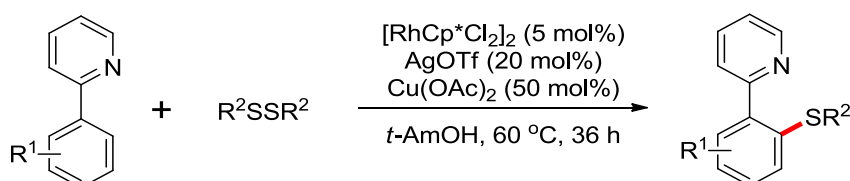
Scheme 150 Rh(III)-catalyzed azidation and nitration of arenes with sodium salts.

Inorganic salts, such as sodium azide, sodium nitrite, have been used to construct the C-N bond via rhodium-catalyzed C-H activation, presenting alternative routes to fulfill the current C-H azidation and nitration reactions (Scheme 150).²¹⁷ Pyridine, pyrimidine, and pyrazole heterocycles were found to be efficient directing groups to control the regioselectivity in the reaction. The authors proposed that the hypervalent iodine reagent was important to generate the active azidation agent $\text{PhI}(\text{N}_3)(\text{OTs})$, which would go through the subsequent electrophilic azidation via a five-membered-ring transition state.



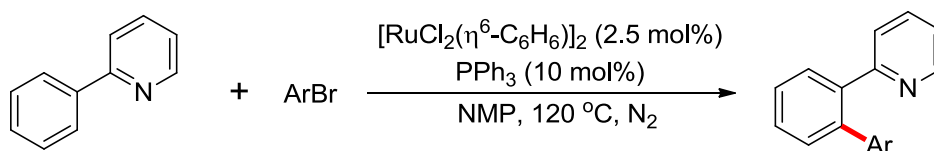
Scheme 151 Rh-catalyzed synthesis of amides from aldehydes and azides.

The rhodium-catalyzed intermolecular direct amidation of aldehyde C-H bonds with *N*-chloroamines was developed by Li and co-workers (Scheme 151a).^{218a} A variety of primary and secondary amines were applied to afford the corresponding amides in moderate to excellent yields in the absence of external oxidants. The first step of the catalytic cycle was supposed to be the heterocycle-directed C-H activation of aldehyde C-H bonds to form the five-membered cyclometalated acyl-Rh(III) complex, which was demonstrated by the X-ray crystallography. Further improvement using azides as the nitrogen source in the Rh(III)-catalyzed amidation of aldehyde was studied by the same group (Scheme 151b).^{218b}

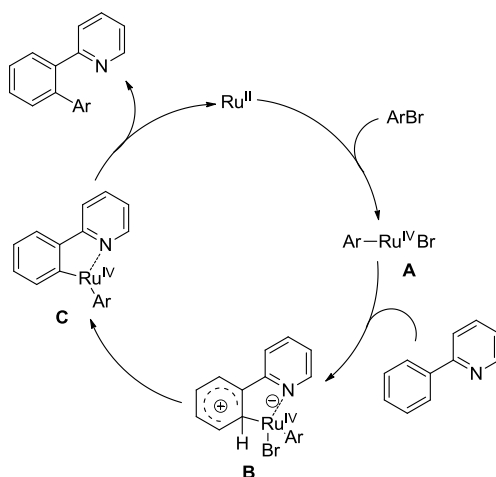


Scheme 152 Rh-Catalyzed directed sulfenylation of arene C-H bonds.

The construction of C-S bond from 2-phenylpyridines with aryl or alkyl disulfides via Rh(III)-catalyzed C-H activation has been reported by Li (Scheme 152).²¹⁹ The selective mono- or dithiolation of arenes could be controlled by the reaction temperature. Significantly, this C-H thioetherification reaction was compatible with many directing groups (pyridine, pyrimidine, pyrazole, and oxime) and various synthetically useful functional groups.

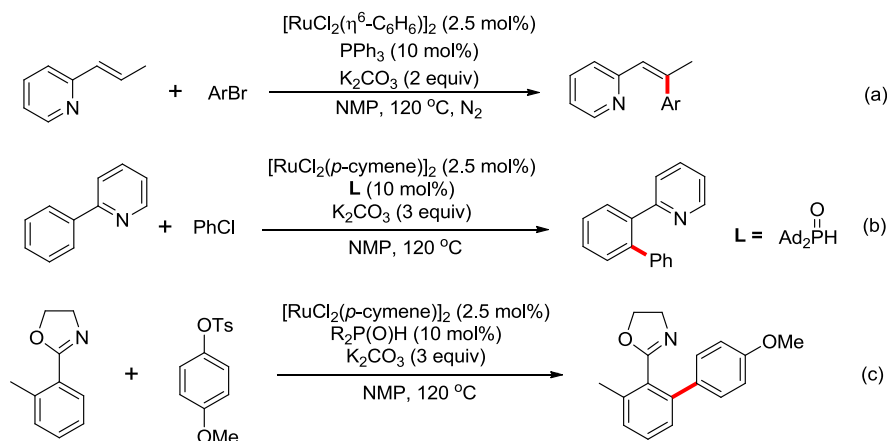


Scheme 153 Ru-catalyzed C-H arylation with arylhalides.

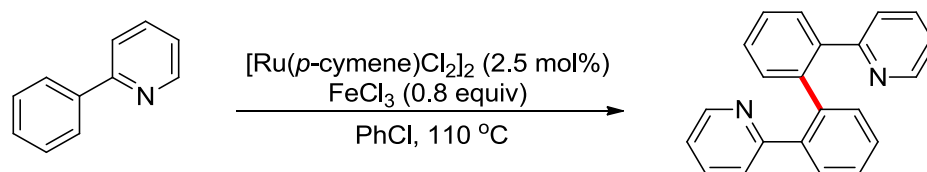


Scheme 154 The plausible mechanism.

Oi and Inoue reported the first example of Ru-catalyzed C-H arylation of 2-arylpyridines using arylhalides (Scheme 153).²²⁰ Bromobenzene, iodobenzene and phenyltriflate were effective arylation reagents in the reaction. The oxidative addition of Ru(II) to ArBr generated the tetra-valent arylruthenium complex **A**, which reacted electrophilically with 2-phenylpyridine to give the zwitterionic intermediate **B**. Elimination of HBr formed the arylated ruthenacycle **C**, which underwent the reductive elimination to afford the product (Scheme 154).

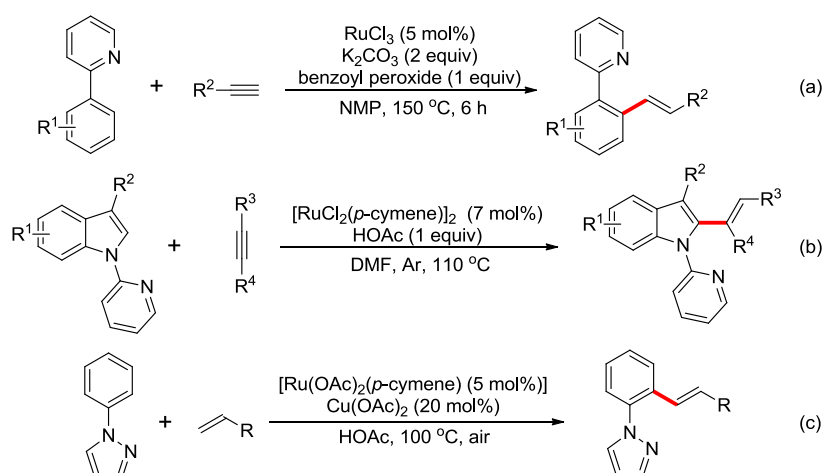


Scheme 155 Ruthenium-catalyzed C-H arylation with different arylation reagents.



Scheme 156 Ruthenium-catalyzed oxidative coupling of 2-arylpyridines.

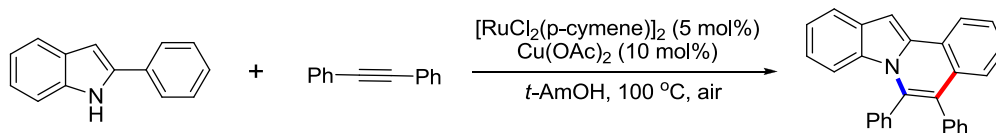
A related example of ruthenium-catalyzed arylation of 2-alkenylpyridines with aryl bromides was developed by the same group later (Scheme 155a).²²¹ By the use of an air-stable secondary phosphine oxide, Ackermann and co-workers further realized the arylation with inexpensive, but less reactive aryl chlorides or aryl tosylates (Scheme 155 b,c).^{222, 223} Meanwhile, the oxidative homocoupling reaction of 2-arylpyridines was reported by Li, in which FeCl₃ was used as an oxidant to regenerate the Ru(II) catalyst (Scheme 156).²²⁴



Scheme 157 Ruthenium-catalyzed C-H alkenylation reaction.

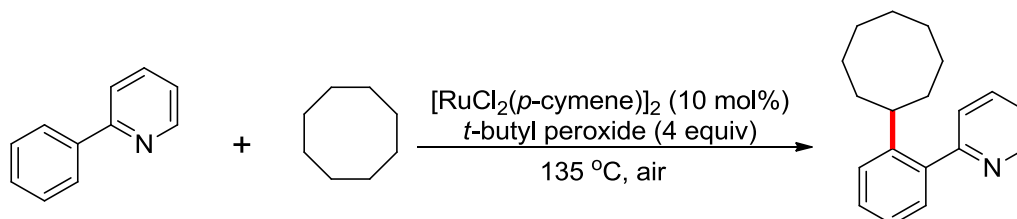
Zhang and co-workers first reported a new catalytic method for the alkenylation of arylpyridines at the *ortho*-C-H bond with terminal alkynes in the presence of 5 mol % of RuCl₃ and 1 equiv of benzoyl peroxide or benzoic acid in NMP at 150 °C, with high stereoselectivity toward (*E*)-stereoisomers. Various terminal alkynes such as aryl terminal alkynes, alkyl terminal alkynes and vinyl terminal alkynes, were tolerated and gave the products in moderate to high yields. However, the internal alkynes were ineffective under these reaction conditions. A plausible mechanism involved the initial formation of a cyclometalated intermediate, regioselective insertion of alkyne, and protonation of the resulting Ru-C bond (Scheme 157a).²²⁵ Very recently, the ruthenium-catalyzed alkenylation of *N*-(2-pyridyl)indoles was achieved by Zeng (Scheme 157b).²²⁶ Various arenes and alkynes, including electron-deficient and electron-rich internal alkynes and terminal alkynes, were compatible in this transformation. Remarkably, the directing group-pyridyl moiety can be easily removed to afford free (N-H) indoles under mild conditions.

Ruthenium-catalyzed C-H alkenylation with styrene and alkyl acrylates was reported by Dixneuf (Scheme 157c).²²⁷ The acetic acid solvent played a key role in the reaction and the yields dramatically decreased without the use of the acetic acid. Importantly, alkenylation with electrophilic acrylates required a stoichiometric amount of oxidant while alkenylation with styrene proceeded with a catalytic amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in acetic acid.



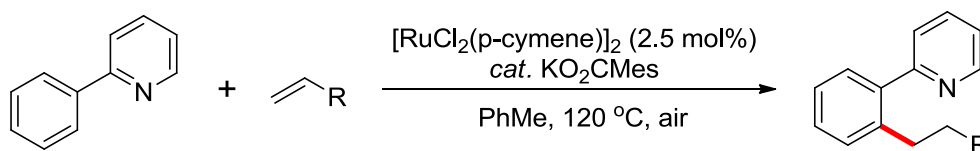
Scheme 158 Ru-catalyzed oxidative coupling of alkynes with 2-aryl-substituted pyrroles.

An oxidative annulation reaction of 2-arylindoles with alkynes by ruthenium-catalyzed C-H bond cleavage was achieved by Ackermann in 2011 (Scheme 158).²²⁸ Remarkably, the stoichiometric amounts of oxidant could be avoided and catalytic amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ were found to be sufficient. Substrates bearing different functional groups, such as fluoro, nitro, ester, ketone or aldehyde substituents, were well tolerated with the catalytic system.



Scheme 159 Ruthenium-catalyzed oxidative coupling of chelating arenes with cycloalkanes.

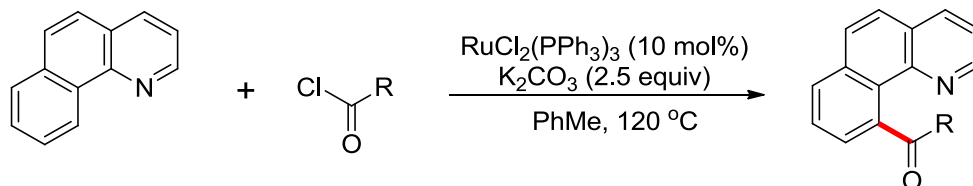
Li and co-workers reported a ruthenium-catalyzed oxidative cross-coupling of chelating arenes with cycloalkanes (Scheme 159).²²⁹ The use of *t*-butyl peroxide as oxidant and cycloalkanes as solvent were crucial to achieve the best yield. Other ruthenium catalysts, such as $\text{Ru}_3(\text{CO})_{12}$, $\text{Ru}(\text{acac})_3$, $[\text{Ru}(\text{cod})\text{Cl}_2]_2$, $\text{Ru}(\text{CO})\text{H}_2(\text{PPh}_3)_3$ and $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$, led to a mixture of mono- and dialkylation products.



Scheme 160 Ruthenium-catalyzed C-H alkylation of arenes.

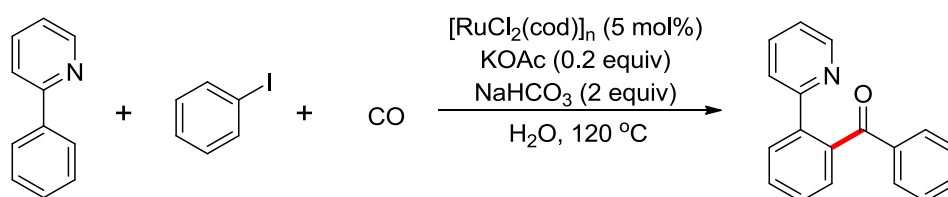
A stable and easy-operated ruthenium catalytic system was developed by Ackermann (Scheme 160).²³⁰ The additives such as metal carboxylates were necessary to generate the

active ruthenium catalyst, and steric KO_2CMes led to the best yield. Notably, unactivated alkenes, such as alkyl alkenes and vinyl silanes, could be used as excellent coupling reagents to provide the alkylated heteroarenes.



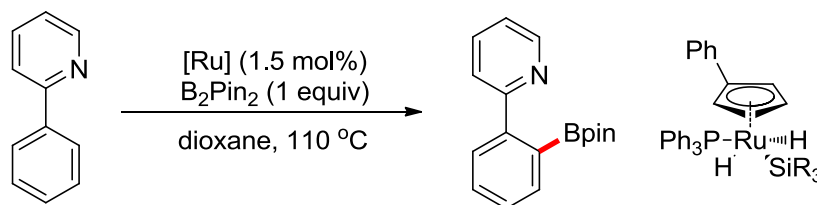
Scheme 161 Ruthenium-catalyzed C-H carbonylation of arenes.

Ruthenium-catalyzed amino- and alkoxy-carbonylations of arenes was described by Kakiuchi and co-workers (Scheme 161).²³¹ The use of carbamoylchlorides and alkyl chloroformates offered an alternative route to synthesize the carbonylation products that required the consume of CO in the traditional method. A broad generality of amide and ester groups were achieved, taking advantage of the wide availability of carbonylating agents. Moreover, alkyl chloroformates, which were inactive in usual Friedel-Crafts conditions, could be used in this direct catalytic alkoxy-carbonylation.



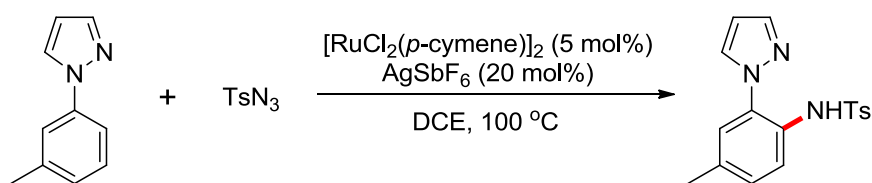
Scheme 162 Ru-catalyzed carbonylative C-C coupling in water.

In 2013, Beller reported a ruthenium-catalyzed carbonylation of arenes in water under CO atmosphere (Scheme 162).²³² The monoarylation products were obtained exclusively under the optimal condition. Interestingly, silver acetate or silver hexafluoroantimonate which had a positive effect on the generation of the active species in the Ru(II)-catalyzed C-H activation, inhibited the reactivity of this catalyst system completely.



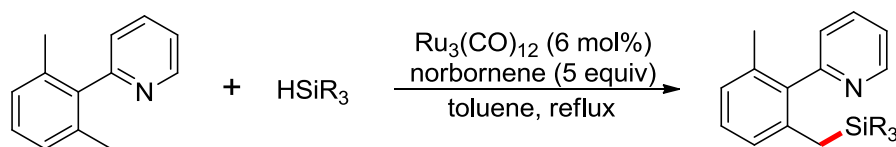
Scheme 163 Ruthenium catalyzed C-H bond borylation.

A new 3-phenylindenyl dihydridosilyl ruthenium complexes was developed to promote the selective *ortho*-borylation of aromatic C-H bonds by Nolan and co-workers (Scheme 163).²³³ The $[\text{RuH}_2(3\text{-phenylindenyl})(\text{SiEt}_3)]$ complex exhibited high efficiency in the C-H activation step to generate the ruthenium(IV) intermediate, which reacted with B_2Pin_2 to form a new ruthenium intermediate, with concomitant releasing of HBpin. The final reductive elimination afforded the desired borylated products. Importantly, the Ir and Rh catalytic system could also be used and the tandem reactions such as a one-pot borylation/Suzuki-Miyaura sequence could be performed.



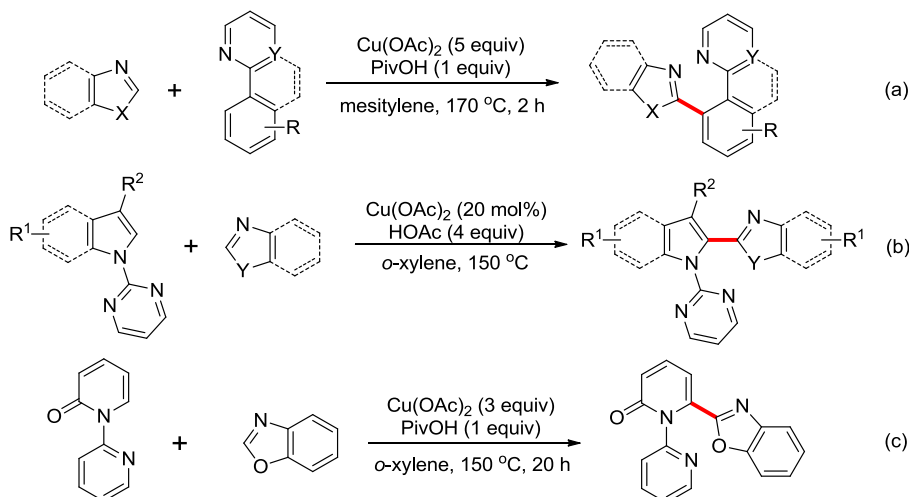
Scheme 164 Ru(II)-catalyzed C-H amidations of heteroaryl arenes.

The ruthenium-catalyzed C-H amidation of arenes with sulfonyl azides was reported by Ackermann and co-workers (Scheme 164).²³⁴ Various alkyl and aryl sulfonyl azides were tolerated to give the products in moderate to high yields. Furthermore, pyrazolyl-, pyrimidyl- or pyridyl-substituted arenes and heteroarenes could successfully be transferred into the corresponding amidation derivatives.



Scheme 165 $\text{Ru}_3(\text{CO})_{12}$ -catalyzed silylation of benzylic C-H bonds with hydrosilanes.

In 2004, Kakiuchi reported a novel $\text{Ru}_3(\text{CO})_{12}$ -catalyzed silylation of benzylic C-H bonds in arylpyridines and arylpyrazoles with hydrosilanes (Scheme 165).²³⁵ Norbornene was used as an important hydrogen acceptor. The silylation took place selectively at the *ortho*-position of CH_3 group rather than the *para*-position, indicating that the coordination of the nitrogen of heterocycle was involved in this silylation reaction. The reaction proceeded exclusively at the methyl group instead of methylene group in an ethyl substituted substrate, which indicated that steric congestion had an important influence on the reactivity of benzylic C-H bonds. This method provided an alternative route for preparing benzylsilane derivatives.

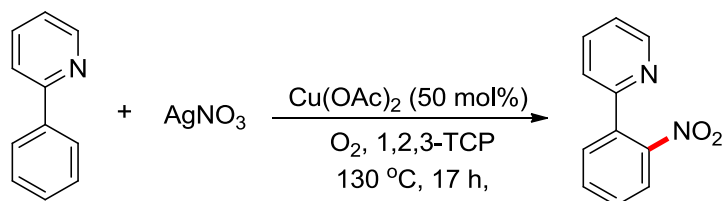


Scheme 166 Copper-mediated/catalyzed intermolecular biaryl coupling reaction.

In the last few decades, late transition metal-catalyzed C-H activation, such as palladium, ruthenium, rhodium, iridium, gold, and platinum, had been extensively studied. However, the relatively high price and considerable toxicity limited their widespread applications. Therefore, more and more chemists shifted their attention to the first-row transition metals, especially copper, iron, and cobalt, which own obvious advantages and unique features. Miura and co-workers reported a copper-mediated intermolecular biaryl coupling reaction (Scheme 166a).²³⁶ The reaction proceeded without palladium catalysts and enabled an unprecedented coupling between 2-arylazines with azoles. Carboxylic acid additives generally improved the reaction efficiency, among which PivOH afforded the best yields. Later, the copper-mediated cross-coupling of indoles and 1,3-azoles was also reported by the same group (Scheme 166b).²³⁷ Compared with the previous work, the use of atmospheric oxygen was found to render the reaction into catalytic manner. More recently, they found that pyridine could be used as a removable directing group in the copper-mediated dehydrogenative arylation of 2-pyridones with 1,3-azoles (Scheme 166c).²³⁸ The authors proposed that the initial cupration of the 1,3-azole and the subsequent chelation of the pyridine moiety to the Cu center afforded the Cu(III) species. The final reductive elimination liberated the product and Cu(I) species, which could be oxidized by molecular oxygen to regenerate the starting Cu(II) species.

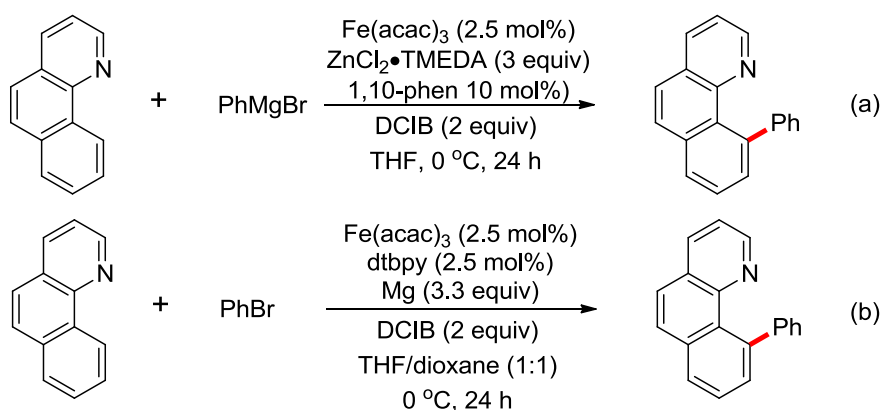
The Cu(II)-catalyzed C-H cyanation, amination, etherification and thioetherification reactions of 2-arylpyridine were investigated by Yu group.²³⁹ A radical-cation pathway was

proposed by the authors: 1) The initial single electron transfer (SET) from the aryl ring to the coordinated Cu(II) led to the cation-radical intermediate. 2) The subsequent intramolecular anion transfer from the Cu(I) complex to the *ortho* position of arene. 3) The final SET led to the generation of *ortho*-functionalized products.



Scheme 167 Cu-mediated C-H nitration of 2-arylpyridines.

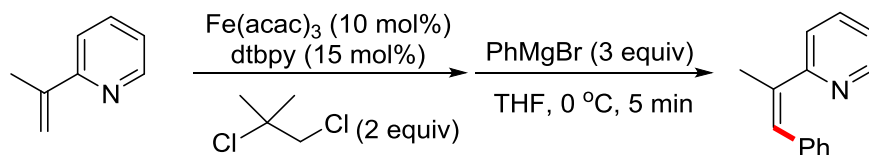
The Cu(II)-mediated C-H functionalization of 2-arylpyridine has been rapidly developed using different anion sources by several groups. For example, Cu(II)-catalyzed *ortho*-cyanation of 2-arylpyridine using different CN sources, such as benzyl nitrile,²⁴⁰ acetonitrile,²⁴¹ azobisisobutyronitrile,²⁴² was achieved. Recently, Liu and co-workers demonstrated that AgNO₃ could provide the nitrate anion in the copper-mediated *ortho*-nitration of (hetero)arenes (Scheme 167).²⁴³



Scheme 168 Arylation of α -benzoquinoline derivatives by iron catalysis.

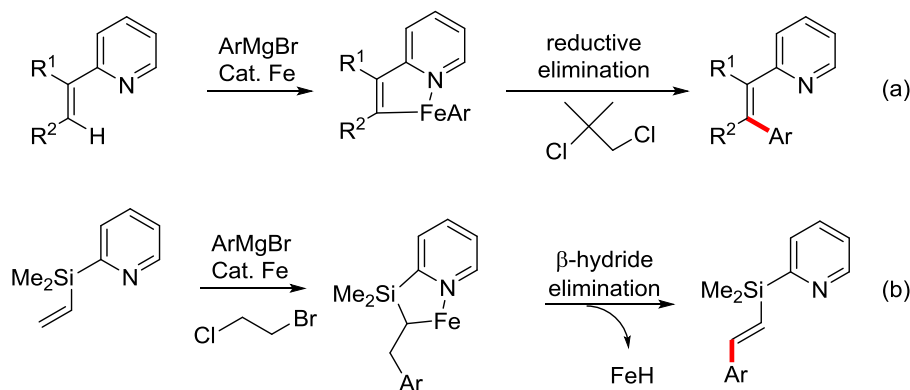
In the last few decades, late transition metal-catalyzed C-H activation, such as palladium, ruthenium, rhodium, iridium, gold, and platinum, had been extensively studied. However, the relatively high price and considerable toxicity limited their applications and possible improvements. Therefore, more and more chemists shifted their attention to the first-row transition metals, especially copper and iron, which own obvious advantages and unique features. A iron-catalyzed direct arylation of α -benzoquinoline with phenylmagnesium bromide was first developed by Nakamura and co-workers in 2008 (Scheme 168).²⁴⁴ The arylation products were obtained using 10 mol% of Fe(acac)₃/phen, 3 equiv of

ZnCl₂·TMEDA and 6 equiv of arylmagnesium bromide at 0 °C. 1,2-Dichloroisobutane (DCIB) had an important role in the reaction as an oxidant. The oxidation state and the counteranion of the iron salt had only a little influence on the catalytic activity and various iron catalysts could be applied in this reaction.



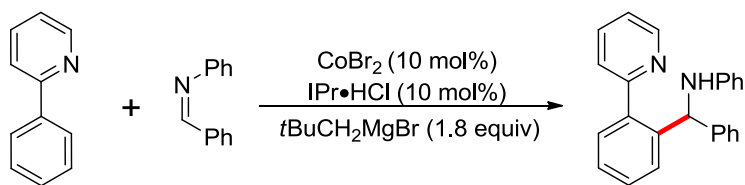
Scheme 169 Iron-catalyzed C-H arylation of 2-vinylpyridines.

In 2011, Nakamura and co-workers reported an iron-catalyzed olefinic C-H arylation with Grignard reagent (Scheme 169).²⁴⁵ A wide range of vinyl groups, such as cyclic and acyclic in the pyridine could be tolerated under the reaction conditions. The solvent had an important influence on the *E/Z* ratio of products, which could be raised from 3/97 to 95/5 when the solvent was changed from PhCl/Et₂O to THF. It was noted that the byproducts could be retarded by the addition of the 4,4-di-*tert*-butyl bipyridine (dtbpy) ligand and the slow addition of the Grignard reagent.



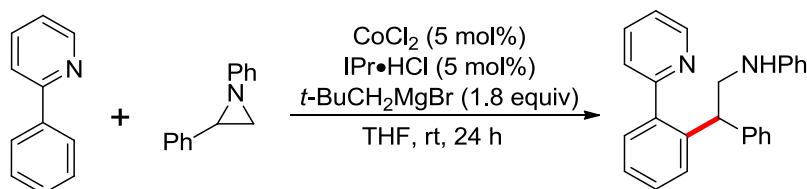
Scheme 170 The proposed mechanism.

Based on the results of the control experiments, the author proposed two different reaction pathways: (a) The C-H bond activation resulted in a five-membered metallacycle which underwent reductive elimination to give the substituted olefin; (b) The five-membered metallacycle underwent the oxidative Heck reaction to give the products (Scheme 170). The aliphatic halides of 1,2-dichloroisobutane and 1-bromo-2-chloroethane were required to oxidize the iron hydride species which led to the formation of the byproduct 2-(ethyldimethylsilyl)pyridine.



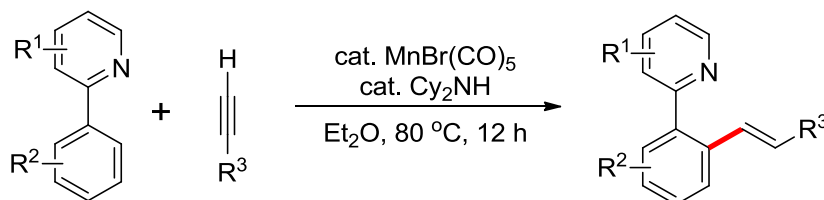
Scheme 171 Cobalt-catalyzed arylation of imines.

Yoshikai and co-workers reported a cobalt-catalyzed arylation of aldimines (Scheme 171),²⁴⁶ in which the polar C=N bond could serve as a reaction partner. The choice of the Grignard reagent of *t*-BuCH₂MgBr was critical, and the use of other alkyl Grignard reagents such as MeMgCl, *n*-BuMgBr, *i*PrMgBr, and Me₃SiCH₂MgCl, resulted in lower yields. The ligand 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (IPr) was indispensable for the reaction and wide functional group was observed.



Scheme 172 Cobalt-catalyzed C-C coupling of arenes and aziridines.

Yoshikai and co-workers reported a cobalt-catalyzed C-H alkylation of 2-arylpyridines with 1,2-diarylaziridines (Scheme 172).²⁴⁷ A cobalt-*N*-heterocyclic carbene catalyst was found to promote *ortho*-C-H functionalization of 2-arylpyridines with 1,2-diarylaziridines through ring-opening alkylation. The reaction afforded the 1,1-diarylethanes bearing 2-amino functional groups in moderate to good yields under mild room-temperature conditions. The combination of a cobalt salt with an NHC ligand as well as a Grignard reagent was indispensable to offer versatile catalytic systems for *ortho*-C-H functionalization of arenes with electrophiles.



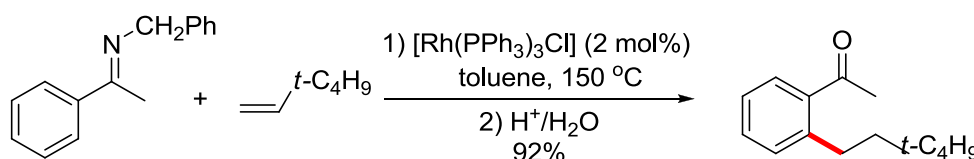
Scheme 173 Mn-catalyzed C-H olefination of 2-arylpyridine with terminal alkynes.

As early as in 1971, Bruce and co-workers reported seminal work on stoichiometric *ortho*-manganation of benzylideneaniline. However, there were only a few examples of Mn-catalyzed C-C bond formation reactions via inert C-H activation. In 2013, Wang and

co-workers demonstrated the first manganese-catalyzed aromatic C-H alkenylations with terminal alkynes (Scheme 173).²⁴⁸ The alkenylate products were obtained by the reaction of 2-phenylpyridine with terminal alkynes in the presence of $\text{MnBr}(\text{CO})_5$ (20 mol%), Cy_2NH (10 mol%) in Et_2O at 80 °C. Importantly, the secondary amines bearing steric bulkiness were found to be beneficial for the C-H activation step. A wide range of functional groups were compatible with the catalytic system. Steric substituents on the benzene moiety showed little influence on the reaction outcome. The reaction occurred readily in a highly chemo-, regio-, and stereoselective manner, delivering *anti*-Markovnikov *E*-configured olefins in high yields.

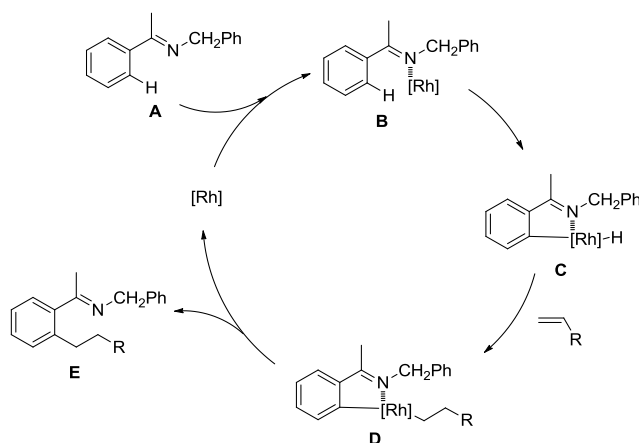
3.2 The C-H functionalization directed by imine

Imines are common reactive functionalities that allow access to a diversity of synthetically useful architectures through demonstrated reactivities. In recent years, the strong coordination ability of imine with transition metals has been found wide applications in challenging C-H bond functionalizations.



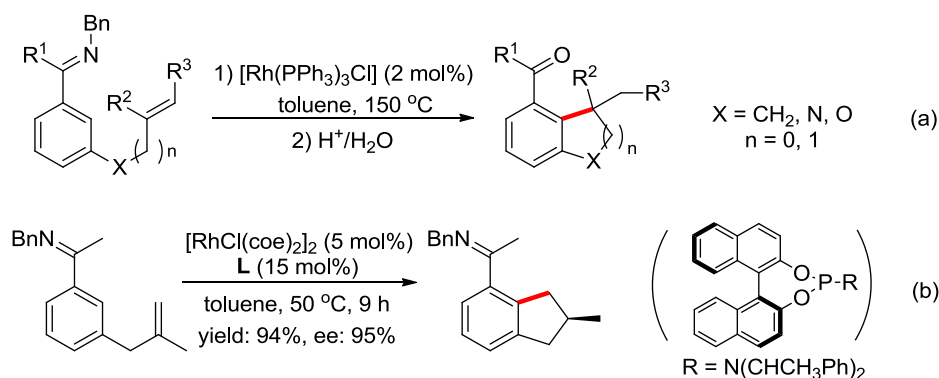
Scheme 174 Rh-catalyzed alkylation of aromatic imines.

The first example of imine directed *ortho*-alkylation of arenes with various olefins was demonstrated by Jun and co-workers in 2000 (Scheme 174).²⁴⁹ Compared with the previous alkylation of aryl ketones by Murai and co-workers, in which ketone was used as the directing group,^{2b} this process exhibited a broad substrate scope of alkenes. The alkenes bearing allylic hydrogens, electron-deficient alkenes, and even internal alkenes, took part in the reaction smoothly to give the corresponding alkylated aryl ketones after acidic hydrolysis. The over alkylation that plagued aryl ketone alkylation could also be avoided in this transformation.



Scheme 175 Proposed mechanism for the *ortho*-alkylation of arenes with olefins.

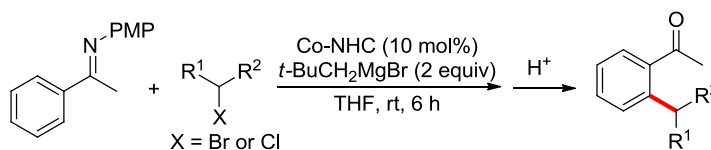
As shown in Scheme 175, the mechanism involved the initial precoordination of the imine nitrogen atom to the Rh(I) center, followed by the activation of an aromatic C-H bond. The resulting metallacycle **C** went through olefin coordination and hydride insertion to give **D**, which underwent reductive elimination to furnish the *ortho*-alkylated product **E**.



Scheme 176 Rh-catalyzed annulation of aromatic imines.

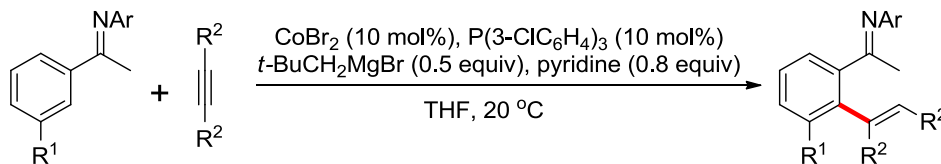
Bergman, Ellman and co-workers demonstrated the imine-assisted intramolecular alkylation of arenes (Scheme 176a).²⁵⁰ Allyl ethers and allylamines tethered to the *ortho*-position could function as efficient olefin coupling partners to undergo the intramolecular annulation to afford the functionalized indane, tetralane, dihydrobenzofuran and dihydroindole derivatives. However, the reaction suffered from the low functional group tolerance and high reaction temperature. After the optimization of the reaction conditions, this intramolecular alkylation reaction could be performed at lower temperature by the use of $[\text{RhCl}(\text{coe})_2]_2$ as catalyst, which allowed the enantioselective cyclization of aromatic imines in the presence of the chiral phosphoramidite ligands (Scheme 176b).²⁵¹ The observed high enantioselectivities were attributed to the unique binding properties of phosphoramidite

ligands with rhodium catalyst.



Scheme 177 Cobalt-catalyzed *ortho*-alkylation of aromatic imines with alkyl halides.

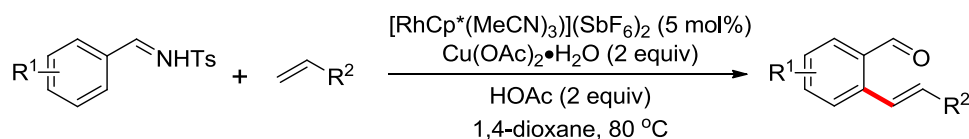
The *ortho*-alkylation of imines using alkyl halides in the presence of a cobalt-*N*-heterocyclic carbene (NHC) catalyst was reported by Yoshikai and co-workers (Scheme 177).²⁵² The choice of different *N*-heterocyclic carbene ligands was crucial for the yields and selectivities of the reaction under mild reaction conditions. These mild conditions afforded the alkylated products in high efficiencies with primary and secondary alkyl chlorides and bromides. The stereochemical outcomes by the use of secondary alkyl halides suggested that the reaction mechanism involved the formation of the alkyl radical through a single-electron transfer from cobalt species.



Scheme 178 Cobalt-catalyzed addition of aromatic imines to alkynes.

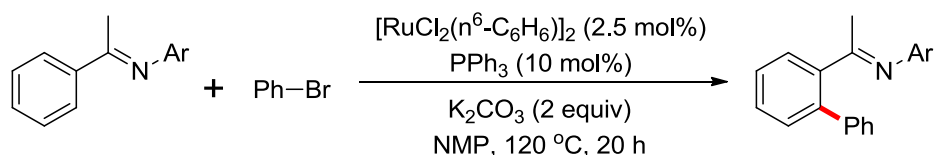
Jun and co-workers reported the first example of the Rh(I)-catalyzed *ortho*-olefination of common aromatic ketimines with alkynes.²⁵³ The product could further undergo the cyclization to result in the generation of isoquinoline derivatives at the high reaction temperature. Recently, Yoshikai group accomplished this addition of aromatic imines to alkynes via cobalt-catalyzed C-H bond activation (Scheme 178).²⁵⁴ A quaternary catalytic system, including cobalt salt, triarylphosphine ligand, Grignard reagent and pyridine, was developed for the transformation. The role of each components of the system has been proposed: 1) the active cobalt intermediate could be stabilized by phosphine ligand; 2) the Grignard reagent may reduce cobalt (II) to give rise to an organocobalt (0) species as the catalytically active species; 3) pyridine appeared to serve as a coligand for the cobalt catalyst. Interestingly, the reaction displayed a unique regioselectivity to form the C-C bond at the more sterically hindered *ortho* positions, which was ascribed to the electron-withdrawing substituents to strengthen a metal carbon bond at the *ortho* position or the coordination

ability of substituents with the metal center in the oxidative C-H activation process. By the use of cobalt catalysts, Yoshikai group also achieved the *ortho*-arylation reaction of aromatic imines with aryl chlorides under their well-established quaternary catalytic system at room temperature.^{246, 255}

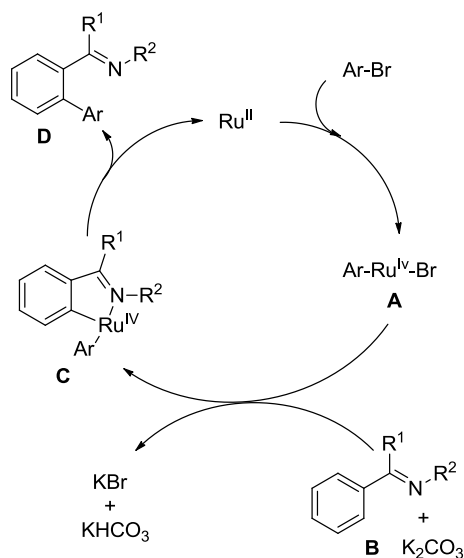


Scheme 179 Rh(III)-catalyzed olefination of *N*-sulfonyl imines.

The application of acrylates and styrenes in the *ortho*-olefination directed by a *N*-Ts imines group was demonstrated by Li and Wu group respectively, in which an excess of copper(II) salt was used as an oxidant (Scheme 179).²⁵⁶ A blocking group was introduced to the *ortho* and *meta* position of the aromatic ring to obtain good isolated yield of mono-olefinated products when styrene was used.^{256a} The *N*-sulfonyl ketimines were further applied to the synthesis of the functionalized pyridines via imine-directed *ortho*-olefination and subsequent annulation by Dong and co-workers.²⁵⁷ It was proposed that the N-S bond of *N*-sulfonyl ketimines served as an internal oxidant.

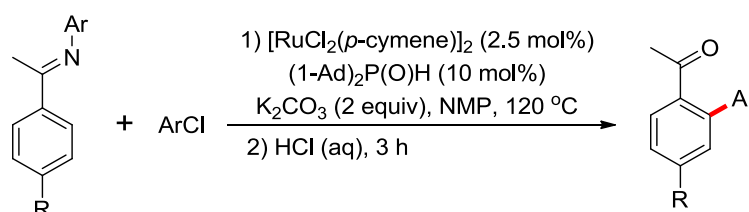


Scheme 180 Ruthenium-catalyzed *ortho*-arylation of aryl imines.



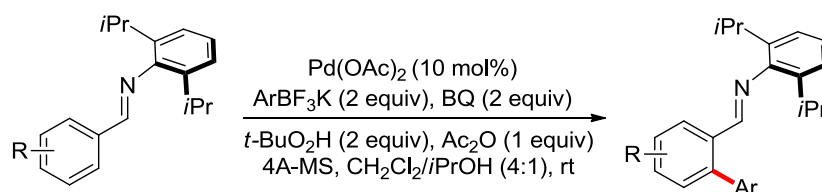
Scheme 181 Proposed mechanism for the *ortho*-arylation of aryl imines.

The ruthenium-catalyzed *ortho*-arylation of aryl imines with aryl and alkenyl bromide was reported by Oi in 2002 (Scheme 180).²⁵⁸ The tetravalent aryl- or alkenyl- ruthenium species should be the key intermediate, which was generated from oxidative addition of aryl bromide to the ruthenium(II) complex. The proposed mechanism was shown as Scheme 181. The coordination of **A** to the imine moiety afforded the arylated ruthenacycle intermediate **C**, followed by the reductive elimination to generate the *ortho*-arylated product **D**.



Scheme 182 Ruthenium-catalyzed arylation using aryl chlorides.

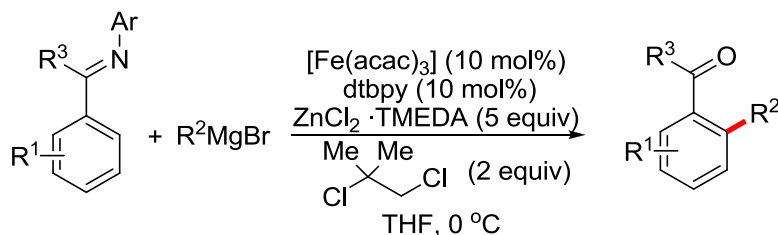
The use of aryl chlorides in the ruthenium-catalyzed arylation of imines was developed by Ackermann (Scheme 182).²²³ Both electron-rich and electron-poor aryl chlorides were tolerated in this reaction and a wide variety of functional groups were compatible, including enolizable ketones, nitriles, and esters. The successful employment of inactive aryl chlorides in the C(sp²)-H arylation was attributed to the use of air-stable, electron-rich phosphine oxides as preligands. The corresponding mono-arylated ketones were isolated upon hydrolysis in high yields.



Scheme 183 Palladium(II)-catalyzed arylation of arenes at room temperature.

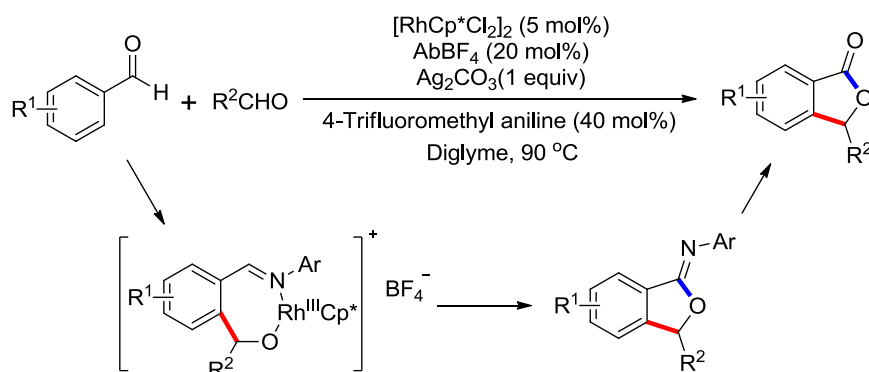
A Pd(II)-catalyzed direct C-H bond arylation on electron-deficient arenes that proceeded at room temperature was described by Gaunt and co-workers (Scheme 183).²⁵⁹ Compared with previous efforts, the increased steric bulk around the aniline moiety was important to increase stability of the imine towards hydrolytic cleavage. The key cyclopalladation intermediate was obtained by the treatment of imine with 1 equivalent of Pd(OAc)₂ at room temperature in methanol, which gave the *ortho*-arylated benzaldimine in excellent yields

when treated with PhB(OH)_2 . Further achievement was made by the use of benzene as a source of the aryl group for this *ortho*-arylation reaction.



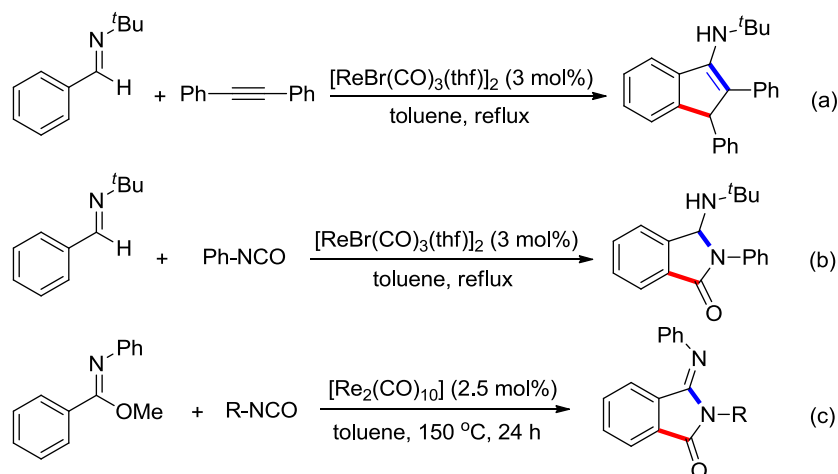
Scheme 184 Iron-catalyzed chemoselective *ortho*-arylation of aryl imines.

Iron-catalyzed coupling of an aromatic imine with a diarylzinc reagent was developed by Nakamura and co-workers (Scheme 184).²⁶⁰ By the use of cheap, ubiquitous and nontoxic iron catalysts, the reaction took place under very mild conditions (0 °C in THF) and tolerated the presence of reactive functional groups, including halides, nitriles, triflate and tosylate groups.



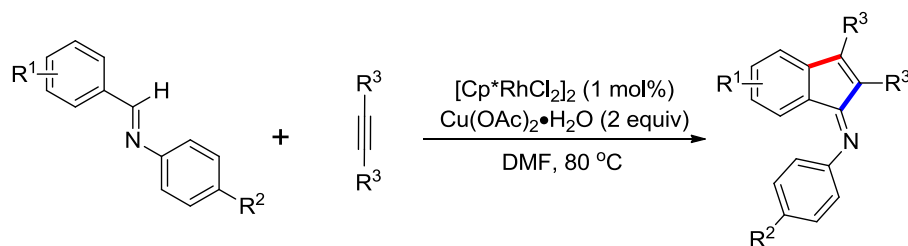
Scheme 185 Rh(III)-amine dual catalysis for the coupling of aldehydes.

The oxidative coupling of aldehydes to form phthalides by Rh(III) catalysis was reported by Seayad and co-workers (Scheme 185).²⁶¹ The presence of catalytic amounts of amines played the key role by reacting with the aldehydes to *in situ* form imine, iminium, or aminated intermediates, which could act as better directing groups, and thus would be able to enhance the reactivity of the Rh-catalyzed *ortho* C-H activation in comparison with the aldehyde functionality.²⁴⁹ Interestingly, primary aryl amines such as 4-trifluoromethylaniline showed the high efficiency, while nucleophilic amines such as *p*-anisidine, pyrrolidine, and cyclohexyl amine gave only trace amount of the products.

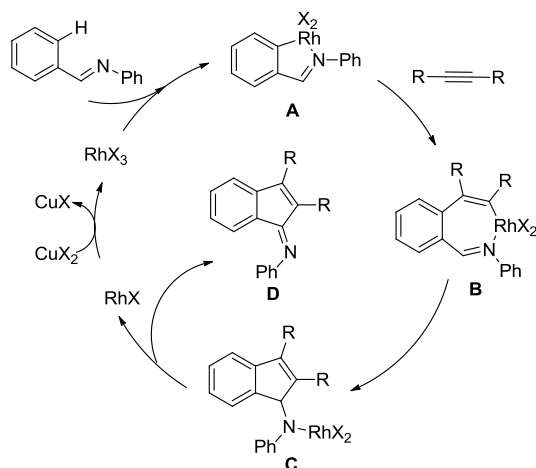


Scheme 186 Rhenium-catalyzed cyclization through C-H bond activation.

The rhenium-catalyzed insertion of aromatic aldimine into isocyanate or acetylene to give phthalimidine or indene derivatives was described by Kuninobu and Takai (Scheme 186a and b).²⁶² These authors proposed a reaction pathway: 1) An *ortho* C-H bond activation by rhenium catalyst; 2) Insertion of the acetylene to rhenium-carbon bond; 3) Intramolecular nucleophilic attack of the formed alkenylrhenium to the carbon atom of the imine; 4) Reductive elimination and 1,3-rearrangement of hydrogen atoms. The directing groups of oxime or hydrazone from an aldehyde did not work. Recently, a new transformation was reported by the same group for the rhenium-catalyzed synthesis of 3-imino-1-isoindolinones (Scheme 186c).²⁶³

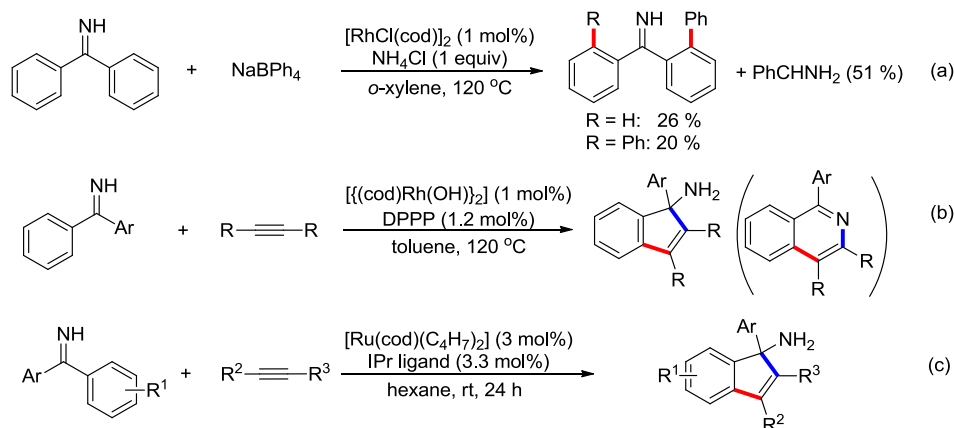


Scheme 187 Rhodium-catalyzed coupling of aromatic imines with internal alkynes.



Scheme 188 The plausible mechanism for the reaction.

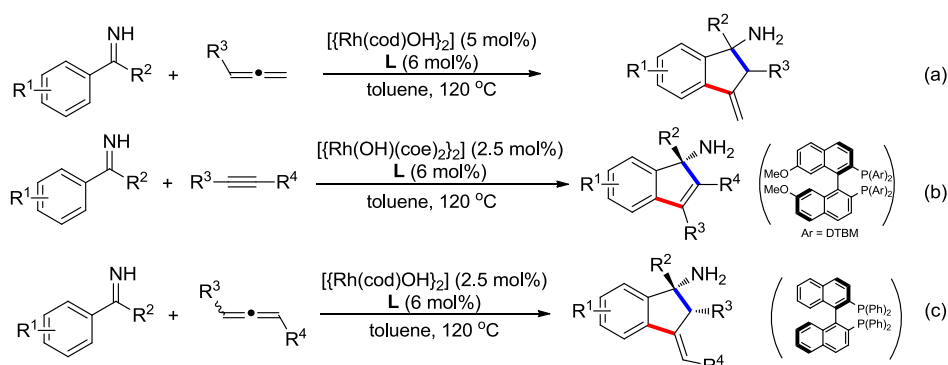
The Rh-catalyzed reaction of aromatic imines with alkynes to achieve indenone imine and isoquinoline derivatives was reported by Satoh and Miura (Scheme 187).²⁶⁴ A plausible mechanism for the reaction of benzylideneaniline with alkynes was illustrated in Scheme 188. The initial coordination of the nitrogen atom of imine to Rh(III)X₃ species led to the regioselective C-H bond cleavage to afford rhodacycle intermediate **A**. The subsequent alkyne insertion formed intermediate **B**, which underwent the intramolecular nucleophilic addition of the amido-rhodium moiety to the imine group to give the intermediate **C**. The β -hydrogen elimination generated the final product and Rh(I)X species, which could be oxidized by a copper(II) salt to regenerate Rh(III)X₃ catalyst.



Scheme 189 Rh(Ru)-catalyzed [3+2] annulation of *N*-unsubstituted aromatic ketimines.

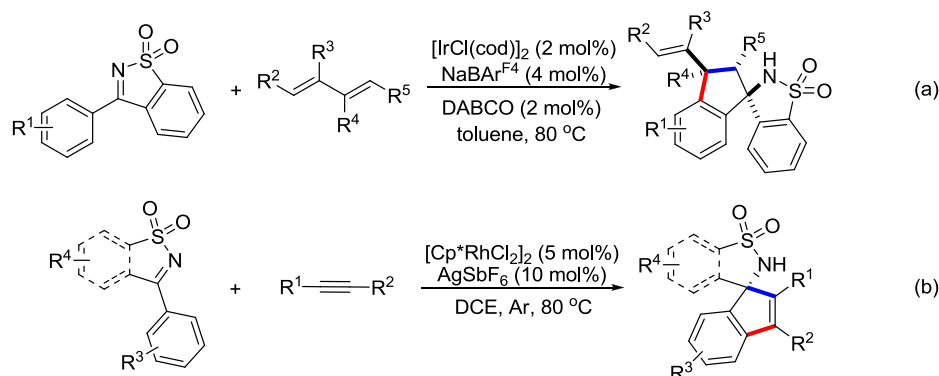
During the study of Suzuki-Miyaura-type cross-coupling of arylboron compounds with aryl halides, Satoh and Miura unexpectedly found the Rh-catalyzed *ortho*-phenylation of the *N*-unsubstituted benzophenone imine (Scheme 189a).²⁶⁵ The subsequent studies by Zhao and

co-workers demonstrated that *N*-unsubstituted aromatic ketimines and internal alkynes could form indenamines through a Rh-catalyzed [3+2] annulation (Scheme 189b).²⁶⁶ Notably, the formation of byproduct implicated that a Rh-catalyzed [4+2] annulation occurred during the reaction to give isoquinolines. The high selectivity of [3+2] versus [4+2] was attributed to the presence of DPPP ligands. Recently, they developed the catalytic system of a Ru(II)/ π -allyl catalyst and *N*-heterocyclic carbene (NHC) ligands to allow this [3+2] annulation to occur at 20-60 °C without the need for other additives (Scheme 189c).²⁶⁷



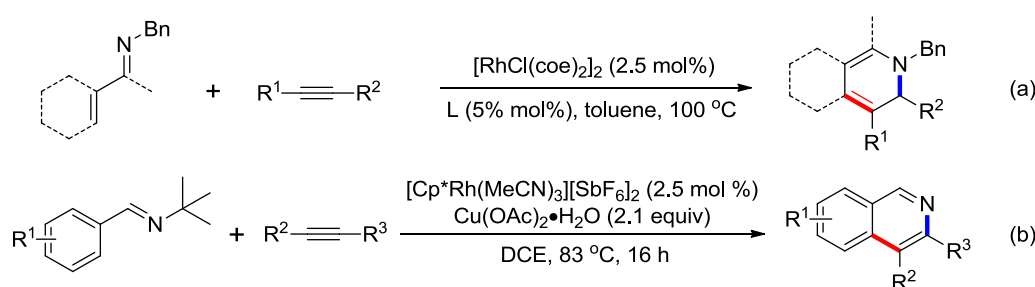
Scheme 190 Rhodium(I)-catalyzed [3+2] annulations of unsubstituted ketimines.

In 2010, Cramer and coworker developed a Rh-catalyzed [3+2] annulation of unsubstituted ketimines with terminal allenes to give the useful substituted indanylamines (Scheme 190a).^{268a} In most cases, a racemic annulation product was obtained and only one example gave the moderate enantioselectivity. The subsequent research by the same group demonstrated that 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) could be used as the effective chiral ligand to provide the excellent enantioselectivity of stereogenic center of the amino group. Both alkynes and racemic allenes were proved to be the excellent coupling partners (Scheme 190b, c).^{268b-c}



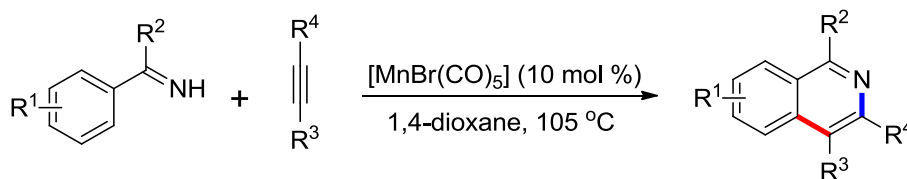
Scheme 191 Rh-catalyzed [3+2] annulation of cyclic *N*-sulfonyl ketimines with 1,3-dienes.

Nishimura and co-workers obtained aminoindane derivatives by iridium-catalyzed [3+2] annulation involving cyclic *N*-sulfonyl ketimines and 1,3-dienes (Scheme 191a).²⁶⁹ The reaction enjoyed high regio- and diastereoselectivity and the deuterium intermolecular competition experiment of k_H/k_D (2.1) revealed that the C-H bond cleavage occurred during the turnover-limiting step. More recently, Dong and co-workers reported an alternative approach, in which spirocyclic benzosultams could be generated through Rh(III)-catalyzed C-H activation of cyclic *N*-sulfonyl ketimines with internal alkynes (Scheme 191b).²⁷⁰ As early as 2012, Li and co-workers had demonstrated that the redox-neutral annulative coupling of *N*-sulfonyl imines with alkynes could be achieved using Ru catalyst.²⁷¹



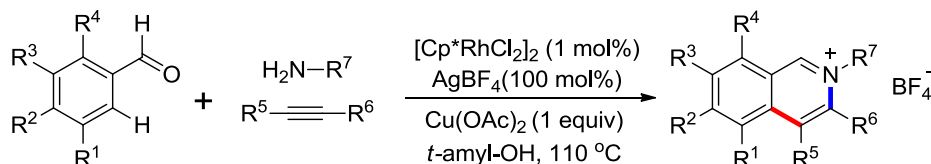
Scheme 192 Rhodium-catalyzed [4+2] annulation reaction.

Direct *ortho*-alkenylation of common aromatic ketimines and its sequential rhodium-catalyzed [4+2] annulation offered a one-pot synthetic protocol of isoquinoline or pyridine derivatives.²⁷² The first application of this strategy was achieved by Jun in 2003 at high temperatures (170 °C).²⁵³ A Rh(I)-catalyzed synthesis of highly substituted dihydropyridines derivatives from alkynes and α,β -unsaturated *N*-benzyl aldimines or ketimines under mild reaction conditions was developed by Bergman and Ellman later (Scheme 192a).^{272a-c} The reaction was proposed to go through the C-H alkenylation/electrocyclization/aromatization sequence, and the isolated rhodium intermediate supported the supposed reaction pathway. In 2009, Fagnou and co-workers made significant contributions to carry out the isoquinoline synthesis via rhodium(III)-catalyzed oxidative cross-coupling/cyclization of aryl aldimines and alkyne, in which $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was used as an oxidant in the Rh(III)/Rh(I) mechanism (Scheme 192b).^{272d} A variety of alkynes could be employed with high regioselectivity, including unsymmetrical alkynes.



Scheme 193 Manganese-catalyzed dehydrogenative [4+2] annulations.

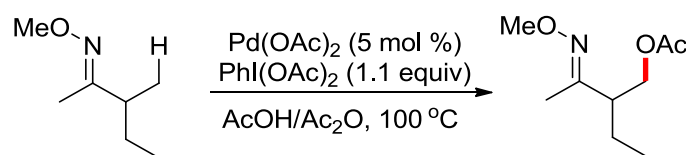
Wang groups presented the first example of manganese-catalyzed C-H dehydrogenative [4+2] annulation of *N*-unsubstituted imines and alkynes to give the isoquinoline. This reaction showed the high efficiency and broad substrate scope (Scheme 193).²⁷³ The key five-membered manganacycle intermediate was prepared and investigated in the subsequent mechanistic study. The C-H bond cleavage induced by catalytic manganese(I) in the rate-determining step was verified through kinetic isotope effect (KIE) experiments.



Scheme 194 Rhodium-catalyzed one-pot synthesis of isoquinolinium salts.

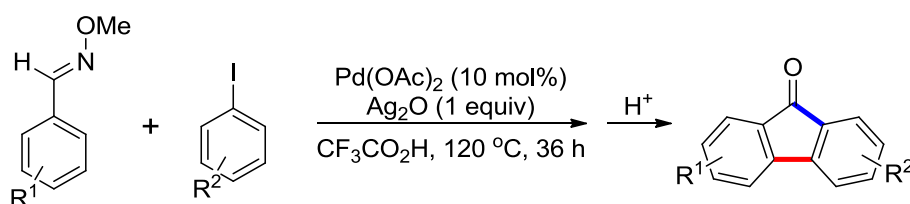
In 2012, Cheng and co-workers demonstrated the regioselective Rh-catalyzed synthesis of substituted isoquinolinium salts from the reaction of benzaldehyde, amines and alkynes. The success was attributed to the coordination of nitrogen atom of the imine, which was generated *in situ* from benzaldehydes and amines, to the rhodium species, followed by the subsequent C-H bond activation (Scheme 194).^{274a} The role of AgBF₄ was crucial for the success of the present catalytic reaction, which provided an inert anion necessary for the isolation of isoquinolinium salt, and removed the chloride on the rhodium complex to facilitate the catalytic reaction. The synthesis of substituted isoquinolinium salts from ketmines^{274b} and Ru-catalyzed synthesis of substituted isoquinolinium salts from benzaldehydes, amines and alkynes^{274c} were reported by the same group.

3.3 The C-H functionalization directed by oxime

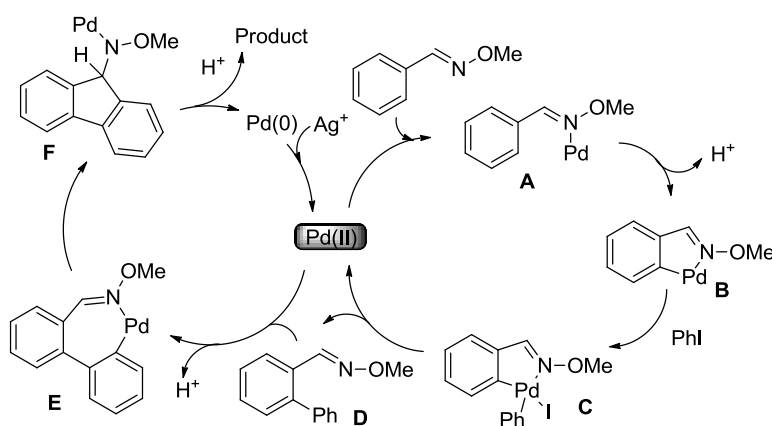


Scheme 195 Palladium-catalyzed oxygenation of unactivated sp³ C-H bonds.

Oximes are important organic scaffolds and widely exist in pharmaceuticals and functional materials. Pioneer work made by Sanford and co-workers demonstrated that the Pd-catalyzed acetoxylation of unactivated sp^3 C-H bonds could be achieved by employment of oxime as the directing group in the presence of stoichiometric oxidant $\text{PhI}(\text{OAc})_2$ (Scheme 195).²⁷⁵ The high selectivity and efficiency of the reaction was attributed to the coordination of *O*-methyl oxime with the palladium catalyst. In general, oxime presented improved stability than imine as directing group under the reaction conditions.



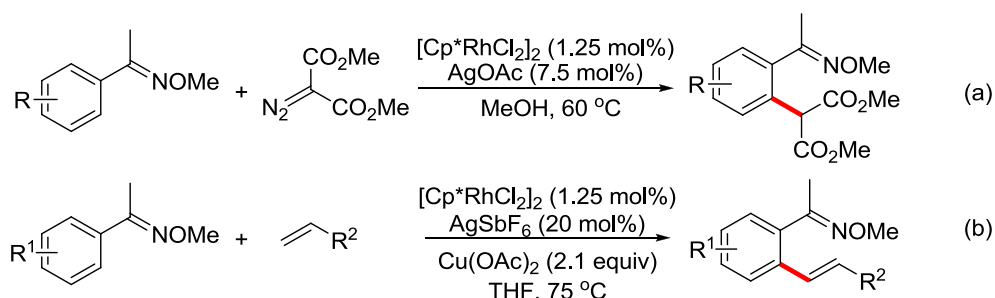
Scheme 196 Palladium-catalyzed cyclization dual C-H activation.



Scheme 197 Proposed mechanism for the reaction.

The palladium-catalyzed oxime-directed arylation of substituted benzaldehyde oxime ethers with aryl halides was reported by Cheng and co-workers for the synthesis of fluorenones (Scheme 196).²⁷⁶ The plausible catalytic pathway was proposed by the authors as shown in Scheme 197. First, the intermediate **B** was formed from the intermediate **A** through the oxime directed C-H activation. The arylation product **D** was achieved via the reductive elimination of Pd(IV) intermediate **C** that was generated from the oxidative addition of the iodobenzene to the Pd(II) intermediated **B**. The second coordination of arylated products **D** to palladium(II) generated the seven-membered palladacycle **E**, which went subsequent intramolecular insertion of C=N group into the Pd-aryl bond to produce intermediate **F**. The final β -elimination afforded the cyclization product. The stoichiometric reaction of prepared

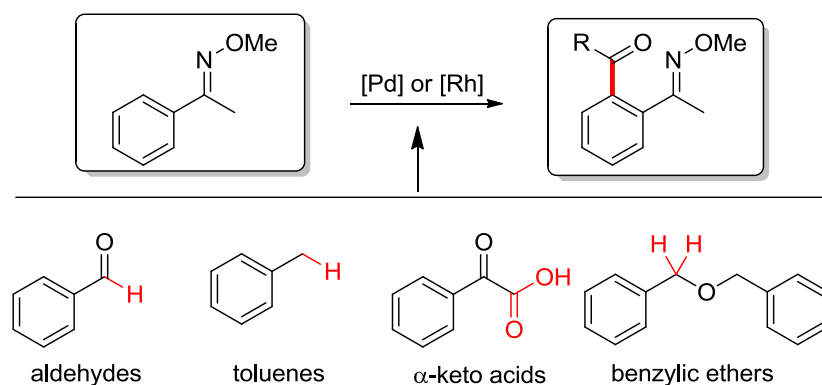
anionic palladacycle **B** with aryl iodide and the reaction of isolated intermediate **D** with aryl iodide resulted in the fluorenone product, which consisted with the proposed mechanism. Subsequent investigation demonstrated that the scope of the arylation reagent could be extended to arylboronic acids²⁷⁷ and simple arenes.²⁷⁸



Scheme 198 Rh-catalyzed alkylation and olefination of aromatic C-H bonds.

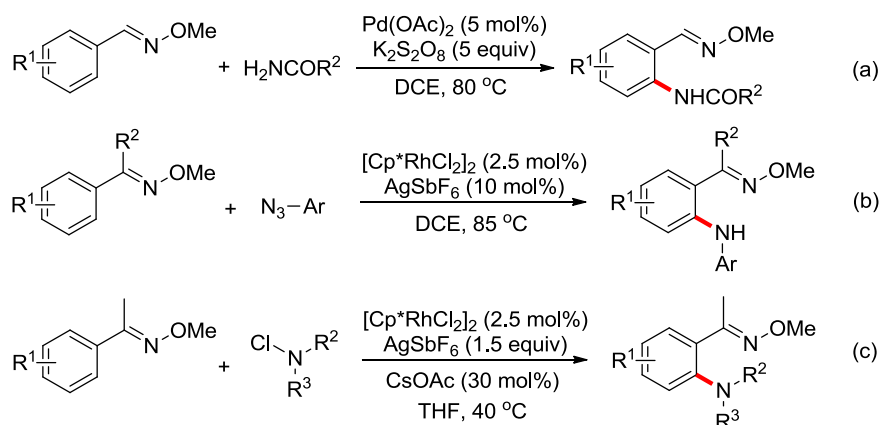
Azamalonates were applied as the coupling reagent to afford α -aryl carbonyl compounds with excellent regioselectivities and functional groups tolerance by Yu and coworkers (Scheme 198a).^{71a} The carbenoid cross-coupling with arene C-H bonds did not require a strongly basic medium and gave the benign N_2 as the only by-product. Two pathways were proposed by the authors, in which the Rh-carbene formation, or 1,2-aryl shift without the Rh-carbene intermediates were both possible. The arylated products could readily be transformed into other useful compounds, such as naphthalenes and isocoumarins.

The Rh(III)-catalyzed oxidative coupling reaction of aryl *O*-methyl oximes with alkenes was reported by Bergman and Ellman group (Scheme 198b).²⁷⁹ The coupling of unactivated terminal alkenes could be accomplished in moderate to good yields. The *para*-cyano aryl oxime gave a poor yield of coupled product (10% by NMR), probably due to coordination of the nitrile to the catalyst.



Scheme 199 Pd-catalyzed *ortho*-acylation of oximes using different coupling reagents.

In 2010, Yu and co-workers developed a Pd-catalyzed *ortho*-acylation of aryl ketone oximes with aldehydes using TBHP as oxidant for the convenient synthesis of 1,2-diacylbenzene oximes (Scheme 199).^{280a} It was believed that a radical process was involved in the reaction and the acyl radicals could be *in situ* generated from the aldehydes with the aid of TBHP. The transformation was proposed to begin with the *ortho*-palladation of *O*-methyl oxime with Pd(OAc)₂ to provide the 5-membered palladacycle, followed by reacting with acyl radicals, which were generated *in situ* by hydrogen atom abstraction of the aldehydes, affording the desired products via Pd(III) or Pd(IV) intermediate. Subsequently, several studies about Pd-catalyzed acylation reaction directed by oximes using different acylating reagents, such as toluenes,^{280b} α -keto acids,^{280c} benzylic ethers^{280d} were successfully reported in the following years. Furthermore, Zhou and Li developed a Rh-catalyzed intermolecular oxidative cross-coupling of simple aldehydes with acetophenone *O*-methyl oxime via C-H bond activation.^{280e} The reaction featured broad substrate scopes, high regioselectivities and mild reaction conditions, providing a complementary route to a wide range of diaryl ketones.

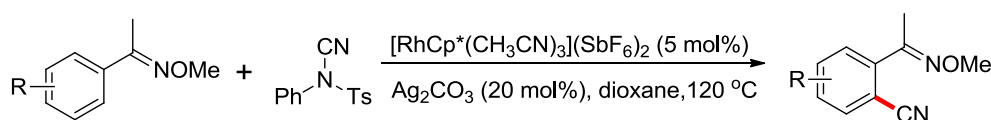


Scheme 200 Palladium-catalyzed intermolecular amidation of oximes.

Palladium-catalyzed C-N bond formation via oxime-directed C-H amidation reactions was reported by Che, Yu and co-workers in 2006 (Scheme 200a).¹⁷¹ Some primary amides, such as carbamates, acetamides, and sulfonamides, could be acted as effective nucleophiles for the reaction. In addition, catalytic amidation of unactivated sp³ C-H bonds with high regio- and chemoselectivities was also achieved under the current protocol. The authors proposed that a key nitrene intermediate generated from the oxidation of benzamide, might

undergo the insertion to the chelation-directed palladacycle to give the final amidated product.

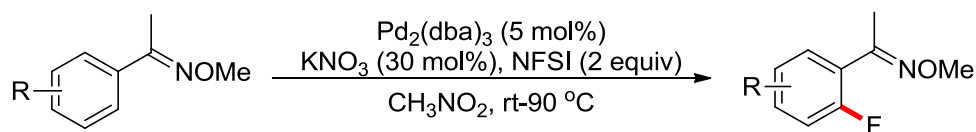
Recently, a Rh-catalyzed direct arene C-H amidation of ketoxime using sulfonyl azides as the amine source was developed by Chang and co-workers (Scheme 200b).¹²⁷ Many aryl ketoximes could be smoothly aminated to give the desired products in moderate to good yields. In addition, phenyl azides bearing not only electron-withdrawing substituents, but also electron-neutral and even electron-donating groups were all tolerant in this amination reaction. The rhodium(III)-catalyzed intermolecular direct amidation of ketoxime employing *N*-chloroamines as amine reagents was demonstrated by Yu and co-workers (Scheme 200c).²⁸¹ It was worth mentioning that monochlorinated primary amines could be well compatible with the Rh-catalyzed amination.^{281b} This protocol presented a notable advancement compared to other related reactions with secondary amines and amides as coupling partners. More recently, Zhou found that readily available *N*-hydroxycarbamates could also be used as a nitrogen source to proceed rhodium(III)-catalyzed C-H amidation.²¹⁵ Liu reported the palladium-catalyzed oxime-assisted aromatic C-H nitration by using of the AgNO₂ as the nitro source.²⁸²



Scheme 201 Rhodium-catalyzed directed C-H cyanation of arenes.

Recently, a Rh-catalyzed C-H cyanation reaction reagent for the synthesis of aromatic nitriles was developed by Fu and co-workers (Scheme 201).²⁸³ The *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) was a less toxic, readily available and easily handled crystalline salt, and could be used as practical cyanation reagent. Ag₂CO₃ was found to be an effective additive and the relatively high temperature was necessary for the high efficiency of the reaction. The kinetic isotope effect (KIE) experiment was conducted to have an understanding of the reaction mechanism and the results indicated a C-H activation process was involved in the rate-determining step. The reaction tolerated a wide range of synthetically important functional groups and a number of aromatic and heteroaromatic nitriles were readily afforded using this method. Furthermore, the obtained nitrile products could be easily transformed into many other synthetically useful groups, providing a

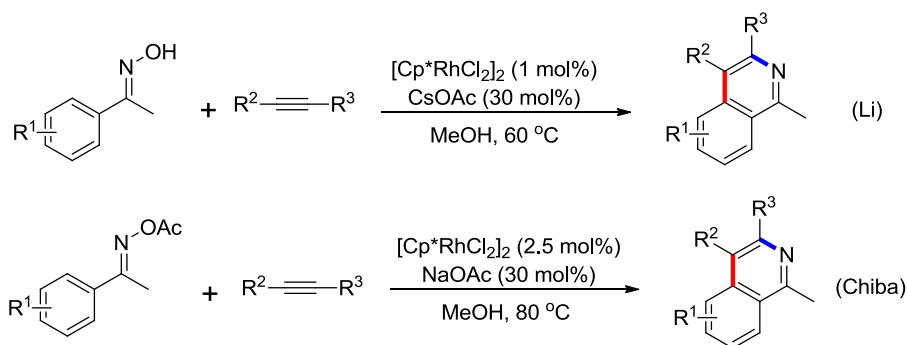
convenient method for the preparation of functional molecules.



Scheme 202 Palladium-catalyzed nitrate-promoted C-H bond fluorination.

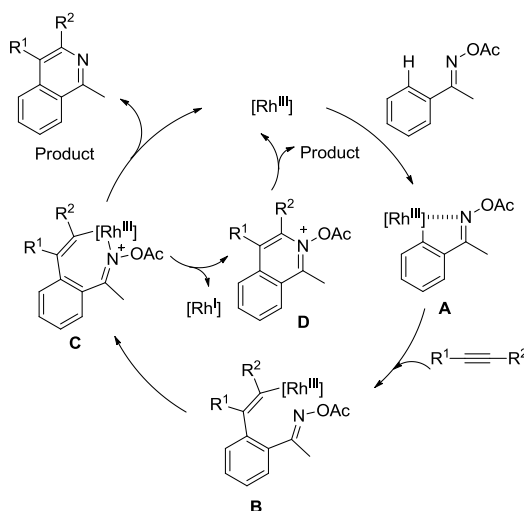
A palladium-catalyzed C-H bond fluorination under mild conditions in the presence of a catalytic amount of simple, cheap, and nontoxic nitrate as the promoter was developed by Xu and co-workers (Scheme 202).²⁸⁴ *O*-Methyl oxime ethers was chosen as an efficient directing group, and both aromatic and olefinic C(sp²)-H bond could be successfully selective fluorination in this transformation. The role of nitrate anion was deemed as a pivotal promoter in the reaction. The author speculated that a highly reactive cationic [Pd(NO₃)]⁺ species generated *in situ* from the Pd precatalyst and nitrate initiated the C-H bond activation process. This elegant selective fluorination reaction was also readily performed on gram scale and no decrease of the yield was observed.

Disulfides could also be used as effective coupling reagents in the Rh-catalyzed C-H thiolation of ketoximes reported by Zhou and Li.^{219a} The mono or dithiolation products were smoothly achieved with good selectivity by using of different oxidants in the reaction, affording a straightforward way for selective construction of aryl thioethers and dithioethers. A Rh(III)-catalyzed, chelation-assisted C-H activation and selenylation of arenes was reported by Wan and Li.²⁸⁵ The oxime, azo, pyridyl and *N*-oxide all could be used as useful directing groups, and electrophilic selenyl chlorides and diselenides were employed as selenylating reagents. The catalytic transformation could tolerate a broad range functional groups and exhibited high efficiency under mild conditions.



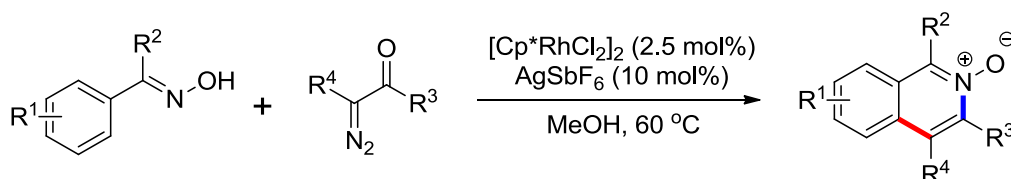
Scheme 203 Rhodium(III)-catalyzed synthesis of isoquinolines.

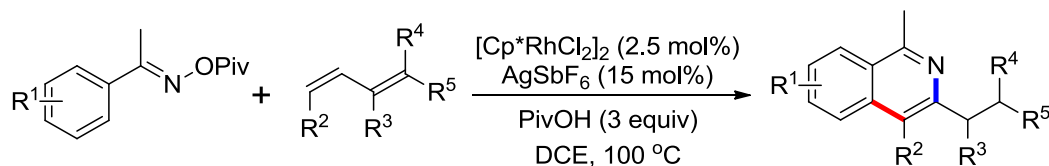
Although the previous Rh-catalyzed oxidative coupling reactions of aryl imines and internal alkynes were extensively investigated, the stoichiometric addition of external oxidants, such as $\text{Cu}(\text{OAc})_2$, was necessary for the reaction to regenerate the active Rh(III) catalyst. The N-O bond of oxime derivatives could act as an internal oxidant to maintain the catalytic cycle, thus providing a redox-neutral reaction condition.²⁸⁶ In 2010, Li^{286d} and Chiba²⁸⁷ independently reported a synthetic method for the synthesis of isoquinolines from aryl ketone oxime derivatives and internal alkynes under the catalytic redox-neutral $[\text{Cp}^*\text{RhCl}_2]_2\text{-NaOAc}$ system (Scheme 203). Several control experiments were performed to shed light on the reaction mechanism and the results revealed that the catalytic cycle was initiated by C-H rhodation process and the C-H activation was likely the rate-determining step.



Scheme 204 Proposed mechanism for the Rh(III)-catalyzed synthesis of isoquinolines.

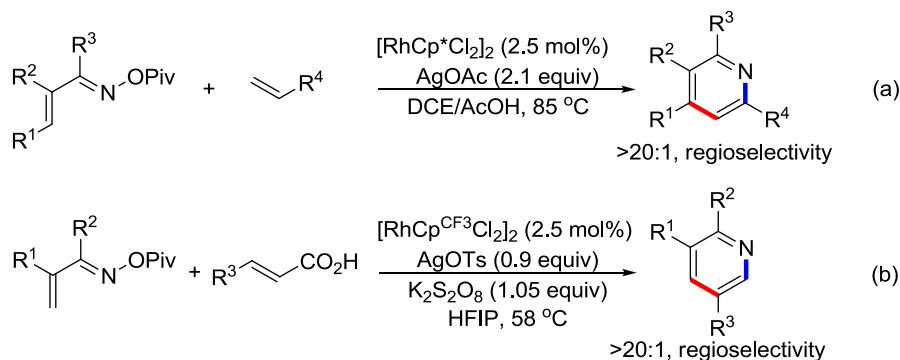
Based on the mechanistic investigations and the relevant results, a plausible mechanism was outlined in Scheme 204. The initial coordination of *O*-acetyloximes with Rh(III) led to the generation of arylrhodium intermediate **A**, followed by insertion into alkynes to afford vinyl rhodium species **B**. The subsequent intramolecular annulation and reductive elimination would provide the *N*-acetoxyisoquinolinium cation **D**, which could serve as an oxidant for the regeneration of the Rh(III) catalyst and afforded the isoquinoline as the final product.



Scheme 205 Rhodium(III)-catalyzed synthesis of isoquinolines *N*-oxides.**Scheme 206** Rhodium(III)-catalyzed synthesis of isoquinolines with diverse 1,3-dienes.

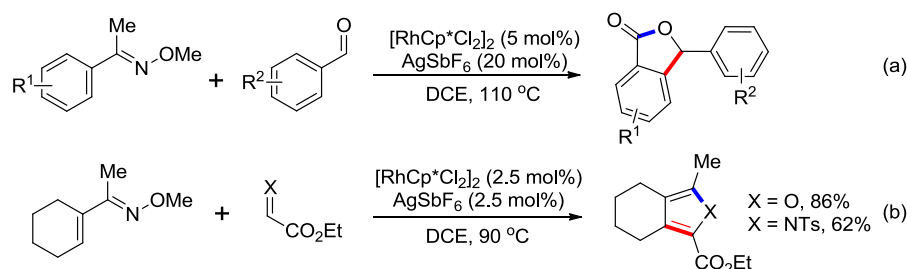
Glorius and co-workers reported the Rh(III)-catalyzed coupling reaction of oximes and diazo compounds to afford multisubstituted isoquinoline and pyridine *N*-oxides (Scheme 205).^{71d} The employment of diazo compounds could act as the equivalents of electron-deficient alkynes in Rh(III)-catalyzed isoquinoline synthesis. Other noteworthy advantages of the reaction were the high regioselectivities and reactivities. This elegant intermolecular annulation reaction for the synthesis of isoquinoline and pyridine *N*-oxides presumably underwent tandem C-H activation, cyclization, and condensation steps in the absence of any external oxidants.

Subsequently, the same group developed a Rh(III)-catalyzed C-H functionalization/aromatization cascade of the aromatic oxime esters with diverse 1,3-dienes to prepare isoquinolines with complete regioselectivity (Scheme 206).²⁸⁸ A variety of important functional groups were compatible, such as halogens (F, Cl, and Br), cyano, nitro, trifluoromethyl, and methoxy groups.

**Scheme 207** Rh(III)-catalyzed substituted pyridines synthesis.

Very recently, Rovis demonstrated the rhodium-catalyzed coupling of α , β -unsaturated oxime esters and alkenes to provide pyridines (Scheme 207a).²⁸⁹ The authors found that high regioselectivity of 6-substituted pyridines could be achieved when electron-deficient alkenes were used as coupling reagents, while unactivated alkenes resulted

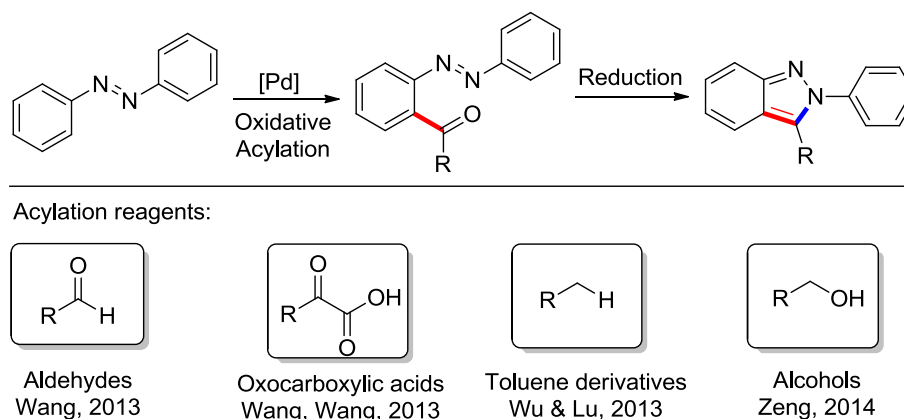
in the mixture of regioisomeric products. They also developed the synthesis of pyridine via the Rh(III)-catalyzed decarboxylative coupling of acrylic acids with unsaturated oxime esters. The carboxylic acid, which would be removed by decarboxylation, served as a traceless activating group, giving 5-substituted pyridines with high regioselectivity. Potassium persulfate ($K_2S_2O_8$) was selected as the best oxidant to avoid the use of superstoichiometric silver reagents, which was usually necessary for the decarboxylation step (Scheme 207b).²⁹⁰



Scheme 208 Rhodium(III)-catalyzed cascade addition and cyclization of benzimidates.

The [3+2] annulation pathway of oxime-directed C-H functionalization to afford phthalide by the use of aldehydes as coupling reagents was demonstrated by Bergman and Ellman (Scheme 208a).²⁹¹ The imine directing group served to capture the alcohol intermediate upon reversible aldehyde addition. Afterwards, the strategy was applied in the synthesis of furans and pyrroles by the same group (Scheme 208b).²⁹² The annulation was initiated by the rhodium(III)-catalyzed addition of an alkenyl C-H bond across an aldehyde C=O or imine C=N bond with subsequent cyclization and aromatization. Annulations with ethyl glyoxylate and the corresponding *N*-tosyl imine provided access to 2-carboxyethyl-substituted furans and pyrroles, respectively. More recently, Li and co-workers demonstrated that isocyanates could be applied in the synthesis of 3-methyleneisindolin-1-ones using aryl ketone *O*-methyl oximes as directing groups via a cascade annulation.²⁹³

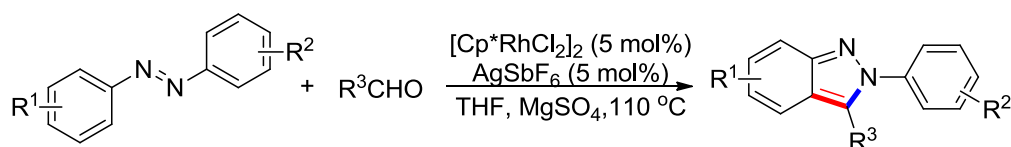
3.4 The C-H functionalization directed by diazo group



Scheme 209 Direct access to acylated azobenzenes via Pd-catalyzed C-H functionalization.

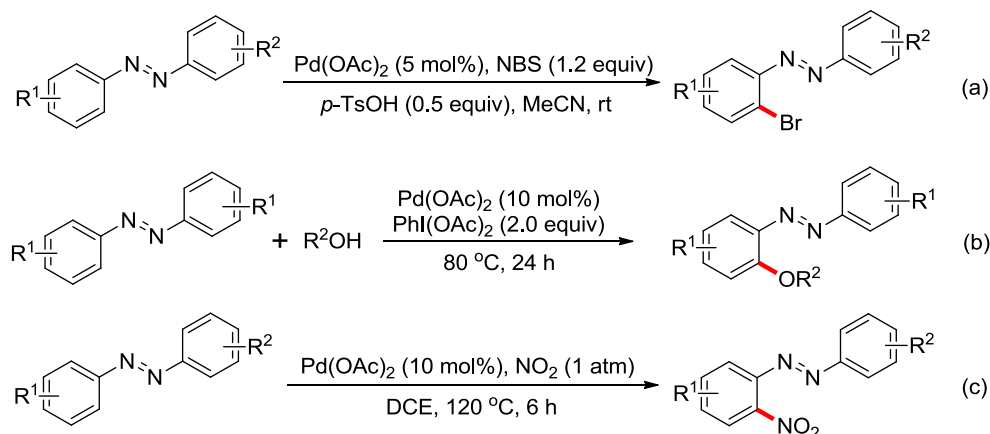
Due to the unique structures of azo moiety in the field of dyes, indicators, photochemical switches and the therapeutic agents, the methods to synthesize *ortho*-substituted azo compounds via C-H activation have been developed in recent years. In the early work by Sanford, the N=N bond of azo group was used as a directing group in the palladium-catalyzed acetoxylation of (*E*)-1,2-diphenyldiazene with $\text{PhI}(\text{OAc})_2$ in CH_3CN at $100\text{ }^\circ\text{C}$.²⁷⁵ Recently, various coupling reagents were developed in the palladium-catalyzed acylation of azobenzenes (Scheme 209).²⁹⁴ For example, Wang demonstrated that azobenzenes could be readily acylated at the *ortho* position through the azo-directed C-H activation.^{294a} The key step of the mechanism was the oxidation of clopalladated intermediate by the reactive benzoyl radical, which was generated from the reaction of benzaldehyde with TBHP. Both electron- and electron-withdrawing groups were tolerated under the acylation conditions. The resulting acylated azobenzenes could be further transformed into synthetically important indazoles through a $\text{Zn}/\text{NH}_4\text{Cl}/\text{MeOH}$ reduction in high yields. They also demonstrated that the α -oxocarboxylic acids could be used as coupling reagents in the palladium-catalyzed decarboxylative *ortho*-acylation of azobenzenes at room temperature.^{294b-d}

Due to the improved stability and availability, much attention has been paid to the use of toluene and its derivatives as acylation reagents. Lu and Wu independently realized the regioselective acylation of azobenzene with toluene, in which the key benzoyl radical was formed in situ from the oxidation of toluene.²⁹⁵ Readily available alcohols were further used as the acyl sources by Zeng and co-workers.²⁹⁶ Notably, the substrate scope could be extended to heteroaryl methanols and aliphatic alcohols, albeit giving low yields.



Scheme 210 Rhodium(III)-catalyzed indazole synthesis.

The direct synthesis of indazole was developed from the rhodium(III)-catalyzed addition of azobenzenes to aldehydes by Ellman and co-workers (Scheme 210).²⁹⁷ The azo moiety served as not only a directing group, but also a nucleophile to trap the initial aldehyde addition product. The regioselective functionalization of unsymmetrical azobenzenes could be controlled by either electronic or steric effects. The major product was obtained by C-H functionalization on the less electron-rich phenyl ring of the azobenzene except for the 4-nitro derivatives. But when *meta*-substitution was introduced to the azobenzene, the C-H activation occurred at the less hindered arene, in which the selectivity was determined by steric effects. A broad range of aldehydes and azobenzenes could participate in the reaction to provide access to a variety of substituted indazoles.

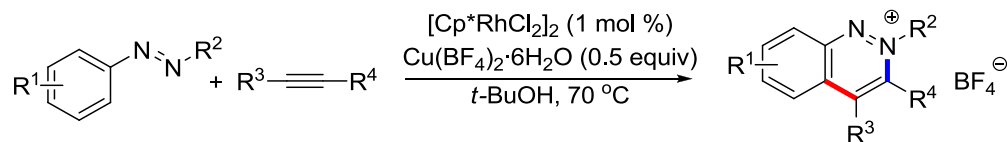


Scheme 211 Palladium-catalyzed direct *ortho*-functionalization of aromatic azo compounds

Tian and co-workers demonstrated the palladium-catalyzed regioselective halogenation of aromatic azo compounds by the use of *N*-bromo-succinimide at room temperature (Scheme 211a).²⁹⁸ The substrate scope was extended to unsymmetrical aromatic azo compounds, in which electron-rich aryl groups prefer to be mono-brominated.

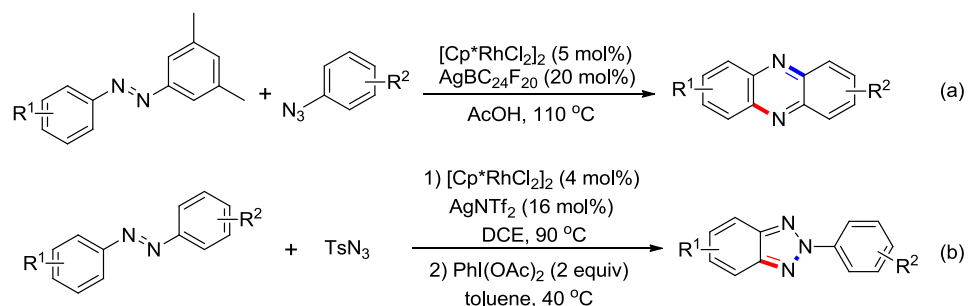
By the use of $\text{PhI}(\text{OAc})_2$ as oxidants, Sun and co-workers realized the palladium-catalyzed *ortho*-alkoxylation of aromatic azo compounds with both primary and secondary alcohols via Pd(II)/Pd(IV) catalytic cycle (Scheme 211b).²⁹⁹ The same group also reported the palladium-catalyzed direct *ortho*-nitration reaction of azoarenes in which NO_2

was used as both nitro source and oxidant for the first time (Scheme 211c).³⁰⁰ When unsymmetrical azoarenes were employed, the reaction took place exclusively on the benzene ring with an electron-donating group in moderate to good yields. The nitration products could be converted into *O*-aminoazoarenes or benzotriazole derivatives by zinc.



Scheme 212 Rhodium(III)-catalyzed synthesis of cinnolinium salts.

Cheng and co-workers developed a rhodium-catalyzed synthesis of cinnolinium salts from azobenzenes and alkynes in good yields (Scheme 212).^{301a} The successful isolation of a five-membered rhodacycle and the result of the subsequent stoichiometric reaction sufficiently supported the proposed C-H activation process. Interestingly, the isomeric ratio of the product using unsymmetrical alkynes appeared to be sensitive to the used metal oxidant, in which a combination of AgBF_4 and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ could greatly improve the regioselectivity. Almost at the same time, a rhodium(III)-catalyzed oxidative C-H activation/cyclization of azo compounds with alkynes for the synthesis of cinnoline and cinnolinium frameworks was demonstrated by You and co-workers.^{301b}

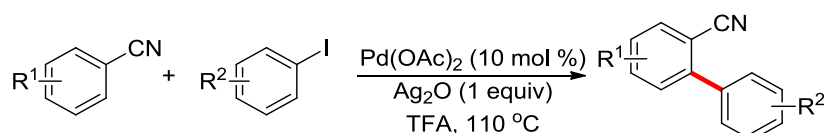


Scheme 213 Rh(III)-catalyzed synthesis of unsymmetrical phenazines.

The [3+3] annulations of aromatic azides with azobenzenes to give phenazines was reported by Ellman (Scheme 213a).³⁰² The transformation proceeded through chelation-assisted *ortho*-amidation, the intramolecular electrophilic aromatic substitution, and aromatization processes. An additional acid was essential for the protonation of rhodacycle intermediate and the electrophilic substitution step. When unsymmetrical azobenzenes were used, regioselective C-N bond formation occurred in the electron-deficient arene. In addition to the azobenzenes, the annulation of aromatic azides with aromatic imines

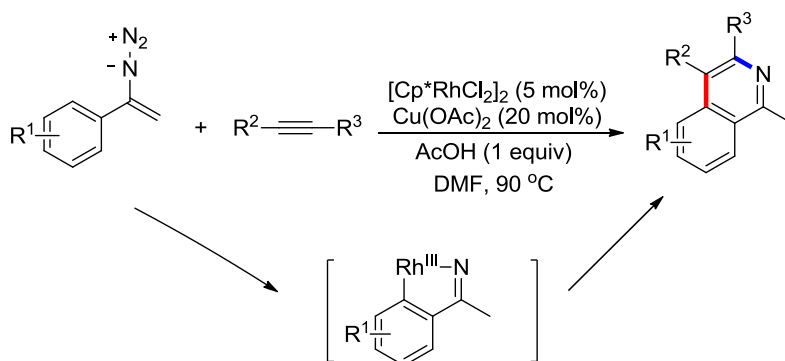
to afford acridines was also demonstrated. In 2014, Lee and other groups further studied the synthesis of benzotriazoles from azobenzenes with *N*-sulfonyl azides. The amidated azobenzenes could go through the subsequent oxidative cyclization in the presence of $\text{PhI}(\text{OAc})_2$ to provide the benzotriazoles in one pot (Scheme 213b).^{303c}

3.5 The C-H functionalization directed by other nitrogen-containing unsaturated bond



Scheme 214 Palladium-catalyzed arylation using cyano as a directing group.

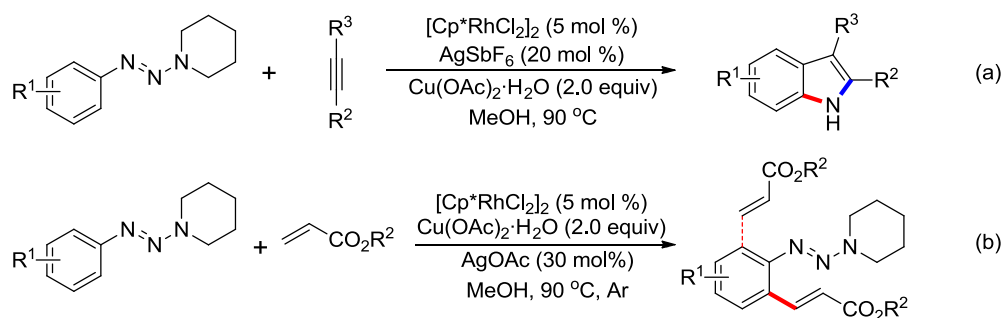
The coordination ability of nitrogen atom in unsaturated bond with transition metals was widely investigated in chelation-assisted C-H functionalizations. Much effort was made by Sun and co-workers, who studied the synthesis of biphenyl-2-carbonitrile derivatives via a palladium-catalyzed C-H arylation of aryl nitriles with aryl halides using cyano as the directing group (Scheme 214).³⁰⁴ Due to the linear configuration of aryl nitriles, it was proposed that the coordination of the π -electron between carbon and nitrogen to palladium was possible. An acidic medium was necessary to promote the transformation and TFA was used as the best solvent. When common functional groups were introduced to the substrates, the directing effect of the cyano group was not influenced. Subsequently, the palladium-catalyzed *ortho*-alkoxylation³⁰⁵ and halogenations³⁰⁶ of aryl nitrile were developed by the same group.



Scheme 215 Rh-catalyzed synthesis of isoquinolines from α -aryl vinyl azides.

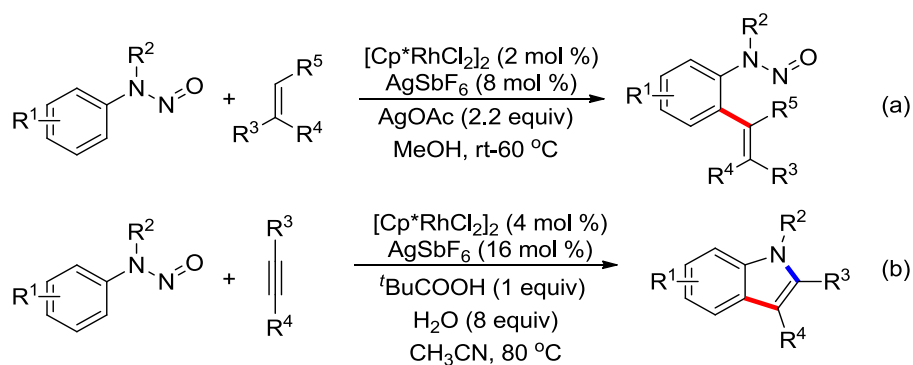
Chiba and co-workers reported the synthesis of highly substituted isoquinolines from

α -aryl vinyl azides and internal alkynes under a rhodium/copper bimetallic catalytic system (Scheme 215).³⁰⁷ The addition of acetic acid (1 equiv) proved to be optimal for the isoquinoline formation, which could reduce the reaction temperature. This method showed wide substrate tolerance for unsymmetrical alkyne, resulting in isoquinoline formation in a regioselective manner. The authors proposed that the reductive formation of imine derivatives from vinyl azides could serve as directing groups to generate a rhodacycle intermediate, which might be followed by a C-C and C-N bond formation sequence to form aza-heterocyclic frameworks.



Scheme 216 Synthesis of indoles through triazene-directed C-H annulations.

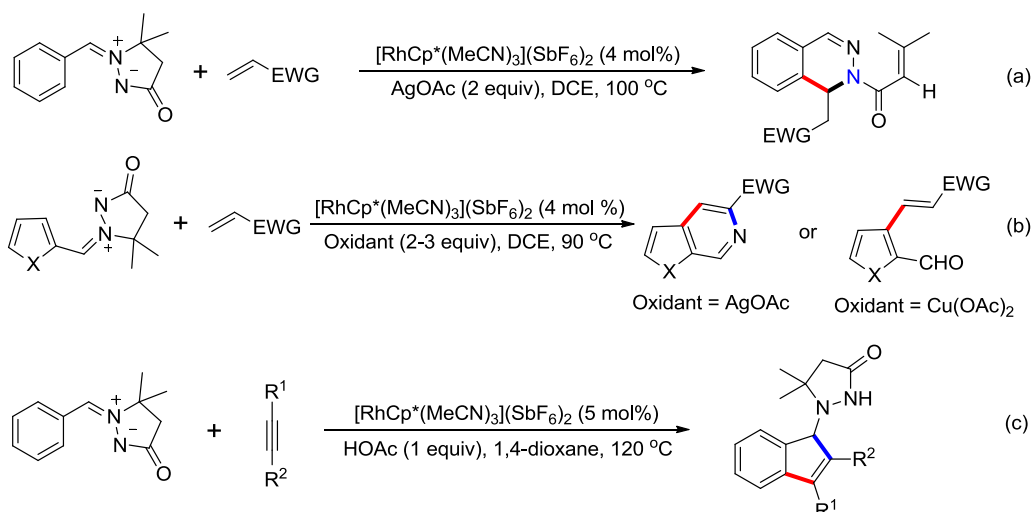
Recently, Wang and co-workers developed a strategy to synthesis indoles through rhodium catalyzed triazene-directed C-H annulation using alkyne (Scheme 216a).³⁰⁸ They proposed that an active Rh(III) acetate species was generated from [Cp*RhCl₂]₂, AgSbF₆, and copper acetate, which could coordinate to the middle nitrogen atom of the triazene moiety. The value of KIE ($k_H/k_D=2.7$) indicated that the C-H activation was the rate-determining step. The N-N bond cleavage might be promoted by HOAc that was in situ generated in the reaction. Excellent regioselectivity was achieved by asymmetrically substituted alkyne. They studied the rhodium-catalyzed olefination of aromatic C-H bond using triazene as a directing group later (Scheme 216b).³⁰⁹ The triazene directing group could be conveniently removed or further transformed into other useful functional groups.



Scheme 217 Rhodium(III)-catalyzed *N*-nitroso-directed C-H olefination of arenes.

The coordination characteristics of the *N*-nitroso moiety as directing group was investigated in the Rh(III)-catalyzed functionalization of arenes.³¹⁰⁻³¹¹ Zhu and co-workers found the unique coordination characteristics of the *N*-nitroso group could enable the use of the unactivated olefins as coupling reagents (Scheme 217a).³¹⁰ During the mechanistic studies, a five-membered rhodacycle was prepared and characterized, in which the nitrogen atom of nitroso coordinated to the Rh centre. The intermolecular kinetic isotope effect experiment gave a KIE value of 4.5, indicating that the C-H activation might be involved in the turnover-limiting step. The synthetic versatility of this method was further demonstrated by the transformation of the *N*-nitroso moiety to amine with high efficiency under mild conditions.

Zhu group and Huang group independently investigated the Rh-catalyzed synthesis of indole from *N*-nitrosoanilines and alkynes (Scheme 217b).³¹² The N-N bond of *N*-nitrosoanilines served as an intramolecular oxidant, which was also observed when *O*-methyl oxime was used as the directing group.²⁸⁶ The electron-rich and electron-deficient substrates showed the equal reactivity in the competition experiment, which supported the concerted metalation-deprotonation (CMD) reaction pathway.



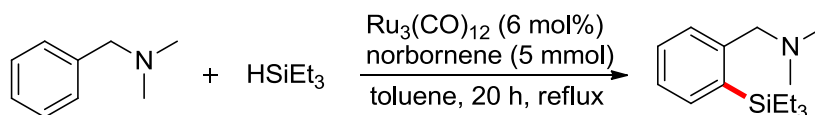
Scheme 218 Rhodium(III)-catalyzed oxidative C-H functionalization of azomethine ylides

In 2012, Li and co-workers reported the Rh(III)-catalyzed oxidative coupling of azomethine ylides with olefins (Scheme 218a,b).^{313a} Depending on the following cascade reactions, the cleavage of C-N or N-N bonds in the azomethine ylides of (hetero)arylaldehydes after the C-H activation was occurred. For example, azomethines of benzaldehydes went through selective C-H and C-N cleavage to produce 1,2-dihydrophthalazines. When different oxidant was used in the reaction, the pyridine or aldehyde derivatives could be smoothly afforded by C-H and N-N cleavage of azomethines of heteroaldehydes. Later, Li and co-workers developed a rhodium(III)-catalyzed oxidative annulation of azomethine ylides with alkynes via C-H activation for the synthesis of indenamines (Scheme 218c).^{313b} The obtained indenamine product could readily be oxidized to an indenone and derivatives under aerobic conditions.

4 The C-H functionalization directed by amine

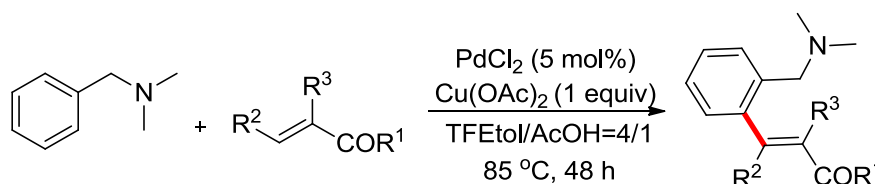
4.1 The C-H functionalization directed by *N,N*-dimethylamino group

Amines are common structural units in both naturally occurring molecules and pharmaceutical agents. The large applications of amines in synthetic, medicinal, materials, and coordination chemistry have fueled interest in the development of methods for their construction. However, the involvement of amines as a directing group in directed C-H functionalization is relatively less studied due to its property of strong Bronsted base.

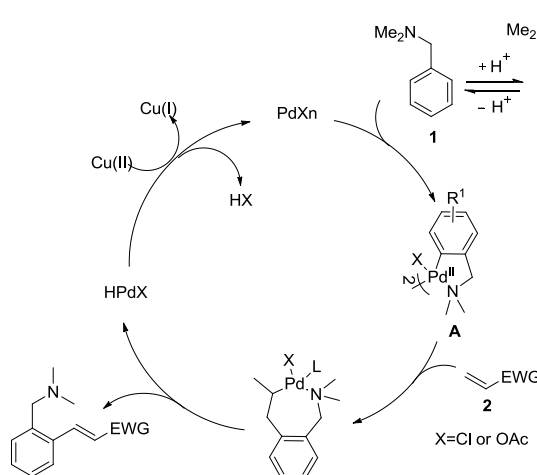


Scheme 219 The *ortho*-silylation of *N,N*-dimethylbenzylamine with triethylsilane.

The first example of utilizing amine as the directing group was reported by Murai and co-workers in 2002 (Scheme 219).³¹⁴ By the use of *N,N*-dimethylaminomethyl group as the directing group, they achieved a Ru-catalyzed C-H silylation reaction of *N,N*-dimethyl-1-phenylmethanamine with triethylsilane via non- π -conjugated chelation-assistance. The norbornene functioned as a hydrogen scavenger and facilitated the reaction process. The result of reaction demonstrated that a catalytic reaction involving aromatic C-H bond cleavage could proceed smoothly, albeit in the non- π -conjugated chelation-assistance manner. It was believed that this protocol was the first example of transition-metal-catalyzed directed C-H functionalization using *N,N*-dimethylbenzylamine as the directing group.



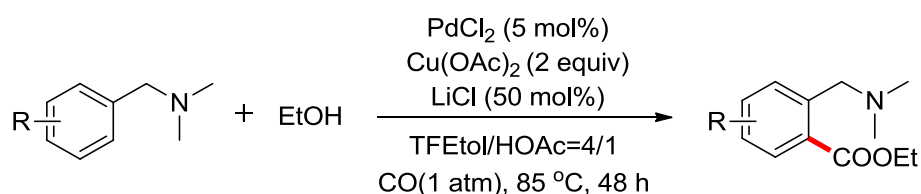
Scheme 220 Pd-catalyzed *ortho*-olefination of *N,N*-dimethylbenzylamine.



Scheme 221 Proposed mechanism of *ortho*-olefination of *N,N*-dimethylbenzylamine.

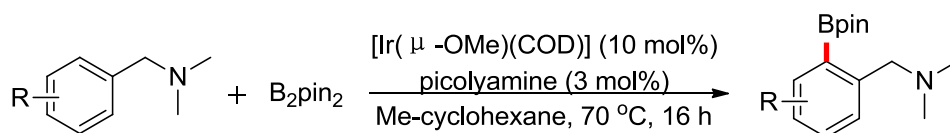
Inspired by Murai's work, the Pd-catalyzed regioselective olefination of substituted *N,N*-dimethylbenzylamines via directed C-H functionalization was developed by Shi and co-workers (Scheme 220).³¹⁵ The acidity of the reaction conditions had a huge influence on the efficiency of the reaction due to the strong Brønsted base property of the

N,N-dimethylbenzylamines. After detailed screening, the combination of 2,2,2-trifluoroethanol (TFEtol) and AcOH was chosen as the best solvent system for the transformation. Mechanistic studies indicated that electrophilic attack on the phenyl ring by the Pd(II) ion assisted by the *N,N*-dimethylaminomethyl group to form intermediate **A** was a key step. The acetic acid played dual important role: tuning the concentration of *N,N*-dimethyl amines through acid-base balance and promoting the dissociation of the anionic ligand from the catalyst center to generate coordinately unsaturated and reactive catalyst species for C–H activation (Scheme 221). In addition, the *N,N*-dimethylaminomethyl group could be further transformed into different useful functional groups.



Scheme 222 Pd(II)-catalyzed *ortho*-carbonylation of *N,N*-dimethylbenzylamines.

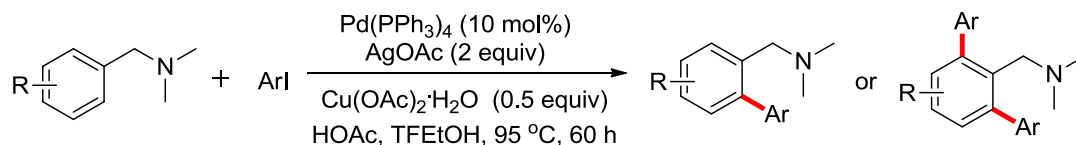
Subsequently, Shi and co-workers developed a LiCl-promoted Pd(II)-catalyzed highly regioselective *ortho*-carbonylation of *N,N*-dimethylbenzylamines via selective aryl C–H activation (Scheme 222).³¹⁶ Compared to Pd(II)-catalyzed other transformations, the carbonylation still faced many challenges because the depalladation process was complicated by reduction of Pd(II) to Pd(0) under CO atmosphere. Further hydrogenation of desired product could achieve *ortho*-methyl benzoate derivatives in one pot. In the reaction, LiCl was found to be the most effective additive and was regarded as Lewis acid to promote the insertion of CO into C–Pd bond. The successful control of the reactivity and binding ability of *N,N*-dimethylbenzylamine through tuning the acidity of the reaction system was crucial.



Scheme 223 Iridium-catalyzed directed C–H borylation.

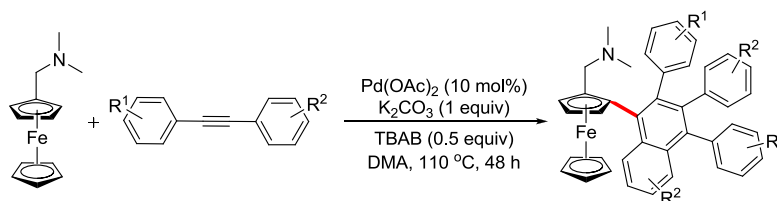
An iridium-catalyzed C–H borylation reaction of benzylic amines using picolyamine as the effective ligand to provide *ortho*-substituted boronate esters was reported by Clark and co-workers (Scheme 223).³¹⁷ The reaction generally featured good yields and high selectivities of the mono *ortho*-borylation products when a basic amine ligand was employed.

Preliminary experiments demonstrated that the partial dissociation of one amine of the hemilabile diamine ligand was necessary for providing the coordination site for *ortho* C-H borylation.



Scheme 224 Palladium-catalyzed C-H *ortho*-arylation of *N,N*-dimethylbenzylamines.

Based on Shi's olefination of *N,N*-dimethylbenzylamines, Zhang and co-workers developed a Pd-catalyzed C-H *ortho*-arylation of various arenes directed by *N,N*-dimethylaminomethyl group (Scheme 220).³¹⁸ The protocol allowed the *ortho*-diarylation of *p*-substituted *N,N*-dimethylbenzylamine using various aryl iodide as coupling partner in the presence of AgOAc and Cu(OAc)₂·H₂O. The exclusive monoarylation of the *meta*-substituted arenes occurred at the less hindered *ortho* position of the dimethylaminomethyl groups owing to the steric effect. The addition of Cu(OAc)₂·H₂O was quite important to the high efficiency of this transformation.

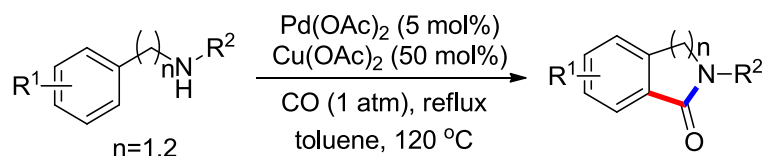


Scheme 225 Pd-catalyzed annulation reaction of *N,N*-dimethylaminomethylferrocene.

A new Pd-catalyzed direct dehydrogenative annulations of *N,N*-dimethylaminomethyl ferrocene with internal alkynes to afford a wide range of ferrocene functionalized naphthalenes was developed by Wu, Cui and co-workers (Scheme 225).³¹⁹ The relatively high reaction temperature was beneficial for the rapid conversion of the substrates and the air was necessary for this transformation. Mechanistic studies demonstrated that *N,N*-dimethylaminomethyl ferrocenium was generated *in situ* and served as a terminal oxidant. This procedure utilized the redox activity of ferrocene to make this approach “greener” and easier to handle. Ferrocene functionalized naphthalenes could also be widely applied in π -conjugated functional materials. Recently, the Pd(II)-catalyzed enantioselective C-H direct acylation of ferrocene derivatives utilizing diphenyl diketone as carbonyl source was developed by Wu and co-workers.³²⁰ A variety of 2-acyl-1-dimethylaminomethyl ferrocenes

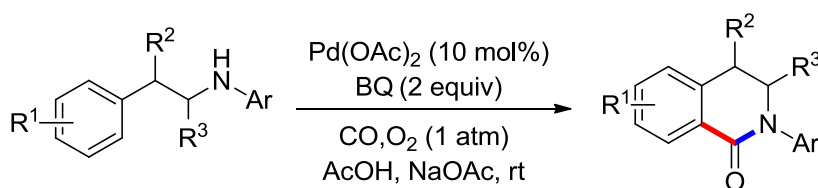
with planar chirality were produced with high enantioselectivity. Additionally, an enantioselective palladium-catalyzed direct functionalization of aminomethylferrocene derivatives with boronic acids was realized by You and Gu.³²¹ Commercially available amino acid Boc-L-Val-OH was found to be the most effective ligand in terms of enantioselectivity and reactivity. This transformation provided a general and practical route for the synthesis of enantiopure ferrocene compounds.

4.2 The C-H functionalization directed by secondary amine



Scheme 226 Pd(II)-catalyzed direct carbonylation for the preparation of benzolactams.

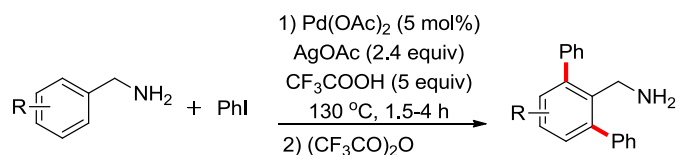
The secondary amine also can be used as a directing group for *ortho* C-H activation. In 2004, Orito and co-workers described a Pd-catalyzed direct aromatic carbonylation in an atmosphere of CO gas (Scheme 226).³²² A broad series of five- or six-membered benzolactams from secondary ω -phenylalkylamines was afforded in high yields. It was proposed that this carbonylation process started from well known *ortho*-palladation and the subsequent insertion of a molecular CO into the resultant cyclopalladation product resulted in the formation of an acylpalladium complex. After a nucleophilic attack of an internal amino group to the carbonyl group, the desired benzolactam products were obtained.



Scheme 227 Pd(II)-catalyzed C-H bond functionalization directed by amine.

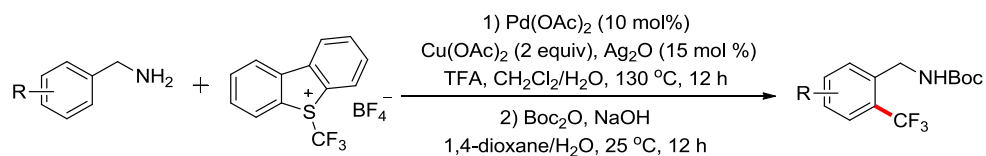
A Pd(II)-catalyzed C-H bond carbonylation and intramolecular cyclization of β -arylethylamines for the synthesis of a diversity of dihydro-2-quinolones was presented by Gaunt and co-workers (Scheme 227).³²³ The carbonylation reaction proceeded smoothly at room temperature and tolerated complex functionality and stereocentres. The use of AcOH as solvent was supposed to suppress the CO mediated reduction of the Pd(II) to palladium black. This useful protocol provided more opportunities for synthetic application of β -arylethylamine motifs.

4.3 The C-H functionalization directed by free amine



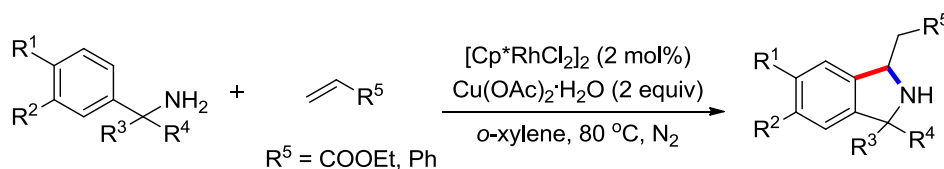
Scheme 228 Direct palladium-catalyzed *ortho*-arylation of benzylamines.

Free amine could be also used as a directing group in catalytic C-H functionalizations. In 2006, Daugulis and co-workers reported a direct Pd-catalyzed *ortho*-arylation of benzylamines in the presence of AgOAc and CF₃COOH (Scheme 228).³²⁴ The reaction proceeded well in trifluoroacetic acid and the amount of acid strongly influenced the reaction. In order to study the properties of directing groups, *N*-trifluoroacetylbenzylamine was treated with iodobenzene under the standard reaction conditions. The desired arylation product did not observed, indicating the free amine should be the directing group.



Scheme 229 Pd(II)-catalyzed *ortho*-trifluoromethylation of benzylamines.

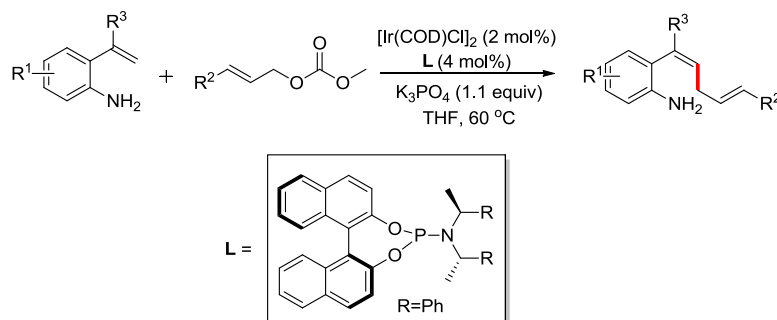
Recently, a Pd(II)-catalyzed *ortho*-C-H trifluoromethylation of *N*-unsubstituted benzylamines utilizing an electrophilic CF₃ reagent was reported by Yu and co-workers (Scheme 229).³²⁵ The presence of H₂O and Ag₂O proved to be crucial for the high yields of the reaction. The oxidative addition of electrophilic trifluoromethylation reagent to the [Ar-Pd(II)] species led to the formation of an octahedral Pd(IV) intermediate and the reductive elimination afforded the final *ortho*-trifluoromethylation product. The reaction was expected to be applicable in medicinal chemistry to prepare diverse functionalized benzylamines.



Scheme 230 Rh-catalyzed dehydrogenative *ortho*-alkenylation of benzylamines.

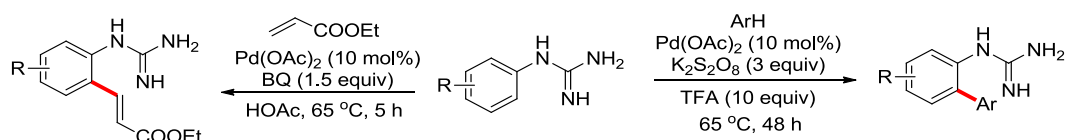
Recently, Miura and co-workers demonstrated that the dehydrogenative *ortho*-alkenylation and cyclization of α,α -disubstituted benzylamines with acrylates could be performed efficiently at room temperature by rhodium or ruthenium catalysis (Scheme

230).³²⁶ Notably, the styrenes could participate in this transformation to give the corresponding stilbenes smoothly by rhodium catalysis.



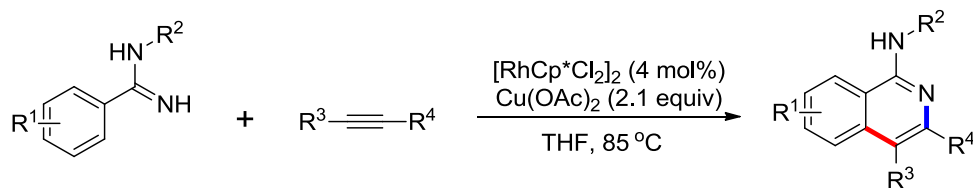
Scheme 231 Ir-catalyzed free amine directed vinyl C-H bond activation of styrenes.

An Ir-catalyzed cross-coupling of styrene derivatives with allylic carbonates via the free amine directed vinyl C(sp²)-H bond activation was originally developed by You and co-workers in 2009 (Scheme 231).³²⁷ The cross-coupling reaction proceeded well under the efficient catalytic system of [Ir(COD)Cl]₂/Feringa's ligand. The unprecedented skipped *Z*, *E* diene products were obtained instead of the possible amination product. Moreover, the *cis*-Heck-type product was formed exclusively and the example offered a complementary method for the preparation of the useful diene compounds. Subsequently, the same group also reported an iridium-catalyzed allylic vinylation and asymmetric allylic amination reactions with *o*-amino styrene derivatives.³²⁸



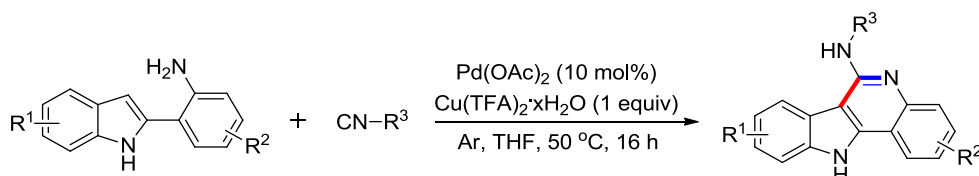
Scheme 232 Pd-catalyzed *ortho*-arylation and olefination of aryl guanidines.

Guanidines are important structural motifs and have been found wide applications in a range of biologically important molecules. In 2012, Yu and co-workers reported a Pd-catalyzed C-H functionalization method for arylation and olefination of arenes using guanidine as the directing group (Scheme 232).³²⁹ The combination of K₂S₂O₈ and TFA was vital for the high efficiency of the arylation, and in contrast, when BQ was identified as oxidant, the best results of olefination were given. It was proposed that the arylation reaction presumably underwent a Pd^{II}/Pd^{IV} pathway and the olefination seemed more likely to follow a Pd⁰/Pd^{II} catalytic cycle.



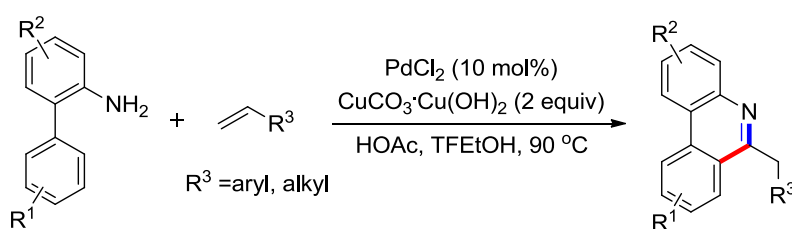
Scheme 233 Rh(III)-catalyzed synthesis of 1-aminoisoquinolines

A Rh(III)-catalyzed oxidative coupling of *N*-aryl and *N*-alkyl benzamidines with alkynes for the synthesis of *N*-substituted 1-aminoisoquinolines with high efficiency was developed by Li and co-workers (Scheme 233).³³⁰ A broad range of functionalized isoquinolines was afforded in moderated to good yields. It was noteworthy that the steric bulk of the C-aryl ring had a vital influence on the reaction selectivity and efficiency.



Scheme 234 Pd(II)-catalyzed cycloamidation with isocyanide insertion.

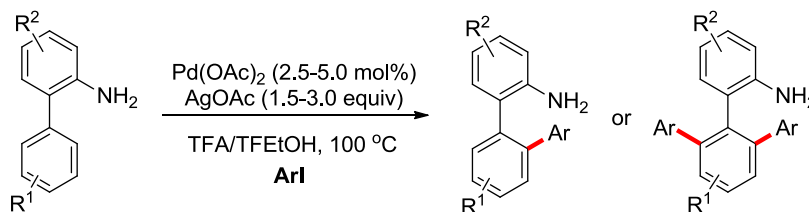
An efficient Pd(II)-catalyzed cycloamidation with isocyanide insertion for the synthesis of 6-aminoindolo[3,2-*c*]quinoline and 4-aminopyrrolo[1,2-*a*]quinoxaline derivatives was described by Zhu and co-workers (Scheme 234).³³¹ The reaction featured broad substrate scope and neutral as well as mild reaction conditions without the racemization of the chiral substrates. Diverse nitrogen heterocycles containing a cyclic amidine subunit could be afforded by this practical method.



Scheme 235 Free-amine-directed alkenylation of C(sp²)-H and cycloamination.

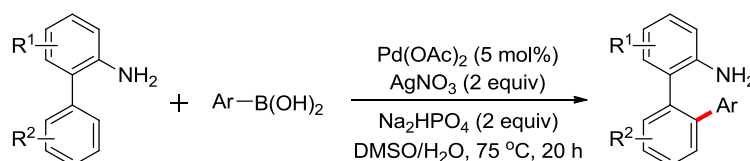
A new method for the palladium-catalyzed free-amine-directed alkenylation of C(sp²)-H bonds and cyclization to give the corresponding functionalized phenanthridines was described by Zhang (Scheme 235).³³² The reaction was highly regioselective and showed good functional-group tolerance. Various alkenes, including electron-deficient alkenes, styrenes and alkyl alkenes, could participate in this transformation. Moreover, the involvement of α -branched styrenes led to the formation of tricyclic compounds with a seven-membered

amine ring. The key six-membered palladacycle was successfully synthesized and shed light on the reaction mechanism. The kinetic isotope experiment indicated that the C-H cleavage might be involved in the catalytic alkenylation and proceed through an electrophilic palladation pathway.



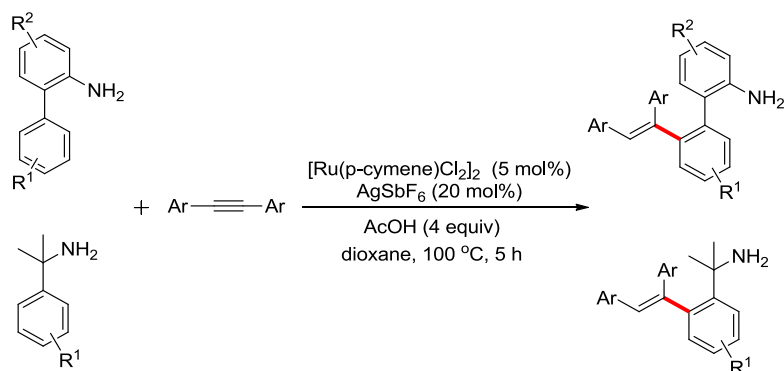
Scheme 236 Free-amine directed arylation of biaryl-2-amines.

Zhang group also developed an efficient protocol for Pd-catalyzed free-amine directed arylation of the C(sp²)-H bond by the use of aryl iodide as arylating agent in the presence of trifluoroacetic acid (Scheme 236).³³³ In this reaction, silver salt might act as a halide scavenger to improve the reaction. The reaction exhibited excellent reactivity and regioselectivity, and a wide range of mono- or diarylated products were prepared after the modification of reaction conditions.



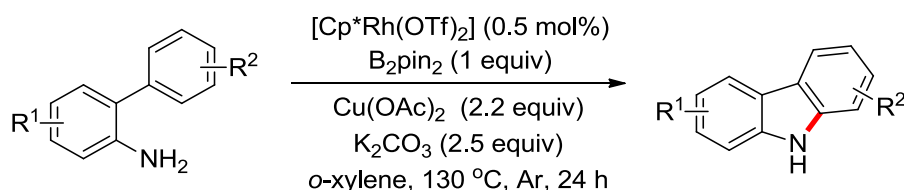
Scheme 237 Pd(II)-catalyzed arylation of arenes with a free amine as directing group.

They developed a palladium-catalyzed free-amine-directed Suzuki-Miyaura-type coupling reaction of biaryl-2-amines with aryl boronic acids in aqueous medium later (Scheme 237).³³⁴ The employment of soluble silver nitrate was a spotlight in the transformation. Silver nitrate was supposed to influence the reaction in two manners: acting as an oxidant to oxidize Pd⁰ to Pd^{II} and serving as a promoter to facilitate the cyclopalladation process. In the presence of silver salts and additional water, high reactivity and chemoselectivity for the formation of carbon-carbon bonds were achieved.



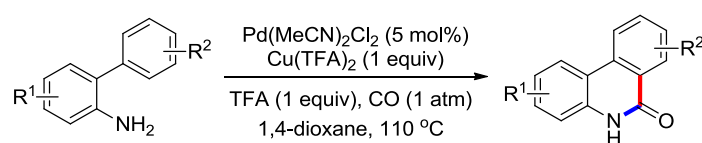
Scheme 238 Ru-catalyzed regioselective C-H alkenylation directed by a free amino group.

At the same time, the ruthenium-catalyzed alkenylation reactions of 2-aminobiphenyls and cumylamine with alkynes directed by free amine group was demonstrated by Murai and co-workers, producing the corresponding regioselectively alkenylated products with high efficiency (Scheme 238).³³⁵ The addition of AcOH was crucial for the reaction, which was supposed to facilitate the C-H bond activation step. Because of their biological activities, the obtained *ortho*-alkenylated α , α -dialkylbenzylamine derivatives including cumylamines had some potential applications in diverse functional molecules.



Scheme 239 Amino-directed Rh(III)-catalyzed synthesis of carbazoles.

A Rh-catalyzed amino-directed C-H bond borylation and Cu(II)-mediated ring closure of the resulting borylated anilines was developed by Yan and Chen to achieve N-H carbazole products (Scheme 239).³³⁶ This reaction adopted a free-amino group as the directing group to form a C-B bond, which undergo the copper-mediated formation of an intramolecular C-N bond. It was the first dehydrogenative cyclization of non-protected 2-aminobiaryl derivatives for the synthesis of medically important non-protected carbazoles in one-pot with good to excellent yields.



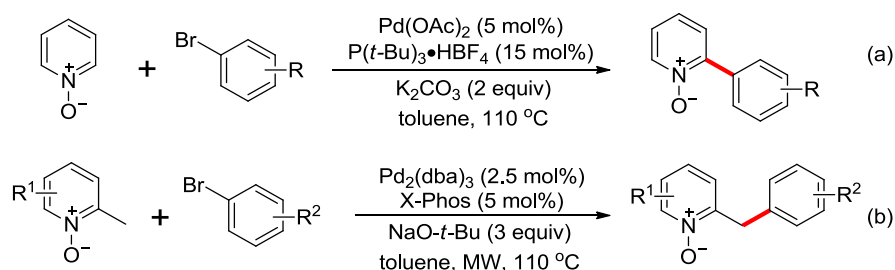
Scheme 240 Palladium-catalyzed C(sp²)-H aminocarbonylation of unprotected *o*-arylanilines.

A Pd-catalyzed C(sp²)-H aminocarbonylation reaction of unprotected *o*-arylanilines under an atmospheric pressure of CO using amine group as a directing group to prepare free

(NH)-phenanthridinones was reported by Zhu and co-workers (Scheme 240).³³⁷ The incompatibility of CO with the oxidative reaction conditions and the formation of urea byproduct were main obstacles in the C-H aminocarbonylation reaction in the presence of free amine group. The addition of 1 equivalent of TFA to increase the electrophilicity of the palladium(II) species might inhibit the side-reaction effectively. A wide variety of free (NH)-phenanthridinone derivatives were successfully synthesized by this strategy and the scope of the reaction could also extend to some *ortho*-heteroarene substituted anilines to give polyheterocycles containing a free (NH)-lactam moiety. Meanwhile, Zhang and co-workers reported a similar Pd-catalyzed aminocarbonylation of *o*-arylanilines under carbon monoxide atmosphere to synthesize various phenanthridinones.³³⁸

5 The C-H functionalization directed by polar N⁺-O⁻ bond

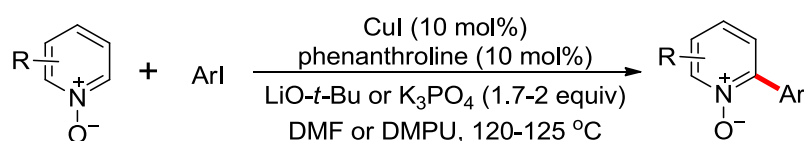
Pyridines are important heterocycles and widely presented in the natural products, pharmaceuticals, and functional materials. However, the *ortho*-functionalization of pyridines through electrophilic aromatic substitution is quite difficult due to its electron-poor nature. In recent years, the pyridine *N*-oxides have served as an attractive platform for the regioselective functionalization of pyridines via transition metal-catalyzed C-H bond cleavage.³³⁹



Scheme 241 Palladium-catalyzed arylation of pyridine *N*-oxides.

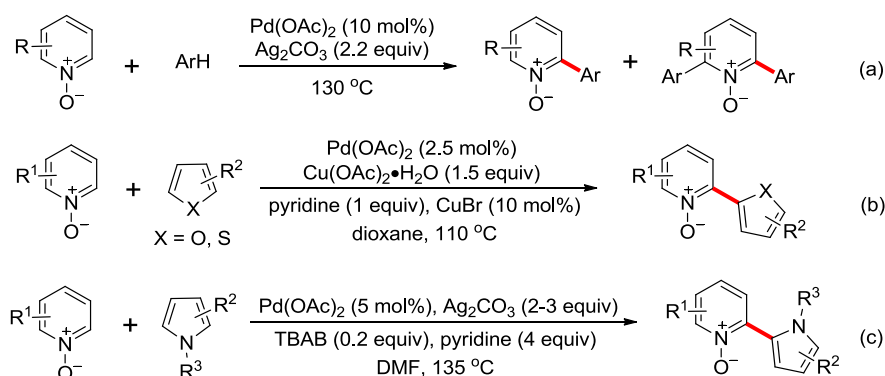
In 2005, Fagnou and co-workers disclosed the palladium-catalyzed regioselective arylation of pyridine *N*-oxides, in which the arylation occurred in excellent yields with complete selectivity at the 2-position with a wide range of aryl bromides (Scheme 241a).^{340a} The presence of both electron-donating and withdrawing groups on the pyridine *N*-oxide made little difference on the efficiency of the transformation. The detected value of intermolecular primary KIE was 4.7, which indicated that the C-H bond cleavage might be involved in the rate-limiting step. Further investigation of mechanism by Fagnou and others revealed that the reaction may undergo a concerted metallation-deprotonation pathway.^{340b-340c}

This palladium-catalyzed direct arylation could also be performed with a broad range of azine and azole *N*-oxides. The arylation of benzylic C(sp³)-H bonds of pyridine *N*-oxides was demonstrated by the same group (Scheme 241b).^{340d} In this case, the arylation took place at the 2-methyl position of pyridine *N*-oxide rather than the *ortho* C(sp²)-H bond, which might be attributed to the easier deprotonation of more acidic benzylic C(sp³)-H bonds under the strong NaO*t*-Bu. The sequential sp²/sp³ arylation of pyridine *N*-oxides under controlled reaction conditions has been achieved by the authors, which was important for the derivation of heterocyclic compounds.



Scheme 242 Copper-catalyzed arylation of pyridine *N*-oxides.

The copper-catalyzed arylation of pyridine *N*-oxide using aryl iodide as coupling reagent was reported by Daugulis and co-workers in 2007 (Scheme 242).^{341a} The acidic pyridine *N*-oxides could be arylated at the 2-position with high selectivity using K₃PO₄ base. If the substrates were less acidic (PK_a 27-35), a stronger lithium alkoxide base was required. A phenanthroline ligand was necessary for this efficient transformation, which could stabilize the copper catalyst and facilitate the halide displacement step. The extension of coupling reagents from aryl iodides to aryl bromides in this arylation was realized by You and co-workers,^{341b} in which pyridine, quinoline, and 2-*p*-tolylpyridine *N*-oxides could smoothly undergo the reaction to afford the desired products in moderate yields.

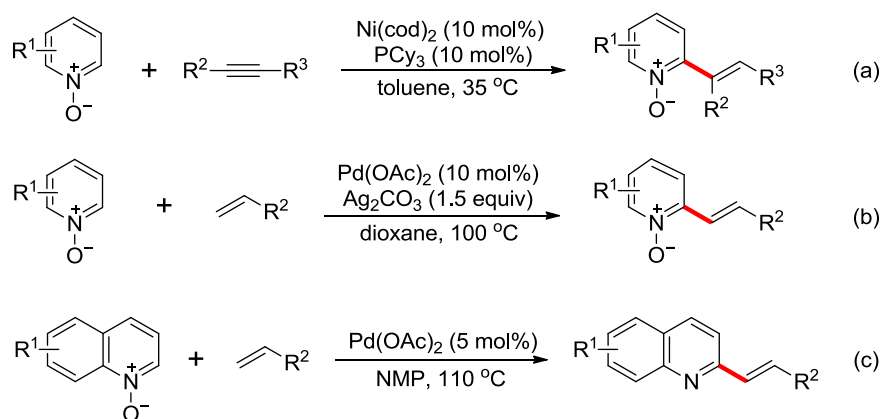


Scheme 243 Palladium-catalyzed (hetero)arylation of pyridine *N*-oxides.

The application of unactivated arenes in the Pd-catalyzed C-H/C-H cross-coupling of pyridine *N*-oxides was reported by Chang and co-workers in 2008 (Scheme 243a).^{342a} In this

work, a range of simple arenes were suitable coupling reagents to give the corresponding monoarylated products with *N*-oxides of pyridine, pyrazine, quinoxaline, quinoline and benzo[h]quinolone at the *ortho*-position in good yields.

The thiophenes or furans were used as coupling reagents in the Pd(II)-catalyzed arylation of pyridine *N*-oxides by You group (Scheme 243b).^{342b} Stoichiometric Cu(II) salts was essential for the transformation and catalytic amount of CuBr was used as an activator to enhance the reactivity. Other *N*-oxides, such as pyrazine, quinoline and isoquinoline, were applicable to this transformation. Later on, the Pd(II)-catalyzed regioselective C3 heteroarylation of indoles and pyrroles with pyridine *N*-oxides was demonstrated by Li and co-workers. (Scheme 243c).^{342c}



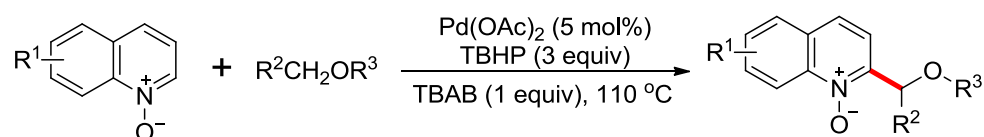
Scheme 244 Transition metal-catalyzed alkenylation of pyridine or quinolone *N*-oxides.

The first Ni(0)-catalyzed alkenylation of pyridine *N*-oxides by the regio- and stereoselective insertion of alkynes was reported by Nakao and Hiyama group in 2007 (Scheme 244a).^{343a} The resulting alkenylated pyridine-*N*-oxides could be readily deoxygenated with PCl₃ to provide 2-alkenylpyridines in excellent yields. Unsymmetric alkynes were excellent substrates to afford (*E*)-2-alkenylpyridine-*N*-oxides, in which the steric repulsion between the bulkier R³ and the pyridyl group might be responsible for the observed good regioselectivities. Primary mechanism investigation revealed that the *N*-oxide moiety played an important role in directing the metal catalyst to the proximal C2-H bond, and also improved the corresponding C-H bond acidity to undergo the oxidative addition to nickel(0).

In 2008, Chang described the Pd(II)-catalyzed selective alkenylation of pyridine *N*-oxides using olefins (Scheme 244b).^{342a} The alkenylation reaction showed broad substrate

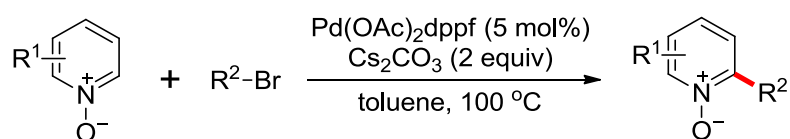
scope: both electron-deficient olefins (conjugated with ester, amide, ketone or diethyl vinylphosphonate groups) and aliphatic olefins smoothly went through the alkenylation at the 2-position of pyridine *N*-oxides. The dialkenylation of the pyridine *N*-oxides was not observed, showing excellent chemoselectivity. A palladium complex was isolated by the treatment of pyridine *N*-oxide with PdCl₂(PPh₃)₂, which demonstrated the interaction between the oxygen atom of the pyridine *N*-oxide and the palladium catalyst. However, the reaction of this palladium complex with olefins failed to provide the alkenylated products under the reaction conditions, suggesting that the *N*-oxide-bound Pd complex was probably a resting species outside the catalytic cycle.

An external-oxidant free condition was developed by Wu and co-workers for the Pd(II)-catalyzed alkenylation of heteroarene *N*-oxides, in which the 2-alkenylated quinolones or 1-alkenylated isoquinolines were produced in chemo- and regioselective manners (Scheme 244c).^{343b} The authors proposed that the initial alkenylatedquinoline-*N*-oxides could act as the oxidant to convert Pd(0) into Pd(II) and complete the catalytic cycle.



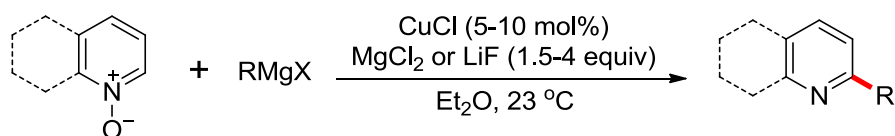
Scheme 245 Palladium-catalyzed alkylation of pyridine *N*-oxides with ethers.

The Pd(II)-catalyzed C-2 alkylation of quinolone *N*-oxides with ethers was demonstrated by Cui, Wu and co-workers in 2013 (Scheme 245).³⁴⁴ A series of quinoline-containing heterocyclic compounds was obtained in moderate to excellent yields using Pd(OAc)₂ as a catalyst and TBHP (*tert*-butyl hydroperoxide) as an oxidant. TBAB (tetrabutylammonium bromide) and H₂O were used as additives in order to obtain the best yield. In the mechanism investigation, the authors proposed that a key Pd(III) intermediate might be involved by the reaction of Pd(II) species with an ether radical, which was generated in situ by the hydrogen *N*-atom abstraction by TBHP.



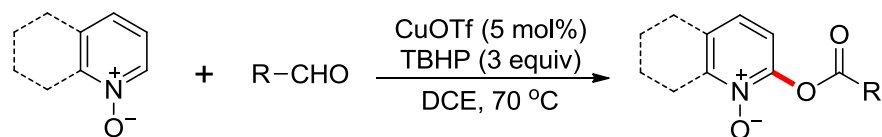
Scheme 246 Palladium-catalyzed alkylation of pyridine *N*-oxides with alkyl bromides.

The use of nonactivated secondary and tertiary alkyl bromides as coupling reagents in the Pd(II)-catalyzed *ortho*-alkylation of pyridine *N*-oxides was reported by Fu and co-workers (Scheme 246).³⁴⁵ The author proposed that the radical-type of C-Br cleavage was engaged in the Pd-catalyzed C-H functionalization reaction, which was consistent with the fact that the primary bromides were less reactive during the transformation. The reaction showed good compatibility with many synthetically relevant functional groups, presenting a good method for the preparation of alkylpyridine derivatives.



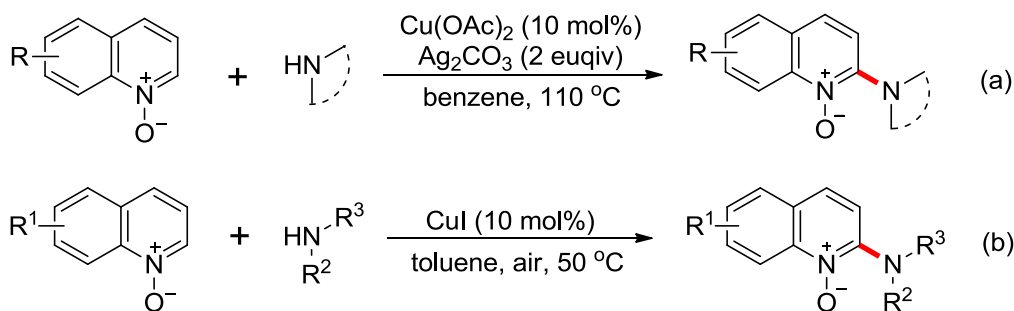
Scheme 247 Copper-catalyzed coupling reaction of heterocyclic *N*-oxides with Grignard reagents

More recently, Larionov reported the Cu(II)-catalyzed coupling reaction of heterocyclic *N*-oxides with Grignard reagents, in which the N-O bond was reduced spontaneously to provide the 2-aryl-, alkyl-, and alkenyl-substituted *N*-heterocycles in good to excellent yields (Scheme 247).³⁴⁶ Both primary and secondary alkylmagnesium halides proved to be suitable nucleophiles in the reaction with substituted quinoline, pyridine, and isoquinoline *N*-oxides. The chemoselective preference for the C2-addition in 4-chloroquinoline *N*-oxides has been exploited for a regioselective synthesis of new structural analogues of amodiaquine and chloroquine.



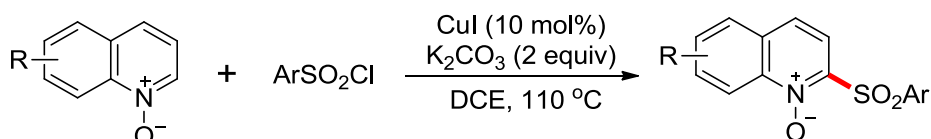
Scheme 248 Copper-catalyzed acetoxylation of quinoline *N*-oxides

The 2-acetoxylation of quinoline *N*-oxides catalyzed by a cheap copper(I) salt via C-H activation was described by Cui, Wu and co-workers (Scheme 248).³⁴⁷ The reaction proceeded smoothly under a nitrogen atmosphere, in which TBHP served as a terminal oxygen source. The authors proposed that quinoline *N*-oxide radical formed by TBHP was an important intermediate in the catalytic cycle. However, electron-deficient aldehydes and heterocyclic aldehydes failed to give the desired products.



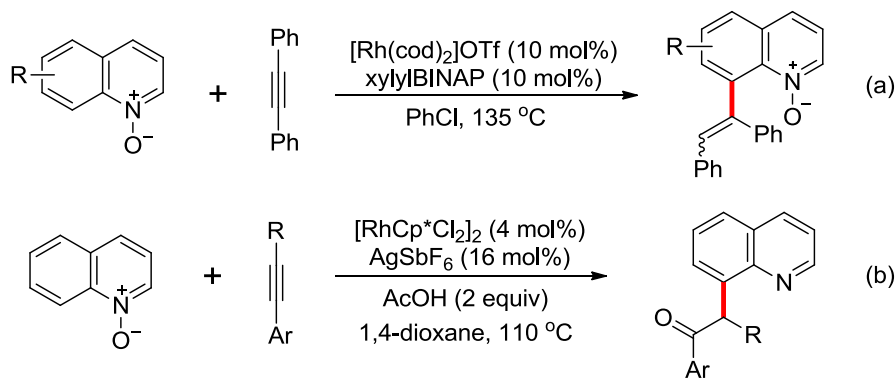
Scheme 249 Copper-catalyzed amidation of quinoline *N*-oxides.

The challenging C-N bond construction of quinoline *N*-oxides with lactams/cyclamines in the presence of the $\text{Cu}(\text{OAc})_2$ catalyst was reported by Li and co-workers in 2013 (Scheme 249a).^{348a} In their reaction, lactams and cyclamines were excellent coupling substrates to provide 2-aminoquinoline derivatives in good yields. The detected intermolecular deuterium kinetic isotope effect value of the amidation was 1.3, suggesting the C-H bond cleavage in quinoline *N*-oxide might not be involved in the rate-limiting step. Later on, Wu, Cui and co-workers developed a simple and efficient method for the direct amination of quinoline *N*-oxides with secondary aliphatic amines via a copper-catalyzed dehydrogenative coupling reaction (Scheme 249b).^{348b} O_2 served as the only oxidant in the catalytic system to give the 2-aminoquinoline derivatives in good yields.



Scheme 250 Copper-catalyzed sulfonylation of quinoline *N*-oxides.

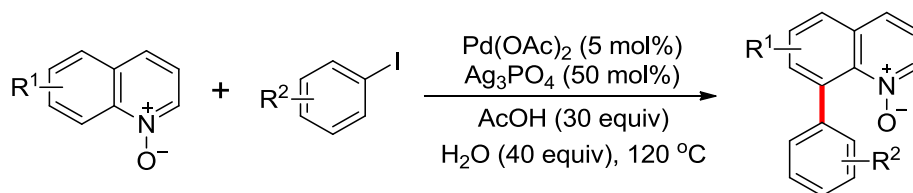
The copper-catalyzed sulfonylation of quinoline *N*-oxides via C-H bond activation was reported by Cui, Wu and co-workers (Scheme 250).³⁴⁹ Commercially available aryl sulfonyl chlorides were used as the sulfonylation reagents to provide various 2-arylsulfonylquinolines in chemo- and regioselective manners. Generally, the reaction efficiency was slightly sensitive to the electronic property of the sulfonyl chlorides, in which the electron-rich substrates gave higher yields. The improved acidity of quinolone *N*-oxides was supposed to promote the deprotonation-metallation of the C-H bond at the 2-carbon under basic conditions. Other heteroarene *N*-oxides, such as pyrazine, pyrimidine, 1-methyl-imidazole, pyridine, and their derivatives, failed to provide the corresponding heterocyclic aromatic sulfone under the reaction conditions.



Scheme 251 Rhodium-catalyzed C-H activation of quinoline *N*-oxides with internal alkynes.

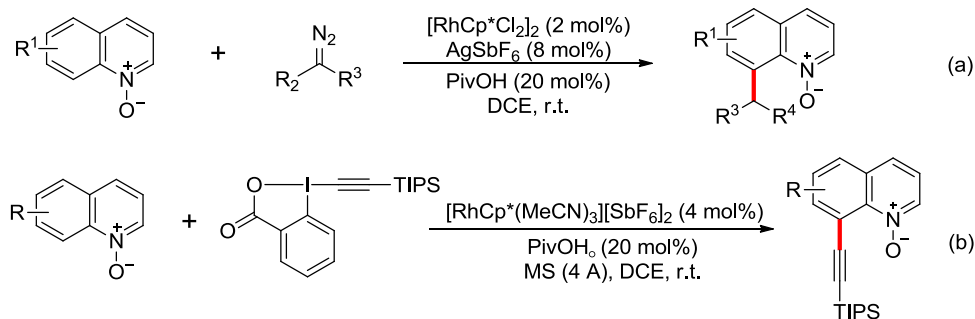
In the above studies, the transition metal-catalyzed *ortho* functionalization of pyridine *N*-oxides was generally supposed to undergo the electrophilic aromatic substitution pathway. Shibata and co-workers demonstrated for the first time that an *N*-oxide could be used as a directing group to promote the rhodium-catalyzed alkenylation at the C-8 position of quinoline *N*-oxides (Scheme 251a).^{350a} The reaction took place at high temperature, leading to an *E/Z* mixture of isomeric products. Based on the preliminary mechanistic study, the authors proposed that C-H bond cleavage occurred at both the C-2 and C-8 positions of the substrate to give two intermediates. But the stable 5-membered metallacycle intermediate preferred to undergo the alkyne insertion, followed by the reductive elimination to afford the alkenylated products.

Li and co-workers developed a rhodium(III)-catalyzed redox-neutral coupling of quinoline *N*-oxide with internal alkynes, leading to the synthesis of substituted acetophenones (Scheme 251b).^{350b} The reaction featured a good functional group tolerance, in which both electron-donating and electron-withdrawing groups in quinoline *N*-oxides were well tolerated to provide the products in moderate to good yields. When the reaction was conducted in the presence of H₂O¹⁸, no ¹⁸O incorporation was observed, implicating with an intramolecular O-atom transfer pathway. The authors proposed a Rh^{III}/Rh^I/Rh^{III} mechanism, in which the N-O bond in quinoline *N*-oxides could readily undergo O-atom transfer to alkynes to afford an α -oxocarbonyl intermediate.



Scheme 252 Palladium-catalyzed C8-H arylation of quinoline *N*-oxides with iodoarenes.

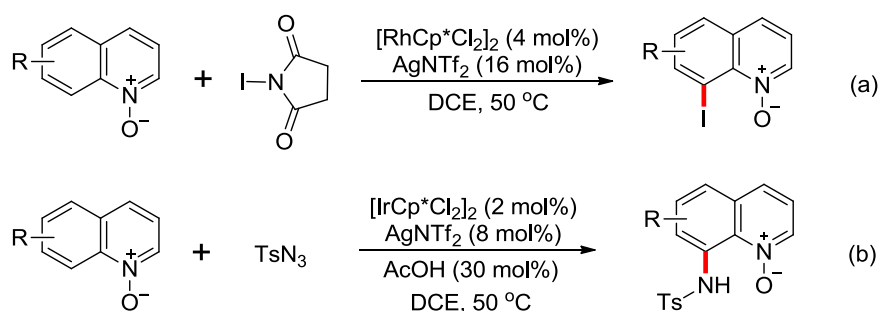
Very recently, Larionov and co-workers reported the Pd(II)-catalyzed C8-H arylation of quinoline *N*-oxides with iodoarenes (Scheme 252).³⁵¹ The method tolerated a number of functional groups in quinolines and iodoarenes. Detailed experiments were carried out to study the reactivity and selectivity of Pd-catalyzed arylation under ligand-free conditions. The observed KIE ($k_H/k_D = 2.0$) indicated that C8-H bond cleavage may be involved in the turnover-determining step. The Hammett analysis suggested that the reaction was accelerated by the electron-withdrawing substituents in the iodoarene and electron-donating substituents in the 5- and 6-positions of the quinoline system. The computational studies by means of DFT demonstrated that the C8 cyclopalladation was the lower energy pathway under phosphine-free conditions and explained the reversal of site selectivity to C2 in the presence of phosphine ligand.



Scheme 253 Rhodium-catalyzed direct C-H alkylation and alkylation of quinoline *N*-oxides.

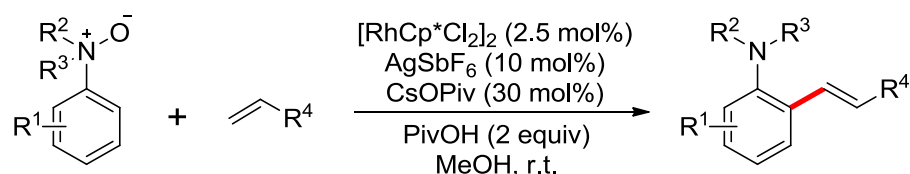
By the use of diazocarbonyl compounds, Chang's group demonstrated the synthetic utility of carbenoid chemistry in the Rh(III)-catalyzed direct C-H alkylation reactions at the C-8 position of quinoline *N*-oxides (Scheme 253a).³⁵² The reaction proceeded efficiently at room temperature with excellent regioselectivity. The common functional groups, such as carbamate, silyloxy, acetoxy, acetal, aldehyde, ketone, and ester, were compatible with the reaction conditions. The authors also realized the introduction of alkynyl moiety at the C-8 position of quinoline *N*-oxides (Scheme 253b). The pregenerated cationic species $[\text{RhCp}^*(\text{MeCN})_3][\text{SbF}_6]_2$ presented high efficiency in the reaction of quinoline *N*-oxides and

1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX) to provide the alkylated products in moderate to good yields. The resulted alkylated and alkynylated quinoline *N*-oxides could easily be deoxygenated with the use of zinc reagent under mild conditions.



Scheme 254 Transition metal-catalyzed iodination and amidation of quinoline *N*-oxides.

The Rh(III)-catalyzed regioselective C-H bond iodination of quinoline *N*-oxides at the 8-position using *N*-iodosuccinimide (NIS) was reported by Chang and co-worker (Scheme 254a).³⁵³ The reaction took place at moderate temperatures in the presence of an in situ generated cationic Cp*Rh(III) catalyst. The authors also achieved the direct C-8 amidation of quinolone *N*-oxide using iridium catalysts (Scheme 254b). An iridacycle complex was isolated from the reaction of quinolone *N*-oxide and [Cp*IrCl₂]₂, revealing that the unique regioselectivity was attributed to the formation of *N*-oxide-chelated iridacycle. Catalytic acetic acid was essential, which was believed to influence the bond strength between the metal and inserted amido moieties and facilitate the proto-demetalation process.



Scheme 255 Rhodium-catalyzed *ortho*-olefination of tertiary aniline *N*-oxides.

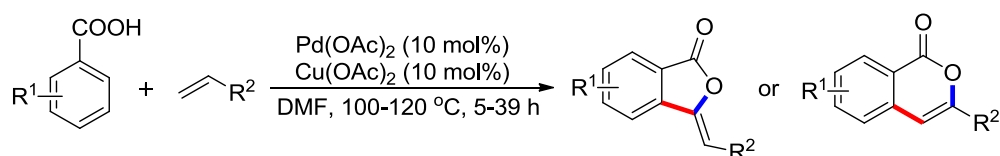
The Rh-catalyzed *ortho*-olefination of tertiary aniline *N*-oxides was reported by You and co-workers. Electron-deficient olefins, such as acrylates, acrylamide, acrylonitrile and vinyl phosphonate could undergo the reaction condition to prepare 2-alkenylated tertiary anilines in good yields (Scheme 255).³⁵⁴ The five-membered cyclometalated Rh(III) complex from the starting material was isolated and its structure was established by X-ray crystallographic analysis, suggesting the directed C-H metalation in the catalytic cycle. The

N-O bond was identified as an internal oxidant to achieve the *ortho* C-H functionalization of tertiary anilines.

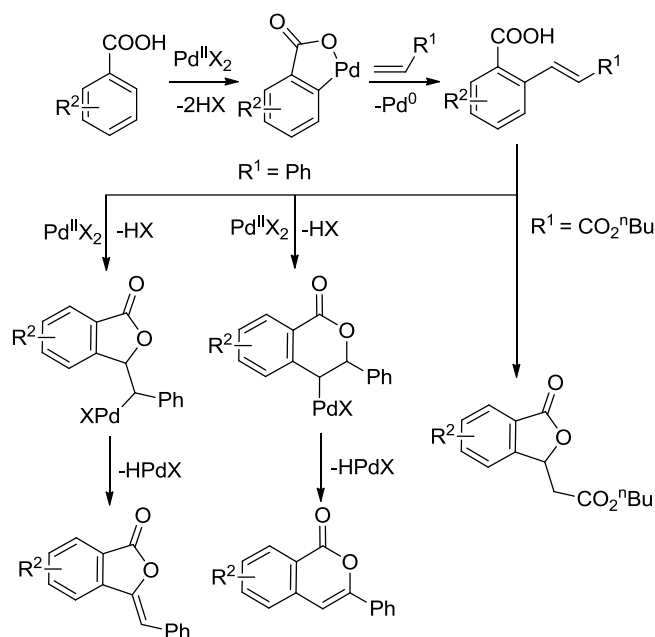
6 The C-H functionalization directed by carboxylic acid

Carboxylic acids widely exist in great structural diversity both from natural and synthetic sources. The weak coordination ability of carboxylic acid to transition metal catalysts renders it an attractive and valuable directing group in C-H bond functionalization reactions. Moreover, carboxylic acid is highly convenient to be removed or transformed to other functional groups through demonstrated reactions.

6.1 Alkenylation of C-H bond and subsequent annulation reaction



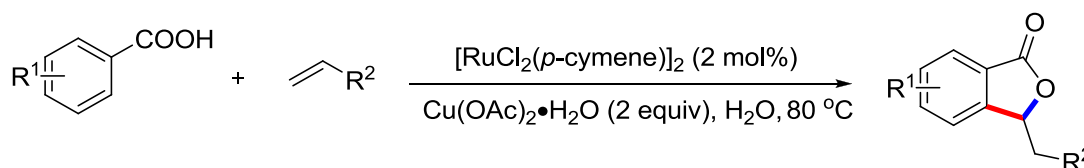
Scheme 256 Palladium-catalyzed carboxylate-directed C-H olefination and subsequent annulation.



Scheme 257 The proposed mechanism.

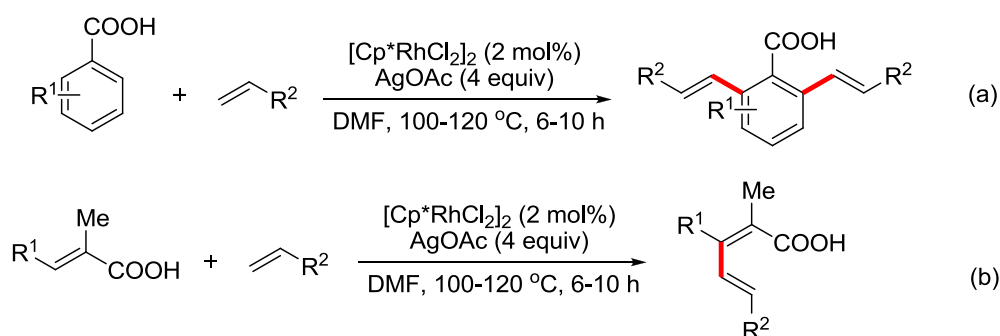
In 1998, the Miura group reported the pioneer work of palladium-catalyzed carboxylate-directed C-H olefination. Benzoic acids and naphthoic acids could react with alkenes to give either phthalides or isocoumarins derivatives in moderate to good yields (Scheme 256).³⁵⁵ The regioselectivity of reaction was presumably determined in the alkene

addition step, in which the nucleophilic cyclization or Wacker-type oxidative cyclization was involved (Scheme 257). When acrylates were used as the coupling reagents, phthalides could be obtained as the single products. Further studies demonstrated that the selectivities of the products between phthalides and isocoumarins could be controlled by the introduction of *ortho*-substituent of benzoic acids, probably due to the steric effect between the neighboring *ortho*-substituent and carboxylate group, which prevented O atom from attacking the distant C2 of the vinyl group.³⁵⁶



Scheme 258 Ru-catalyzed oxidative C-H alkylation of benzoic acids in water.

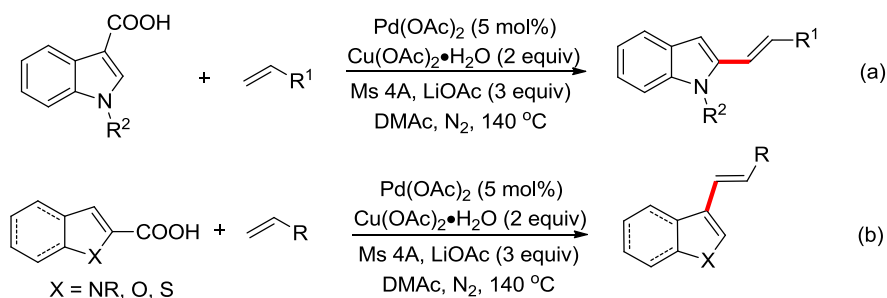
The Ru-catalyzed carboxylate-directed C-H alkenylation was developed by Ackermann and co-workers (Scheme 258).³⁵⁷ Interestingly, the phthalide was generated as the single product from the corresponding benzoic acid and acrylate or acrylonitrile with 2 mol% $[\text{RuCl}_2(p\text{-cymene})]_2$ as the catalyst. It's important that water was used as an environmentally benign reaction medium. The kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} = 3.6$) indicated that the oxidative alkenylation proceeded through an irreversible C-H bond metalation. Recently, the oxidative C-H alkenylation of aromatic sulfonic acids was achieved with an *in situ* generated Ru (II) catalyst by the same group.³⁵⁸



Scheme 259 Rh-catalyzed carboxylate-directed olefination of carboxylic acids.

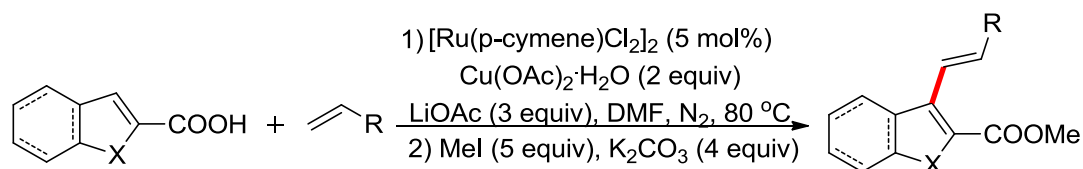
Miura and co-workers demonstrated the Rh-catalyzed carboxylate-directed *ortho*-olefination of benzoic acids with alkenes using silver or copper salts as oxidants (Scheme 259).³⁵⁹ The reaction exhibited broad substrate scope, such as naphthoic acids, α , β -unsaturated carboxylic acids, and heteroarene carboxylic acids. Notably, the directing group

could be readily removed during the olefination reaction or post-treatment with AgOAc/K₂CO₃. Recently, the Rh-catalyzed *ortho*-C-H olefination of arenes directed by the acid group was further developed by Liu group and Miura group.^{360,361} A wide range of acid substrates including substituted thiophene or furan-2-carboxylic acids, 2-substituted benzoic acids, 1-naphthoic acids and aromatic sulfonic acids, could successfully undergo alkenylation with the carboxyl groups intact.



Scheme 260 Rh-catalyzed regioselective olefination of heteroarene carboxylic acids.

The Pd-catalyzed olefination of the heteroarene carboxylic acid, such as indole-3-carboxylic acids, with alkenes to give the corresponding 3-vinylated indoles was also reported by Miura and co-workers (Scheme 260).³⁶² It was proposed that the *ortho*-olefination and the subsequent decarboxylation process were involved in the mechanism. Despite the highly selectivity with respect to C3-vinylation of *N*-methyl-pyrrole-2- and benzofuran-2-carboxylic acids, the selectivity for the vinylation of thiophene and benzothiophene carboxylic acids in the reaction were still problematic, in which the mixtures of 2- and 3-vinylated products were obtained. Furthermore, they demonstrated the Rh(III)-catalyzed synthesis of *meta*-substituted stilbene derivatives via the *ortho*-olefination/decarboxylation of benzoic acids.³⁶³

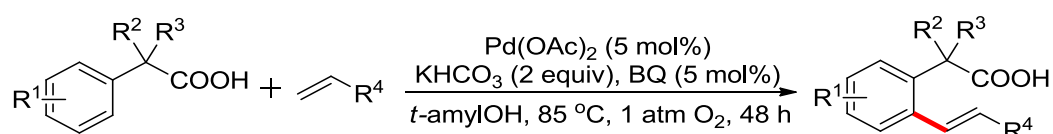


Scheme 261 Ru-catalyzed carboxylate-directed vinylation of heteroaromatic carboxylic acids.

Miura and Satoh demonstrated the Ru-catalyzed vinylation of heteroaromatic carboxylic acids to give the 3-vinylated products. Since the decarboxylation process was sluggish under Ru catalysis, the carboxyl function remained in the obtained vinylated products, which could

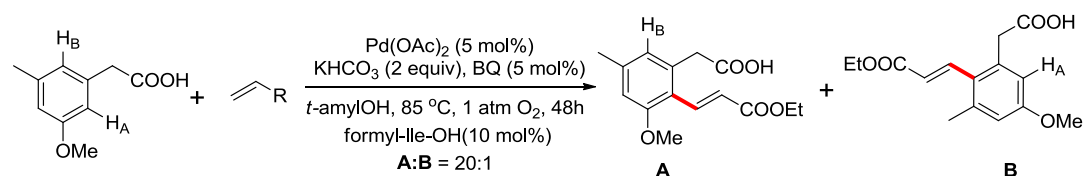
be undergone further catalytic transformations. (Scheme 261).³⁶⁴ A wide variety of heteroaromatic carboxylic acids were well compatible with the reaction conditions.

Using the readily synthesized catalyst $[\text{Cp}^*\text{IrCl}_2]_2$, Ison and co-workers developed the carboxylate-directed reaction of C-H bonds with benzoquinone, affording the benzochromenones as the final products.³⁶⁵ The reaction presented a rare example of C-H functionalization with an electrophilic Ir(III) catalyst, in which the benzoquinone served not only as the coupling reagent but also an intramolecular oxidant to regenerate the Ir(III) catalyst.



Scheme 262 Pd-catalyzed carboxylate-directed C-H olefination under atmospheric O_2 .

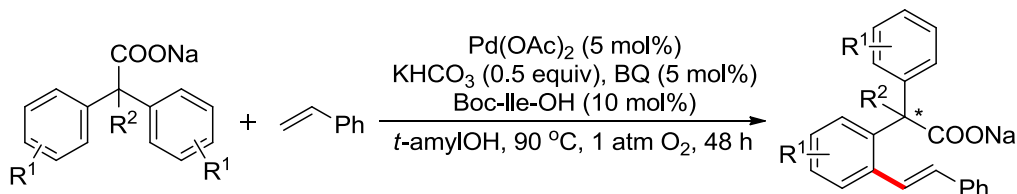
Besides benzoic acid or heteroarene carboxylic acids, the more synthetically useful phenyl acetic acids and 3-phenylpropionic acids could also be used as efficient substrates in the Pd-catalyzed C-H functionalization reactions. In 2010, Yu group developed an operationally simple, atom-economical, carboxylate-directed Pd-catalyzed C-H olefination of phenylacetic acids using O_2 as terminal oxidant (Scheme 262).³⁶⁶ BQ was chosen to be a useful ligand to prevent minor formation of the *meta*- and *di-ortho*-olefinated products. A diversity of phenylacetic acids were involved in this catalyst system to give the desired olefinated products in good to excellent yields. As for the substrates with chiral centers at the α position, the addition of Li_2CO_3 as the base could prevent racemization and give the product with high *ee* value.



Scheme 263 Pd-catalyzed carboxylate-directed C-H olefination enabled by ligand.

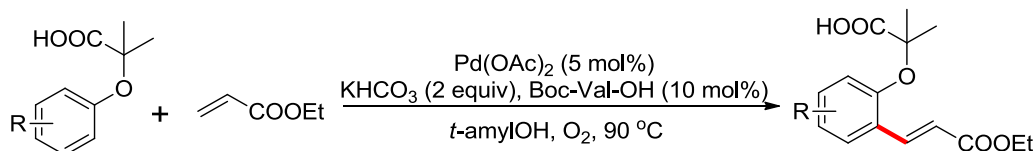
In the same work, Yu group also reported the pioneering ligand-enabled regioselective C-H olefination of phenylacetic acids (Scheme 263).³⁶⁶ The positional selectivities of multiply substituted aromatic rings with two approximately electronically equivalent *ortho*-C-H bonds could be achieved by the addition of specific mono-*N*-protected amino acids. In addition, the

olefination of 3-phenylpropionic acids could also be achieved by using this transformation via the remote coordination.



Scheme 264 Pd-catalyzed carboxylate-directed ligand-induced C-H olefination.

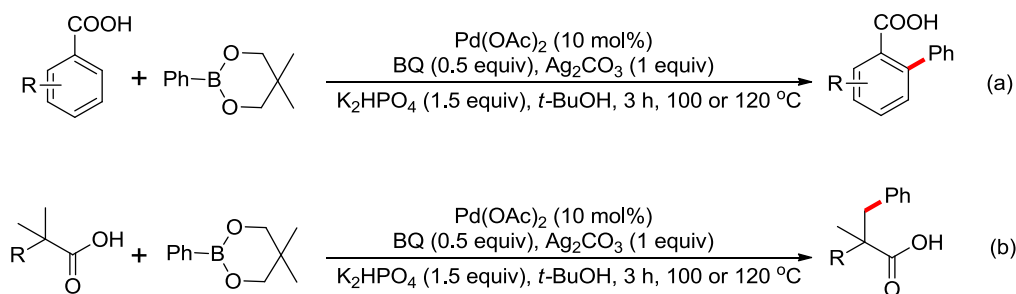
The discovery that amino acid ligand could promote C-H activation provided new opportunities for developing enantioselective C-H activation. In 2010, Yu groups developed a carboxylate-directed enantioselective C-H olefination reaction of α,α -diphenylacetic acids using mono-protected amino acids as effective ligands (Scheme 264).³⁶⁷ Substrates with alkyl, electron-donating, or moderately electron-deficient substituents on the benzene rings coupled with olefin partners such as styrenes or acrylates efficiently, affording the *ortho*-vinylated products in good to excellent yields and enantioselectivities. This new development represented an encouraging step toward the realization of synthetically useful Pd-catalyzed enantioselective C-H activation reactions. Unfortunately, the selectivities were poor for the substrates containing α -hydrogen, which tended to racemize under the reaction conditions.



Scheme 265 Pd-catalyzed *ortho*-C-H olefination of phenol derivatives.

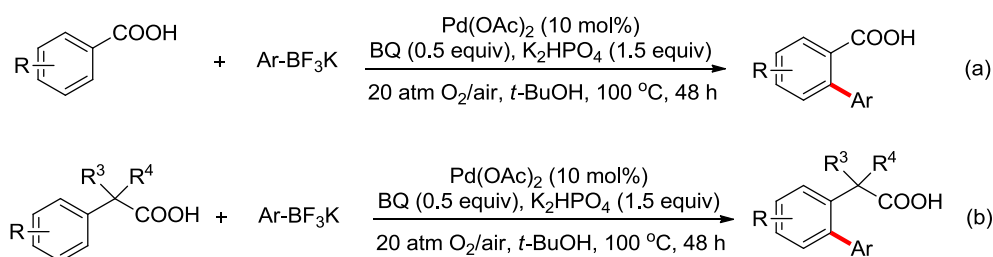
Yu groups have also demonstrated that ligands that can cooperate with the weak coordination of the distal carbonyl group to promote the C-H activation (Scheme 265).³⁶⁸ Therefore, phenol derivatives were olefinated with acrylates in the presence of Pd(OAc)₂ and KHCO₃ under atmospheric oxygen, using Boc-Val-OH as the ligand. These C-H activation reactions applying the distal chelating atoms (six bonds away), which still remain challenging due to the difficulty of forming larger membered palladacycles.

6.2 Arylation of C-H bond

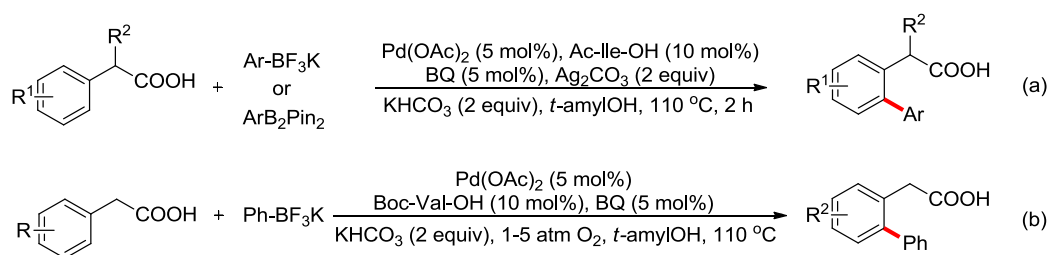


Scheme 266 Pd-catalyzed carboxylate-directed arylation of *ortho*-C-H bond.

The first Pd(II)-catalyzed carboxylate-directed arylation of benzoic acids using phenyl boronates as aryl donors was demonstrated by Yu and co-workers (Scheme 246).³⁶⁹ The generality of this transformation was further demonstrated by β -arylation of aliphatic acids, in which Pd(II)/Pd(IV) catalysis was likely to be involved. Stoichiometric Ag_2CO_3 was used as the oxidant and the use of BQ was crucial for the success of this transformation. The reaction presumably proceeds *via* the *in situ* generation of the corresponding carboxylate, which would bind the Palladium center to undergo the C-H activation/transmetallation/reductive elimination sequence, giving rise to the β -arylated products.



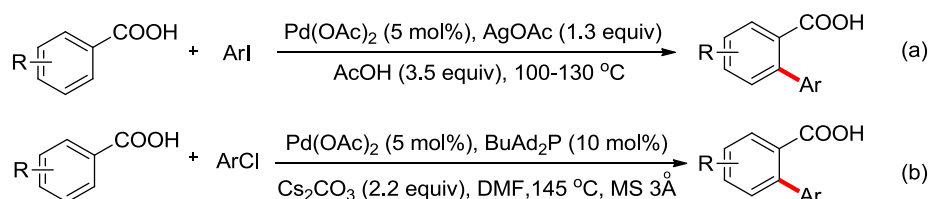
Scheme 267 Pd-catalyzed arylation of benzoic acids and arylacetic acids.



Scheme 268 Ligand-accelerated Pd-catalyzed *ortho*-C-H arylation of phenylacetic acids.

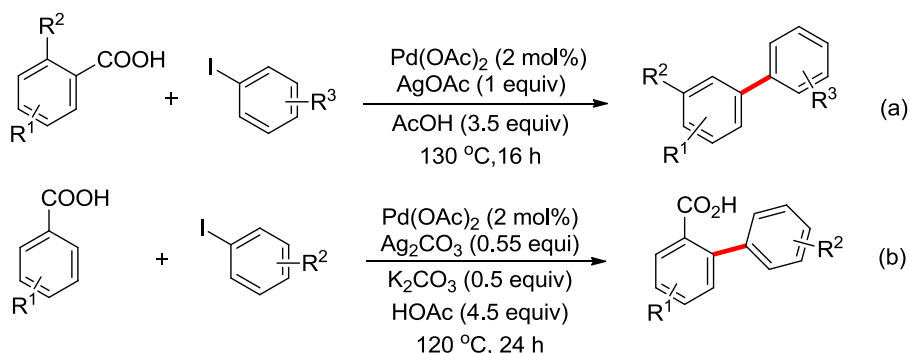
Subsequently, Yu groups reported Pd-catalyzed C-H arylation of benzoic and phenyl acetic acids using aryltrifluoroborates as coupling reagents (Scheme 267).³⁷⁰ This new protocol substantially expanded the scope of reaction, in which the *ortho* C-H arylation of phenylacetic acids and electron-deficient arenes containing α -H was achieved for the first

time. However, the drawbacks of the use of high-pressure O₂ or air, long reaction times, and limited substrate scope, limited the application of this protocol. To overcome these limitations, a ligand-acceleration strategy has been developed by the authors. With the use of Ac-Ile-OH as ligand and Ag₂CO₃ as the oxidant, the coupling of phenylacetic acids with aryltrifluoroborates or pinacol esters of arylboronic acids gave arylation products in nearly quantitative yields (Scheme 268).³⁷¹ Mechanism studies demonstrated that the initial rate of electron-poor phenylacetic acids was improved by the amino acid ligands and the catalytic cycle was proposed to proceed via a concerted metallation/deprotonation pathway.



Scheme 269 Pd-catalyzed carboxylate-directed C-H arylation of benzoic acids.

In 2007, Daugulis group developed the direct *ortho*-arylation of benzoic acids with benzene halides (Scheme 269).³⁷² When iodobenzenes were applied as coupling partners, the acetic acid was used as the solvent to impede the competitive decarboxylation process, and stoichiometric AgOAc was applied for the removal of iodide. The chloride and bromide substitution of benzoic acids were tolerated and the reaction most likely to proceed through a Pd(II)/Pd(IV) pathway. A modified reaction condition allowed the *ortho*-arylation of benzoic acids by the use of chlorobenzene as the coupling partner.

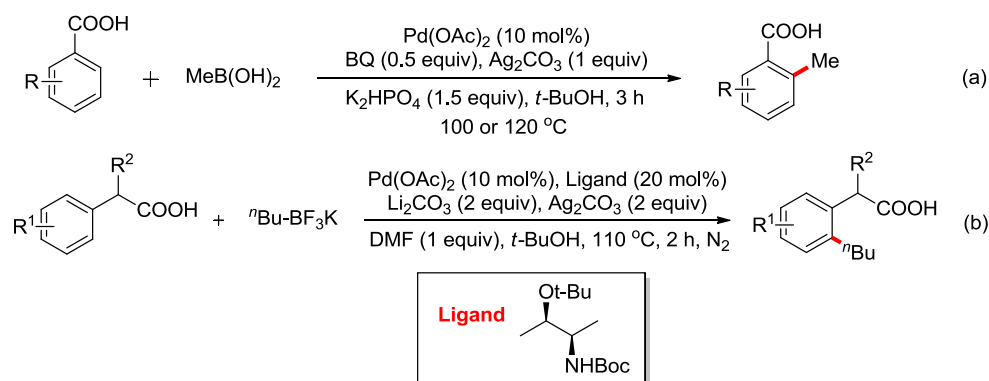


Scheme 270 Pd/Ag-catalyzed *ortho*-C-H arylation of aryl benzoic acids.

In 2011, Larrosa's group reported the first example of the *meta*-C-H arylation and decarboxylation using iodo-arenes as coupling partners in the presence of the Pd(OAc)₂ and Ag₂CO₃ (Scheme 270a).^{373a} Different from the previously reported arylation, the arylation

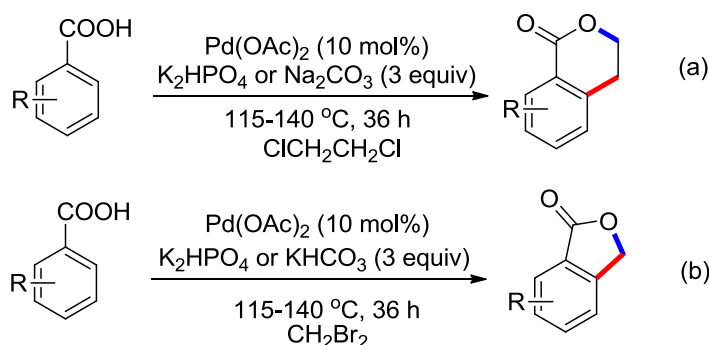
products underwent further the decarboxylation at higher reaction temperature to provide *meta*-substituted biaryl compounds, which would be difficult to be obtained by traditional Friedel-Crafts methods. They found that the use of K_2CO_3 could remarkably suppress the Pd-mediated decarboxylation to give the biaryl carboxylic acids (Scheme 270b).^{373b}

6.3 Alkylation of C-H bond



Scheme 271 Ligand-accelerated Pd-catalyzed *ortho*-C-H alkylation of arylcarboxylic acids.

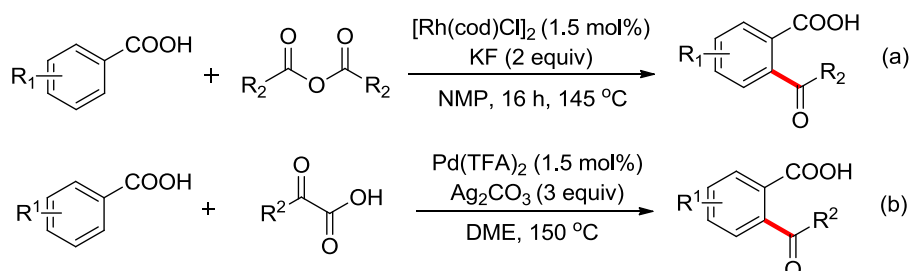
The Pd-catalyzed *ortho*-methylation of benzoic acids using methylboronate as the coupling partner in the presence of benzoquinone and Ag_2CO_3 was reported by Yu group. (Scheme 271a).³⁶⁹ However, the *ortho*-alkylation of arylcarboxylic acid failed when other alkylboron reagents were used as the coupling partner due to the potential β -hydride elimination. This challenge was successfully overcome by Yu and co-workers by using the ligand strategy in 2013. Thus, the Pd-catalyzed ligand-accelerated C-H alkylation of phenylacetic and benzoic acids using alkyl boron reagents was achieved smoothly in the presence of mono-*N*-protected amino acid (MPAA) as the ligand. The accelerated C-H cleavage reactivity was attributed to the additional role of mono-*N*-protected amino acid (MPAA) in the catalysis. Potassium alkyl trifluoroborates and alkyl boronic acids were the compatible coupling partners (Scheme 271b).³⁷⁴ A variety of primary alkyl boron coupling partners, including fragments possessing trifluoromethyl, phenyl, Boc-amine, ester, or ketone functional groups, were compatible. Despite these advances, alkyltrifluoroborates containing α -heteroatoms, olefins, or alkynes did not give the desired coupling products.



Scheme 272 Pd-catalyzed *ortho*-C-H alkylation of benzoic acids.

The Pd-catalyzed sequential alkylation/lactonization reaction of benzoic acids with alkyl halides to afford lactones was described in 2009 by Yu and co-workers (Scheme 272).³⁷⁵ This transformation involved the Pd-catalyzed carboxylate-directed *ortho*-C-H alkylation and subsequent S_N2 substitution. The use of alkyl halides, such as 1,2-dichloroethane, dichloromethane, dibromomethanes, led to the catalytic cycle to be closed in the presence of an inexpensive base instead of Ag^+ salts.

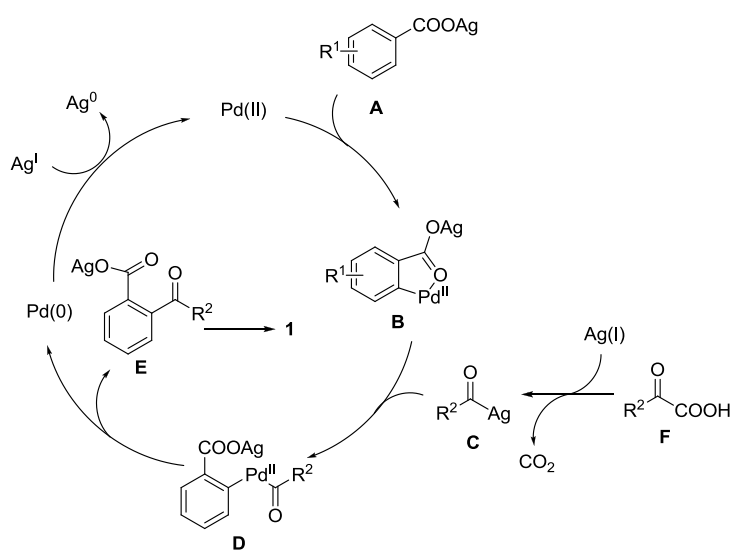
6.4 Acetylation and carboxylation of C-H bond



Scheme 273 Rh and Pd-catalyzed *ortho*-acylation of aromatic carboxylic acids.

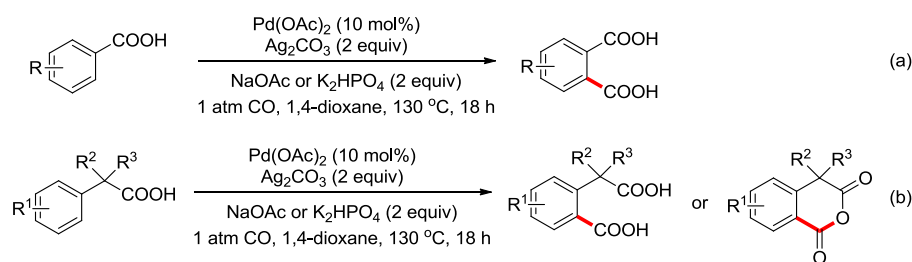
The first example of Rh-catalyzed *ortho*-acylation of aromatic carboxylic acids was reported by Gooßen and co-workers (Scheme 273a).³⁷⁶ The transformations would be of considerable interest due to the *ortho* selectivity when compared with traditional Friedel-Crafts acylation. $[\text{Rh(cod)Cl}]_2$ was found to be the best catalyst to promote the acylation of benzoic acids with anhydrides in the *ortho* position. In the same time, Ge group represented the palladium-catalyzed chemoselective decarboxylative cross-coupling of benzoic acids with α -oxocarboxylic acids (Scheme 273b).³⁷⁷ The method provided an efficient access to 2-acylbenzoic acid derivatives. Ag_2CO_3 was used to generate acyl silver species through the silver-mediated decarboxylation of α -oxocarboxylic acids and reoxidize Pd(0) into Pd(II). The synthesis of pitofenone has been achieved applying this transformation as the

key step.



Scheme 274 Proposed mechanism of the reaction

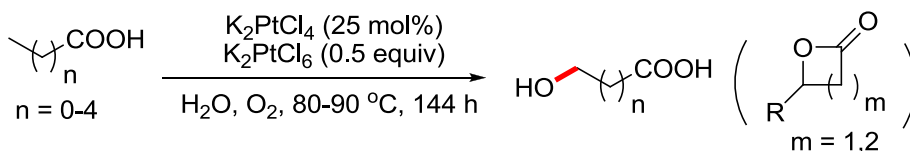
The transformation was proposed to start with the palladation of silver benzoate **A** to produce the Pd(II) intermediate **B**. The subsequent transmetalation step with the acyl silver species **C** which was formed by the silver-mediated decarboxylation of **F**, generated the Pd(II) intermediate **D**. The reductive elimination of **D** provided the silver salt **E** and Pd(0), which could be reoxidized into Pd(II) by Ag_2CO_3 . Protonation of intermediate **E** provided the desired product (Scheme 274).



Scheme 275 Pd-catalyzed C-H carboxylation of benzoic acids or phenylacetic acids with CO.

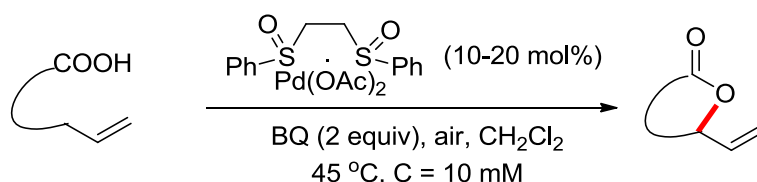
Direct C-H carbonylation using CO has been extensively studied as an expedient route to access carboxylic acid derivatives. In 2008, Yu's group disclosed a new Pd(II)-catalyzed direct carboxylation reaction of aryl and vinyl carboxylic acids using a C-H activation/CO insertion sequence to form dicarboxylic acids (Scheme 275).³⁷⁸ Due to steric effects of substrates, excellent regioselectivities were observed in the carboxylation of *meta*-substituted carboxylic acids. The key cyclepalladated intermediate was characterized and studied.

6.5 Intramolecular oxidative cyclization



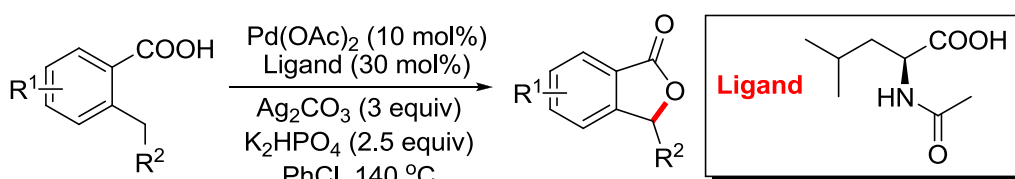
Scheme 276 Pt-catalyzed carboxylate-directed C-H hydroxylation of aliphatic acids.

An early example involving Pt-catalyzed C-H hydroxylation of aliphatic acids was demonstrated by Sen and Kao in 1991 (Scheme 276).³⁷⁹ The β -C-H or γ -C-H of aliphatic acids could be hydroxylated via C-H bond cleavage by carboxylate-chelated Pt(II) species, followed by the cyclization to form lactones. However, the reactions gave only moderate yields and the substrate scope was limited. In 2001, Sames and co-workers developed the catalytic process for the Pt-catalyzed functionalization of α -amino acids in water.³⁸⁰ The work presented a rare example of catalytic heteroatom-directed functionalization of remote alkyl groups in complex substrates. The success was attributed to the chelation of Pt with both the carboxylate and amino groups. In addition, the Pt-catalyzed benzylic C(sp³)-H acetoxylation of *ortho*-alkyl-substituted aromatic carboxylic acids to obtain aryllactone products was reported by Chang group, in which the C-H activation could be assisted by the chelation of the platinum catalyst to the carboxylate group.³⁸¹



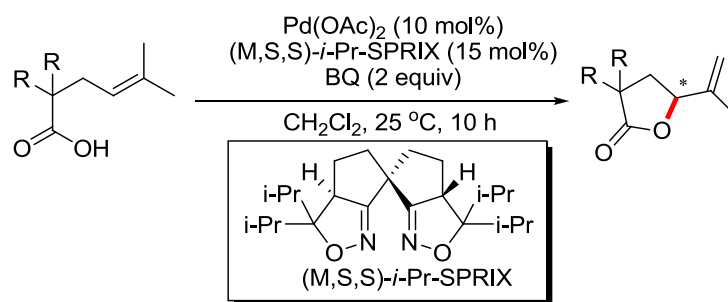
Scheme 277 Pd-catalyzed allylic C-H bond oxidation/macrolactonization.

The Pd-catalyzed macrolactonization of ω -alkenoic acids to furnish 14- to 19-membered alkyl and arylmacrolides via allylic C-H oxidation was reported by White and co-workers (Scheme 277).³⁸² The reaction exhibited remarkable selectivity and a wide range of functional groups were tolerated. Mechanistic studies indicated that the macrolactonization proceeded via a Pd-templated π -allyl carboxylate intermediate.



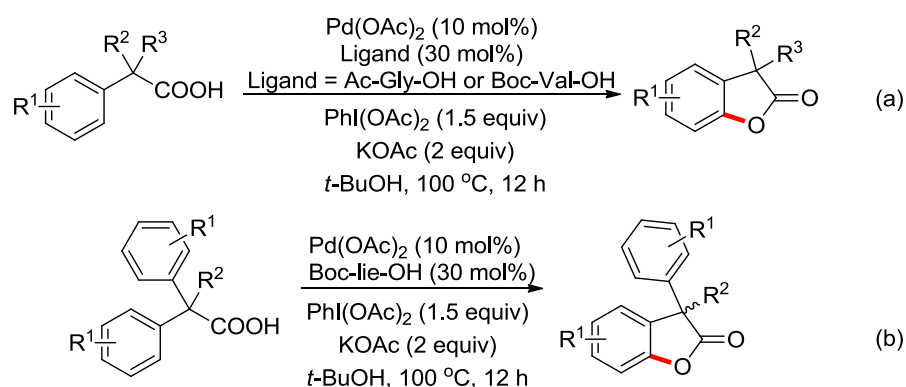
Scheme 278 Pd-catalyzed C(sp³)-H activation/C-O bond formation to produce benzolactones.

Later, a Pd-catalyzed lactonization via benzylic C(sp³)-H oxidation was developed by Martin group (Scheme 278).³⁸³ This Pd-catalyzed processes could be drastically accelerated by the employment of a *N*-protected amino acid as ligands in the synthesis of highly functionalized benzolactones. Mechanistic studies revealed that the transformation proceeded via a Pd(0)/Pd(II) catalytic cycle and the reductive elimination of C(sp³)-O was the rate-limiting step.



Scheme 279 Pd-catalyzed enantioselective intramolecular oxidative cyclization.

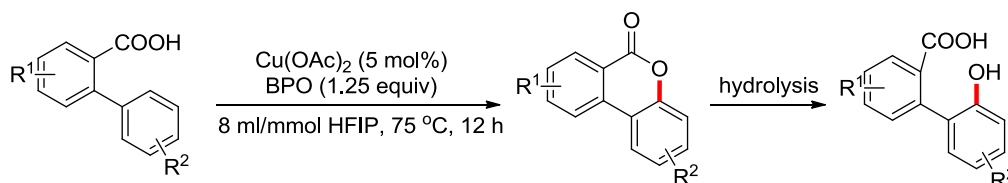
Importantly, the Pd-catalyzed enantioselective allylic C-H functionalization was developed by Sasai's group by the use of chiral ligand spiro-bis(isoxazoline) (SPRIX), in which the 4-alkenoic acids underwent intramolecular oxidative cyclization to give the γ -lactone derivatives with moderate to good enantioselectivities (Scheme 279).³⁸⁴ It was proposed that a π -allyl Pd intermediate was involved in the catalytic process and the carboxylate group played a crucial role in the enantioselective C-H acetoxylation reaction.



Scheme 280 Pd-catalyzed enantioselective intramolecular C-H activation/C-O formation.

The carboxylic group could be used as both a directing and a reacting group in the Pd-catalyzed intramolecular C(sp²)-H activation/C-O bond formation. In 2013, the Wang and co-workers disclosed a novel synthetic method for benzofuranones via carboxylate-directed C-H activation/C-O cyclization with the use of Pd(OAc)₂ as the catalyst and PhI(OAc)₂ as the

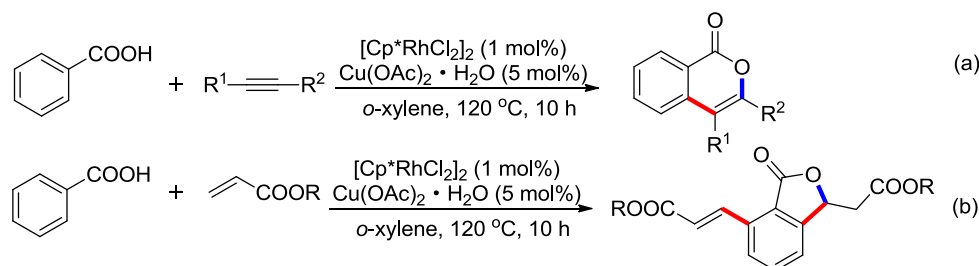
oxidant (Scheme 280a).³⁸⁵ It should be noted that the previous acetoxylation of the C(sp²)-H bond was not observed under the optimized reaction conditions. Moreover, the use of MPAA ligands such as Boc-Ile-OH allowed for the synthesis of benzofuran-2-ones with excellent enantioselectivities, thus providing a complementary strategy to current methods (Scheme 280b).³⁸⁵ This reaction was the first example of Pd-catalyzed enantioselective C-H functionalization through a Pd(II)/Pd(IV) redox catalytic cycle. Simultaneously, Shi group reported the Pd-catalyzed direct lactonization of 2-arylacetic acids through the same reaction sequence, in which amino acids were not needed.³⁸⁶ Subsequently, Wang and co-workers further applied the protocol in the synthesis of biaryl lactone from 2-aryl carboxylic acids.³⁸⁷ The synthetic utility of the new transformation was demonstrated in a concise total synthesis of the natural product cannabinol from commercially available starting materials.



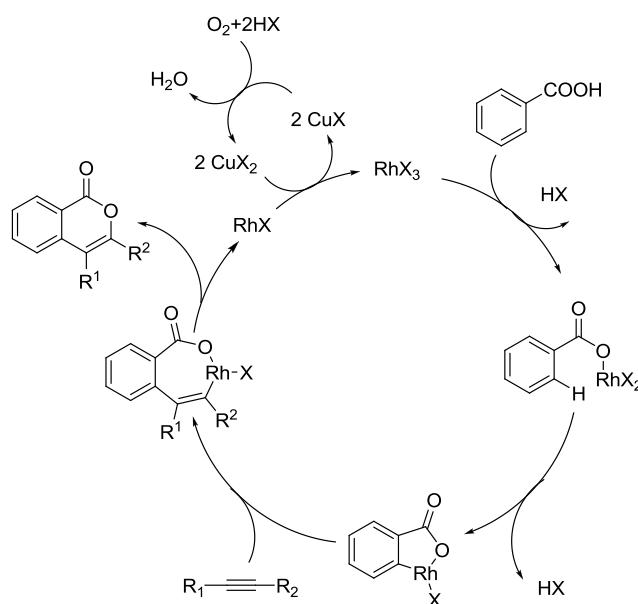
Scheme 281 Cu-catalyzed C(sp²)-H hydroxylation of 2-arylbenzoic acids.

Recently, copper catalysts were studied in the lactonization of 2-arylbenzoic acids, as exemplified by Martin group, who developed a novel C(sp²)-H hydroxylation assisted by benzoic acids in the presence of Cu(OAc)₂ catalyst and BPO oxidant under mild reactions (Scheme 281).³⁸⁸ Mechanistically, a single electron transfer process was likely involved in this transformation, which could be inhibited by radical scavengers such as TEMPO, BHT, and 1,1-diphenylethylene.

6.6 Intermolecular oxidative cyclization

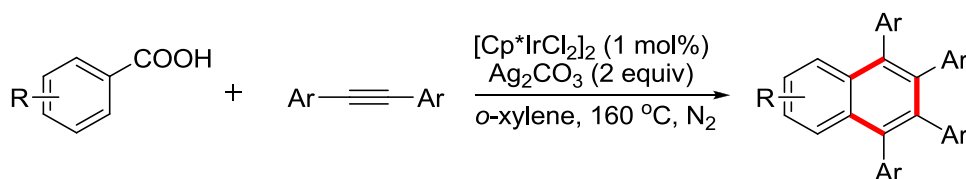


Scheme 282 Rh/Cu-catalyzed carboxylate-directed C-H functionalization reactions.



Scheme 283 Plausible mechanism for Rh-catalyzed isocoumarin synthesis.

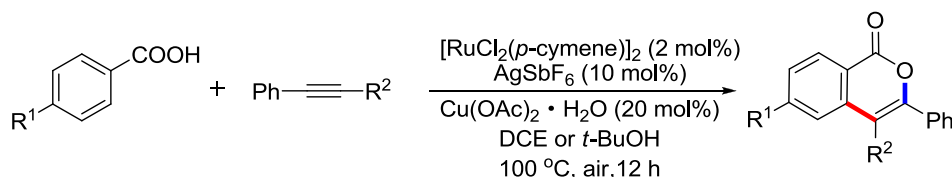
Carboxylate groups can also act as directing groups in the oxidative couplings of benzoic acids and alkynes/alkenes using a Rh-Cu co-catalytic system. In 2007, Muria group developed Rh-Cu system to synthesize isocoumarins from benzoic acids and internal alkynes (Scheme 282a).³⁸⁹⁻³⁹⁰ The reaction produced isocoumarins and proceeded regioselectively with respect to substituted benzoic acids and unsymmetrical internal alkynes. The resulting Rh(I)X species from the reductive elimination step could be oxidized in the presence of the copper cocatalyst under air to regenerate Rh(III)X₃ to render the transformation catalytic (Scheme 283). When acrylates were employed in this transformation, the cyclization was supposed to occur after the first vinylation (Scheme 282b).³⁸⁹ The same group also demonstrated the rhodium-catalyzed coupling of acrylic acids with alkynes to provide corresponding α -pyrone, which proceeded efficiently via the vinylic C-H bond cleavage.³⁹¹ Recently, Li group described the Rh-catalyzed synthesis of sultones via the oxidative coupling of sulfonic acids with internal alkyne.³⁹²



Scheme 284 Ir-catalyzed oxidative coupling of benzoic acids with alkynes.

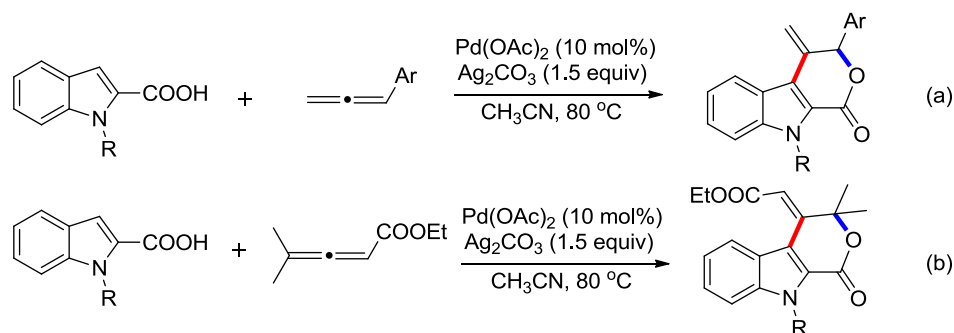
Ir-catalyzed oxidative coupling of benzoic acids with alkynes to produce naphthalene

derivatives was reported by Miura and co-workers, in which 2 equiv of the alkyne should be incorporated (Scheme 284).³⁹³ Different from the rhodium-catalyzed reactions (Scheme 263), the iridium-catalyzed reactions went through the decarboxylation of the seven-membered iridacycle and the subsequent insertion to the second alkyne to afford naphthalene.



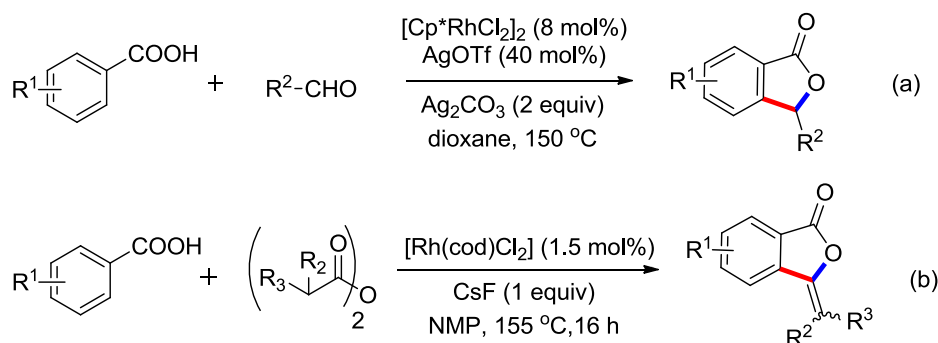
Scheme 285 Rh-catalyzed oxidative coupling of substituted arene or heteroarene carboxylic acids with alkynes.

Jeganmoha's group reported Ru-catalyzed oxidative cyclization of aryl carboxylic acids with alkynes (Scheme 285).³⁹⁴ By the use of Ru/Ag catalyst system, the isocoumarin could be produced as the final product and no naphthalene derivatives were observed. Simultaneously, Ackermann group reported a similar catalyst system to synthesize isocoumarins and α -pyrones through the coupling of carboxylic acids with alkynes in the presence of cationic Ru(II) catalyst.³⁹⁵⁻³⁹⁶ In this reaction, AgSbF₆ was much less effective than KPF₆ for promoting the transformation.



Scheme 286 Pd-catalyzed oxidative annulation of allenes with indole-2-carboxylic acids.

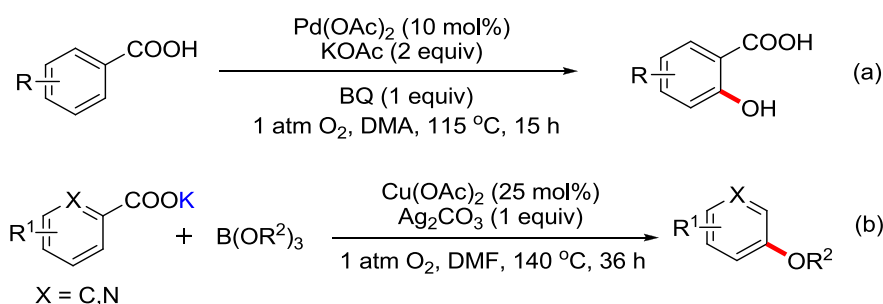
A Pd-catalyzed oxidative annulation of allenes with *N*-alkyl-indole-2-carboxylic acid derivatives via direct C-H functionalization was described by Swamy group in 2012 (Scheme 286).³⁹⁷ The reaction underwent the initial palladation at the C3-position of indole to form the palladacycle intermediate, followed by the subsequent insertion of C-Pd bond into allenes and reductive elimination to generate the lactones in moderate to good yields. This method was fairly general for a wide range of allenes, even terminal substituted allenes.



Scheme 287 Rh-catalyzed carboxylate-directed *ortho*-C-H functionalization with aldehydes.

Besides carbon-carbon multiple bonds, C=O bond can also be inserted by immediate C-M species generated from transition metal-catalyzed C-H cleavage. In 2012, Li group described a novel Rh(III)-catalyzed synthesis of 3-substituted phthalides from benzoic acids and aldehydes (Scheme 287a).³⁹⁸ The reaction should proceed through carboxylate-directed *ortho*-C-H functionalization and subsequent intramolecular cyclization to generate 3-substituted phthalides in moderate to good yields. The initial coordination of Rh(III) species to the carboxylic oxygen atom was attributed to the use of Ag₂CO₃ as the base. In 2013, Gooßen and co-workers reported the [Rh(cod)Cl]₂/CsF catalyst system to promote the straightforward synthesis of 3-alkylidene phthalides from benzoic acids and aliphatic acids or anhydrides in one-pot (Scheme 287b).³⁹⁹

6.7 C-X bond formation

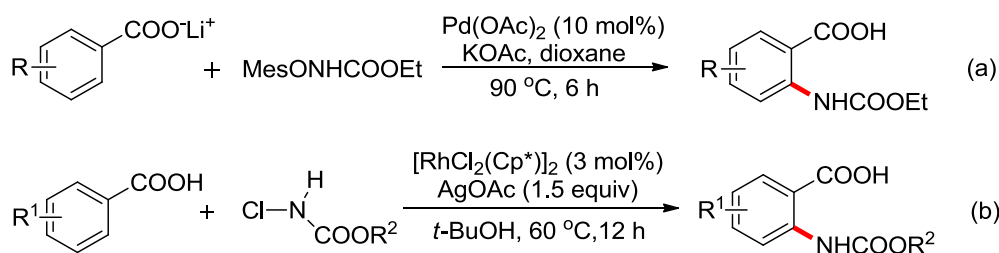


Scheme 288 Pd-catalyzed carboxylate-directed *ortho*-hydroxylation of benzoic acids with O₂.

The C-O bonds are privileged in organic structures, including pharmaceuticals and agricultural chemicals, and C-O bond formation has been a research topic of great importance for C-H activation. In 2009, Yu group discovered a versatile Pd-catalyzed *ortho*-hydroxylation of benzoic acids with O₂ as the oxygen source (Scheme 288a).⁴⁰⁰ The addition of 1 equiv of benzoquinone significantly increased the rate of the hydroxylation and improved the yields of

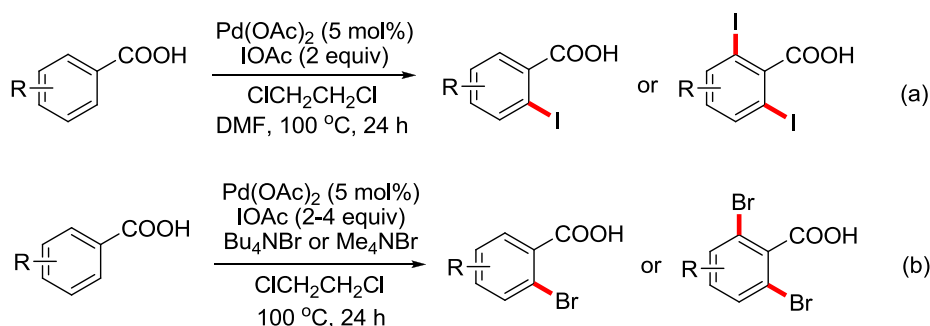
the products. The reaction exhibited many notable advantages, such as wide substrate scope and high atom efficiency. Direct oxygenation of the aryl-Pd species by molecular O₂ was proposed, which was consistent with the labeling results using ¹⁸O₂ and H₂¹⁸O. The method was important in the field of hydroxylation of inert C-H bonds using molecular oxygen

Gooßen group further developed a Cu/Ag-catalyzed C-H alkoxylation of aromatic carboxylates, in which the carboxylate substituent was used as a cleavable directing group (Scheme 288b).⁴⁰¹ Best yields could be achieved performing the reaction under O₂ atmosphere. Benzoates with electron-donating or electron-withdrawing groups could be smoothly converted, and a broad range of functional groups, including keto, cyano, nitro, sulfonyl, *N*-heterocyclic, and even bromo substituents, were tolerated. High selectivity was achieved, in which neither double alkoxylation nor non-decarboxylative alkoxylation was observed. The reaction represented a rare example of an aromatic functionalization, in which the original directing group was removed during the transformation.



Scheme 289 Pd-catalyzed intermolecular C-H amination of benzoic acids.

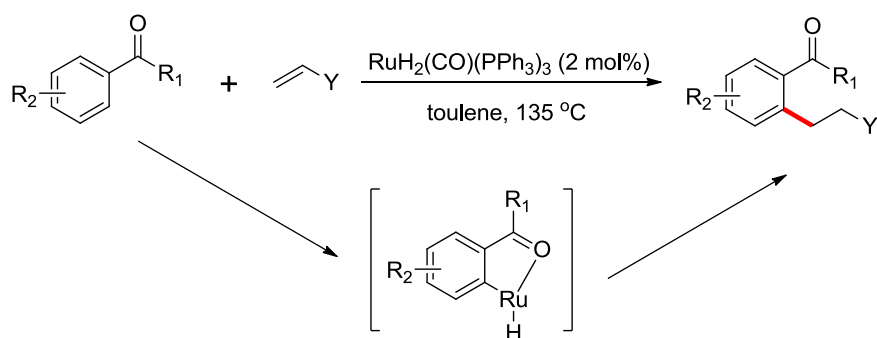
Besides the C-C and C-O bonds, other C-heteroatom bonds could be formed via carboxylate-directed C-H activation. In 2012, Yu groups reported a novel method to synthesize anthranilic acid by intermolecular C-H amination of *N*-arylbenzamides with *O*-benzoyl hydroxylamines in the presence of Pd(OAc)₂ and KOAc (Scheme 289a).⁴⁰² The reaction presented excellent regioselectivity and functional group compatibilities. Mechanism studies demonstrated that the amidation was probably initiated by rate-limiting cyclo-palladation ($k_{\text{H}}/k_{\text{D}} = 2.6$) of the benzoic acids. Recently, a Rh(III)-catalyzed direct *ortho*-C-H amidation/amination of benzoic acids with *N*-chlorocarbamates/*N*-chloromorpholines was also achieved to give anthranilic acids in up to 85% yields with excellent *ortho*-selectivity and functional group tolerance (Scheme 289b).⁴⁰³



Scheme 290 Pd-catalyzed C-H halogenation of benzoic acids assisted by counter cations.

In 2008, Yu and co-workers developed the Pd-catalyzed *ortho* halogenation of carboxylic acids (Scheme 290).⁴⁰⁴ The IOAc was generated *in situ* from PhI(OAc)₂ and I₂, which served as the key iodination reagent in the transformation. When tetrabutylammonium bromide was used, the corresponding brominated products could be afforded with improved monoselectivity. The authors proposed that the large tetraalkyl ammonium cation appeared to assist in the displacement of the monoiodinated (or monobrominated) product from the Pd(II) center to prevent the undesired dihalogenation. Subsequently, the Pd(II)-catalyzed *ortho*-C-H iodination reactions of phenylacetic acids were achieved by the same group.⁴⁰⁵ The synthetic utility of this iodination reaction was further demonstrated by carrying out the subsequent amidation, cyanation, acetylenation and homologation reactions.

7 The C-H functionalization directed by carbonyl group of ketone and aldehyde

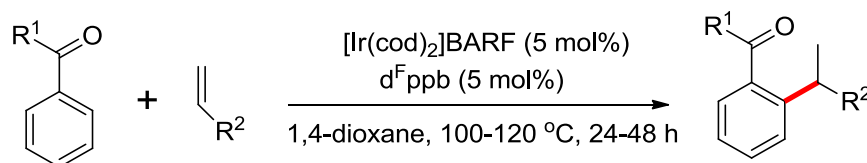


Scheme 291 Ruthenium-catalyzed addition of aromatic C-H bonds to olefins.

Ketones are one of the most common and popular functionalities in organic chemistry. In 1993, Murai and co-workers studied the transition metal catalyzed C-H activation by using ketone as the directing group (Scheme 291).^{2b} It was demonstrated that the *ortho*-alkylation of acetophenones with olefins could be achieved in the presence of low-valent ruthenium

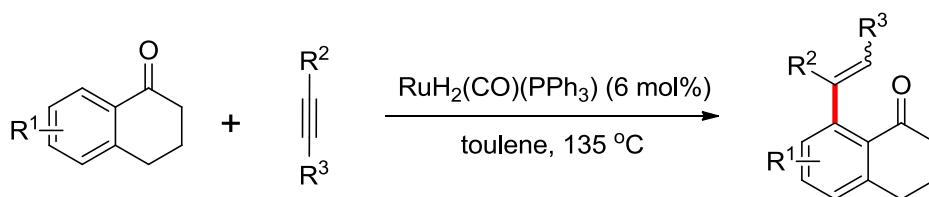
properties of the catalyst by adopting different ligands. These novel protocols were compatible with a wide range of substrates such as heteroaromatic ketones, conjugate enones, and aromatic imines. Subsequently, a simple catalytic system to achieve *ortho*-alkylation of ketones using the cheaper $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ as the catalyst was developed by the same group (Scheme 292).^{408f}

The first rhodium-catalyzed *ortho*-alkylation of ketones with diverse olefins was demonstrated by Brookhart and co-workers in 1999.⁴⁰⁹ The rhodium bis-olefin complex $[\text{C}_5\text{Me}_5\text{Rh}(\text{C}_2\text{H}_3\text{SiMe}_3)_2]$ was identified as an efficient catalyst for the selective addition of olefins to the *ortho* position of aromatic ketones. In contrast to ruthenium-catalyzed *ortho*-alkylation reaction reported by Murai, the rhodium complex was not involved in the carbonyl coordination process for the *ortho* C-H activation, but activation of all sites (*ortho*, *meta*, *para*) of the substrate was observed. The chelation of the carbonyl group to the metal center lowered the barrier for reductive elimination to product.



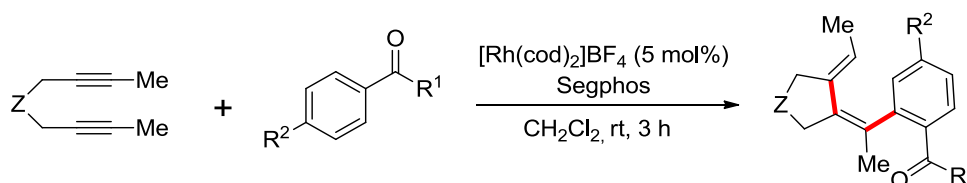
Scheme 293 Iridium-catalyzed hydroarylation of monosubstituted alkenes.

Among previous works reported, the anti-Markovnikov addition product was preferentially formed. Recently, Bower and co-workers developed an efficient system for branch-selective carbonyl-directed *ortho*-alkylation monosubstituted olefins using cationic Ir(I) catalyst (Scheme 293).⁴¹⁰ Ligands had a significant impact on the reaction efficiency and branch selectivity. After detailed screening of the ligands, $\text{d}^{\text{F}}\text{ppb}$, a previously unreported ligand that was the pentafluorophenyl analogue of dppb , was optimal ligand for providing the desired product in quantitative yield with complete branch selectivity. The catalytic system was compatible with a wide range of directing groups and afforded a series of branched hydroarylation products with high efficiency.

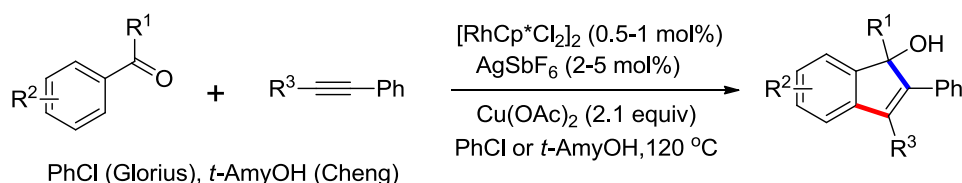


Scheme 294 Ruthenium-catalyzed addition of aromatic C-H bonds to acetylenes.

The ruthenium-catalyzed *ortho*-alkenylation of ketones with various internal acetylenes was described by Murai and co-workers in 1995 (Scheme 294).⁴¹¹ An *E/Z* mixture of 1:1 coupling products was afforded in good yields for symmetrically substituted dialkyl- and diarylacetylenes. The present protocol also provided a useful method for the preparation of diverse substituted vinylsilanes. Subsequently, this reaction was extended to vinylic C-H bonds of α,β -conjugate enones by Murai, giving a variety of conjugated dienones with the assistance of $\text{RuH}_2\text{CO}(\text{PPh}_3)_2$ as the catalyst.⁴¹² Woodgate and co-workers demonstrated a similar alkenylation reaction of fused aromatic ketones. Cyclopenta[*a*]naphthalene derivatives could be yielded through a one-pot insertion-cyclisation sequence.⁴¹³ Cationic iridium-BINAP complex-catalyzed addition *ortho*-C-H bonds in aryl ketones to alkynes was reported by Shibata and co-workers in 2008.⁴¹⁴

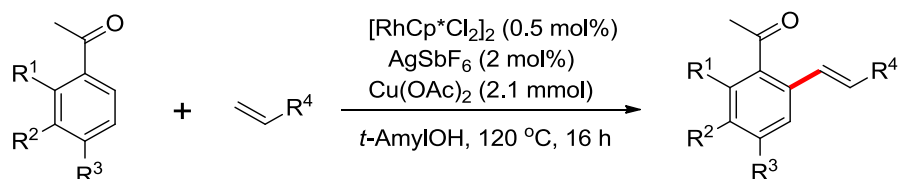
**Scheme 295** Rh-catalyzed cyclization of diynes and enynes.

Tanaka⁴¹⁵ and Shibata⁴¹⁶ independently developed a cationic rhodium(I)-catalyzed cascade reaction of aromatic ketones with 1,6-diynes to give 1,3-dienes in high yields in 2007 (Scheme 295). Carbonyl-directed activation of aromatic and vinylic C-H bonds was regarded as the key step in the transformation. Shibata also pointed out that when ketone substrates were treated with 1,6-enynes, chiral products could be obtained with high *ee* value using a chiral Rh catalyst.

**Scheme 296** Rhodium(III)-catalyzed regioselective synthesis of indenols.

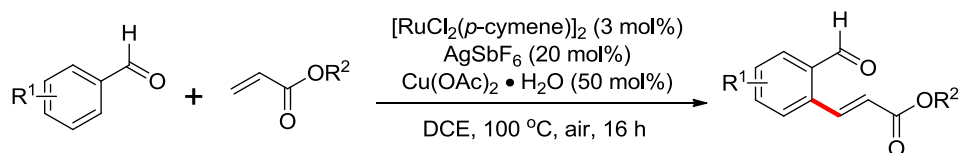
Substituted indenol derivatives are an important structural motif present in various biologically active compounds. Glorius and Cheng group independently developed a rhodium(III)-catalyzed directing group-assisted C-H activation/carbocyclization of aryl ketones with alkynes to afford substituted indenols in good to excellent yields (Scheme

296).⁴¹⁷⁻⁴¹⁸ Glorius found that with regard to electron-neutral and electron-rich phenones bearing protons at dehydrative positions (α or γ), the corresponding fulvene derivatives were successfully afforded after changing PhCl to 1,4-dioxane in higher temperature. Subsequently, Jeganmohan and co-workers also reported a similar reaction of Ru-catalyzed C-H activation of substituted ketones with alkynes, providing substituted indenol derivatives in good to excellent yields.⁴¹⁹



Scheme 297 Rhodium-catalyzed oxidative olefination of C-H bonds.

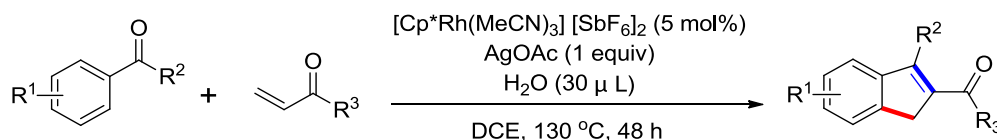
Different from the Ru-catalyzed *ortho*-alkylation reaction of ketones with olefins reported by Murai, rhodium(III)-catalyzed oxidative *ortho*-olefination reaction of aromatic ketones with a wide range of olefins was realized by Glorius and co-workers (Scheme 297).^{69a} This reaction exhibited broad substrate scope and both electron-poor and electron-rich styrenes were well tolerated. Subsequently, a similar olefination reaction of aromatic ketones using $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ as the catalyst was reported by Jeganmohan and co-workers.⁴²⁰



Scheme 298 Ruthenium(II)-catalyzed *ortho*-alkenylation of aromatic and heteroaromatic aldehydes.

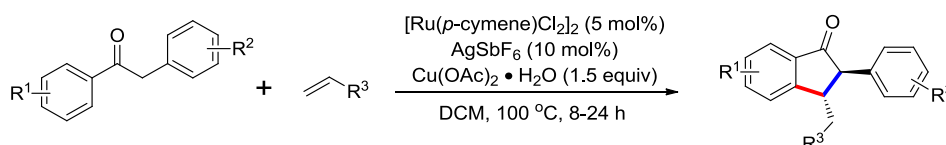
A ruthenium(II)-catalyzed *ortho*-alkenylation of aromatic and heteroaromatic aldehydes with activated alkenes to give substituted alkene derivatives in good to moderate yields was developed by Jeganmohan (Scheme 298).⁴²¹ It was the first example of *ortho*-alkenylation reaction directed by a weakly coordinating aldehyde group. The incident side reaction of decarbonylation of aldehydes, hydroacylation of aldehydes with alkenes, and oxidation of aldehydes to acids were not observed in the reaction. Through a photochemical rearrangement, the obtained alkene products could be further converted into some unusual four-membered cyclic ketones or polycyclic isochromanone derivatives. Based on Jeganmohan's work, Prabhu and co-workers demonstrated a ruthenium(II)-catalyzed highly regioselective

alkenylation of indole at the C-4 position by using an aldehyde functional group as a directing group under mild conditions, giving various biologically active 4-substituted indole derivatives in high yields.⁴²²



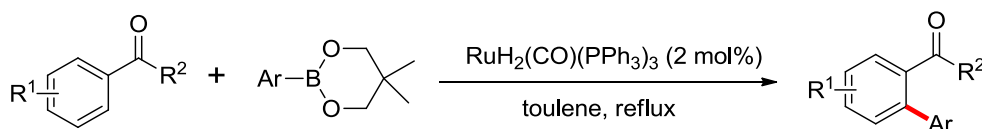
Scheme 299 Rhodium-catalyzed synthesis of indene frameworks.

An unprecedented rhodium(III)-catalyzed direct functionalization of *ortho*-C-H bonds of aromatic ketone derivatives followed by an intramolecular cyclization sequence to prepare indene derivatives was presented by Li and co-workers (Scheme 299).⁴²³ A conjugate addition of α , β -unsaturated ketone and subsequent aldol condensation was regarded to be involved in the cascade reaction. Notably, the reaction was insensitive to air and water, providing a practical and convenient route to synthesize indene derivatives.



Scheme 300 Ruthenium-catalyzed cascade C-H functionalization of phenylacetophenones.

More recently, a ruthenium-catalyzed C-H alkenylation by using arylacetophenones and olefines as substrates was developed by Greaney and co-workers (Scheme 300).⁴²⁴ According to the different choices of substrate and reaction conditions, three orthogonal cascade C-H functionalization processes were undergone to access 1-indanones, indeno indenenes, and indeno furanones through cascade pathways. A wide series of polycyclic architectures could be readily afforded in a single operation with ruthenium-catalyzed multiple C-H functionalization steps.

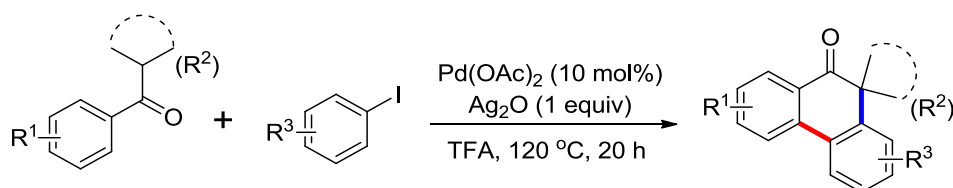


Scheme 301 Ruthenium-catalyzed arylation of aromatic ketones with arylboronates.

A Pd-catalyzed multiple arylation of benzyl phenyl ketones with aryl bromides was developed by Miura and co-workers in 1999.⁴²⁵ In the presence of excess aryl bromides, the α - and two *ortho*- positions of carbonyl group was completely arylated and diphenylmethyl

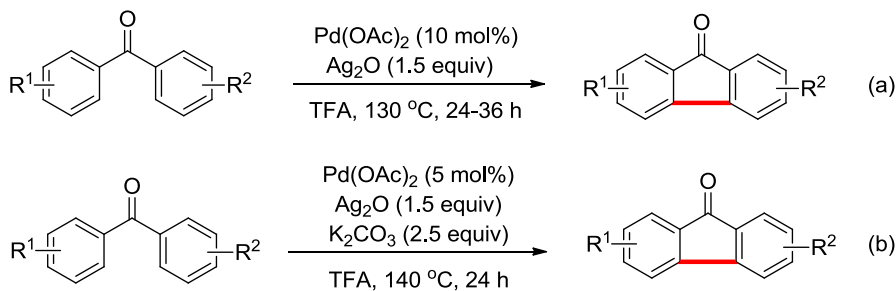
2,6-diphenylphenyl ketone derivatives were predominant products.

The Ru-catalyzed *ortho*-arylation of aromatic ketones using arylboronates as the arylating reagents was reported by Kakiuchi and co-workers in 2003, giving the arylated phenyl ketones with high efficiency and regioselectivity (Scheme 301).^{426a} Further intensive investigations of the reaction by the same group^{426b} indicated that the use of aliphatic ketones, such as pinacolone and acetone, as an additive or solvent dramatically suppressed the undesired reduction of the aromatic ketones, producing the final *ortho*-arylation products in high yields. Detailed mechanistic studies revealed that the pinacolone functioned as a scavenger of *ortho*-hydrogens of the aromatic ketones or as the acceptor of the HB species. The results of kinetic isotope effects showed that the ketone carbonyl group coordinated to the ruthenium catalyst prior to C-H bond cleavage. This useful transformation provided an alternative method for the preparation of biaryl compounds.



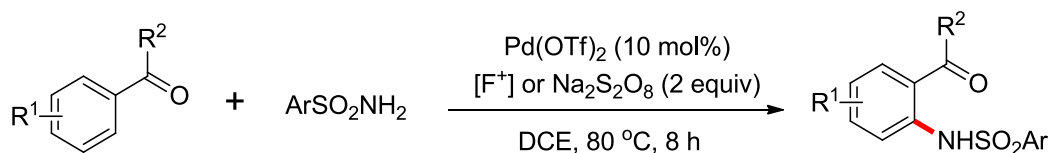
Scheme 302 Synthesis of phenanthrones from *sec*-alkyl aryl ketones and aryl halides.

A palladium(II)-catalyzed novel and mechanistically interesting method for the synthesis of phenanthrone derivatives from *sec*-alkyl aryl ketones and aryl iodides via dual C-H activation and enolate cyclization was developed by Cheng and co-workers (Scheme 302).⁴²⁷ The five-membered palladacycle dimer from the reactions of Pd(OAc)₂ with aryl ketones in TFA was isolated and determined by single crystal X-ray diffraction, affording some evidences of the reaction mechanism. After completing the first C-H activation to deliver the arylation product, further C-H activation of another Pd complex gave seven-membered palladacycle, which underwent enolization, rearrangement and subsequent reductive elimination to give the final product.



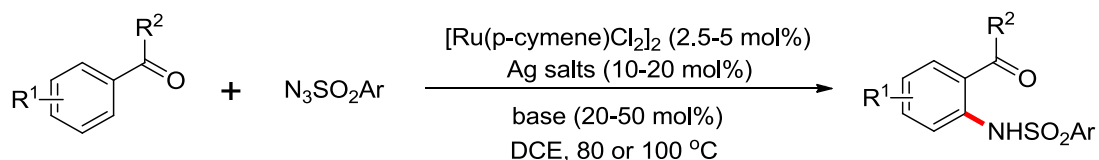
Scheme 303 Pd-Catalyzed dehydrogenative cyclization for the synthesis of fluorenones.

A palladium-catalyzed intramolecular oxidative dehydrogenative cyclization of aromatic ketones to afford the fluorenone derivatives was reported by Cheng⁴²⁸ and Shi,⁴²⁹ independently (Scheme 303). The choice of solvent was crucial for the transformation and trifluoroacetic acid (TFA) was used as the optimal solvent to give the desired fluorenone product in the highest yield. The reaction exhibited broad substrate scope and provided a convenient and effective route toward the synthesis of fluorenone derivatives.



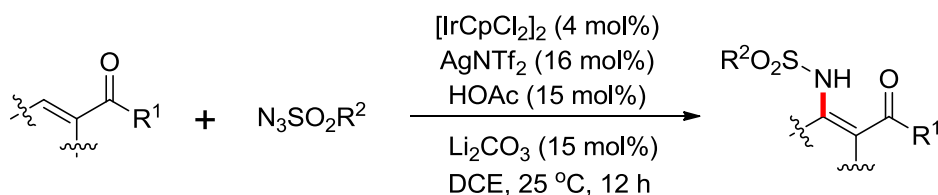
Scheme 304 Palladium-catalyzed intermolecular directed C-H amidation of aromatic ketones.

In contrast to a lot of previous studies on ketone-directed C-C bond formation, ketone-directed construction of C-N bond has rarely been reported. Until 2011, Liu and co-workers made a significant breakthrough on Pd-catalyzed intermolecular oxidative directed C-H amidation of aromatic ketones with amides (Scheme 304).⁴³⁰ The electrical property of Pd species was crucial for the success of this transformation and electron-deficient Pd(OTf)₂ was chosen as the best one. As for ketone substrates, electron-rich ketones could more strongly coordinate to Pd, showing a better performance than that of electron-deficient ketones. Furthermore, the superiority was embodied by the case that ketones with more electron-rich tertiary alkyl groups exhibited a higher efficiency than ketones with a primary or secondary alkyl group. Some relevant mechanical investigations indicated that the reaction might not involve a nitrene intermediate and the C-H activation was presumably the rate-limiting step of the transformation.



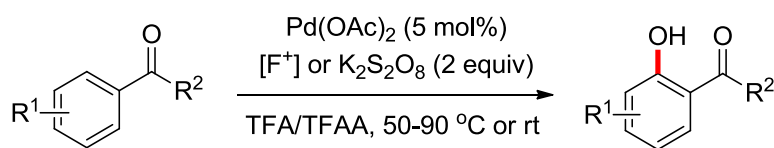
Scheme 305 Ru(II)-catalyzed *ortho*-C-H amidation of aromatic ketones with sulfonyl azides.

More recently, the Ru-catalyzed *ortho*-C-H amination of aromatic ketones by using sulfonyl azides as the nitrogen source was reported by Chang, Sahoo and Jiao, respectively.⁴³¹⁻⁴³³ The reaction featured with high functional group tolerance and a wide range of sulfonylazides could be successfully installed on arylketones, providing a new complementary approach to the practical ketone-directed intermolecular C-N bond formation (Scheme 305). In addition to Chang's amination of ketones, some strong coordinating nitrogen groups such as benzamide, 2-pyridyl, pyrazol, and ketoxime moieties all enabled the *ortho*-C-H amination smoothly in the presence of AgSbF₆ salt and acetate additive.



Scheme 306 The iridium-catalyzed intermolecular C-H amidation of ketone derivatives.

The iridium-catalyzed direct intermolecular C-H amidation of weakly coordinating substrates, particularly of ketone derivatives was developed by Chang and co-workers (Scheme 306).⁴³⁴ During the optimization of reaction, the lithium counteraction was found to have a significantly stronger effect on the transformation than other cations and the combination of lithium carbonate with acetic acid gave the desired products in almost quantitative yield. With the successful isolation of relevant iridacyclic intermediates, some convincing evidences of the mechanistic aspects were proposed and the role of additives was also speculated herein. The facile conversion of ester and ketone functional group further extended the application of this useful transformation.

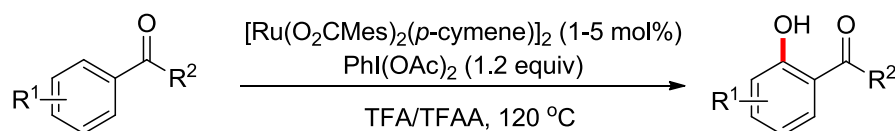


Scheme 307 Palladium-catalyzed *ortho*-C-H bond oxygenation of aromatic ketones.

ortho-Acylphenol is an important structural motif found in diverse bioactive molecules

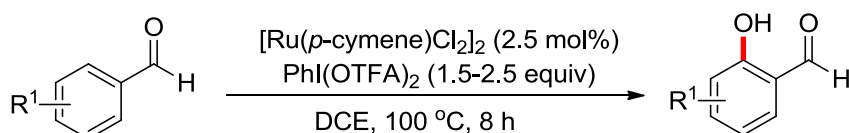
from natural products to drugs and can be readily used for the preparation of various oxygen-containing heterocycles. The Pd-catalyzed regioselective *ortho*-hydroxylations of ketones, benzoates, benzamides, acetanilides, and sulfonamides at room temperature was reported by Rao and co-workers in 2012 (Scheme 307).⁴³⁵ A broad range of functionalized phenols were accessed in high yields by this method. Preliminary mechanistic investigations revealed that the TFA/TFAA solvent system served as both the essential factor for C-H activation and as the oxygen source. The reaction showed excellent reactivity, good functional group tolerance, and high regioselectivity. The obtained phenol derivatives could be easily transformed into some oxygen-containing heterocycles and key intermediates of drugs.

Simultaneously, Dong and co-workers also developed a Pd-catalyzed *ortho*-selective formal hydroxylation of arenes to produce various 2-acylphenols.⁴³⁶ Moreover, a Pd-catalyzed *ortho*-carboxylation of simple aryl ketones to afford an unusual ketal-lactone motif was also disclosed concomitantly. Soon after, the similar research of palladium-catalyzed *ortho*-oxygenation of aromatic ketones by using $\text{PhI}(\text{OTFA})_2$ as oxidant was described by Kwong and co-workers.⁴³⁷



Scheme 308 Ru-catalyzed *ortho*-oxygenation of aromatic ketones.

The Ru-catalyzed *ortho*-oxygenation of aromatic ketones was developed by Ackermann in 2012 (Scheme 308).⁴³⁸ $[\text{Ru}(\text{O}_2\text{CMes})_2(p\text{-cymene})]_2$ was the effective catalyst and $\text{PhI}(\text{OAc})_2$ was used as terminal oxidant to give the desired product in highest yields. The reaction proceeded with excellent functional group tolerance and broad substrate scope.



Scheme 309 Aldehyde-assisted Ruthenium(II)-catalyzed C-H oxygenations.

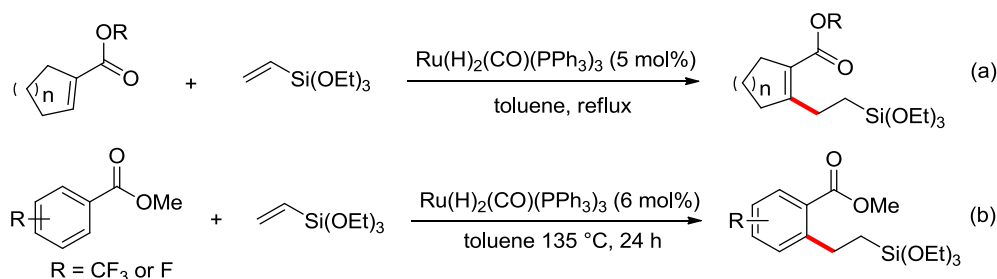
Recently, the Ru-catalyzed *ortho*-C-H oxygenation by using very weakly coordinating aldehydes as directing groups was also developed by Ackermann and co-workers (Scheme 309).⁴³⁹ Among a variety of ruthenium complexes, $[\text{RuCl}_2(p\text{-cymene})]_2$ was the optimal catalyst. The detailed mechanistic studies revealed that the oxygenation reaction initially

occurred by a kinetically relevant C-H metalation and the obtained 2-hydroxy benzaldehydes could be easily converted into various valuable heterocycles.

8 The C-H functionalization directed by ester

8.1 The C-H functionalization directed by ester from acid

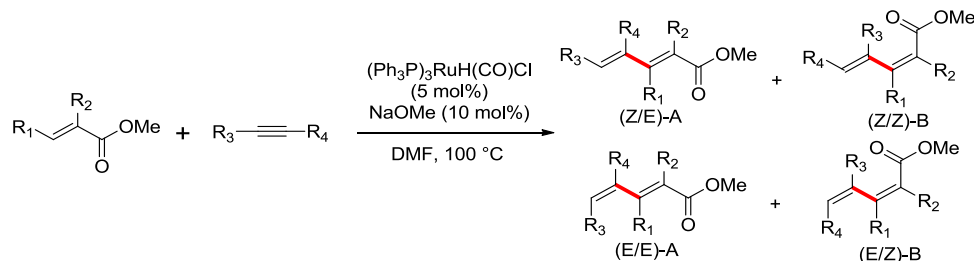
In contrast, the application of ester functionality as the feasible directing group in the transition-metal-catalyzed C-H bond activation has not been widely reported. However, as a weakly coordinating group, the ester moiety serves as a promising and valuable directing group due to its possession of numerous advantages. First, it presents weak coordination to catalysts to induce selective C-H bond cleavage and facilitate the release of the catalyst species. Second, this functional group is omnipresent in numerous natural products and synthetic compounds. Third, the ester unit may be used as a readily manageable protecting group in organic synthesis and it can be converted into various functional groups under ambient conditions.



Scheme 310 Ruthenium-catalyzed addition of aromatic esters to olefins.

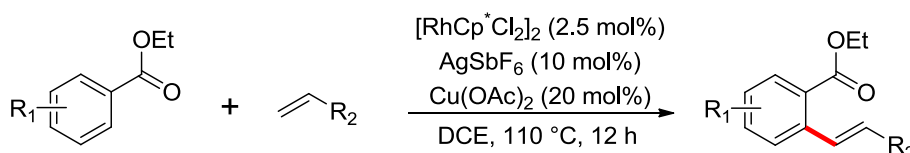
The first transition metal catalyzed ester directed *ortho*-alkylation of functional alkenes was reported in 1995 by Trost and co-workers (Scheme 310a).^{406b} Using Ru(H₂)(CO)(PPh₃)₃ as an efficient catalyst, the methyl-1-cyclopentenecarboxylate or cyclohexenecarboxylate reacted effectively with alkene to give the desired C-H/olefin coupling products. However, the substrates such as methyl benzoates were incompatible with this methodology. Simultaneously, Murai and co-workers also tried this reaction using the same catalyst and substituted alkyl benzoates could be successfully involved in this reaction (Scheme 310b).^{440a} They found that the introduction of an electron-withdrawing group in the aromatic ring dramatically changed the reactivity. The reaction of aromatic ester substituted with CF₃ or F with triethoxyvinylsilane occurred smoothly to give the coupling products. Further studies

showed that the substrates were limited to a benzo- δ -lactone, heteroaromatic esters and aromatic ester substituted with CF₃ or F. Other benzoates with electron-withdrawing groups, such as *o*-CO₂Me, *o*-CN, *o*-NO₂ and *p*-NO₂ failed to afford coupling products.^{440b}



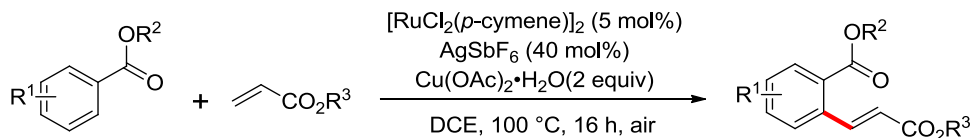
Scheme 311 Ruthenium-catalyzed hydrovinylation of alkynes with alkenes.

Plietker and co-workers revealed a ruthenium-catalyzed broadly applicable hydrovinylation of terminal and internal alkynes with highly substituted electron-deficient olefins (Scheme 311).⁴⁴¹ The efficient ruthenium hydride complex was air and moisture stable, and could be readily prepared from RuCl₃. The addition of catalytic amounts of NaOMe had a significant effect on derivatization of the catalyst based on the important preliminary studies by Murai, rendering the reaction proceed smoothly in the case of some substituted acrylates. Some deuterated experiments were conducted to shed light on the reaction mechanism. A variety of highly substituted 1,3-dienes were obtained using this method in good to excellent yields.

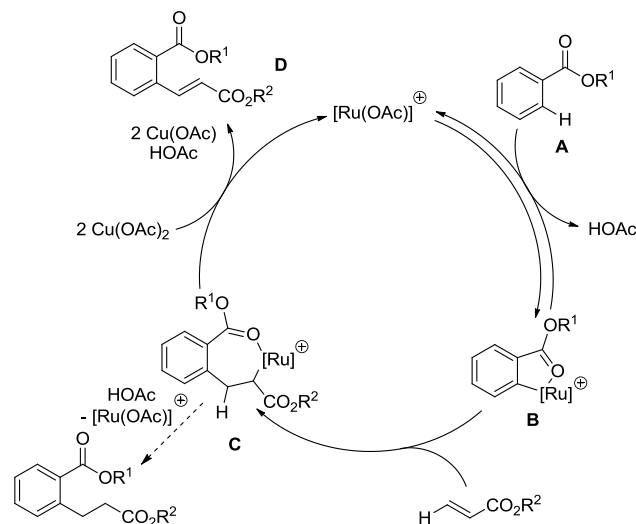


Scheme 312 Rhodium-catalyzed *ortho*-olefination of arene esters.

Chang and co-workers reported a Rh(III)-catalyzed *ortho*-olefination of benzoates under the oxidative conditions (Scheme 312).⁴⁴² They found that an ester moiety could work as an efficient directing group in the Rh(III)-catalyzed olefination reaction. A catalytic copper oxidant was enough for the high yield of the olefination product. The alteration of an alkoxy part of benzoates and the position of an additional substituent on benzoates had little influence on the reaction efficiency. A significant kinetic isotope effect (KIE) based on the deuterated experiment was observed ($k_H/k_D=2.3$), indicating that the C-H bond cleavage at the 2-position of ethyl benzoate was likely involved in the rate-determining step.

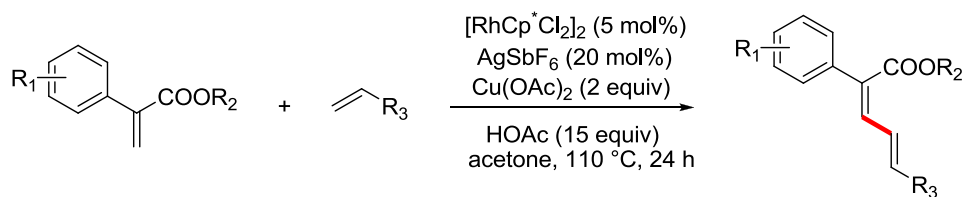


Scheme 313 Ruthenium-catalyzed oxidative alkenylation of aromatic esters.



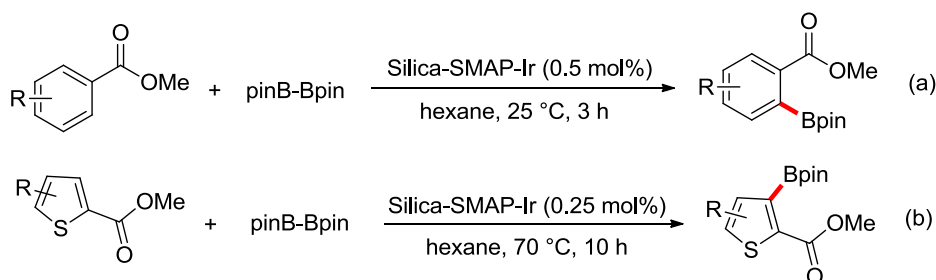
Scheme 314 The proposed mechanism.

Oxidative Fujiwara-Moritani-type alkenylations with weakly coordinating aromatic esters as the directing groups were accomplished by employing a cationic ruthenium(II) complex (Scheme 313). The two-fold C-H bond functionalizations offered a convenient method for the synthesis of various highly substituted alkene derivatives in a highly regio- and stereoselective manner. Jeganmohan⁴⁴³ and Ackermann⁴⁴⁴ independently reported the site-selective ruthenium-catalyzed oxidative alkenylations of arenes bearing weakly coordinating esters. The obtained substituted alkene derivatives could be easily transformed into substituted acrylic acid derivatives in excellent yields. Mechanistic studies were indicative of a reversible acetate-assisted cycloruthenation step to form complex **B**. Subsequent migratory insertion of alkene furnished intermediate **C**, followed by β -hydride elimination gave the desired product **D**, the catalytically active cationic species were regenerated by the oxidation of $\text{Cu}(\text{OAc})_2$ (Scheme 314).



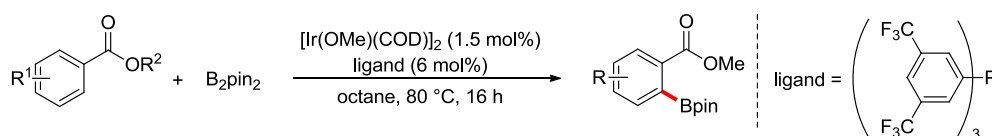
Scheme 315 Ester-directed selective olefination of acrylates by rhodium catalysis.

Very recently, Zhang group successfully developed a general and selective method to prepare conjugated dienes by Rh(III)-catalyzed direct olefination of acrylates with electron-rich alkenes via double C(sp²)-H bond activation (Scheme 315).⁴⁴⁵ It was noteworthy that ester group of acrylates was found to be important to improve the activation of vinylic C-H bond through chelation. Furthermore, this direct cross-coupling reaction exhibited high stereoselectivity to give the (*Z*, *E*) diene isomer as the major product (the ratio of (*Z*, *E*) and (*E*, *E*) isomer is 96/4). This protocol provided an efficient route for the preparation of diverse substituted 1,3-butadienes



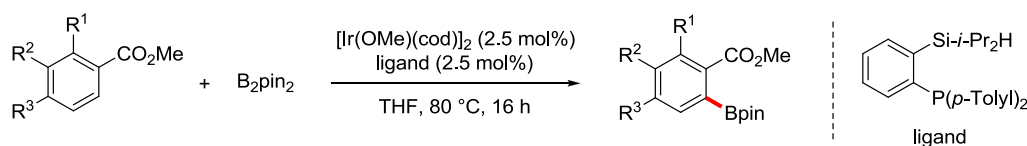
Scheme 316 Ir-catalyzed borylation of functionalized aromatic esters.

Direct borylation of C-H bonds is a highly active recent research subject in the catalytic use of C-H bonds. Sawamura and co-workers reported the ester directed *ortho*-borylation of aromatic C-H bonds with bis(pinacolato)diboron using a solid-supported monophosphine-Ir system. Silica-SMAP-Ir, which was readily formed *in situ* from [Ir(OMe)-(cod)]₂ and Silica-SMAP, showed high activities and selectivities for the borylation of aromatic C-H bonds (Scheme 316a).⁴⁴⁶ The monocoordinating feature of the immobilized phosphine ligand had a obviously positive role in highly efficient *ortho*-directing effects, whereas electronic effects of the strongly σ -donating SMAP ligand might have an additional influence on the catalytic properties. Later, they also developed the ester-directed regioselective borylation of heteroarenes catalyzed by a Silica-supported Iridium complex, a wide range of heteroarenes, including thiophene, pyrrole, furan, benzothiophene, benzofuran, indole, and carbazole derivatives could be well involved in the reaction. (Scheme 316b).⁴⁴⁷



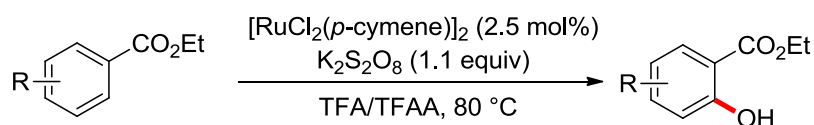
Scheme 317 Iridium catalyzed *ortho*-C-H borylation of benzoate esters.

Miyaura and co-workers disclosed an iridium catalyzed *ortho*-C-H borylation of benzoate ester derivatives with bis(pinacolato)diboron (Scheme 317).⁴⁴⁸ The iridium complexes was readily *in situ* generated from $[\text{Ir}(\text{OMe})(\text{COD})]_2$ and commercial tris[3,5-bis(trifluoromethyl)-phenyl]phosphine. The choice of iridium precursor was crucial for the borylation and $[\text{Ir}(\text{OMe})(\text{COD})]_2$ in non-polar solvent showed the best reactivity. The corresponding aromatic boron compounds were produced in high yields with excellent regioselectivities.



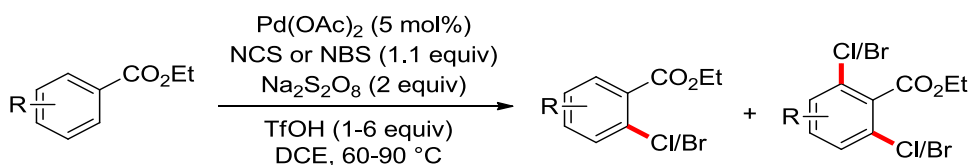
Scheme 318 Iridium-catalyzed *ortho*-borylation of alkyl benzoates.

Compared with Ir-catalyzed borylations using surface supported phosphine ligands, which were the pioneer works by Sawamura, Smith and co-workers developed a novel homogeneous Ir catalysts that could mimic these heterogeneous ones using bidentate silyl ligands that contained *P*- or *N*-donors which were shown to effect *ortho*-borylations for a range of substituted aromatics (Scheme 318).⁴¹⁹ The novel bidentate silyl ligand exhibited high reactivity and a number of substituted methyl benzoates could successfully participate in the reaction, providing the mono- and di-borylated products.



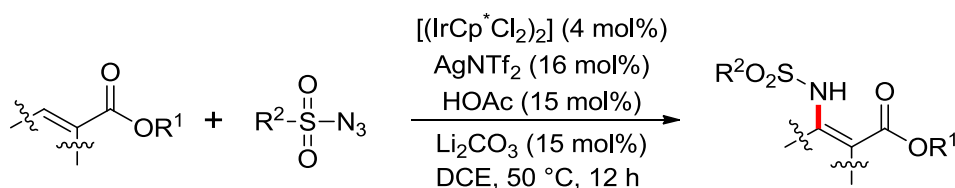
Scheme 319 Ruthenium(II)-catalyzed synthesis of hydroxylated esters.

Rao and co-workers reported the first example of ruthenium(II)-catalyzed *ortho*-hydroxylation of benzoates using ester as an efficient directing group (Scheme 319).⁴⁵⁰ Both the TFA/TFAA cosolvent system and oxidants ($\text{K}_2\text{S}_2\text{O}_8$, Selectfluor, or iodic acid) served as the critical factors in this transformation. The ratio of TFA/TFAA also had an indispensable role in the high yield of the reaction. Higher temperature was necessary for improving the yields. It was possible that the catalytic pathway might undergo a Ru(IV) intermediate, followed by reductive elimination to afford the final product. A wide series of *ortho*-hydroxylated ethyl benzoates could be generated in high efficiency by this method.



Scheme 320 Chlorination/bromination of electron-deficient arenes.

Rao and co-workers reported the first palladium(II)-catalyzed regio- and chemoselective *ortho*-chlorination/bromination reaction of benzoates and 2-phenylacetates (Scheme 320).⁴⁵¹ This method was developed for the synthesis of a broad range of arene chlorides/bromides by the use of NCS/NBS as the halide source. The use of proper oxidant was an essential factor for the regioselectivity of this reaction and $\text{Na}_2\text{S}_2\text{O}_8$ was the best one. In addition, the amount of TfOH also significantly affected both the rate and outcome of the reaction. Mechanistic investigations indicated that the C-H bond cleavage might be involved in the rate-limiting step of this transformation. It should be noted that this protocol was conducted without the need for air- or moisture-free reaction conditions, making the method more convenient and practical.



Scheme 321 Ir-catalyzed amidation with an ester directing group.

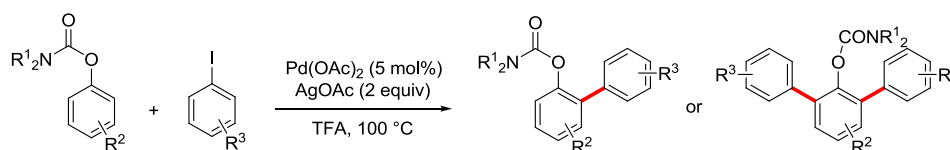
Chang and co-workers described the Ir(III)-catalyzed direct amidation of aryl and alkenyl $\text{C}(\text{sp}^2)\text{-H}$ bonds using esters as viable chelating groups under very mild conditions (Scheme 321).⁴³⁴ The *para*-toluenesulfonyl azide was used as the nitrogen source. A combination of AcOH and Li_2CO_3 would generate lithium acetate and lithium bicarbonate *in situ*, and an acetate ion was expected to coordinate more favorably to the cationic iridium center to form the iridium acetate resting species. The reaction exhibited a broad substrate scope and proceeded under very mild conditions with excellent functional group tolerance. In addition, the protocol could be readily carried out on a gram scale. It was noteworthy that the ester unit could be converted into various functional groups under ambient conditions.

8.2 The C-H functionalization directed by ester from aryl phenol

Because substituted phenols are important organic intermediates with broad synthetic

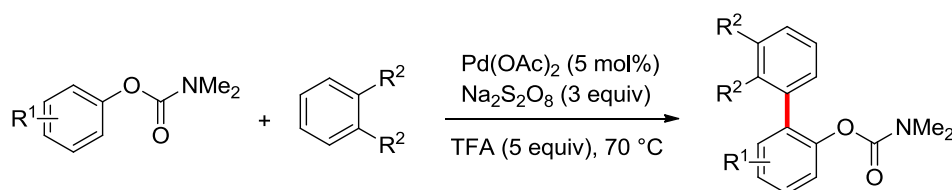
utility, protected phenols (either in the carbamate or ester form) have attracted intensive efforts from the community studying transition metal-catalyzed C-H functionalizations.⁴⁵²

Snieckus and co-workers developed a widespread and popular strategy for accessing elaborate phenol derivatives via directed *ortho*-metalation (DoM) of *O*-phenylcarbamates.⁴⁵³ Notably, the *O*-carbamate not only served as a useful protecting group but also acted as a functional handle for further transformations, including anionic Snieckus-Fries rearrangements⁴⁵⁴ and cross couplings.



Scheme 322 Palladium-catalyzed *ortho*-arylation of carbamate-protected phenols.

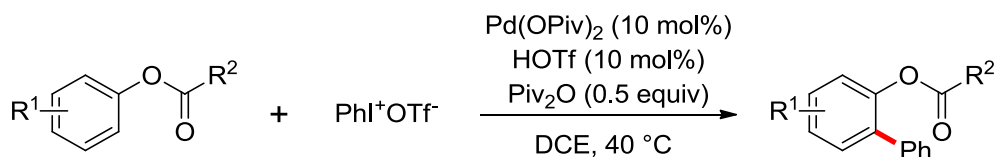
In 2009, Bedford and co-workers reported a palladium-catalyzed *ortho*-arylation of phenols utilizing carbamates as protecting/directing groups (Scheme 322).⁴⁵⁵ Aryl carbamates could be readily prepared and easy to convert back to free phenols. Aryl iodides and diaryliodonium salts were chosen as arylating reagents, in which the former gave both mono- and di-arylated products, whilst the latter favoured mono-arylation. When diaryliodonium salts were used as the arylating reagent, deprotection of the phenol occurred, which could in turn be exploited in the one-pot synthesis of dibenzopyranone derivatives via a novel sequential arylation-deprotection-lactonization process.



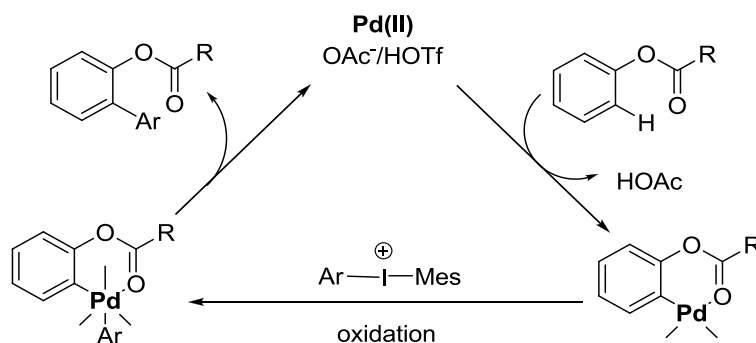
Scheme 323 Palladium-catalyzed *ortho*-arylation of *O*-phenylcarbamates.

Cross-coupling of simple arenes was developed as a green strategy for making biaryl linkages. This arylation involved two aromatic C-H bonds (Ar-H and Ar'-H) undergoing concomitant functionalization to form a new biaryl C-C bond (Ar-Ar'). Dong and co-workers developed an *ortho*-arylation of *O*-phenyl carbamates by employing simple arenes as the cross-coupling partner (Scheme 323).⁴⁵⁶ Na₂S₂O₈ was used as the best effective oxidant and TFA was the optimal additive to promote the efficiency of the reaction. Based on the convincing mechanistic investigations, a possible mechanism was proposed where two C-H

bond activations occurred through a Pd(0)/Pd(II) catalytic cycle involved cyclopalladation and electrophilic metalation, respectively.

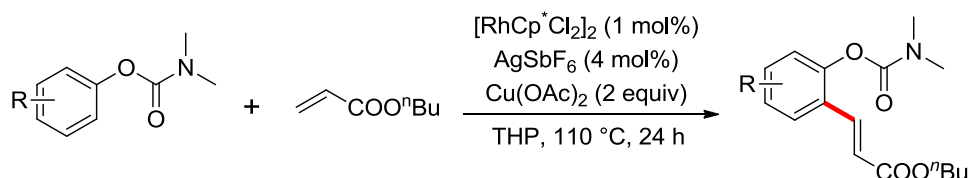


Scheme 324 Pd(II)-catalyzed C-H activation/aryl-aryl coupling of phenol esters.



Scheme 325 The proposed mechanism of the reaction.

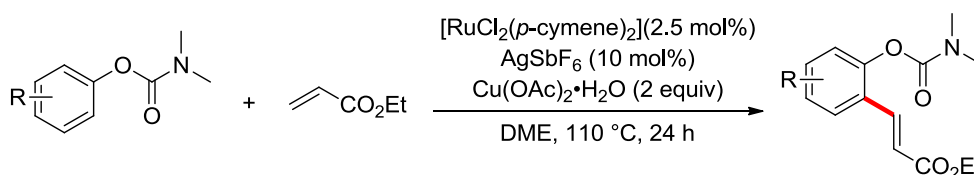
Liu and Fu developed an example of acyloxy-directed Pd(II)-catalyzed *ortho*-C-H arylation reaction of phenol esters (Scheme 324).⁴⁵⁷ This reaction provided a practical strategy for preparing 2-arylphenol derivatives. HOTf was identified as the important additive because the presence of HOTf could tune the electrophilicity of Pd(II) and stabilize the active Pd intermediates. It was notable that the selectivity of mono- versus diarylation could be controlled by modifying the reaction temperature and reactant ratio. In addition, the first palladacycle of phenol ester was successfully isolated and characterized by X-ray crystallography. The plausible mechanism of the arylation reaction possibly involved an acyloxy-directed Pd insertion into the C-H bond and subsequent oxidation of the Pd(II) complex to a Pd(IV) intermediate by $\text{Ar}_2\text{I}^+\text{OTf}^-$, followed by the reductive elimination from the Pd(IV) complex to afford the desired product (Scheme 325).



Scheme 326 Rhodium-catalyzed selective olefination of phenol carbamates.

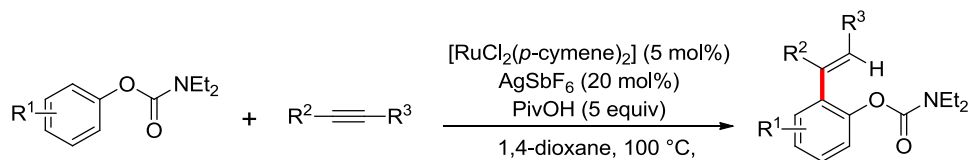
Liu and co-workers further reported a systematic theoretical study of Rh(III)-catalyzed *ortho*-olefination of phenol carbamates (Scheme 326).⁴⁵⁸ This reaction constituted a

complementary method for the Pd-catalyzed processes for the *ortho*-arylation of phenol esters and carbamates. Both substituted styrenes and acrylates well underwent the process to afford the corresponding olefination products in good yields. High regioselectivity was observed for most of the substrates, which favored the C-H functionalization at a sterically less hindered position. Extensive mechanistic studies were conducted and the results indicated that the overall catalytic cycle consisted of three main steps: the C-H activation of arene through the acetate-assisted CMD mechanism, alkene insertion, and β -H elimination. Simultaneously, direct *ortho*-C-H olefination of phenol derivatives catalyzed by rhodium was developed by Loh and co-workers.⁴⁵⁹ Later on, a mechanistic rationale for Rh(III)-catalyzed oxidative heck coupling of phenol carbamates with alkenes was proposed by Huang and Fu.⁴⁶⁰



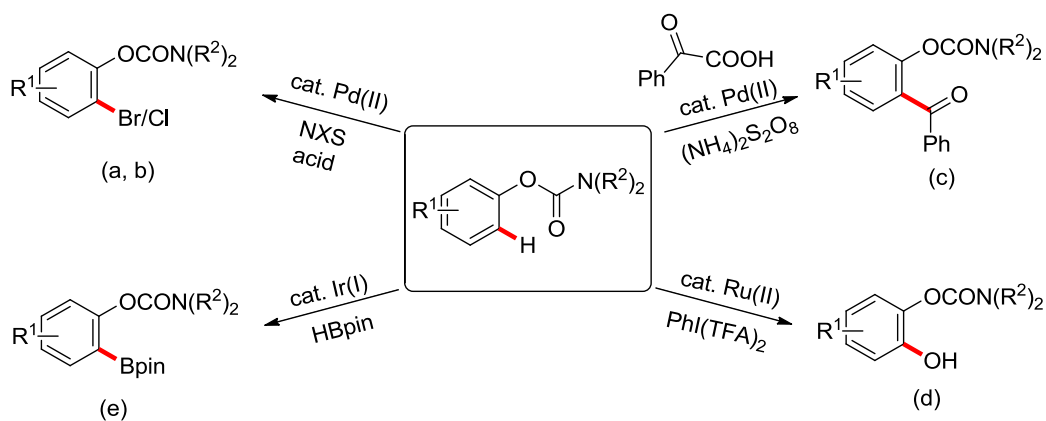
Scheme 327 Ruthenium-catalyzed oxidative C–H alkenylation of aryl carbamates.

The directing ability of the carbamate group was also exploited by Ackermann and co-workers for highly efficient oxidative Fujiwara-Moritani-type alkenylations of aromatic C-H bonds with a less expensive ruthenium catalyst (Scheme 327).⁴⁶¹ The air and moisture stable ruthenium complexes was identified as viable catalysts for environmentally benign twofold C-H bond alkenylations recently. The presence of stoichiometric amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ could proceed the reaction successfully under an atmosphere of ambient air. Intermolecular competition experiments with differently substituted arenes indicated that electron-rich substrates were preferentially converted. Almost at the same time, the similar oxidative *ortho*-alkenylation of phenyl carbamates was independently achieved by Wang and co-workers.⁴⁶² Jeganmohan and co-workers also achieved alkenylations of aryl acetates with acrylates in the presence of catalytic amounts of $[\text{RuCl}_2(p\text{-cymene})_2]$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ with ambient air as the terminal oxidant. Base-mediated cleavage of the directing group in product using K_2CO_3 in MeOH provided the desired *ortho*-alkenylated phenols.⁴⁶³



Scheme 328 Ruthenium-catalyzed hydroarylation of aryl carbamates with alkynes.

A new process for alkenylation of *ortho*-C-H bond of aryl carbamates was developed by Jeganmohan and co-workers with alkynes in the presence of a ruthenium catalyst, AgSbF₆ and pivalic acid, in which highly substituted alkene derivatives could be afforded in good to excellent yields in a highly regio- and stereoselective manner (Scheme 328).⁴⁶⁴ Notably, the regiochemistry of the products was determined by the alkyne substituents. The substrate scope of the present hydroarylation reaction could be easily extended to various substituted aryl carbamates and alkynes.



Scheme 329 Transition metal-catalyzed C-X bonds formation of phenyl carbamates.

By the use of phenyl carbamates as substrates, a series of C-H functionalization reactions, such as C-H bromination, chlorination, decarboxylative acylation, oxygenations, and borylation, were successively reported (Scheme 329). Nicholas and co-workers reported a palladium-catalyzed *ortho*-bromination of aryl-*O*-carbamates using NBS as bromine source via C-H bond activation (Scheme 329a).⁴⁶⁵ A series of cyclometalated palladium complexes derived from *O*-phenylcarbamates with different acids were synthesized and characterized to gain insight into the reaction pathway. A plausible mechanism for the present *ortho*-bromination reaction presumably involved Pd(II)/Pd(IV) catalytic cycle. Initial C-H activation of the carbamate substrate would generate the palladacycle, which could be oxidized by the NBS to give the corresponding Pd(IV) intermediate. Subsequent reductive

elimination from the Pd(IV) manifold to release the desired products.

Most recently, a practical, room-temperature Pd(II)-catalyzed regioselective *ortho*-chlorination/bromination reaction was developed by Rao and co-workers for a facile one-pot synthesis of a broad range of chloro/bromophenol derivatives from easily accessible phenols (Scheme 329b).⁴⁶⁶ NCS or NBS were utilized as halogenation agents in the presence of TfOH. This protocol represented one of the rare examples of mild C-H functionalization at ambient temperature and demonstrated an excellent regioselectivity and reactivity for C-H halogenations.

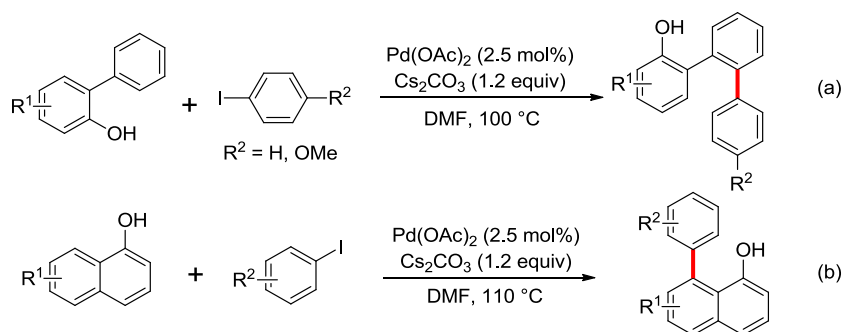
Kim and co-workers described an efficient method for oxidative acylation of *O*-phenyl carbamates with α -oxocarboxylic acids catalyzed by palladium using ammonium persulfate as a convenient oxidant (Scheme 329c).⁴⁶⁷ The presence of a catalytic amount of triflic acid was crucial for the transformation. A wide range of *O*-phenyl carbamates with electron-donating group and halogen groups were favored in the process, whereas substrates with electron-withdrawing groups (e.g., NO₂ and CO₂Et) at the *para*-position failed to deliver the acylation products under the optimal reaction conditions.

Regioselective hydroxylations of *ortho*-C-H bonds in aryl carbamates were achieved by Ackermann and co-workers (Scheme 329d).⁴⁶⁸ By employing [RuCl₂(*p*-cymene)]₂ as the catalyst and PhI(OAc)₂ as the effective oxidant, a number of oxygenation products of phenol derivatives could be obtained with excellent chemo- and *ortho*-selectivities. The intramolecular competition experiments indicated that the carbamates were found to be more potent directing groups as compared to esters, but appeared to be less efficient than the amide substituents.

The directed *ortho*-borylation of phenol carbamates was reported by Sawamura and co-workers with an immobilized monophosphine-Ir catalysis system (Silica-SMAP-Ir) (Scheme 329e).⁴⁶⁹ Compared with the higher reactivity of pinB-Bpin, H-Bpin was used as a boron source in this study in the case of atom economy. Various aryl carbamate derivatives with one or two additional substituents on the aromatic ring were applicable to the reaction. Notably, the directing carbamoyloxy group could also act as a leaving group in the cross-coupling reactions as demonstrated in the synthesis of a terphenyl derivative.

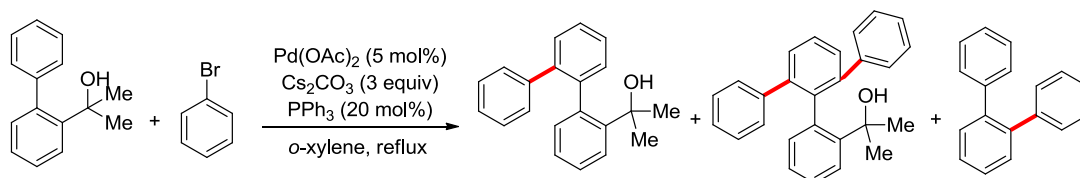
9 The C-H functionalization directed by hydroxyl derivative

Hydroxyl is a very important functional group in organic chemistry, which exhibits weak coordination to transition metals.^{3c} This characteristic enables it to play an important role in several transition-metal-catalyzed transformations.



Scheme 330 Palladium catalyzed arylation of 2-phenylphenols and 1-naphthols.

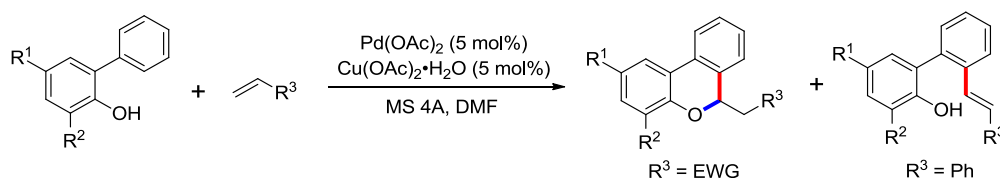
A key application of hydroxyl as directing group in a selective intermolecular arylation of 2-phenylphenols by palladium catalysis was reported by Miura and co-workers (Scheme 330).⁴⁷⁰ This arylation regioselectively took place at the spatially neighboring positions of phenolic function to give the corresponding 2-(2'-arylphenyl)phenol products. The reaction was supposed to be initiated by the oxidative addition of aryl iodide to give an arylpalladium(II) species, which reacted with the phenolate generated the aryl(aryloxy)palladium intermediate. The subsequent C-H activation and reductive elimination afforded the monoarylated product. The coordination of phenolic oxygen to the intermediary arylpalladium(II) species was considered to be crucial for the activation of the C-H bond. The reaction could be extended to 1-naphthols to give the 8-aryl-1-naphthol products. The use of cesium carbonate as the base was important to the success of the formation of phenolate which was soluble in DMF to enhance the rate of deprotonation.



Scheme 331 Palladium-catalyzed arylation of α,α -disubstituted arylmethanols.

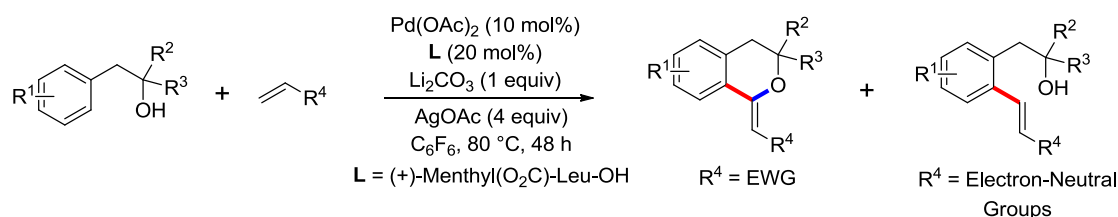
The palladium-catalyzed arylation of 2-(biphenyl-2-yl)-2-propanol with aryl halides was later developed by the same research group (Scheme 331).⁴⁷¹⁻⁴⁷² In this transformation,

both the processes of *ortho*-phenylation and β -carbon elimination occurred in the initial step, and the resulted *ortho*-phenylated product underwent further coupling with aryl halides to give a series of multiple arylation products. One particularly interesting example was the reaction of alcohol with 1,2-dibromo-4,5-dimethylbenzene to afford triphenylene in 60% yield.



Scheme 332 Palladium-catalyzed oxidative cross-coupling of 2-phenylphenols with alkenes.

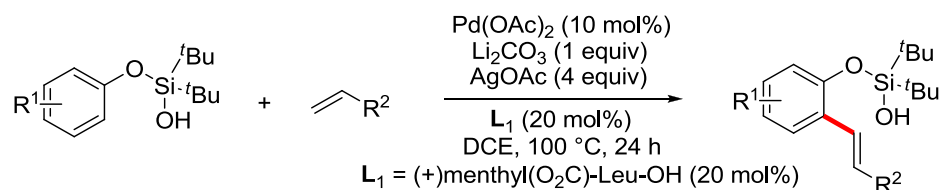
A related precedent for this approach came in the form of a study by Miura and co-workers, who disclosed that 2-phenylphenol could effectively undergo oxidative coupling with alkenes by using a palladium-copper catalyst in air (Scheme 332).⁴⁷³ The subsequent oxa-Michael addition furnished benzopyrans in moderate yields when the electron-deficient alkenes were used as the substrates.



Scheme 333 Pd(II)-catalyzed hydroxyl-directed C-H olefination.

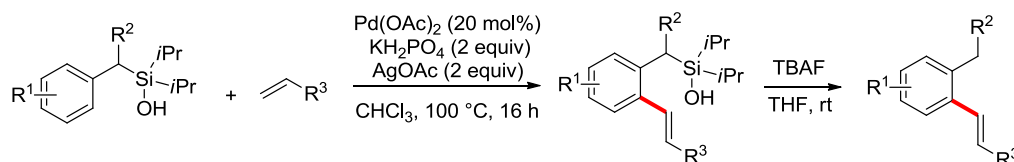
Because many directing groups only effect the C-H activation of proximate bonds via five-membered palladacycles, the range of carbon skeletons that can be accessed are therefore restricted. The use of spatially remote, unprotected tertiary, secondary, and primary alcohols as the directing groups in a Pd(II)-catalyzed *ortho*-C-H olefination was developed by Yu and co-workers (Scheme 333).⁴⁷⁴ They discovered that the mono-*N*-protected amino acid ligands could significantly accelerate the olefination, which represented a rare example of the ligand-promoted C-H activation reaction. Olefination with styrenes and simple olefins gave the corresponding olefinated products without further cyclization. However, the resulted olefination products with electron-deficient alkenes underwent subsequent Pd(II)-catalyzed oxidative intramolecular cyclization to give the corresponding pyran products, which could be

converted into *ortho*-alkylated alcohols after hydrogenolysis.



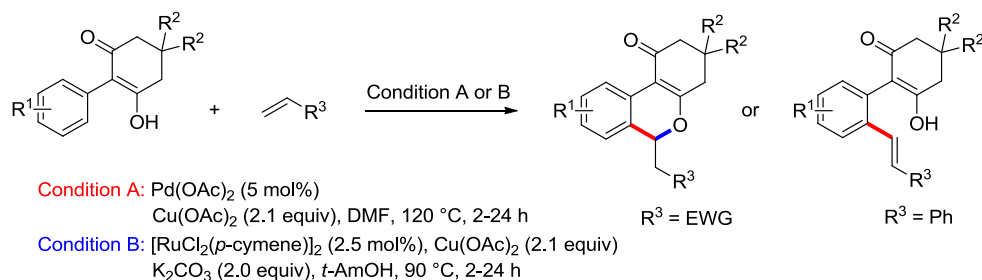
Scheme 334 Pd-catalyzed silanol-directed *o*-alkenylation of phenols.

Although the hydroxyl group has been used as an efficient directing group in C-H bond activation, the direct *ortho*-functionalization of simple phenols is quite difficult because the five- or six-membered metallacycles is unable to be established. Gevorgyan and co-workers designed a traceless/modifiable silicon-tethered directing group (PyDipSi) for *ortho*-acyloxylation and halogenation of arenes.²⁴⁴ By the use of this strategy, they successfully achieved the Pd-catalyzed *ortho*-alkenylation of phenols by the equipment of the phenols with a silanol group (Scheme 334).⁴⁷⁵ The silanol group could be easily removed after the reaction with tetrabutylammonium fluoride (TBAF) in a “semi-one-pot” approach, and the diverse alkenylated phenols could be efficiently prepared in good to excellent yields.



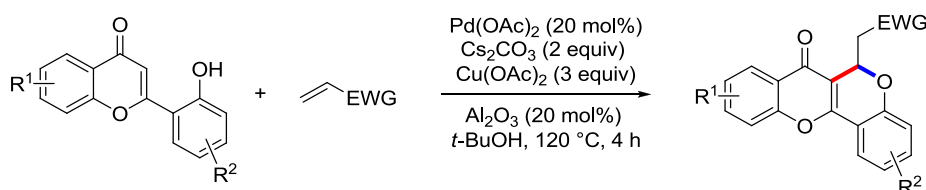
Scheme 335 Pd-catalyzed silanol-directed *o*-alkenylation of alkenes.

Ge and co-workers described a palladium(II)-catalyzed alkenylation of benzyldiisopropylsilanols with olefins (Scheme 335).⁴⁷⁶ In contrast with the procedures of Yu and Gevorgyan, ligand was not required in this transformation, and both the electron-rich and electron-poor arenes showed good reactivity to give the *ortho*-olefinated products in good yields. However, the electron-rich olefins failed to afford the desired olefination product. The *ortho*-alkenyl-substituted alkylarenes could be obtained after the smooth “deprotection” of the olefinated benzyldiisopropylsilanols.



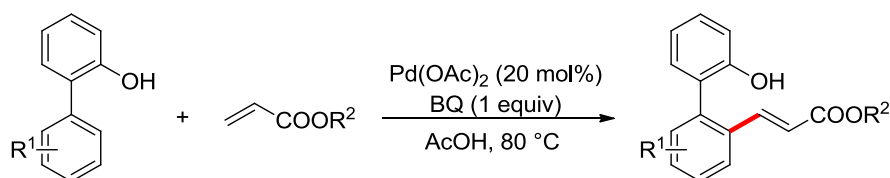
Scheme 336 Pd(II)- or Ru(II)-Catalyzed C-H alkenylation of 2-Aryl-3-hydroxy-2-cyclohexenones.

Given the electronic similarity between the enol group of cyclic 1,3-dicarbonyls and the hydroxyl group of phenols, Lam and co-workers extended the above methodology to the enol-directed oxidative annulation of 2-aryl-3-hydroxy-2-cyclohexenones with terminal alkene. (Scheme 336).⁴⁷⁷ The reaction proceeded not only by the well-established palladium catalysis, but also with ruthenium catalysis. In general, the electron-deficient alkenes such as acrylates delivered benzopyrans, which was formed by the subsequent intramolecular oxa-Michael addition of the alkenylation products. The cyclization was not observed for styrenes and the alkenylated products were isolated in moderate yields.



Scheme 337 Pd(II)-catalyzed C-H alkenylation/C-O cyclization of flavones and coumarins.

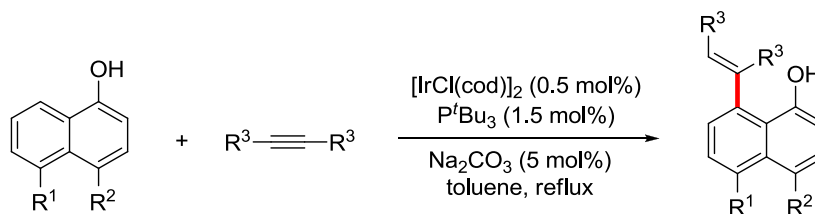
Very recently, a practical and efficient method for the tandem C-H alkenylation/C-O cyclization reactions via the C-H functionalization of flavone derivatives was developed by Hong and co-workers (Scheme 337).⁴⁷⁸ This synthetic process provided a concise access to a variety of flavone-fused benzopyrans.



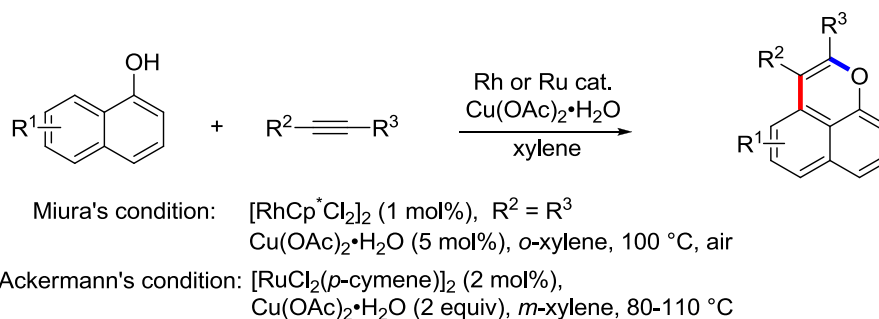
Scheme 338 Palladium-catalyzed alkenylation of 2-arylphenols.

A palladium-catalyzed phenolic hydroxyl-directed alkenylation of 2-arylphenols was reported by Sun and co-workers (Scheme 338).⁴⁷⁹ The reaction proceeded in an atmosphere of

air using the acrylates as coupling partners to give the corresponding coupling products in moderate to good yields. All of the products obtained were proved to be *E* isomers. The electron rich olefin such as styrene or 1-hexene failed to give the desired alkenylation products under the standard reaction conditions.



Scheme 339 Iridium-catalyzed regioselective reaction of 1-naphthols with alkynes.

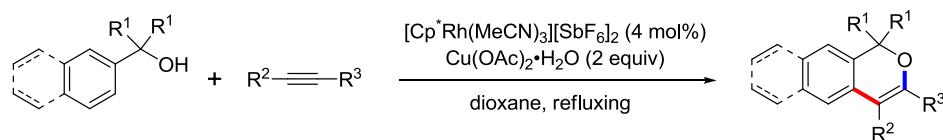


Scheme 340 Rhodium or ruthenium catalyzed oxidative annulation of 1-naphthols.

The metal-catalyzed oxidative annulation of aryl or alkenyl substrates with alkynes via C-H cleavage was proved to be an efficient and atom-economic strategy to access a range of valuable heterocyclic products.^{66b} The reaction of 1-naphthols with internal alkynes in the presence of iridium catalyst to afford the corresponding 8-substituted 1-naphthol derivatives was reported by Miura and co-workers (Scheme 339).⁴⁸⁰ They found that the naphtho[1,8-*bc*]pyran heterocycles were generated with the reaction of 1-naphthols and diarylacetylenes when a rhodium/copper catalytic system in air was employed (Scheme 340).⁴⁸¹ The reaction was supposed to be initiated by the coordination of the phenolic oxygen to rhodium to form a five-membered rhodacycle intermediate via the C-H activation. The insertion of this key intermediate to the alkyne and the subsequent reductive elimination afforded the naphthopyran heterocycles. The Rh(I) species was oxidized by the copper(II) salt to regenerate the Rh(III) catalyst and the oxygen in air achieved the reoxidation of Cu(I) species to CuII. However, the poor site selectivity was observed with unsymmetrical alkynes.

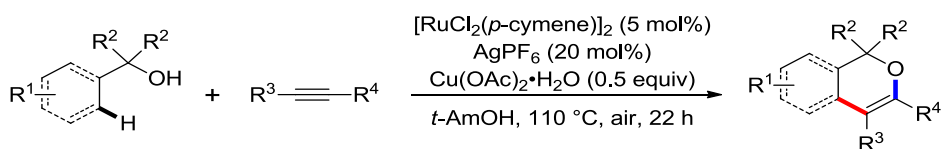
The control of site selectivity in the reaction of 1-naphthols and unsymmetrical alkynes

was demonstrated by Ackermann and co-workers using a ruthenium catalyst (Scheme 340).⁴⁸² The control experiments revealed that the electron-deficient alkynes converted to the product faster than electron-rich alkynes and the C-H bond ruthenation step was reversible. The effective annulation of alkynes were also proved viable with 4-hydroxycoumarin.



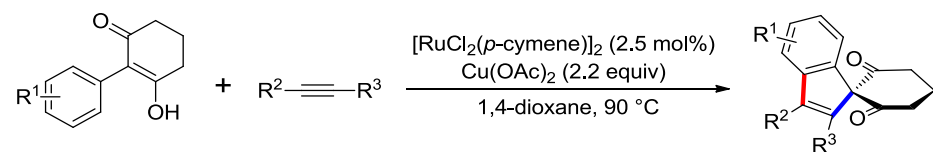
Scheme 341 Rhodium-catalyzed synthesis of isochromene and related derivatives.

The important isochromene derivatives were synthesized by Satoh, Miura and co-workers through the rhodium-catalyzed oxidative coupling of α,α -disubstituted benzyl alcohols with alkynes (Scheme 341).⁴⁸³ This method could be extended to α,α -dimethylallyl alcohols to give the corresponding 2*H*-pyran heterocycles.



Scheme 342 Ruthenium(II)-catalyzed synthesis of isochromenes.

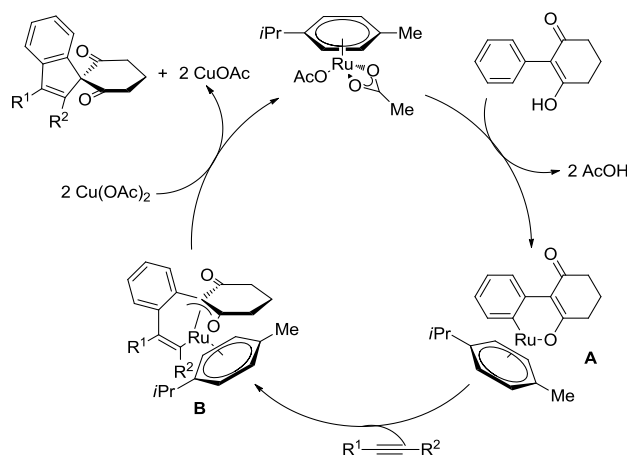
The use of less expensive ruthenium catalysts for the formation of isochromene derivatives was demonstrated by Ackermann and co-workers (Scheme 342).⁴⁸⁴ The highly effective oxidative annulation of alkynes with benzyl alcohols proceeded efficiently under an atmosphere of air. Mechanistic studies indicated that an irreversible, kinetically relevant C-H ruthenation step might be involved in the reaction.



Scheme 343 Ruthenium-catalyzed synthesis of spiroindenes.

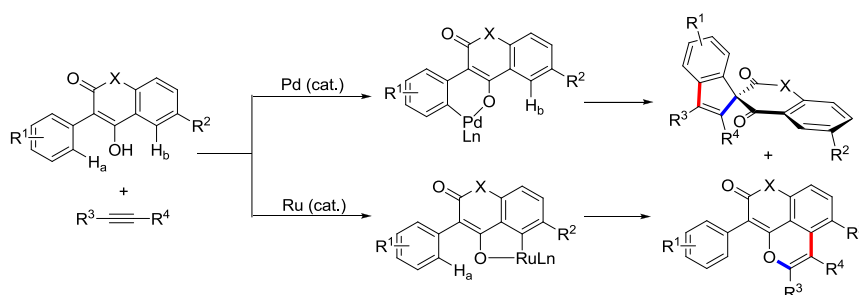
A new mode of Ru-catalyzed oxidative annulation of alkyne involving the functionalization of C(sp³)-H and C(sp²)-H bond was reported by Lam and co-workers (Scheme 343).⁴⁸⁵ This enolate-directed ruthenium-catalyzed oxidative annulation of alkynes with 2-aryl-1,3-dicarbonyl compounds resulted in a diverse range of spiroindenes with high levels of regioselectivity, which were important structures in biologically active compounds. A notable feature of this process was the formation of an all-carbon quaternary center, which

has not been described previously in the alkyne oxidative annulations. A wide range of unsymmetrical alkynes were tolerated and the high regioselectivity with initial C-C bond formation occurring at the alkyne carbon atom of the alkyl substituent was observed. The terminal alkynes gave a complex mixture.



Scheme 344 Possible mechanism for Ru-catalyzed synthesis of spiroindenes.

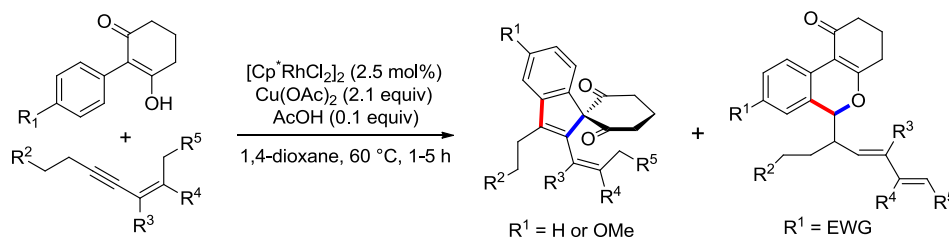
A plausible catalytic cycle was proposed by the authors (Scheme 344). The deprotonation of the cyclic 1,3-dicarbonyl substrate generated an enolate, which was able to direct the cycloruthenation of $[\text{Ru}(\text{OAc})_2(p\text{-cymene})]_2$ complex to form the six-membered ruthenacycle **A**. Coordination and insertion of the alkyne with ruthenacycle **A** gave the unusual eight-membered ruthenacycle **B** with the preference of C-C bond formation at the alkyne carbon atom bearing the alkyl substituent. The reductive elimination released the spiroindene products and the Ru(0) species was oxidized by $\text{Cu}(\text{OAc})_2$ to regenerate the Ru(II) catalyst.



Scheme 345 Annulations of 2-aryl cyclic 1,3-dicarbonyl compounds.

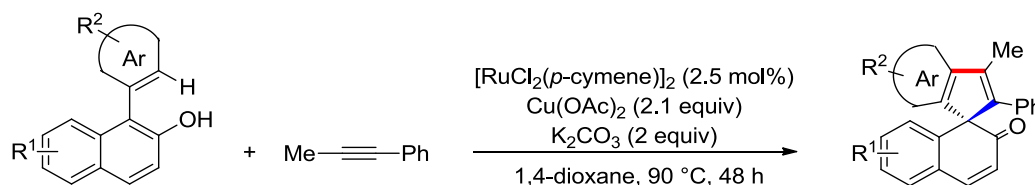
The development of corresponding processes for the synthesis of chiral spiroindenes and benzopyran products was demonstrated by the same research group (Scheme 345).⁴⁸⁶ Site selectivity in the initial C-H functionalization to spiroindene or benzopyran products could be

achieved by the use of palladium- or ruthenium-based catalysts, respectively. A palladium-*N*-heterocyclic carbene complex as the precatalyst mainly resulted in the oxidative annulation with alkynes to provide spiroindenes exclusively. In contrast, a $[\text{RuCl}_2(\textit{p}\text{-cymene})]_2/\text{Cu}(\text{OAc})_2$ catalyst system gave benzopyrans as the major products. This reaction was an elegant example of successful site selectivity control by the suitable choice of catalytic system.



Scheme 346 Oxidative annulation reactions of various 2-aryl-3-hydroxy-2-cyclohexenones with 1,3-enyne.

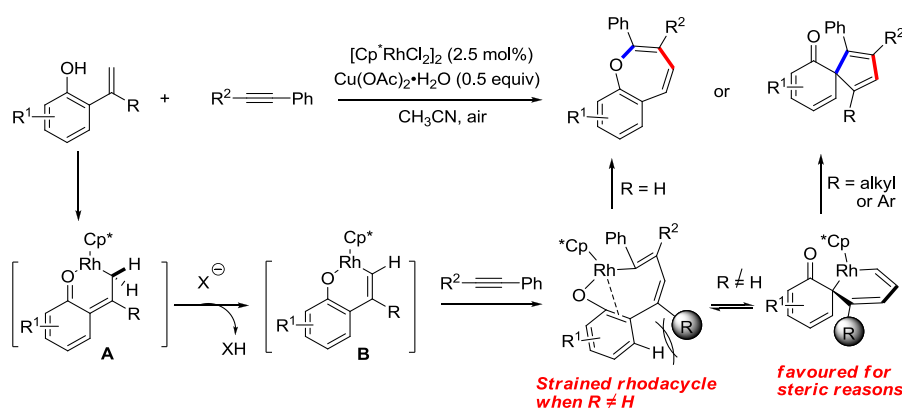
When the 1,3-enynes was used as the substrates of unsymmetrical alkynes in a Rh(III)-catalyzed annulations, besides the expected spiroindene product, a benzopyran compound was isolated as well (Scheme 346).⁴⁸⁷ A reasonable reaction pathway for the one carbon annulation to form the benzopyran compound was presented by the authors and a rare 1,4-migration of Rh(III) species was proposed to be involved in the transformation. The related selectivity was almost determined by the properties of substituent R^1 . The spiroindenes were given as the major products with the electron-donating substituent and the benzopyran compounds were isolated in high yields when the substituent was replaced by the electron-withdrawing groups. The further investigation demonstrated that the enynes containing allylic hydrogens *cis* to the alkyne, which was facilitated the 1,4-Rh(III) migration, were required for the effective oxidative annulation.



Scheme 347 Ru(II)-catalyzed vinylative dearomatization of naphthols.

Recently, Luan and co-workers demonstrated the first example of Ru-catalyzed vinylative dearomatization of α -aryl- β -naphthols through an unprecedented C-H

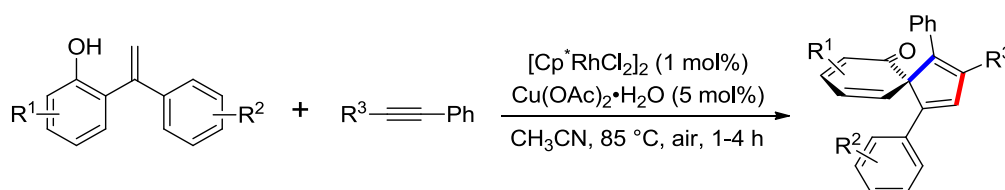
activation/dearomatization tandem process (Scheme 347).⁴⁸⁸ In this transformation, an all-carbon quaternary centre was efficiently constructed by employing the inexpensive $[\text{RuCl}_2(\text{p-cymene})]_2$ as the catalyst and $\text{Cu}(\text{OAc})_2$ as the oxidant. Various symmetrical and unsymmetrical alkynes participated in the reaction selectively and a variety of synthetically important functional groups were found to be tolerable in this process. However, the 2-phenylphenols showed low reactivity and gave the products in extremely low yields. The evolution of dearomatization of naphthyl rings in the substrates compelled by the C-H activation was established. This catalytic method provided a straightforward way to access the useful spirocyclic compounds bearing the spiro[indene-1,1'-naphthalene] skeleton.



Scheme 348 Rhodium(III)-catalyzed C-H functionalization of *o*-vinylphenols.

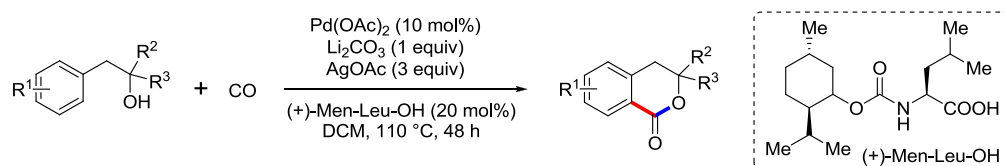
The synthesis of benzoxepines by the rhodium-catalyzed oxidative [5+2] annulation of 2-vinylphenols with alkynes was developed by Mascareñas, Gulías and co-workers (Scheme 348, R=H).⁴⁸⁹ In contrast with the α -aryl- β -naphthols, the dearomatization of phenols was not observed with 2-vinylphenols and a readily [5+2] cycloaddition to alkynes occurred in the presence of $[\text{Cp}^*\text{RhCl}_2]_2$ catalyst and $\text{Cu}(\text{OAc})_2$ oxidant. The reaction took place with high regioselectivity with unsymmetrical alkynes leading to the production of benzoxepines in which the phenyl group was in the carbon tethered to the oxygen group. The mechanistic study gave the evidence of the attack of the conjugated alkene to form the electrophilic Rh complex **A**. The rearomatization resulted in the intermediate **B**, which underwent the insertion to alkynes and liberated the products after the reductive elimination. However, the reaction failed with the substrates with alkyl substituents at the terminal position of the alkene such as (*E*)-2-(prop-1-en-1-yl)phenol. To further study the scope of the process and gain more

mechanistic insights, Mascareñas, Gulías and co-workers explored the performance of alkenylphenol derivatives equipped with a substituent at the internal position of the alkene. They found that a formal [3C+2C] cycloaddition between 2-alkenylphenols and alkynes took place by the rhodium-catalysis under the oxidative conditions to give the spirocyclic products (Scheme 348, R=alkyl or Ar).⁴⁹⁰ These results pointed out the potential of using substituents in key strategic positions of substrates to change reaction outcomes (oxepine vs spirocycle) because of the generation of steric interferences that affected key steps of the mechanism.



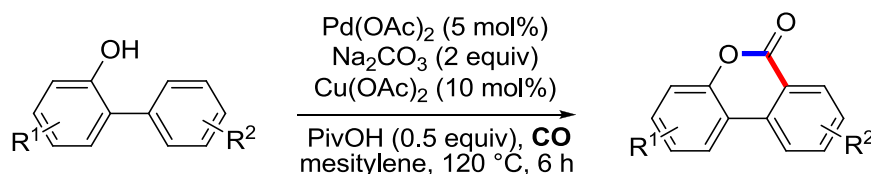
Scheme 349 Rhodium-catalyzed synthesis of spirocyclic enones.

At the same time, Lam and co-workers reported the synthesis of spirocyclic enones by rhodium-catalyzed dearomatizing oxidative annulation of 2-alkenylphenols with alkynes and enynes (Scheme 349).⁴⁹¹



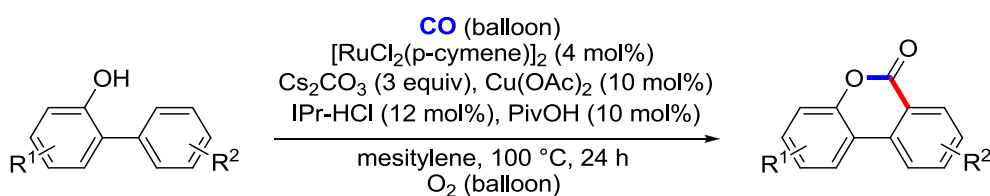
Scheme 350 Hydroxyl-directed C-H carbonylation.

A carbonylation of phenethyl alcohols by palladium catalysis was developed by Yu and co-workers (Scheme 350).⁴⁹² The reaction was significantly improved by the use of the mono-*N*-protected amino acids as the ligands. It was supposed that the amino acids was able to reduce the conversion of Pd(II) to palladium black in the presence of reductive carbon monoxide. Importantly, a histamine release inhibitor was successfully synthesized, which showed the potential of the methodology for the rapid synthesis of an entire library of histamine release inhibitors.



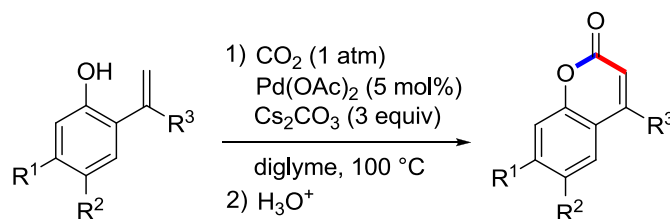
Scheme 351 Palladium-catalyzed directed C-H carbonylation of 2-arylphenols.

The synthesis of dibenzopyranones through Pd-catalyzed phenol-directed C-H activation/carbonylation of 2-phenylphenol derivatives was described by Shi and co-workers (Scheme 351).⁴⁹³ The important combination of carbonylation chemistry and selective C-H activation strategy led to the facile syntheses of dibenzopyranones. The reaction was found to be sensitive to the electronic nature of substituents on the aromatic ring with hydroxyl group, and the electron-neutral groups, such as methyl and phenyl gave higher yields. The mechanistic study revealed that the C-H activation step might go through a $S_{E}Ar$ mechanism. Based on this work, Chuang, Cheng and coworkers reported palladium-catalyzed C-H activation and CO insertion into 2-arylphenols under acid-base free and mild conditions.⁴⁹⁴



Scheme 352 Ruthenium-catalyzed carbonylative C-H cyclization of 2-arylphenols.

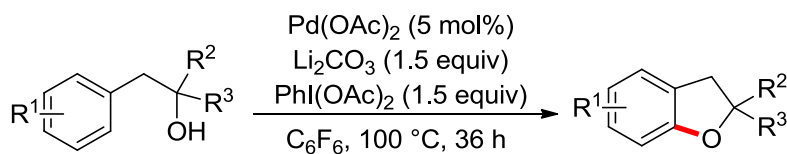
Kondo's group demonstrated a new Ru-catalyzed carbonylative C-H cyclization of 2-arylphenols under relatively mild conditions (Scheme 352).⁴⁹⁵ This method employed a combination of catalytic Ru/N-heterocyclic carbene (NHC) system with a balloon pressure of CO and O₂. Functional groups, such as the alkoxy carbonyl, acetyl groups and the halogen atoms (F, Cl, and Br), were well tolerated.



Scheme 353 Palladium(II)-catalyzed direct carboxylation of alkenyl C-H bonds with CO₂.

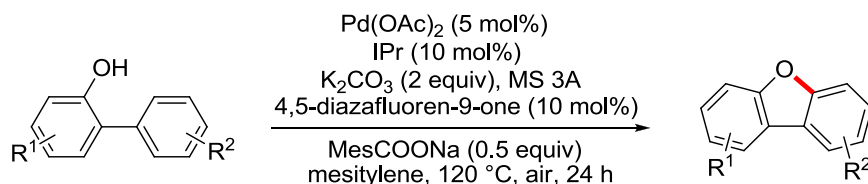
The more challenging Pd-catalyzed carboxylation of unactivated alkenyl C-H bond of 2-hydroxystyrenes using CO₂ was investigated by Iwasawa and co-workers in 2013 (Scheme 353).⁴⁹⁶ Treatment of 2-hydroxystyrenes and a catalytic amount of Pd(OAc)₂ with Cs₂CO₃ under the atmospheric pressure of CO₂ afforded the corresponding coumarins in good yields. The bromophenyl moiety could be tolerated under the reaction conditions, implying that the Pd(0) species might not be formed in the reaction process. The reaction was proposed to undergo

reversible nucleophilic addition of the alkenylpalladium intermediate to CO₂. The substrates bearing various functional groups could provide the desired carboxylation products in good yields. However, β-substituted 2-hydroxystyrenes did not give the desired products under the reaction conditions.



Scheme 354 Pd(II)-catalyzed hydroxyl-directed C-O cyclization.

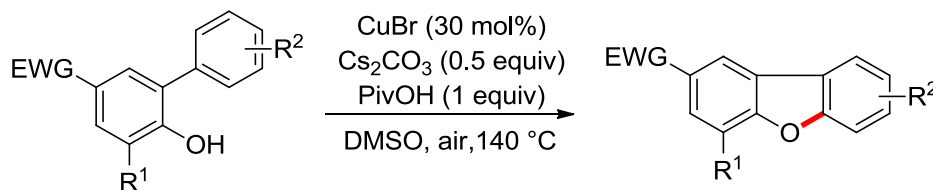
Yu and co-workers developed a new method for the construction of dihydrobenzofurans with Pd(II)-catalyzed C-H activation/C-O cyclization reaction directed by a proximate hydroxyl group (Scheme 354).⁴⁹⁷ The presence of base was essential to reduce the decomposition of the starting material and PhI(OAc)₂ was used as the most effective oxidant for the Pd(II)-Pd(IV) catalytic cycle. It's notable that the *ortho*-brominated substrates could participate in the reaction to afford dihydrobenzofuran products with the remaining of bromide, which provided a useful handle for the subsequent transformations. The process could be applied in the synthesis of natural products and drug molecules containing spirocyclic dihydrobenzofurans.



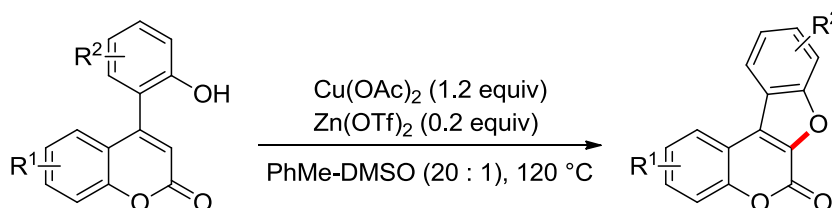
Scheme 355 Palladium-catalyzed phenol-directed synthesis of dibenzofurans.

Later on, Liu and co-workers reported a practical phenol-directed C-H activation/C-O cyclization reaction as an efficient route to substituted dibenzofurans (Scheme 355).⁴⁹⁸ The addition of sodium pivalate (PivONa) could significantly improve the reaction and air was used as the oxidant for the Pd(0)/Pd(II) catalytic cycle. The X-ray diffraction analysis of a four-coordinate Pd(II) complex carrying an anionic pivalate ligand provided clear evidence that the phenol group coordinated with Pd(II) as a neutral σ donor. The mechanism investigation revealed that the turnover-limiting step of the reaction was found to be the reductive elimination instead of C-H activation. Yoshikai and co-workers reported a similar Pd-catalyzed process involving 3-nitropyridine as a ligand and *tert*-butyl peroxybenzoate as

an oxidant.⁴⁹⁹ The mechanistic experiment suggested that the reaction involved Pd(II)-mediated C-H bond cleavage as the rate-limiting step.

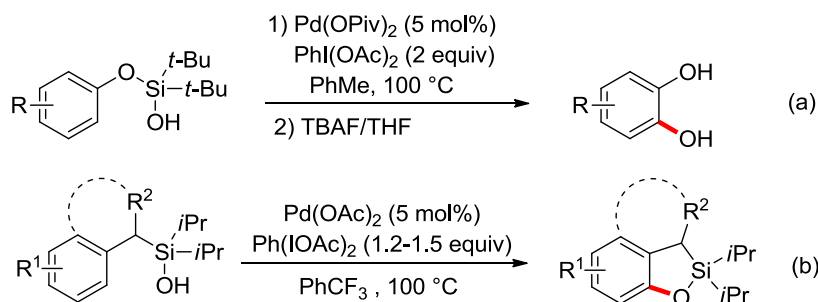


Scheme 356 Cu-catalyzed oxidative C(sp²)-H cycloetherification of *o*-Arylphenols.



Scheme 357 Synthesis of heterocyclic-fused benzofurans via C-H functionalization of flavones and coumarins.

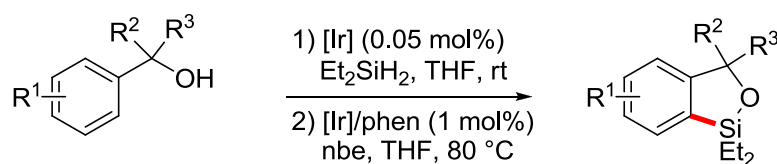
The Cu(I)-catalyzed process for the synthesis of dibenzofuran derivatives was developed by Zhu and co-workers (Scheme 356).⁵⁰⁰ A catalytic amount of CuBr could promote the cycloetherification reaction using Cs₂CO₃ and PivOH as additives under the air atmosphere. The presence of a strong *para*-electron-withdrawing group (e.g., NO₂) on the phenol was essential for the success of the reaction. Hong and co-workers further extended the methodology to the C-H functionalization of chromones and coumarins, providing the straightforward process for the preparation of heterocyclic-fused benzofurans with good functional group tolerance (Scheme 357).⁵⁰¹



Scheme 358 Pd-catalyzed silanol-directed C-H oxygenation.

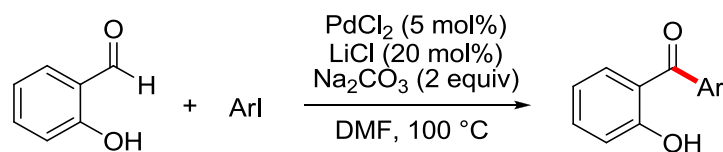
The Pd-catalyzed silanol-directed *ortho*-C-H oxygenation of phenols derivatives was presented by Gevorgyan and co-workers (Scheme 358a).⁵⁰² The reaction presented high site selectivity and a broad functional group tolerance. Both electron-neutral and electron-poor

phenols could undergo the Pd-catalyzed C-H acetoxylation/C-O cyclization reaction to form silacycle, followed by the desilylation to furnish catechol products. The corresponding ^{18}O -labeling studies demonstrated that the acetoxyated product was involved in the stepwise route in stead of the direct C-O reductive cyclization from the starting silanol. The same group further discovered that the benzyloxysilanol could be used as substrates in the efficient synthesis of oxasilacycles, which were valuable intermediates containing an easily cleavable Si-O bond and a modifiable C-Si bond (Scheme 358b).⁵⁰³



Scheme 359 Iridium-catalyzed arene *ortho*-silylation by formal hydroxyl-directed C-H activation.

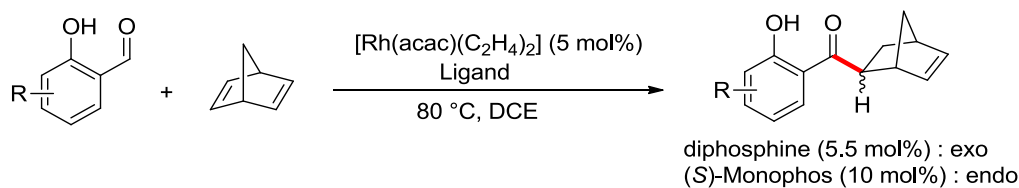
Hartwig demonstrated the Ir-catalyzed *ortho*-silylation of phenol derivatives, in which the *in situ* generated diethyl(hydrido)silyl ethers went through the dehydrogenative cyclization to form benzoxasilole products (Scheme 359).⁵⁰⁴ The transformation proceeded with low catalyst loadings (1 mol%), and a range of functional groups were found to be compatible with the reaction conditions. The synthetic utility was further demonstrated by the conversions of the benzoxasilole products to phenol and biaryl derivatives by Tamao-Fleming oxidation and Hiyama cross coupling.



Scheme 360 Palladium-catalyzed coupling reaction of salicylaldehydes with aryl iodides.

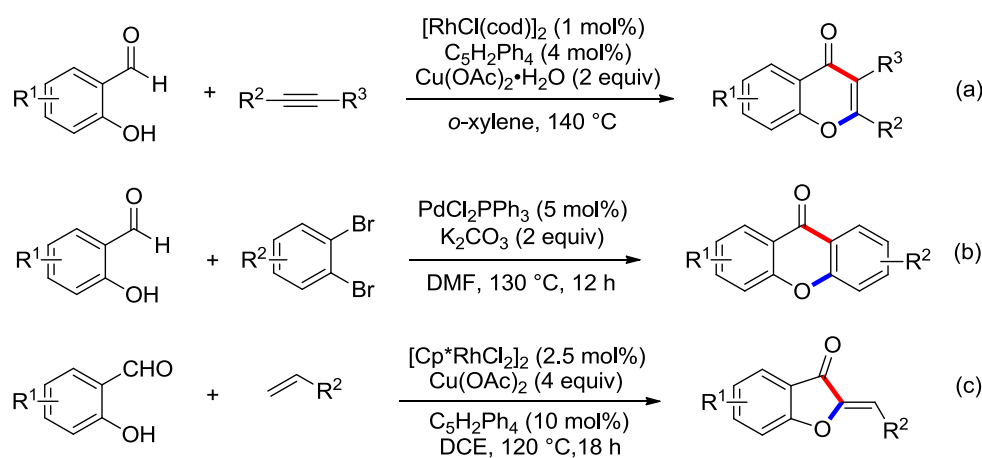
The Pd-catalyzed hydroxyl-directed aldehyde C-H bond cleavage could be involved as the key step in the cross-coupling reactions of salicylaldehydes with aryl iodides, which provided new routes for the synthesis of 2-aryloxyphenols derivatives. In 1996, Miura and co-workers reported the Pd-catalyzed coupling of salicylaldehydes with phenyl iodides to produce biaryl ketones, in which the phenolic function could act as a good anchor for the catalytic intermolecular C-C coupling (Scheme 360).⁵⁰⁵ The addition of LiCl (20 mol%) could promote the reaction and enhance the yield of the product. Further more, Miura and co-workers

developed the coupling reaction of salicyl aldehydes with alkynes/alkenes/allenes using a rhodium-based catalyst system.⁵⁰⁶ Various alkynes, alkenes or allenes were applicable to the process, affording the corresponding ketones. Tanaka, Suemune and coworkers reported the Rh-catalyzed hydroacylation between salicylaldehyde and alkenyl nitriles at room temperature, in which the additional effect of the CN ligand on transition metal-catalyzed reactions was observed.⁵⁰⁷



Scheme 361 Rhodium-catalyzed intermolecular hydroacylation with salicylaldehydes.

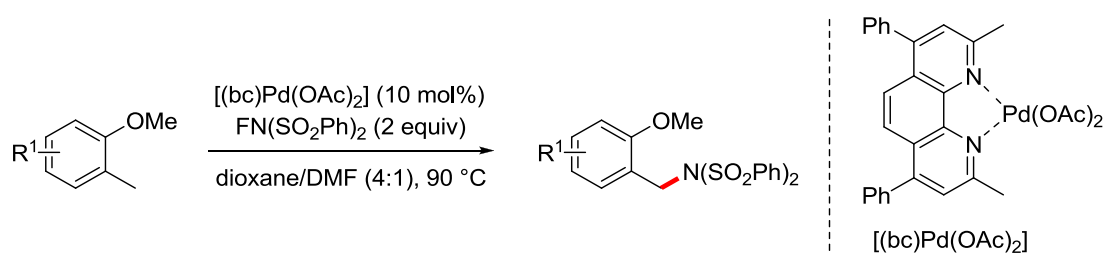
Rhodium-catalyzed asymmetric intermolecular hydroacylation reaction of norbornenes with salicylaldehydes was developed by Bolm and co-workers (Scheme 361).⁵⁰⁸ It was found that monodentate phosphoramidite ligands gave rise to endo products, while bidentate phosphine ligands catalyzed the reaction to form exo products predominantly.



Scheme 362 Rhodium-catalyzed coupling of salicylaldehydes.

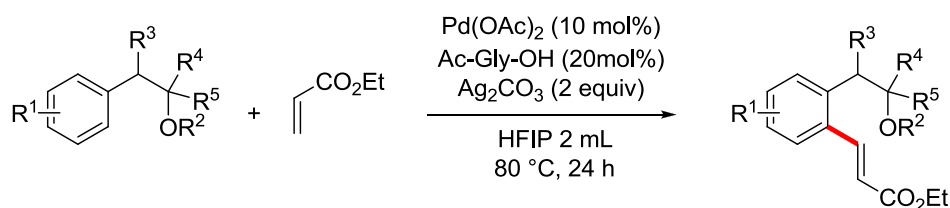
The rhodium-catalyzed oxidative coupling of salicylaldehydes with internal alkynes was achieved with the cleavage of the aldehyde C-H bond to provide 2,3-disubstituted chromone derivatives by Miura, Satoh and coworkers (Scheme 362a).⁵⁰⁹ A cyclopentadiene ligand $\text{C}_5\text{H}_2\text{Ph}_4$ was crucial for the success of the transformation, which was supposed to stabilize the unstable Rh(I) species during the reoxidation step to prolong the lifetime of the catalyst. Later, the synthesis of xanthenes was reported by Peng group via Pd-catalyzed annulation of 1,2-dibromoarenes and salicylaldehydes (Scheme 362b).⁵¹⁰ Recently, Glorius group reported a

Rh(III)-catalyzed regioselective dehydrogenative Heck reaction of aldehyde C-H bonds with different classes of olefins to afford aurone derivatives (Scheme 362c).⁵¹¹ Both aldehyde C-H olefination and oxidative cyclization were involved in the mechanism in the presence of a hydroxy directing group. When less electrophilic olefin substrates such as styrene and ethylene were used, the reaction could afford only olefinated products without the further cyclization even when the amount of oxidant was increased. A variety of salicylaldehydes could be converted to the desired aurone derivatives, and this method can be applied to the synthesis of lonchocarpin and 4-methoxylonchocarpin.



Scheme 363 Palladium-catalyzed C-H amidation of 2-methylphenyl ethers.

Álvarez and Muñiz developed an aryloxy-directed palladium-catalyzed oxidative amidation of C(sp³)-H bonds with NFSI as the decisive reagent (Scheme 363).¹⁷² By the use of the preformed bathocuproine palladium complex [(bc)Pd(OAc)₂], a series of 2-methylanisole derivatives could undergo selective C(sp³)-H amidation under the optimized conditions.



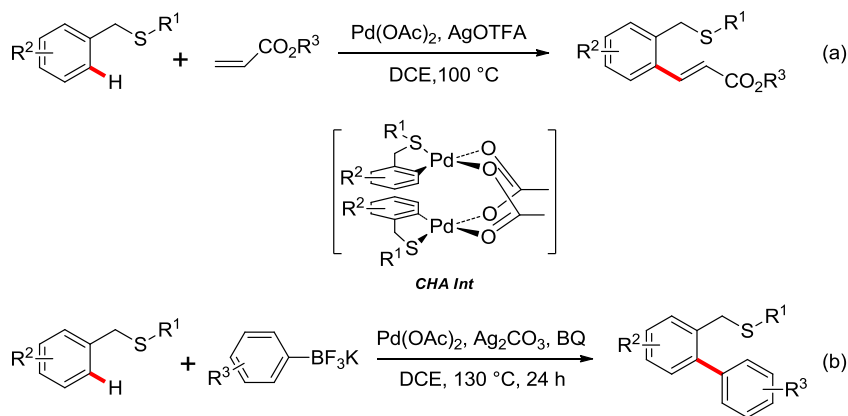
Scheme 364 Ether-directed *ortho*-C-H olefination with a palladium(II)/monoprotected amino acid catalyst.

Yu group demonstrated a new method for the functionalization of a major class of ethers, namely aryloxy ethers (Scheme 364).⁵¹² They successfully achieved an aliphatic ether-directed C-H olefination via a six-membered cyclopalladation which was promoted by monoprotected amino acid ligands (MPAA). This reaction provided a new method for chemically modifying readily available and synthetically useful ethers.

10 The C-H functionalization directed by S, P, Si-containing functional

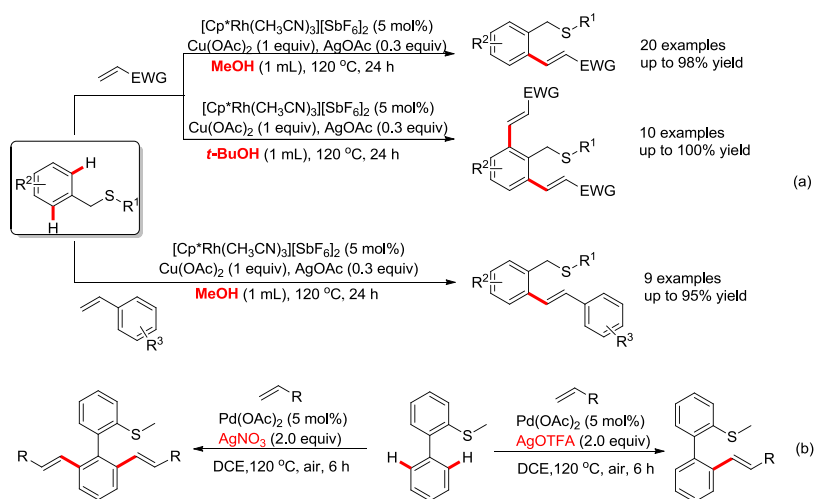
group

10.1 The C-H functionalization directed by thioether and sulfoxide



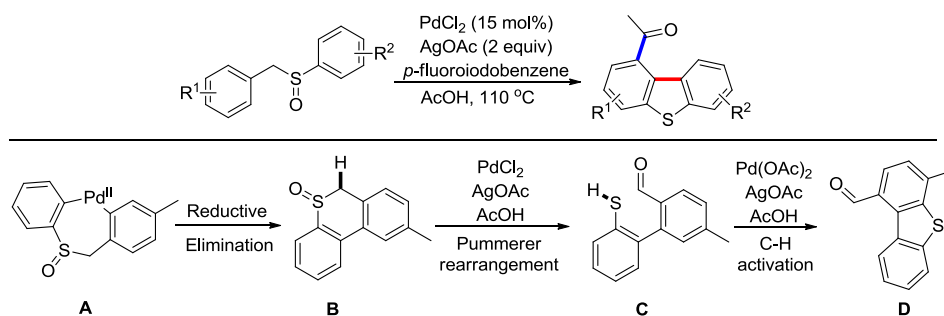
Scheme 365 Pd-catalyzed *ortho*-alkenylation and arylation directed by thioether.

Sulfur compounds have attracted much attention of the chemists in organic synthesis, coordination chemistry, biomaterials, and functional materials. Many of the sulfur containing molecules present the unique properties and thus have found wide applications in pharmaceuticals and functional materials. The straightforward synthesis of sulfur containing molecules is highly desirable. However, the investigation of using sulfur containing functional groups as directing groups in C-H activation poses the challenge due to their ability to poison metal catalysts in some cases. In 2012, Zhang and co-workers developed a Pd-catalyzed thioether directed C-H alkenylation of arenes, which should be the first example of employing thioether as the directing group in direct C-H functionalization reactions (Scheme 365a).⁵¹³ Using AgOTFA as oxidant, the reaction of arylthioethers and acrylic esters was carried out in DCE to afford the dialkenylation products. It was found that the length of the tether group between arene and sulfur exerted a drastic effect on the reaction, and the benzyl thioethers showed the best efficiency. Besides, the authors succeeded in isolating a key five-membered palladacycle intermediate, which demonstrated sulfur was indeed the anchoring atom. It should be noted that the thioether could be easily removed, which is an important issue for the application of the chelation-assisted C-H activation strategy. Furthermore, the thioether can be readily transformed to other useful functionalities. The palladium-catalyzed thioether-assisted C-H arylation of arenes was reported by the same group later using Ag₂CO₃ as oxidant and BQ as additive at 130 °C in DCE (Scheme 365b).⁵¹⁴



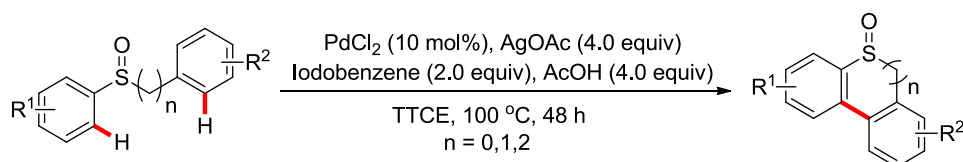
Scheme 366 Thioether directed controllable alkenylation of arenes.

The rhodium-catalyzed thioether-directed *ortho*-alkenylation of arenes was reported by Shi and co-workers (Scheme 366a).⁵¹⁵ With benzyl-(methyl)sulfane as the model substrate, both methyl acrylate and butyl acrylate gave the corresponding products in high yields. Impressively, positional selectivities of multiply substituted aromatic rings with two approximately electronically equivalent *ortho*-C-H bonds could be controlled by using different solvents: MeOH favored mono-alkenylation whereas *t*-BuOH favored dialkenylation using the Cu(OAc)₂ as oxidant and AgOAc as additive. When styrenes were used as the resource of olefin, the mono-alkenylation products were obtained in DCE. However, the homobenzyl methyl sulfide showed very low reactivity in their rhodium catalytic system. After intensive screening of the reaction conditions, they found the combination of palladium catalyst with silver salt led to the formation of the alkenylated product of biphenyl-2-yl(methyl)sulfane in good yields (Scheme 366b).⁵¹⁶ Interestingly, the selectivity of the mono-alkenylation and di-alkenylation could be controlled by the choice of oxidant. The mono-alkenylated arenes were obtained as the major products when AgOTFA was used as an oxidant, and the di-alkenylated arenes were given as the products in the presence of 2 equiv AgNO₃.



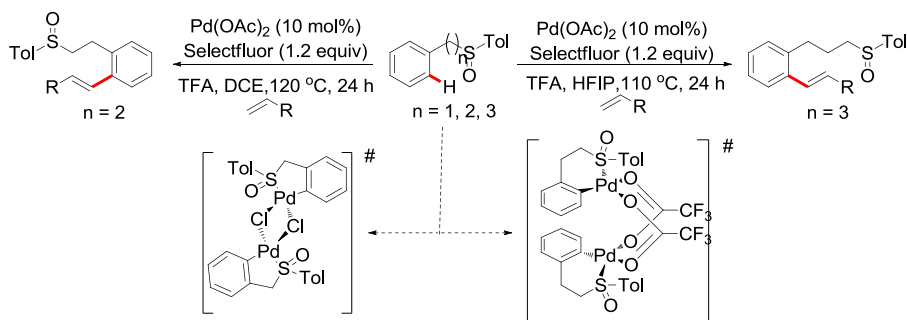
Scheme 367 Palladium-catalyzed synthesis of dibenzothiophenes from aryl sulfoxides.

The palladium-catalyzed double C-H activation of simple benzyl phenyl sulfoxides to synthesize dibenzothiophenes was described by Antonchick and co-workers (Scheme 367).⁵¹⁷ They proposed that the sulfoxide functionalized as a directing group to undergo the first *ortho*-C-H activation in the benzyl phenyl ring. The second C-H activation gave the intermediate **A**, which underwent the reductive elimination to give the sulfur-bridged six-membered polycycle **B**. However, polycycle **B** was unstable under the acidic reaction condition and took place the Pummerer rearrangement to produce the thiophenyl derivative **C**, which underwent the palladium-catalyzed cyclization to afford the dibenzothiophenes. It was unusual that aryl iodide played important role in this transformation and the reaction was sluggish without the use of aryl iodide.



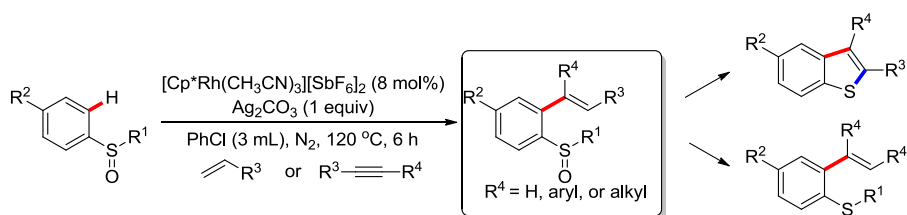
Scheme 368 Pd-catalyzed synthesis of sulfur-bridged polycycles.

The sulfur-bridged six-membered polycycle was prepared by Zhang and co-workers by using the less acidic reaction conditions. They found when the amount of acetate acid was decreased to 4 equivalents, the Pummerer rearrangement could be thoroughly suppressed and the five-, six-, and seven-membered sulfur-bridged polycycles could be isolated by using the different sulfoxide substrates (Scheme 368).⁵¹⁸ The solvent had a significant effect on the reaction efficiency and TTCE gave the best results. A sulfide-bridged six-membered pyrene-thienoacene molecule was synthesized readily using this method, and the preliminary study revealed its excellent fluorescence performance to give a photoluminescence quantum yield as high as 0.48.



Scheme 369 Palladium(II)-catalyzed sulfoxide directed *ortho*-olefination of arenes

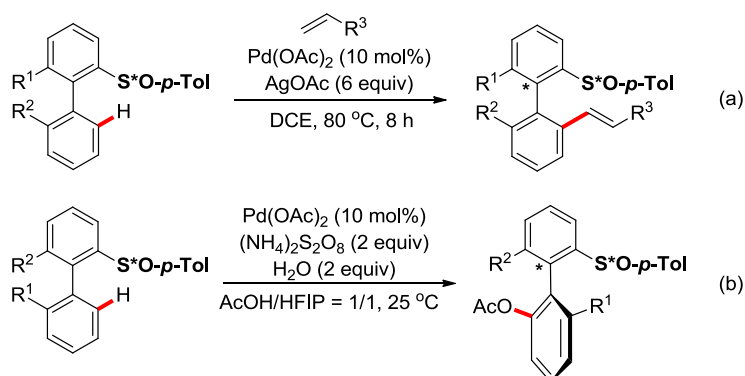
Sulfoxide directed *ortho*-alkenylation of arenes was disclosed by Zhang and co-workers (Scheme 369).⁵¹⁹ Because the Pd(OAc)₂/AgOTFA system for thioether-assisted *ortho*-olefination was inactive to its sulfoxide analogues, much effort was made to find the effective catalytic system for sulfoxide substrates. Fortunately, after extensive optimization of the reaction conditions, the use of Selectfluor as oxidant was found to be superior, and various *ortho*-alkenylated products were obtained with broad substrate scope in high yields. It was established that five-membered and six-membered palladacycles of sulfoxide could be formed, which led to the successful *ortho*-olefination of benzyl and 2-phenylethyl sulfoxide substrates. Importantly, 3-phenylpropenyl sulfoxide with a three carbon tether length could participate in the *ortho*-alkenylation smoothly, showing the excellent directing property of sulfoxide group. The sulfoxide group could be easily transformed to other functionalities such as hydroxyl and aldehyde.



Scheme 370 Rhodium(III)-catalyzed *ortho*-alkenylation of arenes

The rhodium-catalyzed *ortho*-alkenylation of phenyl sulfoxides using alkenes or alkynes as substituent sources was developed by Satoh, Miura, and co-workers (Scheme 370).⁵²⁰ Both acrylates and internal alkynes showed good reactivity to give the *ortho*-alkenylated phenylsulfoxides. Although solid mechanism evidence was not presented, the authors believed the oxygen rather than sulfur was the anchoring atom to form a more stable five-membered rhodacycle key intermediate. Further transformation of the sulfoxide group to

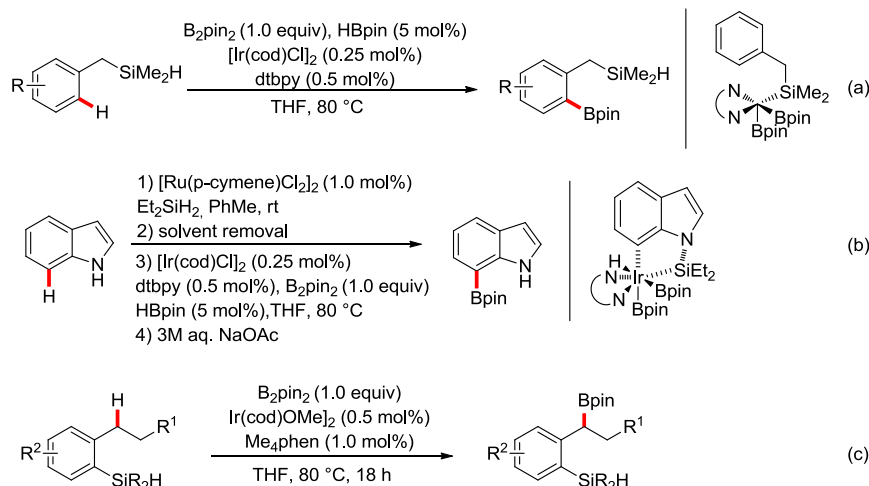
sulfide and useful diphenylbenzothiophenes after the alkenylation was achieved by convenient reduction or treatment of the sulfoxide with acid respectively.



Scheme 371 Atropodiastereoselective C-H functionalization using chiral sulfoxide.

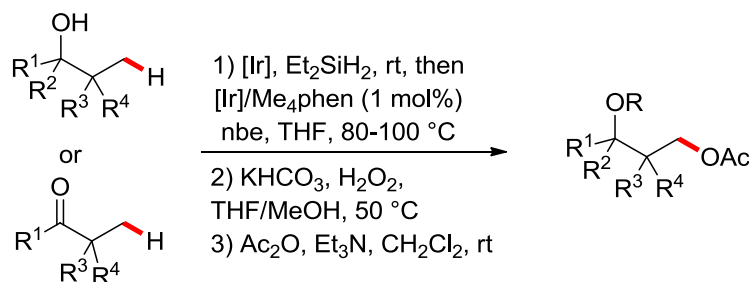
The exploit of chiral sulfoxide as both directing group and chiral auxiliary was explored by Colobert and co-workers. They found 2-*p*-tolylsulfanylbiaryl derivatives could be olefinated with methyl acrylate in the presence of 10 mol% Pd(OAc)₂ and 6 equiv AgOAc at 80°C, using DCE as the solvent (Scheme 371a).⁵²¹ An atropodiastereoselective olefination was desired by the introduction of the chiral sulfoxide group in the biaryl. However, a relatively low atropodiastereoselectivity was observed under the reaction conditions, in which an 80 °C temperature was required for the olefination. The high temperature might make the rotation of the olefinated product around the biaryl axis and led to the low stereoselectivity. Nevertheless, this work showed the possibility of asymmetric C-H bond functionalization by the use of a chiral sulfoxide. In the light of this concept, the stereoselective acetoxylation and iodination of biaryls was successful achieved through a mild C-H activation/DKR (dynamic kinetic resolution) sequence by Colobert and co-workers (Scheme 371b).⁵²² The replacement of PhI(OAc)₂ by persulfate oxidant/acetic acid drastically improved the efficiency of the reaction and the acetoxylation could be performed at room temperature. Mechanistic studies suggested that the isomerization of the diastereomeric mixture of biaryl substrates might occur when bridging palladacyclic intermediates with decreased configurational stability were generated. This was a successful example to access atropisomeric scaffold by direct C-H functionalization strategy.

10.2 The C-H functionalization directed by Si-containing functional group



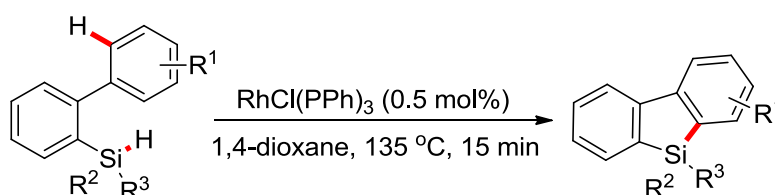
Scheme 372 Iridium-catalyzed silyl-directed borylation.

The hydrosilanes were explored by Hartwig and co-workers to function as the directing groups in an Ir-catalyzed *ortho*-borylation of benzyldimethylsilane. The formation of a bisboryl monosilyl complex through the reaction of hydrosilane and $[\text{Ir}(\text{cod})\text{Cl}]_2$ in the presence of B_2pin_2 was supposed to be the key intermediate, which allowed the selective *ortho*-C-H bond activation and functionalization (Scheme 372a).⁵²³ Substrates with more readily cleavable silicon linkers such as silyl ether and silylamine worked well under the reaction conditions to give the corresponding *ortho*-borylation products. It should be emphasized that the preparation of these siloxide or silylamine substrates and the borylation reaction could be performed in one pot. This method provided a valuable novel route for the synthesis of borylated products from benzylic silanes, phenols, and anilines. By the use of the similar strategy, a change in borylation selectivity of indoles from 2-position to 7-position was accomplished (Scheme 372b).⁵²⁴ The directed borylation reaction at 7-position of the indole framework tolerated a variety of substituents such as halogen, cyano group, and alkoxy and benzyloxy groups at the 3-, 4-, and 5-positions. Extension of this strategy to alkylarylsilane brought out the successful iridium-catalyzed borylation of secondary benzylic C-H bonds in the presence of 3,4,7,8-tetramethyl-1,10-phenanthroline as the ligand (Scheme 372c).⁵²⁵



Scheme 373 Iridium-catalyzed silyl-directed borylation.

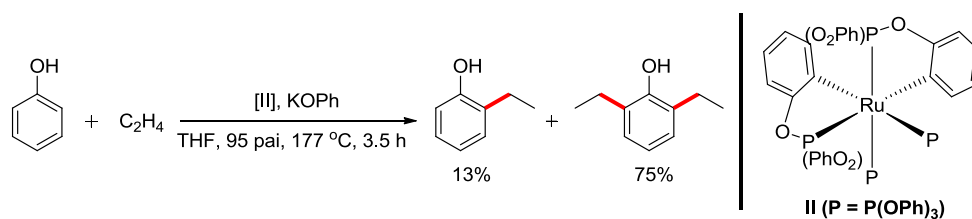
In 2012, Hardwig and co-workers achieved the site-selective functionalization of aliphatic C-H bonds by the combination of an iridium-phenanthroline catalyst and a dihydrosilane reagent (Scheme 373).⁵²⁶ The site-selective γ -functionalization of primary C-H bonds was controlled by a hydroxyl group, and the scope of the reaction encompassed alcohols and ketones bearing different substitution patterns and auxiliary functional groups. Importantly, this superior method was suitable for the site-selective functionalization of complex natural products under mild conditions.



Scheme 374 Rhodium-catalyzed synthesis of silafluorene derivatives.

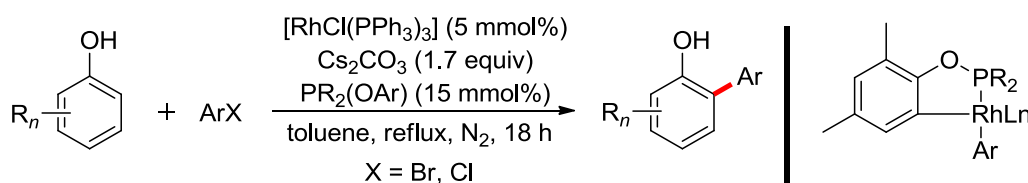
The Rh-catalyzed synthesis of silafluorenes from biphenylhydrosilanes was described by Kuninobu, Takai and co-workers (Scheme 374).⁵²⁷ The pathway by a Friedel-Crafts-type reaction was excluded. The oxidative addition of rhodium into the hydrosilane was supposed to be the important step, which allowed the subsequent selective C-H activation through binding the rhodium to deliver selectively the catalyst to the proximal C-H bond. This dehydrogenation reaction could be applied for the synthesis of the ladder-type bis-silicon-bridged *p*-terphenyl compounds.

10.3 The C-H functionalization directed by P-containing functional group

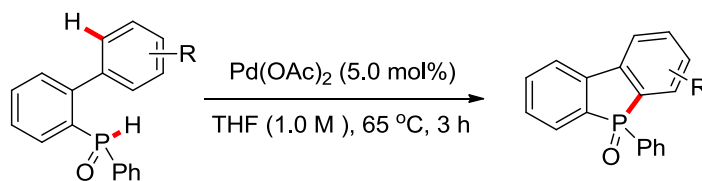


Scheme 375 Catalytic C-C bond formation via *ortho*-metalated complexes.

Phosphorous is one of the most important atoms in organic compounds and can be found in a wide range of organic molecules such as natural products, polymers, liquid crystals, and ligands. The utility of the phosphate group as a directing group in C-H activated reactions was reported as early as 1986 by Lewis and Smith (Scheme 375).^{2a} They found that the regioselective mono and double *ortho*-alkylations of phenol with ethylene could be achieved by using a *ortho*-metalated ruthenium phosphite complex. The initial exchange of the aryloxy moieties of the phosphite ligands with phenols led to the formation of an *ortho*-metalated ruthenium complex via the phosphorus-assisted the C-H bond cleavage. The subsequent substitution of phosphite by ethylene, insertion of ethylene into the Ru-C bond, and finally reductive elimination gave the ethylated product. This was the first time that the *ortho*-metalated complex was used for catalytic C-C bond formation via C-H cleavage.

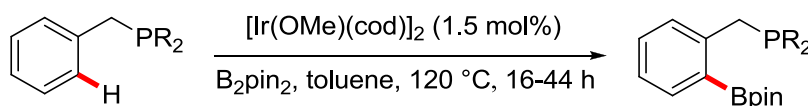
**Scheme 376** The rhodium complex catalyzed *ortho*-arylation of phenols.

The use of Wilkinson's catalyst with an appropriate phosphinite cocatalyst as the catalytic system for *ortho*-arylation of phenols was reported by Bedford and co-workers in 2003 (Scheme 376).⁵²⁸ In this transformation, the facile *orthometalation* occurred through the aryloxy group incorporation into the phosphinite cocatalyst phosphorus donors to give low-strain five-membered metallacycles. The cocatalyst influenced the reaction significantly; the reaction worked with the aryl dialkylphosphinite very well, but the bulky triarylphosphite ligand required a large excess of aryl bromide and the homocoupled biphenol was observed. A variety of aryl halides could be selectively coupled with phenols, leading to the synthesis of 2-arylated phenols. The similar chemistry was reported by Oi, Inoue, and co-workers.⁵²⁹ The direct *ortho* arylation of phenols with aryl bromides was accomplished by using a rhodium complex and hexamethylphosphorous triamide (HMPT).



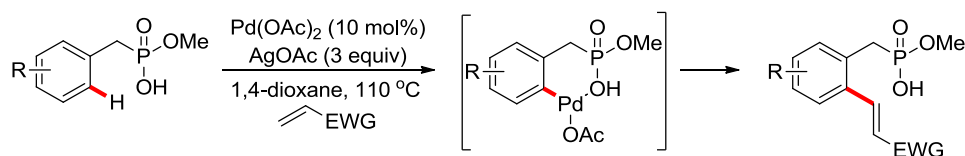
Scheme 377 Palladium-catalyzed synthesis of dibenzophosphole oxides.

In 2011, Kuninobu, Takai and co-workers explored a new strategy for the synthesis of dibenzophosphole oxides as shown in Scheme 377.⁵³⁰ In the presence of a catalytic amount of palladium(II) acetate, the dehydrogenation of phosphine-hydrogen and carbon-hydrogen bond of the secondary hydrophosphine oxides occurred through the palladium-catalyzed successive P-H and C-H bond cleavage steps. The palladium species formed from the oxidative addition of Pd(0) to P-H bond or from the elimination of P-H bond with Pd(OAc)₂ played the key role for the activation of C-H bond. By the use of this strategy, a ladder-type dibenzophosphole oxide was synthesized by the double intramolecular dehydrogenative cyclization.



Scheme 378 Iridium-catalyzed phosphine-directed *ortho* C-H borylation of arenes

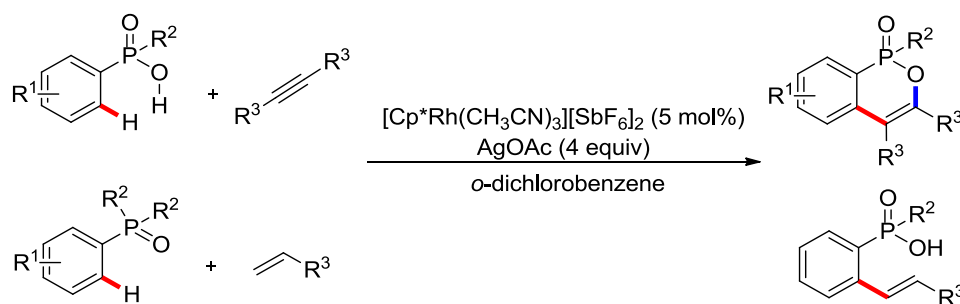
An elegant *ortho*-C-H borylation of aryldiphenylphosphines catalyzed by iridium was developed by Clark and co-workers (Scheme 378).⁵³¹ In this reaction, the phosphine was used as a directing group to assist the activation of C-H bond and the diamine ligand was crucial for the displacement of the borylated substrate to allow catalyst turnover. The use of toluene as a solvent could improve the mono-substituted product. The resulted boronate ester was air sensitive and an air-stable crystalline product was obtained by the protection of the phosphine with borane. It was quite easy to remove the protecting group and pure ambiphilic phosphine boronate esters were obtained. This method provided an efficient new route to a variety of ambiphilic ligands.



Scheme 379 Palladium(II)-catalyzed *ortho*-olefination of benzylic phosphonic esters.

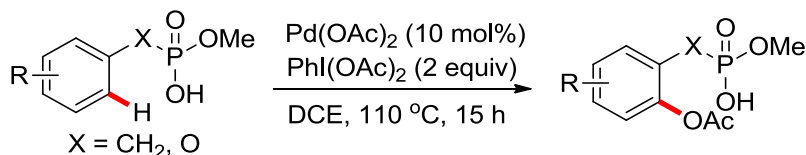
The phosphonic acid and its derivatives have extensively served as essential compounds

in organic, bioorganic, and medicinal chemistry. The Pd-catalyzed direct *ortho*-olefination of the benzylic phosphonic acid monoesters with ethyl acrylate or alkene was developed by Kim and co-workers in 2013 (Scheme 379).⁵³² The reaction was carried out in presence of Pd(OAc)₂ catalyst using AgOAc as oxidant to give a mixture of mono- and bisolefinated products. The benzylic phosphonic acid monoesters with electron-withdrawing substituents could give the moderate yields, but the reaction was incomplete for the substrates with an electron-donating substituents. the most important step for the reaction was supposed to be the formation six-membered palladacycle by the assistant of the phosphoryl-hydroxyl group through the coordination of oxygen atom. The following insertion of C-Pd into double bond and β-hydrogen elimination generated the *ortho*-alkenylated product.



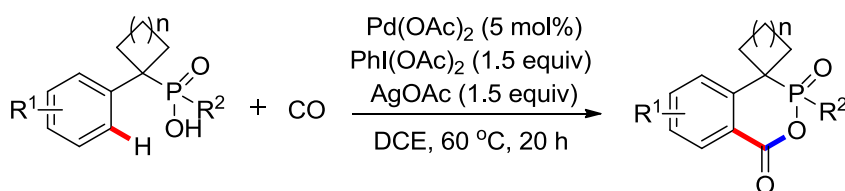
Scheme 380 Rh(III)-catalyzed oxidative coupling through phosphinoxy group directed C-H bond cleavage.

The Rh-catalyzed *ortho*-alkenylation of phenylphosphinic acids with alkynes was reported by Satoh, Miura and co-workers (Scheme 380).⁵³³ They found that phenylphosphinic acids could react with internal alkynes under rhodium catalysis efficiently to give the corresponding phosphaisocoumarin derivatives. The key step of this transformation involved the coordination of hydroxyl group in phenylphosphinic acids to the Rh(III) center and subsequent cyclorhodation to form a stable five-membered rhodacycle intermediate. This phosphinoxy group directed oxidative coupling could be successfully extended to alkenes and a variety of *ortho*-alkenylated arylphosphine products were obtained. The similar chemistry using different phenylphosphinic or alkenylphosphonic acids was described by Lee and co-workers.⁵³⁴



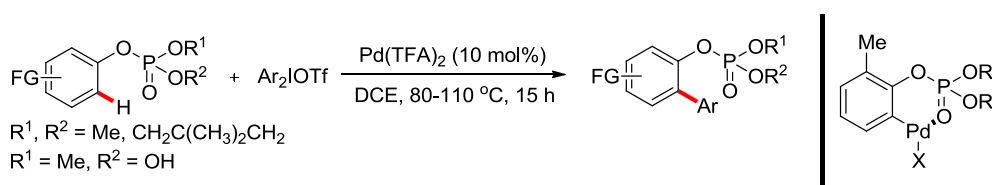
Scheme 381 *ortho*-Acetoxylation of phosphonic monoacids via Pd(II) catalysis.

The *ortho*-acetoxylation using the phosphoryl-hydroxyl directing group under Pd(OAc)₂ catalyzed was reported by Kim and co-workers (Scheme 381).⁵³⁵ In this transformation, the solvent played the key role. The use of 1,2-dichloroethane (DCE) significantly improved the reaction efficiency to give the product in high yields. Other solvent, including dioxane, MeOH, DMSO, DMF, AcOH and toluene, gave the poor yields. However, the reaction exhibited a relatively lower selectivity. Mono-acetoxyated products were obtained when the benzylic phosphonic and aryl phosphoric monoacids with substituents at the *ortho*- or *meta*-position. However, a mixture of mono- and di-acetoxyated products was resulted when using the *para*-substituted substrates.



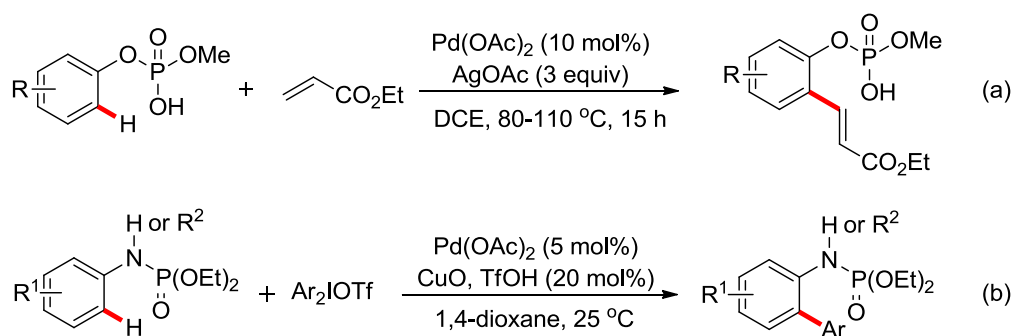
Scheme 382 Phosphaannulation by Pd-catalyzed carbonylation of C-H bonds.

The Pd-catalyzed *ortho*-carbonylation and phosphaannulation of phosphonic and phosphinic acids was developed by Lee and co-workers (Scheme 382).⁵³⁶ The substituents at the α -positions of ethyl hydrogen benzylphosphonates influenced remarkably the efficiency of the reaction. The phosphinic acid substrates with one substituent or without substituent in the α -position were inactive. Only the substrates with two-substituents in the α -position conducted the reaction smoothly to give the phosphaannulation product in high yields. Similar with the above phosphonic substrate, the hydroxyl group was supposed to be the directing group.



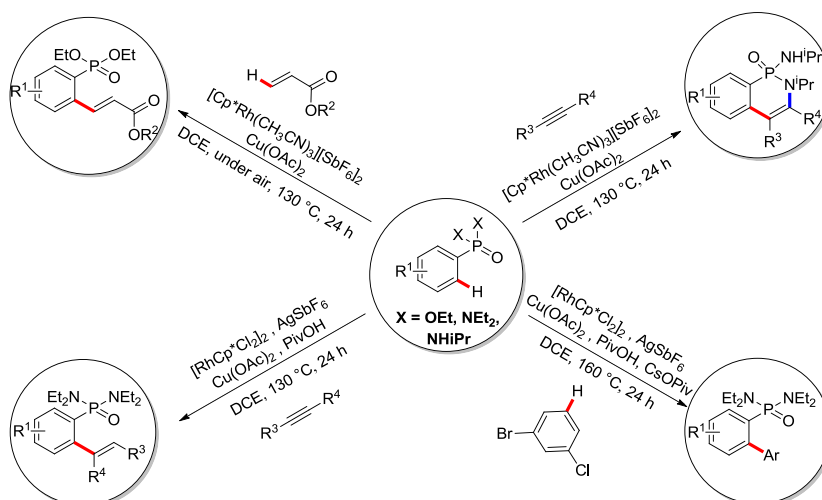
Scheme 383 Pd(II)-catalyzed *ortho*-arylation of aryl phosphates.

The Pd(II)-catalyzed arylation of aryl phosphates and aryl hydrogen phosphates using the phosphoryl as the *ortho*-directing group was developed by Kim and co-workers (Scheme 383).⁵³⁷ Various functionalized aryl groups were introduced to the *ortho*-position of organophosphates to successfully synthesize the biaryl compounds. They proposed that the mechanism of this reaction underwent the Pd(II)/Pd(IV) catalytic pathway and the key step of this transformation involved the weak coordination of the P=O bond with Pd(II) to generate the six-membered palladacycl intermediate. The Ar₂IOTf was used as both arylation reagent and oxidant in this reaction. Later on, a similar transformation of *ortho*-arylation via Pd(OTf)₂·2H₂O catalyzed C-H bond activation with phosphate as directing group was reported by Kang and co-workers.⁵³⁸



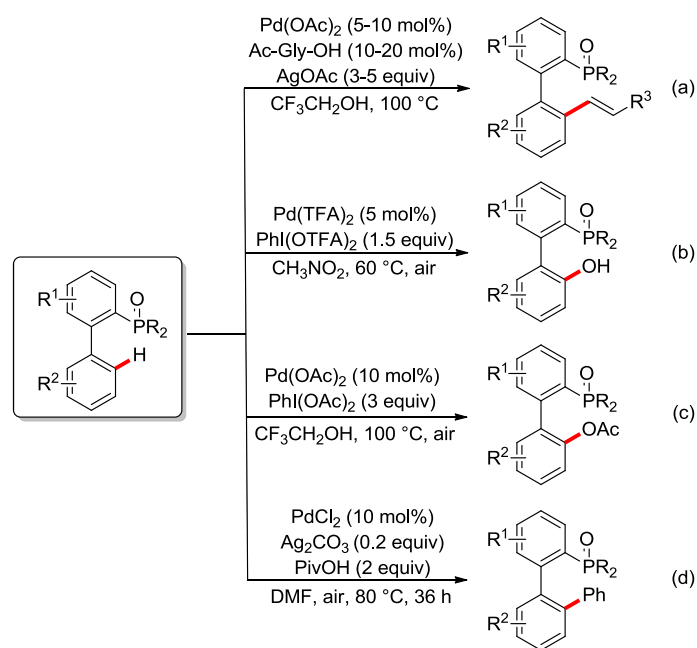
Scheme 384 Palladium-catalyzed *ortho*-alkenylation of mono-phosphoric acid and *ortho*-arylation of phosphoramidate.

An efficient Pd-catalyzed *ortho*-alkenylation was subsequently described by Lee and co-workers using a mono-phosphoric acid-directing group (Scheme 384a).⁵³⁹ This reaction offered a new approach to synthesize various the *ortho*-alkenylated phosphoric products. Importantly, various alkenes, including the electron-deficient alkenes, styrene, vinyl sulfone, vinyl phosphate, and phenyl vinyl ketone derivatives, could be successfully employed to give the *ortho*-alkenylation products. The Pd(II)-catalyzed arylation of phosphoramidate in the presence of TfOH and CuO was reported by the same research group (Scheme 384b).⁵⁴⁰



Scheme 385 Phosphoryl-related directing groups in rhodium(III) catalysis.

The Rh(III)-catalyzed oxidative C-H activation using the phosphoryl-related directing groups was demonstrated by Glorius and co-workers.⁵⁴¹ After modification of the reaction conditions, the *ortho*-alkenylation, the *ortho*-arylation, and the oxidative cyclization products could be obtained by rhodium catalysis. The catalytic process was supposed to undergo the five-membered rhodacycle intermediate generated by coordination of rhodium with the phosphoryl group. Almost at the same time, Kim⁵⁴² and Lee⁵⁴³ reported the similar transformations respectively. The Ru-catalyzed *ortho*-alkenylation of the phenylphosphine oxides with alkynes have been described by Satoh, Miura and co-workers.⁵⁴⁴ The corresponding (*o*-alkenylphenyl)phosphines was the useful ligands. The added acid was supposed to play the role in the step of reductive elimination to promote the reaction (Scheme 385)



Scheme 386 Pd-catalyzed *ortho*-functionalization of diphenylphosphine oxide.

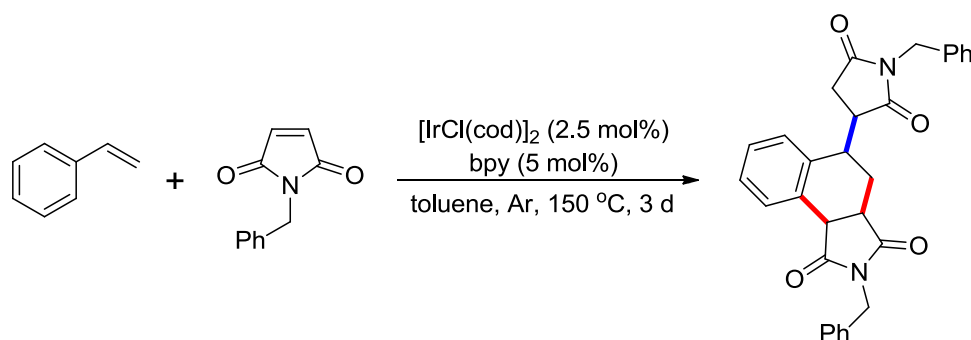
The application of palladium-catalyzed phosphine oxide as directing group was described by Yang and co-workers. They initially reported an alkenylation of diarylphosphine oxides with diverse alkenes. They found that the amino acid ligand Ac-Gly-OH could significantly improve the alkenylation to afford the useful alkene-phosphine ligands in high yields. In addition, a seven-membered cyclopalladium intermediate might be involved in this transformation via Pd(II)/Pd(IV) catalytic pathway (Scheme 386a).⁵⁴⁵ Later on, they reported the palladium-catalyzed hydroxylation⁵⁴⁶ and acetoxylation⁵⁴⁷ of diarylphosphine oxides (Scheme 386b, c). Very recently, they developed a palladium-catalyzed arylation of diarylphosphine oxides to give the terphenyl electron-rich phosphorus compounds (Scheme 386d).⁵⁴⁸

11 The C-H functionalization assisted by bidentate directing group

The π -bonds are the most common functional groups in organic molecules and play an indispensable role in organic synthesis. Because several metal complexes with unsaturated π -bonding ligands are known in the literature, such as Zeise's salt, $\text{Ni}(\text{COD})_2$, $\text{Pd}_2(\text{dba})_3$ and $[\text{RuCl}_2(p\text{-cumene})_2]_2$, it is unsurprising that such ligands can also be used as directing groups in these reactions. The π -bond coordination is generally weaker than σ -bond coordination with regard to metals because π -bonding electron pairs tend to be lower in energy than lone pairs. However, recent work has demonstrated that π -coordinating functional groups can assist

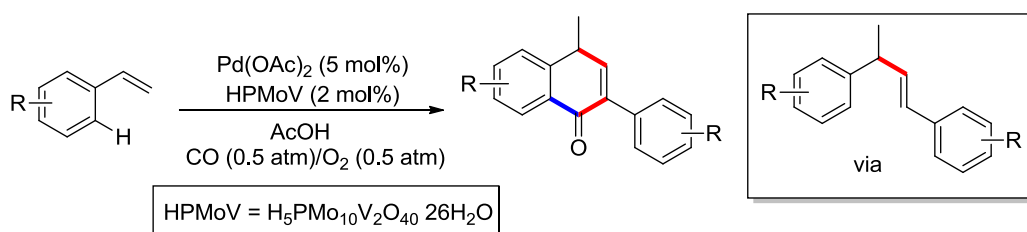
in guiding metal complexes for site-selective C-H bond activation.⁵⁴⁹

11.1 The C-H functionalization assisted by alkene



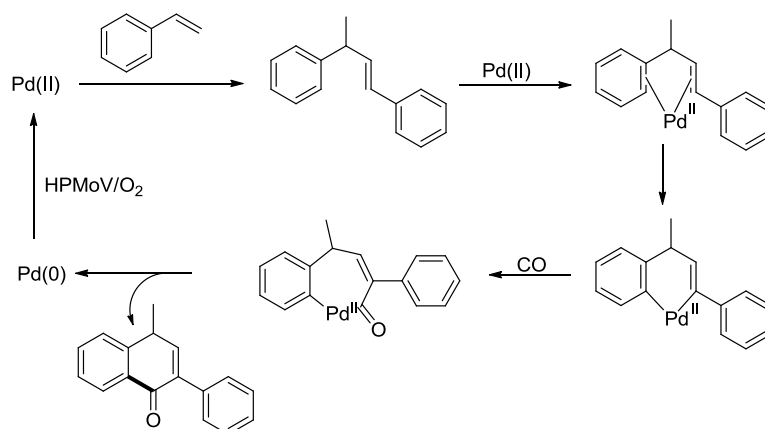
Scheme 387 Iridium-catalyzed π -bond-assisted C-H activation.

Kiyooka and co-workers demonstrated π -bond coordination-assisted C-H bond activation by using iridium complexes (Scheme 387).⁵⁵⁰ The styrene reacted with *N*-benzylmaleimide in the presence of $[\{\text{IrCl}(\text{cod})\}_2]$ and 2,2'-bipyridine (bpy) in toluene at 150 °C for 3 days to give product in 63% yield, in addition to various byproducts. The reaction was likely to be initiated by the coordination of styrene to iridium complex to form the coordinatively unsaturated intermediate, which underwent oxidative addition to the *ortho*-C-H bond to afford the C-H activation intermediate.



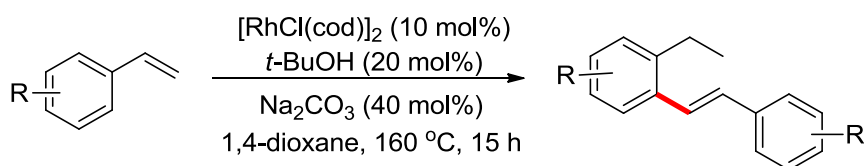
Scheme 388 Palladium-catalyzed carbonylation of styrenes.

In 2007, a palladium-catalyzed carbonylation of styrenes and carbon monoxide to produce arylnaphthalene-1(4H)-ones in the presence of $\text{Pd}(\text{OAc})_2$ combined with $\text{H}_5\text{PMo}_{10}\text{V}_2\text{O}_{40} \cdot n\text{H}_2\text{O}$ was described by Ishii and co-workers (Scheme 388).⁵⁵¹ Styrenes substituted with electron-withdrawing groups failed to give the product. The reaction was found to proceed in two stages involving the head-to-tail dimerization of styrenes, followed by carbonylation of the resulting dimers.



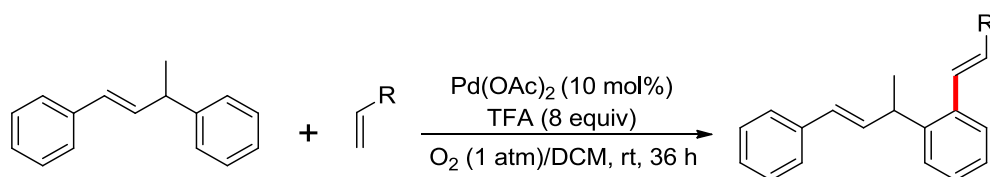
Scheme 389 Mechanism for the carbonylation of styrenes.

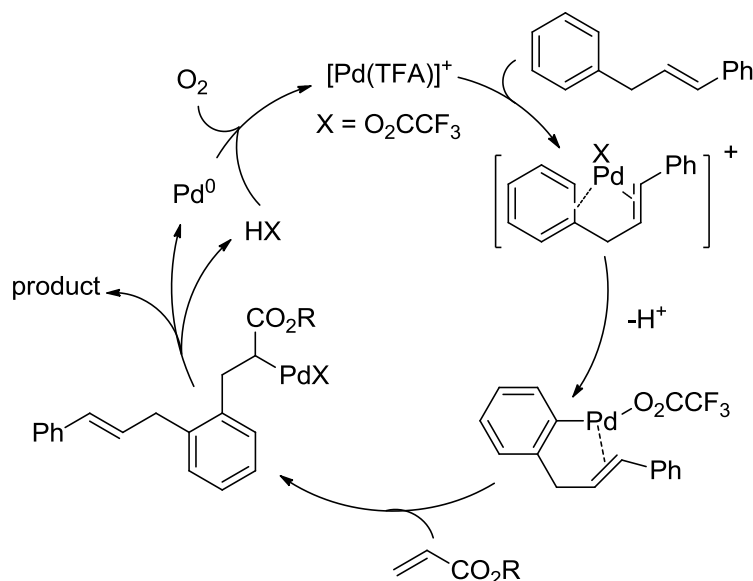
A possible mechanism for this transformation was depicted in Scheme 389. First, but-1-ene-1,3-diyldibenzene coordinated to $\text{Pd}(\text{OAc})_2$ at two of the $\text{C}=\text{C}$ double bonds and facilitated *ortho*-C-H activation of the aryl group to give palladacycle intermediate. Insertion of CO into the Pd-C bond followed by reductive elimination afforded product and palladium(0). The palladium(0) species was then oxidized back to the active palladium(II) species by HPMoV/O_2 .



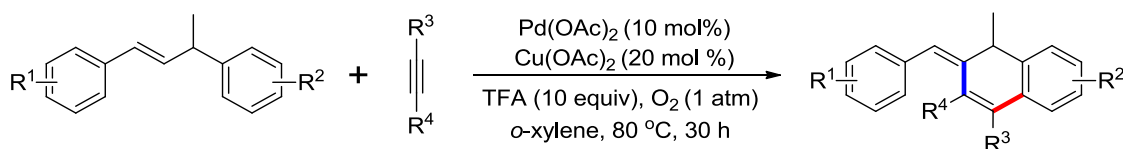
Scheme 390 Rhodium-catalyzed dimerization of styrenes through *ortho*-C-H bond cleavage.

The rhodium-catalyzed dimerization of styrenes involving *ortho*-C-H bond cleavage was reported by Tobisu and Chatani (Scheme 390).⁵⁵² In contrast to the conventional head-to-tail, tail-to-tail, or head-to-head dimers, they found the unusual dimerization product in moderate yields after reacting various styrenes in the presence of 10 mol% $[\{\text{RhCl}(\text{cod})\}_2]$, 20 mol% *t*-BuOH, and 40 mol% Na_2CO_3 in 1,4-dioxane. In this reaction the new carbon-carbon bond was formed between the benzene ring at the 2-position and the vinylic carbon. The reaction represented the first rhodium catalyzed *ortho* C-H functionalization of styrenes.



Scheme 391 Palladium-catalyzed allylic double bond assisted C-H olefination.**Scheme 392** Proposed mechanism for the allylic double-bond-assisted olefination reaction.

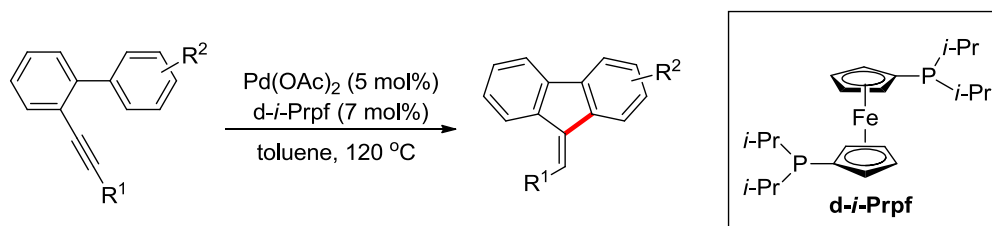
In 2012, Cheng and Gandeepan demonstrated a Pd-catalyzed allylic C=C bond directed oxidative *ortho*-olefination of arenes (Scheme 391).⁵⁵³ The reaction proceeded under mild conditions and used oxygen as an oxidant to give *ortho*-olefinated allylarenes in good to excellent yields. The choice of solvent and oxidant was crucial for the success of the present catalytic reaction. TFA appeared to be the best additive for this catalytic reaction. The reaction was highly selective and effectively cleaved the *ortho* C-H bond of the arene attached to the allylic C=C bond. No C-H activation was observed when using vinylic or butenylic C=C bonds as directing groups. The proposed mechanism was shown in Scheme 392.

**Scheme 393** Palladium-catalyzed olefin assisted C-H activation.

Recently, Cheng's group reported the synthesis of highly substituted naphthalenes from substituted allylarenes and internal alkynes by using a catalytic amount of Pd(OAc)₂ (Scheme 393).⁵⁵⁴ The reaction of allylarene with an alkyne gave substituted naphthalenes in good yields in the presence of 10 equivalents of TFA under oxygen atmosphere. This reaction also worked in the absence of Cu(OAc)₂ with decreasing efficiency and no reaction was observed

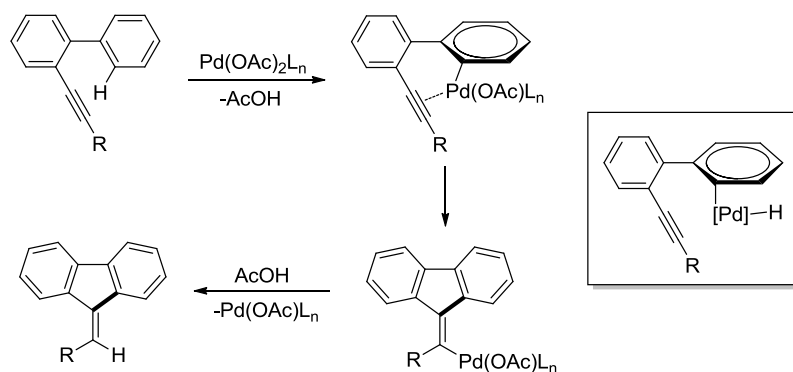
without TFA. Two regioisomeric products were produced when Unsymmetrical alkynes were used as starting materials. Substrates with *meta* substituents selectively underwent C-H activation at less hindered sites owing to steric hindrance. This reaction proceeded through the π -coordination of the allylic carbon-carbon double bond to Pd(II) and *ortho*-selective C-H bond activation.

11.2 The C-H functionalization assisted by alkyne

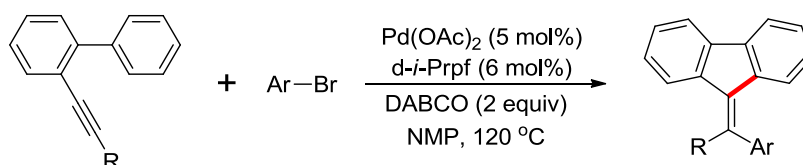


Scheme 394 Palladium-catalyzed intramolecular C-H activation of *o*-alkynylbiaryls.

In 2008, Gevorgyan and Chernyak discovered the palladium catalyzed exclusive 5-exo-dig hydroarylation of *o*-alkynylbiaryls (Scheme 394).⁵⁵⁵ The method allowed for efficient cyclization of a variety of *o*-alkynylbiaryls possessing electron-neutral and electron-deficient aryl rings into the corresponding 9-benzylidene-9*H*-fluorenes. The reaction proceeded through alkyne-assisted C-H activation instead of the more common Friedel-Crafts-type electrophilic aromatic substitution, which predominantly followed 6-endo-dig carbocyclization.⁵⁵⁶ Based on the high efficiency of the cyclization of substrates bearing electron deficient aryl rings and the observed high values of kinetic isotope effects, as well as on the exclusive *cis*-selectivity of cyclization, a plausible mechanism involving the C-H activation motif had been proposed for this transformation.

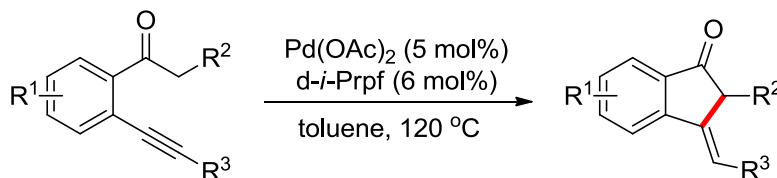


Scheme 395 Mechanism for the palladium-catalyzed C-H activation of *o*-alkynylbiaryls.



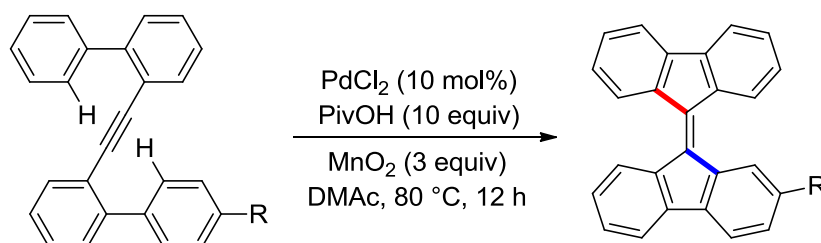
Scheme 396 Palladium-catalyzed arylation of *o*-alkynylbiaryls.

The mechanistic studies suggested the possible catalytic cycle outlined in Scheme 395. Coordination of the alkyne to the palladium complex, followed by activation of the aromatic C-H bond, afforded *ortho*-palladation intermediate. Intramolecular migratory insertion of the alkyne into the Pd-C bond provided the vinylpalladium species, which gave the final product and regenerated the catalyst. This reaction could also be applied to the synthesis of fluorenes that were fully substituted at C-10 by adding an aryl bromide and slightly modifying the reaction conditions (Scheme 396).⁵⁵⁷



Scheme 397 Palladium-catalyzed carbocyclization of *ortho*-alkynyl ketones.

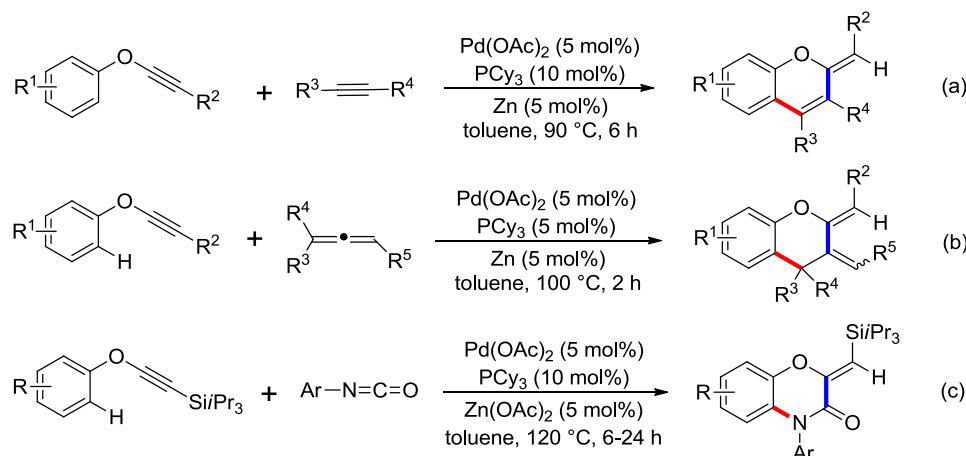
Later on, the same group further extended this strategy to synthesize alkylideneindanones as single *E* stereoisomers in good to excellent yields from *ortho*-alkynyl ketones (Scheme 397).⁵⁵⁸ It was demonstrated that the Pd-catalyzed regio- and stereoselective carbocyclization of *o*-alkynyl ketones, featuring the carbopalladation of the triple bond with Pd enolate species.



Scheme 398 Palladium-catalyzed synthesis of 9,9'-bifluorenylidenes.

Recently, Jin and co-workers developed a novel palladium-catalyzed alkyne directed dual C-H activation of bis-biaryl alkynes to form the important products 9,9'-bifluorenylidene derivatives in high yields with a broad range of functional group compatibility (Scheme 398).⁵⁵⁹ The use of the PdCl₂ catalyst combined with the MnO₂ and PivOH was vital for the

accomplishment of the catalytic cycle sufficiently. The unexpected mechanistic evidence indicated that this transformation was in sharp contrast with the previously reported hydroarylation. The reaction seemed to proceed through an unusual mechanism involving alkyne-directed dual C-H activation followed by carbopalladation with a C-C triple bond.

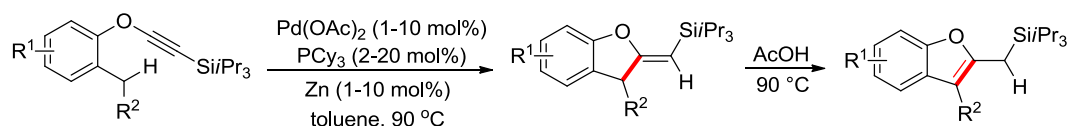


Scheme 399 Palladium-catalyzed cycloaddition of alkynyl aryl ethers.

A palladium(0)-catalyzed C-H activation assisted by alkyne coordination from alkynyl aryl ethers and internal alkynes for the synthesis of 2-methylidene-2H-chromenes was reported by Hiyama and co-workers (Scheme 399a).⁵⁶⁰ In this reaction, the alkynoxy group acted as a directing group to promote *ortho* C-H functionalization. The presence of oxygen and alkyne moieties in substrates was essential for the success of the annulation. PCy₃ was the most efficient ligand for the transformation catalyzed by Pd(OAc)₂/Zn system. Other phosphine ligands, such as PPh₃ and PBU₃, were less effective, whereas the presence of bulky silyl substituents on the alkyne groups was also imperative. A wide variety of alkynes were compatible with the reaction conditions, and it was noteworthy that unsymmetrical alkynes afforded single regioisomer products. Deuterium-labeling experiments indicated that the arylpalladium hydride complex formed by oxidative addition was a key intermediate in the reaction.

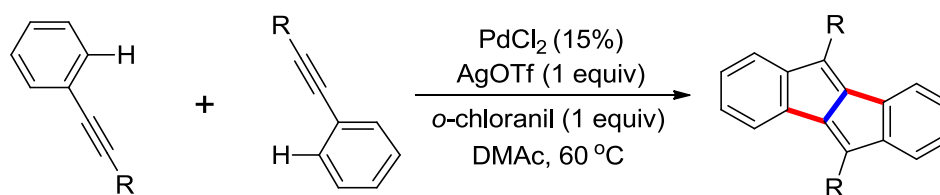
By using of the same strategy, Hiyama and co-workers demonstrated the palladium(0)-catalyzed cycloaddition reaction of alkynyl aryl ethers and allenes to form 2,3-bismethylidene-2,3-dihydro-4H-1-benzopyrans in good yields (Scheme 399b).^{561a} It was seemed that an arylpalladium hydride complex intermediate was involved in the reaction. Insertion of the allene into the Pd-C bond followed by intramolecular migratory insertion to

the alkynyl moiety offered the final product. Recently, this group constituted a further improvement of this kind of reaction by the use of isocyanates as the coupling partner (Scheme 399c).^{561b} The palladium-catalyzed reaction of alkynyl aryl ethers with isocyanates via C-H activation gave methyldene-2*H*-1,4-benzoxazin-3(4*H*)-one derivatives in moderate to good yields.



Scheme 400 Palladium-catalyzed hydrobenzylation of *ortho*-tolylalkynyl ethers.

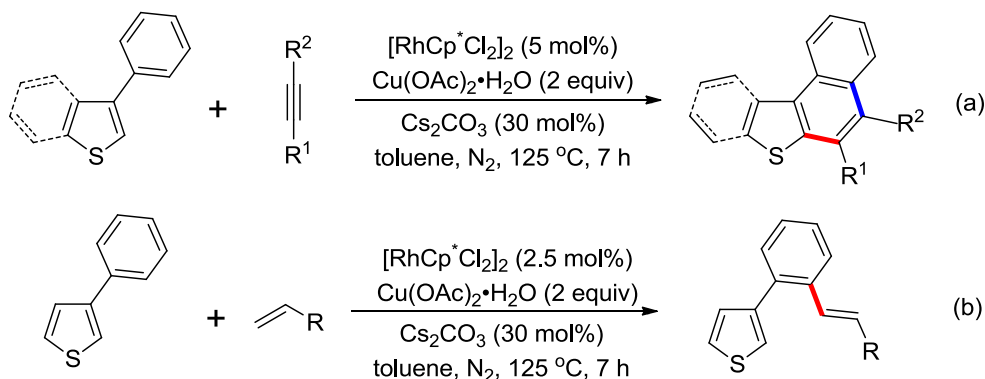
Hiyama and co-workers also extended their alkynyl-assisted C-H activation strategy for the synthesis of functionalized benzofurans through intramolecular sp^3 -C-H activation (Scheme 400).⁵⁶² The reaction of silyl-substituted *ortho*-tolylalkynyl ethers in the presence of zinc metal gave the *Z*-exocyclic alkylidene product in high yield and the product could be readily transformed into benzofuran upon treatment with acetic acid. The alkynoxy moiety containing bulky substituents could act as a directing group and play a key role in the present transformation. It was noteworthy that $Zn(OAc)_2$, generated *in situ* from the reaction of $Pd(OAc)_2$ with Zn, could effectively promote the cyclization process. The control experiment indicated that *in situ* generated $Zn(OAc)_2$ acted as a Lewis acid and acetate ion donor to facilitate the cleavage of benzylic C-H bond.



Scheme 401 Palladium-catalyzed annulation reaction of arylacetylenes.

A palladium-catalyzed C-H activation and annulations reaction from diarylacetylenes for the synthesis of dibenzo[*a,e*]pentalenes was demonstrated by Segawa and co-workers (Scheme 401).⁵⁶³ A mechanistic study indicated that the new annulation occurred through alkyne-directed, *ortho*-selectively electrophilic aromatic C-H palladation. Both symmetric diarylacetylenes and unsymmetric arylacetylenes were all applicable to this reaction and afforded the corresponding products.

11.3 The C-H functionalization directed by arene π -bond coordination



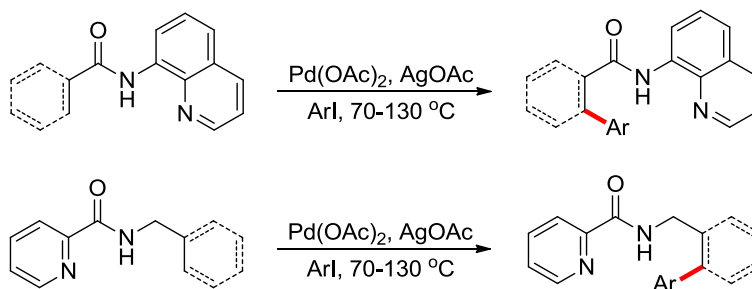
Scheme 402 Rhodium(III)-catalyzed thiophene-assisted annulation and C-H olefination.

Besides alkenes and alkynes group, the heterocycles π bond can also be used as directing group. Miura and co-workers demonstrated a rhodium(III)-catalyzed C-H activation reaction by using the thiophene π bond as a directing group.⁵⁶⁴ This strategy could be used to synthesize substituted naphthothiophenes through annulation of 3-phenylthiophenes with alkynes (Scheme 402a). Alkenylation of 3-phenylthiophene could also occur through the same procedure (Scheme 402b).

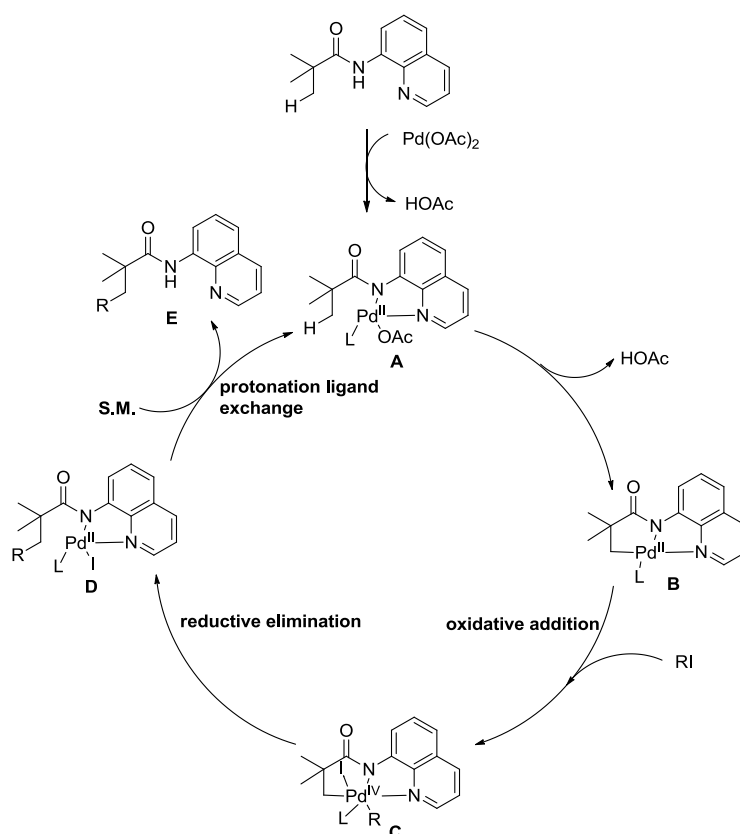
12 The C-H functionalization assisted by bidentate directing group

Despite the great advances in the field of catalytic directed C-H bond functionalization, a large number of transformations remain to be discovered and some inherent limitations still exist. To extend the concept of directed C-H bond functionalization beyond its limits, the development of new types of directing groups is the crucial point for achieving the catalytic transformations that cannot be completed with existing directing groups. Besides the monodentate directing group, the bidentate directing groups are found to promote the activation of C-H bonds via the formation of stable metallacycle and show a rigid coordination to transition metal. The stoichiometric amount of metallacycle of the bidentate directing groups has been well studied previously.⁵⁶⁵

12.1 Arylation of C-H bond



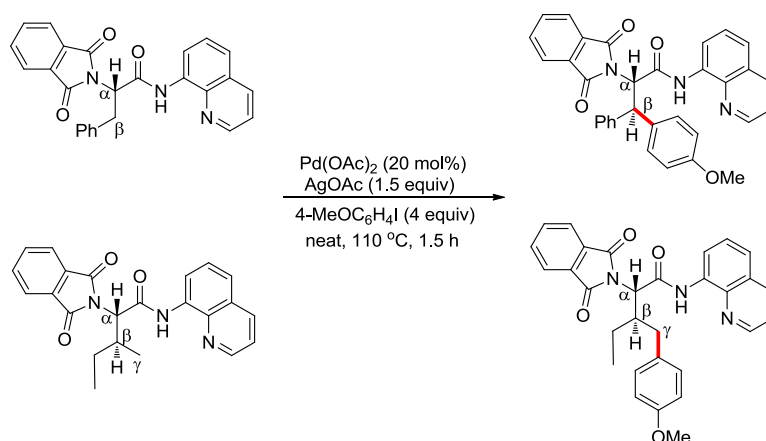
Scheme 403 Palladium-catalyzed arylation of C-H bonds assisted by a bidentate directing group.



Scheme 404 Proposed mechanism of Pd-catalyzed arylation of C-H bond.

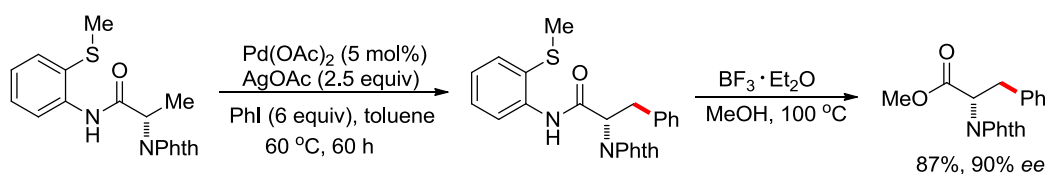
In 2005, Daugulis and co-workers first demonstrated the palladium-catalyzed C-H functionalization of C(sp³)-H and C(sp²)-H bonds by utilizing the bidentate directing group (Scheme 403).⁵⁶⁶ They showed that an 8-aminoquinolyl directing group could promote the palladium-catalyzed arylation of C(sp³)-H and C(sp²)-H bonds, thus offering an elegant method for the functionalization of various aliphatic and aromatic acids or amides. Significantly, the selective activation of C(sp³)-H bonds, which was very difficult to be achieved, could be performed smoothly by the use of the bidentate system. It was believed

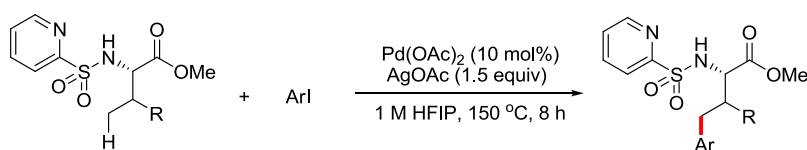
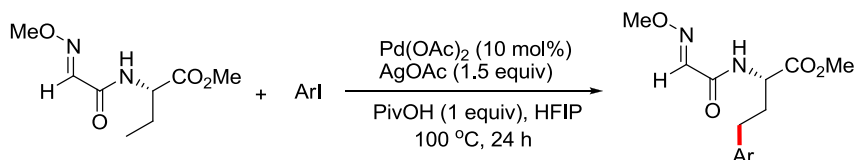
that the double coordination of the metal by those auxiliaries would facilitate the reaction by stabilizing Pd(IV) species, which was suspected to be involved as the key step in the mechanism.⁵⁶⁷ As shown in Scheme 404, the coordination of amide to a Pd(II) species followed by a ligand exchange process generated palladium complex **A**, which gave rise to the intermediate **B** by a cyclometalation process via a concerted metalation-deprotonation mechanism.^{568, 1n} The oxidative addition of intermediate **B** with an aryl iodide followed by reductive elimination generated the intermediate **D**, which produced the desired product **E** upon protonation and regenerated the Pd(II) intermediate **A** by ligand exchange. This methodology opened up a new avenue of research in the C-H functionalization.



Scheme 405 Palladium-catalyzed β - and γ -C(sp³)-H arylation.

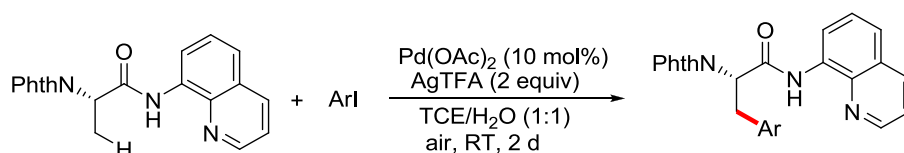
After this pioneering example, Corey and co-workers successfully employed this strategy for the synthesis of a broad range of unnatural (S)- α -amino acids (Scheme 405).⁵⁶⁹ The diastereoselective arylation of β -C(sp³)-H in α -amino acid derivatives was smoothly achieved. When the β -hydrogen was attached to a tertiary carbon, the rate of C-H activation drastically decreased and the arylation of the γ -methyl C-H bond occurred due to the bulky nature of the substrate. For instance, *N*-phthaloylated phenylalanine amide performed in this reaction with *p*-iodoanisole by producing β -C-H arylation product in a yield of 91%, while a fascinating γ -CH₃ arylation product was isolated in 87% yield by employing the isoleucine derivative in the reaction with *p*-iodoanisole under the same conditions.



Scheme 406 Palladium-catalyzed β -C(sp³)-H arylation.**Scheme 407** Palladium-catalyzed γ -C(sp³)-H arylation.**Scheme 408** 2-Methoxyiminoacetyl-directed γ -arylation of C(sp³)-H bond.

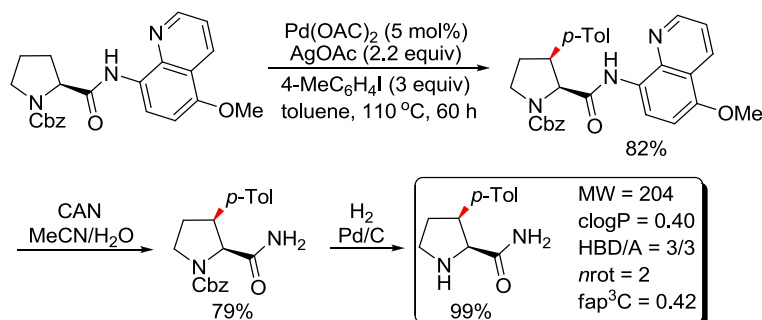
The scope of this reaction to a range of *N*-protected phthaloyl nonnatural α -amino acids and aryl partners was extended to Tran and Daugulis (Scheme 406).⁵⁷⁰ They found that a high selectivity of monoarylation could be achieved when 2-thiomethylaniline was employed as a directing group. Meanwhile, the use of an 8-aminoquinolyl directing group allowed for the diarylation of methyl groups and diastereoselective monoarylation of methylene groups of the amino acids. The acetoxylation and alkylation of C-H bonds in amino acid derivatives could also be furnished with the assistance of an 8-aminoquinolyl directing group. *N*-(2-Pyridyl)sulfamide as a new directing group in the palladium-catalyzed arylation of amino acid derivatives was studied by Carretero and co-workers (Scheme 407).^{571, 161} A variety of *N*-(2-pyridyl)sulfonamide amino acid derivatives, including α -quaternary amino acids and β -amino acids, reacted with iodoarenes in the presence of Pd(OAc)₂ to provide γ -arylated products in good yields. An unprecedented remote C(sp³)-H arylation of dipeptides was occurred, illustrating the compatibility of the method with the peptidic bonds. Notably, the auxiliary could be easily removed by treatment with zinc/NH₄Cl to give amino acid derivatives. The key role of a bimetallic γ -metalated five-membered ring palladacycle complex of the (2-pyridyl)sulfonyl unit was demonstrated.

Ma and co-workers developed an effective protocol for palladium-catalyzed direct γ -arylation of substituted 2-aminobutanates by employing 2-methoxyiminoacetyl (MIA) as the directing group (Scheme 408).⁵⁷² In comparison with Carretero's work, this reaction resulted in a better selectivity and higher yield.



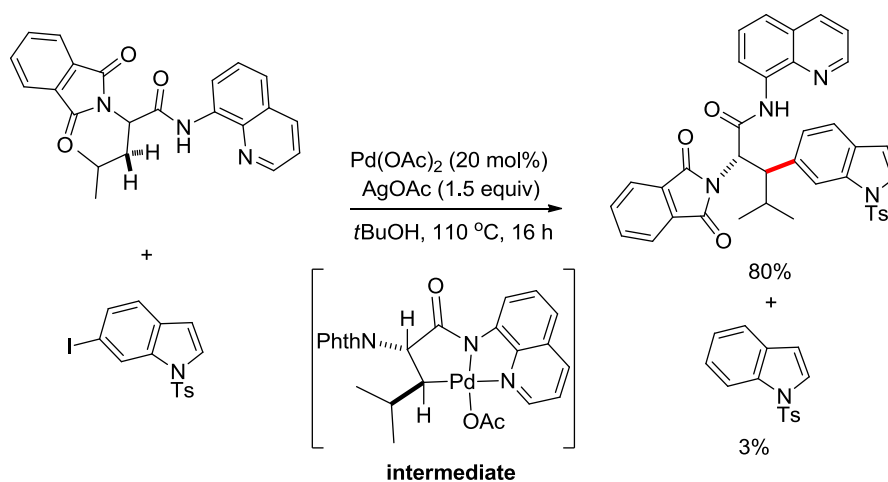
Scheme 409 Palladium-catalyzed trifluoroacetate-promoted C(sp³)-H bonds arylation.

Palladium-catalyzed mono-arylation of unactivated β -C(sp³)-H bonds was developed by Chen and co-workers via the palladium-catalyzed *N*-quinolylcarboxamide-directed coupling of phthaloyl alanine with aryl iodides under very mild reaction conditions (Scheme 409).⁵⁷³ A broad range of aryl iodides, including unprotected phenol and indole derivatives, could be selectively installed into the β -methyl group to produce various natural and unnatural aromatic α -amino acid compounds. From an operational perspective, these mono-arylation reactions were compatible with broad functional groups, insensitive with water and air, and could be operated in a gram scale. The further C-H functionalization in a diastereoselective of these monoarylated compounds could be performed smoothly, thereby providing various β -disubstituted aromatic α -amino acids which were difficult to synthesize by other ways.

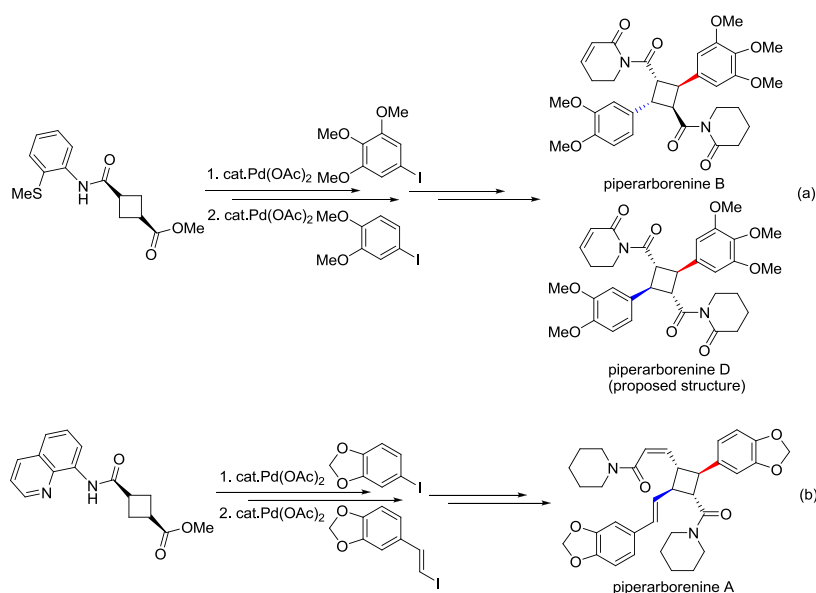


Scheme 410 Palladium catalyzed C(sp³)-H arylation of proline.

The stereospecific installation of (hetero)aryl and vinyl substituents at the unactivated 3-position of *N*-protected prolines via Pd-catalyzed C-H functionalization was independently developed by Bull⁵⁷⁴ and Zhang⁵⁷⁵ (Scheme 410). These methods enabled the efficient preparation of small yet complex enantiopure *cis*-2,3-disubstituted pyrrolidines. It was noteworthy that in Bull's report the products could be isolated as a single stereoisomer (>98% *ee*). The reaction was operative under an air atmosphere and was also successful on a larger scale. This 3-arylation reaction occurred in high yields with aminoquinolyl and methoxyaminoquinolyl directing groups which could be readily removed to give primary amide derivatives. The subsequent removal of the *N*-protected groups via hydrogenolysis afforded the 2-amido-3-aryl pyrrolidines as the *cis*-isomers.



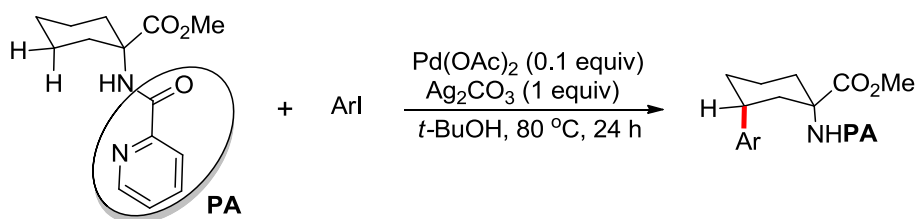
Scheme 411 Palladium-catalyzed synthesis of celogentin C.



Scheme 412 Palladium catalyzed total synthesis of piperarborenines.

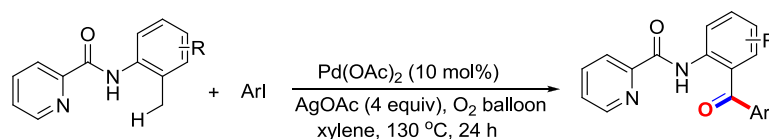
Based on the previous study involved Pd-catalyzed C-H bond arylation of amino acid derivatives, Chen and coworkers synthesized the celogentin C by an efficient and stereoselective palladium-catalyzed indolylolation of the β -C-H bond in *N*-Phth Leu (Scheme 411).⁵⁷⁶ They proposed that the quinoline moiety served as a chelating auxiliary for palladium coordination, and promoted the formation of *trans*-palladacycle intermediate. The palladium(II) intermediate presumably underwent cross-coupling with an aryl iodide partner to provide the final arylated product, which had an *erythro* stereochemical preference. Based on this, they successfully achieved the high-yielding and stereoselective 6-indolylolation of *N*-phthaloyl leucine. In light of the model reaction, the total synthesis of the celogentin C in a total of 23 steps from simple amino acid building blocks was completed. This was the first

example of utilizing the bidentate chelation strategy for the total synthesis of a natural product. Later, Baran and co-workers reported the example of sequential Pd-catalyzed C-H arylation in an unactivated cyclobutane ring with two different aryl iodides to complete the total synthesis of pipericyclobutanamide B (Scheme 412a).⁵⁷⁷ They recently described a concise total synthesis of pipericyclobutanamide A based on the bidentate directing system of sequential palladium-catalyzed arylation/vinylation of the C(sp³)-H bonds with aryl iodide and styrenyl iodide (Scheme 412b).⁵⁷⁸ These examples demonstrated the power of guided C-H functionalization to enable the fundamentally new approach to natural product synthesis.



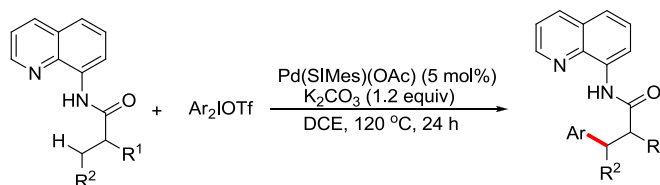
Scheme 413 Picolinamide-directed palladium-catalyzed C(sp³)-H arylation.

The strategy of bidentate auxiliary-directed C-H functionalization had been applied in arylation of aromatic and aliphatic amines.⁵⁷⁹ In 2011, Chen's group developed a practical synthetic strategy based on the picolinamide-directed palladium-catalyzed arylation and alkenylation of the remote C(sp³)-H bonds in a variety of aliphatic amines (Scheme 413).⁵⁸⁰ A broad range of aryl iodides were used successfully in this transformation. *O*-TIPS, NO₂, tosylamide, and CO₂Me groups were tolerated well under the reaction conditions, and the use of iodophenol gave the desired product in moderate yield. More importantly, various disubstituted cyclic vinyl iodides could participate in the reaction to afford the alkenylated products in moderate to good yields, which could undergo the further transformations. Interestingly, the installation of a methylene hydroxy group in the *ortho*-position of the picolinamide (PA) auxiliary made this directing group much easier to be removed under mild conditions. This modified PA directing group was exploited in the formal synthesis of (+)-obafluorin.



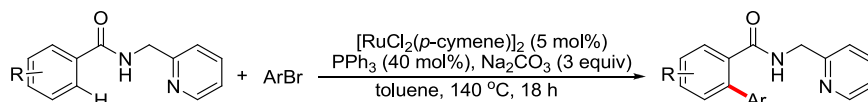
Scheme 414 Palladium-catalyzed arylation/oxidation of a benzylic C-H bond.

A palladium-catalyzed benzylic C-H arylation/oxidation of aniline substrates by the utilization of picolinamide as the directing group was reported by Zhang and co-workers (Scheme 414).⁵⁸¹ This reaction could take place under argon or air, but dioxygen atmosphere was superior. Screening of the additives indicated that AgOAc gave the best yield. Other palladium catalysts such as PdCl₂, Pd(CH₃CN)₂Cl₂, and Pd(PPh₃)₂Cl₂ also worked in this transformation but delivered lower yields. Control experiments confirmed that the palladium catalyst and silver additive were necessary in this process. The transformation tolerated a broad range of substrates, and aryl iodides as well as arenes bearing both electron-withdrawing and electron-donating substituents could well participate in the transformation to give the corresponding diarylketones in moderate to good yields. The control experiments indicated that a Pd(II)/Pd(0) process might be involved in the reaction.



Scheme 415 Pd-catalyzed C(sp³)-H arylation with diarylhyperiodonium salts.

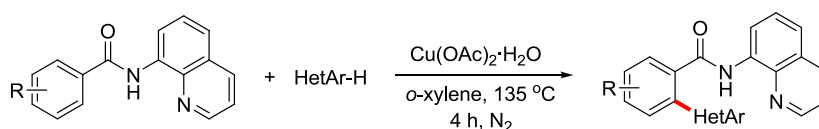
For the arylation of C-H bonds, different aryl resources other than aryl iodides have been explored.⁵⁸² Shi and co-workers reported a successful example of Pd-catalyzed primary and secondary C(sp³)-H arylation by using diarylhyperiodonium salts as the arylation reagents (Scheme 415).⁵⁸³ Various acid derivatives and different diarylhyperiodonium reagents were compatible with this reaction. They hypothesized that the trifluoromethanesulfonate anion might participate in the rate-limiting proton-abstraction step. To evaluate the reactivity of the corresponding ArI from Ar₂IOTf, the PhI was used as the substrates and the reaction was sluggish under the standard reaction conditions. This method could be applied to direct arylation of naturally important structural units such as the derivatives of amino acids and oleic acid.



Scheme 416 Ruthenium-catalyzed C-H arylation of aromatic amides.

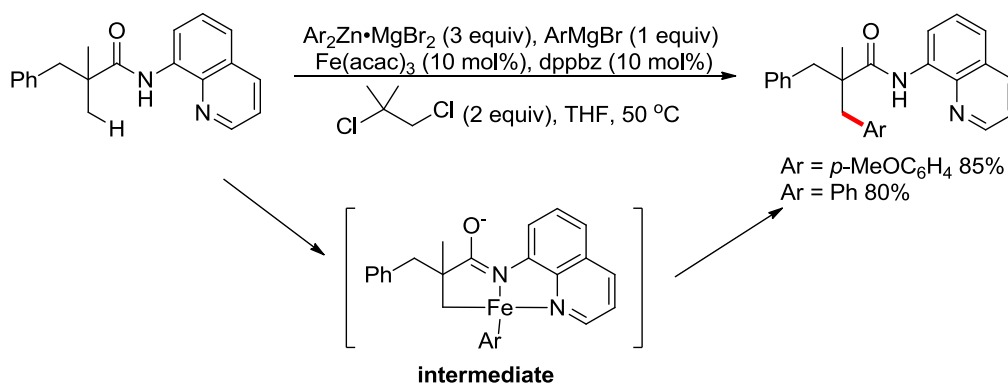
The Ru(II)-catalyzed *ortho*-arylation of aromatic amides with a bidentate directing group

was reported by Chatani and co-workers (Scheme 416).⁵⁸⁴ The presence of a bidentate directing group, such as 2-pyridynylmethylamino or 8-aminoquinoline was essential for the arylation to proceed smoothly. A variety of aryl bromides as well as heteroaromatic bromides were applicable to the arylation reaction. The use of phenyl chloride as coupling reagent gave the corresponding product in low yield. This reaction proceeded in a highly selective manner at the less hindered C-H bonds of *meta*-substituted aromatic amides, indicating that the regioselectivity was controlled by the steric nature of substrates. Although the reaction mechanism for Ru(II)-catalyzed arylation was not elucidated, the electronic effects of substituents on the efficiency of the reactions were examined in detail.

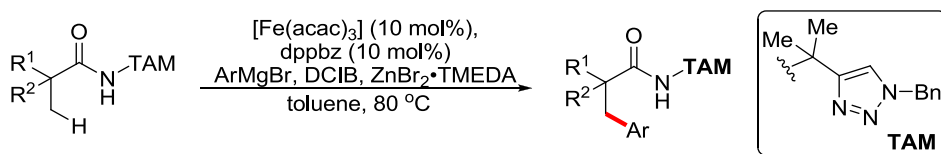


Scheme 417 Copper-mediated oxidative arylation of a C(sp²)-H bond.

A copper-mediated C-H/C-H coupling of benzoic acid derivatives and 1,3-azoles with the assistance of bidentate directing groups was developed by Miura and co-workers (Scheme 417).⁵⁸⁵ After extensive screening, the 8-aminoquinoliyl group showed excellent directing properties among the bidentate directing groups to allow the C-H/C-H coupling efficiently. A better result was achieved when anhydrous Cu(OAc)₂ was used. In addition, the relatively acidic NH was also believed to play a pivotal role during the transformation. Through the mechanism investigation, the C-H bond cleavage of benzoxazole was found to occur reversibly, while the benzamide was an irreversible process under the reaction conditions. The authors proposed that stoichiometric Cu(OAc)₂ was necessary to provide the azolylcopper intermediate, followed by the generation of the Cu(III) complexes before reductive elimination. A variety of 1,3-azoles were applicable to this direct C-H/C-H coupling, and both electron-rich and electron-deficient 5-aryloxazoles benzoxazoles underwent the arylation smoothly.



Scheme 418 β -Arylation of carboxamides via iron-catalyzed C(sp³)-H bond activation.

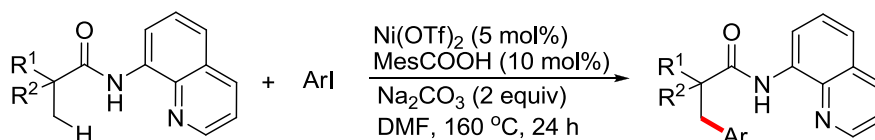


Scheme 419 Iron-catalyzed C(sp³)-H arylation by triazole assistance.

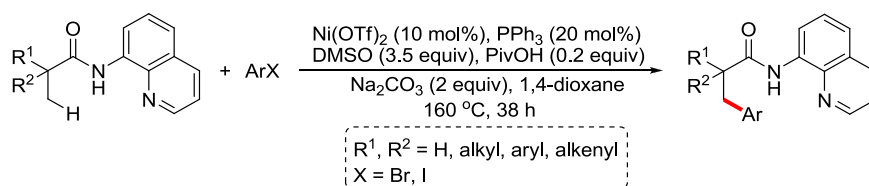
The iron-catalyzed β -arylation of 2, 2-disubstituted propanamide with an organozinc reagent in the presence of an organic oxidant and a biphosphine ligand was disclosed by Nakamura's group (Scheme 418).⁵⁸⁶ The 8-aminoquinoliny (NH-Q) directing group and 1,2-bis(diphenylphosphino)benzene (dppbz) ligand were found to be essential for the transformation. The success of the reaction was mostly attributed to the careful design of the ligand. For example, the bidentate ligand 1,2-bis(diphenylphosphino)-ethane (dppe), which was similar to dppbz except for its slightly larger bite angle and a more flexible backbone, gave the product in 9% yield. The reaction was also sensitive to the structure of the substrate. For instance, cyclohexanecarboxamide and cyclopentanecarboxamide participated in the reaction smoothly to give the corresponding products, whereas the corresponding cyclobutane- and cyclopropanecarboxamides failed to give the desired products. They proposed that the CH₃-C-C(=O) bond angle might be crucial for efficient C-H activation, and a wider or smaller angle resulted in the formation of a chelation intermediate less stable. The overwhelmingly higher reactivity of a methyl group over a benzylic group excluded a radical mechanism that previously observed in iron catalysis,⁵⁸⁷ and the high sensitivity of the yield to the structure of the substrates and the ligands suggested the involvement of organoiron intermediate in the crucial step. Kinetic isotope effect (KIE) experiments with a primary KIE of 2.4 indicated that the cleavage of the C-H bond might be the rate-determining step of the

reaction.

A novel triazolylmethylmethyl (TAM) amide-based bidentate auxiliary was developed in the iron-catalyzed arylation of unactivated C(sp³)-H bonds by Ackermann and co-workers (Scheme 419).⁵⁸⁸ Detailed optimization studies revealed that this C-H functionalization was viable with a catalyst system consisting of FeCl₃ as the metal source and dppe as the ligand. The triazole auxiliary proved to be superior to the hitherto employed bidentate directing groups, such as the widely used 8-aminoquinolyl auxiliary, under the reaction conditions. The iron catalytic system could also be applied in the direct β-arylation of α,β-unsaturated amide derivatives.



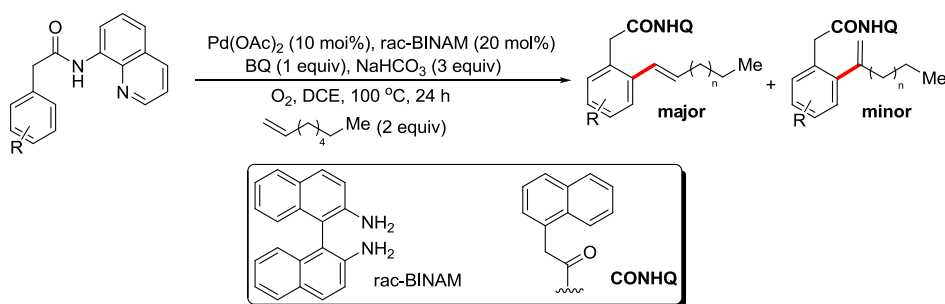
Scheme 420 Nickel-catalyzed arylation of C(sp³)-H bonds.



Scheme 421 Ni(II)-catalyzed arylation of unactivated β-C(sp³)-H bond arylation.

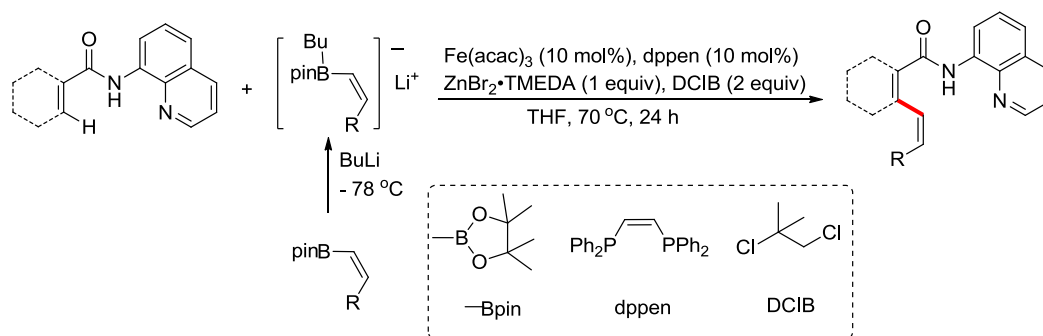
The Ni-catalyzed β-arylation of aliphatic amides with aryl iodides was achieved by Chatani and coworkers (Scheme 420).⁵⁸⁹ The base and the additive of benzoic acid was crucial for the efficiency of the reaction, and the choice of Na₂CO₃ and MesCOOH gave the best yield. Various nickel complexes, including Ni(II) and Ni(0) catalysts, showed a high catalytic activity for this transformation. To gain insights into the mechanism for the reaction, the deuterium-labeling experiments were carried out, which revealed that the C-H bond cleavage step was fast and reversible. The detailed mechanistic investigation and the control experiments illustrated that the reaction proceeded through a Ni(II)/Ni(IV) catalytic cycle. Shortly after, an analogous chemistry with a broad scope of aryl halides as substrates was demonstrated by You and co-workers (Scheme 421).⁵⁹⁰

12.2 Alkenylation of C-H Bond



Scheme 422 Palladium-catalyzed aryl C-H olefination with unactivated, aliphatic alkenes.

Due to the easy β -hydrogen elimination, the olefination of unactivated aliphatic alkenes remains a big challenge in palladium-catalyzed coupling reactions.^{591, 315} Recently, The palladium-catalyzed *ortho* C-H bond olefination of phenylacetic acid derivatives using unactivated aliphatic alkenes with high regio- and stereoselectivities was reported by Maiti and co-workers (Scheme 422).⁵⁹² Compared with the previous Pd-catalyzed C-H olefination, this significant breakthrough of the restricted substrate scope, in particular non compliance of unactivated aliphatic olefins was owing to bidentate directing strategy. A racemic 1,1'-binaphthyl-2,2'-diamine (*rac*-BINAM) ligand was supposed to enhance the catalytic activity of active Pd(II) species. The versatility of this operationally simple method was illustrated through the sequential C-H olefination in synthesizing divinylbenzene derivatives.

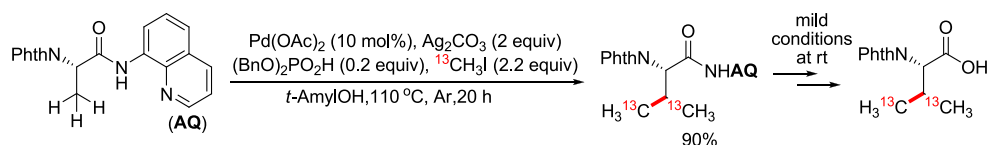


Scheme 423 Iron-catalyzed C(sp²)-H bond alkenylation.

By the use of organoborate reagent as the olefinic coupling partner, Nakamura and co-workers demonstrated an efficient protocol for the C-H alkenylation of a quinolinyl amide in the presence of iron and zinc catalysts (Scheme 423).⁵⁹³ They found that a stoichiometric organoiron(III) in the absence of DCIB was quite effective to give the product in nearly quantitative yield, indicating that the phenyliron(III) intermediate played the key role in the alkenylation. The zinc salt was crucial to promote the transfer of the organic group from the

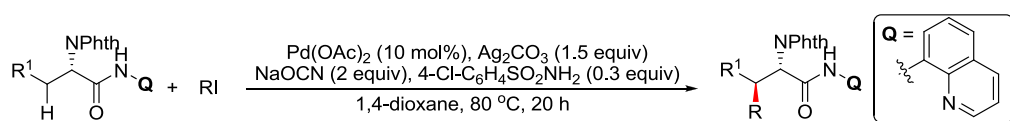
boron atom to iron(III) catalyst. This reaction allowed the coupling of a variety of aromatic, heteroaromatic and olefinic substrates with alkenyl and aryl boron compounds under mild oxidative conditions.

12.3 Alkylation of C-H Bond



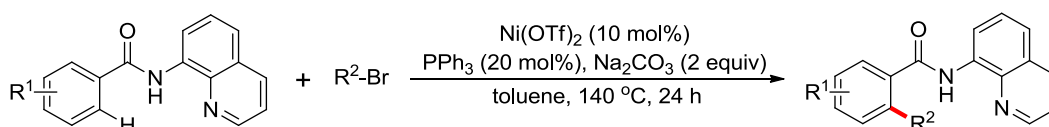
Scheme 424 Pd-catalyzed alkylation of unactivated methylene C(sp³)-H bonds.

Compared with the C-H bond arylation and alkenylation reactions, the direct alkylation of C-H bonds with unactivated alkyl halides remains in early stage of development. During the past years, Chen's group reported a series of Pd-catalyzed alkylation reactions of C(sp²)-H and C(sp³)-H bonds directed by the PA group [PA = picolinamide].⁵⁹⁴ In 2013, Chen and co-workers reported the Pd-catalyzed alkylation of unactivated methylene C(sp³)-H bonds of aminoquinolyl aliphatic carboxamides with α -haloacetate and methyl iodide (Scheme 424).⁵⁹⁵ This reaction was highly efficient with the tolerance of a wide range of functional groups. The reaction enabled a streamlined strategy for the synthesis of various natural and unnatural amino acids, particularly β -alkylated α -amino acids, in a diastereoselective manner. With simple isotope-enriched reagents, they also provided a convenient and powerful solution to site-selectively incorporate isotopes into the carbon scaffolds of amino acid substrates. They postulated that the C-H alkylation reaction proceeded through a C-H palladation/coupling sequence and that a Pd(II)/(IV) manifold was operative. Notably, (BnO)₂PO₂H was the most effective additive among the carboxylic acid and organic phosphate tested. It was proposed that (BnO)₂PO₂H could form a soluble complex with Ag₂CO₃ to improve the concentration of Ag⁺ in the reaction medium, and might also serve as a ligand for palladium during the oxidative addition and reductive elimination steps. They also suspected that (BnO)₂PO₂H could facilitate the protonolysis of the Pd-complexed alkylated intermediate to promote the release of the target product, thus accelerating the turnover of Pd catalyst.



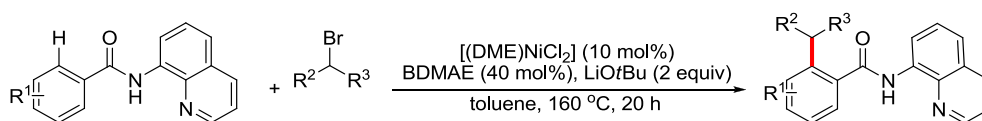
Scheme 425 Palladium(II)-catalyzed alkylation of unactivated methylene C(sp³)-H bonds.

A sulfonamide-promoted palladium(II)-catalyzed alkylation of unactivated β -methylene C(sp³)-H bonds of α -amino acid substrates with alkyl iodides was reported by Shi and co-workers (Scheme 425).⁵⁹⁶ The reaction tolerated a diverse array of functional groups and proceeded with high diastereoselectivity. Alkyl iodides bearing β -hydrogen atoms could be used as substrates under the optimized reaction conditions. This transformation provided a versatile strategy for the stereoselective synthesis of unnatural β -disubstituted α -amino acids. Interestingly, a series of stoichiometric and catalytic experiments indicated that the presence of 4-Cl-C₆H₄SO₂NH₂ and NaOCN were crucial for the reaction to proceed efficiently.



Scheme 426 Ni-catalyzed *ortho*-alkylation of benzamides.

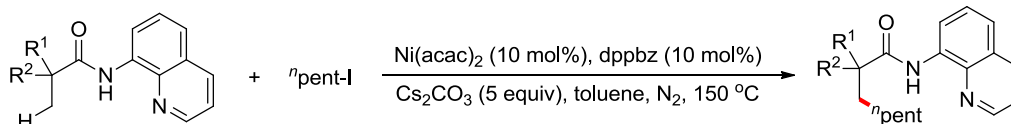
A new Ni-catalyzed 8-aminoquinoline directed *ortho* C-H bond alkylation of benzamides and acrylamide derivatives with unactivated primary alkyl halides was developed by Chatani and co-workers (Scheme 426).⁵⁹⁷ This reaction represented the first example of Ni-catalyzed *ortho* alkylation of amide derivatives with high functional group compatibility and proceeded in a highly selective manner at the less hindered C-H bond when the *meta*-substituted aromatic amides were employed. The deuterated experiment indicated that cleavage of the C-H bond appeared to be a reversible and rapid step, which was not the rate-determining step.



Scheme 427 Nickel-catalyzed C-H bonds alkylation with secondary alkyl bromides.

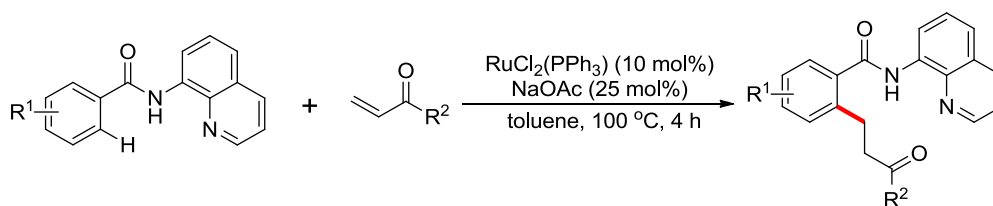
Compared with the primary alkyl halides, C-H functionalizations with secondary alkyl halides are considered to be more difficult because of their reluctance to undergo oxidative additions to transition metals and the subsequent β -hydride eliminations. In 2014, Ackermann developed a nickel-catalyzed C-H bonds alkylation with challenging secondary alkyl bromides and chlorides. Catalytic nickel precursors [(DME)NiCl₂] in combination with BDMAE[bis(2-dimethylaminoethyl)ether] and LiOtBu in toluene was proved as the optimal conditions (Scheme 427).⁵⁹⁸ In this synthesis, a robust nickel(II) catalyst enabled C-H

transformation with cyclic and acyclic alkyl bromides and chlorides with ample substrate scope. Notably, this versatile nickel(II) catalyst also formed the basis for unprecedented trifluoroethylations of unactivated C-H bonds.

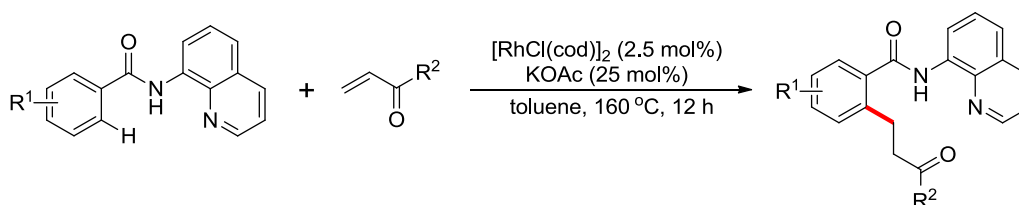


Scheme 428 Nickel-catalyzed site-selective alkylation of unactivated C(sp³)-H bonds.

A highly regioselective alkylation of 2,2-disubstituted propionamide with 8-aminoquinolinyl group as the amide moiety via a nickel-catalyzed C(sp³)-H bond functionalization process was demonstrated by Ge and co-workers (Scheme 428).⁵⁹⁹ It was also found that not only alkyl iodides but also alkyl bromides or chlorides with the addition of CsI could participate in the reaction to generate the corresponding products. However, both secondary alkyl halides and benzyl bromide failed to give the corresponding products, presumably due to the steric effect or the unstability of the intermediate. Moreover, this reaction showed a predominant preference for C(sp³)-H bonds of methyl groups via a five-membered ring intermediate over the C(sp²)-H bonds of arenes in the cyclometalation step. The deuterium-labeling experiment indicated that the cyclometalation of amide with a nickel species was the rate-determining step. The addition of TEMPO resulted in the decreased yield and 2,2,6,6-tetramethyl-1-(pentyloxy)piperidine was isolated as the major product, which was consistent with the radical involving Ni(II)/Ni(III) catalytic cycle.



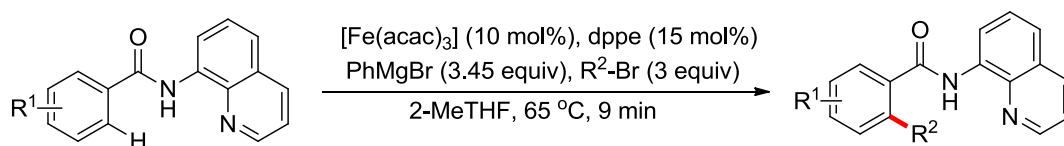
Scheme 429 Ruthenium-catalyzed *ortho*-C-H bond alkylation of aromatic amides.



Scheme 430 Rhodium-catalyzed alkylation of C-H bonds in aromatic amides.

Besides the alkyl halides, various α,β -unsaturated carbonyl compounds could be

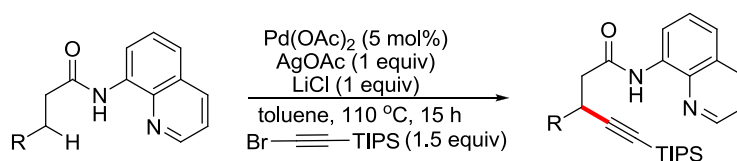
employed alkylation reaction. For instances, Chatani and co-workers developed Ru(II) (Scheme 429) and Rh(I)-catalyzed (Scheme 430) alkylation of *ortho* C(sp²)-H bonds in aromatic amides with the assistance of bidentate directing groups.⁶⁰⁰ These reactions had a broad substrate scope, in which acrylic esters, acrylamide, fumarate, maleate, and phenyl vinyl sulfone could be tolerated. The transformation provided a fast and economical access to the functionalizable molecular backbones, which could be achieved by the potential transformation of the amide moiety to various functional groups.



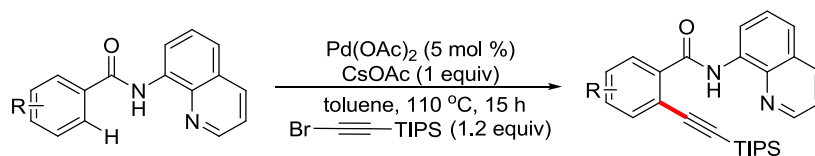
Scheme 431 Iron-catalyzed C(sp²)-H alkylation of carboxamides with primary electrophiles.

Following the pioneering work by Nakamura and co-workers, Cook's group disclosed a robust iron-catalyzed *ortho* alkylation of aryl amides in mild reaction conditions (Scheme 431).⁶⁰¹ In particular, this reaction did not require a co-oxidant and could be accomplished in less than 10 min, proceeding in high yields with exceptional regioselectivity. Although several Grignard reagents were viable in the reaction, phenylmagnesium bromide offered the highest conversion rate to the product. In addition, the rate of Grignard reagents addition was critical to the success of the reaction (i.e., dropwise additions over less than nine minutes compromised the yield of the reaction). In contrast to Pd-, Co-, and Ni-catalyzed C-H alkylations, the reaction provided exclusively the monosubstituted products without any detectable dialkylation product. Moreover, the presence of a *meta* substituent provided very high levels of regioselectivity, favoring the less-hindered position. The small intermolecular KIE ($k_{\text{H}}/k_{\text{D}} = 1.5$) and the large intramolecular KIE ($k_{\text{H}}/k_{\text{D}} = 2.9$) observed in the control experiment implied that substrate coordination was irreversible and occurred prior to C-H cleavage.

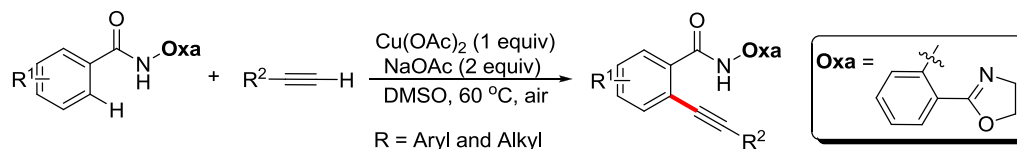
12.4 Alkylation of C-H Bond



Scheme 432 Palladium-catalyzed C(sp³)-H bonds alkylation.



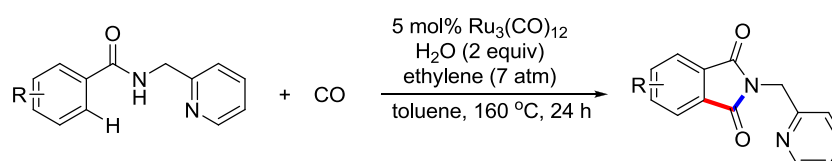
Scheme 433 Palladium-catalyzed C(sp²)-H bonds alkylation.



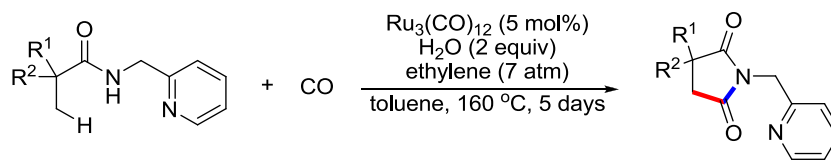
Scheme 434 Cu(II)-mediated *ortho* C(sp²)-H alkylation with terminal alkynes.

Alkynes are powerful building blocks in chemical synthesis due to the diverse reactivity of carbon-carbon triple bonds toward addition, cycloaddition, and metathesis reactions.⁶⁰² Encouraged by the success of C-H bonds functionalizations in recent years, chemists have paid much attention to the direct alkylation of C-H bonds.⁶⁰³ Chatani and co-workers accomplished the palladium catalyzed alkylation of unactivated C(sp³)-H bonds (Scheme 432).⁵⁷³ These reactions allowed for the straightforward introduction of an ethynyl group into aliphatic acid derivatives. The reaction tolerated a variety of functional groups and could be applied to the natural-product-based substrates, thus offering a new method for preparing complex alkyne components in a more straightforward manner. Furthermore, this Pd-catalyzed strategy for alkylation of C-H bonds could be extended to the transformation of benzoic acid derivatives (Scheme 433).⁶⁰⁵ Alternatively, Yu and co-workers recently developed Cu(II)-promoted *ortho* alkylation of arenes and heteroarenes with terminal alkynes to prepare aryl alkynes (Scheme 434).⁶⁰⁶ This reaction tolerated a variety of arenes and terminal alkynes bearing different substituents. More importantly, aliphatic alkynes, including *n*-pentyl-, *tert*-butyl-, cyclopropyl-, and cyclohexyl-substituted acetylenes, were all compatible with the reaction conditions, thus by providing an alternative synthetic disconnection to Sonogashira coupling. Moreover, the resulted alkylation benzoic acids could be converted to various useful heterocycles and valuable synthons.

12.5 Annulation of C-H Bond

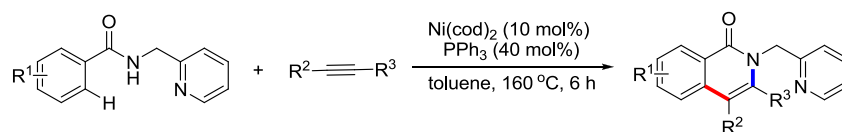


Scheme 435 Ruthenium-catalyzed carbonylation at *ortho* C-H bonds in aromatic amides.



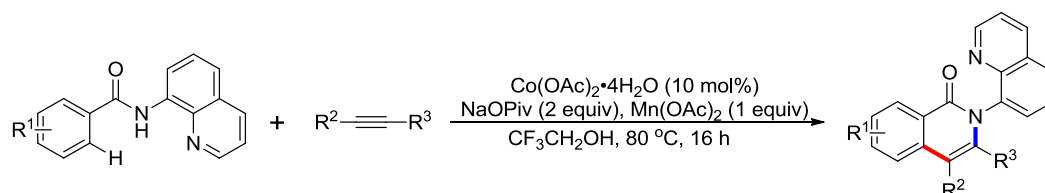
Scheme 436 Carbonylation of unactivated C(sp³)-H bonds by ruthenium carbonyl.

Bidentate auxiliary assisted transition-metal-catalyzed C-H bonds functionalization have also emerged as a powerful tool for the synthesis of heterocycles.⁶⁰⁷ In 2009, Chatani and co-workers^{608a-b} demonstrated the Ru-catalyzed carbonylation of aromatic, aliphatic amides to synthesize phthalimides and pyrrolidine-2,5-dione derivatives with tolerance of a variety of functional groups (Scheme 435 and Scheme 436). In these processes, the choice of ethylene and H₂O as additives was crucial to result in an effective catalytic system. Notably, for the carbonylation of unactivated C(sp³)-H bonds, the reaction proceeded selectively at a methyl C-H bond over a methylene C-H bond.



Scheme 437 Ni-catalyzed *ortho* C-H bonds functionalization with alkynes.

The Ni-catalyzed oxidative annulation of aromatic amides with alkynes to produce isoquinolones has also been disclosed (Scheme 437).^{608c} This transformation represented the first example of Ni-catalyzed transformations of *ortho* C-H bonds by utilizing chelation assistance. Various functional groups in aromatic ring of amides were tolerated under the reaction conditions, and substrates with an electron-donating group were less reactive than those with an electron-withdrawing group. Moreover, a highly regioselective result was achieved when the unsymmetrical alkynes were used as substrates.

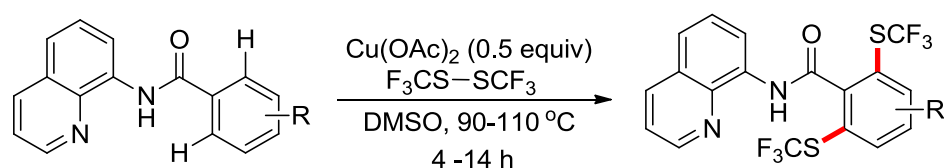


Scheme 438 Cobalt-catalyzed C(sp²)-H bond alkenylation with alkynes.

A cobalt catalyzed coupling of alkynes with C(sp²)-H bonds was demonstrated by Daugulis and co-workers (Scheme 438).⁶⁰⁹ Both terminal and internal alkynes were

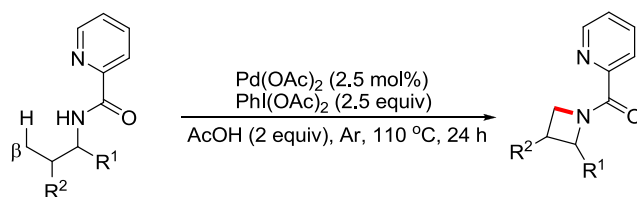
compatible in the reaction. The reaction proceeded more efficiently in trifluoroethanol, presumably due to higher solubility of the cobalt catalyst. Furthermore, this reaction demonstrated the first use of cobalt catalysis by employing bidentate, monoanionic auxiliaries. Subsequently, with the modified catalytic system, they accomplished the cobalt-catalyzed aminoquinoline-directed *ortho*-functionalization of C(sp²)-H bonds with alkenes and carbon monoxide to synthesize six-membered and five-membered nitrogen-containing heterocycles.⁶¹⁰

12.6 C-X Bond Formation

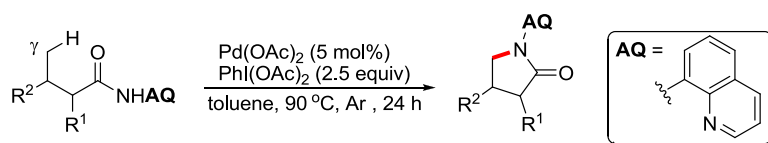


Scheme 439 Copper-promoted sulfenylation of C(sp²)-H bonds.

In addition to the Pd-catalyzed arylation, alkenylation and alkylation using removable bidentate directing groups, the challenging carbon-heteroatom bonds formation through C-H bond activation was also developed. Daugulis and co-workers reported a copper mediated, auxiliary-assisted direct sulfenylation of β -sp² C-H bonds of benzoic acid derivatives and γ -C(sp²)-H bonds of benzylamine derivatives (Scheme 439).⁶¹¹ The reaction showed high generality, excellent selectivity toward *ortho* C-H bonds, as well as good functional group tolerance. This method provided a novel and straightforward way to form C-S bond, thereby accomplishing the preparation of aryl trifluoromethyl thioethers.



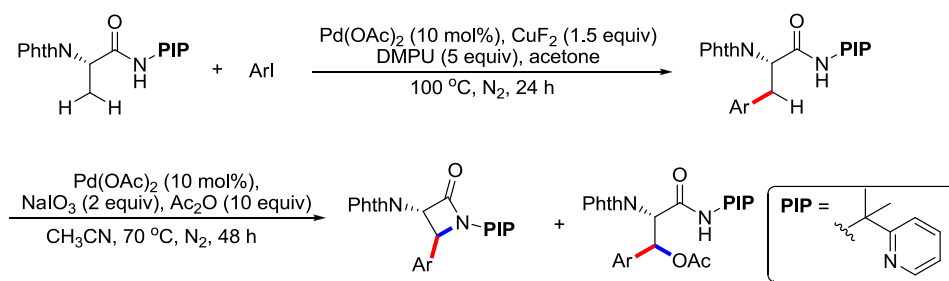
Scheme 440 Palladium-catalyzed intramolecular amination of C(sp³)-H bonds.



Scheme 441 Palladium-catalyzed intramolecular amination of γ C(sp³)-H bonds.

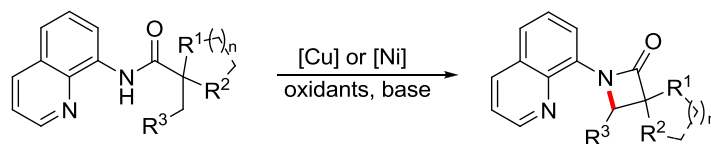
The C-N bonds construction⁶¹² by palladium-catalyzed C-H bond intramolecular amination

reactions of unactivated C(sp³)-H and C(sp²)-H bonds of amine substrates to form azetidines, pyrrolidines, and indulines has been studied (Scheme 440).⁶¹³ For instances, Chen and co-workers developed a novel protocol for the synthesis of pyrrolidones and indolinones by the palladium-catalyzed intramolecular amination of unactivated C(sp³)-H and C(sp²)-H bonds at the γ position of secondary-amide precursors (Scheme 441).⁶¹⁴ These lactamization reactions were efficient, versatile and only inexpensive reagents were required. Notably, combining these reactions with other palladium-catalyzed C(sp³)-H functionalization reactions in a sequential manner could provide the alternative to diverse pyrrolidinone products from readily accessible carboxylic acid.



Scheme 442 Palladium(II)-catalyzed sequential C(sp³)-H monoarylation/amidation.

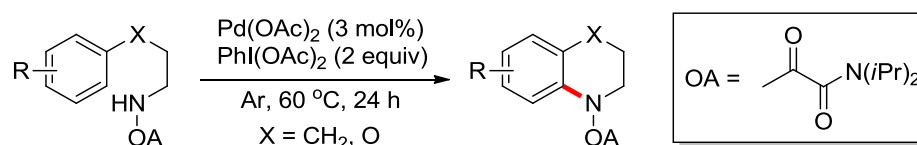
A palladium(II)-catalyzed sequential C(sp³)-H monoarylation/amidation for stereoselective synthesis of α -amino- β -lactams from simple anilines derivatives was developed by Shi and co-workers (Scheme 442).⁶¹⁵ The *N,N*-bidentate PIP amide directing group was found to be effective in both controlling selectivity in the arylation step for monoarylation and enhancing reactivity in the amination step. This procedure tolerated a wide range of functional groups, and the desired products were obtained in moderate to high yields. This procedure showed the power of sequential C-H functionalization to streamline the synthesis of complex, enantiomerically pure heterocycles from readily available starting materials.



Scheme 443 Copper or nickel-catalyzed the intramolecular amidation of aliphatic amides.

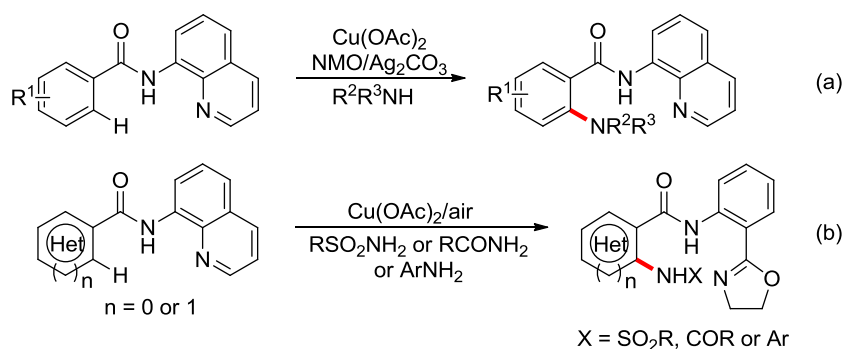
The copper and nickel-catalyzed intramolecular dehydrogenative amidation of aliphatic amides was reported by Kanai and Ge, respectively (Scheme 443).⁶¹⁶ The amination reactions occurred at a terminal methyl group, as well as at the internal benzylic position of an alkyl

chain. More importantly, β -lactams could be obtained in high yields even on gram scale.



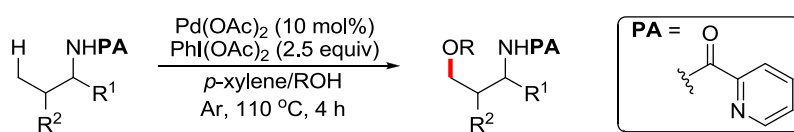
Scheme 444 Palladium-catalyzed intramolecular amination.

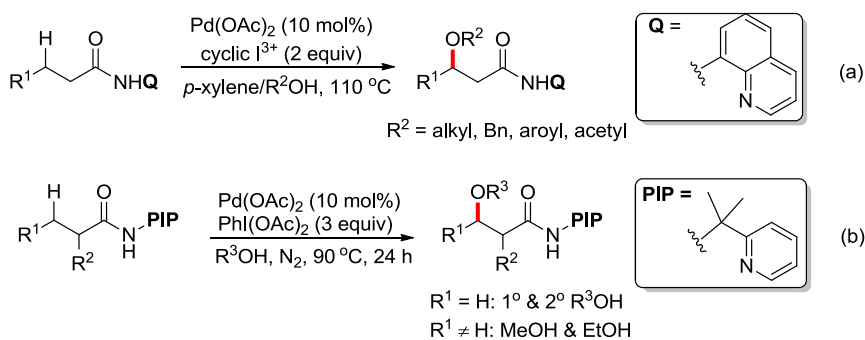
A palladium-catalyzed intramolecular amination of $C(sp^2)$ -H and $C(sp^3)$ -H bonds assisted by an accessible *N,O*-bidentate auxiliary was developed by Yao and Zhao (Scheme 444).⁶¹⁷ The oxalyl amide derivative was used as a newly bidentate directing group for the first time. Through this strategy, both $C(sp^2)$ -H and $C(sp^3)$ -H bonds at δ - and ϵ - positions were effectively activated. Some pharmaceutical-important nitrogen-containing heterocycles, such as tetrahydroquinolines (THQs), benzomorpholines (BMPs), pyrrolidines, and indulines could be smoothly synthesized. In addition, the developed directing group could be easily introduced and removed under mild reaction conditions.



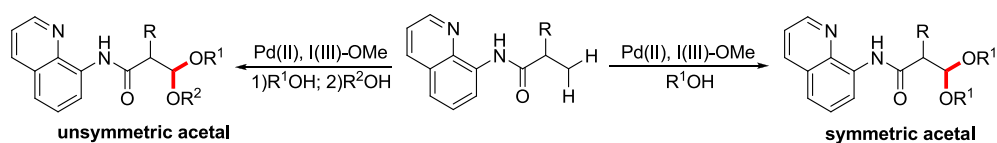
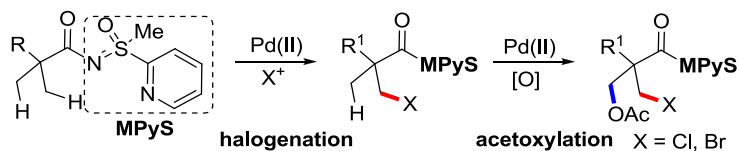
Scheme 445 Cu(II)-catalyzed or -promoted $C(sp^2)$ -H bonds amination.

The intermolecular $C(sp^2)$ -H bonds amination catalyzed or promoted by copper was reported by Daugulis and Yu, respectively (Scheme 445).⁶¹⁸ The exceptional compatibility of this amination with multiple heteroatoms present in both reactants rendered this reaction highly valuable for the synthesis of medicinally important compounds, such as 2-benzamidobenzoic acids and *N*-phenylaminobenzoates, by using readily available benzoic acids (Scheme 445b). Remarkably, a variety of sulfonamides, amides, and anilines could be tolerated in this reaction to give the desired products.



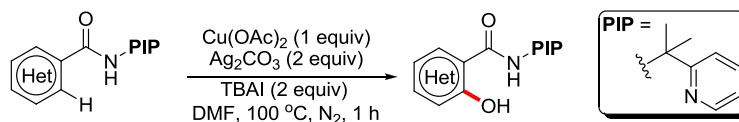
Scheme 446 Pd-catalyzed alkoxylation of unactivated γ -C(sp³)-H.**Scheme 447** Palladium-catalyzed C(sp³)-H alkoxylation of unactivated methylene.

Chen's group reported the efficient synthesis of alkyl ethers by the functionalization of unactivated sp³- and sp²- hybridized C-H bonds. Picolinamide-protected amine substrates underwent facile alkoxylation at the γ or δ positions with a range of alcohols, including *t*-BuOH, to give alkoxyated products under the Pd(OAc)₂-catalyzed, PhI(OAc)₂-mediated reaction conditions. This reaction featured a broad substrate scope, inexpensive reagents, and convenient operating conditions and highlighted the emerging value of unactivated C-H bonds, particularly the C(sp³)-H bond of methyl groups (Scheme 446).⁶¹⁹ In addition to the unactivated methyl C(sp³)-H bonds,⁶²⁰ the palladium-catalyzed alkoxylation of unactivated methylene positions was achieved using hypervalent iodine as the oxidants by Rao and Shi, respectively (Scheme 447).⁶²¹ These reactions were complementary to previous methods for the synthesis of dialkyl ethers.

**Scheme 448** Pd(II)-catalyzed double unactivated C(sp³)-H alkoxylation.**Scheme 449** Palladium catalyzed halogenation/acetoxylation on two β -CH₃ moieties.

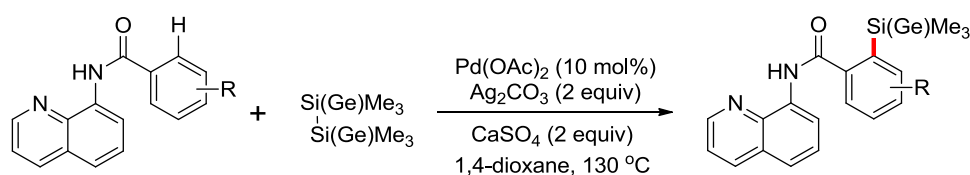
Subsequently, Rao and co-workers developed a Pd(II) catalyzed double unactivated C(sp³)-H alkoxylation to prepare symmetric or unsymmetric acetals with the addition of Ag₂CO₃ as the co-oxidant (Scheme 448).⁶²² Sahoo and co-workers demonstrated the

unprecedented halogenation and acetoxylation sequence on two β -CH₃ moieties by using S-methyl-S-2-pyridyl-sulfoximine as directing group, providing access to highly functionalized quaternary carbon centers bearing carboxylic acids (Scheme 449).⁶²³



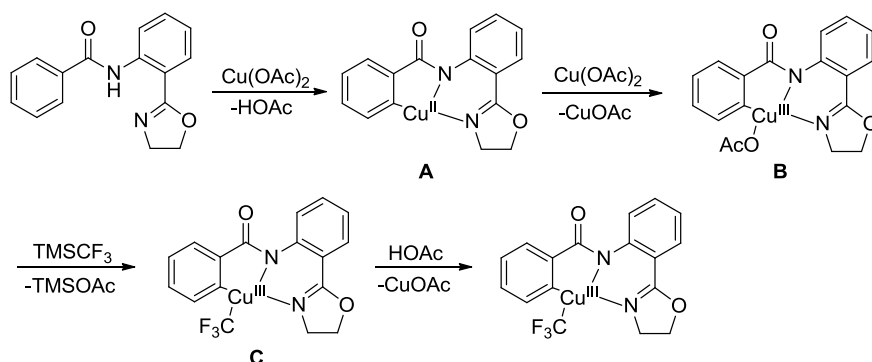
Scheme 450 Copper-mediated hydroxylation of arenes and heteroarenes.

Very recently, Shi and co-workers demonstrated an effective copper-mediated hydroxylation of arenes and heteroarenes directed by their newly developed PIP directing group (Scheme 450).⁶²⁴ This method was scalable and compatible with a wide range of functional groups and heteroarenes, providing an operationally simple protocol for the synthesis of *o*-hydroxybenzamides. This new directing group was applied in the synthesis of benzoisothiazolones via Cu(II)-mediated C-S/N-S bond formation. The direct diversifications of the benzoisothiazolone products into a variety of sulfur-containing compounds were also investigated.⁶²⁵



Scheme 451 Palladium-catalyzed C(sp²)-H silylation and germanylation.

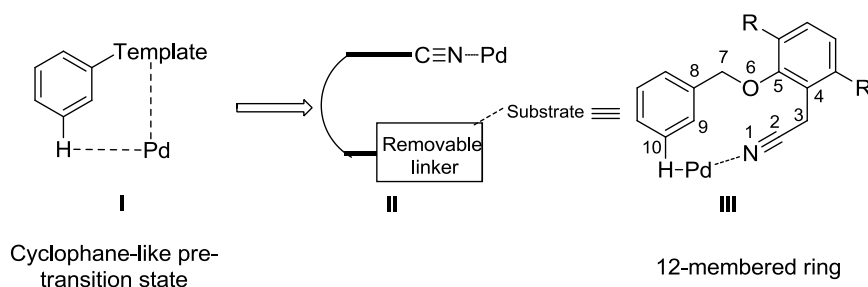
The direct C-H bond functionalization for the synthesis of organosilanes has become more and more attractive during the development of new methods for efficient strategic installation of silyl groups into organic compounds. Several transition metals such as Sc, Ru, Rh, Ir, and Pt catalyzed silylation of aromatic, vinylic, allylic, and aliphatic C-H bonds have made innovative contributions to this field.^{626, 235} Kanai's group demonstrated a palladium-catalyzed regioselective silylation of C(sp²)-H and C(sp³)-H bonds of benzamides and carboxamides with the aid of 8-aminoquinoline as a directing group (Scheme 451).⁶²⁷ Silver salts were superior to other oxidants and calcium sulfate was the best choice of additive. Moreover, this study gave the first example of transition-metal-catalyzed germanylation of C(sp²)-H bonds and intermolecular C(sp³)-H silylation at the internal positions of alkyl chains.



Scheme 452 Plausible mechanism of copper(II)-promoted *ortho*-C-H trifluoromethylation.

Intrigued by the previous reports,^{29, 65, 166, 325, 628} Yu and co-workers established a method for the copper(II)-mediated *ortho*-trifluoromethylation of arenes, including heteroarenes, with TMSCF₃. This copper(II)-promoted C-H activation reaction has taken advantage of the oxazoline-based bidentate auxiliary to complete the transformation within 30 minutes. Significant isotope effects observed in both of intra- and intermolecular kinetic isotope experiments indicated that a copper-mediated C-H cleavage step was involved in the rate-determining step (Scheme 452).^{629, 585a} Initially, copper(II) complex coordinated to the substrate, followed by the C-H activation and disproportionation of intermediate **A** to yield a chelated organocopper(III) complex **B**. Subsequent transmetalation of the organocopper(III) species with TMSCF₃ afforded Cu(III)-CF₃ intermediate **C**, then reductive elimination would deliver the desired *ortho*-trifluoromethylated arene.

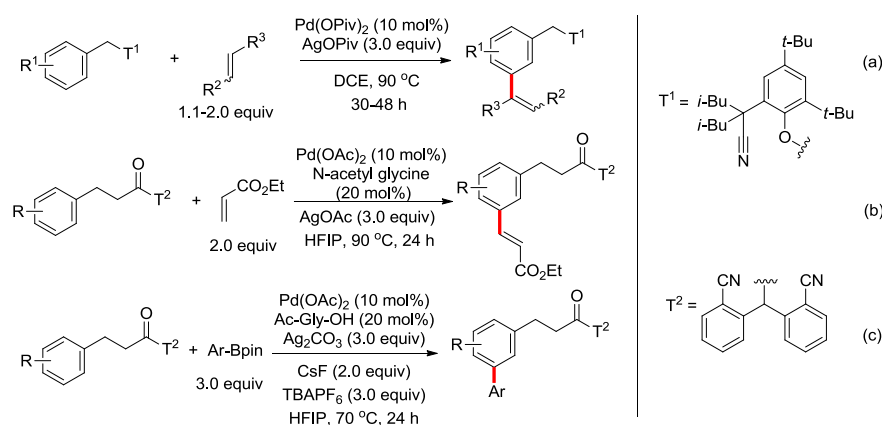
13 The remote *meta*-C-H bond activation



Scheme 453 Remote *meta*-C-H activation using an 'end-on' template.

As shown above, functionalization of *ortho* arene C-H bonds could be achieved by chelation-directed metalation with different directing groups *via* five or six membered cyclometalation (Scheme 453). However, the remote control of site selectivity, especially *meta*-selective functionalization of electron-rich aromatic rings, is still one of the greatest challenges in this active research field. The breakthrough in this area was achieved by Yu and

co-workers in 2012.⁶³⁰ They designed a class of easily removable nitrile-containing templates that direct the activation of distal *meta*-C-H bonds (more than ten bonds away) of a tethered arene through the formation of a macropalladacycle. The template was designed based on the weak interaction between Pd(II) and anitrile group, and the nitrile group coordinated in an ‘end-on’ coordination geometry which relieved the strain of a macrocyclic cyclophane-like pre-transition state of the *meta*-C-H activation event.

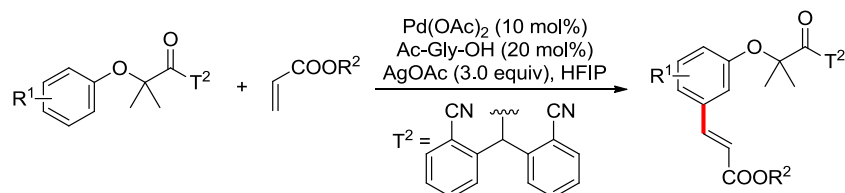


Scheme 454 Template-directed *meta*-selective C-H olefination and arylation.

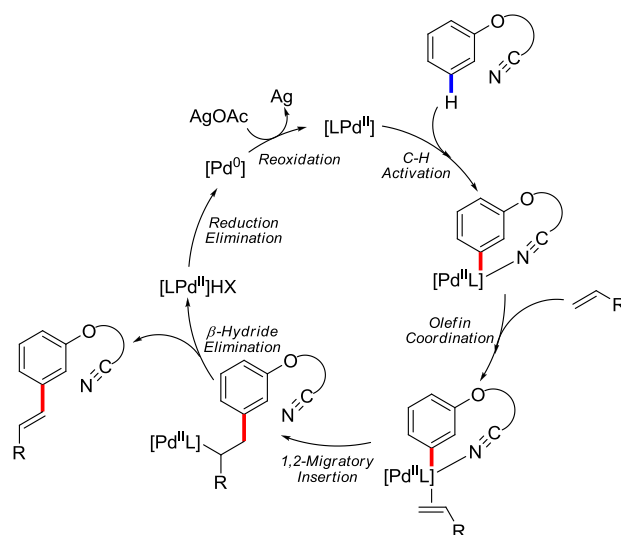
In this pioneering report, Yu and co-workers demonstrated the new mode of C-H activation that nitrile-containing templates deliver palladium to the vicinity of tethered arene substrates to promote C-H olefination of distal *meta*-C-H bonds.⁶³⁰ This reaction proceeded with excellent selectivity and high functional group compatibility. In addition, this template overrode the intrinsic electronic and steric biases as well as *ortho*-directing effects with two broadly useful classes of arene substrates (toluene derivatives and hydrocinnamic acids) (Scheme 454a, b). Unlike in conventional directed *ortho*-C-H olefination reactions where the coordinated directing group could prevent sterically hindered olefins from binding, in this case the nitrile group on the template was weakly coordinated to the [Pd(II)-Ar] intermediate and could be effectively displaced by disubstituted olefins, allowing carbopalladation to proceed. Finally, the template could be readily removed to afford *meta*-alkylated toluenes or hydrocinnamic acids in excellent yields.

Later on, they developed *meta*-C-H arylation and methylation of 3-phenylpropanoic acid and phenolic derivatives using organoborons as coupling partners (Scheme 454c).⁶³¹ The combination of a weakly coordinating U-shaped template and mono-protected amino acid

ligand was crucial for the cross-coupling of C-H bonds with organoborons. Tetrabutylammonium (TBA) salts showed a dramatic influence on the catalytic performance of palladium in cross coupling reactions for the ability of surfactants to prevent undesired agglomeration of Pd(0) species to form unreactive palladium black. Furthermore, the anionic counterion played an important role in stabilizing cationic palladium intermediates.

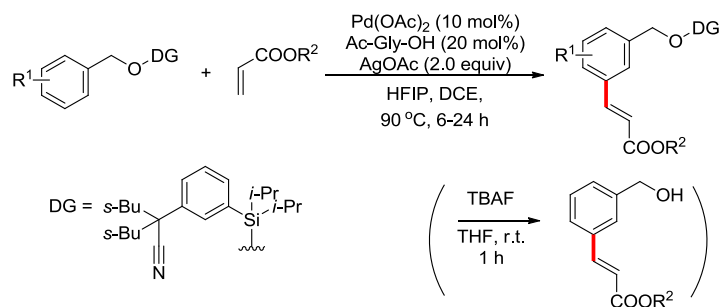


Scheme 455 Remote *meta*-C-H olefination of electron-rich phenol derivatives.



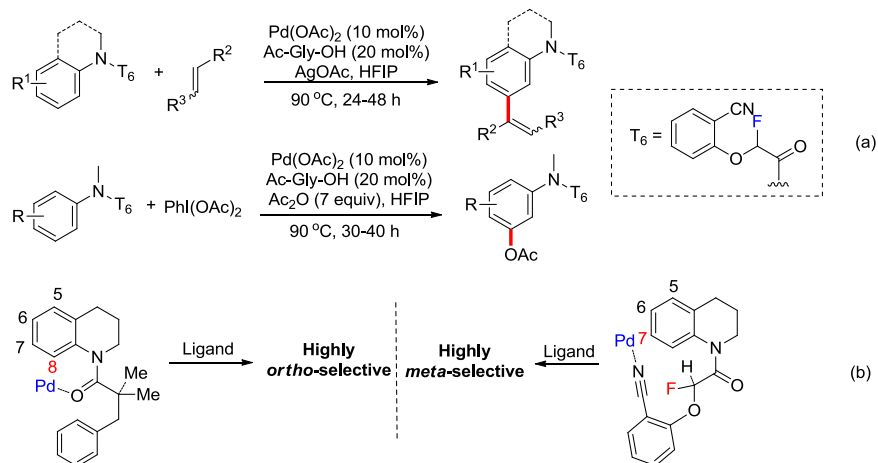
Scheme 456 The catalytic cycle of *meta*-C-H olefination.

Recently, they investigated the *meta*-C-H olefination of electron-rich phenol derivatives (Scheme 455).³⁶⁸ The end-on coordinating nitrile template was easily introduced to α -phenoxyacetic acids which was derived from the phenol. This palladium catalyzed olefination proceeded with high *meta*-selectivity in the presence of the Boc-Val-OH ligand. The reaction was unprecedented and orthogonal to previous electrophilic substitution of phenols in terms of regioselectivity. This protocol was successfully applied to the parent α -phenoxyacetic acids of drug molecules fenofibrate, clofibrate, and etofibrat. To gain insights into the mechanism for the reaction, an intermolecular isotope kinetic experiment was carried out and a significant kinetic isotope effect ($k_H/k_D = 3.8$) was observed, indicated that the C-H cleavage might be involved in the rate-determining step. A tentative catalytic cycle could also be proposed (Scheme 456).



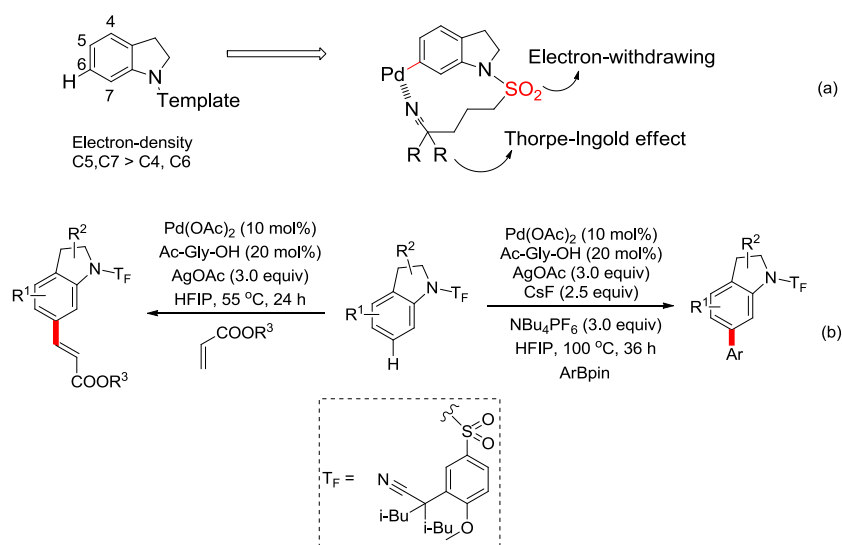
Scheme 457 Remote *meta*-C-H olefination of using a nitrile-based directing group and cleavable si-tether.

Based on Yu's nitrile-based directing groups, Tan and co-workers reported *meta*-selective C-H olefination using silicon-tethered nitrile-based directing group (Scheme 457).⁶³² The directing group with a silicon atom attachment could be synthesized in three steps from inexpensive starting materials and easily removed by tetrabutylammonium fluoride at room temperature, allowing for a facile installation/deprotection strategy increasing the synthetic practicality of this template. To investigate the substrates scope, they found that the bis-substituted products produced simultaneously by the use of 2-substituted substrates. The alkenylation of 3-substituted substrates clearly showed the method was applicable to a wide variety of functional groups. *meta* Selectivity decreased slightly with 4-substituted compounds due to steric hindrance. Various olefin partners revealed that electron-deficient olefins bearing amide, ketone, and sulfone groups produced functionalized compounds with moderate yields and high selectivity. Moreover, 1,2-disubstituted *trans*-methyl crotonate also proceeded well, affording a single stereoisomer as the major product. An additional advantage of this chemistry was the potential to reuse the silicon-directing group.



Scheme 458 Remote *meta*-C-H olefination and acetoxylation of tetrahydroquinolines, anilines and benzylamines.

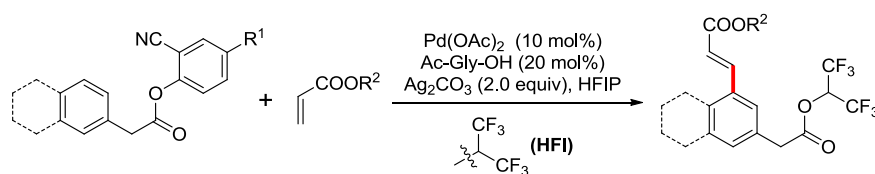
Very recently, Yu and co-workers reported the first olefination and acetoxylation of remote *meta*-C-H bonds as far as 11 bonds away-of tetrahydroquinolines, anilines and benzylamines by using a new recyclable template (Scheme 458a).⁶³³ The template could be readily installed through acylation of the amine substrates with the commercially available 2-(2-cyanophenoxy)-2-fluoroacetic acid. This template was able to direct the *meta* selective C-H functionalization of bicyclic heterocycles via a highly strained, tricyclic-cyclophane-like palladated intermediate. X-ray and nuclear magnetic resonance studies revealed that the conformational biases induced by a single fluorine substitution in the template could be enhanced by using a ligand to switch from *ortho*- to *meta*-selectivity (Scheme 458b). Directed by this versatile template, the remote *meta*-C-H bond activation of tetrahydroquinoline, benzoxazines, anilines, benzylamines, 2-phenylpyrrolidines and 2-phenylpiperidines proceeded smoothly under Pd(OAc)₂/Ac-Gly-OH/Ag salt system.



Scheme 459 *meta*-C-H olefination, arylation of indolines using nitrile containing templates.

However, the previously developed templates for amines did not give *meta*-selectivity for indoline substrates, presumably due to both conformational and electronic properties of indolines. To override this intrinsic site-selectivity, Yu and co-workers designed a novel nitrile-containing template based on two key principles: first, a more electron-withdrawing template would reduce the electron density at the *ortho*- and *para*-positions of the indoline

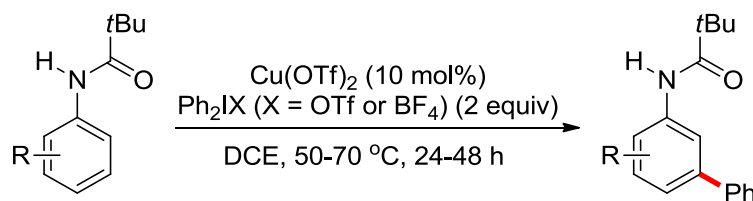
substrate, and second, a maximization of the Thorpe-Ingold effect in the template backbone would enhance the directing power of the nitrile (Scheme 459a). This new template was attached to the indolyl nitrogen *via* a removable sulfonamide linkage. The *meta*-C-H olefination, arylation, and acetoxylation of indolines was achieved by using this template (Scheme 459b).⁶³⁴ The combination of the nitrile template and a monoprotected amino acid ligand was crucial for the *meta*-selective C-H functionalization of electron-rich indolines that showed highly reactive toward electrophilic palladation at the *para*-positions. This method provides a useful tool for the preparation of a wide range of *meta*-substituted indoline derivatives, including biologically important natural products and drug molecules.



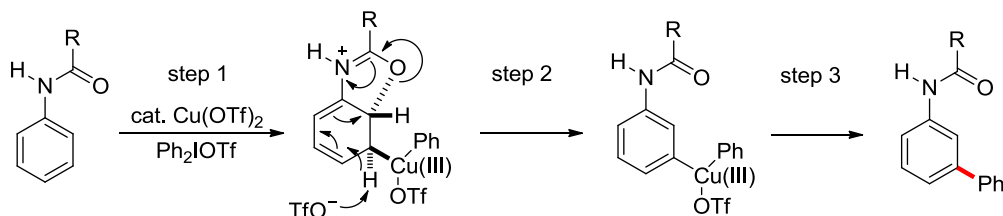
Scheme 460 *meta*-selective arene C-H bond olefination of arylacetic acid using a nitrile-based directing group.

Maiti and co-workers reported a *meta*-selective C-H bond olefination using a 2-hydroxybenzotrile template attached with a phenylacetic acid derived scaffold. (Scheme 460).⁶³⁵ Introduction of an electron-donating methoxy (OMe) substituent at the *para* position to the hydroxyl group in the template (in Scheme 460, R¹ = OMe) enhanced the reactivity, and the selective desired monoalkenylated product was obtained in moderate to good yield, which was easily transferred to *trans*-esterification compounds in (CF₃)₂CHOH (1,1,1,3,3,3-hexafluoro-2-propanol, HFIP). This palladium-catalyzed protocol was applicable to a wide range of substituted phenylacetic acids and tolerated a variety of functional groups. The directing group (2-hydroxy-5-methoxybenzotrile) could be easily installed and removed to form pharmaceutically relevant phenylacetic acid derivatives.

There is another type of *meta* C-H activation achieved via regular *ortho* C-H activation followed by functionalization at the *para* position to the M-C bond, and herein result in a formal *meta* C-H activation. Recently, extensive and significant progress toward *meta*- or *para*-selective C-H functionalizations has aroused much interest of chemists.⁶³⁶



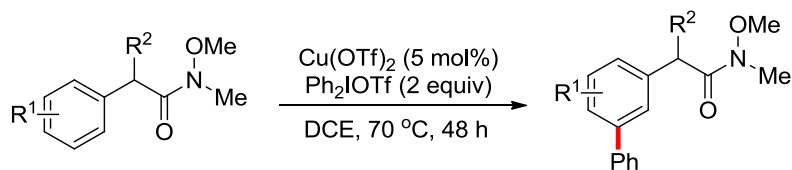
Scheme 461 Copper-catalyzed *meta*-arylation reaction of pivanilide.



Scheme 462 The plausible mechanism of copper-catalyzed *meta*-arylation reaction.

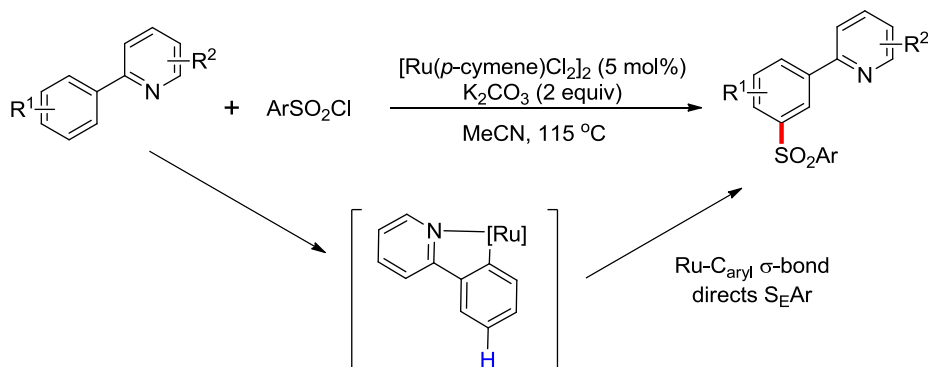
A copper-catalyzed *meta*-arylation reaction of anilide using Ph_2IOTf as the arylating agent was developed by Gaunt and co-workers, which was highly different from usual *ortho*-C-H bond functionalization (Scheme 461).⁶³⁷ The elegant C-H bond functionalization strategy provided a direct method to afford the *meta* isomer on highly versatile electron-rich aromatic structures. The nature of the acyl group of anilide had an obvious influence on the yield of the reaction but without changing the *meta*-selectivity. The protocol showed many notable features, such as simple operation, mild conditions, broad substrate scope and exclusive regioselectivity. Although the precise mechanism of the reaction was unclear, a highly electrophilic Cu(III)-aryl species was proposed to be involved in the reaction (Scheme 462). The Cu(III)-aryl species was regarded as a Lewis acid to activate the aromatic ring to undergo an anti-oxy-cupration process across the 2,3 position on the arene ring. The Cu(III)-aryl species was placed at the *meta* position via the dearomatizing process, followed by rearomatizing deprotonation and reductive elimination to deliver the desired product.

In 2011, Wu and co-workers⁶³⁸ described their theoretical study of the novel mechanism of the copper-catalyzed anilide *meta* C-H bond arylation reaction reported by Gaunt. The density functional theory (DFT) calculations and experimental investigations were carried out to elucidate the reaction mechanism. A Heck-like four-membered-ring transition state involving a Cu(III)-Ph intermediate was considered to be involved in the *meta* arylation reaction process.



Scheme 463 Cu(II)-catalyzed *meta*-selective arylation of α -aryl carbonyl compounds.

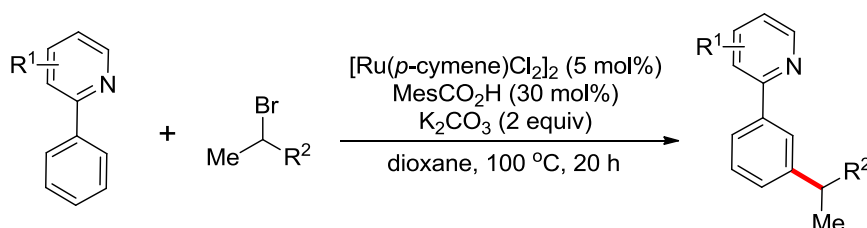
A copper-catalyzed *meta*-selective arylation of the α -aryl carbonyl scaffold with diaryliodonium salts using a remote and versatile Weinreb amide group as the directing group was developed by Gaunt and co-workers (Scheme 463).⁶³⁹ The location of the carbonyl group was supposed to have a significant role in determining the site selectivity of the reaction. Moreover, the arene nucleophilicity of the electronically neutral α -aryl carbonyl motif was different to the electron-rich anilide. A range of simple alkyl substituted α -arylketones could work well in the *meta*-arylation reaction. Interestingly, the *meta*-arylation reaction proceeded well with the exquisite selectivity even in the absence of the copper catalyst, just at the elevated temperature. Hence the Cu(III)-aryl intermediate that previously proposed in their original working model was not that convincing. The precise mechanism still required to be further investigated.



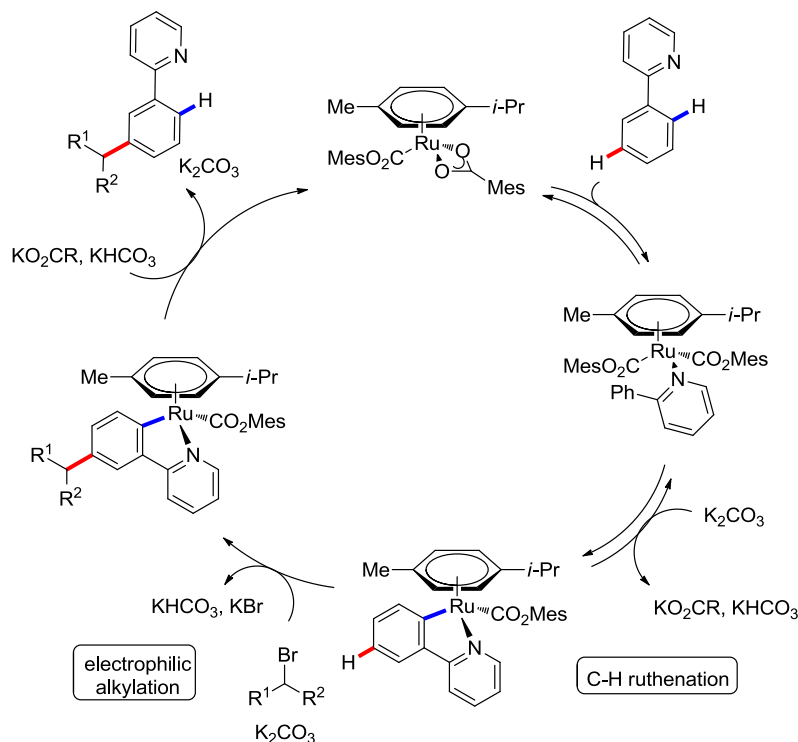
Scheme 464 Ruthenium-catalyzed *meta* sulfonation of 2-phenylpyridines.

A ruthenium-catalyzed selective *meta* sulfonation of 2-phenylpyridines was demonstrated by Frost and co-workers (Scheme 464).⁶⁴⁰ The mechanistic pathway of the reaction is quite different from the Gaunt's work and the catalytic chelation-assisted cyclometalation was proposed to be involved in the Ru catalyzed *meta* sulfonation reaction. It was surmised that the chelating group might facilitate the formation of a stable Ru-C_{aryl} σ bond that could induce a strong *para*-directing effect. In addition, the observed kinetic isotope effect indicated that the C-H bond cleavage was the rate-determining step in the catalytic

cycle. The reaction was the first example of a catalytic σ -activation process.



Scheme 465 Ruthenium-catalyzed *meta* selective C-H bond alkylation.



Scheme 466 The plausible mechanism of ruthenium-catalyzed *meta*-alkylation

This first ruthenium-catalyzed direct C-H bond alkylation with excellent levels of unusual *meta*-selectivity under nonacidic reaction conditions was disclosed by Ackermann and co-workers (Scheme 465).⁶⁴¹ The ruthenium(II) biscarboxylate complexes proved to be the key factor of the highly *meta* selective alkylation and the carboxylic acid MesCO₂H was indispensable. A wide variety of arenes with ample scope could be smoothly compatible with the reaction system. Isotope labeling experiments suggested that an initial reversible *ortho*-C-H bond cyclometalation was involved in the reaction process and the *meta*-C-H bond cleavage was not supposed to be kinetically relevant. It was rationalized that a S_EAr-type alkylative substitution occurred in the *meta*-position, facilitated by the strong activation and the *ortho*-/*para*-directing effect induced by the Ru-C(sp²)- σ bond. The relevant mechanistic studies were also conducted and the possible catalytic cycle was proposed (Scheme 466).

Initially, the cyclometalated complex was reversibly formed via C-H ruthenation. A S_EAr -type alkylation of the aromatic substrates with the secondary alkyl halides activated by cyclometalation occurred to generate a *ortho* or *para* functionalization of the Ru-C(sp²) bond. Finally, proton-demetalation process delivered the desired *meta*-substituted product and regenerated the catalytically active Ru(II) species.

14 Conclusion and outlook

The field of transition-metal-catalyzed group directed C-H bond functionalization reactions has expanded rapidly over the last ten years. Various functionalities have been designed and employed as directing groups successfully for C-C bonds or C-heteroatom bond formation. A broad range of useful transformations, including arylation, olefination, alkylation, alkynylation, carbonylation, amination, halogenations, and so on, have appeared in the literatures. Owing in part to their good functional group compatibility and high efficiency, these reactions have been utilized rapidly in the syntheses of complex molecules.

Despite the impressive number of contributions and results obtained, there are still significant demand and great room for further development in this area. For instance, comparing with the huge number of functionalities existing in the organic molecules, the directing properties of many functionalities, especially the less basic ones, are unknown and waiting for investigation. In many cases the directing groups are not an intrinsic part of the substrate and/or product, which need to be installed and removed, or converted to the final desired functional group. It will be important to develop the more general methods that are applicable to a broad spectrum of functionalities or removable directing groups. On the other hand, the most of current chelation-directed metalation of C-H bonds limited to *ortho*-selectivity or β -selectivity. The control of the positional selectivity of C-H cleavage, especially to achieve the remote C-H functionalization, is remains an outstanding challenge. Moreover, most of the efficient catalytic systems for C-H activation rely on expensive precious metals. The development of more powerful novel catalytic processes adopting the inexpensive, environmentally benign, and relatively nontoxic metals is of significance for the widespread application of the direct C-H functionalization methodology. It also should be noted that the asymmetric C-H activation still in its infancy and its true potential remains

open ended. To address all of these issuers, the evolution of new system that allows the access to a greater diversity of products is highly desirable. Generally, the mechanistic investigations will allow the thorough understanding of C-H activation process and conclude the disciplines of the complex interplay between catalyst, ligands, solvent, additives, and substrates, and thus guide the design and discovery of new highly active and selective catalytic systems. Nevertheless, due to the highly sustainable nature of direct C-H bond functionalizations, the advances in this area will change the way of the functional molecule construction and speed up the industrial applications.

Acknowledgements

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