ACS Catalysis
Review
pubs.acs.org/acscatalysis

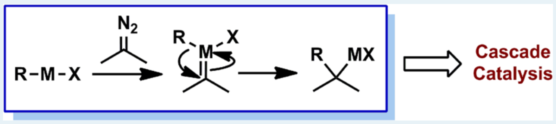
# Catalytic Cascade Reactions Involving Metal Carbene Migratory Insertion

Ying Xia,[†] Yan Zhang,[†] and Jianbo Wang*[,†,‡]

[†]Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

[‡]State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

**ABSTRACT:** Transition-metal-catalyzed cross-coupling reactions involving a carbene migratory insertion process have been developed rapidly during the past ten years. Such a type of coupling reactions provides useful methodologies for the construction of carbon−carbon and carbon−heteroatom bonds. On the basis of the carbene migratory insertion process, catalytic cascade reactions have also been designed and developed, affording versatile methods for the construction of complex molecules. In this review, four types of transition-metal-catalyzed cascade reactions involving the carbene migratory insertion process are discussed.



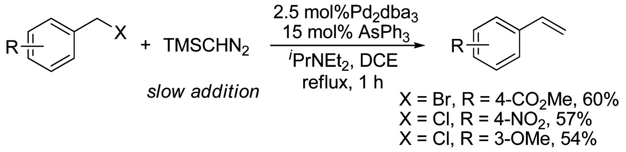
**KEYWORDS:** *catalysis, cascade reaction, carbene, migratory insertion, coupling reaction*

## 1. INTRODUCTION

Metal carbene is an important intermediate in many catalytic reactions.[1,2] Generally, the most common precursors of metal carbenes are diazo compounds, including relatively stable α-diazocarbonyl compounds[3] or the nonstabilized diazo compounds that are usually generated in situ from *N*-tosylhydrazones under basic conditions.[4,5] Typically, the metal carbene generated from diazo compounds undergoes a series of transformations, such as X−H (X = C, Si, O, S, N, etc.) insertions, cyclopropanations, ylide formations, 1,2-migration, and others.[3,6−10]

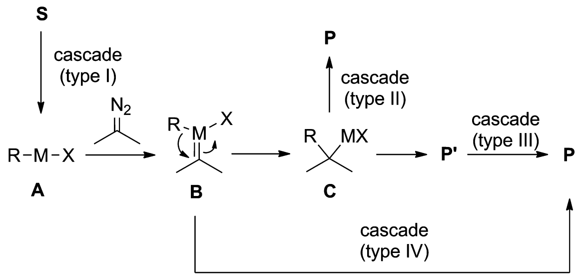
Apart from the traditional transformations, metal carbene can undergo a migratory insertion process.[11−14] In such a process, a ligand (usually a coupling partner moiety) can migrate from the metal to the carbenic carbon and generate a new metal species. The metal carbene migratory insertion process, which is merged with the cross-coupling process, leads to the development of an array of novel cross-coupling reactions. The first catalytic cross-coupling reaction involving a carbene migratory insertion process was realized in 2001 by Van Vranken and co-workers (Scheme 1)[15] by using a palladium complex as the catalyst. Although the reaction has a limitation both in substrates scope and in low efficiency, this pioneering work opens up new possibilities for novel cross-coupling reactions based on the carbene migratory insertion process. Barluenga and co-workers first reported the Pd-catalyzed cross-coupling of aryl halides with *N*-tosylhydrazones, which were safer than diazo compounds as the carbene precursors and allowed the direct functionalization of carbonyl groups.[16] Wang and co-workers then applied the palladium carbene migratory insertion process in the oxidative cross-coupling of carbene precursors with nucleophiles, including boronic acids[17] and terminal alkynes.[18] The same group also expanded the metal carbene migratory insertion process from palladium to copper.[19] These novel coupling reactions provide useful methodologies for the carbon−carbon and carbon−heteroatom bond constructions.[11−14]

**Scheme 1. The First Catalytic Cross-Coupling Involving Carbene Migratory Insertion**



As shown in Scheme 2, transition-metal-catalyzed cross-coupling reactions based on carbene migratory insertion include the following common process: (1) metal species **A** decomposes the diazo compound to generate metal carbene species **B**; (2) **B** undergoes migratory insertion to produce a new metal species, **C**; (3) release of the coupling product regenerates the transition metal catalyst.

**Scheme 2. Cascade Process Involving Carbene Migratory Insertion**



Received: August 11, 2013
Revised: October 1, 2013
Published: October 2, 2013

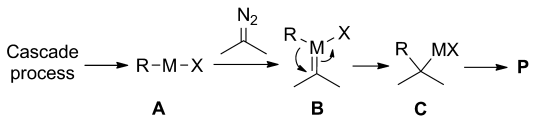
Along with the development of cross-coupling reactions involving metal carbene migratory insertion process, various catalytic cascade reactions have been developed during the past few years. These cascade reactions can be roughly categorized into four different types, as shown in Scheme 2. The metal species **A** may be derived from starting material **S** through a cascade process, or the metal species **C**, which is generated from metal carbene **B**, may undergo a further cascade process to afford product **P**. These two are termed type I and type II cascade reactions in this review, respectively. In addition, the coupling product **P′** may further undergo a cascade process to afford the final product, **P**. This transformation is termed a type III cascade reaction. The type IV cascade reaction includes at least two independent transformations (autotandem catalysis).

The obvious advantages of cascade reactions are step economy and waste reduction. In addition, cascade reactions enable one to exploit the reaction intermediates, which are not practical or facile to isolate. Moreover, cascade reactions are highly efficient for complex molecule construction. In this article, we will discuss only the catalytic cascade reactions involving the metal carbene migratory insertion process. Catalytic cascade reactions based on other metal carbene reactions, such as X−H insertions or ylide transformations, are not in the scope of this review.[3,6−10]

## 2. TYPE I CASCADE REACTION

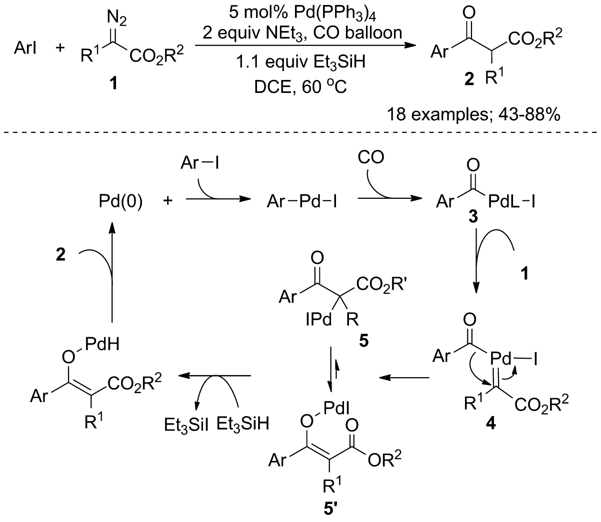
In the transition-metal-catalyzed cross-coupling reactions based on carbene migratory insertion, the metal species **A**, which reacts with the diazo compound to give metal carbene **B**, is typically generated from oxidative addition either with electrophiles or from transmetalation with a nucleophile, or though C−H activation. When metal species **A** is formed from a cascade process, a subsequent similar transformation occurs, leading to the type I cascade reaction (Scheme 3).

**Scheme 3. General Process of Type I Cascade Reaction**



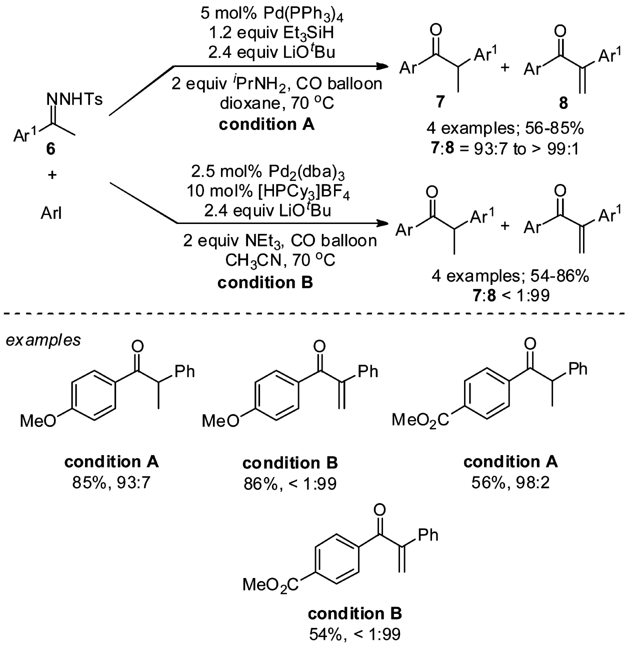
This type of cascade reaction was first reported in the palladium-catalyzed carbonylation and acyl migratory insertion tandem process. The generation of acylpalladium species via palladium-catalyzed carbonylation of aryl halide or pseudohalide is an important process in organic synthesis.[20] In 2010, Wang and co-workers reported a multicomponent reaction of aryl iodide, CO, diazo compound and triethylsilane in the presence of palladium catalyst.[21] In this reaction, the generated acylpalladium intermediate **3** can smoothly decompose the $\alpha$-diazocarbonyl compound **1** to produce the palladium carbene intermediate **4**, which undergoes migratory insertion to generate C-bound enolate **5**. Enolate **5** is isomerized to $\eta^2$-O,O-bound intermediate **5′**. Subsequently, transmetalation with $Et_3SiH$ and reductive elimination affords the product ketoester compound **2** (Scheme 4).

**Scheme 4. Pd-Catalyzed Carbonylation/Acyl Migratory Insertion Cascade Reaction**



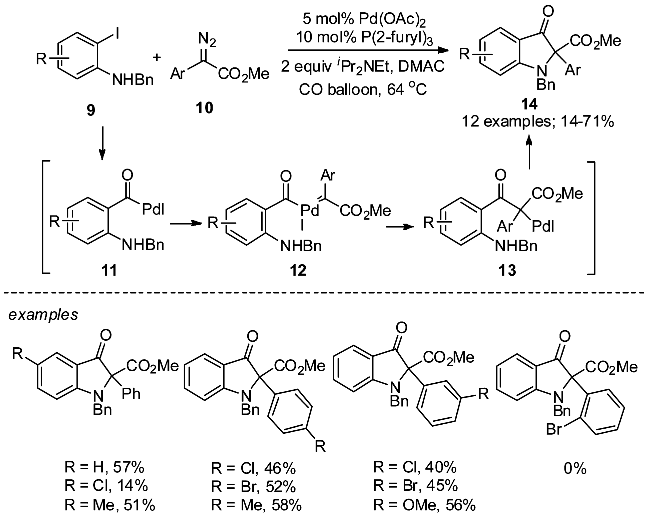
Interestingly, when *N*-tosylhydrazones **6** are used as the carbene precursors, two types of products could be obtained with high chemo-selectivity through the control of reaction condition. In the absence of the ester group of the carbene precursor, the similar O-bound intermediate **5** is not predominant, and the equilibrium of O- or C-bound intermediate can be controlled by the phosphine ligand.[22] The C-bound enolate **5** undergoes $\beta$-hydride elimination, affording the unsaturated ketone **8**, and the O-bound species undergoes a process similar to that of the diazo compound to give saturated ketone **7** (Scheme 5). The selected examples are illustrated in Scheme 5. Although *N*-tosylhydrazones bearing an electron-withdrawing group give only moderate yields, the chemoselectivity of the two sets of reactions is excellent.

**Scheme 5. Pd-Catalyzed Carbonylation/Acyl Migratory Insertion Cascade with *N*-Tosylhydrazone as the Carbene Precursor**



Recently, a similar tandem process was successfully applied in the construction of 3-indolone derivatives by Liang and co-workers.[23] In this transformation, the palladium-catalyzed carbonylation of aryl iodide **9** generates acylpalladium species **11**. Intermediate **11** decomposes the diazo compound **10** to give palladium carbene **12**, followed by a similar acyl migratory insertion. At this point, isomerization of C-bound intermediate **13** and the subsequent intramolecular nucleophilic substitution by the amino group leads to the final product **14** (Scheme 6).

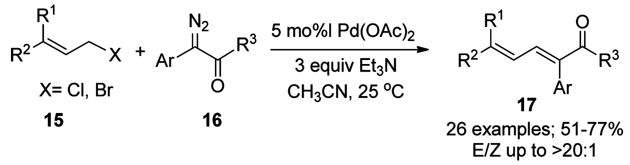
**Scheme 6. Pd-Catalyzed Carbonylation/Acyl Migratory Cascade Reaction for 3-Indolone Synthesis**



The scope of this cascade reaction is quite limited, and ortho-substituted diazoacetate fails to give the corresponding product. In addition, only moderate yields have been obtained in most cases. Nevertheless, this reaction provides a rapid approach to construct these useful scaffolds.

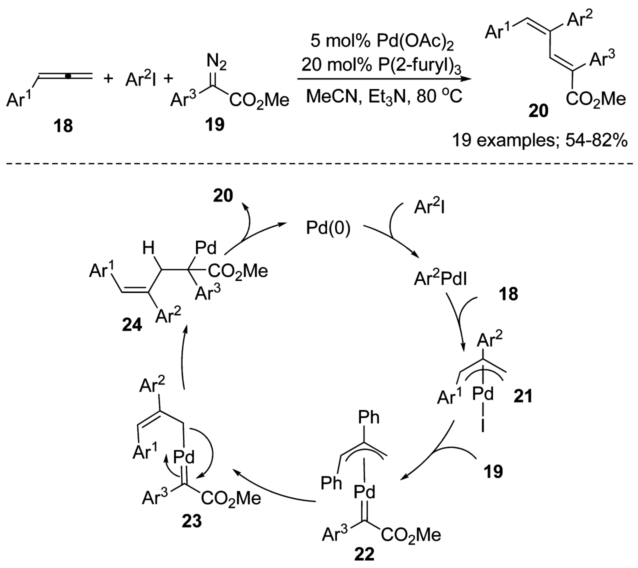
The $\pi$-allylic palladium species are important intermediates in palladium-catalyzed reactions.[24] In 2008, Wang and co-workers reported the Pd-catalyzed coupling reaction of allyl halides **15** with $\alpha$-diazocarbonyl compounds **16**, and the product 1,3-diene derivatives **17** were obtained in good yields and with good to excellent stereoselectivities. The mechanism most likely involves an allyl group migratory insertion of palladium carbene (Scheme 7).[25]

**Scheme 7. Pd-Catalyzed Coupling of Allyl Halides with Diazo Compounds**

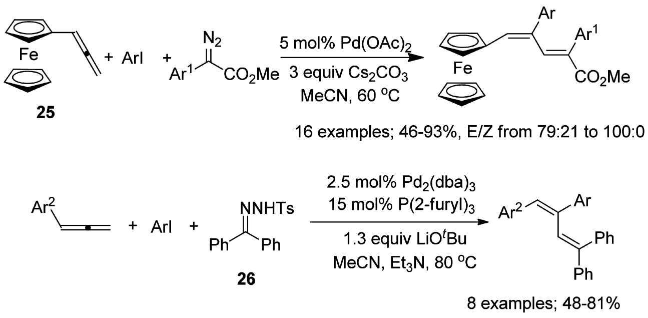


Very recently, this allyl migratory insertion process was successfully applied in the three-component reaction of allenes, aryl iodides and diazo compounds (Scheme 8).[26] In this transformation, the arylpalladium(II) species generated from oxidative addition undergoes carbopalladation to the allene **18**, leading to a $\pi$-allyl palladium intermediate **21**. Then the $\pi$-allyl palladium species decomposes the diazo compound **19** to generate palladium carbene intermediate **22**, which might undergo isomerization to $\eta^1$-allyl palladium intermediate **23**. Finally, migratory insertion of the allyl group and $\beta$-hydride elimination affords the product **20**. Interestingly, the product is highly stereoselective, with *E*,*E* configuration. This has been explained by the attractive $\pi$−$\pi$-stacking interaction[27] in the transition state of the syn $\beta$-hydride elimination (from **24** to **20**). The scope of the substrates was further extended to ferrocenyl allenes **25** and *N*-tosylhydrazones **26** under slightly modified reaction conditions (Scheme 9).

**Scheme 8. Pd-Catalyzed Carbopalladation/Allyl Migratory Insertion Cascade Reaction**

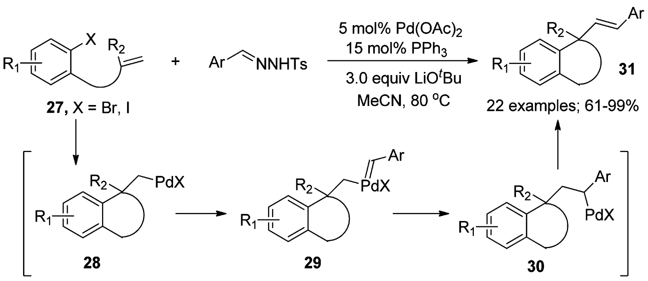


**Scheme 9. Further Substrates Scope for Pd-Catalyzed Carbopalladation/Allyl Migratory Insertion Cascade Reaction**



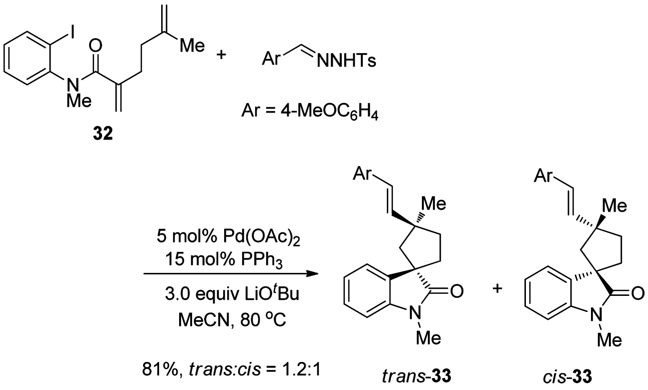
Recently, Gu and co-workers reported a Pd-catalyzed Heck-type cascade reaction of aryl halides **27** and *N*-tosylhydrazones (Scheme 10).[28] This reaction is initiated by the oxidative addition and intramolecular alkene insertion to generate the alkyl palladium species **28**, which undergoes palladium carbene formation, alkyl migratory insertion, and $\beta$-hydride elimination to afford the products **31** with good to excellent yields. In

**Scheme 10. Pd-Catalyzed Intramolecular Alkene Insertion/Alkyl Migratory Insertion Cascade Reaction**



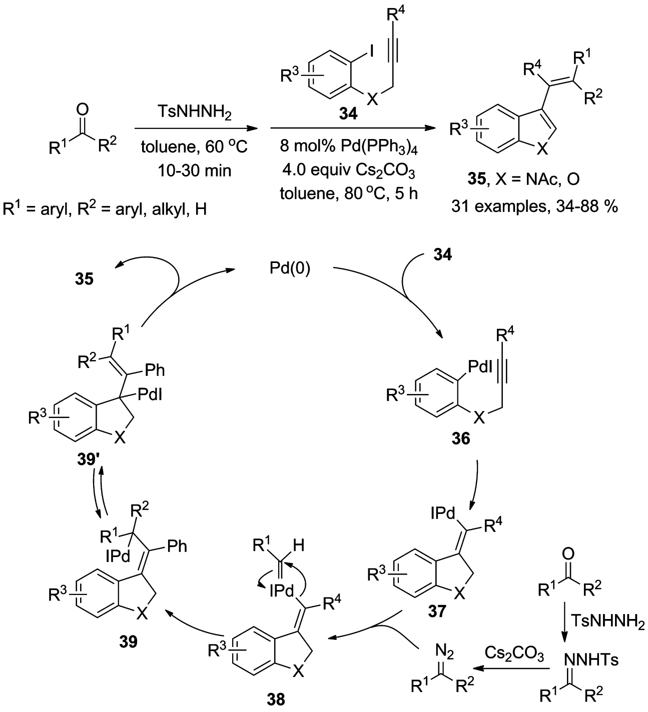
addition, when the aryl halide component has two alkene moieties (**32**), double alkene insertion occurs to produce the spiro compounds **33** in 81% yield with a 1.2:1 diastereoselectivity (Scheme 11).

**Scheme 11. Pd-Catalyzed Intramolecular Double Alkene Insertion to Synthesize Spiro Compounds**



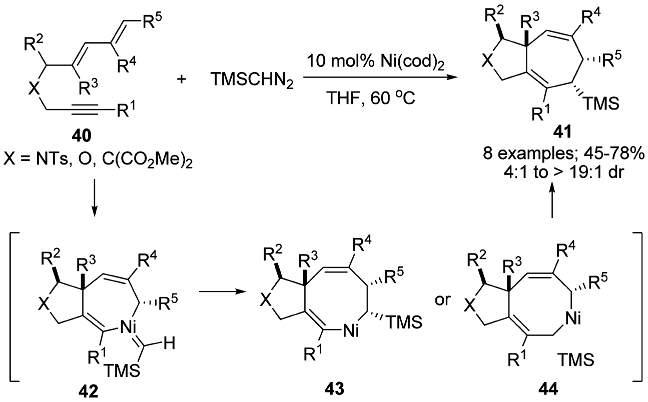
At the same time, Wang and co-workers developed a Pd-catalyzed cyclization and carbene migratory insertion cascade reaction by employing aryl iodides **34** and the in situ-formed *N*-tosylhydrazones as the substrates. In this transformation, the aryl palladium species **36** generated by the oxidative addition of **34** undergoes intramolecular alkyne insertion to produce an alkenyl palladium species **37**. Then the Pd-carbene is formed by decomposition of the in situ-generated diazo compound, subsequently followed by alkenyl migratory insertion and *β*-hydride elimination to afford the final product **35**. This reaction provides a general approach to the stereoselective synthesis of 3-vinylindoles and 3-vinylbenzofurans (Scheme 12).[29]

**Scheme 12. Pd-Catalyzed Intramolecular Alkyne Insertion/Alkenyl Migratory Insertion Cascade Reaction**



Apart from the palladium catalyst, Montgomery and co-workers have reported a Ni-catalyzed [4 + 2 + 1] cycloaddition, which is considered to belong to the type I cascade reaction. In this reaction, dienynes **40** were employed as substrates, and TMSCHN$_2$, as the carbene precursor, and the [4 + 2 + 1] cycloaddition products **41** were obtained in moderate to good yields (Scheme 13).[30] One of the mechanisms proposed by the authors includes oxidative cyclization of Ni(0) with dienyne **40** and decomposition of the diazo compound to generate metallacycloheptadiene carbene species **42**. Subsequent carbene migratory insertion produces metallacycles **43** or **44**; and finally, reductive elimination affords the product **41** with regeneration of the Ni catalyst. However, a mechanism that involves the [3,3]-sigmatropic rearrangement of divinylcyclopropane intermediates is also likely, which is supported by the stereochemical studies.[30]

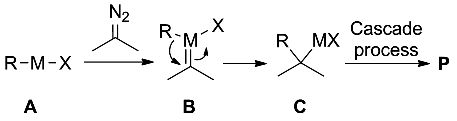
**Scheme 13. Nickel-Catalyzed [4 + 2 + 1] Cycloadditions**



## 3. TYPE II CASCADE REACTION

In the transition-metal-catalyzed carbene migratory insertion coupling reactions, the generated alkyl metal species **C** from the carbene migratory insertion usually undergoes *β*-hydride elimination or protonation.[11−14] In the type II cascade reaction, the alkyl metal species **C** undergoes a further cascade process instead of *β*-hydride elimination (Scheme 14).

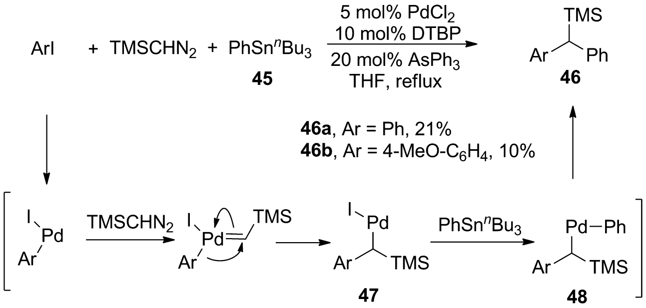
**Scheme 14. General Process of the Type II Cascade Reaction**



### 3. 1. Type II Cascade Reaction Based on Benzyl Palladium Species.

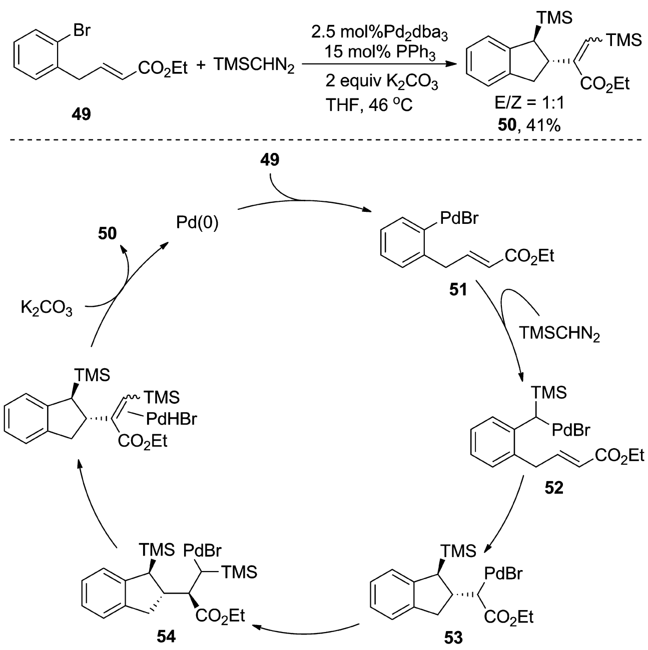
In Van Vranken's seminal work, they reported a palladium-catalyzed three-component reaction of aryl iodides, trimethylsilyldiazomethane (TMSCHN$_2$), and tributylphenyltin **45** (Scheme 15).[15] In this cascade reaction, the benzyl palladium species **47** generated from migratory insertion undergoes transmetalation with tin reagent, followed by reductive elimination to afford the final product benzhydryl derivatives **46**. The reaction needs slow addition of both TMSCHN$_2$ and tin reagent and the use of toxic ligand AsPh$_3$. The target products **46** were obtained only in low yield. Nevertheless, this reaction was the first example to employ the alkyl palladium species generated from migratory insertion in

### Scheme 15. Pd-Catalyzed Migratory Insertion/Stille Coupling Cascade Reaction



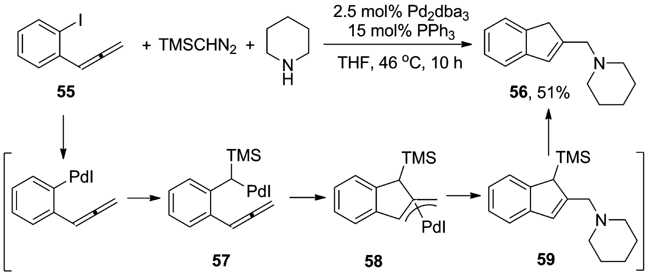
the cascade reaction, demonstrating the potential for the construction of two separate bonds at the carbonic carbon simultaneously.

### Scheme 16. Cascade Catalysis Involving Intramolecular Carbopalladation to Alkene



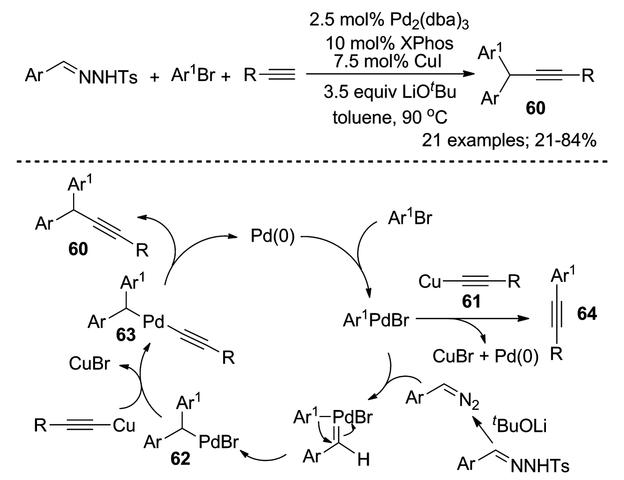
More recently, the same group reported that the benzyl palladium species generated from carbene migratory insertion could undergo carbopalladation to an intramolecular alkene (Scheme 16).[31] This reaction used aryl bromide containing an α,β-unsaturated ester moiety **49** and TMSCHN$_2$ as the substrates, through a series of cascade process, affording the indane derivatives **50** in moderate yields. Mechanistically, the carbene insertion of aryl palladium species **51** generates benzyl palladium species **52**, then the intramolecular carbopalladation occurs to form intermediate **53**. At this point, the second carbene migratory insertion may take place, and subsequent β-hydride elimination leads to the anti configuration product **50**. Apart from the major product **50**, other products were also obtained from this cascade reaction.

### Scheme 17. Carbopalladation of Benzyl Palladium Species to Allene



This paper also provided an example of migratory insertion and carbopalladation cascade reaction by using *o*-iodide aryl allene **55**, TMSCHN$_2$, and piperidine as substrates (Scheme 17).[31] In this reaction, the benzyl palladium species **57** undergoes carbopalladation of the intramolecular allene moiety to generate $\eta^3$-allylpalladium intermediate **58**. Then nucleophilic substitution by piperidine leads to the indene **59**, which is unstable under the reaction conditions and undergoes nucleophilic proto-desilylation to afford the final product **56** with moderate yield.

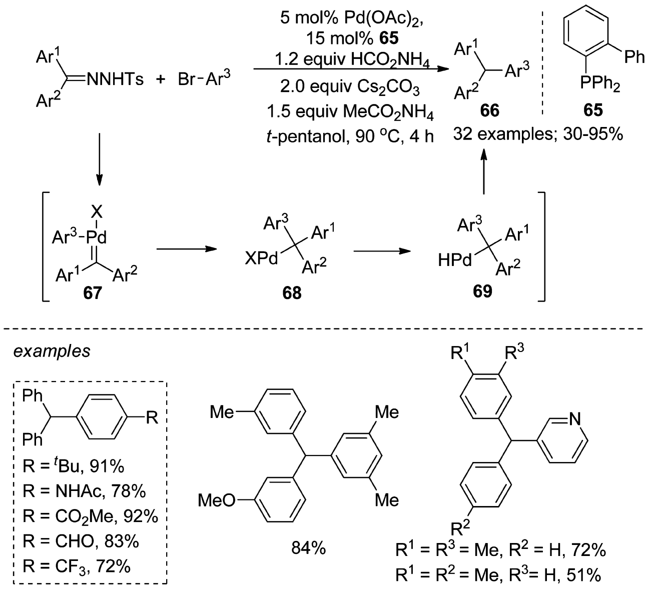
### Scheme 18. Pd-Catalyzed Migratory Insertion/Sonogashira Coupling Cascade Reaction



In 2010, Wang and co-workers reported a three-component reaction of *N*-tosylhydrazone, terminal alkyne, and aryl halide, in which the migratory insertion and the Sonogashira alkynylation are combined (Scheme 18).[32] This reaction uses *N*-tosylhydrazone as the carbene precursor, and benzyl palladium species **62** (bearing no β-hydride), generated from carbene migratory insertion, undergoes transmetalation with the in situ-formed copper acetylide **61** to give **63**. Subsequently, reductive elimination affords the benzhydryl acetylene derivatives **60** and regenerates the palladium catalyst. The key issue in this reaction is the suppression of the direct Sonogashira coupling to form **64**.

More recently, the same group reported a palladium-catalyzed cascade migratory insertion/reduction reaction by using *N*-tosylhydrazones and aryl bromides as substrates and ammonium formate as the hydride source (Scheme 19).[33] In this reaction, the palladium carbene intermediate **67** undergoes migratory insertion to give benzyl palladium species **68** (bearing no β-hydride). At this point, the ligand exchange with formate anion occurs, followed by decarboxylation to give palladium-hydride complex **69**. Finally, the reductive elimination affords the product **66** and regenerates the palladium catalyst. The phosphine ligand **65** plays an important role in

**Scheme 19. Pd-Catalyzed Migratory Insertion/Reduction Cascade Reaction**

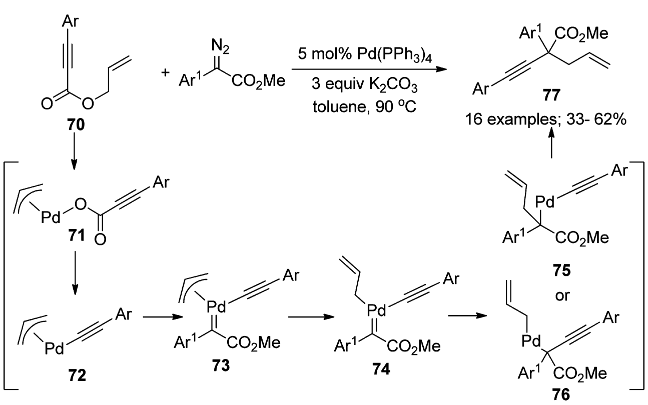


this transformation, and the more bulkiness or more electron-rich ligands give poor results.

In this reaction, the direct reduction of aryl bromide is suppressed by ammonium acetate, and the cascade migratory insertion/reduction products are obtained in good to excellent yields. This approach provides a general route for the synthesis of triarylmethanes. Moreover, this cascade reaction demonstrates the concept of employing *N*-tosylhydrazone as an alkyl metallic reagent equivalent in Pd-catalyzed reaction, leading to the formal C($sp^3$)−C($sp^2$) single bond formation. A similar palladium-catalyzed migratory insertion and reduction sequence by using ethyl diazoacetate (EDA) as the carbene precursor was reported at the same time.[34]

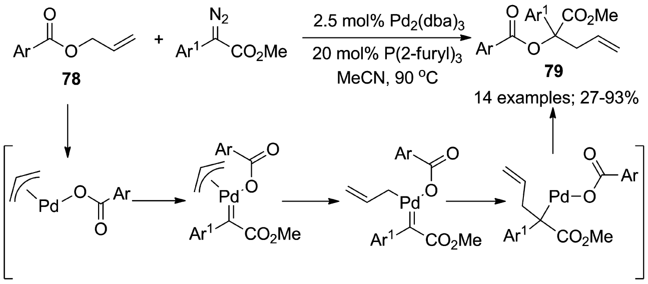
Another cascade reaction, which employed the benzyl palladium species generated from migratory insertion, was reported by Liang and co-workers in 2012 (Scheme 20).[35] They use aryldiazoacetates and allyl 3-arylpropiolate **70** as the substrates. Through oxidative addition, decarboxylation, and decomposition of the diazo compound, the palladium carbene intermediate **73** is generated and isomerizes to $\eta^1$-allylpalladium intermediate **74**. Interestingly, the palladium carbene species **74** has two carbon ligands, which can undergo migratory insertion reactions, generating palladium species **75** or **76**. Finally, reductive elimination affords the product 1,5-enynes **77**.

**Scheme 20. Pd-Catalyzed Decarboxylation/Migratory Insertion/Reductive Elimination Cascade Reaction**



When allylic benzoates derivatives **78** are used in place of allyl 3-arylpropiolates **70**, a similar decarboxylation process does not occur. Instead, a migratory insertion and directly reductive elimination cascade process took place to generate product **79** with an O-substituted quaternary carbon center in good yields (Scheme 21).

**Scheme 21. Pd-Catalyzed Migratory Insertion/Reductive Elimination Cascade Reaction**

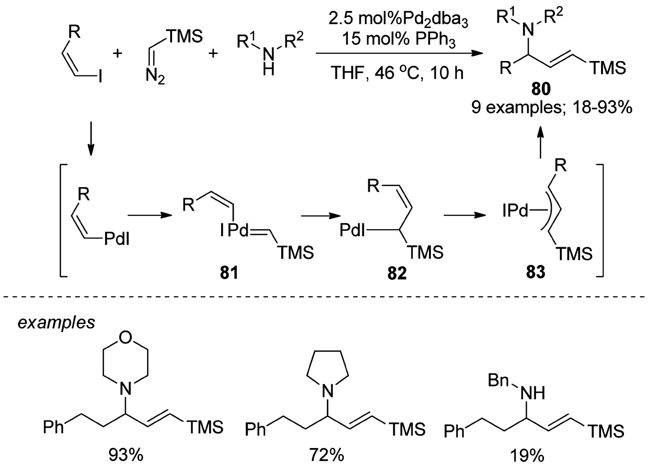


### 3.2. Type II Cascade Reaction Based on Allyl Palladium Species.

The above palladium-catalyzed type II cascade reaction was mainly based on the benzyl palladium species generated from carbene migratory insertion. Apart from the benzyl palladium species, $\pi$-allylpalladium species generated from the carbene migratory insertion process can attend a series of allylic substitution reactions.

In 2007, Van Vranken and co-workers reported a three-component reaction of vinyl halides, $TMSCHN_2$, and amines to generate allyl amines in the presence of palladium catalyst (Scheme 22).[36] The mechanism of this reaction is proposed to involve the formation of a palladium carbene intermediate **81**, which undergoes migratory insertion of a vinyl moiety to the carbenic carbon. The $\eta^1$-allylpalladium species **82** then isomerizes to $\eta^3$-allylpalladium intermediate **83**, which subsequently undergoes nucleophilic substitution by the amine, leading to the allyl amines **80** as the products. This reaction is limited to cyclic secondary amines, terminal vinyl iodides and $TMSCHN_2$ as carbene precursor. Nevertheless, it is the first

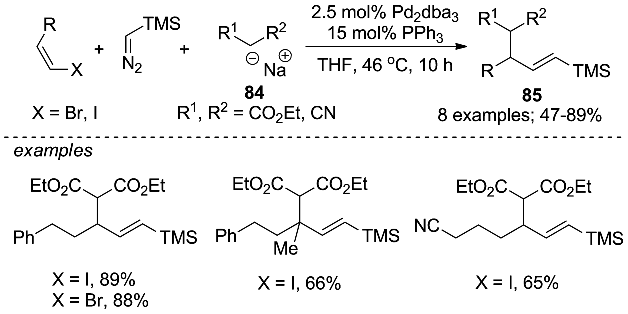
**Scheme 22. Pd-Catalyzed Three-Component Reaction of Vinyl Halides, $TMSCH_2$, and Amines**



example to employ the allyl palladium species generated from carbene migratory insertion in the cascade reaction.

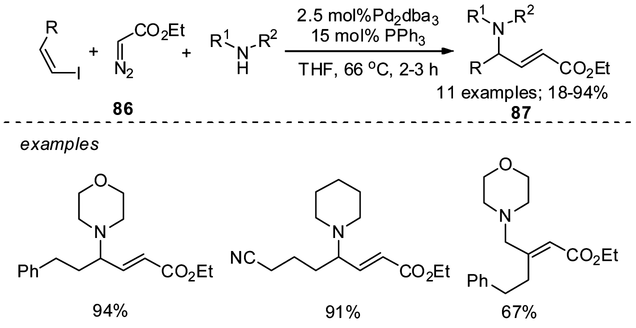
Recently, a similar cascade reaction was reported in which the $\eta^3$-allylpalladium species generated from carbene migratory insertion were trapped by stabilized carbanions **84** as nucleophiles (Scheme 23).[37] The vinyl bromides and iodines are both suitable substrates, affording the corresponding vinylsilanes **85** in moderate to excellent yields.

### Scheme 23. Pd-Catalyzed Three-Component Reaction of Vinyl Halides, TMSCH$_2$, and Carbon Nucleophiles



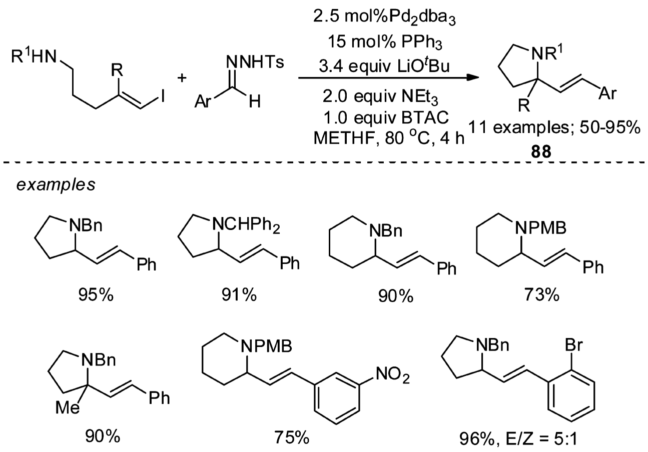
To further demonstrate the application of the migratory insertion/nucleophilic substitution cascade reaction, Van Vranken and co-workers used ethyl diazoacetate (EDA) **86** instead of TMSCHN$_2$ as the carbene precursor (Scheme 24).[38] The similar three-component reaction afforded $\alpha,\beta$-unsaturated $\gamma$-amino esters **87**.

### Scheme 24. Pd-Catalyzed Three-Component Reaction of Vinyl Halides, $\alpha$-Diazoesters, and Amines

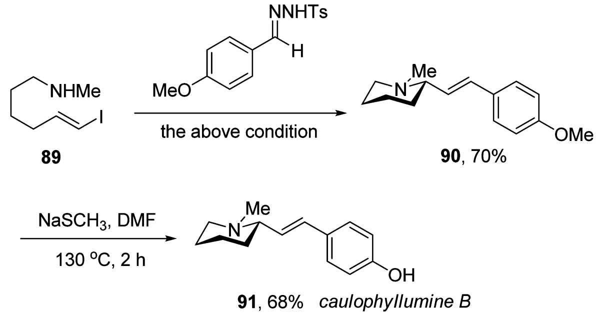


In 2012, the same group reported the use of $N$-tosylhydrazones as carbene precursors in a similar cascade reaction (Scheme 25). In this transformation, the generated $\eta^3$-allyl palladium species is trapped by the intramolecular amino group, leading to the formation of pyrrolidine and piperidine ring systems.[39] The cascade reaction is compatible with a wide range of functional groups on the amino moiety and the substituents on $N$-tosylhydrazone. The target product is obtained in good to excellent yields. In addition, the cascade reaction is successfully applied in the synthesis of alkaloid natural product caulophyllumine B (Scheme 26).

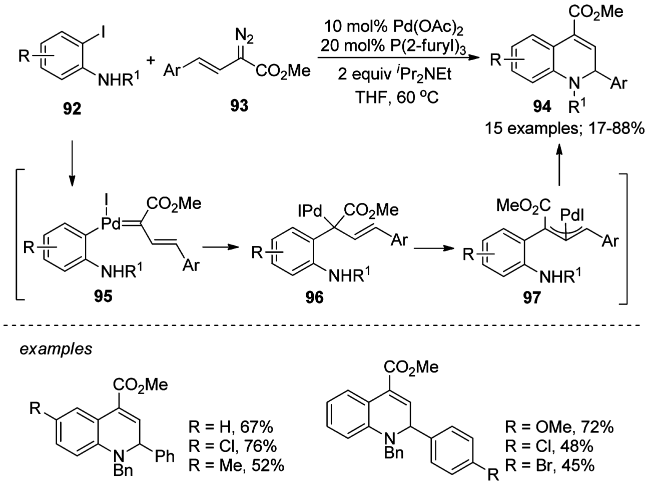
### Scheme 25. Pd-Catalyzed Carbenylative Amination with $N$-Tosylhydrazones



### Scheme 26. Pd-Catalyzed Carbenylative Amination in the Synthesis of (±)-Caulophyllumine B



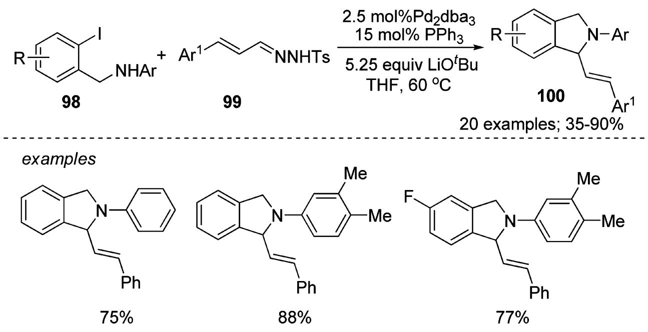
### Scheme 27. Pd-Catalyzed Cascade Reaction for the Synthesis of Cyclic $\alpha,\beta$-Unsaturated $\gamma$-Amino Ester



The $\eta^3$-allylpalladium species can also be generated from reaction of aryl halide with vinyl-substituted diazo compounds. Very recently, the Liang group reported a palladium-catalyzed cascade reaction of $N$-substituted-2-iodoaniline **92** with aryl vinyldiazoacetate **93**, affording cyclic $\alpha,\beta$-unsaturated $\gamma$-amino ester **94** as the product (Scheme 27).[23] The mechanism of this reaction is proposed to involve the formation of palladium vinyl carbene intermediate **95**. Then migratory insertion generates $\eta^1$-allyl palladium species **96**, which undergoes isomerization to $\eta^3$-allyl palladium species **97**. The intermediate **97** is then trapped by the intramolecular amino group, affording the final product **94**.

Subsequently, the same group reported similar Pd-catalyzed cascade reaction for the synthesis of isoindoline derivatives by using $N$-(2-iodobenzyl) anilines **98** and $\alpha,\beta$-unsaturated $N$-tosylhydrazones **99** as the substrates (Scheme 28).[40] The mechanism is also believed to proceed via the intramolecular

**Scheme 28. Pd-Catalyzed Cascade Reaction for the Synthesis of Isoindoline Derivatives**

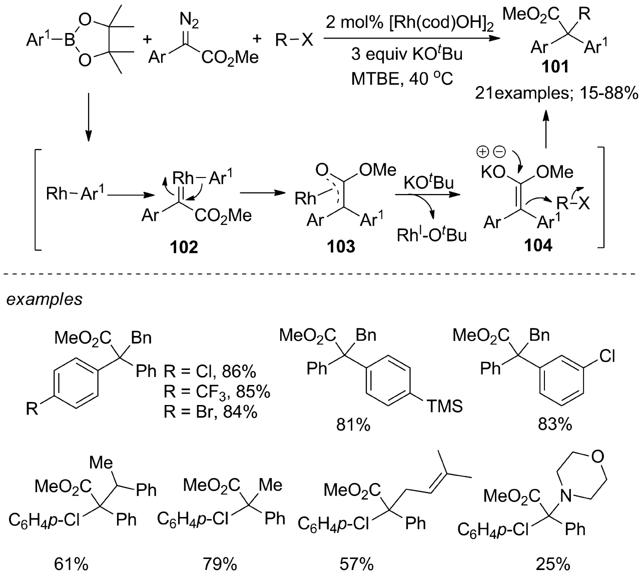


substitution of the internal benzyl amino moiety as nucleophile to $\eta^3$-allyl palladium species. The scope of this reaction was examined by a wide range of substrates bearing different functional groups, and the corresponding isoindoline products **100** were obtained in moderate to good yields under mild reaction conditions.

### 3.3. Type II Cascade Reaction Based on Rhodium and Copper Catalysts.

In 2011, the Yu group reported a Rh(I)-catalyzed three-component reaction of $\alpha$-aryldiazoesters, arylboronates, and alkyl halides (Scheme 29).[41] The mechanism of this reaction involves transmetalation with arylboronates to generate arylrhodium(I) species, formation of rhodium carbene intermediate **102**, and carbene migratory insertion to afford oxa-$\pi$-allylrhodium complex **103**. At this point, potassium enolate **104** is generated from **103** by exchanging with KO$^t$Bu, which is then trapped by electrophiles to afford the final product **101** with a quaternary carbon center.

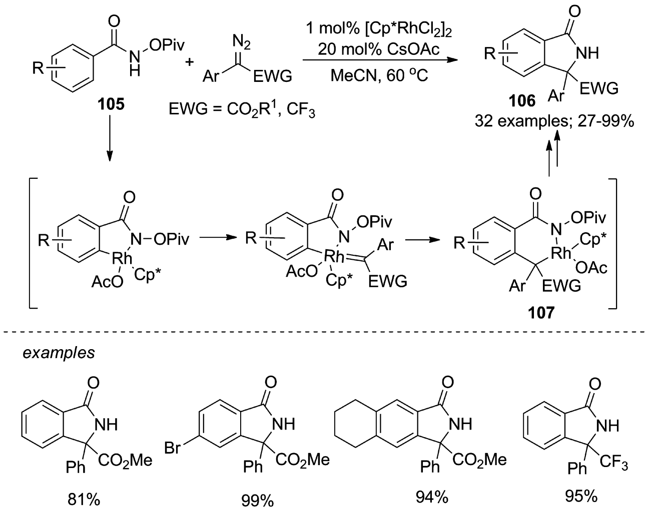
**Scheme 29. Rh(I)-Catalyzed Cascade Reaction for the Construction of an All-Carbon Quaternary Center**



The electrophiles in this cascade reaction include benzyl bromides, methyl iodide, and allyl bromide, and the corresponding products are obtained in moderate to good yields. This study demonstrates an interesting example of Rh(I)-catalyzed carbene migratory insertion reactions, which is contrary to the classic Rh(II)-catalyzed carbene transfer reaction.[3,6−10] Notably, this cascade reaction generates two separate C−C bonds in the carbenic carbon, resulting in an all-carbon quaternary center in the products.

The Rh(III) complex can also decompose the diazo compounds to generate metal carbene species, which may undergo similar migratory insertion process. Such a concept was first explored by Yu and co-workers, who reported a Rh(III)-catalyzed intermolecular carbenoid functionalization of aromatic C−H bonds by using $\alpha$-diazomalonates as carbene precusors.[42] In 2013, Rovis and co-workers developed a Rh(III)-catalyzed reaction of benzamides **105** and diazo compounds, leading to the formation of isoindolones **106** as the products (Scheme 30).[43] This reaction involves C−H activation, rhodium carbene formation, and migratory insertion, generating intermediate **107**, which further undergoes reductive elimination to form the C−N bond and regenerate the Rh(III) catalyst with the aid of the internal oxidant *N*-OPiv moiety.[44] Mechanistic study suggests that C−H activation is the rate-determining step, and this step is irreversible.

**Scheme 30. Rh(III)-Catalyzed Cascade Reaction for the Synthesis of Isoindolones**

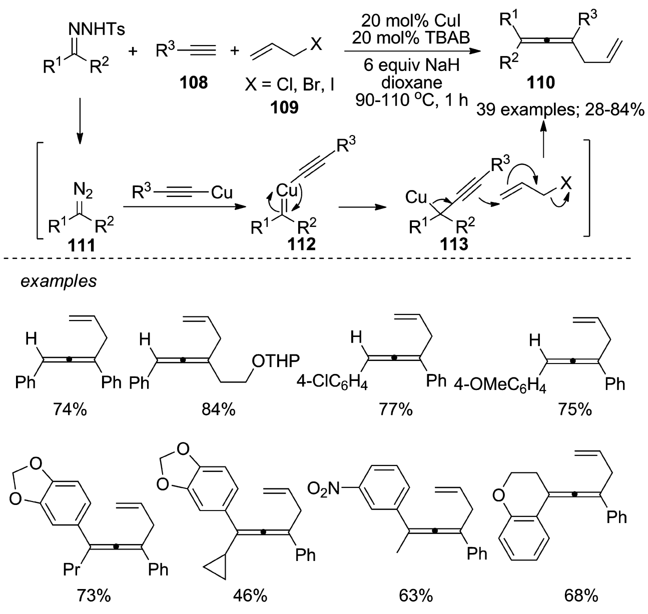


This Rh(III)-catalyzed cascade reaction tolerates a wide range of benzhydroxamic acids and diazo compounds, affording the products with a tetra-substituted carbon center under mild reaction conditions. This approach provides a new method for the synthesis of isoindolone derivatives.

On the other hand, Wang and co-workers reported a series of copper-catalyzed coupling of terminal alkynes with *N*-tosylhydrazones, in which the protonation of propargyl copper species generated from migratory insertion affords allenes or functionalized alkynes.[19] Very recently, the same group has demonstrated that the nucleophilic propargyl copper species can be trapped by allyl halides (Scheme 31). In this way, a three-component reaction of *N*-tosylhydrazones, terminal alkynes **108**, and allyl halides **109** has been developed, leading to the formation of polysubstituted allenes **110**.[45]

This cascade reaction affords tri- and tetra-substituted allyl allenes in moderate to good yields. For the synthesis of tetra-substituted allenes, *N*-tosylhydrazones derived from ketones need 1,10-phenanthroline as the ligand. In this transformation, excess NaH was required to trap the proton, suppressing the directly protonated two-component reaction.

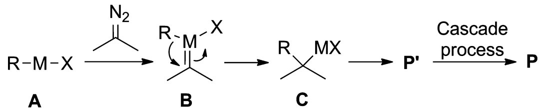
**Scheme 31. Cu(I)-Catalyzed Cascade Reaction for the Synthesis of Allyl Allenes**



## 4. TYPE III CASCADE REACTION

The coupling product **P**′ generated from the carbene migratory insertion coupling reaction in some cases is reactive under the reaction conditions, which may undergo further transformation to afford the final product **P**. Such a cascade process is termed a type III cascade reaction (Scheme 32). Interestingly, this type of cascade reaction is all based on cumulenes as the intermediates, including ketenes, ketenimines, and allenes, which are reactive intermediates widely used in organic synthesis.[46]

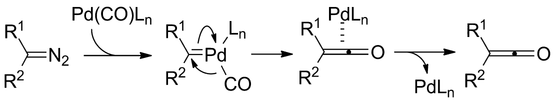
**Scheme 32. General Process of Type III Cascade Reaction**



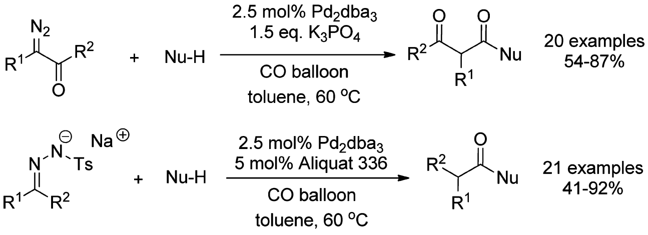
**4. 1. Type III Cascade Reaction Based on Ketene or Ketenimine.** In 2011, Wang and co-workers developed an efficient catalytic approach to ketene intermediate via carbonylation of the palladium carbene species with CO.[47] The mechanism of this transformation involves the decomposition of a diazo compound by the CO-complexed palladium species, the migratation of the CO ligand to the carbenic carbon, and ketene formation by releasing the palladium catalyst (Scheme 33). This transformation provides an efficient catalytic method to generate ketene species under mild conditions.[48]

Both the $\alpha$-diazocarbonyl compounds and *N*-tosylhydrazones can be used as carbene precursors to generate ketene intermediates, which could be trapped by amines, alcohols, and phenols as nucleophiles to afford amides or esters (Scheme 34). In addition, when imines are used as nucleophiles, a formal cycloaddition product can be obtained. When $\alpha$-diazocarbonyl compounds are used as the carbene precursors, the generated acylketene intermediates undergo formal [4 + 2] cycloaddition with imines to produce 1,3-dioxin-4-one derivatives **114**. The ketenes without adjacent acyl group will undergo formal [2 + 2] cycloaddition with imines, affording $\beta$-lactam derivatives **115** with excellent trans diastereoselectivity (Scheme 35). DFT calculation indicates that the palladium complex is involved in the [2 + 2] cycloaddition process, which affects the diastereoselectivity of the product.

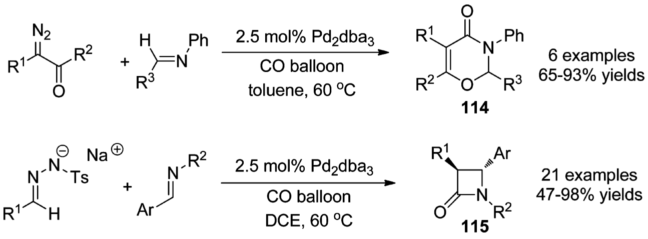
**Scheme 33. Pd-Catalyzed Carbonylation of Diazo Compound: Ketene Intermediate Formation**



**Scheme 34. Pd-Catalyzed Carbonylation/Nucleophilic Addition Cascade Reaction**

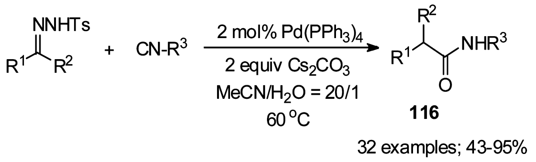


**Scheme 35. Pd-Catalyzed Carbonylation/Formal Cycloaddition Cascade Reaction**



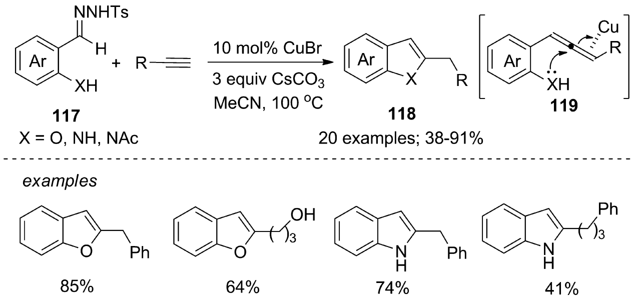
Cai, Ding, and co-workers subsequently reported a similar palladium-catalyzed reaction by using isocyanides in place of CO to generate ketenimines, which is then trapped by $H_2O$ as the nucleophile to afford the amides **116** as the final products (Scheme 36).[49] This reaction tolerates a wide range of *N*-tosylhydrazones and isocyanides, and the corresponding products are obtained with moderate to good yields. However, only $H_2O$ can act as the nucleophile to trap the generated ketenimine intermediates, and attempts to use other nucleophiles failed.

**Scheme 36. Pd-Catalyzed Amidation of *N*-Tosylhydrazones with Isocyanides**



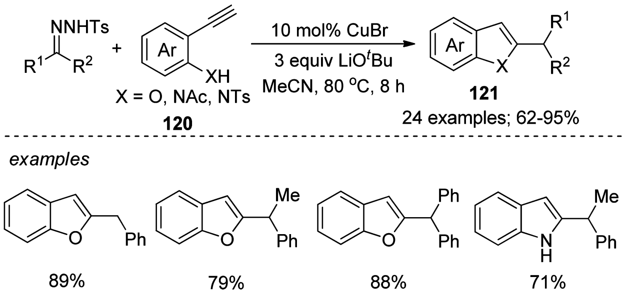
**4. 2. Type III Cascade Reaction Based on Allene.** The Cu-catalyzed coupling reactions of terminal alkynes with *N*-tosylhydrazones generates allenes.[19] If there is an internal nucleophilic group, subsequent cascade cyclization may occur. In 2011, Wang and co-workers reported a CuBr-catalyzed coupling of *N*-tosylhydrazones derived from *o*-hydroxy- or *o*-aminobenzaldehydes **117** and terminal alkynes, providing a useful method for the synthesis of 2-substituted benzofurans and indoles **118** (Scheme 37).[50] This reaction may proceed through nucleophilic cyclization of the internal hydroxy or an amino group to the generated allene moiety, which was shown as **119**. This cascade reaction affords a variety of 2-substituted benzofurans and indoles in moderate to good yields under ligand-free conditions.

### Scheme 37. CuBr-Catalyzed Synthesis of Benzofurans and Indoles through Cascade Reaction



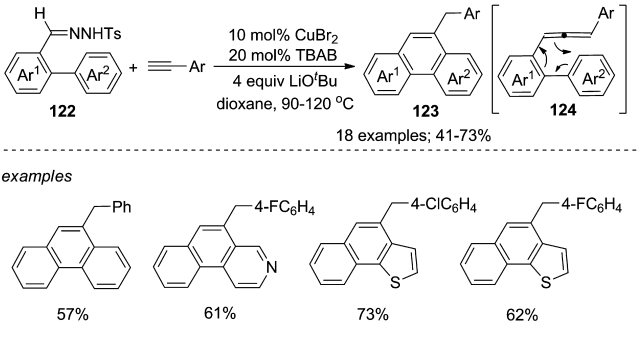
Then, Zhou and co-workers reported a similar Cu-catalyzed cascade reaction for the synthesis of benzofurans and indoles (Scheme 38).[51] The reaction also proceeds via the allene intermediates, in which the internal nucleophiles exist on the terminal alkynes moiety (**120**). Apart from primary alkyl-substituted benzofurans, this reaction can also afford a variety of secondary alkyl substituted benzofurans **121**, which cannot be synthesized through the above-mentioned method shown in Scheme 37.

### Scheme 38. CuBr-Catalyzed Synthesis of Benzofurans and Indoles from Terminal Alkynes Bearing Internal Nucleophile



In 2011, Wang and co-workers reported another Cu-catalyzed cascade reaction by using terminal alkynes and *N*-tosylhydrazones derived from *o*-formyl biphenyls **122** as the substrates (Scheme 39).[52] In this transformation, the allene intermediate **124** undergoes 6$\pi$ electrocyclization and aromatization to form the final product, 9-benzyl-substituted phenanthrenes, **123**. The yields are moderate in most cases. Nevertheless, the reaction uses simple and inexpensive $CuBr_2$ catalyst without adding ligand, which makes this method attractive in the synthesis.

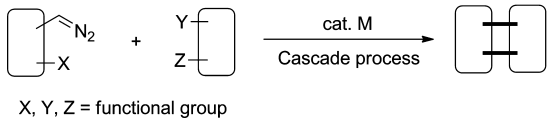
### Scheme 39. $CuBr_2$−Catalyzed Synthesis of Phenanthrenes through Cascade Reaction



## 5. TYPE IV CASCADE REACTION

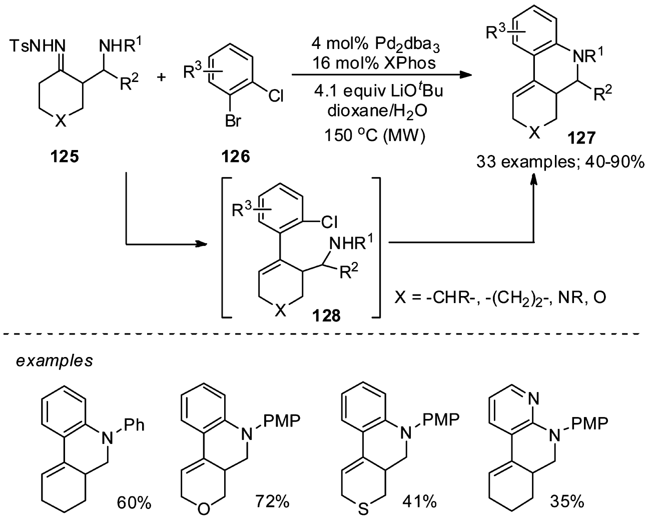
The type IV cascade reaction includes at least two independent transformations in the presence of a single catalyst, one of which contains the carbene migratory insertion process as the key step (Scheme 40). Such a cascade reaction belongs to autotandem catalysis.[53,54] Thus, part or all of the reaction partners have at least two functional groups, and two or more chemical bonds are formed in the same reaction system, leading to the facile construction of complex molecules.

### Scheme 40. General Process of Type IV Cascade Reaction



In 2011, Barluenga and co-workers reported a palladium-catalyzed autotandem reaction involving a migratory insertion coupling process (Scheme 41).[55] This reaction used tosylhydrazones **125** derived from $\beta$-aminoketones with *o*-bromochlorobenzene derivatives **126** as the substrates, affording quinoline derivatives **127** as the product in moderate to good yields. The mechanism of this reaction is believed to involve C−C bond formation to produce intermediate **128**, followed by intramolecular C−N bond formation.

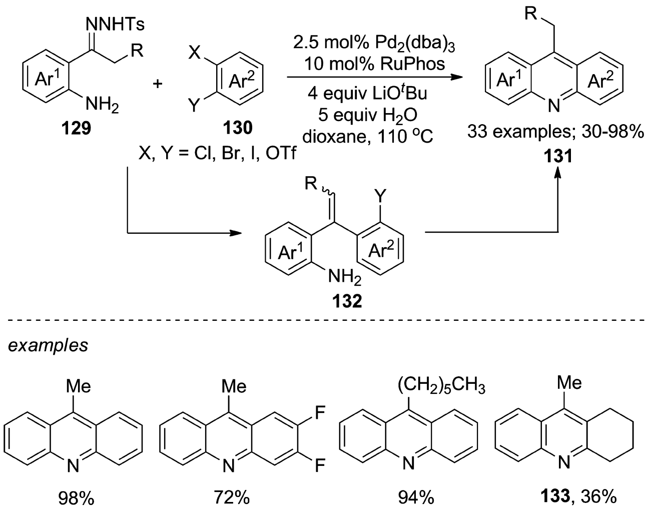
### Scheme 41. Pd-Catalyzed Synthesis of Quinoline Derivatives through a C−C/C−N Bonds Formation Sequence



The starting material $\beta$-aminoketones can be easily obtained in enantiomerically enriched form through asymmetric organocatalyzed Mannich reactions.[56] Thus, the combination of organocatalysis with the palladium autotandem catalysis provides a useful method for the construction of the quinoline skeleton in enantiomerically enriched form.

Wang and co-workers later reported a palladium-catalyzed autotandem reaction by using *N*-tosylhydrazones derived from *o*-aminoarylketones **129** and *o*-dihalobenzenes **130** as the substrates (Scheme 42).[57] In this transformation, a C=C bond and a C(sp$^2$)−N bond are created in one-pot fashion to construct the acridine skeleton in the presence of the single palladium complex. Mechanistic study indicates that reaction likely follows a pathway with a faster C=C bond formation and subsequent intramolecular C−N bond formation. Thus, the reaction involves the intermediate **132**. This intermediate was independently prepared, and it could, indeed, be transformed to **131** in quantitative yield under the identical reaction conditions.

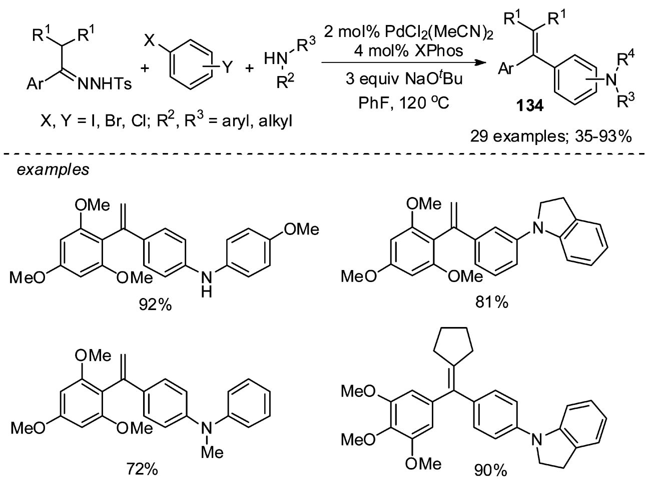
### Scheme 42. Acridine Synthesis through Pd-Catalyzed Autotandem Reaction



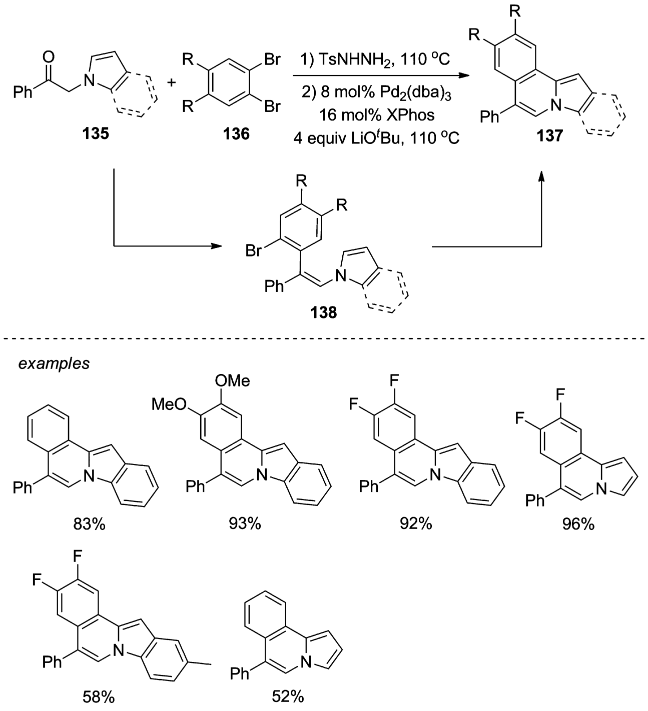
This cascade reaction has broad scope for both coupling substrates, affording a series of highly functionalized acridine derivatives with yields up to 98%. In addition, quinoline derivative **133** can also be obtained in this reaction, and the low yield might be ascribed to the migratory insertion of a vinyl group, rather than an aryl moiety. Moreover, the regioselective synthesis of acridines could be achieved by employing unsymmetrical *o*-dihalobenzenes.

The autotandem reaction of successive C−C and C−N bond formation is also successfully applied in the Pd-catalyzed three-component reaction of *N*-tosylhydrazones, dihaloarenes, and amines (Scheme 43).[58] This cascade reaction involves an intermolecular C−N cross-coupling process, which is different from the autotandem reactions described in Scheme 42. Good to excellent yields are obtained by exploring a wide range of substrates. The products 1,1-diarylethylene derivatives **134** bearing various nitrogen substituents at the aromatic ring are promising molecules with biological activity.

### Scheme 43. Synthesis of 1,1-Diarylethylenes through Pd-Catalyzed Auto-Tandem Reaction



### Scheme 44. Pd-Catalyzed Autotandem Reaction to Pyrroloisoquinolines



Very recently, Valdés and co-workers developed another palladium-catalyzed autotandem reaction to synthesize pyrroloisoquinoline derivatives **137** from *α*-*N*-azoleketones **135** and 1,2-dibromobenzenes **136** (Scheme 44).[59] This reaction is an excellent example of the Pd-catalyzed C−C/C−C autotandem process, which involves the carbene migratory insertion process to generate intermediate **138** and subsequent intramolecular C−H arylation to form a C(sp$^2$)−C(sp$^2$) bond. The *Z*-configuration in *N*-alkenylazole **138**, which is necessary for the following C−H arylated process, may be attributed to the ortho-stereodirecting effect.[60]

## 6. CONCLUSION

Transition-metal-catalyzed cascade reactions involving the carbene migratory insertion process has attracted significant interest in recent years. These reactions are categorized into four different types in this review article. The transition metals, which catalyze these transformations, are focused mainly on palladium and copper, with only two examples of rhodium. Generally, more than one C−X (X = C, H, C, O, N) bond is formed in these cascade reactions, providing useful methods for rapid construction of complex molecules.

The development of such cascade reactions also promotes the understanding of carbene migratory insertion process. Very recently, Wang and co-workers reported the employment of conjugated ene−yne-ketones as carbene precursors to participate in the cross-coupling reaction involving the carbene migratory insertion process.[61] This reaction demonstrates that the cross-coupling reaction with carbene migratory insertion is not limited to diazo or tosylhydrazone chemistry. From the accumulated reports, we consider that carbene migratory insertion is a rather general process that can merge with other transition-metal-catalyzed process in a single catalytic system. It is thus expected that many more useful catalytic cascade reactions based on this concept will be developed in the future.

## AUTHOR INFORMATION

### Corresponding Author

*Phone: (8610)-6275-7248. Fax: (8610)-6275-1708. E-mail: wangjb@pku.edu.cn.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This project is supported by the 973 Program (No. 2012CB821600) and Natural Science Foundation of China (No. 21272010).

## ABBREVIATIONS

TMS, trimethylsilyl; dba, *trans,trans*-dibenzylideneacetone; cod, 1,5-cyclooctadiene; Cp*, pentamethylcyclopentadienyl; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; RuPhos, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; EDA, ethyl diazoacetate; DTBP, 2,6-di-*tert*-butyl-4-methylpyridine; DCE, 1,2-dichloroethane; DMAC, *N,N*-dimethylacetamide; MTBE, *tert*-butyl methyl ether; METHF, 2-methyltetrahydrofuran; BTAC, benzyl triethylammonium chloride; Piv, pivaloyl; TBAB, *tetra*-butyl ammonium bromide; Aliquant 336, tri-*n*-octylmethylammonium chloride.

## REFERENCES

(1) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(2) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326−3350.

(3) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577−6605.

(4) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735−4740.

(5) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479−1492.

(6) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.

(7) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1797−1815.

(8) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269.

(9) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.

(10) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935.

(11) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015−1026.

(12) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486−7500.

(13) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560−572.

(14) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236−247.

(15) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219−5225.

(16) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587−5590.

(17) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566−1567.

(18) Zhou, L.; Ye, F.; Ma, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3510−3514.

(19) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114−1117.

(20) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114−4133.

(21) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139−1142.

(22) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245.

(23) Zhou, P.-X.; Zhou, Z.-Z.; Chen, Z.-S.; Ye, Y.-Y.; Zhao, L.-B.; Yang, Y.-F.; Xia, X.-F.; Luo, J.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 561−563.

(24) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(25) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198−4200.

(26) Xiao, Q.; Wang, B.; Tian, L.; Yang, Y.; Ma, J.; Zhang, Y.; Chen, S.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9305−9308.

(27) Krenske, E. H.; Houk, K. N. *Acc. Chem. Res.* **2013**, *46*, 979−989.

(28) Liu, X.; Ma, X.; Huang, Y.; Gu, Z. *Org. Lett.* **2013**, *15*, 4814−4817.

(29) Liu, Z.; Xia, Y.; Zhou, S.; Wang, L.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 5032−5035.

(30) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609−2614.

(31) Kudirka, R.; Van Vranken, D. L. *J. Org. Chem.* **2008**, *73*, 3585−3588.

(32) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *132*, 13590−13591.

(33) Xia, Y.; Hu, F.; Liu, Z.; Qu, P.; Ge, R.; Ma, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2013**, *15*, 1784−1787.

(34) Titanyuk, I. D.; Beletskaya, I. P. *Synlett* **2013**, *24*, 355−358.

(35) Chen, Z.-S.; Duan, X.-H.; Zhou, P.-X.; Ali, S.; Luo, J.-Y.; Liang, Y.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1370−1374.

(36) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047−2049.

(37) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909−1911.

(38) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677−3680.

(39) Khanna, A.; Maung, C.; Johnson, K. R.; Luong, T. T.; Van Vranken, D. L. *Org. Lett.* **2012**, *14*, 3233−3235.

(40) Zhou, P.-X.; Luo, J.-Y.; Zhao, L.-B.; Ye, Y.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 3254−3256.

(41) Tsoi, Y.-K.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *13*, 5370−5373.

(42) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565−13568.

(43) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364−5367.

(44) Guimond, N.; Gorelsky, S. L.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449−6457.

(45) Ye, F.; Hossain, M. L.; Xu, Y.; Ma, X.; Xiao, Q.; Zhang, Y.; Wang, J. *Chem.—Asian J.* **2013**, *8*, 1404−1407.

(46) Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013**, *13*, 7287−7342.

(47) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330−4341.

(48) Zhang, Z.; Zhang, Y.; Wang, J. *ACS Catal.* **2011**, *1*, 1621−1630.

(49) Zhou, F.; Ding, K.; Cai, Q. *Chem.—Eur. J.* **2011**, *17*, 12268−12271.

(50) Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 968−971.

(51) Xiao, T.; Dong, X.; Zhou, L. *Org. Biomol. Chem.* **2013**, *11*, 1490−1497.

(52) Ye, F.; Shi, Y.; Zhou, L.; Xiao, Q.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5020−5023.

(53) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379.

(54) Wasike, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020.

(55) Barluenga, J.; Quiñones, N.; Cabal, M.-P.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 2350−2353.

(56) Rodríguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888−2891 and references cited therein.

(57) Huang, Z.; Yang, Y.; Xiao, Q.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2012**, 6586−6593.

(58) Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M. *Org. Lett.* **2013**, *15*, 148−151.

(59) Florentino, L.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2013**, *19*, 10506−10510.

(60) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510−513.

(61) Xia, Y.; Qu, S.; Xiao, Q.; Wang, Z.-X.; Qu, P.; Chen, L.; Liu, Z.; Tian, L.; Huang, Z.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 13502−13511.