Diazo Compounds and *N*-Tosylhydrazones: Novel Cross-Coupling Partners in Transition-Metal-Catalyzed Reactions

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CONSPECTUS

Transition-metal-catalyzed carbene transformations and cross-couplings represent two major reaction types in organometallic chemistry and organic synthesis. However, for a long period of time, these two important areas have evolved separately, with essentially no overlap or integration. Thus, an intriguing question has emerged: can cross-coupling and metal carbene transformations be merged into a single reaction cycle? Such a combination could facilitate the development of novel carbon—carbon bond-forming methodologies.

Although this concept was first explored about 10 years ago, rapid developments in this area have been achieved recently. Palladium catalysts can be used to couple diazo compounds with a wide variety of organic halides. Under oxidative coupling conditions, diazo compounds can also react with arylboronic acids and terminal alkynes. Both of these coupling reactions form carbon—carbon double bonds. As the key step in these catalytic processes, Pd carbene migratory insertion plays a vital role in merging the elementary steps of Pd intermediates, leading to novel carbon—carbon bond formations.

Because the diazo substrates can be generated *in situ* from *N*-tosylhydrazones in the presence of base, the *N*-tosylhydrazones can be used as reaction partners, making this type of cross-coupling reaction practical in organic synthesis. *N*-Tosylhydrazones are easily derived from the corresponding aldehydes or ketones. The Pd-catalyzed cross-coupling of *N*-tosylhydrazones is considered a complementary reaction to the classic Shapiro reaction for converting carbonyl functionalities into carbon—carbon double bonds. It can also serve as an alternative approach for the Pd-catalyzed cross-coupling of carbonyl compounds, which is usually achieved via triflates.

The combination of carbene formation and cross-coupling in a single catalytic cycle is not limited to Pd-catalyzed reactions. Recent studies of Cu-, Rh-, Ni-, and Co-catalyzed cross-coupling reactions with diazo compounds or *N*-tosylhydrazones show that these transformations also work with other transition metals, demonstrating the generality of the diazo compounds as new cross-coupling partners in transition-metal-catalyzed coupling reactions.
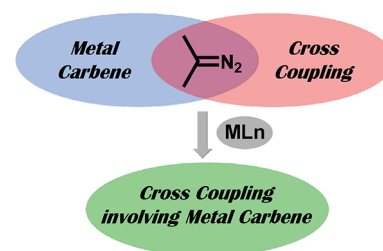
Introduction

Diazo compounds have found wide applications in modern synthetic organic chemistry.[1] In particular, transition-metal-catalyzed reactions of diazo compounds generate metal carbene species, which can undergo diverse reactions (Scheme 1). Extensive investigations of the transition-metal-catalyzed reactions of diazo compounds have led to the development of an array of very valuable synthetic methodologies. Although significant progress has been made in this field, the discovery and development of highly efficient catalytic tran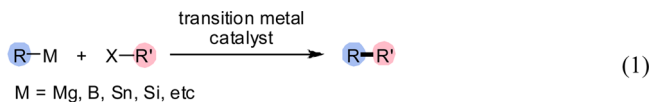sformations via transition metal carbene intermediates are still one of the most important and attractive areas in the research of modern synthetic methodology.

On the other hand, transition-metal-catalyzed cross-coupling reactions have been established as indispensable tools for the carbon—carbon and carbon—heteroatom bond formations in modern synthetic organic chemistry.[2] A typical transition-metal-catalyzed cross-coupling reaction is the reaction that joins two molecular fragments using a transition metal as catalyst (eq 1). The electrophilic partners employed in the coupling reaction are usually halides or pseudohalides, while the nucleophilic coupling partners are

SCHEME 1. Metal Carbene Reactions
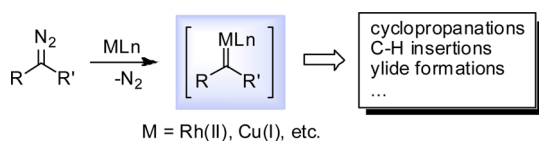
typically organometallic reagents for carbon–carbon bond formation, except the Heck-type reaction, in which C=C double bonds serve as the nucleophilies. In the case of carbon–heteroatom bond formations, the nucleophiles are amines, alcohols, phenols, thiophenols, etc. The exploration of new cross-coupling partners for transition-metal-catalyzed reactions has been one of the major tasks of the organic synthesis community in the last decades.

$$R-M \ + \ X-R' \xrightarrow[\text{catalyst}]{\text{transition metal}} R-R' \qquad (1)$$

M = Mg, B, Sn, Si, etc

Both transition-metal-catalyzed cross-couplings and carbene transformations have now been developed into standard methodologies in organic synthesis. However, these two major domains in organometallic chemistry and organic synthesis have so far evolved essentially independently, and there is little overlap between them. It is thus highly interesting to consider a catalytic cycle that integrates both cross-coupling and carbene processes. Such integration may result in new carbon–carbon bond forming methods that are distinct from both classic cross-coupling and carbene transformation.

The explorations toward this goal in the past decade have demonstrated that this is indeed the case. An array of novel Pd-catalyzed reactions with diazo compounds as cross-coupling partners has now been established.[3] These reactions are mechanistically different from the classic Pd-catalyzed cross-coupling reactions (Scheme 2, cycle I versus cycle II). Oxidative insertion initiates the catalytic cycle for both cases, generating organopalladium species **A**. In the standard cross-coupling reactions, intermediate **A** follows the ligand exchange–reductive elimination sequence (cycle I), while in the presence of a diazo substrate, **A** reacts with the diazo substrate to form a palladium carbene species **C**. Subsequently, migratory insertion of the carbene ligand to the palladium–carbon bond leads to the formation of a new Pd species **D**, which undergoes further reactions, typically β-hydrogen eliminations.

The migratory insertion of Pd carbene in cycle II is found to be general in terms of the migratory groups, which include

SCHEME 2. Standard Cross-Coupling versus the Coupling Involving a Carbene Process



Standard Coupling   Coupling involving Carbene
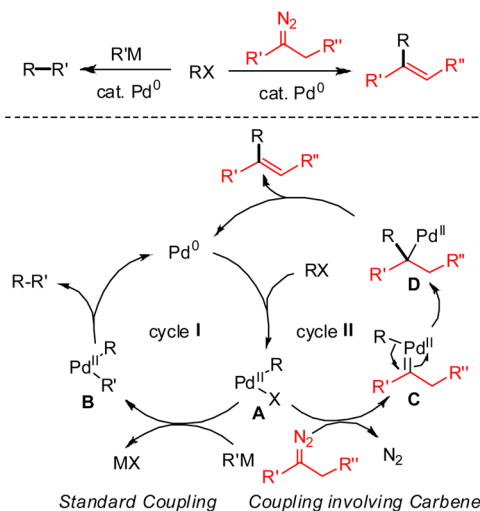
aryl, vinyl, benzyl, acyl, allyl, allenyl, alkynyl, propargyl, and cyclopropyl. Moreover, this type of cross-coupling is not limited to palladium catalysts. Copper, rhodium, nickel and cobalt catalysts are also effective for similar couplings. This Account will focus on the most recent advances in this rapidly growing area with some limited background introduction.[3]

Early Studies on Pd-Catalyzed Cross-Coupling with Diazo Compounds

Despite the great success of palladium as catalyst in cross-coupling reactions, the Pd-catalyzed reactions that involve Pd carbene as reactive intermediates have only been sporadically documented in the literature.[4] In 2003, the first Pd(II) complex of a non-heteroatom stabilized carbene ligand was reported.[5] However, the inertness of this complex precluded the detailed study into its chemical properties. In contrast, Pd-catalyzed reactions of diazo compounds have been examined quite long ago.[1] The studies have indicated different reaction patterns in the case of Pd-catalyzed reaction of diazo compounds compared with the corresponding Rh(II)- or Cu(I)-catalyzed reactions. For instance, in Pd-catalyzed cyclopropanation of diazomethane, it was proposed that the reaction proceeds through electrophilic addition by Pd-olefin complexes to diazomethane, rather than through a Pd-carbene intermediate.[6]

The first catalytic cross-coupling involving a Pd carbene migratory insertion process was reported in 2001 by Van Vranken and co-workers.[7] They used benzyl halides as electrophiles and (trimethylsilyl)diazomethane (TMSCHN₂) as the carbene precursor. The reaction afforded the styrene derivatives in moderate yields (Scheme 3).
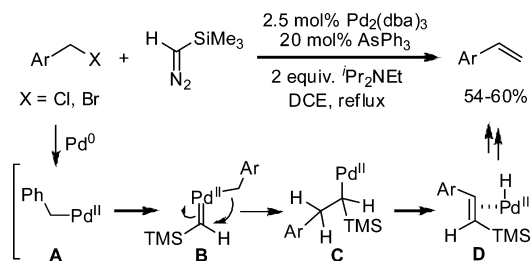
In the proposed mechanism, the Pd(II) species **A** is first generated through oxidative addition (Scheme 3). Then, **A** reacts with TMSCHN$_2$, and Pd(II) carbene species **B** is formed via dinitrogen extrusion. Subsequently, migratory insertion takes place to form a new Pd(II) species **C**, from which β-hydrogen elimination occurs. Finally, the sequence of insertion/β-silicon elimination/reductive elimination delivers the final product and regenerates the Pd(0) catalyst.

Van Vranken's pioneering work opens up new possibilities for both diazo compounds and Pd-catalyzed cross-coupling.[8] However, these reactions have not attracted much attention in the following years, presumably due to the limited scope and low efficiency of the reactions in the initial studies.

Pd-Catalyzed Cross-Coupling with *N*-Tosylhydrazones

Diazo compounds bearing no electron-withdrawing substituent on the diazo carbon, such as diazoalkanes and aryl-substituted diazomethane derivatives, are generally unstable and difficult to handle. To expand the substrate scope and, more importantly, to make this novel Pd-catalyzed coupling reaction practically useful in organic synthesis, other sources that can generate unstable diazo compounds *in situ* have to be considered. In this context, *N*-tosylhydrazones have been proven to be very useful for the *in situ* generation of nonstabilized diazo compounds through Bamford—Stevens reaction (eq 2).
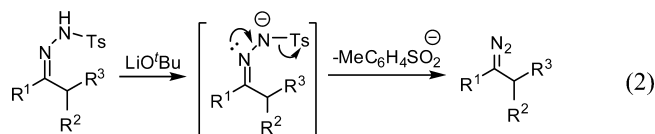
Barluenga and co-workers first demonstrated the application of *N*-tosylhydrazones in the Pd-catalyzed cross-coupling with aryl halides in the presence of base (Scheme 4).[9] The reaction is catalyzed by Pd$_2$(dba)$_3$ with Xphos (2-dicyclohexylphosphino-2′,4′,6′-triisopropyl biphenyl) as ligand. The tosylhydrazones are derived from cyclic ketones, aryl

SCHEME 4. Pd-Catalyzed Cross-Coupling of *N*-Tosylhydrazones
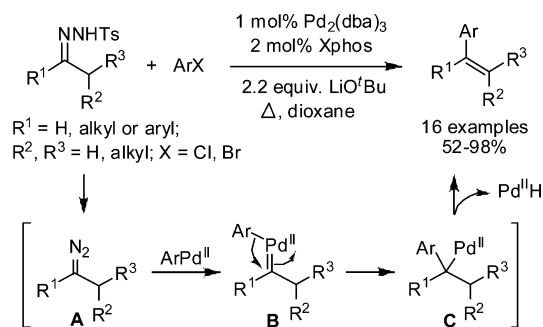
ketones, or alky carboxyaldehydes. Either aryl bromides or aryl chlorides can undergo the transformation smoothly. The reaction also shows good functional group compatibility.

The reaction is proposed to be initiated by oxidative addition of aryl halide to Pd(0) species to form an aryl palladium(II) complex. The Pd(II) carbene **B** is then produced by dediazoniation of the *in situ* generated diazo compound **A**. Migratory insertion of the carbene to Pd—aryl bond leads to the formation of Pd(II) intermediate **C**, which is followed by β-hydrogen elimination to afford the alkene products.

Following Barluenga's seminal report, an array of Pd-catalyzed cross-coupling reactions with *N*-tosylhydrazones has been developed.[3b,c,10−12] Since *N*-tosylhydrazones are readily available from the corresponding ketones or aldehydes, this type of cross-coupling is expected to find applications in organic synthesis.

Cross-Coupling of Diazoacetate with Aryl- or Vinylhalides

In 2007, our long-standing interest in the chemistry of diazo compounds led us to study the Pd-catalyzed cross-coupling reactions of diazo compounds. Initially, we tried to combine aryl or vinyl iodides (very common electrophiles in cross-coupling) with ethyl diazoacetate (EDA, a very common diazo compound) in a Pd-catalyzed reaction system. The cross-coupling of vinyl iodides and EDA with Pd(PPh$_3$)$_4$ as catalyst and triethylamine as an additive afforded α,β-unsaturated α-diazoesters (Scheme 5).[13] Surprisingly, the diazo group remains intact in this reaction, which is contrary to the general conviction that diazo functionality decomposes readily when exposed to transition metals. The coupling reaction works similarly with aryl iodides.

The mechanism of this reaction is proposed to follow the pathway of a conventional Pd-catalyzed coupling reaction (Scheme 6). Oxidative addition generates the Pd(II) intermediate **A**, to which EDA coordinates to form complex **B**. Deprotonation then occurs to afford complex **C**, which is

SCHEME 5. Selected Examples of Pd-Catalyzed Cross-Coupling of Vinylhalides with EDA
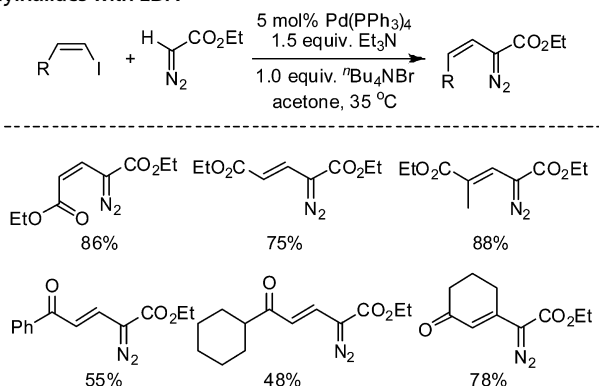
SCHEME 6. The Mechanism of Pd-Catalyzed Cross-Coupling of Iodides with EDA
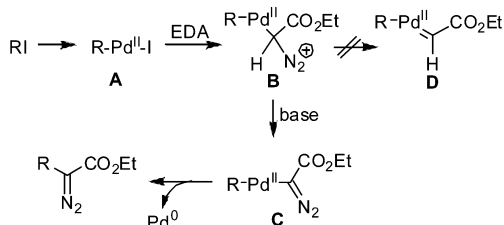
followed by reductive elimination to give the coupling product. Notably, nitrogen extrusion (that is, the formation of **D**), which is usually a very facile process for transition-metal-complexed diazo compounds, does not occur from complex **B**. This fact implies that the back-electron-donation from Pd to form a Pd carbene is not a facile process. This may explain the experimental observations that Pd-catalyzed dediazoniation usually requires forced conditions as compared with the corresponding Cu(I)- and Rh(II)-catalyzed reactions.

This reaction seems to represent the first example of using a diazo compound as a simple nucleophilic partner in Pd-catalyzed cross-coupling reaction. It provides a straightforward approach to introduce the diazo functionality to the organic molecule.[14] Frantz and co-workers have reported similar Pd-catalyzed cross-coupling of enol triflates and EDA. The reaction has been used in a tandem cross-coupling electrocyclization process to synthesize pyrazole derivatives.[15a] More recently, Reissig and co-workers have reported Pd-catalyzed coupling of pyrid-4-yl nonaflates with methyl diazoacetate.[15b]

Cross-Coupling of Diazo Compounds or N-Tosylhydrazones with Arylboronic Acids

We subsequently studied the Pd-catalyzed oxidative cross-coupling between boronic acids and α-diazocarbonyl

SCHEME 7. Pd-Catalyzed Oxidative Cross-Coupling between Boronic Acids and α-Diazocarbonyl Compounds
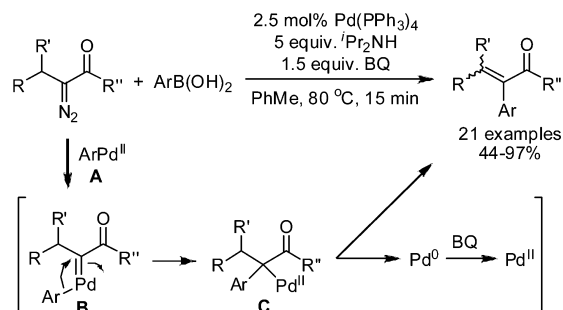
compounds, which afforded α-aryl α,β-unsaturated carbonyl compounds as products (Scheme 7).[16] The reaction requires benzoquinone (BQ) as the oxidant to regenerate the Pd(II) catalyst. Interestingly, the diazo functionality, which is prone to undergo oxidation, is not directly oxidized by BQ.

The possible mechanism for this reaction involves the following main steps: (i) transmetalation with the arylboronic acid gives the intermediate **A**; (ii) dediazoniation of the α-diazocarbonyl substrate generates the Pd carbene complex **B**; (iii) migratory insertion of the aryl group to the carbenic carbon forms the intermediate **C**; (iv) β-hydrogen elimination provides the final product with the generation of Pd(0); (v) oxidation of the Pd(0) species regenerates the Pd(II) catalyst (Scheme 7).
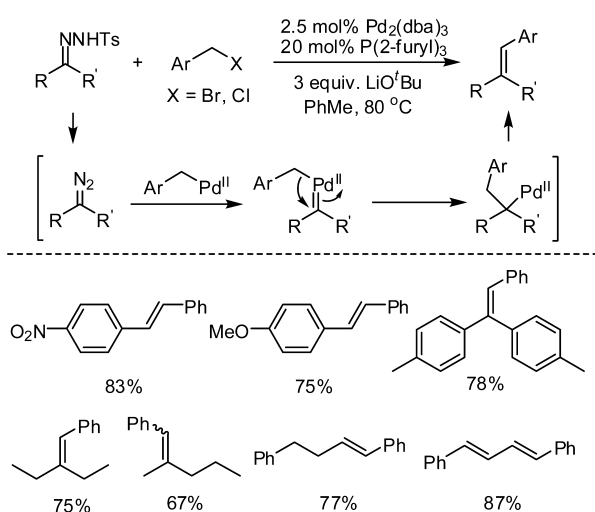
Furthermore, we have developed a similar transformation with N-tosylhydrazones and arylboronic acids.[17] With catalytic Pd(PPh$_3$)$_4$, LiO^{t}Bu as the base, and CuCl (10 mol %) combined with O$_2$ as the oxidant, the oxidative cross-coupling reaction can provide di-, tri-, and tetrasubstituted alkenes in moderate to good yields (eq 3).
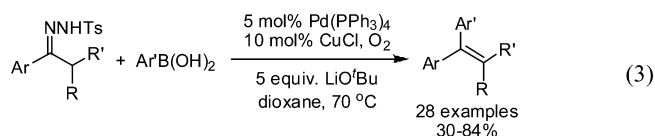
In the reaction mechanism shown in Scheme 7, the Pd(II) intermediate **A** can be generated through oxidative addition of Pd(0) to ArX, instead of through oxidation and transmetalation with arylboronic acids. Thus, Pd-catalyzed cross-coupling of α-diazo carbonyl compounds with aryl halide is expected to proceed in similar manner but without oxidant. This has been proven to be the case.[18]

Cross-Coupling of Diazo Compounds or N-Tosylhydrazones with Benzyl Halides and Allyl Halides

Both allyl- and benzylpalladium species are common intermediates in Pd-catalyzed reactions. Thus, it is also expected
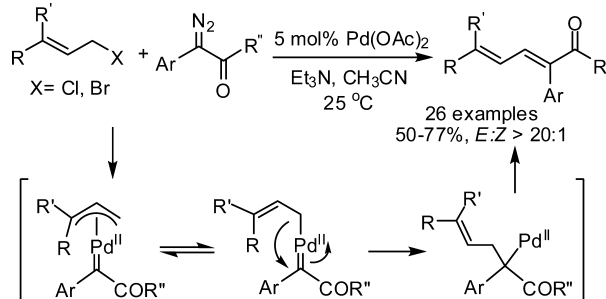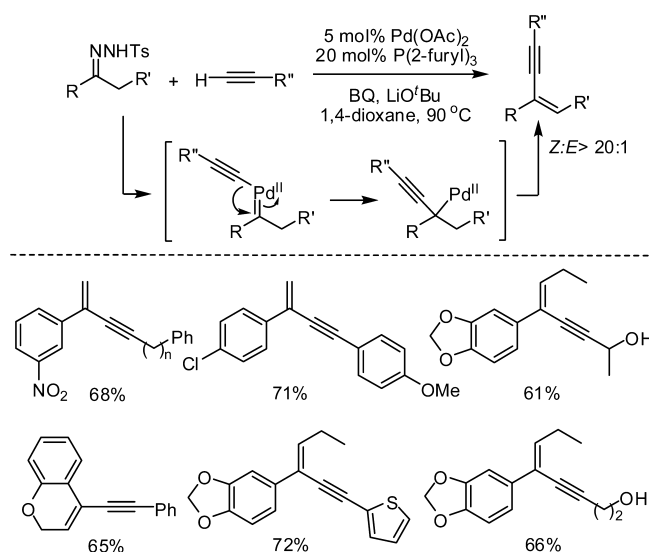
SCHEME 8. Selected Examples of Pd-Catalyzed Cross-Coupling between Benzylhalides and N-Tosylhydrazones

$$\text{2.5 mol\% Pd}_2\text{(dba)}_3 \quad 20 \text{ mol\% P(2-furyl)}_3 \quad 3 \text{ equiv. LiO}^t\text{Bu} \quad \text{PhMe, 80 }^\circ\text{C}$$

83%   75%   78%

75%   67%   77%   87%

SCHEME 9. Pd-Catalyzed Cross-Coupling of Diazo Compounds with Allylhalides

$$X = \text{Cl, Br} \quad 5 \text{ mol\% Pd(OAc)}_2 \quad \text{Et}_3\text{N, CH}_3\text{CN} \quad 25 \text{ }^\circ\text{C}$$

26 examples
50–77%, *E:Z* > 20:1

SCHEME 10. Selected Examples of Pd-Catalyzed Oxidative Cross-Coupling of N-Tosylhydrazones with Terminal Alkynes

$$5 \text{ mol\% Pd(OAc)}_2 \quad 20 \text{ mol\% P(2-furyl)}_3 \quad \text{BQ, LiO}^t\text{Bu} \quad 1,4\text{-dioxane, 90 }^\circ\text{C}$$

Z:E > 20:1

68%   71%   61%

65%   72%   66%

to introduce the diazo substrates in the Pd-catalyzed reactions involving these species. In 2009, we reported the Pd-catalyzed cross-coupling reaction involving N-tosylhydrazones and benzyl halides (Scheme 8).[19] This coupling reaction is effective with a variety of benzyl bromides and chlorides bearing electron-donating or electron-withdrawing groups, giving di- and trisubstituted olefins in high yields with excellent stereo-selectivities. Similar reactions with EDA or aryldiazoacetates have been reported by Van Vranken[8a] and Yu,[20] respectively.

Similarly, we have found that allyl halides react efficiently with aryldiazoacetates or aryldiazoacetone derivatives when catalyzed by Pd(OAc)₂ in the presence of Et₃N, affording 1,3-diene derivatives in good yields and with excellent stereoselectivities (Scheme 9). Both allyl chlorides and allyl bromides worked well in this reaction. The reaction mechanism is similar to those previously described. Notably, the migratory group in this case is the allyl group. However, an alternative mechanism involving direct attack of the diazo substrate on the allyl ligand of the π-allylic palladium species cannot be strictly excluded.[21]

Cross-Coupling of Diazo Compounds or N-Tosylhydrazones with Terminal Alkynes
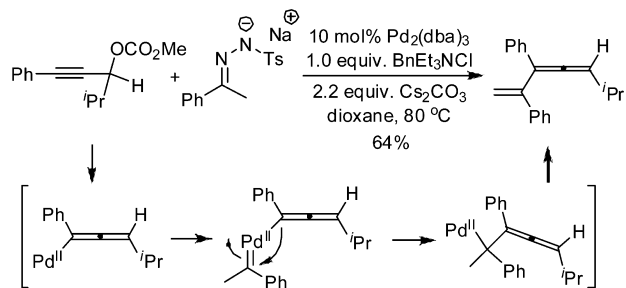
Terminal alkynes are widely used in Pd-catalyzed Sonogashira cross-coupling reactions, which is a powerful method to introduce an alkynyl group to organic molecules. We found that under oxidative conditions, terminal alkynes can also couple with diazo compounds or 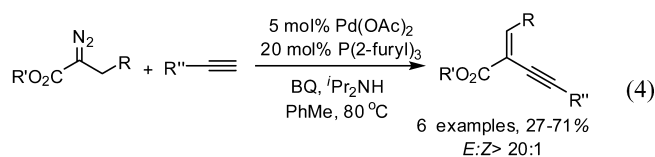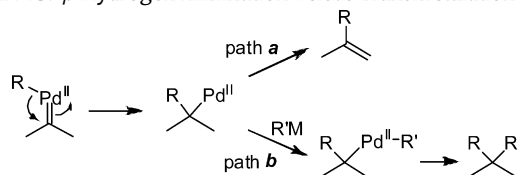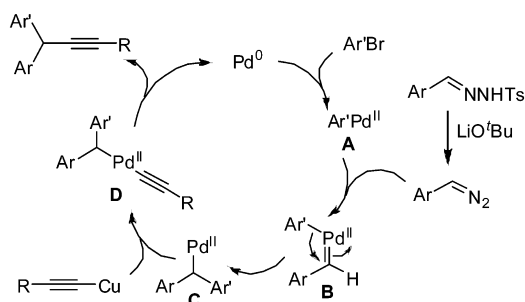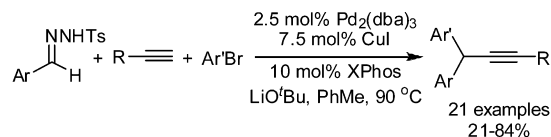N-tosylhydrazones, affording conjugated enyne products (Scheme 10).[22] It is noteworthy that this reaction expands the migratory group in Pd carbene to the alkynyl group.

In this oxidative cross-coupling, the weak electron-rich ligand P(2-furyl)₃ in combination with Pd(OAc)₂ affords the optimal results. The reaction shows wide substrate scope for both N-tosylhydrazone and terminal alkyne components. Various *ortho*-, *para*-, and *meta*-substituted aromatic N-tosylhydrazones can be used to produce the desired conjugated enynes in moderate to good yields. Both electron-donating and electron-withdrawing groups on the aromatic ring are tolerated. Aliphatic, aromatic, and heteroaryl alkynes are all suitable substrates.

α-Diazocarbonyl compounds can also be utilized in lieu of N-tosylhydrazones as coupling partners under slightly modified conditions (eq 4). The treatment of terminal alkynes with a series of α-diazocarbonyl compounds in the presence of ⁱPr₂NH furnished the corresponding

SCHEME 11. Migratory Insertion of Allenyl Group in Pd-Catalyzed Reaction

SCHEME 12. Migratory Insertion Cyclopropyl Group in Pd-Catalyzed Reaction

enyne products in moderate to good yields with high stereoselectivity.

$$R'O_2C \overset{N_2}{\diagdown} R + R'' \!\!=\!\! \xrightarrow[\substack{BQ,\,^iPr_2NH \\ PhMe,\,80\,^\circ C}]{\substack{5\ mol\%\ Pd(OAc)_2 \\ 20\ mol\%\ P(2\text{-furyl})_3}} \quad (4)$$

6 examples, 27–71%
E:Z > 20:1

Migratory Insertion of Allenyl and Cyclopropyl Groups

From the above-discussed reactions it can be seen that the migratory groups of the Pd carbene are quite general, which include aryl, vinyl,[8] benzyl, and allyl groups. It is thus reasonable to expect other migratory groups in this type of reaction. In 2011, Liang and co-workers reported the reaction in which the allenyl migratory insertion of Pd carbene is involved (Scheme 11).[12]

More recently, we have demonstrated that cyclopropyl migratory insertion is also possible in the Pd carbene transformation (Scheme 12).[23] This reaction constitutes an interesting access toward cyclopropylmethyl palladium species, which has been known to undergo ring-opening rearrangement through β-carbon elimination.

Three-Component Cross-Coupling Reactions

In the catalytic cycle of the cross-coupling reactions described above, the alkyl palladium species, which are formed by migratory insertion, typically undergo β-hydrogen elimination to give rise to the final products with the formation of C=C double bond (Scheme 13, path a). However, when the β-hydrogens are not available,[24] it may be possible to undergo a cascade process, such as a transmetalation with an organometallic reagent and subsequent reductive elimination to form two separate C−C single bonds in a carbenic center (Scheme 13, path b).

Such cascade reactions have been previously explored by Van Vranken and co-workers.[7,8d] Based on a similar concept, we have recently developed three-component

SCHEME 13. β-Hydrogen Elimination versus Transmetalation

SCHEME 14. Pd-Catalyzed Three-Component Cross-Coupling Reaction

coupling reactions of *N*-tosylhydrazones, terminal alkynes, and aryl halides (Scheme 14).[25] Aryl bromides have to be used in order to avoid the competing process of direct Sonogashira cross-coupling between aryl halides and terminal alkynes. The use of more reactive aryl iodides mainly yields Sonogashira coupling products.

In the reaction mechanism, arylpalladium intermediate **A**, which is formed through the oxidative addition of Pd(0) to aryl bromide, may undergo a competing transmetalation with copper acetylide generated *in situ*. In reactions with aryl bromides, Pd(II) species **A** preferentially follows the alternative pathway to react with the *in situ* generated diazo substrate, leading to the formation of Pd(II) carbene **B**. Subsequently, migratory insertion affords alkyl palladium species **C**. Since there is no β-hydrogen available in

SCHEME 15. Pd-Catalyzed Decarboxylation–Migratory Insertion–Reductive Elimination Cascade

SCHEME 16. Pd-Catalyzed Carbonylation/Acyl Migratory Insertion Cascade
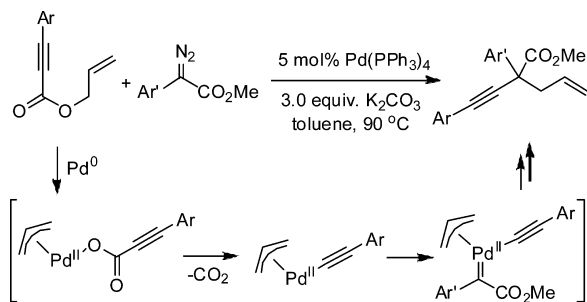
palladium species **C**, transmetalation with copper acetylide is then followed to give **D**. Finally, reductive elimination provides the benzhydryl acetylenic product. This process demonstrates the possibility to incorporate carbene migratory insertion with other elementary processes of Pd-catalyzed reaction.

More recently, Liang and co-workers reported a very interesting reaction that involves a decarboxylation–migratory insertion–reductive elimination cascade (Scheme 15).[26] The reaction uses allylic alkynoates and aryldiazoacetates as cross-coupling partners, affording 1,5-enynes in moderate yields. This reaction represents an efficient method to construct a quaternary carbon center.

## Pd-Catalyzed Reaction of Diazo Compounds or *N*-Tosylhydrazones in the Presence of Carbon Monooxide

As a powerful method for introducing carbonyl functionality, insertion of a CO ligand to form a reactive acylpalladium intermediate is a fundamental process in organopalladium chemistry. The Pd-catalyzed carbonylation of aryl halides or pseudohalides is now widely applied in organic synthesis.[27] To further explore the reaction of Pd carbene migratory insertion, we have conceived that incorporation of diazo compounds or *N*-tosylhydrazones into the Pd-catalyzed carbonylation process may be a valuable endeavor. Such an assumption has led to some interesting transformations incorporating both carbonylation and carbene processes.

In 2010, we reported a four-component coupling reaction involving diazo compounds, aryl iodides, and triethylsilanes in the presence of carbon monoxide, affording the 2-methyl-3-oxo-3-arylpropanoates in moderate to good yields (Scheme 16).[28] The reaction is proposed to involve an acyl group migratory insertion of Pd carbene.

In the course of our study on Pd-catalyzed carbonylation of diazo compounds, we observed a highly efficient direct
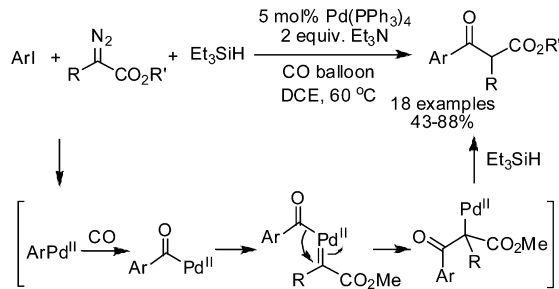
SCHEME 17. Pd-Catalyzed Carbonylation–Staudinger Cycloaddition: β-Lactam Synthesis
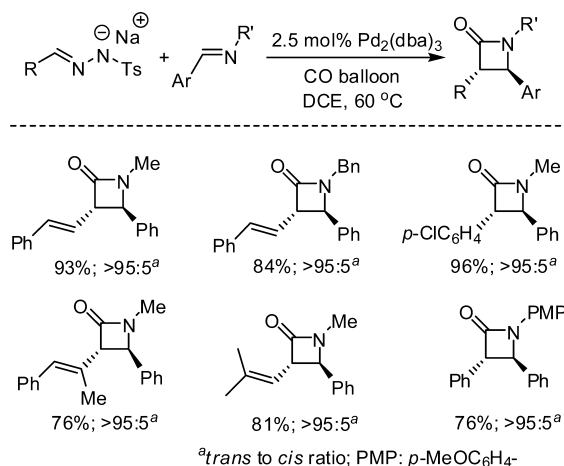
carbonylation of Pd carbene leading to ketene species, which are very useful intermediates in organic synthesis. Conventionally, ketenes are produced from acyl halides through base-promoted dehalogenation.[29] In our reaction, ketene intermediates are formed *in situ* from α-diazocarbonyl compounds or *N*-tosylhydrazone salts with a palladium catalyst under atmospheric pressure of CO (eq 5).[30,31] This straightforward carbonylation provides a novel and practical approach toward efficient catalytic generation of ketene species under mild conditions.
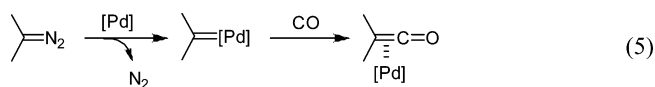
The ketene intermediates undergo further reactions with various nucleophiles such as alcohols, amines, or imines. Furthermore, this catalytic carbene formation can be successfully used in diastereoselective β-lactam synthesis (Scheme 17). DFT calculation on the reaction mechanism has suggested that Pd is involved in the [2 + 2] cycloaddition process and affects the diastereoselectivity of the β-lactam products.[30]

SCHEME 18. Pd-Catalyzed Amidation of *N*-Tosylhydrazones with Isocyanides
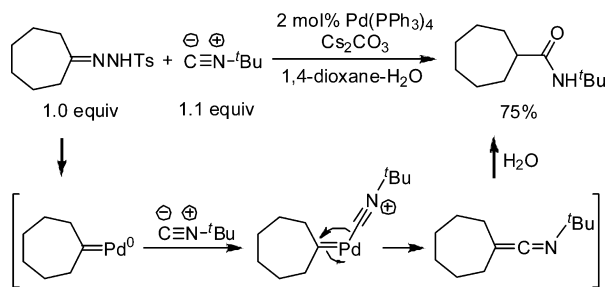
Interestingly, if CO is replaced by isocyanides for a similar Pd-catalyzed reaction, the analogous reaction occurs leading to the amidation of *N*-tosylhydrazones (Scheme 18).[32]

Cross-Coupling Reactions Catalyzed by Other Transition Metals

From the reactions described above, it is seen that Pd-catalyzed cross-coupling can be nicely incorporated with carbene processes. With such combinations, novel transformations that are distinct from both classic cross-coupling and carbene reaction can be expected. Is this chemistry only limited to palladium? Since both in cross-coupling and in carbene chemistry there are many transition metals that are effective as catalysts, it is reasonable to predict that this chemistry may be expanded by using other transition metals. Recent studies have demonstrated that copper,[33−39] rhodium,[40] and nickel and cobalt[41] can also catalyze similar transformations.

Copper-Catalyzed Reactions. It is well-known that Cu(I)-catalyzed carbene transfer reaction with alkene or alkyne usually occurs to afford cyclopropanation or cyclopropenation products.[1,42] However, in the Cu(I)-catalyzed reaction of *N*-tosylhydrazones and terminal alkynes in the presence of base, allenes are formed as the products, while the anticipated cyclopropenation products are not observed (Scheme 19).[33] With this reaction, trisubstituted allenes can be directly synthesized through a transition-metal-catalyzed cross-coupling of two fragments. The Cu(I)-catalyzed coupling reaction may follow a similar reaction pathway as the corresponding Pd-catalyzed reaction. The key step is the migratory insertion of alkynyl ligand in Cu(I) carbene **B**. Compared with the Pd-catalyzed reaction (see Scheme 10), the difference is that β-hydrogen elimination does not occur from Cu(I) species **C**; instead the Cu(I) species is protonated to afford allene as the product. Fox and co-workers have also reported similar Cu-catalyzed allene formation with diazo compounds.[34] Moreover, a Cu(I)-catalyzed cascade coupling/cyclization of

SCHEME 19. Cu(I)-Catalyzed Coupling of *N*-Tosylhydrazones with Terminal Alkynes: Synthesis of Trisubstituted Allenes
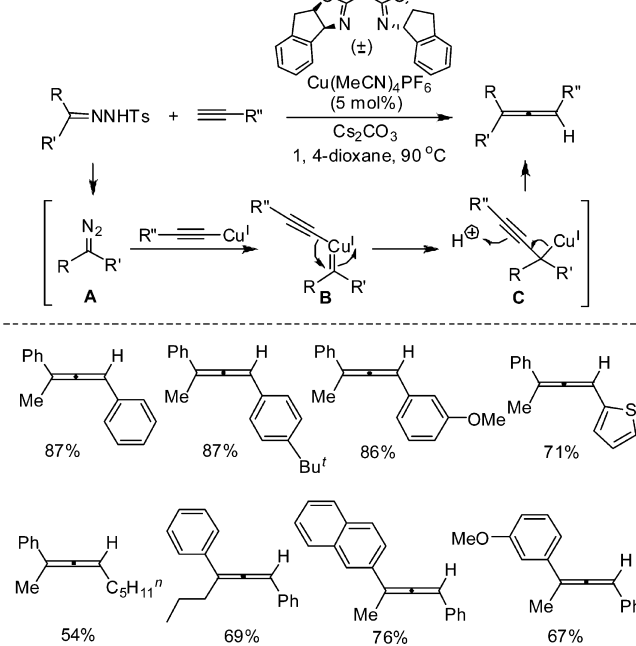
**SCHEME 20.** Cu-Catalyzed Synthesis of Benzofurans, Indoles, and Phenanthrenes
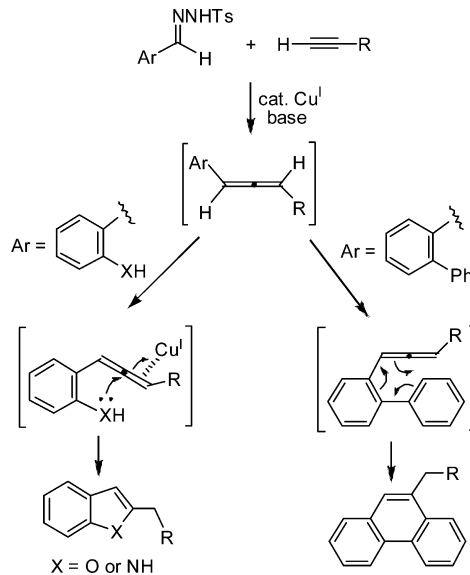
terminal alkynes with diazoacetates has been reported to follow a similar pathway.[35]

Since the allene moiety can be further activated by Cu(I) catalyst, this coupling reaction has been utilized in cascade process for the synthesis of benzofurans[36] and phenanthrenes (Scheme 20).[37]

The sequence of migratory insertion/protonation from Cu(I) carbene, as outlined in eq 6, provides a new

SCHEME 21. Cu-Catalyzed C(sp)–C(sp³) Bond Formation
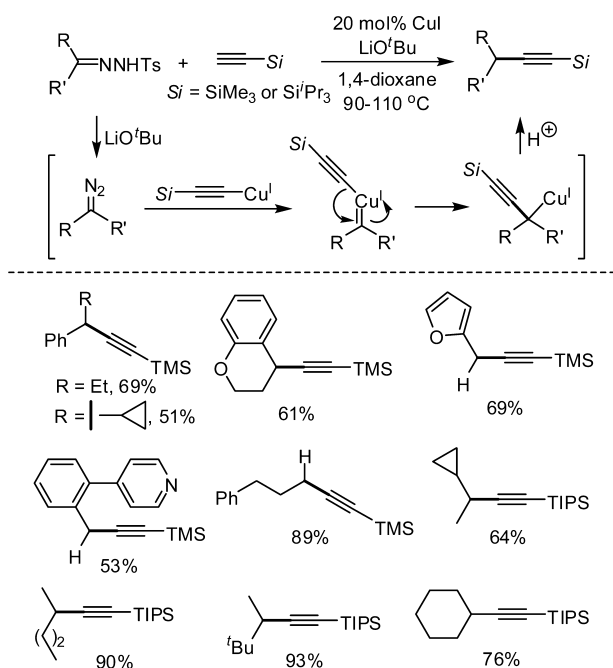
possibility for C(sp²)–C(sp³) and C(sp)–C(sp³) single bond formation.

(6)
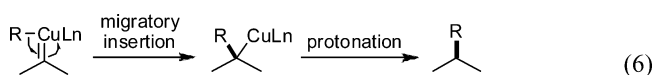
In the Cu-catalyzed reaction of *N*-tosylhydrazones and terminal alkynes, when trialkylsilylethyne is used as the substrate, the ethynylation product was isolated as the major product without detectable formation of allene products (Scheme 21).[38] This result demonstrates the potential of this type of cross-coupling reaction for the construction of C(sp)–C(sp³) bonds, which has been a challenging problem in the past decade.[43] Further examination of the reaction scope has revealed that the reaction works with a wide range of *N*-tosylhydrazones derived from either aromatic and aliphatic aldehydes or ketones. This reaction can be considered as an effective method for converting the carbonyl functionality into an ethynyl group, which is an otherwise troublesome transformation.

Another example to demonstrate the potential of the process shown in eq 6 is the copper-catalyzed direct benzylation or allylation of 1,3-azoles with *N*-tosylhydrazones (Scheme 22).[39] The C−H bond functionalization by the secondary benzyl group, which is difficult with other transition metal-catalyzed direct C−H bond functionalization methods, can be achieved with this reaction.

SCHEME 22. Cu(I)-Catalyzed Direct Benzylation or Allylation of 1,3-Azoles with *N*-Tosylhydrazones
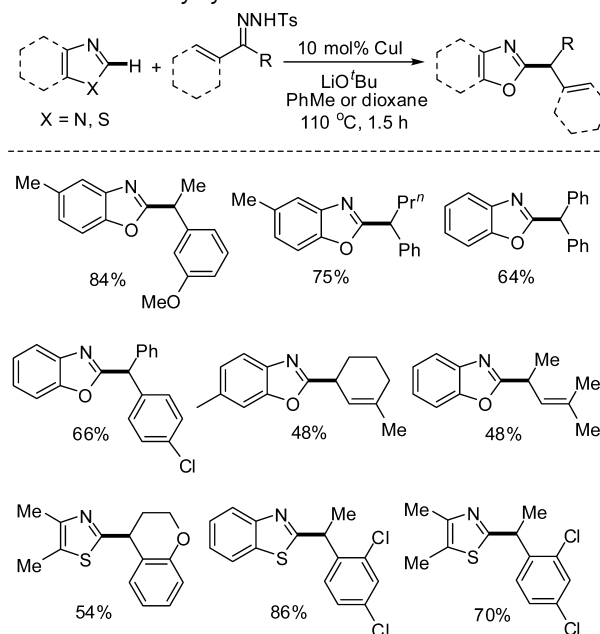

SCHEME 23. Rh(I)-Catalyzed One-Pot Three-Component Reaction
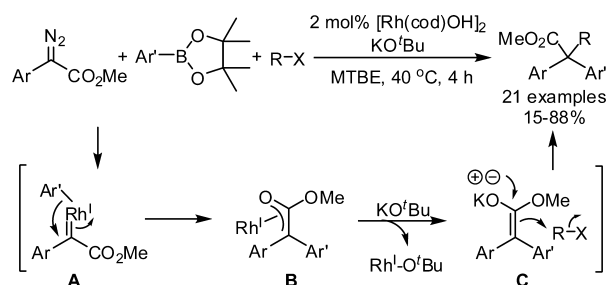
Rh-Catalyzed Reactions. Rh(II) catalysts, similar to Cu(I) catalysts, have been well-established in carbene transformations.[1] However, most Rh(II) carbene transformations follow the classic carbene transfer mechanism. Interestingly, Yu and co-workers have reported Rh(I)-catalyzed three-component coupling reaction of arylboronates, diazoesters, and alkyl halides. The reaction involves an aryl migratory insertion of Rh(I) carbene **A** to form oxa-π-alkylrhodium species **B**, which undergoes transmetalation and alkylation with alkyl halides. This reaction is an interesting approach toward the construction of a quaternary carbon center (Scheme 23).[40]

Ni- and Co-Catalyzed Reaction. In Cu(I)-catalyzed direct alkylation of 1,3-azoles, the coupling reaction only works with benzylation and allylation (Scheme 22).[39] Recently Hirano and Miura have extended this type of 1,3-azole direct C−H bond functionalization to more general alkyl groups by using Ni(II) or Co(II) catalysts (eqs 7 and 8).[41] These

transformations demonstrate that similar migratory insertion also occurs with Ni(II) or Co(II) carbene species.


$$(7)$$

$$(8)$$
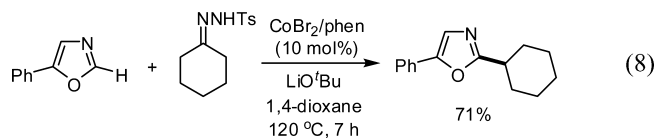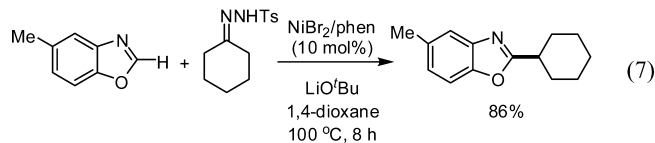
Summary

In conclusion, we have demonstrated in this Account that metal carbene and cross-coupling reactions can be merged resulting in various novel transformations. The carbene migratory insertion, which leads to C—C bond formation, seems to play a key role in these transformations. Migratory insertion is one of the most important elementary steps in organometallic chemistry, particularly in Pd-catalyzed transformations (Scheme 24). The alkene insertion into a Pd—C bond, the key step in Heck—Mizoroki reaction, is the insertion of a two-carbon unit, while carbonylation with CO involves a one-carbon unit insertion. The carbene insertion is comparable to CO insertion, which is also a one-carbon insertion. Because CO insertion has been widely exploited as powerful tool for introducing one-carbon fragments, the analogous carbene insertion may prove to be another general and useful approach to introduce one-carbon fragments.[44]

From the perspective of synthetic applications, the introduction of N-tosylhydrazones as the cross-coupling partners makes this type of C—C bond forming reaction practically useful. For example, when one considers the cross-coupling starting with ketones or aldehydes, the classic way is to first convert the carbonyl functionality into triflates, then to carry out the coupling reaction (Scheme 25). Now the same transformation can be realized in an alternative way through N-tosylhydrazone. The advantage of the latter approach is the easy formation and handling of the bench-stable N-tosylhydrazones.

It is also interesting to compare the Pd-catalyzed cross-coupling of N-tosylhydrazones with the widely applied Shapiro reaction (Scheme 26).[45] In the case of Shapiro reaction, the N-tosylhydrazone is converted to a vinyl anion by a strong base, typically butyllithium. The vinyl anion then reacts with an electrophile (E), usually a proton or a carbonyl
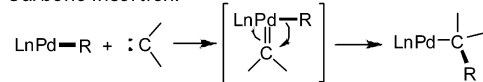
SCHEME 24. Comparison of Migratory Insertions
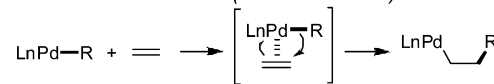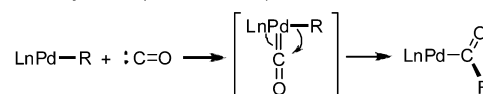
SCHEME 25. Cross-Coupling with Carbonyl: Triflate Approach versus N-Tosylhydrazone Approach
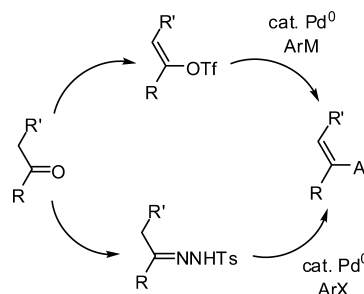
SCHEME 26. Alkene Synthesis from N-Tosylhydrazone: Shapiro Reaction versus Pd-Catalyzed Cross-Coupling
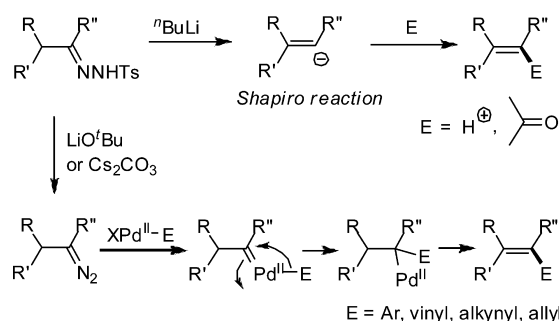
group. The most important application of Shapiro reaction in organic synthesis is to convert carbonyl functionality to C=C double bond.

In the Pd-catalyzed reaction, a diazo compound is generated from N-tosylhydrazone, which is dediazonized by the Pd catalyst to form a Pd carbene. Migratory insertion, followed by β-hydrogen elimination, affords the alkene product. As in the Shapiro reaction, the C=C double bond is generated in Pd-catalyzed reaction. However, the difference between Shapiro reaction and Pd-catalyzed reaction is that

SCHEME 27. Deoxygenative Transformation of Carbonyl Group into C=C or C−C Bonds
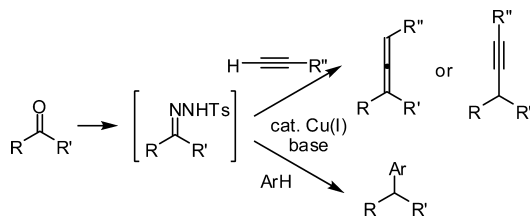
in the latter case, the E group can be aryl, vinyl, alkynyl, and so on, while in the Shapiro reaction, the E group can only be H or RCH(OH). In this sense, it can be considered that the Pd-catalyzed reaction is complementary to the classic Shapiro reaction in the alkene synthesis from *N*-tosylhydrazones.

Finally, it has also been demonstrated in this Account that Cu- and some other transition-metal-catalyzed coupling reactions of *N*-tosylhydrazones undergo a similar metal carbene migratory insertion process. Unlike the Pd-catalyzed reactions, the alkyl metal species generated from carbene migratory insertion does not have the propensity to undergo β-hydrogen elimination in these cases, and instead the reactions lead to the formation of protonated products. This type of reactions can be considered as efficient deoxygenative cross-coupling, which converts carbonyl functionality of aldehyde or ketone to allenyl, aryl, or ethynyl groups into C−C or C=C bonds (Scheme 27).

BIOGRAPHICAL INFORMATION

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REFERENCES

1 For selected reviews, see: (a) Ye, T.; McKervey, M. A. Organic Synthesis with α-Diazo Carbonyl Compounds. *Chem. Rev.* **1994**, *94*, 1091–1160. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (c) Zhang, Z.; Wang, J. Recent Studies on the Reactions of α-Diazocarbonyl Compounds. *Tetrahedron* **2008**, *64*, 6577–6605.

2 Negishi, E.-i. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002.

3 For reviews, see: (a) Zhang, Y.; Wang, J. Recent Development in Pd-Catalyzed Reaction of Diazo Compounds. *Eur. J. Org. Chem.* **2011**, 1015–1026. (b) Barluenga, J.; Valdés, C. Tosylhydrazones: New Uses for Classic Reagents in Palladium-Catalyzed Cross-Coupling and Metal-Free Reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486–7500. (c) Shao, Z.; Zhang, H. N-Tosylhydrazones: Versatile Reagents for Metal-Catalyzed and Metal-Free Cross-Coupling Reactions. *Chem. Soc. Rev.* **2012**, *41*, 560–572.

4 For an example, see: Trost, B. M.; Hashmi, A. S. K. On the Mechanism of the TCPC^HFB-Catalyzed Metathesis of 1,6-Enyne: Evidence for Alkylidenepalladium Intermediates. *Angew. Chem., Int. Ed.* **1993**, *32*, 1085–1087.

5 Bröring, M.; Brandt, C. D.; Stellwag, S. The First Pd(II) Complex of a Non-heteroatom Stabilized Carbene Ligand. *Chem. Commun.* **2003**, 2344–2345.

6 Doyle, M. P. Catalytic Methods for Metal Carbene Transformations. *Chem. Rev.* **1986**, *86*, 919–939.

7 Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. Palladium-Catalyzed Insertion Reactions of Trimethylsilyldiazomethane. *Tetrahedron* **2001**, *57*, 5219–5225.

8 (a) Greenman, K. L.; Van Vranken, D. L. Palladium-Catalyzed Carbene Insertion into Benzyl Bromides. *Tetrahedron* **2005**, *61*, 6438–6441. (b) Devine, S. K. J.; Van Vranken, D. L. Palladium-Catalyzed Carbene Insertion into Vinyl Halides and Trapping with Amines. *Org. Lett.* **2007**, *9*, 2047–2049. (c) Devine, S. K. J.; Van Vranken, D. L. Palladium-Catalyzed Carbene Insertion and Trapping with Carbon Nucleophiles. *Org. Lett.* **2008**, *10*, 1909–1911. (d) Kudirka, R.; Van Vranken, D. L. Cyclization Reactions Involving Palladium-Catalyzed Carbene Insertion into Aryl Halides. *J. Org. Chem.* **2008**, *73*, 3585–3588. (e) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. Palladium-Catalyzed Insertion of α-Diazoesters into Vinyl Halides to Generate α,β-Unsaturated α-Amino Esters. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677–3680. (f) Khanna, A.; Maung, C.; Johnson, K. R.; Luong, T. T.; Van Vranken, D. L. Carbenylative Amination with N-Tosylhydrazones. *Org. Lett.* **2012**, *14*, 3233–3235.

9 Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. N-Tosylhydrazones as Reagents for Cross-Coupling Reactions: A Route to Polysubstituted Olefins. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587–5590.

10 (a) Barluenga, J.; Tomá-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. Pd-Catalyzed Cross-Coupling Reactions with Carbonyls: Application in a Very Efficient Synthesis of 4-Arylte-trahydropyridines. *Chem.—Eur. J.* **2008**, *14*, 4792–4795. (b) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. Synthesis of Enol Ethers and Enamines by Pd-Catalyzed Tosylhydrazide-Promoted Cross-Coupling Reactions. *Chem.—Eur. J.* **2009**, *15*, 13291–13294. (c) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. Arylation of α-Chiral Ketones by Palladium-Catalyzed Cross-Coupling Reactions of Tosylhydrazones with Aryl Halides. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856–6859. (d) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F. Synthesis of Dienes by Palladium-Catalyzed Couplings of Tosylhydrazones with Aryl and Alkenyl Halides. *Adv. Synth. Catal.* **2010**, *352*, 3235–3240. (e) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. Synthesis of 2-Arylacrylates from Pyruvate by Tosylhydrazide-Promoted Pd-Catalyzed Coupling with Aryl Halides. *Chem.—Eur. J.* **2010**, *16*, 12801–12803. (f) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. Synthesis of Polysubstituted Olefins by Pd-Catalyzed Cross-Coupling Reaction of Tosylhydrazones and Aryl Nonaflates. *Org. Lett.* **2011**, *13*, 510–513.

11 (a) Tréguier, B.; Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. Expeditious Synthesis of 1,1-Diarylethylenes Related to isoCombretastatin A-4 (iso CA-4) via Palladium-Catalyzed Arylation of N-Tosylhydrazones with Aryl Triflates. *Tetrahedron Lett.* **2009**, *50*, 6549–6552. (b) Messaoudi, S.; Tréguier, B.; Hamze, A.; Provot, O.; Peyrat, J.—F.; De Losada, J. R.; Liu, J.-M.; Bignon, J.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. Isocombretastatins A versus Combretastatins A: The Forgotten isoCA-4 Isomer as a Highly Promising Cytotoxic and Antitubulin Agent. *J. Med. Chem.* **2009**, *52*, 4538–4542. (c) Brachet, E.; Hamze, A.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. Pd-Catalyzed Reaction of Sterically Hindered Hydrazones with Aryl Halides: Synthesis of Tetra-Substituted Olefins Related to iso-Combretastatin A4. *Org. Lett.* **2010**, *12*, 4042–4045. (d) Rasolofonjatovo, E.; Tréguier, B.; Provot, O.; Hamze, A.; Morvan, E.; Brion, J.-D.; Alami, M. Palladium-Catalyzed Coupling of N-Tosylhydrazones with ortho Substituted Aryl Halides: Synthesis of 4-Arylchromenes and Related Heterocycles. *Tetrahedron Lett.* **2011**, *52*, 1036–1040.

12 Chen, Z.-S.; Duan, X.-H.; Wu, L.-Y.; Ali, S.; Ji, K.-G.; Zhou, P.-X.; Liu, X.-Y.; Liang, Y.-M. Palladium-Catalyzed Coupling of Propargylic Carbonates with N-Tosylhydrazones: Highly Selective Synthesis of Substituted Propargylic N-Sulfonylhydrazones and Vinylallenes. *Chem.—Eur. J.* **2011**, *17*, 6918–6921.

13 Peng, C.; Cheng, J.; Wang, J. Palladium-Catalyzed Cross-Coupling of Aryl or Vinyl Iodides with Ethyl Diazoacetate. *J. Am. Chem. Soc.* **2007**, *129*, 8708–8709.

14 Maas, G. New Syntheses of Diazo Compounds. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186–8195.

15 (a) Babinski, D. J.; Aguilar, H. R.; Still, R.; Frantz, D. E. Synthesis of Substituted Pyrazoles via Tandem Cross-Coupling/Electrocyclization of Enol Triflates and Diazoacetates. *J. Org. Chem.* **2011**, *76*, 5915–5923. (b) Eidamshaus, C.; Hommes, P.; Reissig, H. —U. Palladium-Catalyzed Coupling of Pyrid-4-yl Nonaflates with Methyl Diazoacetate. *Synlett* **2012**, *23*, 1670–1674.

16 Peng, C.; Wang, Y.; Wang, J. Palladium-Catalyzed Cross-Coupling of α-Diazocarbonyl Compounds with Arylboronic Acids. *J. Am. Chem. Soc.* **2008**, *130*, 1566–1567.

17 Zhao, X.; Jing, J.; Lu, K.; Zhang, Y.; Wang, J. Pd-Catalyzed Oxidative Cross-Coupling of N-Tosylhydrazones with Arylboronic Acids. *Chem. Commun.* **2010**, *46*, 1724–1726.

18 Peng, C.; Yan, G.; Wang, Y.; Jiang, Y.; Zhang, Y.; Wang, J. Palladium-Catalyzed Coupling Reaction of α-Diazocarbonyl Compounds with Aromatic Boronic Acids and Halides. *Synthesis* **2010**, 4154–4164.

19 Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. Pd-Catalyzed C═C Double Bond Formation by Coupling of N-Tosylhydrazones with Benzyl Halides. *Org. Lett.* **2009**, *11*, 4732–4735.

20 Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. Palladium-Catalyzed Cross Coupling Reaction of Benzyl Bromides with Diazoesters for Stereoselective Synthesis of (E)-α,β-Diarylacrylates. *Org. Lett.* **2009**, *11*, 469–472.

21 Chen, S.; Wang, J. Palladium-Catalyzed Reaction of Allyl Halides with α-Diazocarbonyl Compounds. *Chem. Commun.* **2008**, 4198–4200.

22 Zhou, L.; Ye, F.; Ma, J.; Zhang, Y.; Wang, J. Pd-Catalyzed Oxidative Cross-Coupling of N-Tosylhydrazones or Diazoesters with Terminal Alkynes: A New Route to Conjugated Enynes. *Angew. Chem., Int. Ed.* **2011**, *50*, 3510–3514.

23 Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. Cyclopropylcarbinylpalladium Species from Carbene Migratory Insertion: New Routes to 1,3-Butadienes. *Org. Lett.* **2012**, *14*, 922–925.

24 Zhou, L.; Liu, Y.; Zhang, Y.; Wang, J. Pd-Catalyzed Coupling of Hydroxy α-Diazocarbonyl Compounds with Aryl Iodides: A Migratory Insertion/β-Hydroxy Elimination Sequence. *Chem. Commun.* **2011**, *47*, 3622–3624.

25 Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. Pd-Catalyzed Three-Component Coupling of N-Tosylhydrazone, Terminal Alkyne, and Aryl Halide. *J. Am. Chem. Soc.* **2010**, *132*, 13590–23591.

26 Chen, Z.-S.; Duan, X.-H.; Zhou, P.-X.; Ali, S.; Luo, J.-Y.; Liang, Y.-M. Palladium-Catalyzed Divergent Reactions of α-Diazocarbonyl Compounds with Allylic Esters: Construction of Quaternary Carbon Centers. *Angew. Chem., Int. Ed.* **2012**, *51*, 1370–1374.

27 For a recent review on Pd-catalyzed carbonylations, see Brennführer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133.

28 Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. Palladium-Catalyzed Carbonylation/Acyl Migratory Insertion Sequence. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139–1142.

29 Tidwell, T. T. Ketene Chemistry after 100 Years: Ready for a New Century. *Eur. J. Org. Chem.* **2006**, 563–576.

30 Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. Pd-Catalyzed Carbonylation of Diazo Compounds at Atmospheric Pressure: A Catalytic Approach to Ketenes. *J. Am. Chem. Soc.* **2011**, *133*, 4330–4341.

31 Zhang, Z.; Zhang, Y.; Wang, J. Carbonylation of Metal Carbene with Carbon Monoxide: Generation of Ketene. *ACS Catal.* **2011**, *1*, 1621–1630.

32 Zhou, F.; Ding, K.; Cai, Q. Palladium-Catalyzed Amidation of N-Tosylhydrazones with Isocyanides. *Chem.—Eur. J.* **2011**, *17*, 12268–12271.

33 Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. Coupling of N-Tosylhydrazones with Terminal Alkynes: Synthesis of Trisubstituted Allenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114–1117.

34 Hassink, M.; Liu, X.; Fox, J. M. Copper-Catalyzed Synthesis of 2,4-Disubstituted Allenoates from α-Diazoesters. *Org. Lett.* **2011**, *13*, 2388–2391.

35 Zhou, L.; Ma, J.; Zhang, Y.; Wang, J. Copper-Catalyzed Cascade Coupling/Cyclization of Terminal Alkynes with Diazoacetates: A Straightforward Route for Trisubstituted Furans. *Tetrahedron Lett.* **2011**, *52*, 5484–5487.

36 Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. CuBr-Catalyzed Coupling of N-Tosylhydrazones and Terminal Alkynes: Synthesis of Benzofurans and Indoles. *Org. Lett.* **2011**, *13*, 968–971.

37 Ye, F.; Shi, Y.; Zhou, L.; Xiao, Q.; Zhang, Y.; Wang, J. Expeditious Synthesis of Phenanthrenes via CuBr₂-Catalyzed Coupling of Terminal Alkynes and N-Tosylhydrazones derived from O-Formyl Biphenyls. *Org. Lett.* **2011**, *13*, 5020–5023.

38 Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. C(sp)—C(sp³) Bond Formation through Cu-Catalyzed Cross-Coupling of N-Tosylhydrazones and Trialkylsilylethynes. *J. Am. Chem. Soc.* **2012**, *134*, 5742–5745.

39 Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. Copper-Catalyzed Direct Benzylation or Allylation of 1,3-Azoles with N-Tosylhydrazones. *J. Am. Chem. Soc.* **2011**, *133*, 3296–3299.

40 Tsoi, Y.-K.; Zhou, Z.; Yu, W.-Y. Rhodium-Catalyzed Cross-Coupling Reaction of Arylboronates and Diazoesters and Tandem Alkylation Reaction for the Synthesis of Quaternary α,α-Heterodiaryl Carboxylic Esters. *Org. Lett.* **2011**, *13*, 5370–5373.

41 Yao, T.; Hirano, K.; Satoh, T.; Miura, M. Nickel- and Cobalt-Catalyzed Direct Alkylation of Azoles with N-Tosylhydrazones Bearing Unactivated Alkyl Groups. *Angew. Chem., Int. Ed.* **2012**, *51*, 775–779.

42 For a recent report on an unusual Cu(I)-catalyzed reaction of α-aryldiazoesters with terminal alkynes, see: Park, E. J.; Kim, S. H.; Chang, S. Copper-Catalyzed Reaction of α-Aryldiazoesters with Terminal Alkynes: A Formal [3 + 2] Cycloaddition Route Leading to Indene Derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 17268–17269.

43 For a recent example, see: Vechorkin, O.; Godinat, A.; Scopelliti, R.; Hu, X. Cross-Coupling of Nonactivated Alkyl Halides with Alkynyl Grignard Reagents: A Nickel Pincer Complex as the Catalyst. *Angew. Chem., Int. Ed.* **2011**, *50*, 11777–11781.

44 Jellema, E.; Jongerius, A. L.; Reek, J. N. H.; de Bruin, B. C1 Polymerisation and Related C—C Bond Forming `Carbene Insertion' Reactions. *Chem. Soc. Rev.* **2010**, *39*, 1706–1723.

45 (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405–507. (b) Adlington, R. M.; Barrett, A. G. M. Recent Applications of the Shapiro Reaction. *Acc. Chem. Res.* **1983**, *16*, 55–59.