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Directing group-assisted transition-metal-catalyzed vinylic C–H bond functionalization

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Transition-metal-catalyzed C–H bond activation represents one of the most attractive research areas in organic synthesis. In contrast to the great developments made in directed C–H bond functionalization of arenes, the directing group-assisted activation of non-aromatic vinylic C–H bonds still remains challenging. During the recent years, significant progress has been made in this fascinating field with various functionalized alkenes, heterocycles and carbocycles being obtained. This article will focus on the recent achievements in the field of directing-group-assisted vinylic C–H bond functionalization.

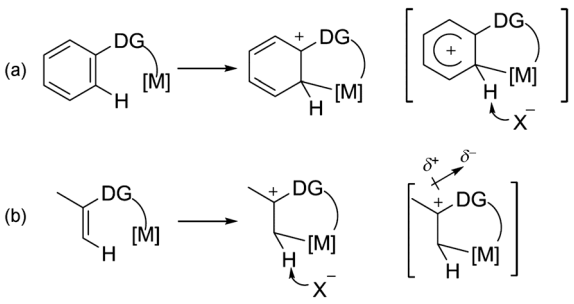
transition-metal-catalysis, organic synthesis, C–H bond functionalization, vinylic C–H bond

1 Introduction

The transition-metal-catalyzed activation of C–H bond is one of the most attractive research fields in modern organic synthesis [1]. The C–H bond activation of cost-effective hydrocarbons can obviate troublesome prefunctionalization and reduce the production of toxic by-products. Therefore, great efforts have been made in the field of transition-metal-catalyzed C–H bond activation over the last decade.

In comparison to the aryl C–H bond functionalization reactions, which have been extensively studied, activation of non-aromatic vinylic C–H bonds is more challenging [2]. Factors from several angles may help comprehending this phenomenon. First, the directing groups (DGs) on the alkenes (for example, carbonyl groups) could activate the olefins towards competitive transformations, such as conjugate addition, which are not at play for aromatic system. Second, the resulted positive charge via electrophilic attack of metal on the aromatic system can be stabilized by the delocalization of aromatic ring (Scheme 1(a)), which is not seen for alkenes. And the electron-withdrawing DG is not contributive either (Scheme 1(b)). Besides, the substituents on the double bond may bring in steric hindrance for the reaction on C–H bond.

Owing to the diverse reactivity of alkenes, the vinylic C–H bond activation would be appealing as on efficient tool for organic synthesis, while it remains less developed. Incorporating directing-groups to alkenes allows site-selective decoration of vinylic C–H bonds, making functionalization of C=C double bonds more flexible. In transition-metal-catalyzed transformations, the cyclic vinylmetal species is



Scheme 1 Comparison of arylic and vinylic C–H bond activation.

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commonly involved in these directing-group-assisted vinylic C–H activation strategies. As is illustrated in Scheme 2, the cyclic vinylmetal species **A**, which is formed through the assistance of directing group, can further react to construct C–C or C–X bonds, leading to functionalized alkenes **B** or annulated compounds **C**. These structures can be found in numerous pharmaceutical compounds and natural products. This review will focus on the directing-group-assisted activation of vinylic C–H bonds catalyzed by transition-metal catalysts.

2 Csp^2–Csp bond formation through directed vinylic C–H bond activation

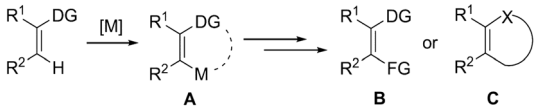
Conjugated 1,3-enynes are widely encountered frameworks in organic chemistry and material sciences [3]. Through the vinylic C–H activation protocol, C=C double bonds can be alkynylated by reacting with alkynylation reagents.

In 2014, Glorius *et al*. [4] developed the synthesis of enynes via directed vinylic C–H activation strategy (Scheme 3). They selected TIPS-EBX as an electrophilic alkynylation reagents and diisopropylbenzamide as the directing group for the alkynylation of cinnamamides. Different substituents on the aromatic ring are tolerated. In this reaction, two possible mechanisms are proposed. Upon the vinylic C–H bond activation, alkyne moiety of **2** coordinates to rhodium complex **A** to give intermediate **B**. With subsequent addition of rhodium complex **A**, 2-iodobenzoic acid is expelled to give a carbene species **C**. The final product is obtained via carbene rearrangement/reductive-elimination sequence of **D**. Another feasible pathway involves regio-selective carborhodation, which generates alkenyl-rhodacycle **E**. α-Elimination of 2-iodobenzoic acid gives rhodium vinylidene **F**. Concerted or stepwise vinyl-migration and elimination affords the final product.

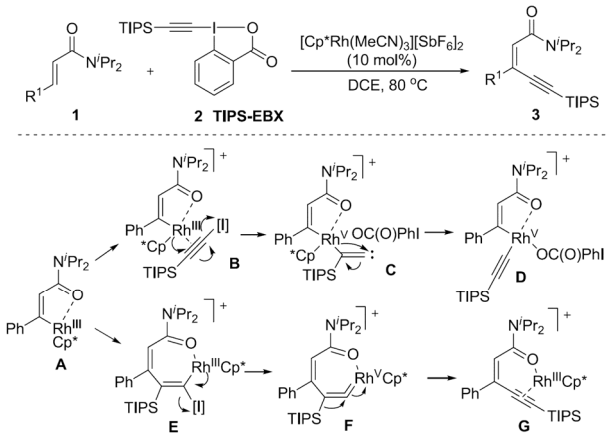
In an Rh- and Ir-catalyzed C–H alkynylation of arenes, as reported by Li and co-workers [5], they showed several examples about Ir-catalyzed alkynylation of acrylamide derivatives with TIPS-EBX reagents in moderate to good yields (Scheme 4).

Recently, Loh *et al*. [6] developed a complementary reaction for α-substituted acrylamides using Ts-amide DG (Scheme 5). Presumably due to the weakly coordinating ability of Ts-imide group, the highly reactive ligated catalyst can be formed to react with the substrates.

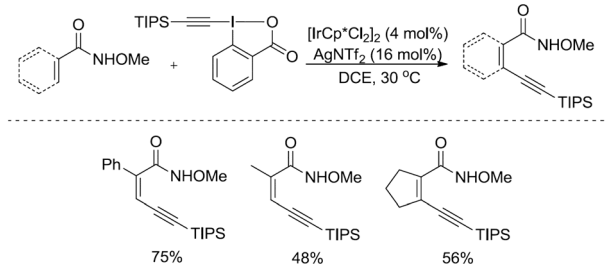
Furthermore, some cyclic or acylic α,β-disubstituted acrylamide derivatives are all compatible by switching the



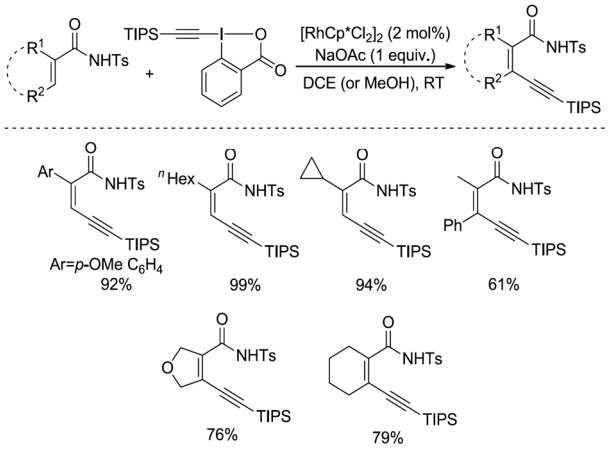
Scheme 2 Functionalization of vinyl C–H bonds via directed C–H bond activation.



Scheme 3 Rh(III)-catalyzed alkynylation of acrylamides to 1,3-enynes.



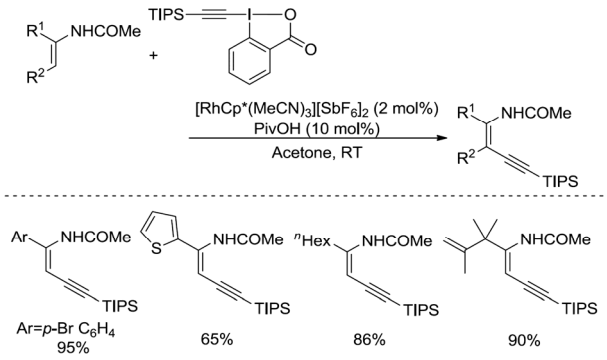
Scheme 4 Ir(III)-catalyzed alkynylation of acrylamide derivatives.



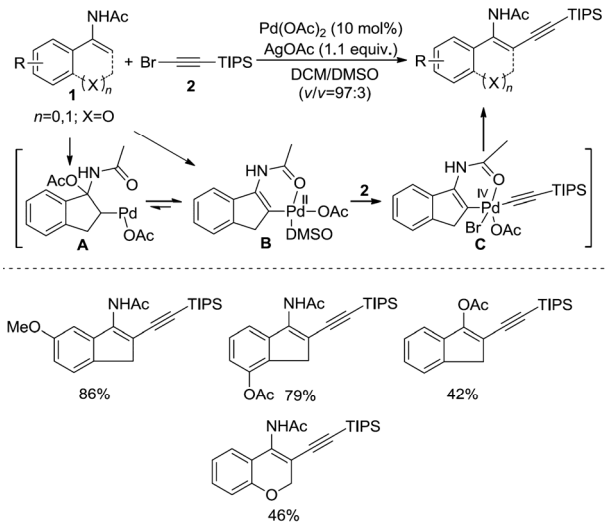
Scheme 5 Rh(III)-catalyzed alkynylation of acrylamide derivatives to 1,3-enynes.

solvents, which shows potential applications in 1,3-enynes synthesis (Scheme 6) [7].

Haloacetylenes can also act as electrophilic alkynylation agents. In 2014, Loh *et al*. [8] reported a Pd-catalyzed alkynylation of cyclic *N*-vinylacetamide employing alkynyl-bromides (Scheme 7). Both electron-donating and electron-withdrawing groups on the phenyl ring are tolerated in this transformation. A mechanism is proposed as shown in Scheme 7. Vinylpalladium species **B** is formed through the vinylic C–H bond activation or a subsequent addition-



Scheme 6 Rh(III)-catalyzed alkynylation of enamides to 1,3-enynes.

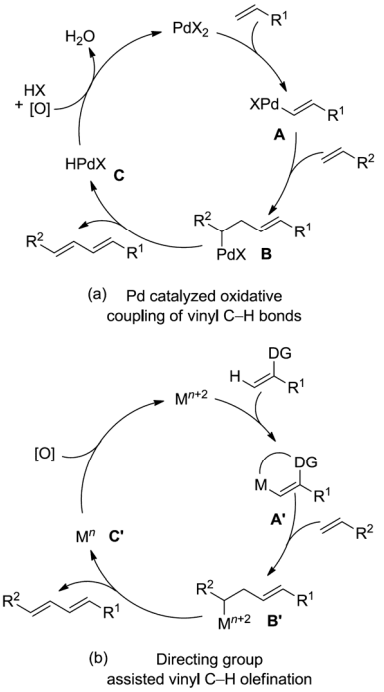


Scheme 7 Pd(II)-catalyzed directed alkynylation of *N*-vinylacetamides.

elimination step. Oxidative addition of alkynylbromide to intermediate **B** gives the Pd(IV) species **C**, which undergoes reductive elimination to the product.

3 Csp^2–Csp^2 bond formation through directed vinylic C–H bond activation

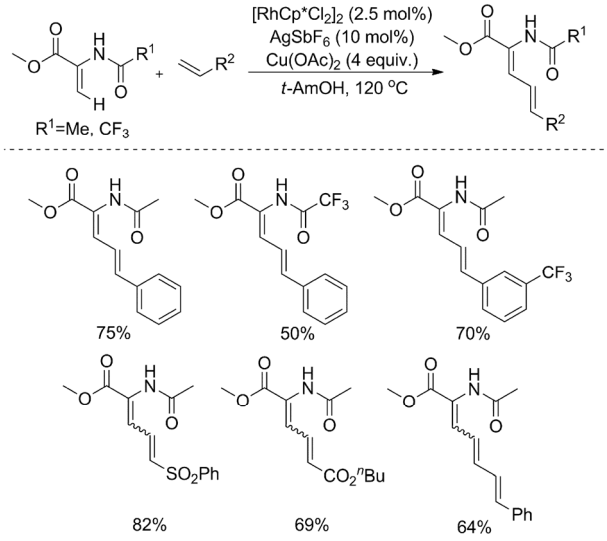
Conjugated diene and polyene structures exist in large scales of pharmaceutical compounds and natural products [9]. These highly unsaturated structures could be obtained by the construction of Csp^2–Csp^2 bond following vinylic C–H bond activation protocol. Recently, diene synthesis through Pd-catalyzed oxidative Heck reaction of two vinylic C–H bonds has been extensively studied [10] (Scheme 8(a)). These reactions are initiated by vinylpalladium intermediate **A** with subsequent alkene insertion/β-H elimination. In contrast to this type of reactions, under the assistance of directing groups (DGs), transition-metals can be placed at a proximal C–H site to facilitate the formation of cyclic vinylmetal intermediate **A′** to achieve functionalization of vinylic C–H bonds (Scheme 8(b)).



Scheme 8 Synthesis of dienes via oxidative Heck reaction (a) or directed vinylic C–H activation (b).

In 2011, Glorius and co-workers [11] developed the Rh-catalyzed olefination of vinylic C–H bonds with directing-group-assisted strategy (Scheme 9). They reported that α- and β-substituted acrylamides and acrylesters could be converted into the corresponding linear butadienes. They then studied the Rh-catalyzed functionalization of methyl 2-acetamidoacrylates in detail. A variety of styrenes with different substituents could be well tolerated along with other coupling partners.

In the same year, Loh *et al*. [12] reported a Pd-catalyzed



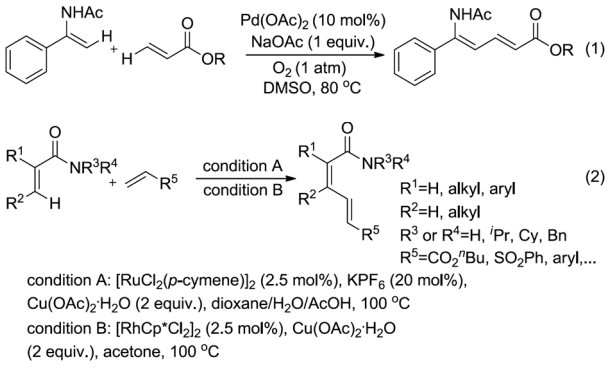
Scheme 9 Rh(III)-catalyzed olefination of acrylamides and acrylates with styrenes and acrylates.

olefination of enamides with acrylates using oxygen as oxidant (Scheme 10, Eq. (1)). Both cyclic and acyclic enamides afforded the products in moderate to good yields with acrylates as coupling partners. They isolated a cyclic vinylpalladium complex, which was believed as the key intermediate and its structure was confirmed by X-ray analysis. In 2012, the same group developed Ru- and Rh-catalyzed olefination of acrylamides with acrylates. The reaction shows a wide functional-group compatibility with good efficiency (Scheme 10, Eq. (2)) [13].

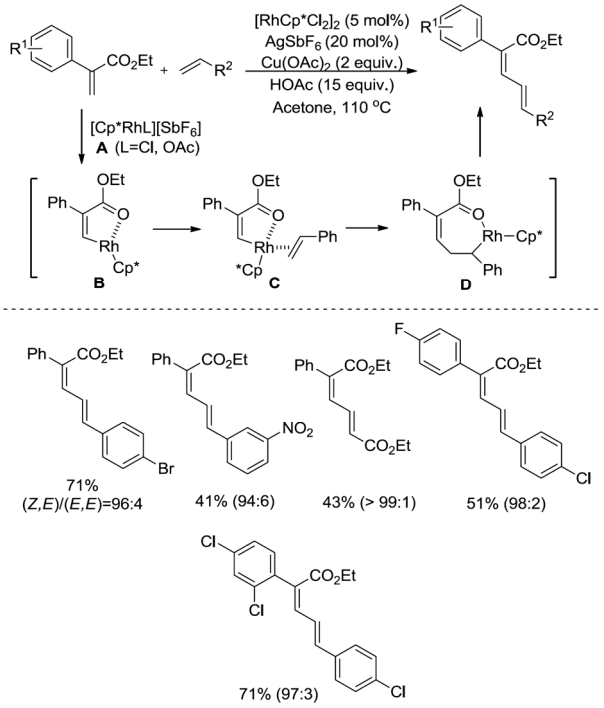
In addition to the amide groups, the weakly-coordinating ester groups can also act as DGs to promote the olefination reaction. In 2014, Zhang and co-workers [14] investigated the ester-directed Rh-catalyzed olefination of 2-aryl acrylates with styrenes (Scheme 11). This reaction exhibited excellent stereo-selectivity to form (*Z,E*)-diene isomers with electron-donating and electron-withdrawing groups on both sides. The mechanism indicates that after the formation of active Rh(III) species **A**, a cyclic vinylrhodium intermediate **B** is formed with the assistance of ester groups. The alkene then inserts into **B** to give Rh-intermediate **D**, the subsequent β-H elimination releases the product and Rh(I) species, which is oxidized to Rh(III) by copper species.

By installing a directing group on enolates, Glorius *et al*. [15] developed an Rh-catalyzed C–H olefination of enolates (Scheme 12). A variety of α-aryl, alkyl and cyclic enolates were alkenylated using carbamate directing group. As for the coupling partners, methyl acrylates, acrylonitriles and vinyl ketones were all compatible. The olefination products of enolates can be further converted into the corresponding α-alkenylated ketones.

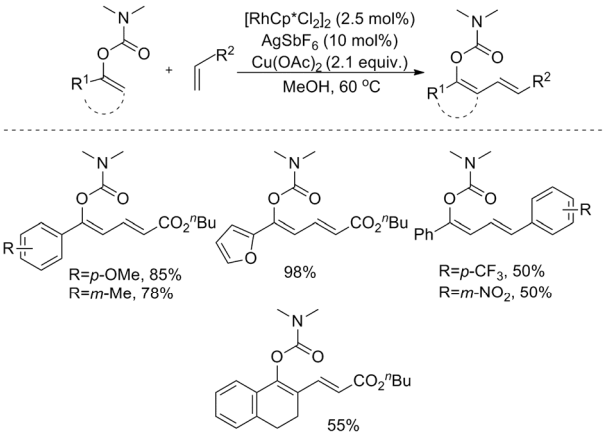
Polyenes, for example, [3]dendralenes (cross-conjugated trienes), are highly unsaturated compounds of great importance. These trienes have received great attention for their occurrence in various natural compounds [16]. In 2013, Glorius *et al.* [17] reported the synthesis of [3]dendralenes by Rh-catalyzed vinyl C–H activation of acrylamides with allenyl carbinol carbonates (Scheme 13). A variety of acrylamides and their coupling partners with different substituted patterns are compatible with good efficiency. The transformation is initiated by a C–H activation step giving



Scheme 10 Transition-metal-catalyzed olefination of alkenes with terminal alkenes.



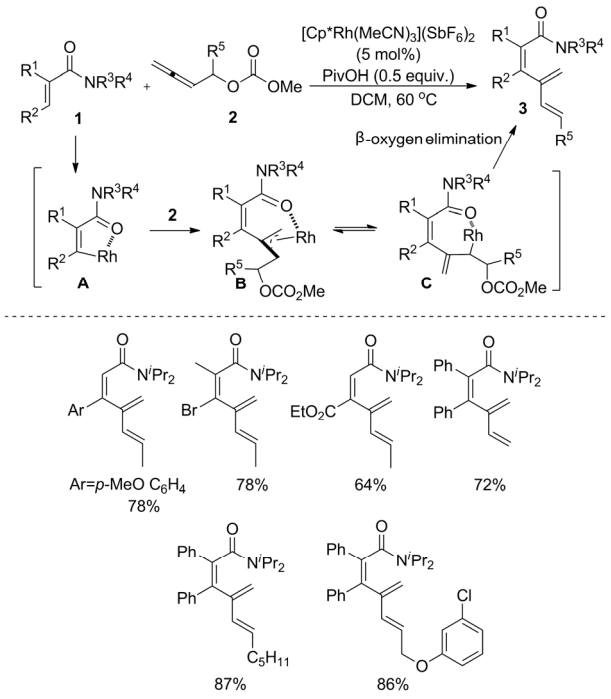
Scheme 11 Ester-directed selective olefination of acrylates by Rh(III) catalysis.



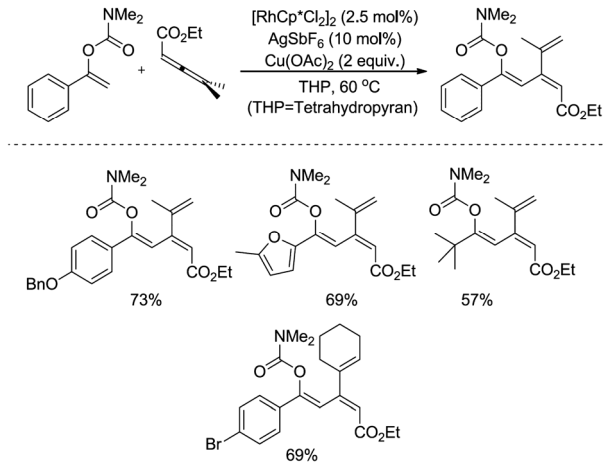
Scheme 12 Rh(III)-catalyzed olefination of ketone-containing molecules.

vinylrhodium intermediate **A**. The Rh–C bond of **A** then adds to allene moiety to produce complex **B** or **C**. Subsequent β-oxygen elimination produces the final product.

In 2014, Fu and co-workers [18] reported that enolate esters can also react with allenes to afford highly conjugated trienes using Rh catalysts (Scheme 14). In this reaction, enolate esters of dimethylcarbamates coupled with various substituted allenes such as ethyl 4-methylpenta-2,3-dienoate to give conjugated trienes with high regioselectivity and functional-group compatibility. The reaction proceeds through the similar C–H activation/allene insertion/β-H elimination procedure.



Scheme 13 Rh (III)-catalyzed C–H activation/functionalization of acrylamides with allenyl carbinol carbonates.



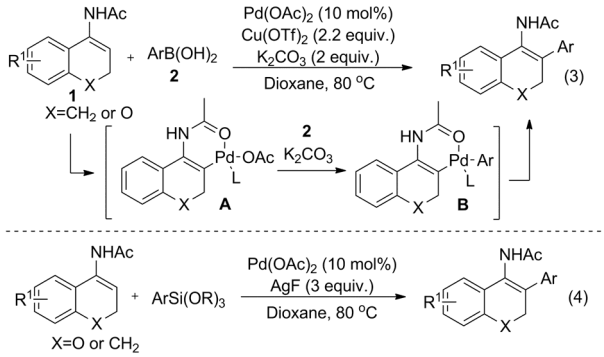
Scheme 14 Rh(III)-catalyzed C–H activation of enolate esters with allenes to conjugated olefins.

In recent years, Pd-catalyzed coupling of arenes with alkenes, or Fujiwara-Moritani reaction, to give styrenes has been well explored [19]. However, alkenes are usually involved as the second coupling partners after aryl C–H bond activation. With the assistance of DGs, alkenes can be transformed into vinylmetal species to react with aryl-transfer reagents or even arenes, which represents a different reaction mode for alkenyl arylation.

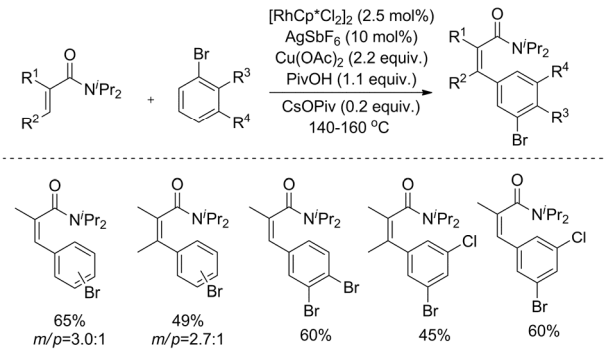
In 2009, Loh and co-workers [20] developed a Pd-catalyzed arylation of cyclic enamides with aryl boronic acids through vinyl C–H activation (Scheme 15, Eq. (3)). Both electron-donating and electron-withdrawing group substituted arylboronic acids can furnish the products in good to high yields despite the substituted patterns of enamides. The reaction is initiated by the six-membered palladacycle **A**. The subsequent transmetallation/reductive-elimination gives the product. Besides, they also developed Pd-catalyzed arylation employing organosilane reagents, which show great functional group tolerance (Scheme 15, Eq. (4)) [21]. The six-membered vinylpalladium species is also involved in the reaction mechanism.

Instead of using aryl-transfer reagents, in 2012, Glorius and co-workers [22] developed the Rh-catalyzed dehydrogenative alkene-arene coupling reaction utilizing directed vinylic C–H activation strategy (Scheme 16). In contrast to the traditional oxidative olefination of arenes to give *E*-products, this method affords *Z*-arylated olefins. Various mono- or di-substituted acrylamides coupled with bromobenzene in moderate to good yields with a ratio between *meta*/*para* isomers, while β-substituted acrylamides reacted in lower yields. Only one isomer could be obtained due to the steric hindrance when 1,3-disubstituted arenes were employed. The isomerization test and competition experiments suggested that a C–H bond activation pathway is involved.

Arylated alkenes can also be obtained via decarboxylative coupling. In 2014, Shi *et al*. [23] reported an Rh-catalyzed pyridinyl-group-assisted C–H functionalization of cyclic enamines employing simple carboxylic acids as cou-



Scheme 15 Pd(II)-catalyzed arylation of cyclic enamides with arylboronic acids and arylsilanes.



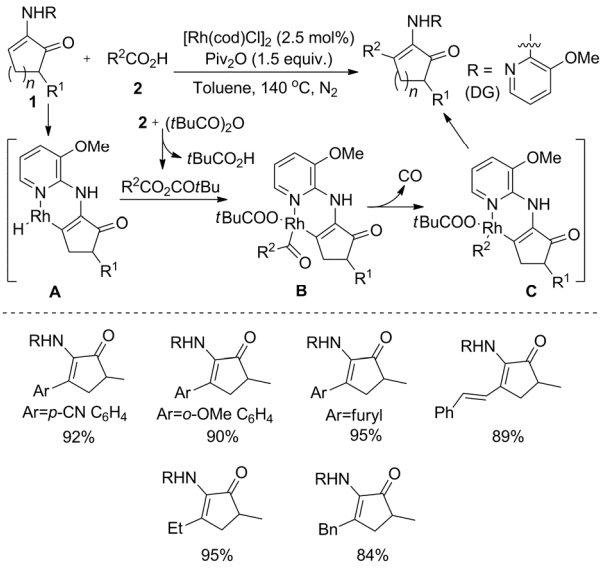
Scheme 16 Rh(III)-catalyzed dehydrogenative alkene-arene coupling reaction.

pling partners (Scheme 17). The substrates of enamines could bear various functional groups such as phenyl, furyl, alkenyl, and alkyl groups, which showed great versatility of this method. In the mechanism, the alkenyl C–H bonds is activated by Rh(I) with the assistance of pyridinyl group to form the vinylrhodium **A**. The carboxylic acid reacts with $(t\text{BuCO})_2\text{O}$ and then with **A** to give intermediate **B**. Decarbonylation of **B** gives rhodium species **C** which affords the final product via reductive elimination.

4 Csp^2–Csp^3 bond formation through directed vinylic C–H bond activation

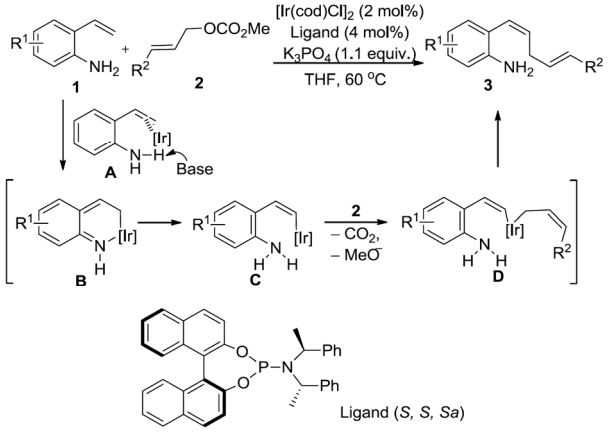
Apart from the Csp^2–Csp and Csp^2–Csp^2 bond formation through vinylic C–H bond activation, the construction of Csp^2–Csp^3 bond could also be carried out via this strategy, for example, the allylic alkylation and trifluoromethylation reaction. These transformations are also very important C–C bond forming reactions in synthetic organic chemistry.

In 2009, You *et al*. [24] reported an Ir-catalyzed allylic alkylation of *o*-aminostyrenes employing allylic carbonates (Scheme 18). The leaving group of the allyl precursors is crucial for the reaction patterns. The reactive allyllic precursors, such as allyl diethyl phosphates, could afford allylic amination products. This reaction shows great functional group tolerance to both sides. Mechanistic experiments excluded the [3,3]-sigmatropic rearrangement pathway of amination products. In the reaction mechanism, 2-vinylaniline coordinates to Ir-complex to produce the dearomatization intermediate **B** by base-assisted deprotonation. Aromatization of **B** gives iridium species **C**, which undergoes subsequent oxidative addition to allyl carbonates to afford complex **D**. Finally, reductive elimination of **D** affords the product.

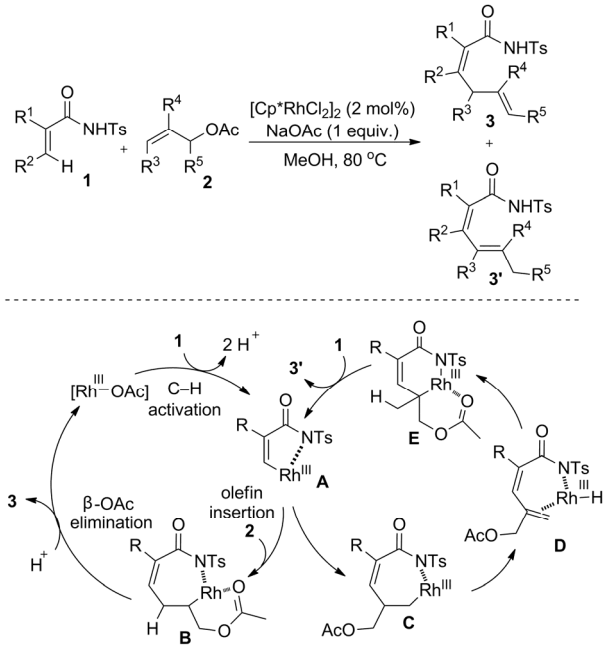


Scheme 17 Rh(I)-catalyzed alkenyl C–H functionalization of cyclic enamines with carboxylic acids.

In 2014, Loh *et al*. [25] reported their investigation on the Rh(III)-catalyzed vinyllic C–H bond allylation of acrylamides bearing weakly coordinating Ts-imide directing-group with different allyl acetate electrophiles (Scheme 19). Acrylamides bearing different substituents and cyclic acrylamides are all compatible with the 1,3-diene products being detected in some cases. As for the mechanism, it is proposed that after the formation of active Rh(III) species **A**, vinyl rhodium species **B** is generated through assisted C–H bond activation via a concerted-metalation-deprotonation (CMD) process. The insertion of allyl C=C bond to **B** produces the seven-membered rhodacycle **C**, which is stabilized by acetoxyl group. Subsequent β-OAc elimination of **C** gives the product. The formation of dienes could be explained by a pathway via regioselective-reversed insertion



Scheme 18 Ir(I)-catalyzed allylic vinylation of 2-vinylaniline with allylic carbonates.



Scheme 19 Rh(III)-catalyzed allylation of acrylamides with allyl acetates.

of allyl acetates with subsequent hydride-elimination/reinsertion/β-OAc elimination sequence.

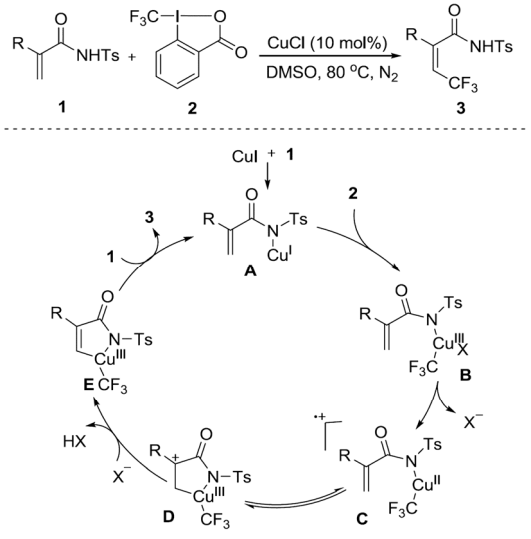
Owing to the unique properties of the trifluoromethyl group [26], trifluoromethylated molecules have attracted wide attention in many fields. With the assistance of DGs, the trifluoromethylation of alkenes can occur in regio- and stereo-selective manner.

In 2013, Loh *et al.* [27] reported the Cu-catalyzed alkenyl trifluoromethylation of acrylamides using Togni-reagent (Scheme 20). Ts-imide group was proved as a suitable directing group via screening of various DGs. Different substituted α-aryl acrylamides and α-alkyl acrylamides are all compatible. Control experiments suggested a SET pathway might be involved in the mechanism. For the reaction mechanism, it is suggested that Cu(I) first exchanges ligand with **1** to afford intermediate **A**, which is then oxidized to Cu(III) species **B** by Togni reagent. An intramolecular single-electron transfer (SET) step forms cationic radical intermediate **C**, which further affords intermediate **D**. The hydrogen-elimination of **D** produces species **E** which gives the product through reductive elimination.

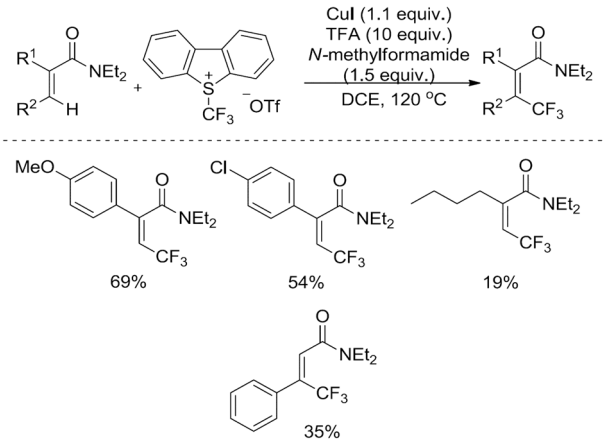
In the same year, a Cu(I)-mediated trifluoromethylation of acrylamides employing Umemoto's reagent was reported by Besset *et al.* [28] (Scheme 21). The reaction with various α-substituted acrylamides afforded the corresponding trifluoromethylation products in moderate to good yields, while the reaction with α-alkyl or α,β-biphenyl substituted acrylamides was in relatively low efficiency.

5 Csp^2–X bond formation through directed vinyl C–H activation

In addition to the C–C bond formation methods described above, C–X bonds construction could also be achieved through the directed vinylic C–H bond activation strategy,



Scheme 20 Cu(I)-mediated trifluoromethylation of acrylamides.



Scheme 21 Cu(I)-mediated olefinic trifluoromethylation of acrylamides with Umemoto's reagent.

which makes the functionalization of various acrylamides, enamides and alkenes more flexible and effective.

Construction of C–O bonds via the oxidation of unactivated sp^2 C–H bonds constitutes one of the fundamental transformations in organic synthesis [29]. Alkoxylation and acetoxylation represent two forms of these C–O construction methods.

As for the acetoxylation reactions, several efficient methods have been developed to introduce acetoxyl group to arenes. Despite these progresses, the acetoxylation of vinyl C–H bonds assisted by directing groups has not been reported. In 2014, Zhang *et al.* [30] developed the Rh-catalyzed *Z*-acetoxylation of enamides with $Cu(OAc)_2{\cdot}H_2O$ serving as both oxidant and source of acetate (Scheme 22). As electron-rich enamides may be hydrolyzed to ketones in the reaction, the acetoxylation efficiency could be improved by removing the water of the solvents with P_2O_5 and employing anhydrous $Cu(OAc)_2$ salts. Pivaloxylated or benzoxylated products could be obtained with the corresponding copper salts. Deuteration experiments suggest that the carbometalation of vinylic C–H bond is reversible, while KIE experiments indicate that the C–H cleavage is not a rate-determining step. In the mechanism, a six-membered rhodacycle **A** is first generated via reversible directing-group-assisted carbometalation and subsequent hydrogen abstraction. The acetate coordinates to Rh to form intermediate **B**, which undergoes reductive elimination to give the final product and release Rh(I) species. Finally, $Cu(OAc)_2$ oxidizes Rh(I) to Rh(III) species to complete the catalytic cycle.

Compared with acetoxylation, phenoxylation, and direct hydroxylation, the alkoxylation is more challenging. Presumably because of the easy transformation of alkanols to aldehydes or ketones and the tendency of β-H elimination of alkoxyl-metal species. Very recently, Song and coworkers [31] developed a cobalt-catalyzed Csp^2–H bond alkoxylation of aromatic and olefinic carboxamides (Scheme

23). In this alkoxylation reaction, various substituted benzamides are well tolerated with $Co(OAc)_2·4H_2O$ being employed as the catalyst. Linear and branched alcohols are also compatible. As for olefinic carboxamides, the reaction is carried out under mild reaction conditions and argon atmosphere. Radical quenchers inhibit the reaction and KIE experiments indicate that C–H bond cleavage is not the rate-determining step. Based on these experiments, it is proposed that oxidative substitution of arenes and alkenes mediated by the SET step is very possible.

As for other functionalization of vinyllic C–H bonds, in 2013, Loh and co-workers [32] reported the Pd-catalyzed pyridinyl group assisted sulfonylation of olefinic C–H bonds (Scheme 24). As organosulfones are also very important intermediates in organic chemistry, this reaction can served as an efficient approach to this type of compounds. In this reaction, various vinyl pyridines and enamides are sulfonylated in moderate to good yields with a series of organosulfonyl chlorides being employed. In the mechanism, a cyclic vinylpalladium species **A** or **B** is proposed to form initially. This vinylpalladium species then reacts with sulfonic chlorides to produce Pd(IV) complex **C** or **D**. Reductive elimination of them gives the products and regenerates the Pd(II) catalyst.

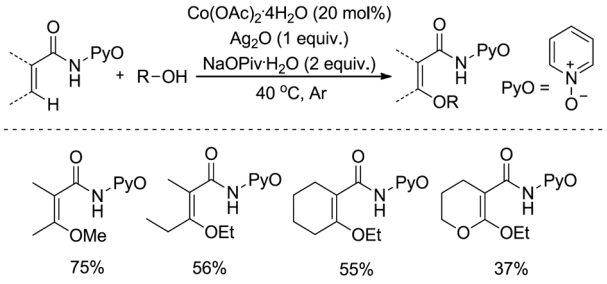
In 2013, Glorius and co-workers [33] reported the Rh-catalyzed halogenation of vinyl C-H bonds of acrylamides using *N*,*N*-diisopropylamide as a directing group (Scheme 25). They found that a series of substituted acrylamides could be iodinated or brominated to produce Z-halo acrylamides by reacting with NIS or NBS. Moreover, the iodination reaction using NIS was more robust to different substituted acrylamides. Robustness screen experiments showed that a variety of synthetically useful functional groups and moieties could be tolerated.

6 Annulation reactions through directed vinyllic C–H bond activation

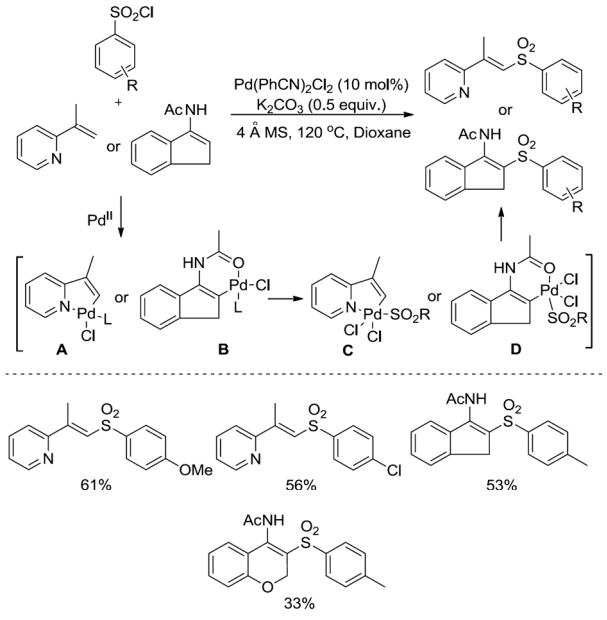
In the above-discussed developments, alkenyl functionalizations are carried out through directed vinylic C–H bond activation, such as olefination, alkynylation, and halogenation [33]. Moreover, when olefin substrates with O or N atom-contained DGs are employed, the annulation reactions with unsaturated coupling partners may occur to afford annulated products. Various useful heterocycle or carbocycles structures, such as pyrones, pyrroles, coumarins and so on, can thus be obtained from this annulation pathway, In view of their applications in pharmaceutical chemistry, material science, and natural products, the synthesis of these cyclic structures via vinylic C–H bond activation/annulation pathway has drawn considerable attentions from chemists.

In 2008, Ellman *et al*. [34] reported the synthesis of dihydropyridines (DHPs) from imines and alkynes via a C–H alkenylation/electrocyclization/aromatization sequence (Scheme 26). A variety of aldimines and ketimines could react with alkynes to afford the DHP products in moderate to good yields when $(DMAPh)PEt_2$ was employed as the ligand. Unsymmetrical alkynes could produce single regioisomers with bulky substituent proximal to the N-atom of DHPs. Furthermore, substituted pyridines are produced through the oxidation of DHPs with subsequent debenzylation.

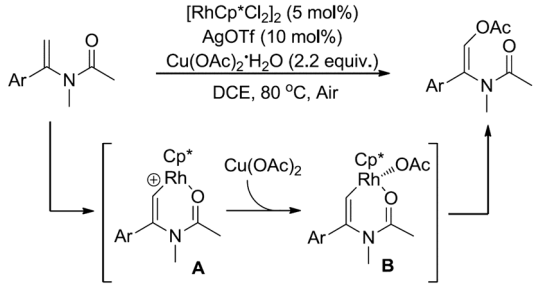
In about the same time, the synthesis of pyridines from



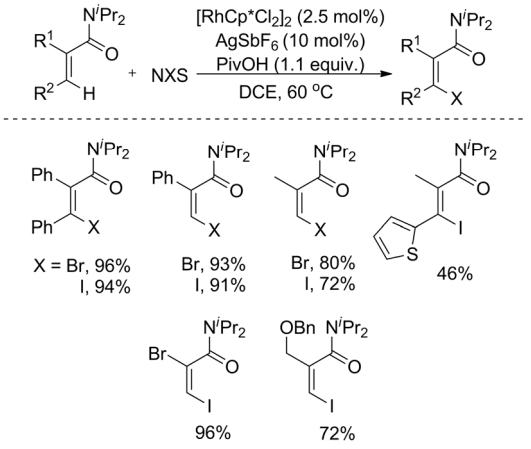
Scheme 23 Co(II)-catalyzed alkoxylation of aromatic and olefinic carboxamides.



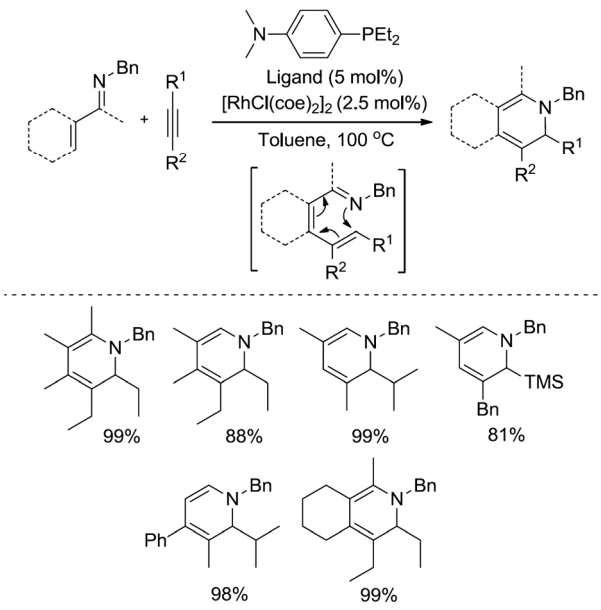
Scheme 24 Pd(II)-catalyzed sulfonylation of alkenyl C–H bonds using organosulfonyl chlorides.



Scheme 22 Rh(III)-catalyzed acetoxylation of vinylic C–H bonds.



Scheme 25 Rh(III)-catalyzed halogenation of vinyl C–H bonds.

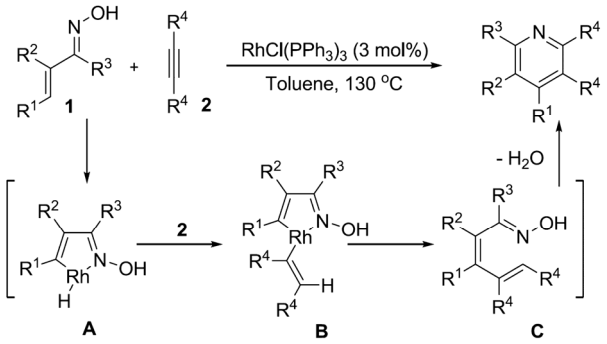


Scheme 26 Rh(III)-catalyzed synthesis of dihydropyridines from imines and alkynes.

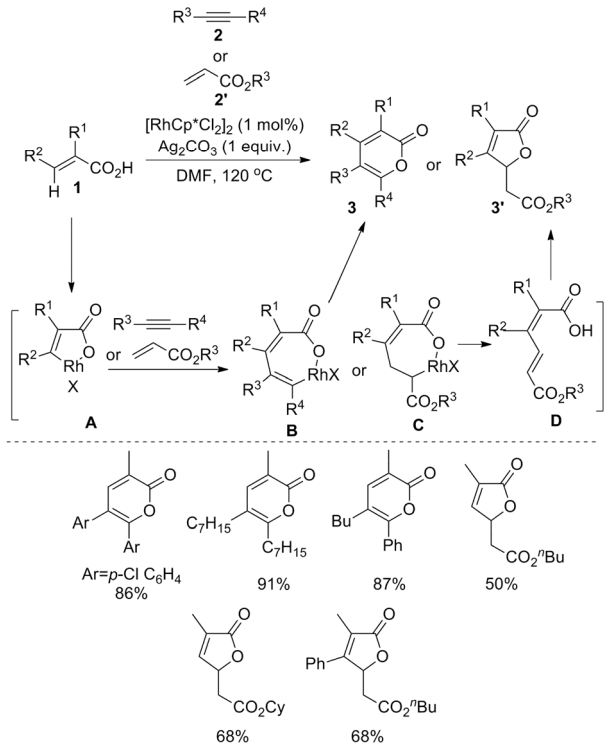
α,β-unsaturated ketoximes with alkynes through the assisted vinylic C–H bond activation under Rh catalysis was developed by Cheng *et al*. [35] (Scheme 27). Various alkyl-substituted α,β-unsaturated ketoximes could react with alkynes to give the corresponding pyridines in moderate to good yields. As for the mechanism, it is proposed that the oxime nitrogen first coordinates to Rh-catalyst to activate the vinylic C–H bonds with a subsequent oxidative insertion. The Rh–H bond then adds to alkynes to afford the species **B**, which undergoes reductive elimination to afford intermediate **C**. The final product **C** is then formed through 6π-electrocyclization and subsequent elimination of water.

In 2009, Miura *et al*. [36] reported the synthesis of α-pyrones and butenolides through the Rh-catalyzed annulation of acrylic acids with internal alkynes and acrylates (Scheme 28). The reaction shows good regioselectivity towards acrylic acids and unsymmetrical alkynes. This annulation is initiated by coordination of carboxyl oxygen to Rh(III) catalyst. The subsequent cyclorhodation at vinylic β-position gives intermediate **A**. The alkyne or alkene inserts to **A** to give the corresponding seven-membered rhodacycle **B** or **C**. The reductive elimination of **B** or β-hydrogen elimination of **C** followed by nucleophilic cyclization affords the α-pyrone or butenolide products.

In 2010, Li and co-workers [37] reported the synthesis of 2-pyridones and iminoesters through the Rh-catalyzed oxidative annulation of acrylamides with alkynes (Scheme 29, Eq. (5)). Various *N*-aryl acrylamides bearing electron-donating or electron-withdrawing groups on the phenyl ring



Scheme 27 Rh(I)-catalyzed synthesis of substituted pyridines from α,β-unsaturated ketoximes and alkynes.

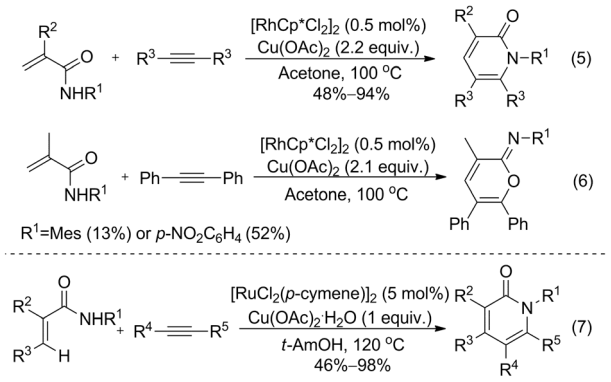


Scheme 28 Rh(III)-catalyzed oxidative coupling of acrylic acids with alkynes and alkenes.

could react with internal alkynes to produce pyridones. Iminoester isomers could also be obtained depending on the steric and electronic properties of the *N*-aryl groups (Scheme 29, Eq. (6)). In 2011, Hofmann *et al*. [38] developed an improved method for the pyridone synthesis under Ru-catalysis in which asymmetric dialkyl-substituted alkynes could be employed, affording the products with high regioselectivity (Scheme 29, Eq. (7)).

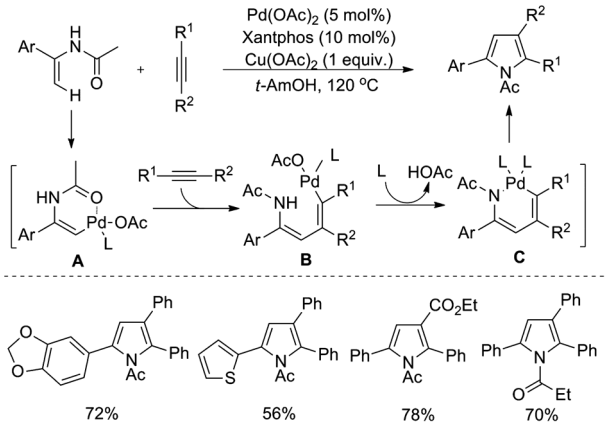
In 2014, Guan *et al*. [39] reported the synthesis of pyrroles through oxidative annulation of enamides with alkynes employing $Pd(OAc)_2$ and Xantphos as the catalyst and ligand, respectively (Scheme 30). The transformation showed high functional group tolerance towards both sides. Moderate yields are obtained when using dialkyl alkynes. The reaction is initiated by alkenyl C–H bond activation to form alkenyl palladium intermediate **A**, which produces species **B** via alkyne insertion. Intermediate **B** undergoes an intramolecular cyclization to generate a palladacycle **C**. Reductive elimination of **C** releases the final product and Pd(0) species, which is oxidized by Cu(II) to activate Pd(II) catalyst to complete the catalytic cycle.

In addition to enamides and acryl acid derivatives, phenols with vinyl moieties could also undergo oxidative annulation to afford O-heterocycle moieties. In 2013, Gulias and co-workers [40] reported the Rh-catalyzed [5+2] cycloadditions of *o*-vinylphenols with alkynes to afford benzoxepines (Scheme 31). Symmetrical diaryl alkynes bearing electron-rich or electron-deficient substituents lead to the annulated products in good yields with high regioselectivity. This reaction also showed good substrate scope towards various substituted vinylphenols. KIE effect suggests that the C–H bond cleavage is involved in the rate-limiting-step. For the mechanism, it is proposed that ligand replacement of the catalyst **A** by substrate **1** affords intermediate **B**. ACMD step or electrophilic attack of alkene to Rh(III) with a subsequent deprotonation produces the rhodacycle **D**. The alkyne then inserts into **D** to give intermediate **E**, which undergoes reductive elimination to afford the product and releases the Rh(I) species, this species could be oxidized to the active Rh(III) catalyst.

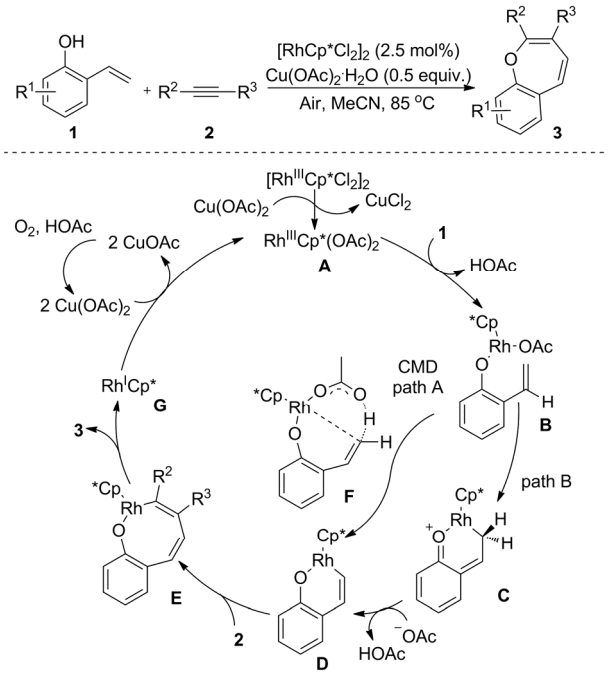


Scheme 29 Rh(III)-catalyzed oxidative coupling of acrylamides with alkynes.

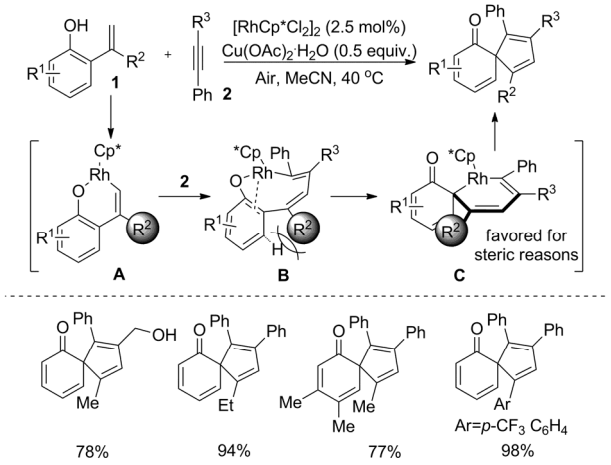
In a continued study, Gulias *et al*. [41a] found that the dearomatizing [3+2] annulation with alkynes could occur when α-substituted *o*-vinylphenols were employed (Scheme 32). This transformation shows high regioselectivity for unsymmetrical alkynes. Substituents at the α-position of the alkene motif are necessary for this annulation. The same eight-membered-cyclorhodacycle **B** produced by alkyne insertion is also involved. The substituent in the alkene moiety creates a steric clash to generate a more favored rhodacycle **C**, which undergoes reductive elimination to afford spirocyclic products. At the same time, a similar reaction has been reported by Lam *et al.* [41b], in which the conjugated enynes could also be excellent substrates for the annulation.



Scheme 30 Pd(II)-catalyzed oxidative coupling of enamides with alkynes.



Scheme 31 Rh(III)-catalyzed synthesis of benzoxepines from 2-vinylphenols.

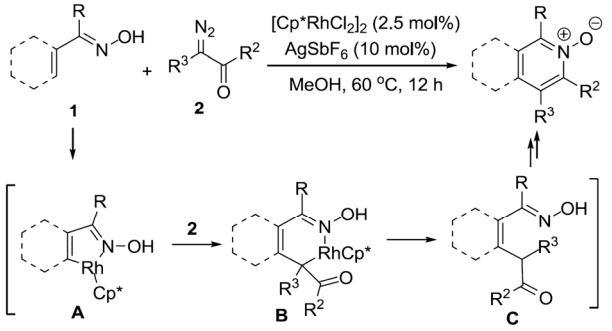


Scheme 32 Rh(III)-catalyzed dearomatizing annulation of 2-vinylphenols and alkynes.

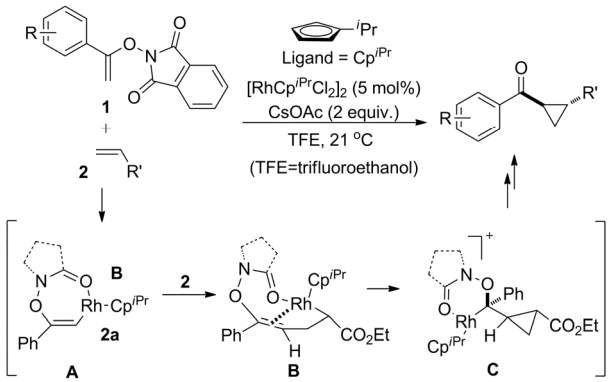
Diazo compounds are also employed as the substrates for the incorporation into the annulation reactions [42]. In 2013, Glorius *et al*. [43] reported the synthesis of multi-substituted isoquinoline and pyridine *N*-oxides from oximes and diazo compounds via sp^2 C–H bond activation of aryl and vinyl C–H bonds (Scheme 33). Reactions with various α,β-unsaturated oximes gave the corresponding pyridine *N*-oxides in good to excellent yields. This intermolecular annulation is initiated by C–H bond cleavage to give species **A**. The migratory insertion of diazo compound and protonolysis affords the intermediate **C**. After that, the tautomerization of **C** with the subsequent 6π-electrocyclization and elimination of water could afford the final products.

In 2014, Rovis *et al*. [44] developed an Rh-catalyzed [2+1] annulation of *N*-enoxyphthalimide with acrylates to produce cyclopropane compounds (Scheme 34). The authors reasoned that the seven-membered rhodacycle **A** could act as one-carbon component. The isopropylcyclopentadienyl ligand has been found to give the products in high *trans*-selectivity and reactivity via ligands tuning. In the mechanism, it is proposed that an irreversible vinyllic C–H bond activation first gives rhodacycle **A**. Then alkene inserts into **A** to form Rh species **B**, which undergoes intramolecular carborhodation in a 3-*exo*-*trig* form to generate intermediate **C**. Subsequently, a sequence of β-H elimination and other steps follow to give the final products.

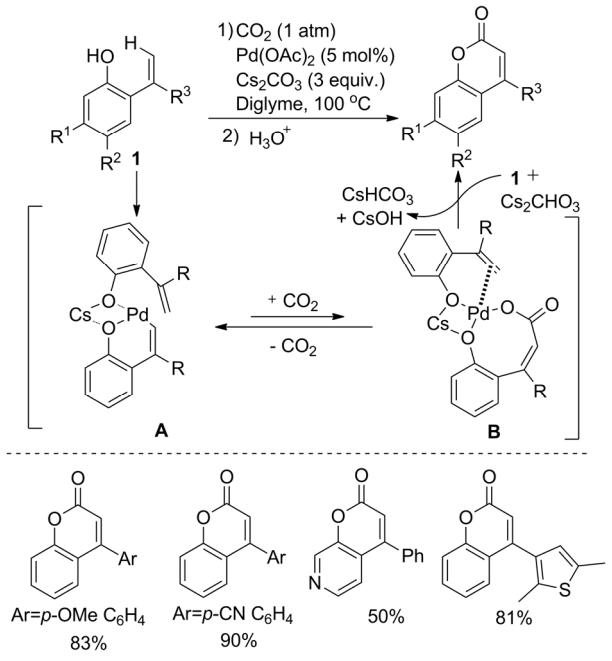
Besides the annulation of olefins with alkynes or alkenes that produces carbocycle and heterocycle compounds, the gaseous substrates CO, CO_2 is also incorporated to afford the cyclic α,β-unsaturated carbonyl compounds. In 2013, Iwasawa *et al*. [45] reported the synthesis of coumarins by incorporating CO_2 as the carboxyl source (Scheme 35). α-Aryl-2-hydroxystyrene reacts with CO_2 under Pd catalysis to give coumarins with various substituents on the phenyl ring. Mechanistic experiments suggest the equilibrium between the vinylpalladium species **A** and the carboxylation



Scheme 33 Rh(III)-catalyzed vinyl C–H activation of oximes with diazo compounds.



Scheme 34 Rh(III)-catalyzed cyclopropanation of *N*-enoxyphthalimides with alkenes via [2+1] annulation.



Scheme 35 Pd-catalyzed direct carboxylation of 2-vinylphenols with CO_2.

intermediate **B**, in which **A** is more favored. In the reaction

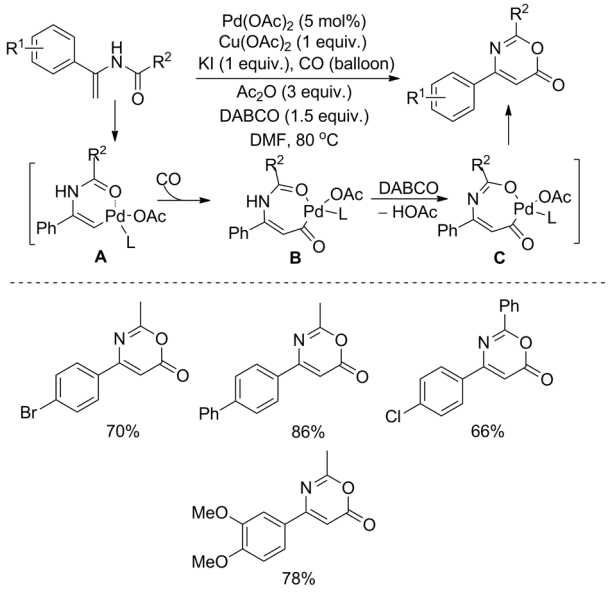
mechanism, the six-membered vinylpalladium intermediate **A** is formed through olefinic C–H bond activation which undergoes reversible carboxylation to produce carboxylated intermediate **B**. Species **B** reacts with another substrate and the base to afford the coumarin product and regenerates the active species **A**.

In 2013, Guan *et al*. [46] reported the synthesis of 1,3-oxazin-6-ones via Pd-catalyzed oxidative carbonylation of enamides (Scheme 36). This annulation reaction requires KI for the improvement of the efficiency. The electronic nature of the substituents on the aryl ring has little influence on the efficiency of the annulation reaction. *N*-propionyl and *N*-benzoyl amide directing groups are also compatible with the reaction. For the mechanism, it is proposed that upon the formation of vinylpalladium species **A**, CO inserts into **A** to afford acylpalladium intermediate **B**. Then **B** transforms to intermediate **C** with the assistance of base. Subsequent reductive elimination of **C** affords the product and Pd(0), which is oxidized by Cu(II) to complete the catalytic cycle.

7 Conclusions

Among the various C–H bond activation methods, the directing-group-assisted strategy enables the site-selective functionalization of the C–H bonds. These directing groups act as chelators to transition-metal-catalysts to enhance the reactivity at a proximal C–H site. Compared to the great achievements of directed aryl C–H bond activation, activation of vinylic C–H bond is rather challenging, which is due to the increased reactivity of the alkenes in the presence of the directing groups.

Despite these potential challenges, vinylic C–H bond activation has achieved significant progress in recent years. A variety of C–C bonds and C–X bonds can be constructed through the directed vinylic C–H bond functionalization strategy. In particular, various highly unsaturated and annulated moieties such as enynes, dienes, polyenes, pyrroles and coumarins, which are found as the key structures in numerous bioactive compounds, organic materials and natural products, can be accessed effectively via the assisted vinylic C–H bond activation. Although significant progresses have been made in this area, the development of efficient transformations for olefin functionalization is still in its infancy, and further progress will be expected in this fascinating field.



Scheme 36 Pd(II)-catalyzed oxidative carbonylation of the alkenyl C–H bonds of enamides.

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