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Some recent advances in transition-metal-catalyzed *ortho* SP^2 C–H functionalization using Ru, Rh, and Pd

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In the past decade, transition-metal-catalyzed C–H functionalization by weak coordination has emerged as a practical and powerful tool to access many valuable chemicals. Two classes of weakly coordinating directing groups, commonly occurring functional groups, and easily removable auxiliaries, have been found to be efficient and practical for C–H activation reactions. This mini-review contains examples of recent research advances on transition-metal-catalyzed SP^2 C–H functionalization via weak coordination, using Ru, Rh, and Pd. A number of weakly coordinating functional groups (e.g., ketone, ester, carbamate, tertiary amide, ether, thioether, alcohol, and some others) are covered. As the field of transition-metal-catalyzed C–H functionalization continues to develop and more synthetically useful chemo-, regio-, and enantioselective reactions catalyzed by transition metal via weak coordination are discovered, this promising and attractive strategy will play a more important role in modern organic synthesis.

transition metal catalysis , SP^2 C–H functionalization, weak coordination, *ortho*-selectivity, directing group

1 Introduction

Traditional approaches to specific transformations of selected molecules always strongly rely on prefunctionalized chemicals to control selectivity and reactivity. The selective cleavage of C–H bonds in organic compounds and the direct conversion of C–H bonds into C-heteroatom bonds will undoubtedly present a faster and atom-economical strategy for organic synthesis. Transition metals, especially palladium-atalyzed C–H bond activation toward the synthesis of aromatic and heteroaromatic compounds with various directing goups, have proven since 2004 to be highly selective and atom-economical. Many reviews and accounts have recently been published to cover this exciting topic [1]. The majority of those works have focused on using nitrogen-containing directing goups. By contrast, much less research has been devoted to weakly coordinating directing groups (an area of study pioneered by Prof. Jin-Quan Yu's group). Recently, an elegant review of "C–H functionalization by weak coordination" was summarized by Yu's group [2] in an article mainly about palladium cataylsis with weakly coordinating carboxylic acids and amides. In light of the many reported examples of various metals and space constraints, herein we focus on reviewing some reactions catalyzed by Ru, Rh, and Pd with a few specific weakly coordinating directing groups. Our main interest is in the use of commonly occurring functional groups (e.g., ketone, ester, carbamate, tertiary amide, ether, thioether, alcohol, and somes) to direct C–H cleavage through weak coordination. We hope this mini-review will complement other reviews in the field of transition-metal-catalyzed C–H bond functionalization.

2 Ru catalysis

An early example of employing transition metal to catalyze

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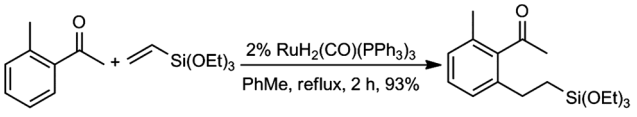
C–H functionalization via weak coordination was reported by Murai and coworkers [3] in 1993. An organometallic ruthenium complex-$RuH_2(CO)(PPh_3)_3$ was used to cleave C–H bonds in a variety of aromatic systems, which led to addition to alkenes by C–C bond formation (Scheme 1). The weakly coordinating ketone group was adopted as an efficient directing group for this reaction. The catalyst operated with a high degree of efficiency, selectivity, and generality that make it a valuable tool for constructing carbon-carbon bond in organic synthesis.

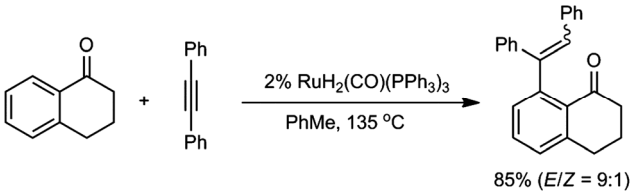
In 1995, with this similar system (Ru catalyst and weakly coordinating aromatic ketones), the Murai group [4] developed a new method enabling a direct, catalytic addtion of C–H bonds in aromatic ketones across C–C triple bonds which results an addition to alkynes by C–C bond formation. This approach could provide a quick access to vinyl derivatives with *E*-isomers as major products (Scheme 2).

In 2003, Kakiuchi and coworkers [5] reported a new C–C bond formation method by the ruthenium(0)-catalyzed *ortho* arylation of aromatic ketones with arylboronates (Scheme 3). $RuH_2(CO)(PPh_3)_3$ was used as the catalyst in that reaction, which involved the oxidative addition of a C–H bond in aromatic ketones to a ruthenium(0) center and an ensuing transmetalation pathway to provide biaryl compounds. This reaction represents the first example of the catalytic coupling of C–H bonds with organometallic compounds through the oxidative addition of C–H bonds.

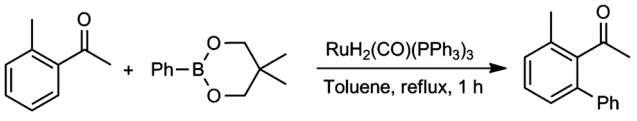
In 2006, Darses and coworkers [6] disclosed a new methodology that generated *in situ* a highly active ruthenium catalyst for C–H bond activation from stable and easily available ruthenium(II) sources (Scheme 4). Through chelating with the ketone group, depending on the substrates, this *in-situ*-generated catalyst showed similar or higher activity than the Murai catalyst for constructing a new C–C bond. The electronic and steric properties of this catalyst can be fine-tuned by changing the ligands, which allows the functionalization of various substrates.



Scheme 1 Ruthenium-catalyzed C–H/olefin coupling directed by a ketone group.



Scheme 2 Ruthenium-catalyzed C–H/alkyne coupling directed by a ketone group.

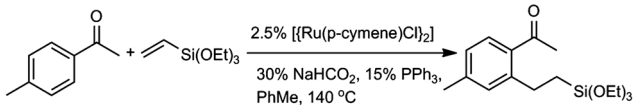


Scheme 3 Ruthenium-catalyzed C–H arylation directed by a ketone group.

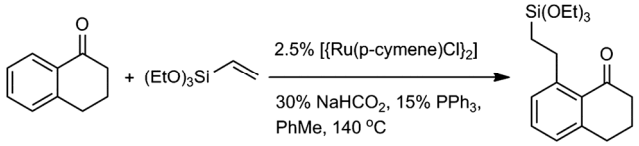
In 2009, the Darses group [7] reported another example of *in-situ* generation of a highly active ruthenium catalyst from a stable and readily available ruthenium(II) source; this catalyst effectively promoted C–H bond activation with ketone as the directing group (Scheme 5). This approach showed that, depending on the electronic and steric nature of the ligand, aromatic ketones could be facilely functionalized by a reaction with either vinylsilanes or styrenes to make C–C bonds through weak coordination.

In 2012, Ackermann and coworkers [8] developed a ruthenium-catalyzed C(sp^2)–H-bond oxygenation reaction with arenes bearing weakly coordinating ketones to provide *ortho*-hydroxylated aryl ketones (Scheme 6). These reactions were achieved with oxone, $K_2S_2O_8$, or $PhI(OAc)_2$ as the terminal oxidant and $[RuCl_3(H_2O)n]$ or well-defined $[Ru(O_2CMes)_2(p\text{-cymene})]$ as the catalyst.

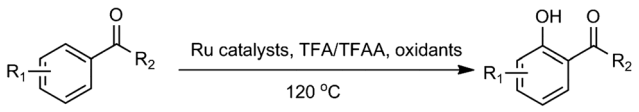
In 2013, the Rao group [9] independently reported the development of a Ru(II)-catalyzed regio- and chemoselective phenol from easily accessible arenes (Scheme 7). In this study, a variety of aromatic ketones were converted into corresponding 2-acyl phenols via a combination of Ru(II) catalysts ($[RuCl_2(p\text{-cymene})]_2$), oxidants (mainly $K_2S_2O_8$), and TFA/TFAA at relatively milder temperatures (50–80 °C). The practicality of this new methodology has been proven by gram-scale synthesis of a few different 2-acylphenols. Its synthetic utility has also been exemplified in further applications in heterocycle synthesis and a direct



Scheme 4 Ruthenium-catalyzed C–H/olefin coupling directed by a ketone group.



Scheme 5 Ruthenium-catalyzed C–H/olefin coupling directed by a ketone group.



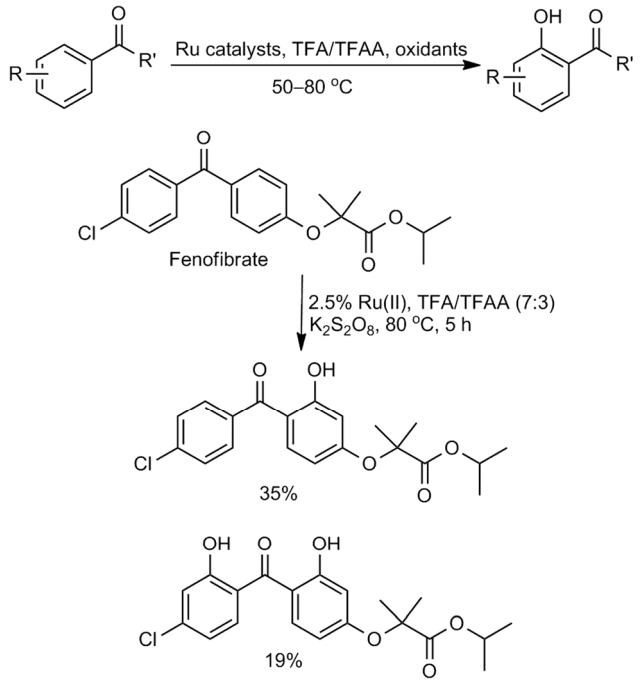
Scheme 6 Ruthenium-catalyzed C(sp^2)–H bond oxygenation directed by a ketone group.

modification of Fenofibrate (a prescription drug commonly used to reduce triglyceride and cholesterol levels).

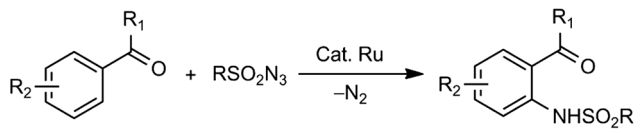
In 2013, the Chang [10], Jiao [11] and Sahoo [12] groups independently reported a ruthenium(II)-catalyzed direct sp^2 C–H amidation of weakly coordinating ketones by using sulfonyl azides as the nitrogen source (Scheme 8). The catalytic system typically includes $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$/$AgNTf_2$, and $NaOAc/Cu(OAc)_2$. These reactions, which demonstrate good functional-group tolerance and high yields, provide a new approach to constructing an intermolecular C–N bond through ketone-directed C–H activation without employing an extra oxidant.

In 1996, Murai and coworkers [13] disclosed a ruthenium($RuH_2(CO)(PPh_3)_3$)-catalyzed addition to double bonds of aromatic and heteroaromatic esters at the *ortho* C–H bonds (Scheme 9). The weakly coordinating ester group behaved as an effective directing group for this highly regioselective reaction. Lactones of different ring sizes were also tried under these conditions. It was found that five-membered lactone did not provide any desired product at all, whereas six-membered lactone did give corresponding product although the reaction took a long time. The success of the six-membered lactone may be because of the instability of the postulated strained cyclometalated intermediate from five-membered lactone. In 2001, the same group reported a mechanistic study [14] of $RuH_2(CO)(PPh_3)_3$-catalyzed addition of C–H bonds in aromatic esters to olefins by deuterium-labeling experiments and measurement of the ^{13}C kinetic isotope effect. Results revealed rapid equilibrium among the intermediates prior to the reductive elimination; in addition, the ^{13}C NMR kinetic isotope effect suggested that C–C bond formation is the rate-determining step in this reaction.

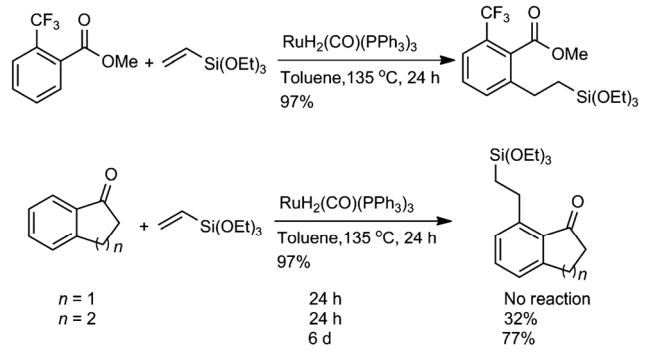
In 2007, Uemura and coworkers [15] reported an effective conjugate addition reaction of terminal alkynes to α- and β-unsaturated carbonyl compounds under the catalysis of a ruthenium complex $[Ru_3(CO)_{12}]$ in the presence of [PPN]Cl (Scheme 10). Both of these weakly coordinating ester and ketone groups can efficiently promote this transformation to provide alkynyl esters/ketones in good yields. Interestingly, the combination of $Ru_3(CO)_{12}$ and LiI promotes the linear codimerization of alkynes with acrylates to give corresponding conjugate dienes in satisfactory yields. It was believed that these two different reaction pathways could be tuned by changing the halide ions (either a chloride or an iodide) with other conditions being kept almost the same.



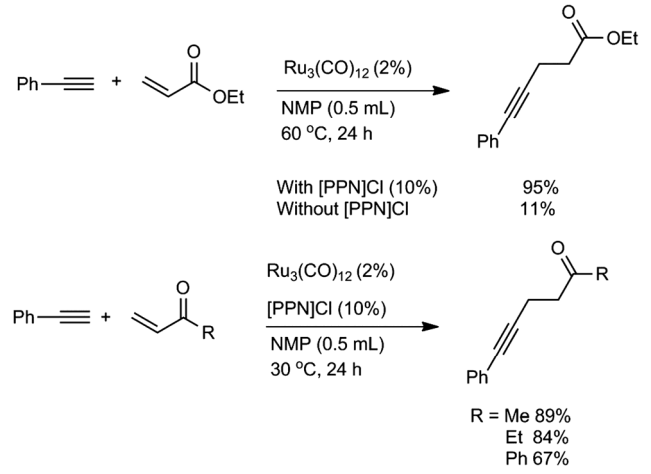
Scheme 7 Ruthenium catalyzed C–H bond oxygenation directed by a ketone group.



Scheme 8 Ruthenium-catalyzed C–H amidation directed by a ketone group.



Scheme 9 Ruthenium catalyzed C–H/olefin coupling directed by an ester group.



Scheme 10 Ruthenium-catalyzed olefin/alkyne coupling directed by an ester group.

In 2009, the Plietker group [16] reported a broadly applicable hydrovinylation of both terminal and internal alkynes with electron-deficient olefins bearing weakly coordinating ester and tertiary amide groups (Scheme 11). The reactions were catalyzed by an air-and-moisture-stable ruthenium hydride complex, which can be readily prepared in one step with $RuCl_3$ and NaOMe prior to use. A variety of highly substituted 1,3-dienes were smoothly produced in good to excellent yields under these reaction conditions. The vinylation of terminal alkynes proceeded with excellent stereo- and regioselectivity in favor of the linear *Z*-products. It was found that the *E*-configured alkene displayed a significantly higher reactivity than the *Z*-configured isomer under these conditions. The authors proposed that alkyne activations proceeds via hydrometallation with a Ru-H species and that alkene activation requires the bonding of a *cis*-H atom to a carbonyl group for the C–H activation.

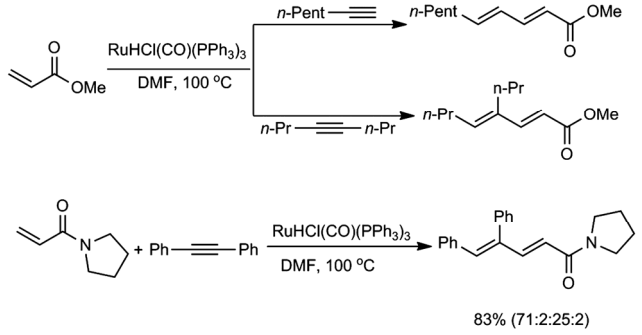
In 2012, the Ackermann group [17] reported *ortho*-selective ruthenium-catalyzed oxidative alkenylations of arenes containing weakly coordinating esters. Cationic ruthenium(II) complexes such as $[RuCl_2(p\text{-cymene})]_2$ can effectively promote cross-dehydrogenative C–H bond functionalizations between aryl- and alkenyl-substituted esters with cocatalytic amounts of $Cu(OAc)_2\ 3H_2O$ (Scheme 12). Air was utilized as the terminal oxidant in this reaction. The directing ability of the ester groups in the *ortho* C–H alkenylation reaction was well illustrated as highly chemo- and diastereoselective as well as site-selective.

In 2012, the Rao group [18] developed a unique Ru(II)-catalyzed *ortho* hydroxylation for the synthesis of multifunctionalized arenes from easily accessible benzoates (Scheme 13). The ester group of benzoates served as an effective directing group in this transformation's C–H hydroxylation reaction with potassium persulfate, selectfluor, or iodic acid as oxidants. The TFA/TFAA cosolvent system and oxidants both served as the critical success factors for this C–O bond formation reaction, which demonstrated excellent reactivity, good functional group tolerance, and high yields.

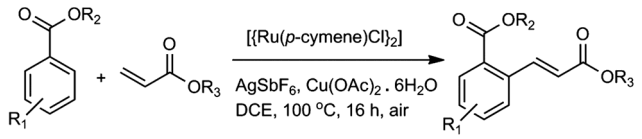
In 2013, the Wang [19] (Scheme 14) and Jeganmohan [20] (Scheme 15) groups independently developed a ruthenium-catalyzed aerobic oxidative *ortho*-C–H alkenylation of phenyl carbamates with alkenes. A variety of substituted alkene derivatives were produced in good to excellent yields in a highly regio- and stereoselective fashion through weakly coordinating carbamate groups. Further treatment with a base such as NaOH, $LiOH{\cdot}H_2O$ or K_2CO_3 would quantitatively furnish the corresponding phenol derivatives.

In 2013, a ruthenium-catalyzed $C(sp^2)$–H bond oxygenation of phenol derivatives with a weakly coordinating carbamate group was reported by the Ackermann group [21] (Scheme 16). Direct hydroxylations of aryl carbamates proceeded with high catalytic efficacy as well as excellent chemo- and regioselectivities (*ortho*-position in this case). These researchers also found that, by contrast, the ruthenium-(II) catalyst promoted direct C–H bond functionalization on anisole derivatives with *para*-selectivity.

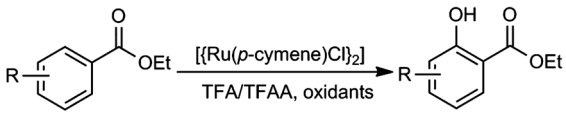
In 2012, Ackermann and coworkers [22] disclosed a ruthenium-catalyzed C–H hydroxylations on arenes that bear weakly coordinating tertiary amides (Scheme 17). These intermolecular oxidative C–O bond formations were obtained with $PhI(OAc)_2$ as the oxidant and $[RuCl_3(H_2O)_n]$ as an effcient catalyst. This C–H hydroxylation reaction oculd be accomplished with only a low catalyst loader (e.g.,



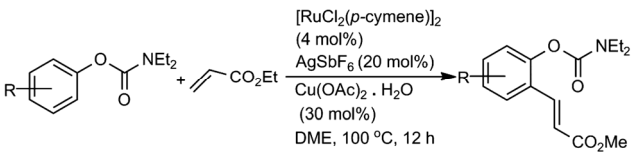
Scheme 11 Ruthenium-catalyzed olefin/alkyne coupling directed by ester and tertiary amide groups.



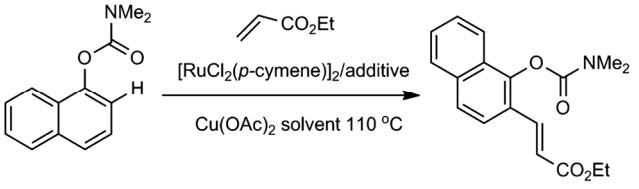
Scheme 12 Ruthenium-catalyzed C–H alkenylation directed by an ester group.



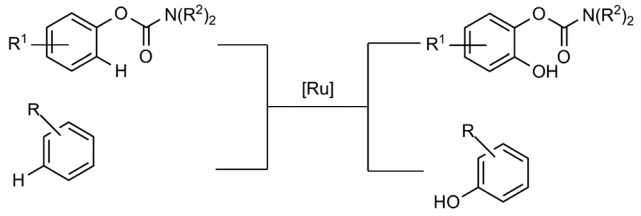
Scheme 13 Ruthenium-catalyzed C–H hydroxylation directed by a ketone group.



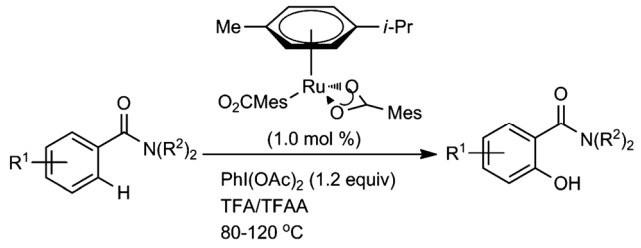
Scheme 14 Ruthenium-catalyzed C–H alkenylation directed by a carbamate group.



Scheme 15 Ruthenium-catalyzed C–H alkenylation directed by a carbamate group.



Scheme 16 Ruthenium-catalyzed C–H hydroxylation directed by a carbamate group.

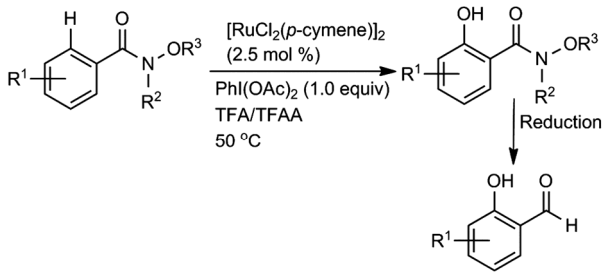


Scheme 17 Ruthenium-catalyzed C–H hydroxylation directed by a tertiary amide group.

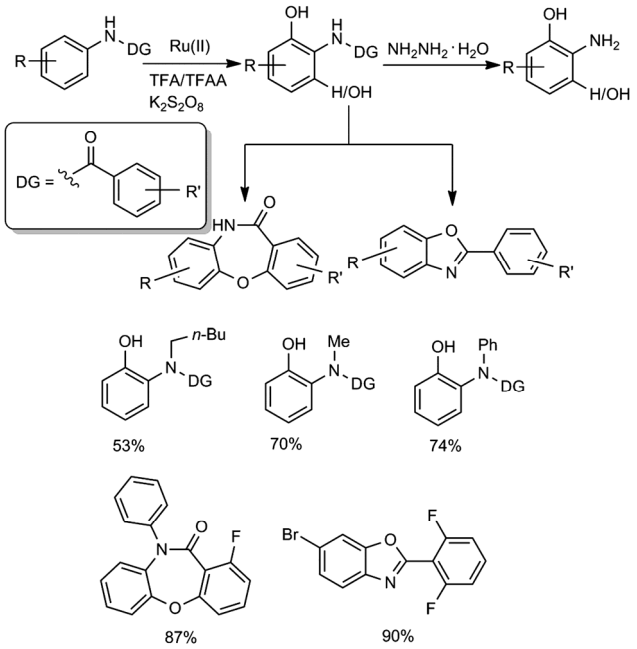
1.0 mol%) of a ruthenium(II) biscarboxylate [$Ru(O_2CMes)_2$(*p*-cymene)]$_2$ with a broad substrate scope and satisfactory yields.

In 2012, the Ackermann group [23] also reported a C–H bond oxygenation of weakly coordinating aryl Weinreb amides (Scheme 18). A ruthenium catalyst such as [$RuCl_2$(*p*-cymene)]$_2$ effectively promoted the synthesis of *ortho*-hydroxylated Weinreb amides with a broad scope, under quite mild reaction conditions. Finally, the reduction of aryl Weinreb amides with $LiAlH_4$ smoothly provided the corresponding *ortho*-hydroxy benzaldehydes in good yields.

In 2013, a practical directing-group strategy was developed by Rao and coworkers [24] for the synthesis of a broad range of 2-aminophenols and 2-aminobenzene-1,3-diols through Ru-catalyzed C–H hydroxylation of weakly coordinating tertiary aryl amides (Scheme 19). Both mono- and dihydroxylation products were smoothly obtained in satisfactory yields by using different equivalents of oxidants. This reaction shows excellent reactivity, regioselectivity, and good functional-group tolerance. The synthetic utilities of corresponding directing groups were well illustrated in the ready removal of directing groups and the following



Scheme 18 Ruthenium-catalyzed C–H hydroxylation directed by a Weinreb amide group.



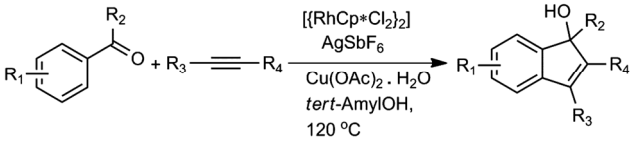
Scheme 19 Ruthenium-catalyzed C–H hydroxylation directed by an amide group.

synthesis of heterocycles (e.g., dibenzoxazepine and benzoxazole derivatives).

3 Rh catalysis

In 2011, Cheng and coworkers [25] reported a rhodium-catalyzed, chelation-assisted C–H activation of aryl ketones with alkynes to afford substituted indenols in good to excellent yields (Scheme 20). This catalytic reaction employed weakly coordinating ketone as a practical directing group for C–H activation. This catalytic reaction was highly regioselective with unsymmetrical alkynes to give corresponding indenol products through a sequential C–H activation/carbocyclization step. The authors proposed that $Cu(OAc)_2$ not only involved oxidation of the reduced rhodium species to regenerate the active Rh(III) species but also, possibly, provided the acetate source as ligands for the active rhodium species in the reaction.

By utilizing weakly coordinating aryl ketone as the directing group, in 2011 the Glorius group [26] discovered a new approach to the preparation of diversely functionalized indenol and fulvene derivatives via an Rh-catalyzed C–H activation of phenone derivatives and their subsequent coupling with internal alkynes (Scheme 21). By carefully dif-

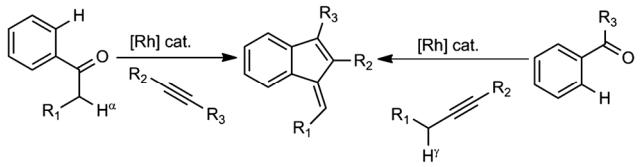


Scheme 20 Rhodium-catalyzed indenols synthesis directed by a ketone group.

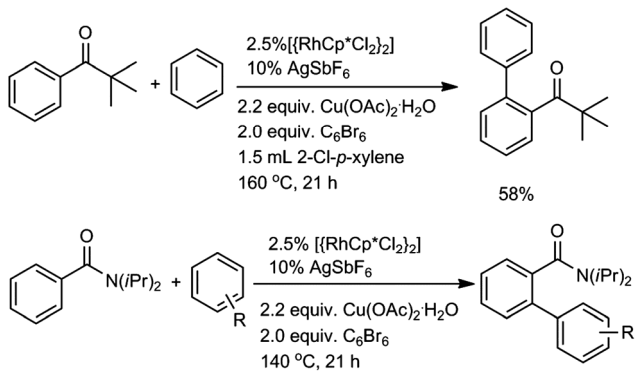
ferentiating between the α- and the γ-route, the authors were able to regioselectively access indenol and fulvenes that bore diverse functional groups with high efficiency. Although it was suggested that the initial C–H activation step is not an electronically discriminating process, this method can serve as a very useful protocol for the synthesis of 5-membered carbocyclic-ring-containing molecules.

In 2012, Glorius and coworkers [27] developed a new Rh(III)-catalyzed dehydrogenative cross-coupling reaction between simple benzene derivatives. Among those examples, weakly coordinating aromatic tertiary amides or ketones can be successfully employed to provide corresponding biaryl product in a highly regio- and chemoselective pattern (Scheme 22). Both arenes and heteroarenes can be effectively adopted in those cross-coupling reactions. A key feature of the catalyst system was its combination of $Cu(OAc)_2$ with C_6Br_6, which is a relatively less-common additive in this type of CDC transformation.

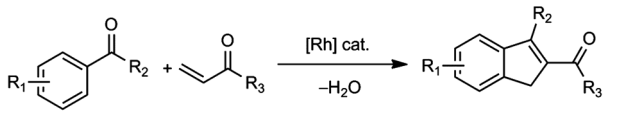
In 2013, the Li group [28] successfully developed a catalytic synthesis of indene derivatives through a Rhodium(III)-catalyzed functionalization of an aromatic *ortho* C–H bond directed by weakly coordinating ketone groups (Scheme 23). This cascade reaction, which involved a conjugate addition of α- and β-unsaturated ketone and subsequent aldol condensation, provided a unique approach to constructing indene scaffold in a single step. Interestingly, this reaction could be conducted efficiently in the presence of water and under an atmosphere of air, which provides an operationally practical and cleaner approach to accessing indene derivatives.



Scheme 21 Rhodium-catalyzed indenols and fulvenes synthesis directed by a ketone group.



Scheme 22 Rhodium-catalyzed dehydrogenative cross-coupling reaction between simple benzene derivatives directed by ketone and tertiary amide groups.

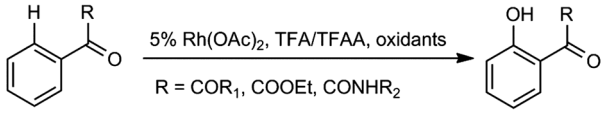


Scheme 23 Rhodium-catalyzed indenes synthesis directed by a ketone group.

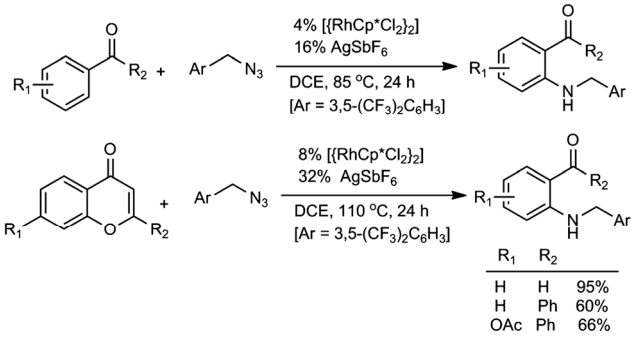
In 2013, Rao and coworkers [9] employed $Rh(OAc)_2$ as an effective catalyst for regio- and chemoselective synthesis of phenol from easily accessible arenes bearing weakly coordinating ketone groups (Scheme 24). Compared to $[RuCl_2(p\text{-cymene})]_2$, the overall catalytic activity of $Rh(OAc)_2$ was found to be similar in terms of selectivity, efficiency, and substrate scope. A number of aromatic ketones could be readily converted into corresponding 2-acyl phenols by employing a combination of Rh(II) catalysts, oxidants, and TFA/TFAA. Compared with commonly used Rh(III) and Rh(I) catalysts in a C–H activation study, this represents a rare demonstration that Rh(II) can efficiently promote this type of C–H funcationalization.

In 2013, Chang and coworkers [29] developed a new Rh(III)-catalyzed reaction for the insertion of an amino group into arene C–H bonds with a weakly coordinating ketone group (Scheme 25). Alkyl azides were adopted as the nitrogen source. Benzyl and aliphatic azides bearing a wide range of functional groups of high biological interest both reacted readily with a range of substrates containing ketone chelating groups. Remarkably, the authors found that chromone and flavones could also be regioselectively aminated in satisfactory yields. This transformation provided a convenient route to obtaining synthetically and medicinally useful amino-containing chemicals.

In 2012, the Glorius group [30] reported a general and practical strategy for the *ortho* bromination and iodination of arenes with a cationic Rh(III) catalyst (Schemes 26 and 27). In their studies, weakly coordinating tertiary benzamide,



Scheme 24 Rhodium-catalyzed C–H hydroxylation directed by a ketone group.

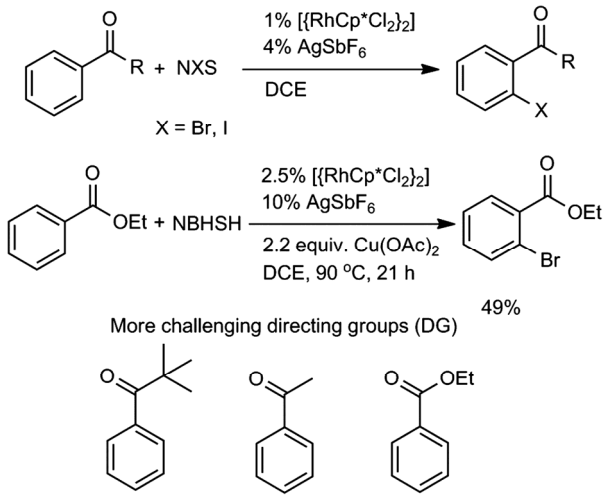


Scheme 25 Rhodium-catalyzed C–H amination directed by a ketone group.

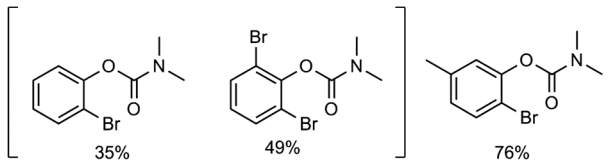
aryl ketone, ester, and carbamate substrates were found to be efficient to promote *ortho* C–H bond activation to provide *ortho*-halogenation products. The typical reaction condition used NBS/NIS in the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ as oxidant, and PivOH as additive. Based on their observations, the authors proposed two plausible mechanistic pathways. One pathway involved a nucleophilic addition type reaction to NXS to directly lead to halogenated product. Another possibility was that the rhodacycle intermediate would potentially be oxidized to Rh(V) complex in the presence of NXS, which would then undergo reductive elimination to provide halogenated product and regenerate the Rh(III) catalyst.

In 2011, Chang and coworkers [31] discovered that an ester can be employed as an efficient chelating group to direct an *ortho*-alkenylation reaction via the regioselective C–H bond activation under oxidative Rh(III)-catalytic conditions (Scheme 28). This discovery represents one of the few examples that show the directing ability of readily available ester groups in rhodium ($[RhCp^*Cl_2]_2$)-promoted C–H bond functionalization. The authors also found that a carboxaldehyde unit could work as a directing group to enable *ortho*-olefination, albeit in moderate yields and with no corresponding hydroacylation adduct observed under the same conditions. A significant amount of side-product (hydrodecarbonylation products) were formed, which accounted for the low product yields in benzaldehydes.

In 2011, the Liu [32] (Scheme 29) and Loh [33] (Scheme 30) groups independently reported a practical protocol for



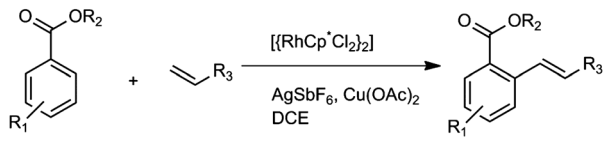
Scheme 26 Rhodium-catalyzed C–H bromination and iodination directed by tertiary benzamide, ketone, and an ester group.



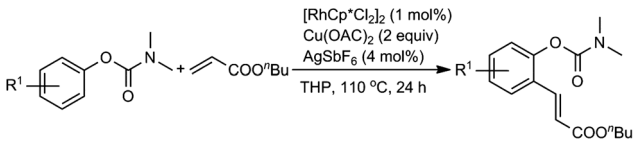
Scheme 27 Rhodium-catalyzed C–H bromination directed by a carbamate group.

the Rh(III)-catalyzed *ortho* C–H activation/olefination of weakly coordinating phenol carbamates. A good regioselectivity was observed, with a broad range of phenol carbamates enabling efficient coupling with acrylates and styrenes. Notably, (methylsulfonyl)ethene and diethyl vinylphosphonate could be employed as the substrates. By contrast, the coupling of unactivated, aliphatic alkenes could not be promoted by this method. Because this reaction exhibited different reactivity than Pd-catalyzed *ortho*-arylation reaction of phenol esters, it presents a new way to access *ortho*-substituted phenols.

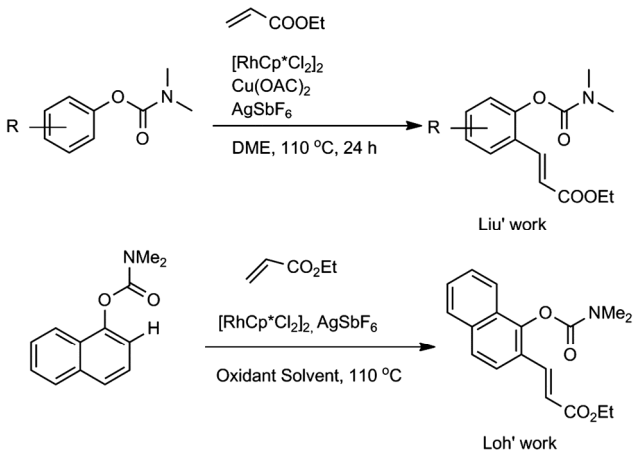
In 2013, the Fu group [34] reported a computational study on the mechanism of Rh(III)-catalyzed oxidative Heck coupling of phenol carbamates with alkenes (Scheme 31). Their study was mainly focused on addressing two questions: whether this reaction would proceed via the arene activation-first or alkene activation-first mechanism, and how the C–H activation occurs. Calculation results indicated that the arene activation-first mechanism was more favorable than the alkene activation-first mechanism. The potential catalytic cycle therefore involves three main steps:



Scheme 28 Rhodium-catalyzed C–H alkenylation directed by an ester group.



Scheme 29 Rhodium-catalyzed C–H alkenylation directed by a carbamate group.

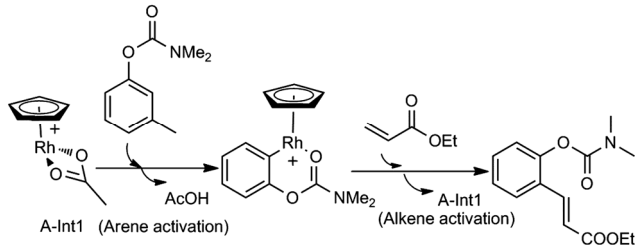


Scheme 30 Rhodium-catalyzed C–H alkenylation directed by a carbamate group.

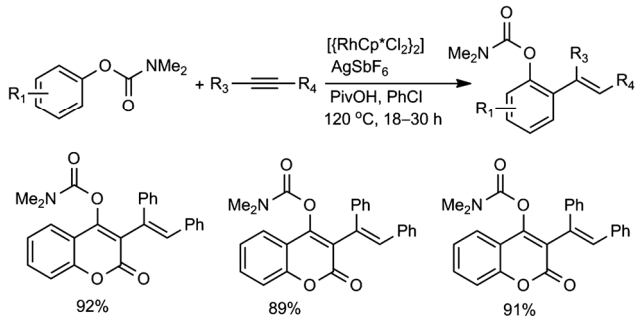
the C–H activation of arene, alkene insertion, and β-H elimination. Based on this study, these researchers proposed that the arene C–H bond was activated by the concerted metallationdeprotonation (CMD) mechanism, which was also the rate-determining step of this Rh(III)-catalyzed oxidative Heck reaction.

In 2013, the Wang group [19] reported a new method to access *ortho*-olefinated phenyl carbamates via a rhodium(III)-catalyzed alkyne hydroarylation of weakly coordinating phenyl carbamate with internal alkynes through direct C–H activation (Scheme 32). The reactions were found to be highly regio- and stereoselective for the formation of corresponding products. The authors also applied this protocol to carbamate-protected 4-hydroxycoumarin, resulting in production of the desired *ortho*-olefinated products in high yields.

In 2012, Zhang and coworkers [35] discovered a palladium-catalyzed C–H alkenylation reaction of aromatic thioethers, which proceeded via an acetate-bridged dinuclear Pd(II) intermediate (Scheme 33). The authors demonstrated the potential of weakly coordinating thioethers as effective directing groups in Pd(II)-catalyzed C–H activation. The synthetic utility of this transformation was shown by the ready preparation of various cinnamic esters with different alkene coupling partners in high yields. Further chemical transformations were conducted to easily remove the thioether directing group or convert it into other useful functional groups. In 2013, the same group [36] reported the development of a new palladium catalysis method for *ortho*-arylation of arenes through thioether-assisted C–H bond activation (Scheme 34). Potassium aryltrifluoroborate was



Scheme 31 Mechanism study of rhodium-catalyzed C–H alkenylation reaction directed by a carbamate group.

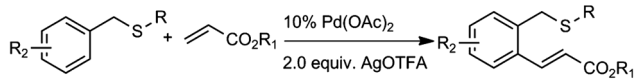


Scheme 32 Rhodium-catalyzed C–H alkenylation directed by carbamate group.

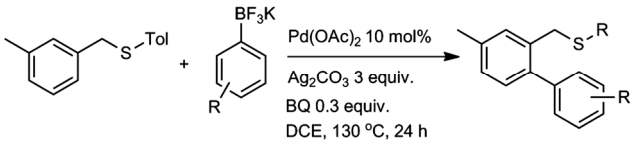
emplyed as the coupling partner. This new reaction provides convenient and efficient access to the preparation of a variety of sulfur-containing biaryl compounds.

In 2011, the Antonchick group [37] developed a highly efficient double C–H activation directed by a weakly coordinating sulfoxide group (Scheme 35). A variety of dibenzothiophenes were smoothly prepared from simple benzyl phenyl sulfoxides in a cascade reaction by the abstraction of four hydrogen atoms in total. Based on their investigations, the authors proposed a plausible mechanism. The first step involved a sulfoxide-group-directed double C–H activation to give the cyclic sulfoxide intermediate. An ensuing Pummerer reaction provided a mercaptoaldehyde. Finally, the following S–H/C–H activation and the formation of a new C–S bond gave the desired dibenzothiophene products.

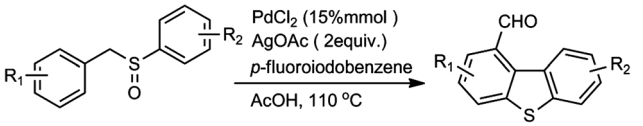
In 2013, the Shi group [38] reported an sp^3-hybridized-thioether-directed C–H alkenylation through Rh(III) catalysis (Scheme 36). An excellent regioselectivity was consistantly observed with all substrates containing weakly coordinating thioether groups. This new method demonstrated a broad substrate scope and good yield. Interestingly, it was observed that both mono- and difunctionalized products could be obtained selectively by tuning the solvents in this transformation. The authors also showed that sequential



Scheme 33 Palladium-catalyzed C–H alkenylation directed by thioether group.



Scheme 34 Palladium-catalyzed C–H arylation directed by a thioether group.



Scheme 35 Palladium-catalyzed dibenzothiophenes synthesis directed by a sulfoxide group.

Scheme 36 Rhodium-catalyzed C–H alkenylation directed by a thioether group.

alkenylation with two different alkenes could be achieved and well controlled. It was also shown that a further reduction of product with Raney Ni in ethanol could readily provide phenylpropanoic acid derivatives (and toluene derivatives).

4 Pd catalysis

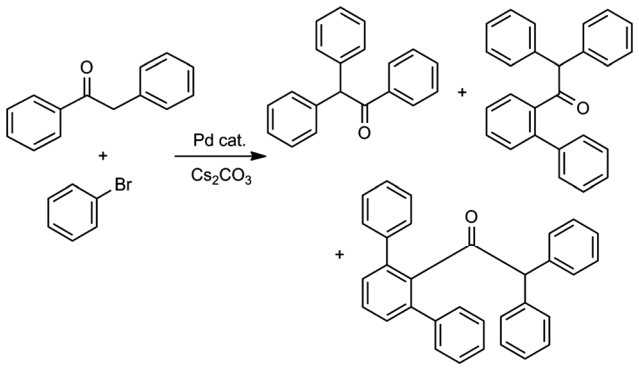
In 1999, the Muria group [39] reported an early example of palladium-catalyzed *ortho* C–H arylation directed by a weakly coordinating ketone group (Scheme 37). Arylation products of aryl ketones were smoothly obtained with the treament of excess amount of aryl bromides in the presence of Cs_2CO_3. Both the *ortho*- and α-positions of the ketone group could undergo arylation reaction. Depending on the substrates and reaction conditions, di-, tri-, or tetraarylation compounds could be produced.

In 2010, the Cheng group [40] discovered a new method for the synthesis of phenanthrone derivatives from *sec*-alkyl aryl ketones and aryl iodides (Scheme 38). The reaction was catalyzed by palladium acetate in trifluoroacetic acid with weakly coordinating ketone groups, which behaved as a practical directing group in this *ortho* aromatic C–H bond activation via five-membered metallacycles. The roles of Ag_2O were suggested to be a likely oxidant, a halide scavenger, and a base. When a *sec*-alkyl ketone was used, a dual C–H activation and enolate cyclization occurred, to afford a corresponding cyclization product. By contrast, primary alkyl aryl ketones when employed would not undergo a further cyclization step.

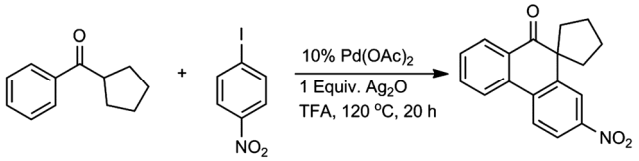
In 2011, Liu and coworkers [41] reported a palladium-catalyzed directed *ortho* C–H amidation of aromatic ketones with both sulfonamides and amides (Scheme 39). This ketone-directed C–H amidation provided a convenient access to 2- and 3-alkyl indoles and 2-aminophenyl ketones. The cyclopalladation complexes of ketones were characterized by X-ray crystallography. It was proposed that the use of an electron-deficient Pd complex, $Pd(OTf)_2$, served as a key factor for this C–H functionalization. Based on their experimental results, these authors suggested that this reaction would be unlikely through a nitrene intermediate.

In 2012, the Cheng [42] and Shi [43] groups independently developed an efficient approach to the synthesis of fluorenones by Pd-catalyzed oxidative cyclization of diaryl ketones (Scheme 40). Both reactions employed $Pd(OAc)_2$ and Ag_2O in the presence of TFA. This oxidative dehydrogenative C–C coupling demonstrated good functional-group compatibility and high yields. Results of a preliminary mechanistic study strongly indicated that a possible concerted metalation-deprotonation (CMD) process, rather than the electrophilic substitution, was involved in the rate-determining step. This possibility could exclude a potential Nazarov cyclization pathway. The plausible mechanism could involve a weakly coordinating ketone-group-assisted *ortho*-C–H activation, the subsequent formation of a six-membered palladacycle, and a final reductive elimination.

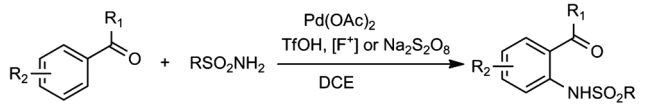
In 2012, the Rao [44] (Scheme 41) and Dong [45] (Scheme 42) groups independently reported a Pd(II)-catalyzed regioselective phenol synthesis from easily accessible aryl compounds bearing different weakly coordinating groups (e.g., ketones, esters, and sulfonamides). Interestingly, it was found that this C–H hydroxylation could be conducted at room temperature via the coordinating ketone and ester groups. A preliminary mechanistic investigation revealed that the TFA/TFAA solvent system served as a key C–H activation factor and as the oxygen source. The Rao



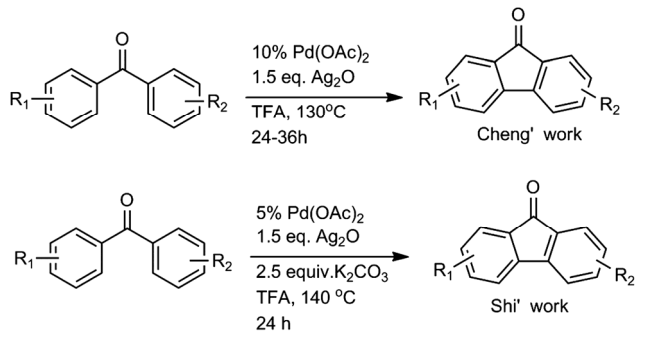
Scheme 37 Palladium-catalyzed C–H arylation directed by a ketone group.



Scheme 38 Palladium-catalyzed C–H arylation directed by a ketone group.



Scheme 39 Palladium-catalyzed C–H amidation directed by a ketone group.



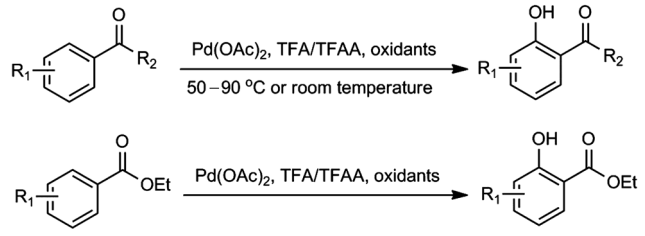
Scheme 40 Palladium-catalyzed intermolecular dehydrogenative C–C coupling directed by a ketone group.

group demonstrated the utility of this method in the synthesis of a variety of heterocyclic compounds and direct modification of a drug (ibuprofen). The Dong group discovered a Pd-catalyzed *ortho*-carboxylation of simple aryl ketones to access a ketal-lactone motif, which illustrates the high efficiency of weakly coordinating ketone-directed C–H bond activation. In 2013, the Kwong group [46] (Scheme 43) also independently reported a ketone-directed Pd-catalyzed oxygenation of simple arenes under similar reaction conditions.

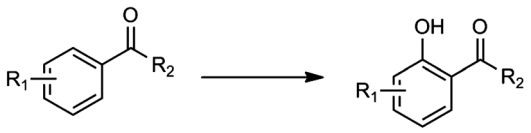
In 2013, the Rao group [47] developed a new palladium (II)-catalyzed *ortho*-chlorination/bromination reaction to access a broad range of arene halides with electron-deficient arenes (Scheme 44). Among these examples, ketone and ester groups were employed as the effective directing groups for promoting *ortho* C–H activation. It was observed that both the co-oxidant and TfOH served as important success factors for regio- and chemoselective C–H activation. A preliminary evaluation of relative directing group (DG) abilities was carried out to give some insight into the priority ordering of DG abilities. Results showed that NHAc > CONHR > C=O > SO_2NHR > CO_2Et, $CONR_1R_2$, $SO_2NR_1R_2$. This knowledge of diverse DGs' abilities may be useful for the design and synthesis of chlorine-containing molecules, which involves C–H activation assisted by directing groups.

In 2010, Liu and coworkers [48] developed a practical Pd(II)-catalyzed *ortho* C–H arylation reaction with weakly coordinating phenol esters under mild conditions (Scheme 45). The method can provide a useful strategy for preparing a variety of 2-arylphenol derivatives; as noted, the reaction was not sensitive to moisture or air. This reaction presents a rare example of acyloxy-directed Pd insertion into C–H bonds promoted by oxygen-only groups. The authors also revealed a cyclopalladation complex formed from a simple phenol ester which was characterized by X-ray crystallography.

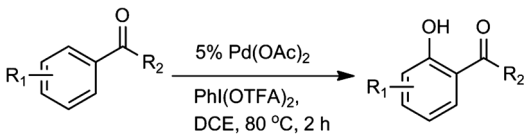
In 2009, the Bedford group [49] discovered new palladium-catalyzed *ortho*-arylation reactions of carbamate-protected phenols with aryl iodides or diaryliodonium salts (Scheme 46). The carbamate functional group served as an



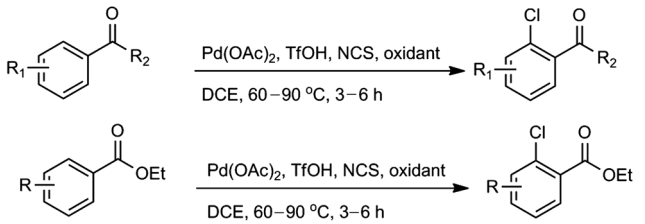
Scheme 41 Palladium-catalyzed C–H hydroxylation directed by ketone and ester groups.



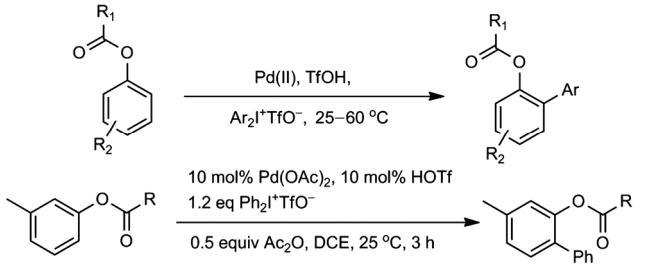
Scheme 42 Palladium-catalyzed C–H hydroxylation directed by a ketone group.



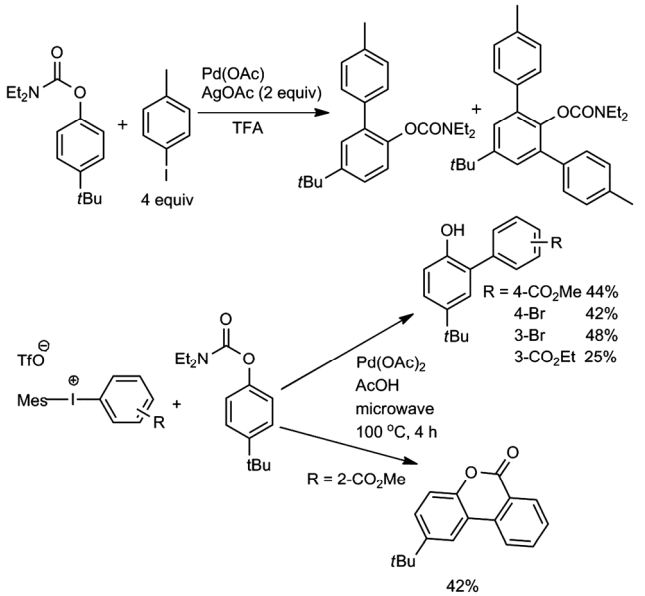
Scheme 43 Palladium-catalyzed C–H hydroxylation directed by a ketone group.



Scheme 44 Palladium-catalyzed C–H chlorination and bromination directed by ketone and ester groups.



Scheme 45 Palladium-catalyzed C–H arylation directed by an ester group.



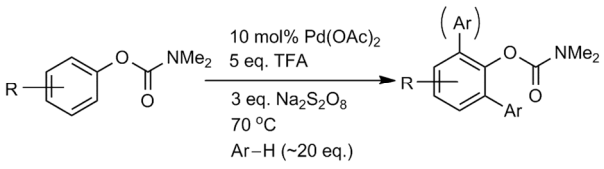
Scheme 46 Palladium-catalyzed C–H arylation directed by a carbamate group.

excellent directing group for this palladium-catalyzed direct arylation reaction, which provides either protected or free-substituted phenol derivatives. When aryl iodides were used, both mono- and di-arylated products were obtained. By contrast, monoarylated products were favored with diaryliodonium salts.

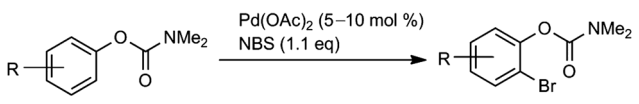
In 2010, Dong and coworkers [50] reported an ortho-arylation of *O*-phenylcarbamates that employed simple arenes as the cross-coupling partner and sodium persulfate as the terminal oxidant (Scheme 47). The efficiency of carbamate as a directing group was well demonstrated in this catalytic C–H functionalization reaction. A broad range of 2-arylphenol derivatives could be readily prepared by this new method. The authors isolated and characterized the first cyclopalladate, which was prepared from an *O*-phenylcarbamate as a bimetallic Pd species containing a weak Pd-Pd interaction. Based on their results, the authors proposed a mechanism in which two C–H bond activations may occur via cyclopalladation and electrophilic metalation, respectively.

In 2012, the Nicholas group [51] reported a palladium-catalyzed *ortho*-bromination reaction of *O*-aryl carbamates to give the corresponding *ortho*-brominated carbamates (Scheme 48). Originally, amine adducts of cyclopalladate complexes derived from the *O*-phenyl carbamates were prepared by the authors. However, instead of undergoing any C–N bond formation under oxidative conditions, *ortho*-brominated products were obtained with NBS in good yields.

In 2014, Rao and coworkers [52] disclosed the development of a room-temperature palladium(II)-catalyzed *ortho*-chlorination/bromination reaction that can provide convenient access to 2-chloro/bromophenol derivatives from simple phenols (Scheme 49). The new C–H halogenation reaction demonstrated excellent regioselectivity and reactivity, and high yields. The reaction represents a rare example of mild C–H functionalization at room temperature. The efficiency and practicality of this reaction was further proven by gram-scale synthesis and a one-pot protocol for preparation of 2-chloro/bromophenols.



Scheme 47 Palladium-catalyzed C–H arylation directed by a carbamate group.

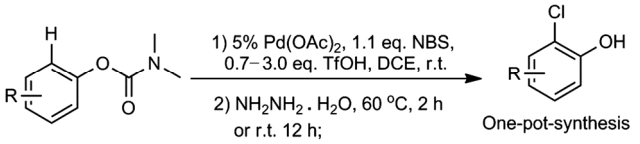


Scheme 48 Palladium-catalyzed C–H bromination directed by a carbamate group.

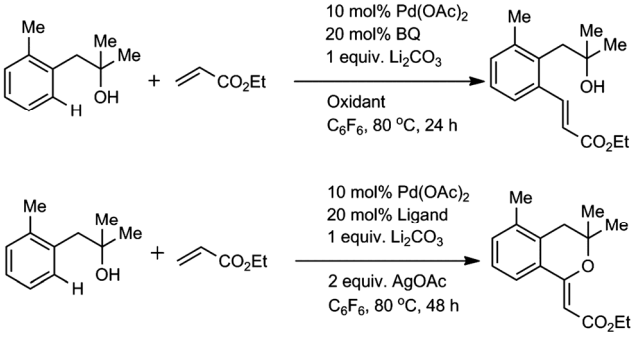
In 2010, Yu and coworkers [53] developed a practical palladium(II)-catalyzed olefination reaction which was directed by alcohol in a solvent of C_6F_6 (Scheme 50). The reaction was effectively promoted by the use of monoprotected amino acids, which supplied a rare example of a ligand-promoted C–H activation reaction. For most substrates, a cascade olefination/oxidative cyclization always affords corresponding pyran products. However, when styrenes and simple olefins were adopted in this reaction, only the olefinated products were obtained without further cyclization. As the authors proposed, a plausible mechanism may involve a hydroxyl-directed insertion of Pd(II) and an ensuing olefin coordination, 1,2-migratory insertion, and a following β-hydride elimination to generate the uncyclized intermediate in a Pd(0)/Pd(II) catalytic cycle.

In 2010, the Yu group [54] discovered a Pd(II)-catalyzed C–H activation/C–O cyclization reaction directed by a weakly coordinating hydroxyl group (Scheme 51). A variety of dihydrobenzofurans could be smoothly produced in good yields via this new method. Notably, the authors further demonstrated the application of the transformation in the synthesis of two spirocyclic dihydrobenzofuran derivatives, which often serves as a common structure motif in natural products. Based on their experiments, the authors proposed that the hydroxyl moiety would coordinate with Pd(II) as a neutral σ donor and suggested that the reaction underwent a Pd(II)/(IV) catalytic cycle in the presence of oxidants.

More recently, Davies and coworkers [55] demonstrated the applicability of C–H functionalization in the streamlined synthesis of complex molecules (Scheme 52). A series of 2,3-dihydrobenzofurans were prepared in a highly regio-, diastereo-, and enantioselective fashion by a sequential C–H functionalization transformations that included a Rh(II)-



Scheme 49 Palladium-catalyzed C–H chlorination directed by a carbamate group.

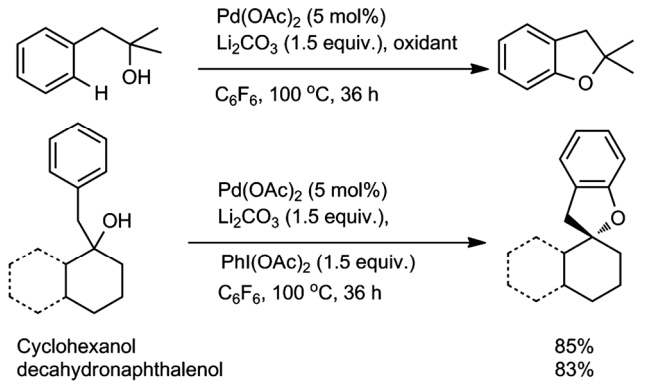


Scheme 50 Palladium-catalyzed C–H olefination directed by an alcohol group.

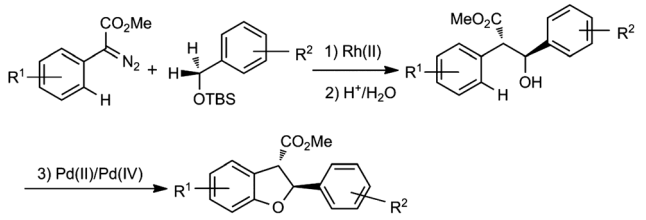
catalyzed enantioselective intermolecular benzylic C–H insertion and a Pd(II)-catalyzed alcohol-directed C–H activation/C–O cyclization. It is expected that further development of selective C–H functionalization methods will have great impact upon future studies of organic synthesis.

In 2013, the Lam group [56] discovered new catalytic C–H alkenylation reactions with 2-aryl-3-hydroxy-2-cyclohexenones and various alkene partners (Scheme 53). Notably, it was revealed that this hydroxy-directed reaction could be efficiently promoted by both palladium catalysis and ruthenium catalysis to provide corresponding benzopyrans in satisfactory yields via a cascade olefination/ cyclization.

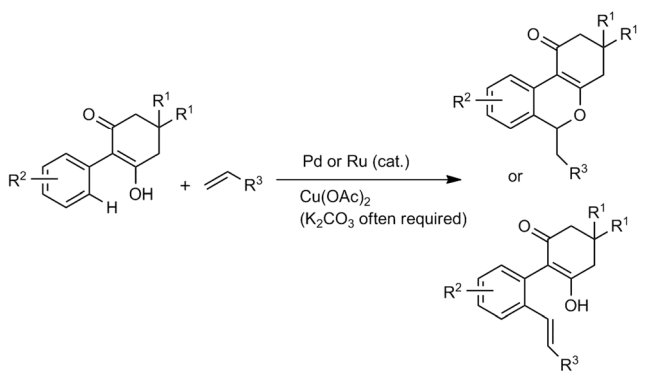
In 2011, the Liu group [57] reported a Pd(II)-catalyzed phenol-directed C–H activation/C–O cyclization reaction



Scheme 51 Palladium-catalyzed C–H activation/C–O cyclization directed by an hydroxyl group.



Scheme 52 Palladium-catalyzed C–O cyclization directed by an hydroxyl group.



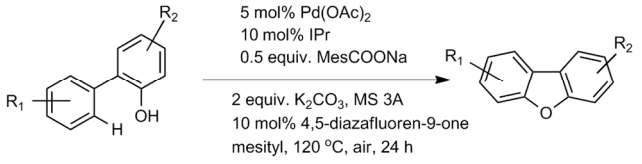
Scheme 53 Palladium-catalyzed C–H alkenylation directed by an hydroxyl group.

that undergoes a Pd(0)/Pd(II) catalytic cycle with simple air as the oxidant (Scheme 54). This new reaction demonstrated a good functional-group tolerance and satisfactory yields. The authors also showed a good compatibility of this C–O cyclization method with the known C–N cyclization in their stuy. Interestingly, C–O reductive elimination instead of C–H activation was found to be the turnover-limiting step.

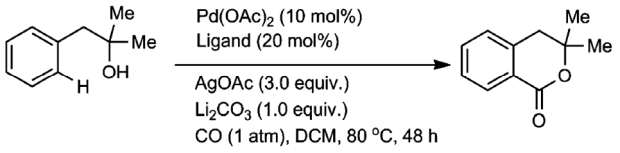
The Yu group [58] developed a Pd(II)-catalyzed *ortho*-C–H carbonylation reaction with phenethyl alcohol substrates in 2011 (Scheme 55). This represents a rare example of C–H functionalization directed by a weakly coordinating hydroxyl group. The synthetic utility of this reaction was well shown by a simple-step access to 1-isochromanone derivatives. The authors further demonstrated the applicability of the reaction by synthesizing a histamine-release inhibitor. One notable advantage of this reaction was that both the hydroxyl directing group and the coupling partner (CO) were totally incorporated into the desired moleucles without the need of additional manipulations. In addition, the mono-N-protected amino acid ligands used in this transformation played an important role.

In 2011, Gevorgyan and coworkers [59] discovered a novel semi-one-pot Pd(II)-catalyzed C–H oxygenation of phenols via sequential C–H acetoxylation/acid-catalyzed transesterification and cyclization steps (Scheme 56). One key feature of this reaction was that its regioselectivity could be well directed by using a weakly coordinating silanol functional group. This new approach provided ready access to efficient and regioselective synthesis of substituted catechol derivatives, some of which are difficult to prepare with known methods. Unlike the known alcohol- or phenol-directed C–O cyclization methods, in which the oxygen atom comes from the directing group, in this transformation the oxidant serves as the oxygen source.

In 2013, a palladium-catalyzed ether-directed C–H olefination with monoprotected amino acid ligands (MPAA) was reported by the Yu group [60] (Scheme 57). The potential of weak coordination as a practical tool was well demonstrated by this alkylether-directed aryl C–H activation



Scheme 54 Palladium-catalyzed C–H activation/C–O cyclization directed by a phenol group.

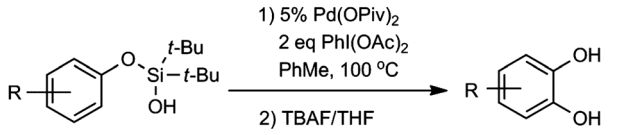


Scheme 55 Palladium-catalyzed C–H carbonylation directed by an alcohol group.

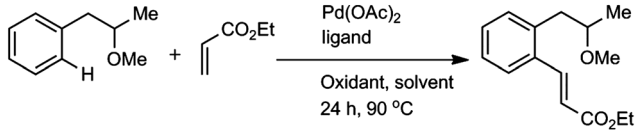
reaction. A variety of novel cinnamate compounds could be readily produced from corresponding arylethyl ethers with this new method. The authors further demonstrated the utility of the reaction by releasing a free hydroxy group via a simple demethylation of the methyl ether products with BBr_3.

In 2012, the Cheng group [61] reported an effective Pd-catalyzed C=C double-bond-assisted selective *ortho*-C–H olefination of arenes with various olefin partners (Scheme 58). Remarkably, the reactions could proceed at room temperature using dioxygen gas as the terminal oxidant in the presence of TFA (8 equiv.). Dioxygen gas was noted to be better than other typically used oxidants such as Ag_2O and $Cu(OAc)_2$. The reaction represents the first example to employ an allylic alkenyl double bond as a practical directing group for C–H activation. The authors also found that a β-C=C bond instead of an α-C=C bond was critical for this *ortho*-C–H bond activation of arenes.

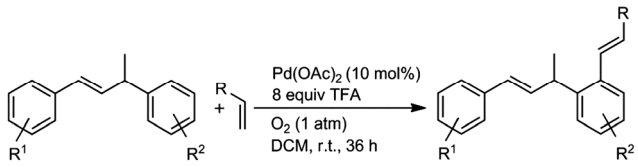
In 2012, Hiyama and coworkers [62] disclosed a palladium(0)-catalyzed cycloaddition of alkynyl aryl ethers with internal alkynes, which would provide substituted 2-methylidene-2*H*-chromene compounds by *ortho* C–H activation (Scheme 59). The reaction demonstrates a good



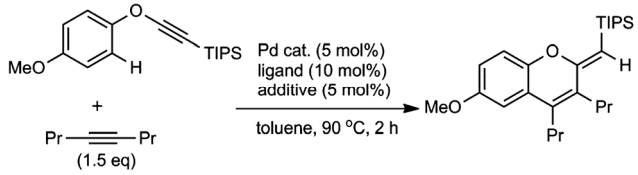
Scheme 56 Palladium-catalyzed C–H oxygenation directed by a silanol group.



Scheme 57 Palladium-catalyzed C–H olefination directed by an ether group.



Scheme 58 Palladium-catalyzed C–H olefination directed by an allylic alkenyl group.



Scheme 59 Palladium-catalyzed cycloaddition directed by an alkynoxy group.

functional-group tolerance and reactivity. The weakly coordinating alkynoxy group effectively works as a directing group in this transformation. Based on deuterium-labeling experiment data, the authors suggested that the arylpalladium hydride complex served as a key intermediate through oxidative addition.

5 Conclusions

Since the early 1990s, transition-metal-catalyzed C–H functionalization with weakly coordinating directing groups has gradually become a practical and powerful tool for the synthesis of many valuable chemicals. Since 2004, two types of weakly coordinating directing groups including commonly occurring functional groups (e.g., ketone, ether, or ester) and easily removable auxiliaries (e.g., amide) have well demonstrated their efficiency and feasibility in C–H activation reactions. One remarkable advantage of using a common and weakly coordinating functional group is that both the directing group and the coupling partner can be naturally integrated into the desired compounds without additional chemical manipulations. As the field of metal-catalyzed C–H functionalization moves forward, we believe that more transition-metal-catalyzed regio-, chemo-, and enantioselective reactions by weak coordination will be developed. We also expect that this attractive and promising strategy will play a more important role in modern organic synthesis.

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