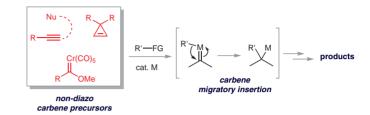
Account

Transition-Metal-Catalyzed Cross-Coupling with Non-Diazo Carbene Precursors

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Abstract Transition-metal-catalyzed cross-coupling reactions through metal carbene migratory insertion have emerged as powerful methodology for carbon–carbon bond constructions. Typically, diazo compounds (or in situ generated diazo compounds from *N*-tosylhydrazones) have been employed as the metal carbene precursors for this type of cross-coupling reactions. Recently, cross-coupling reactions employing non-diazo carbene precursors, such as conjugated ene-yne-ketones, allenyl ketones, alkynes, cyclopropenes, and Cr(0) Fischer carbenes, have been developed. This account will summarize our efforts in the development of transition-metal-catalyzed cross-coupling reactions with these non-diazo carbene precursors.

- 1 Introduction
- 2 Cross-Coupling with Ene-yne-ketones, Allenyl Ketones, and Alkynes
- 3 Cross-Coupling Involving Ring-Opening of Cyclopropenes
- 4 Palladium-Catalyzed Cross-Coupling with Chromium(0) Fischer Carbenes
- 5 Conclusion

Key words cross-coupling, catalysis, carbene migratory insertion, metal carbene, C–C bond formation

1 Introduction

Metal carbene species are versatile intermediates or reagents in organometallics and in organic synthesis.¹ In addition to the traditional metal carbene transformations, the combination of metal carbenes and transition-metal-catalyzed cross-coupling has recently been recognized as powerful methodology for the construction of carbon–carbon and carbon–heteroatom bonds.² In general, the transitionmetal-catalyzed cross-coupling reactions involving metal carbenes present two features (Scheme 1): first, metal carbene precursors are employed as the cross-coupling partners; second, in the reaction mechanism a metal carbene migratory insertion process is considered as the key C-C bond-forming process.

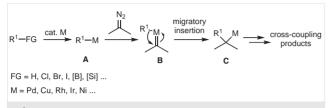
The metal carbene species are typically generated from the interaction of metal catalysts and carbene precursors. Diazo compounds or N-tosylhydrazones (the precursors for in situ generated diazo compounds) are the most convenient and widely used carbene precursors.^{2,3} Mechanistically, the cross-coupling transformation involving a metal carbene follows the catalytic pathway shown in Scheme 1. The organometallic species A is generated from classic crosscoupling steps, such as oxidative addition, transmetalation, and C-H bond activation, which is followed by the reaction with diazo substrate to generate metal carbene intermediate **B**. The intermediate **B** then undergoes migratory insertion of the R group from the metal center to the unsaturated carbenic carbon, generating a C-C bond. The migratory insertion thus generates a new organometallic species C, which undergoes further transformations to produce the final cross-coupling products.

Although diazo compounds are very useful precursors to generate metal carbene species, they suffer some apparent drawbacks such as instability, explosiveness, and toxicity. Thus, significant efforts have been devoted to investigating alternative carbene precursors, and various carbene precursors have been developed in the past few years.⁴ Some of these alternative carbene precursors have also been explored in carbene-based cross-coupling reactions. It has now been established that a range of non-diazo carbene precursors also generate metal carbene intermediates to participate in the cross-coupling reaction. These reactions do not only provide products with diverse structural features, but also validate the generality of the cross-coupling based on metal carbene migratory insertion. In this account, we will provide the overview of our own efforts in

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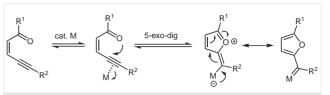
the development of transition-metal-catalyzed cross-coupling reactions of non-diazo carbene precursors.



Scheme 1 Cross-coupling reactions based on metal carbene migratory insertion

2 Cross-Coupling with Ene-yne-ketones, Allenyl Ketones, and Alkynes

Transition-metal catalysts can activate alkynes to trigger an inter- or intramolecular nucleophilic attack to generate metal carbene species.⁵ In particular, conjugated eneyne-ketones have been reported to produce metal carbene intermediates at the alkyne moiety by transition-metalcatalyzed cycloisomerization. The 5-exo-dig cyclization of conjugated ene-yne-ketone generates metal carbene species, which can undergo various metal carbene transformations (Scheme 2).⁶ We thus conceived that the conjugated ene-yne-ketone could serve as an effective carbene precursor in the cross-coupling reactions based on migratory insertion.

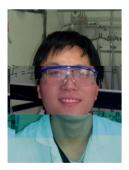


Scheme 2 Generation of a metal carbene from ene-yne-ketone

Along this line, we developed a Pd-catalyzed cross-coupling reaction employing an ene-yne-ketone as the carbene precursor, that afforded 2-vinyl-substituted furan rings in good yields (Scheme 3).⁷ A series of benzyl, allyl, and aryl halides (**2**, **3**, and **7**) were tolerated as the cross-coupling partners. When the alkyne moiety was connected with a bulky group such as a *tert*-butyl or triisopropylsilyl group, the *Z*/*E* isomer selectivity of product **4** could be improved. The coupling reaction gave furyl-containing 1,3-diene products **5** when allyl bromides were used as the coupling partners.

Regarding the reaction mechanism, it has been proposed that the reaction is initiated by oxidative addition of organic halides to palladium(0) species **9** to form an organopalladium(II) species **10**, which then triggers the 5-exo-dig cyclization by coordinating to the alkyne moiety to generate the furyl palladium(II) carbene intermediate **11**. The migratory insertion process of **11** occurs to give a new organopalladium(II) intermediate **12**, which undergoes β -hydride elimination to afford the alkene product and reproduce the Pd(0) catalytic species (Scheme 4). DFT calculation

Biographical Sketches



Kang Wang was born in Shandong Province. He obtained his B.S. degree in 2013 at the School of Chemistry and Chemical Engineering at Shandong University. He then became a graduate student in Jianbo Wang's group at Peking University. He obtained his Ph.D. degree in July 2018. The

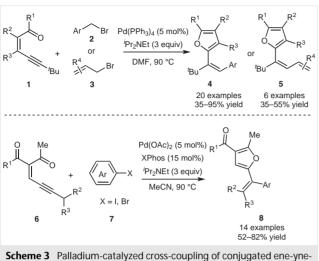
research of his Ph.D. thesis focused on transition-metalcatalyzed cross-coupling with chromium(0) Fischer carbene complexes.

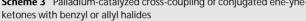


Jianbo Wang received his B.S. degree from Nanjing University of Science and Technology in 1983 and his Ph.D. from Hokkaido University (under the supervision of Prof. H. Suginome) in 1990. He was a postdoctoral associate at the University of Geneva from 1990 to 1993 (with Prof. C. W. Jefford) and University of Wisconsin-Madison from 1993 to 1995 (with

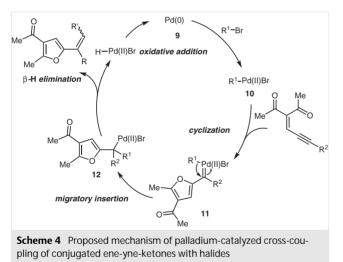
Prof. H. E. Zimmerman and F. A. Fahien). He began his academic career at Peking University in 1995. His research interests have been focused on catalytic metal carbene transformations.

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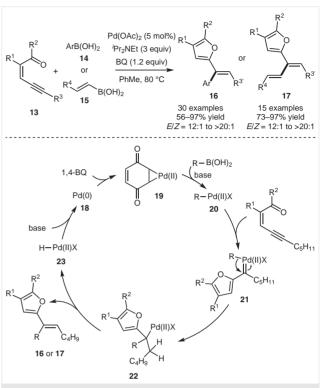




reveals that the palladium carbene formation is the ratelimiting step and the Pd(II) carbene migratory insertion step occurs readily with a very low energy barrier of less than 5 kcal/mol.



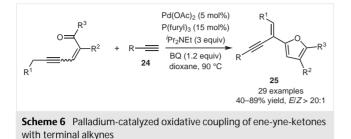
Encouraged by this work, we further explored the palladium-catalyzed oxidative coupling of conjugated ene-yneketones **13** with aryl and vinyl boronic acids **14** or **15** (Scheme 5).⁸ This reaction also show ed excellent functional group tolerance towards various substituted aryl and alkenyl boronic acids. Conjugated ene-yne-ketones bearing various substituents, such as an ester and a sulfonyl group, were also compatible. Compared with the poor E/Z selectivity that was obtained when aryl halides were employed as the coupling partners,⁷ decent *E*-isomer selectivity was observed in this oxidative coupling reaction in almost all the cases.



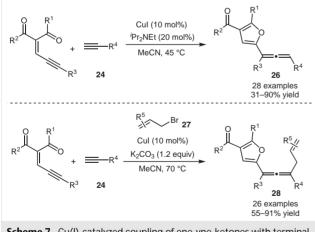
Scheme 5 Palladium-catalyzed oxidative coupling reaction of conjugated ene-yne-ketones with organoboronic acids

We have proposed a similar reaction mechanism. Thus, the oxidative coupling reaction is initiated by the oxidation of palladium(0) species **18** by 1,4-benzoquinone oxidant. The formed palladium(II) catalytic species **19** undergoes transmetalation with organoboronic acid to produce the organopalladium intermediate **20**, which then activates the ene-yne-ketone substrate to trigger cyclization to produce the furyl palladium carbene intermediate **21**. Migratory insertion of **21** affords intermediate **22**, which further undergoes β -H elimination to give the alkene products. The disassociated Pd(II) species is converted to Pd(0) catalytic species **18** to enter the next catalytic cycle.

Then, we extended this oxidative coupling strategy to a palladium-catalyzed alkyne–alkyne coupling (Scheme 6). We reasoned that the alkyne substrates would form alkynyl palladium species which could activate the ene-yne-ketone to generate the furyl palladium carbene species.⁹ Migratory insertion of the Pd carbene gives the propynyl palladium intermediate, followed by β -hydride elimination to afford furyl-substituted 1,3-enyne product. Indeed, the alkyne substrates **24** and differently substituted ene-yne-ketones occurred readily to give the expected 1,3-enyne products **25**. The coupling reaction tolerates a range of aryl-, alkyl-, or silyl-substituted alkyne substrates.

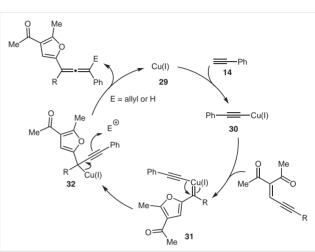


It is worth mentioning that, for the same alkyne substrates and ene-vne-ketone carbene precursors, different transition-metal catalysts may result in different transformations and give different products. Thus, with copper iodide as the catalyst, the cross-coupling between alkynes and ene-yne-ketones gave furyl-substituted allene as the products (Scheme 7).¹⁰ This reaction exhibited a good substrate scope; a series of aryl and heteroaryl-substituted terminal alkynes 24 as well as primary, secondary, and tertiary alkyl-substituted terminal alkynes were all tolerated to give various trisubstituted allenes 26. The reaction also proceeded smoothly in a gram-scale experiment under the standard conditions. We also extended this methodology to the synthesis of tetrasubstituted allenes 28 by introducing allyl bromides as the electrophiles to trap the nucleophilic alkyl copper intermediate.¹¹ The three-component reaction of alkyne, ene-yne-ketone, and allyl bromide 27 proceeded effectively with good functional group compatibility.



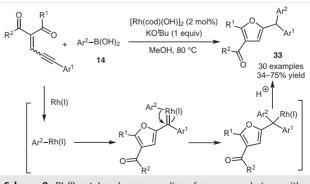
Scheme 7 Cu(I)-catalyzed coupling of ene-yne-ketones with terminal alkynes

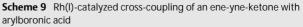
We have proposed the following mechanism as shown in Scheme 8. The copper acetylide **30** is generated from the alkyne substrate and Cu(I) species **29** with the assistance of a base. The ene-yne-ketone then undergoes cyclization to form Cu(I) carbene intermediate **31** by the activation by copper species **30**. After that, copper carbene **31** undergoes migratory insertion to form the propynyl copper intermediate **32**. Regioselective protonation occurs at the triple bond carbon atom to give the trisubstituted allene product. When the nucleophilic propynyl copper intermediate **32** is trapped by allyl bromide, the tetrasubstituted allene product is obtained.



Scheme 8 Proposed reaction mechanism for Cu(I)-catalyzed crosscoupling of an ene-yne-ketone with an alkyne

Because we and other groups have demonstrated that Rh(I) catalysts are also efficient in carbene-involved crosscoupling, we presumed that the conjugated ene-yne-ketones should also undergo a similar cross-coupling reaction under Rh(I) catalysis. Indeed, we further developed the Rh(I)-catalyzed cross-coupling of ene-yne-ketone and organic boronic acid (Scheme 9).¹² Mechanistically, a similar Rh(I) carbene formation and a subsequent metal carbene migratory insertion process are involved in the catalytic cycle. Compared with the Pd(II)-catalyzed coupling of ene-yneketone and boronic acid which gives furyl-substituted alkene product with β -hydride elimination as the terminating step, the Rh(I)-catalyzed transformation affords furancontaining triarylmethane product **33** with protonation as the terminating step.

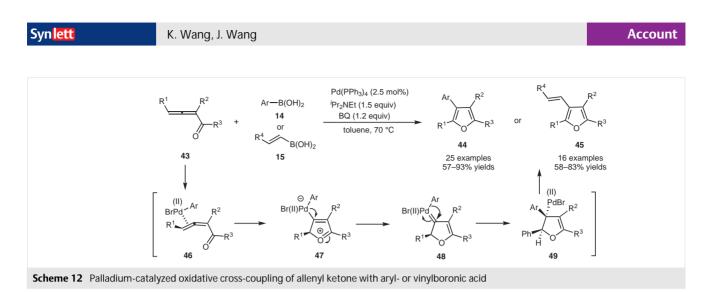




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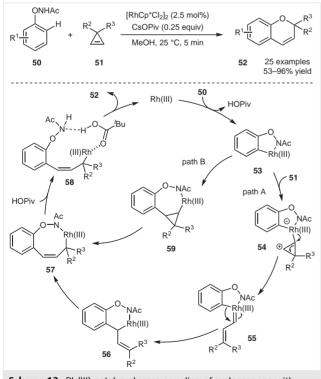
In addition to the conjugated ene-yne-ketone, which undergoes intramolecular cyclization to generate the palladium carbene species, an alkyne moiety alone can also be utilized as metal carbene precursor with the assistance of an intermolecular nucleophile (Scheme 10).¹³ Typically, under gold catalysis the alkyne undergoes carbene transformations, such as ylide formation, X–H insertion and cyclopropanation, through the in situ generated α -oxo gold carbenes.¹⁴ The α -oxo carbene is formed through the activation of the triple bond by the gold catalyst, which triggers the nucleophilic attack followed by the oxidation of alkynes by the N–O bond oxidants.



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activation (Scheme 13).¹⁸ This annulation reaction is highly efficient and can proceed within five minutes at room temperature with a range of different cyclopropenes and *N*-phenxoyacetamides, affording the corresponding 2*H*-chromene products **52** in good to excellent yields.

Two probable reaction mechanisms have been proposed to explain this rhodium-catalyzed transannulation reaction (Scheme 13, paths A and B). They share the same C–H activation process which gives the rhodacycle intermediate **53**. In path A, the cyclopropene substrate is coordinated to the rhodium center to generate intermediate **54**, which then undergoes ring-opening to give the vinyl rhodium carbene intermediate **55**. Subsequent migratory insertion and 1,3-



Scheme 13 Rh(III)-catalyzed cross-coupling of cyclopropene with *N*-phenxoyacetamide

allyl migration reaction give intermediate **57**. Then, the acid-assisted N–O bond cleavage and C–O bond formation sequence (through intermediate **58**) would produce the 2*H*-chromene product. In pathway B, the cyclopropene inserts into the aryl–rhodium bond to form the seven-membered rhodacycle **59**. The subsequent β -carbon elimination process gives the same intermediate **57**. Notably, recent DFT calculation suggests that the aryl–rhodium bond insertion/ β -carbon elimination sequence is more likely to be involved in the reaction mechanism.¹⁹

Moreover, we developed the palladium-catalyzed crosscoupling of cyclopropenes 60 with aryl iodides, affording conjugated 1,3-butadiene products 61 (Scheme 14).²⁰ The cyclopropene substrates bearing two identical aliphatic chains produced E/Z mixtures of 1,3-dienes with almost 1:1 ratio. Other cyclopropene substrates gave the 1,3-diene products with the E-configured isomers as the only or major products. Mechanistically, the aryl palladium species 62 is formed from the oxidative addition step of aryl iodide with the Pd(0) species. Intermediate 62 forms a vinyl palladium carbene intermediate 63 through a ring-opening reaction. The subsequent migratory insertion and B-H elimination then produces the 1,3-diene products. Alternatively, intermediate 62 can insert into the carbon-carbon double bond to form the cyclopropyl palladium intermediate 63 which then undergoes β -carbon elimination to form the same allyl palladium intermediate (65 or 65'). The subsequent β-H elimination affords product 61 and releases the palladium catalyst.

4 Palladium-Catalyzed Cross-Coupling with Chromium(0) Fischer Carbenes

In the past 50 years, Fischer carbene complexes have been extensively explored as valuable reagents in organometallics and in organic synthesis.²¹ Among the various stable metal carbene complexes, chromium(0) Fischer carbene complexes have found wide applications because of their diverse reactivity. A prominent example is the Dötz annula-

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which will be followed by migratory insertion. This type of catalytic transformation should open up new opportunities for the application of chromium(0) Fischer carbene complexes in organic synthesis.

Scheme 16 Transition-metal-catalyzed cross-coupling with chromium(0) Fischer carbene

In the beginning, we studied the palladium-catalyzed cross-coupling reaction of vinyl-substituted chromium(0) carbene complexes which were reported to undergo rhodium- or nickel-catalyzed [3+2] cyclization with unsaturated components such as alkynes and allenes.²⁴ In 2017, we reported the palladium-catalyzed [3+3] annulation reaction of vinyl chromium(0) carbenes **68** with 2-iodophenols **69**catO93 Tw (a

tion of chromium(0) Fischer carbene complexes with alkynes, which has been extensively applied in the synthesis of densely functionalized arenes.^{21,22}

In addition to the traditional reactions, chromium(0) Fischer carbene complexes (66) can transfer their carbene ligands to other transition metals to generate new metal carbene intermediates 67, which undergo further processes to afford various products under catalytic conditions (Scheme 15). The transition metals that have been explored in this type of carbene transfer include palladium, copper, nickel, rhodium, and gold.^{23,24} Transition-metal-catalyzed self-dimerization, cyclopropanation, and cyclization reactions of chromium(0) carbene complexes have been developed on the basis of the carbene transfer process.23 Although the catalytic carbene transfer process generates reactive metal carbene intermediates, the type and scope of transformations based on such a process are still rather limited. We reasoned that it would be desirable to explore a new type of transformations with chromium(0) Fischer carbene complexes under catalytic conditions.

Scheme 15 Transition-metal-catalyzed carbone transfer reactions of chromium(0) Fischer carbone complexes

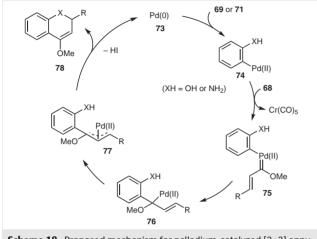
In this context, we have recently initiated a program to study the possibility of employing stable chromium(0) Fischer carbene complexes as the sources of reactive metal carbenes for carbene-based cross-coupling reactions (Scheme 16). The chromium(0) Fischer carbene complex is expected to undergo carbene transfer with organometallic species to generate a new metal carbene intermediate,

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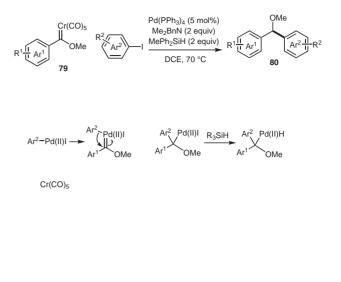
intermediate **75**. The migratory insertion of palladium carbene **75** generates allyl palladium(II) species **77** which is trapped intramolecularly by the nucleophilic hydroxyl group (or amido group) to produce six-membered-ring product **78**.



Scheme 18 Proposed mechanism for palladium-catalyzed [3+3] annulation of vinyl chromium(0) Fischer carbenes

In order to extend this type of transformation with chromium(0) carbenes, we further performed experimental and mechanistic studies on the palladium-catalyzed reductive cross-coupling of aryl halides with aryl chromium(0) carbenes.²⁶ With hydrosilanes as the hydrogen sources and reductants, the coupling products **80** could be obtained through reductive coupling with various substituted aryl chromium(0) carbenes **79** and aryl iodides (Scheme 19). We reasoned that the formation of palladium(II) carbene and its migratory insertion step might be involved in the reaction pathway (path **A**). How ever, an alternative mechanism which involves nucleophilic attack of the hydride source to the electrophilic carbenic carbon of chromium(0) carbene follow ed by transmetalation and reductive elimination cannot be ruled out (path **B**).

A mechanistic experiment employing stoichiometric benzyl palladium species 81 as the coupling partner supports the palladium carbene pathway, as only a palladium carbene migratory insertion process can lead to the observed vinyl ether products 82 (Scheme 19). Moreover, a Hammett linear free energy correlation study afforded a substantially large negative reaction constant ($\rho = -2.93$), implicating that an electron-donating group on the aryl group of the chromium(0) carbene can promote the coupling reaction. This result also supports the palladium carbene pathway. Since the carbene ligand is transferred from a zero-valued chromium(0) center to a positively charged palladium(II) center in the carbene formation process, the carbenic carbon thus becomes more electron-deficient. Therefore, electron-donating groups promote the carbene transfer process.



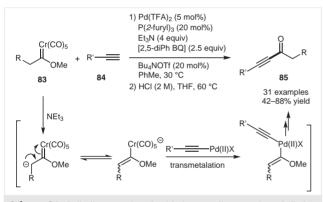
Scheme 19 Palladium-catalyzed reductive coupling reactions of aryl chromium(0) Fischer carbenes with aryl iodides

To gain further insights, we also carried out a computational study on the reaction mechanism. The DFT calculation reveals that the palladium carbene intermediate IM2 is formed through the dimetallacyclopropane transition state TS1. The total energy barrier for the palladium(II) carbene formation process is 26.7 kcal/mol (Scheme 20). The subsequent migratory insertion is a facile process with an energy barrier of 5.1 kcal/mol. After that, the concerted hydrogen transfer, depalladation, and Pd-Si bond formation sequence takes place to release the coupling products, crossing over the transition state TS2 with an energy barrier of 27.9 kcal/mol. The resulting I-Pd-S species IM4 undergoes reductive elimination to regenerate the Pd(0) catalytic species. Both carbene transfer and hydrogen transfer processes are the rate-limiting steps in the transformation. Overall, this reductive coupling provides experimental and theoreti-

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cal evidence for the palladium-catalyzed cross-coupling of the chromium(0) Fischer carbene complex that involves carbene transfer and migratory insertion.

Furthermore, we explored the oxidative cross-coupling of alkynes with alkyl-substituted chromium(0) Fischer carbene complex (Scheme 21).²⁷ In contrast to the typical benzannulations between alkyne and alkyl chromium(0) carbene complex,²⁸ the presence of a palladium catalyst completely redirected the reaction path toward cross-coupling. A range of substituted terminal alkynes **84** were efficient coupling partners in the palladium-catalyzed coupling reaction with various alkyl chromium(0) carbene complexes **83**. Mechanistic experiments implicate that a pathway involving a sequential deprotonation and transmetalation process is more likely, which is in sharp contrast with the palladium carbene migratory insertion and β -hydride elimination pathway.



Scheme 21 Palladium-catalyzed oxidative coupling reaction of alkyl chromium(0) carbene with terminal alkyne

5 Conclusion

In this account, we have introduced the transformations that employ a range of non-diazo carbene precursors in cross-coupling reactions. The conjugated ene-yne-ketones, allenyl ketones, cyclopropene derivatives along with chromium(0) Fischer carbene complexes have been proved as effective metal carbene precursors to participate in the cross-coupling with migratory insertion as the key step. A range of coupling partners, such as organic halides, boronic acids, terminal alkynes as well as C–H bond activation substrates, were employed in the cross-coupling reactions with the transition-metal catalysis of palladium, rhodium, and copper.

These coupling reactions with non-diazo carbene precursors not only introduce some new synthetic methodologies, but also validate the generality of the metal carbene migratory insertion process. In addition to the cross-coupling transformations described in this account, a series of cross-couplings employing other metal carbene precursors have also been developed by other groups.^{3a} It can be expected that carbene-based cross-coupling with other nondiazo substrates will continue to emerge in the coming years.

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