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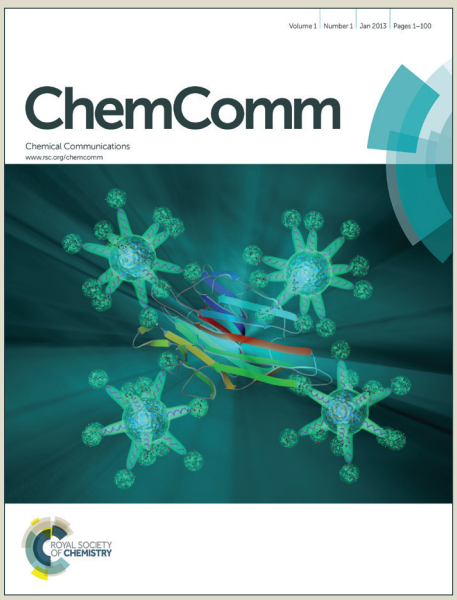

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FEATURE ARTICLE

C-H Bond Functionalization Based on Metal Carbene Migratory Insertion

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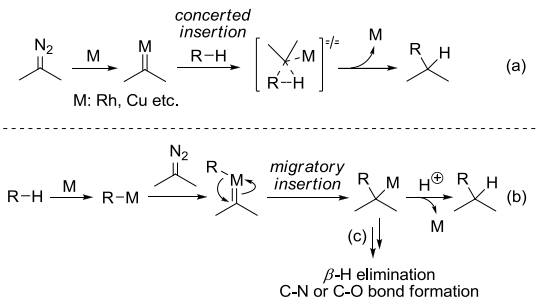
Abstract. Cross-coupling reactions involving metal carbene migratory insertion have been established as a new type of coupling reactions with diazo compounds as the reaction partners. Since 2011, an inspiring evolvement has been made in that the carbene migratory insertion process is successfully merged into C-H bond activations. Along this line, a series of investigations have been documented in the past few years. This feature article summarizes the developments in this area.

1. Introduction

Metal carbenes represent useful and versatile intermediates in modern organic synthesis.[1] In particular, these species play vital role in transition-metal-catalyzed carbene transfer reactions, in which diazo compounds are usually served as the carbene precursors.[2] In the presence of transition metal catalysts, diazo compounds generate metal carbene species with extrusion of N_2. The metal carbene intermediate thus generated undergoes diverse transformations, such as X-H insertions, cyclopropanations, ylide formations, 1,2-shifts and other reactions.[2] In contrary to these traditional reactions of metal carbenes, a new type of metal carbene transformations which involves cross-coupling process with diazo compounds as the coupling partners has emerged recently.[3] Compared to the classic reactions, this type of cross-coupling reactions is characterized by carbene migratory insertion process in the carbon carbon bond forming step. These transformations provide a new methodology for the construction of C-C or C-X bonds.[3,4]

On the other hand, transition-metal-catalyzed C-H bond activations have been one of the attractive research topics in the last several years.[5] Various cross-coupling partners, such as alkenes, alkynes, and allenes have been extensively investigated in the transition-metal-catalyzed C-H bond activations. Although significant progress has been achieved in this field, the development of new substrates which can be used as the cross-coupling partners in C-H bond activation is still highly desirable. In this context, it is conceivable that diazo compounds may be utilized as the cross-coupling partners in C-H bond activation. Notably, carbene insertion into C-H bond represents one of the classic metal carbene transformations.[6] In the case of classic sp^3 C-H bond insertion, the reaction follows a concerted mechanism, while for the aromatic sp^2 C-H insertion the mechanism is considered as electrophilic substitution. In both cases, electron-rich C-H bonds react preferentially (Scheme 1, a). On the contrast, the C-H bond activation involving metal carbene migratory insertion follows a different reaction mechanism, in which the C-H bond metalation is the initial step. In these cases, the electron-deficient C-H bonds usually react preferentially. Thus, this type of formal C-H bond insertions is complementary to the classic electrophilic sp^2 C-H insertion process (Scheme 1, b). Moreover, the organometallic species generated from metal carbene migratory insertion may undergo other reaction pathways, such as β-H elimination and C-N or C-O bond forming reactions (Scheme 1, c). This feature article summarizes the recent developments in this area.

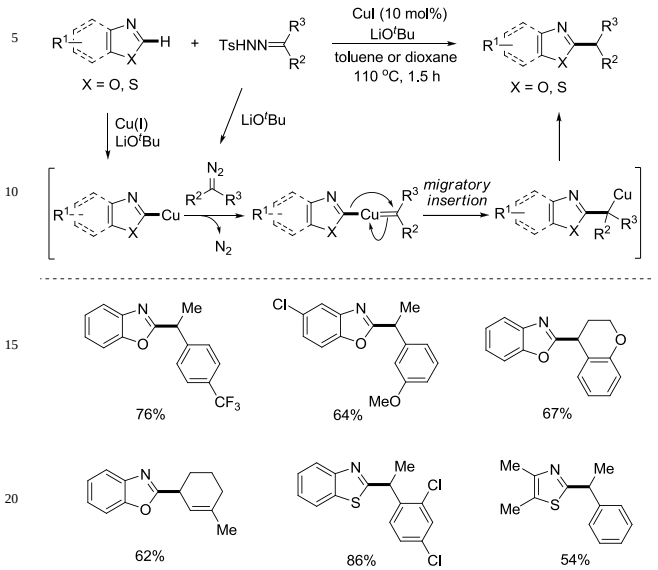


Scheme 1 Classic C-H bond insertion of metal carbene (a) *vs* C-H bond activation based on metal carbene migratory insertion (b, c)

2. The reactions terminated by protonation

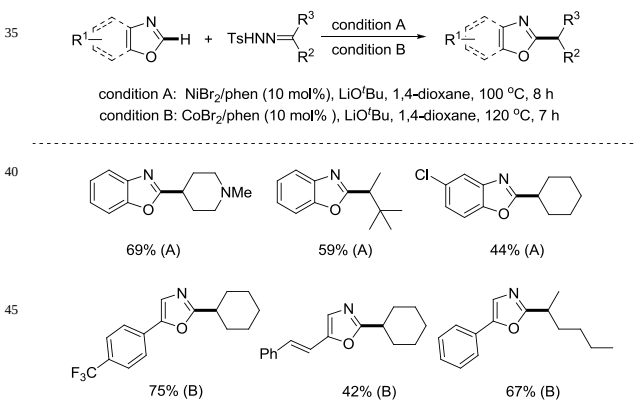
The early example which realizes C-H bond functionalization through carbene migratory insertion process is dated back to 2011. Wang and co-workers reported a copper catalyzed C-H bond functionalization of 1,3-azoles with *N*-tosylhydrazones (Scheme 2).[7] It has been well known that diazo compounds can be produced *in situ* from *N*-tosylhydrazones under basic conditions.[8] This C-H bond functionalization reaction provides a useful and convenient method for benzylation or allylation of 1,3-azoles, which is difficult to achieved through other transition-metal-catalyzed C-H bond activation methods. However, this reaction is

only limited to 1,3-oxazoles or 1,3-thiazoles. Control experiments indicate that direct carbene C-H insertion is not a likely mechanism.



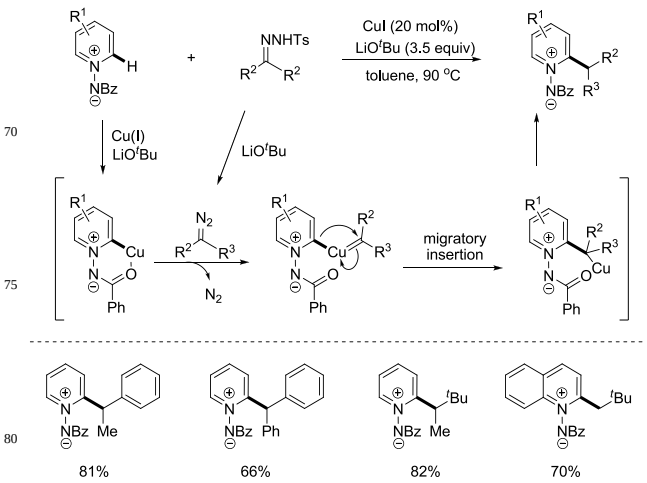
Scheme 2 Cu(I)-catalyzed direct benzylation or allylation of 1,3-azoles with *N*-tosylhydrazones.

Nickel and cobalt complex are also competent catalysts to promote this transformation. In 2012, Hirano and Miura reported a similar C-H functionalization of 1,3-azole with *N*-tosylhydrazones derived from alkyl ketones (Scheme 3).[9] These reactions are characterized by their compatible with various unactivated secondary alkyl groups which are not efficiently accessed by the copper-catalyzed procedure shown in Scheme 2.



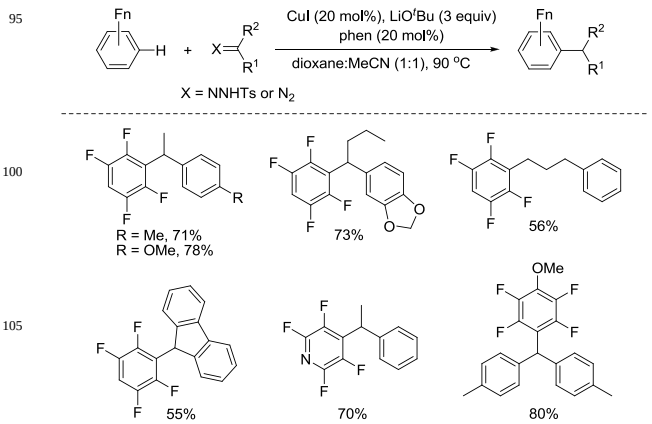
Scheme 3 Nickel- and cobalt-catalyzed direct C-H alkylation of 1,3-azoles with *N*-tosylhydrazones

Subsequently, Wang and co-workers developed a C-H bond functionalization reaction of *N*-iminopyridinium ylides with *N*-tosylhydrazones (Scheme 4).[10] This reaction is initiated by direct C-H bond activation to generate a Cu(I) pyridinium ylide intermediate, which undergoes copper carbene formation, migratory insertion and protonation to afford the final products with good to excellent yields. The *N*-iminobenzoyl (NBz) moiety served as directing group which controlled the regioselectivity. Computational study was carried out in order to gain insights into the reaction mechanism, in particular the migratory insertion step. The DFT calculation confirms the Cu carbene formation and the subsequent migratory insertion. The latter overcomes an energy barrier of 12.5 kcal/mol.



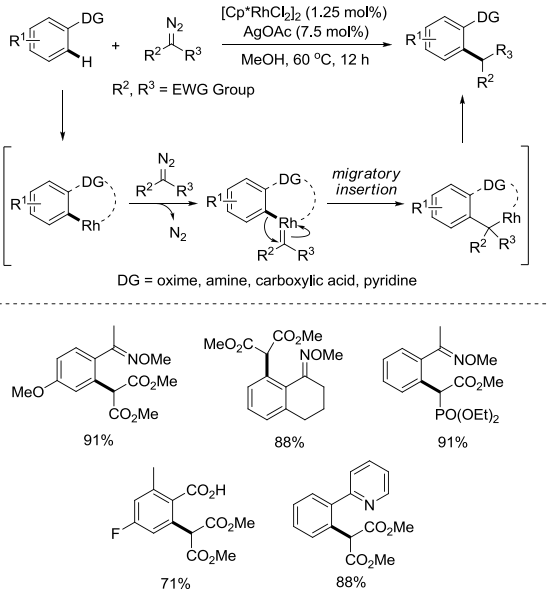
Scheme 4 Cu(I)-catalyzed direct *ortho*-alkylation of *N*-iminopyridinium ylides with *N*-tosylhydrazones.

More recently, the similar Cu(I)-catalyzed C-H bond functionalization approach has been applied to alkylation of polyfluoroarenes (Scheme 5).[11] Polyfluoroarenes are a representative class of F-containing molecules that have found wide applications in various fields. The alkylation of polyfluoroarenes through direct C-H bond functionalization remains a challenging problem. The Cu(I)-carbene based approach provides a unique solution to this problem.



Scheme 5 Cu(I)-catalyzed direct C-H bond alkylation of polyfluoroarenes

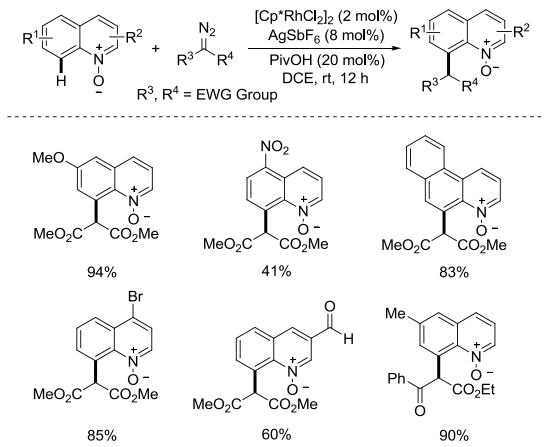
It is worth mentioning that the reactions shown above are all limited to hetero aromatic substrates. As for the C-H activation of more general aromatic substrates, directing group strategy is a common practice to enhance both reactivity and regioselectivity. In 2012 Yu and co-workers developed the first directing group assistant Rh(III)-catalyzed C-H bond activation with diazomalonates (Scheme 6).[12,13]



Scheme 6 Rh(III)-catalyzed functionalization of aromatic C-H bonds by *α*-diazomalonates.

This reaction has been successfully expanded to non-heterocyclic aromatic substrates. The mechanism is proposed to involve rhodacyclic intermediate formed through electrophilic C-H bond cleavage. Then coordination with diazo compounds followed by N_2 extrusion generates a Rh(III)-carbene species, which undergoes migratory insertion and protonation, leading to the final product. However, an alternative pathway, which proceeds through intramolecular 1,2-aryl shift with simultaneous N_2 extrusion, cannot be strictly ruled out. In this pathway, Rh(III) carbene is not involved as intermediate. Subsequently, Li and Wan expanded this reaction by exploiting pyrazole, pydimidine, and pyridine as the directing groups.[14]

Very recently, Chang and co-workers demonstrated the application of this carbene chemistry in direct C-H bond functionalization of quinoline *N*-oxides (Scheme 7).[15] This reaction achieved regioselective C-H bond functionalization of quinoline *N*-oxides at room temperatures. A wide range of

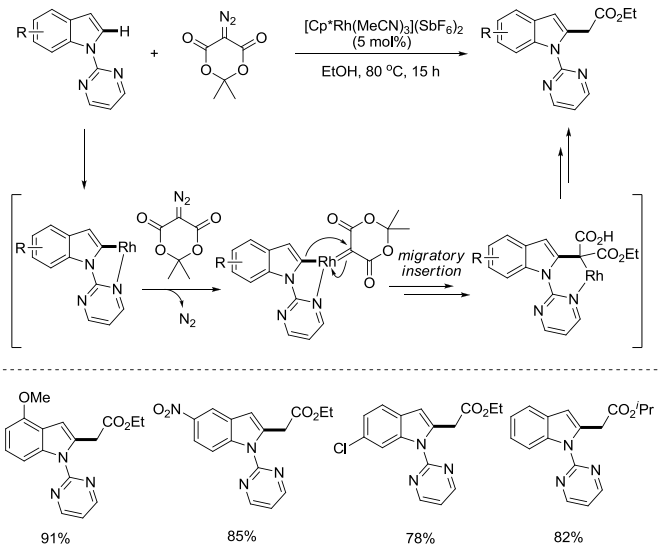


Scheme 7 Rh(III)-catalyzed C-H activation of quinoline *N*-oxides with diazomalonates.

substrates are tolerated and the final product can be further functionalized with installed *N*-oxides directing groups.

In the reaction mechanism, the five-membered rhodacycle intermediate, which is generated through C-H bond cleavage, reacts with diazo substrates to give Rh(III)-carbene intermediate. Similar migratory insertion occurs, followed by final protonation process to give the desired product. Kinetic isotope effect experiment is conducted to afford a k_H/k_D value of 5.0, which indicates that the C-H bond cleavage may be involved in the rate-limiting step.

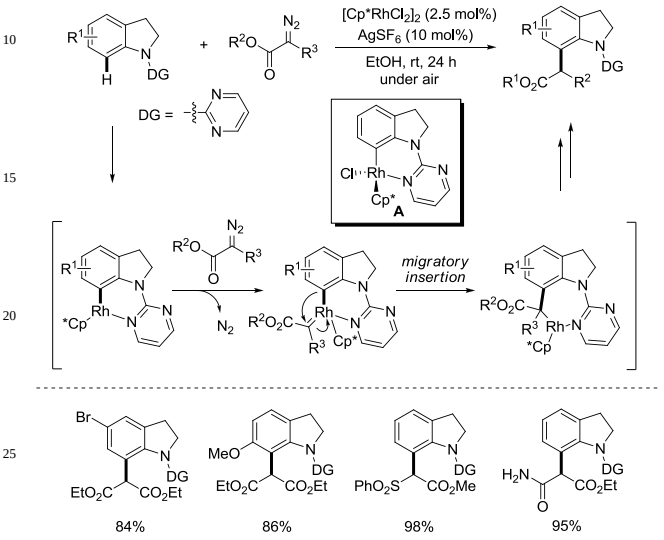
Another C-H bond activation based on carbene migratory insertion has been reported by Yi, Xu and co-workers (Scheme 8).[16] They selected *α*-diazotized Meldrum's acid as carbene source and achieved C2–H functionalization of indoles. This reaction is characterized by its decarboxylation process upon completion of carbene migratory insertion. Notably, alcohol plays a crucial role in this transformation. Under $[Cp^*Rh(MeCN)_3](SbF_6)_2$/EtOH catalytic system, a wide range of 2-acetate substituted indoles was obtained in good to excellent yields. The competition experiments between electronically different indoles shows that electron-rich indoles are more favored than the electron-deficient ones, indicating that the C-H bond activation undergoes an electrophilic metalation process. Moreover, the 2-acetate indoles can be further alkenylated at the C7-position with Rh(III)/Cu(II) catalytic system.



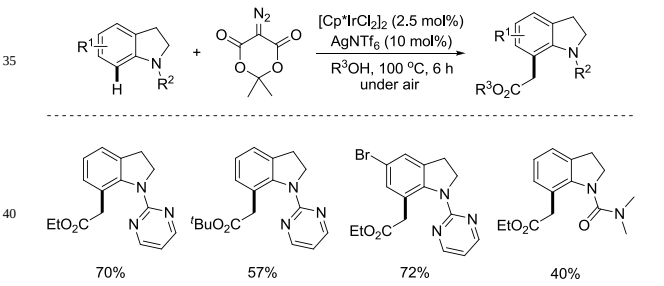
Scheme 8 Rh(III)-catalyzed C2-selective carbene functionalization of indoles.

By installing pyrimidyl as the directing group, indoles are successfully functionalized at C2-position with carbene insertion. More recently, Yang, Zhou and co-workers reported Rh(III)- and Ir(III)-catalyzed C7 alkylation of indolines with diazo compounds employing the same directing group (Scheme 9 and Scheme 10).[17] The reaction can be performed under mild reaction conditions and various indolines are compatible in this transformation. Interestingly, 7-acetate substituted indolines can be produced in moderate to good yields when an Ir(III) catalyst is employed. The diazo derivatives of Meldrum's acid are used in the iridium catalyst system. In addition to indolines, carbazoles are also found to be suitable substrates for the reaction. Mono-

and bis-functionalized products can be selectively obtained by changing the equivalents of the diazo substrates. To shed light into the reaction mechanism, a stable cyclometalated Rh(III) complex **A** was isolated and it was characterized by X-ray crystallography. This complex was found to catalyze the reaction to deliver the expected products. Thus, this complex is likely involved as an active species in the catalytic cycle.

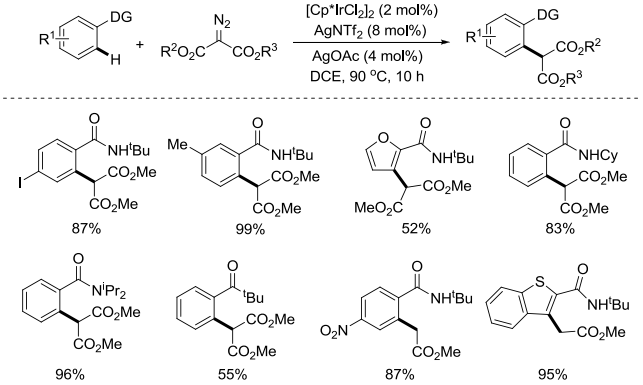


Scheme 9 Rh(III)-catalyzed C7 alkylation of indolines with diazo compounds



Scheme 10 Ir(III)-catalyzed C7 alkylation of indolines with diazo derivative of Meldrum's acid.

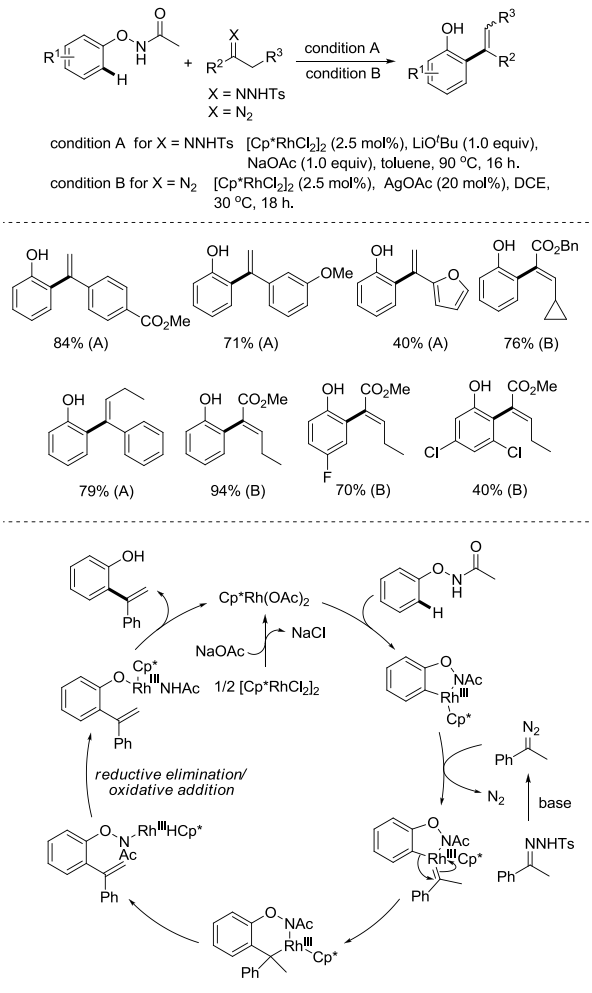
In addition to rhodium catalyst, other transition metals are also explored in this area. Recently, Wang and co-workers reported a versatile aromatic C-H bond functionalization *via* Ir(III) catalysts (Scheme 11).[18] A wide variety of substrates are submitted to this transformation, affording the desired products in good to excellent yields. It is worth mentioning that mono- and bis-functionalized products can be selectively accessed by simply changing the equivalents of the diazo substrates. Besides, decarboxylation occurs accompanied with the C-H bond functionalization when mono-*tert*-butyl diazomalonate or di-*tert*-butyl diazomalonate are employed as the substrates. Mechanistic studies have revealed that the reaction is favored for electro-donating substrates, indicating that the electrophilic metalation may be involved in the catalytic cycle. The KIE data have suggested that the cleavage of the C−H bond is not involved in the rate-limiting step but most likely occur before the cleavage of C-H bond.



Scheme 11 Ir(III)-catalyzed aromatic C-H bond functionalization with diazomalonates.

3. The reactions terminated by *β*-H elimination

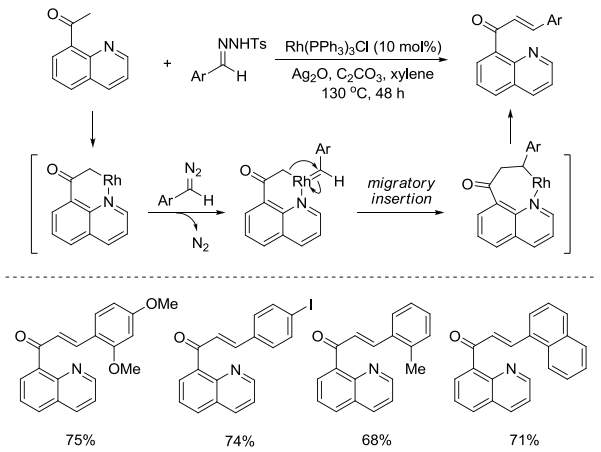
For all the reactions described above, the catalytic cycles are terminated by direct protonation of cyclic rhodium intermediates. In contrast to these reactions, Wang and co-workers recently



Scheme 12 Rh(III)-catalyzed C-H activation of *N*-phenoxyacetamides with *N*-tosylhydrazones or diazoesters.

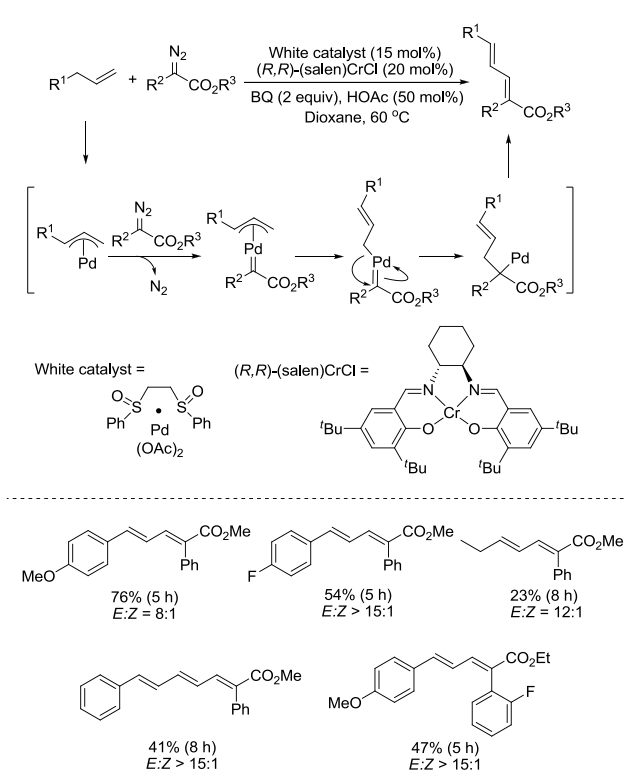
reported a Rh(III)-catalyzed C-H activation of *N*-phenoxyacetamides with *N*-tosylhydrazones or diazoesters intermediate undergoes *β*-hydride elimination, reductive elimination and oxidation of the resultant Rh(I) to Rh(III) (Scheme 12).[19] This transformation is characterized by the utilization of oxidizing *N*-oxyacetamide as the directing group, which contains an N-O bond.[20] Under the optimized reaction conditions, the diazo compounds which either directly used or generated *in situ* from *N*-tosylhydrazones are employed as the coupling partners, affording the *ortho*-alkenyl phenols in good to excellent yields and with excellent stereoselectivity. Notably, the *ortho*-alkenyl phenols are not easily accessed with other methods. The reaction mechanism follows similar pathway as described above, except that upon the completion of migratory insertion, *β*-hydride elimination, reductive elimination and oxidation to generate active Rh(III)-catalyst are followed, instead of direct protonation as shown above.

In contrast to Rh(III) complexes that have been proved as efficient catalysts in this area, Rh(I) catalyst is also evaluated recently (Scheme 13). Wang and co-workers reported a Rh(I)-catalyzed C-H bond functionalization of (quinolin-8-yl)methanone with *N*-tosylhydrazones.[21] The mechanism of this reaction involves C-H bond cleavage to generate cyclic Rh(I) species, formation of Rh(I) carbene intermediate, and carbene migratory insertion to afford a seven-membered rhodacycle complex. This intermediate undergoes *β*-hydride elimination to release the product and simultaneously to regenerate the active catalyst with the aid of Ag_2O. Although a variety of *N*-tosylhydrazones are applicable in this reaction, the other reaction component is only limited to (quinolin-8-yl)methanone, which hampers the further application of this transformation. Nevertheless, this reaction represents a rare case of C(sp^3)-H bond activation in this area.



Scheme 13 Rh(I)-catalyzed C-H bond activation of (quinolin-8-yl)methanone with *N*-tosylhydrazones.

Palladium complexes represent other powerful catalysts for the C-H bond activation, which has also been explored in the C-H bond functionalization with diazo compounds. Gong and co-workers have integrated allylic C-H bond activation with carbene migratory insertion with palladium catalyst (Scheme 14).[22] The Pd-catalyzed allylic C-H bond functionalization with diazoesters gave conjugated polyene derivatives in moderate to good yields with excellent stereoselectivities. In the reaction mechanism, *π*-allylic palladium intermediate, which is formed through C-H bond activation, reacts with diazoesters to give allyl palladium carbene intermediate. With migratory insertion process and the subsequent *β*-H elimination, the final product is generated and the corresponding palladium(0) is released. It is worth mentioning that (salen)CrCl plays crucial role in this reaction, which is proposed as a Lewis acid to assist the formation of *π*-allylic palladium carbene.



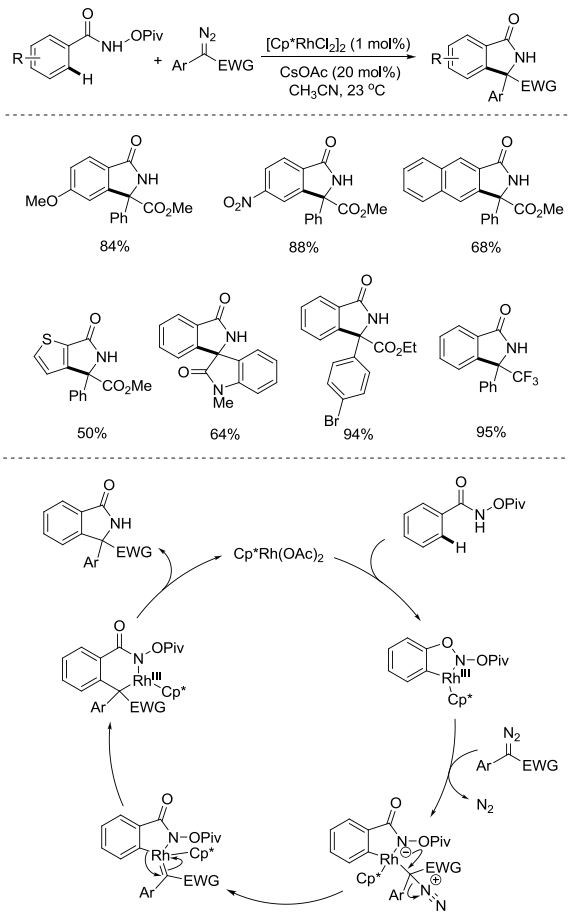
Scheme 14 Allylic C−H bond activation with diazoesters synergistically catalyzed by palladium/Lewis acid.

4. The reactions terminated by C-N bond formation

From the reactions described above, the catalytic cycle is terminated by either protonation or *β*-hydride elimination to afford the final products. However, the organometallic intermediate generated from migratory insertion process may undergo alternative process such as C-N bond formations instead of protonation or *β*-hydride elimination.

In 2013, the Rovis group reported a Rh(III)-catalyzed C-H activation of *N*-methoxybenzamides with donor/acceptor diazo compounds (Scheme 15).[23] The reaction provides a new access to isoindolones bearing a quaternary carbon center in high yields. A broad range of benzhydroxamicacids and diazo compounds including substituted 1-aryl-2,2,2-trifluorodiazoethanes are tolerated in this reaction. The reaction mechanism is similar to those previously described, except for the reductive elimination step for the final product formation. It should be noted that N-O bond in amide acts as internal oxidant, which obviates the use of external oxidant. This is similar to the reaction described in Scheme 11. In mechanistic studies, the competition experiments between electronically differentiated amides suggest that the C-H activation favors more acidic C-H bonds. Another competition experiment between diazo compounds indicates that electron-

deficient substrate is superior to electron-rich one for this reaction, which suggests that migratory insertion step favors more electron-deficient diazo compounds due to their increased electrophilicity. The KIE studies indicate that the reaction may follow a concerted metalation deprotonation (CMD) mechanism. Additionally, the deuterium experiment suggests that C-H bond activation is largely irreversible on the time scale of the reaction.

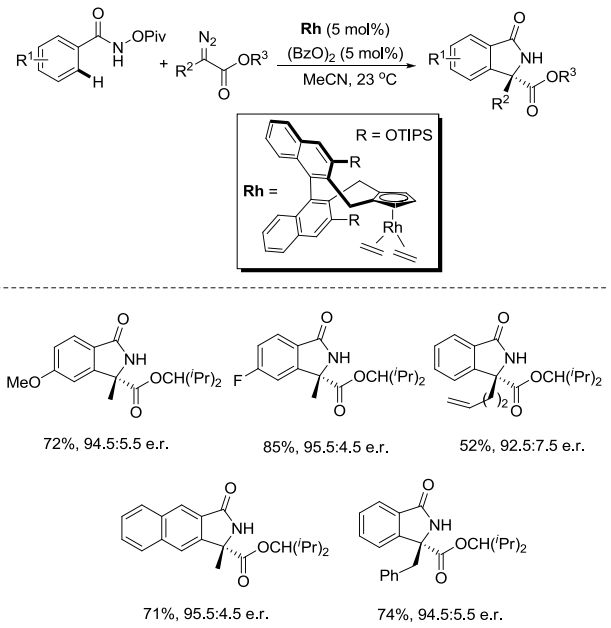


Scheme 15 Rh(III)-catalyzed C-H bond activation of benzamides with donor/acceptor diazo compounds.

The asymmetric version of this type of transformations has been developed by Cramer's group (Scheme 16).[24] A C_2-symmetric disubstituted Cp ligand with a chiral backbone is introduced to enable the asymmetric induction in the synthesis of isoindolones. Notably, the size of two substituents on the diazo carbon has significant effect on the enantioselectivity. Increase the sizes of the substituents afford improved enantioselectivity. Additionally, weak alkyl donor-acceptor diazo derivatives are superior to aryl ones in selectivity.

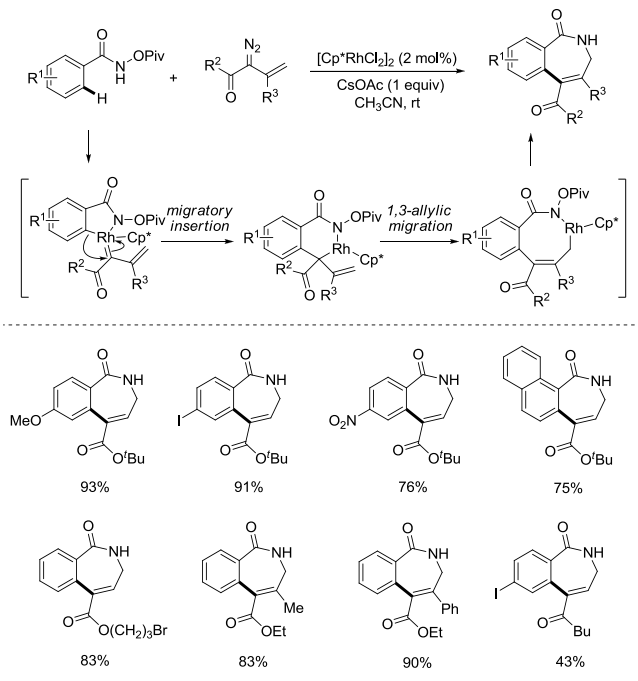
More recently, the Yu group reported a similar reaction of *N*-alkoxybenzamides with *α*-diazoesters.[25] In the study, the rhodacyclic complex is isolated and characterized by X-ray crystallography, which provides a direct proof that C-H/N-H cyclometallation is a key step in the catalytic cycle.

Following the Rovis's seminal work,[23] Cui and co-workers employed vinylcarbenoids as three-carbon components in Rh(III)-catalyzed C-H bond activations (Scheme 17).[26] This reaction is effective with a variety of *N*-alkoxybenzamides and vinylcarbenoids, giving azepinones in high yields. The mechanism of this reaction is proposed to involve C-H activation,



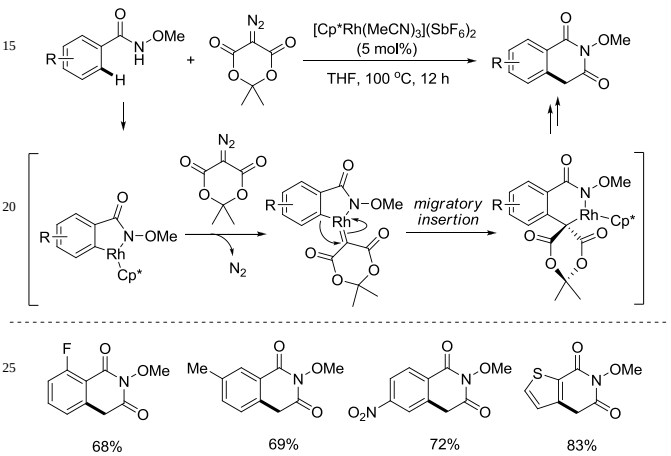
Scheme 16 Asymmetric synthesis of isoindolones by chiral cyclopentadienyl-Rh(III)-catalyzed C-H functionalizations.

rhodium carbene formation, and migratory insertion. In contrary to Rovis's work, the six-membered rhodacycle intermediate undergoes 1,3-allylic migration before the reductive elimination step. Thus, the vinylcarbenoids are served as three-carbon coupling partners. More recently, the same group expanded this C-H bond activation to the indoles and pyrroles using the same directing group.[27] The alkynes, alkenes and diazo compounds are smoothly coupled in the reaction and delivered a variety of five- and six-membered fused heterocycles.



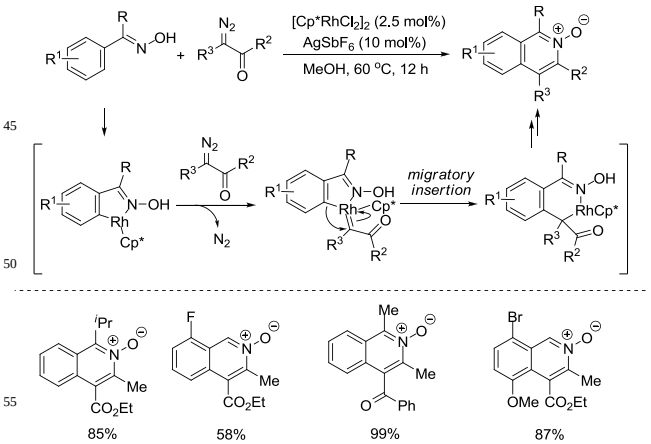
Scheme 17 Rh(III)-catalyzed C-H bond activation of benzamides with vinylcarbenoids.

Another report of carbene insertion C–H activation/cyclization was demonstrated by Yi, Xu and co-workers. They developed the one-pot synthesis of *N*-methoxyisoquinolinediones with the *N*-methoxybenzamides and *α*-diazotized Meldrum's acid as the substrates *via* Rh(III)-catalysis (Scheme 18).[28] The formation of *N*-methoxyisoquinolinediones is also explained by a pathway of C-H activation/metal carbene formation/migratory insertion. Upon protonation, a rhodium-bonded intermediate is formed. The subsequent addition/elimination/decarboxylation processes give the final product with the release of active Rh(III) catalyst. It should be mentioned that the C-N bond formation is from a cascade process in this and the following examples, which differs from the above-mentioned C-N reductive elimination process.



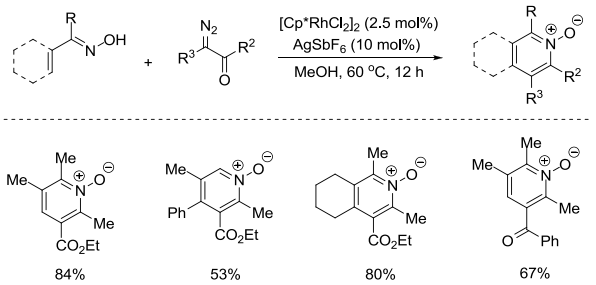
Scheme 18 Rh(III)-catalyzed C–H bond activation/carbene insertion/cyclization for the synthesis of *N*-methoxyisoquinolinediones.

As *N*-methoxybenzamides are extensively explored in C-H bond activations based on carbene migratory insertion, Glorius and co-workers reported the synthesis of *multi*-substituted isoquinoline *N*-oxides from aromatic oximes and diazo compounds through C-H bond activation (Scheme 19).[29] This reaction proceeds smoothly under relatively mild reaction conditions, and the KIE experiment implies C−H activation may be involved in the rate-limiting step.



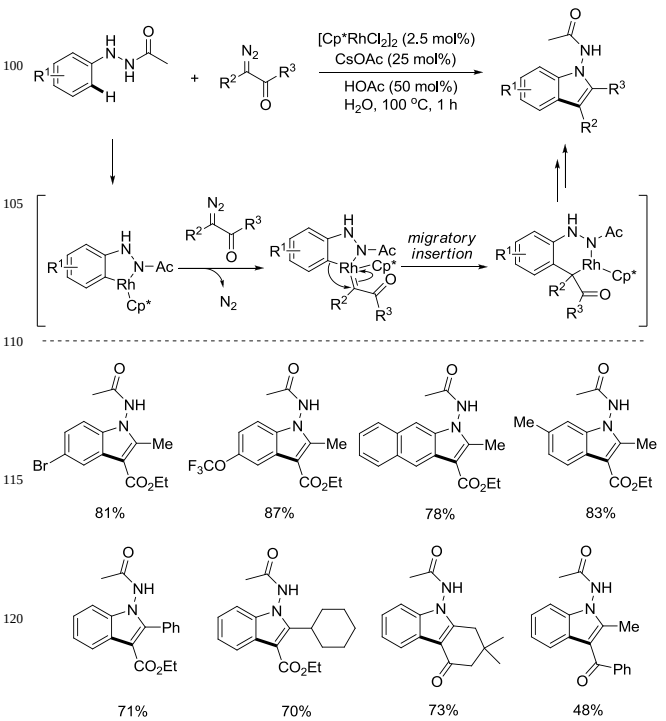
Scheme 19 Rh(III)-catalyzed synthesis of *multi*-substituted isoquinoline *N*−oxides from oximes and diazo compounds.

Not only isoquinoline *N*-oxides could be accessed by this method, but also pyridine *N*-oxides could be produced in good to excellent yields. When aromatic oximes are replaced by *α, β*-unsaturated oximes, the reaction works smoothly under standard reaction conditions (Scheme 20).[29] Compared to the previous report, this is the first example which covers vinyl C(sp^2)-H activation. For the synthetic application, *N*-oxides are important and useful building blocks since they can be easily converted into pyridine- or isoquinoline-containing compounds.



Scheme 20 Rh(III)-catalyzed vinyl C-H activation of oximes with diazo compounds for the synthesis of pyridine *N*−oxides.

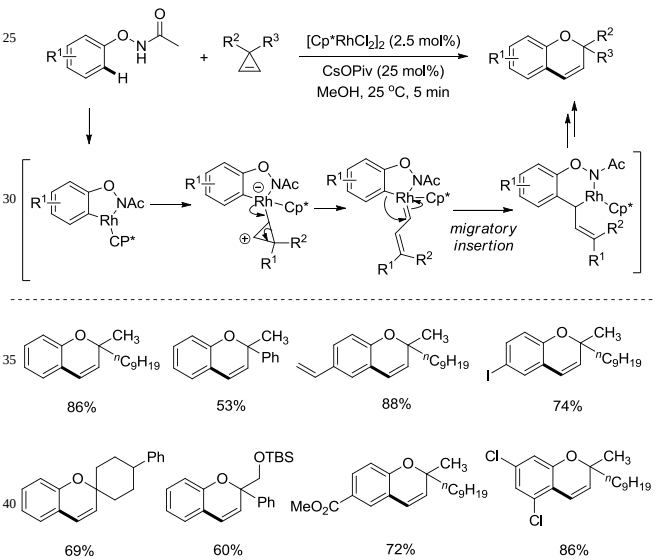
Another Rh(III)-catalyzed C-H activation with diazo compounds has been recently reported by Wang and co-workers (Scheme 21).[30] With 2-acetyl-1-arylhydrazines and diazo compounds as substrates, this coupling reaction provides a direct approach for the synthesis of 1-aminoindole derivatives. Various substrates with different substituents are tolerated in this intermolecular annulation. This transformation is also characterized by the use of water as solvent. This coupling reaction may follow a similar reaction pathway as the above mentioned work from Glorius's group.[29] In mechanistic studies, the KIE experiment data suggest that C-H bond cleavage is involved in the rate-determining step. Notably, the acetyl group in the product can be easily deprotected under acidic conditions, which is advantageous for the further application of the products.



Scheme 21 Rh(III)-catalyzed synthesis of 1-aminoindole derivatives from 2-acetyl-1-arylhydrazines and diazo compounds.

5. The reaction with cyclopropenes as the carbene precursors

Apart from diazo compounds, cyclopropenes also serve as the carbene precursors which can generate vinyl metal carbene species.[31] Therefore, it is conceivable to incorporate cyclopropenes into the C-H bond activation. Along this line, Wang and co-workers have recently reported an Rh(III)-catalyzed C-H bond functionalization of *N*-phenoxyacetamides with cyclopropenes (Scheme 22).[32] This reaction provides an efficient method for the synthesis of *2H*-chromene. Notably, this work illustrates that cyclopropene can be used as a three-carbon unit in Rh(III)-catalyzed C-H bond activations. One of the possible reaction pathways is that the cyclopropene is initially activated by rhodacycle intermediate formed through C-H bond activation. Then, ring opening occurs with the formation of vinylrhodium(III) carbene intermediate. With 1,3-allylic migration and intramolecular substitution, the final products are obtained with high efficiency. Through mechanistic experiments, it is found that the C-H bond activation step is largely irreversible under the standard reaction conditions. Moreover, the results from KIE studies indicate that the C-H bond-cleavage process is presumably involved in the rate-determining step.



Scheme 22 Rhodium(III)-catalyzed transannulation of cyclopropenes with *N*-phenoxyacetamides through C-H activation.

6. Conclusion

In conclusion, the cross-coupling reactions involving metal carbene migratory insertion and the transition-metal-catalyzed C-H bond activations can be merged into a single catalytic cycle as demonstrated by various examples summarized in this feature article. Owing to the rapid evolvement of these two areas, this combination is expected to develop further in the coming years. Diazo compounds and their precursor *N*-tosylhydrazones, which are served as one-carbon coupling partners, represent the most common carbene sources applied in this type of reactions.

As for the transition-metal catalysts, rhodium complexes are the most widely used catalysts in C-H bond activation based on metal carbene migratory insertion. Other transition metals, such as palladium and iridium, are much less investigated. On the other hand, C(sp^3)-H bond activation is more challenging than C(sp^2)-H ones and there are only few examples with regard to the C(sp^3)-H bond activation based on metal carbene process so far reported in the literature. Finally, asymmetric catalysis represents another formidable challenge in this area. Further developments along those lines are thus expected in the coming years.

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Notes and references

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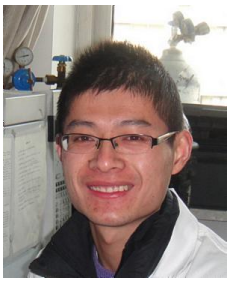

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