Recent Advances in Palladium-Catalyzed Bridging C–H Activation by Using Alkenes, Alkynes or Diazo Compounds as Bridging Reagents

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Abstract Transition-metal-catalyzed direct inert C–H bond functionalization has attracted much attention over the past decades. However, because of the high strain energy of the suspected palladacycle generated via C–H bond palladation, direct functionalization of a C–H bond less than a three-bond distance from a catalyst center is highly challenging. In this short review, we summarize the advances on palladium-catalyzed bridging C–H activation, in which an inert proximal C–H bond palladation is promoted by the elementary step of migratory insertion of an alkene, an alkyne or a metal carbene intermediate.

1 Introduction

Transition-metal-catalyzed direct inert C–H bond functionalization has been recognized as a concise method to construct molecules with diverse functionalities from read-
Palladium-catalyzed alkene bridging C–H activation through the formation of a thermodynamically stable metallacycle has gained much attention. However, this process remains largely limited to C–H bonds that are located three bonds away from the directing atom because of the preferential formation of five-membered (or larger) metallacycles. In this context, the direct transformation of a C–H bond located in a close proximal position is challenging, as the formation of small and strained metallacycles is energetically unfavorable. Migratory insertion is a fundamental step that occurs in many transition-metal-catalyzed reactions, and a longer bridging arm can be created after this elementary step. This short review will focus specifically on palladium-catalyzed bridging C–H activation, which provides viable solutions for the functionalization of inert C–H bonds that are located in close proximity. Herein, we summarize the advances in this area. Mechanistic rationale, synthetic potential, scope and limitations are included. The reactions are classified according to the bridging reagents employed: (1) palladium-catalyzed alkene bridging C–H activation, (2) palladium-catalyzed alkyne bridging C–H activation, and (3) palladium-catalyzed carbene bridging C–H activation. Palladium and norbornene/norbornadiene co-catalyzed functionalization of (hetero)arenes is a prominent example of alkene bridging C–H activation. Related work on these topics has already been discussed in recent reviews.

2 Palladium-Catalyzed Alkene Bridging C–H Activation

Alkenes are ubiquitous feedstock chemicals which have found broad applications by the synthetic community. The palladium-catalyzed arylation or alkenylation of alkenes is referred to as the Heck reaction, a simplified catalytic cycle of which is displayed in Scheme 1. Oxidative addition of a low-valent palladium catalyst to an organic (pseudo)halide affords intermediate 2. Coordination of 2 to olefin 3, followed by syn-migratory insertion gives adduct 4. Adjusting to the proper configuration by C–C bond rotation in 4 furnishes 5. Next, syn-β-hydride elimination gives a new substituted alkene 6 and releases the palladium hydride species. Reductive elimination of 7 closes the catalytic cycle and regenerates the active catalyst.

When a syn-hydride is not available, the synthetic intermediate 5 can be trapped by other reagents. In this context, a variety of cascade reactions initiated by Heck-type migratory insertion have been developed in the past decades. The progress made on palladium-catalyzed C–C double migratory insertion enabling functionalization of a proximal C–H bond is summarized in the following section.

2.1 Intramolecular Reactions

By employing bifunctional compounds as reactants, Larock and co-workers achieved the synthesis of fused polycyclic compounds through intramolecular migratory insertion of the C–C double bond in intermediate 10 can be considered as the alkene bridging process, which is crucial for the following 1,4-palladium translocation through the five-membered palladacycle 12. A subsequent intramolecular C–H bond palladation would give intermediate 14, which upon reductive elimination eventually affords the polycyclic product 9. Obviously, the creation of a bridging arm through intramolecular alkene migratory insertion is critical for the subsequent two-fold C–H bond activation. This intriguing cascade reaction offers a concise method to construct complex molecules from easily accessible reactants.
picted in Scheme 3, the reaction was initiated by oxidative addition of 15. Intramolecular migratory insertion of the α,β-unsaturated double bond could accomplish the alkene bridging process to give intermediate 18, which possessed a suitable configuration for the following 1,4-Pd shift to furnish 19 or 20. Selective C(sp^3)-H (R^1 = Me) or C(sp^2)-H (R^1 = H) bond activation and reductive elimination then gives fused oxindoles 16 or 17, respectively. Of note, a C(sp^3)-H bond activation was preferred to form seven-membered palladacycles (R^1 = Me and R^2 = aryl). A related transformation from 21 into 22 was also demonstrated by Loh and Xu. They found that the regioselectivity could be altered by the substituents on the double bond.

The five-membered palladacycle generated through intramolecular alkene bridging C–H activation could be trapped by a range of external reagents under appropriate conditions. In 2010, Jia and co-workers reported a water-controlled regioselective alkene bridging C–H functionalization. According to their deuterium labeling experiments, alkene bridging C–H activation occurred to produce a five-membered palladacycle 26. At this stage, addition of water led to a regioselective protonation to give product 24 with the functional group located on the methylene carbon atom. Whereas without adding water as the co-solvent, functionalization of the phenyl ring to give 25 was observed. In this reaction, several nucleophiles, including K_4[Fe(CN)_6]·3H_2O, styrene, methyl acrylate, unactivated ole-

fins and aryl boronic acids, could react with compound 23. When DMF was employed as the solvent, a sequence involving alkene migratory insertion enabled a 1,4-palladium shift/intramolecular arylation to occur to give polycyclic products in moderate to high yields (Scheme 4).

In 2014, Lautens and co-workers demonstrated that the palladium(II) intermediate generated by intramolecular alkene bridging C–H activation could react with a variety of (hetero)aryl iodides to produce fused biaryls 27 with high structural complexity (Scheme 5). Compared with Jia’s work, they found that five-membered palladacycle 26

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could be functionalized at both positions connected to palladium atom. Employment of the complex [Pd(crotyl)QPhosCl] as the precatalyst was essential to suppress formation of the by-product arising from dimerization of 28.

According to the results they obtained, two plausible pathways were proposed. For path a, oxidative addition of palladacycle 26 to aryl iodide 28 might give the palladium(IV) intermediate 29, which upon aryl–aryl reductive elimination could generate intermediate 30. As an alternative pathway, transmetalation might occur between 26 and intermediate 31 to give the bis-palladium(II) intermediate 29. Aryl–aryl reductive elimination in 29 would also furnish 30 (path b, Scheme 5). At this stage, an intramolecular arylation occurring through a seven-membered palladacycle 32 would afford the fused biaryl products 27. A related reaction was reported by Li and co-workers in 2016 by employing the simple palladium salt [Pd(cod)Cl₂] as the precatalyst. Yang and Liang have applied this strategy for oxidation synthesis, and two aryl groups derived from 28 were incorporated in the final products. In their subsequent study, Lautens and co-workers found that intermediate 26 could be trapped by Me₃SiI or Me₃GeI, thus disilylation or digermylation of 23 could be easily realized. Shortly after this study, Liang and Yang reported a palladium-catalyzed domino Heck-disilylation and borylation of alkene-tethered 2-(2-halophenyl)-1H-indoles.

Yao and Lautens have explored the reactivity of a five-membered palladacycle toward arynes. Similar to the catalytic cycle displayed in Scheme 5, the palladium intermediate generated through intramolecular alkene bridging C–H activation could react with benzyne to form a seven-membered palladacycle akin to 32. Reductive elimination would then give the fused products. As depicted in Scheme 6, a range of polycyclic products was obtained in moderate to high yields.

In their subsequent studies, Lautens and co-workers described a regioselective insertion of an unsymmetrical alkyne into the five-membered palladacycle 47. The utilization of a phosphine ligand, P(2-F₃-C₆H₄)(H₂)₃, with the right balance of both electronic and steric characters was critical to achieve high efficiency. By contrast, the reaction using the electron-neutral ligand PPh₃ resulted in no conversion of the both reactants 43 and 44, and when P(o-tol)₃ was used as the ligand, low conversion was observed. Similarly, the σ-alkyl palladium species 46 was produced via an intramolecular Heck-type cyclization. The elongation of a two-atom bridging arm could deliver the palladium catalyst close to the C(sp²)–H bond, thus furnishing a thermodynamically stable palladacycle 47. After a sequence of coordination, migratory insertion of 44 and reductive elimination, products 45 were obtained regioselectively (Scheme 8). For the reactant 43, an alkyl group was always situated at the α-position relative to the carbonyl group (R = alkyl).

Very recently, Yang and Liang reported a new method for the synthesis of fused isoquinolinediones and isoquinolinones through a cascade reaction of compounds 36 with 2-bromobenzoic acid (37) (Scheme 7, top). Mechanistically, a Heck-type cyclization of 36 in presence of a suitable palladium catalyst could accomplish the alkene bridging process. The generation of a two-atom bridging arm would facilitate the proximal C–H bond palladation to furnish a fused five-membered palladacycle 39. Oxidative addition of 39 and 37 led to the formation of a spiro palladium(IV) intermediate 40. A consecutive reductive elimination and decarboxylation then gave another seven-membered palladacycle 41. The final isoquinolinedione or isoquinolinone products were produced via reductive elimination of 41. The carbonyl group in 36 was crucial for this domino process to occur (Scheme 7, bottom). As depicted, the preparation of fused benzofuran or oxindole derivatives from substrates 42a–d failed when using this reaction.
According to Lautens’ previous work, replacement of the alkyl substituent with an aryl group switched the chemoselectivity to produce a spirooxindole.\(^{21}\)

![Scheme 8 Palladium-catalyzed intramolecular alkene bridging C–H activation and alkyne insertion](image)

In 2014, Shi and co-workers found that the palladacycle 26 could react with di-tert-butylaziridinone (49) to form a spiro palladium(IV) intermediate 51. After releasing one equivalent of tert-butyl isocyanate, indolines 50 bearing a tert-butyl group could be obtained (Scheme 9).\(^{22}\) In this reaction, a nitrene intermediate 52 was probably involved. In analogy with the work of Lautens (see Scheme 8), when the alkyl substituent (\(R = \text{alkyl}\)) on the olefin was replaced by an aryl group, a spiroindoline was obtained selectively.

![Scheme 9 Palladium-catalyzed intramolecular alkene bridging C–H activation and formal nitrene insertion](image)

### 2.2 Intermolecular Reactions

The main obstacle in developing palladium-catalyzed intermolecular alkene bridging C–H activation lies in the facile \(\beta\)-hydride elimination to form substituted olefins. As mentioned previously, when a syn-\(\beta\)-hydrogen atom is not available, the \(\sigma\)-alkyl palladium(II) intermediate could participate in the following cascade reactions. Based on this principle, studies on reactions mediated by palladium and norbornene (or its analogues) have attracted significant attention. As shown in Scheme 10, the formation of the five-membered palladacycle 54 is promoted by Heck-type migratory insertion of a palladium(II) intermediate with norbornene (53). This type of transformation, which is referred to as the Catellani reaction, is an important example of palladium-catalyzed alkene bridging C–H activation. Due to space limitations and the fact that related advances having been discussed in recent elegant reviews,\(^{6}\) we will focus on reactions employing olefins other than norbornene-type alkenes in this section.

![Scheme 10 Simplified reaction mode of the Catellani reaction](image)

In 2001, Carretero and co-workers discovered the first palladium-catalyzed cascade arylation of an acyclic alkene when they tested the activity of \(\beta\)-substituted vinylsulfone 55 with phenyl iodide (28a).\(^{\text{11}}\) According to their systematic examination of the reaction conditions, they found that the utilization of \(\text{Ag}_2\text{CO}_3\) as the base, a sulfone-containing \(\alpha,\beta\)-unsaturated alkene and an excess amount of 28a were important to achieve high selectivity to form dihydrophenanthrenes 56 instead of the normal

![Scheme 11 Palladium-catalyzed intermolecular alkene bridging C–H activation using a vinylsulfone as the bridging reagent](image)
Heck-type products. As can be seen, this reaction was quite efficient for bond formation as four new C–C bonds were created in a single step. Mechanistically, oxidative addition of the palladium(0) catalyst to phenyl iodide in the presence of Ag₂CO₃ would give the cationic phenylpalladium(II) intermediate 57. Next, syn-insertion of 55 into 57 would afford sulfonylalkylpalladium intermediate 58, thereby accomplishing the alkene bridging process. The cationic nature of 58 might account for the fast C–H activation to produce the five-membered palladacycle 59. Intermediate 59 then reacts with a second equivalent of phenyl iodide to give another cationic α-sulfonylalkylpalladium species 58. The repetition of the same mechanistic sequence would lead to the formation of intermediates 59 and 60. A third C–H bond activation could give the seven-membered palladacycle 61, and reductive elimination of 61 would eventually afford the product 56. The critical role played by the cationic nature of the palladium species was evidenced by the reaction of vinylsulfone 55b with 28a under the standard conditions, which gave the normal Heck product exclusively (Scheme 11, middle). Replacing the sulfonyl group with an ester or ketone group also led to a switch of the chemoselectivity (Scheme 11, bottom).

An elegant palladium-catalyzed alkene bridging C–H activation using other olefins as bridging reagents was reported by Wang and Hu. According to their studies, a variety of substituted 1,6-dienes 62 could be successfully applied as modular bridging arms to react with different aryl halides 28, achieving selective ortho-C(sp²)–H bond activation of aryl halides 28. The selectivity toward the cascade reaction sequence that outcompeted with the traditional Heck reaction is noteworthy, and which might be attributed to the existence of the second alkenyl tether that could easily participate in cascade syn migratory insertion, and further promote the intramolecular C–H bond palladation to furnish a thermodynamically stable seven-membered palladacycle 66. Reductive elimination of 66 could give the final polycyclic products 63 (Scheme 12). In this reaction, 1,6-diene 62 was involved in a two-fold migratory insertion of a palladium(II) species (64 and 65), acting as a modular four-atom bridging reagent to facilitate the cascade reaction. As depicted, different protogenic groups (R¹), substituents on the alkene termini (R² and R⁴) and functional groups on the phenyl ring (Ar) were compatible with the current cascade reaction, and the corresponding polycyclic products were obtained in moderate to excellent yields.

In 2005, Ohno and Tanaka demonstrated that enallenes could participate in palladium-catalyzed bridging C–H bond arylation reactions. They found that different (hetero)-aryl halides 28 could participate in the cascade cyclization reaction with substituted enallenes 67, and that the presence of a substituent on the alkene terminus (R²) was essential to inhibit the undesired β-H elimination to form the Heck-type products. Based on their findings, two reaction modes were proposed to explain the stereoselectivity of the reaction (Scheme 13).

### 3 Palladium-Catalyzed Alkyne Bridging C–H Activation

Alkynes have been frequently used as substrates for palladium-catalyzed carbopalladation reactions. These types of reactions normally involve following general steps (Scheme 14). First, oxidative addition of a low-valent palladium catalyst to a suitable organic halide leads to the formation of a palladium(II) species 71. Subsequently, this organometallic species reacts with alkynes through a syn carbopalladation pathway to generate a vinyl palladium(II) intermediate 72. Herein, we refer to the syn migratory insertion of the alkyne to 71 to generate the vinyl palladium(II) species 72 as the alkyne bridging process. The trapping of 72 by appropriate reagents leads to the formation of a variety of functional products.
3.1 Intermolecular Reactions

In 1989, Heck reported the preparation of 2,3-diphenylindenone via a palladium-catalyzed coupling of o-iodobenzaldehyde with diphenylacetylene. Following this report, Larock and co-workers re-examined this reaction and expanded the scope to produce a broader range of indenone derivatives. In analogy to the aforementioned alkene bridging C–H activation, the reaction was proposed to be initiated by oxidative addition of a Pd(0) species to aryl halide to generate aryl palladium(II) intermediate. Intramolecular C–H bond palladation of the aldehyde moiety would furnish a six-membered palladacycle. Reductive elimination of then affords substituted indenones. This process was highly regioselective for indenones containing tertiary alkyl or other hindered groups, with the major isomer bearing the more sterically demanding group at the 2-position of the indenone. When less hindered alkynes were employed, the corresponding products were obtained with low regioselectivity. Recently, Satyanarayana and Ramesh identified that by using L-proline as a ligand, this reaction could be carried out in aqueous medium. The excellent regioselectivity allowed this reaction to serve as a key step in the synthesis of a neolignan.

In addition to alkynes, arynes are also competent bridging reagents participate in Pd-catalyzed annihilations. Larock and co-workers reported a Pd-catalyzed annihilation of arynes with o-haloarene-carboxaldehyde 73 to provide fluoren-9-ones 80 in good yields. Arynes were produced in situ through the reaction of 2-(trimethylsilyl)aryl triflates 79 with CsF. A plausible pathway is depicted in Scheme 16. The reaction of the Pd(0) catalyst with the aryne formed in situ from 79 afforded palladacycle 81, which could further react with aryl halide 73 to furnish the Pd(IV) intermediate. Reductive elimination of 82 would then give arylpalladium(II) intermediate 83. Intramolecular C–H bond activation of the aldehyde moiety would furnish a six-membered palladacycle. Reductive elimination of 84 would give fluoren-9-ones 80. Interestingly, the reaction of 3-methoxybenzylamine exhibited very high regioselectivity, and 3-methoxyfluoren-9-one was obtained as the major product. The high regioselectivity might be attributed to the directing effect arising from weak coordination of the methoxy group to the palladium atom in 82. Thus Pd appeared to add to the more hindered end of the triple bond of the aryne formed in situ from 79.
As is already known, the palladium-catalyzed reaction of aryl halides 28 with alkynes 74 could lead to the direct formation of a potential five-membered palladacycle 88. Trapping intermediate 88 with appropriate reagents could give a range of products with rich structural diversity (Scheme 18).

Hexamethyldisilane is commercially available and has been widely employed as a trimethylsilyl source in organosilicon chemistry. Zhang and co-workers reported that the addition of hexamethyldisilane into palladacyclic species 88 could afford a range of vinylsilanes 89 (Scheme 19, a). The same group also discovered that intermediate 88 could be trapped by di-tert-butyldiaziridinone 49 to give substituted indoles 90 bearing a tert-butyl group on the nitrogen atom (Scheme 19, b). More recently, Habibi and Jafarpour used simple and readily accessible amines as nitrogen sources to reaction with palladacycle 88, giving N-aryl-substituted indoles 90 in a highly efficient manner (Scheme 19, c). By using CH3Br2 as the reaction partner, Zhang and co-workers uncovered a valuable method for the preparation of benzofulvenes 91 through the alkylation of intermediate 88 (Scheme 19, d). Using this novel protocol as a platform, Liang and Yang developed a simple and convenient approach for the construction of phenanthrene frameworks 92 via a palladium-catalyzed domino alkyne insertion/C–H activation/decarboxylation sequence (Scheme 19, e).

In 2003, during an exploration on the palladium-catalyzed reactions of aryl iodies with internal alkynes for the synthesis of tetrasubstituted naphthalenes 85, Miura and co-workers found that the reaction of 1-iodonaphthalene (28b) with diethyl acetylenedicarboxylate (74b) gave diethyl acenaphthylene-1,2-dicarboxylate (93a) as the major product (Scheme 20, top). Recently, Yamamoto and co-workers described a similar formal [3+2] annulation by using 4-iodo-2-quinolone 28c as the reactant. They found that
slow addition of the activated alkyne 74c could suppress the formation of the [2+2+2] annulation product effectively without adding phosphine ligands. In analogy to the aforementioned work, alkyne 74c acted as a bridging reagent to facilitate formation of the six-membered palladacycle 94 via an intramolecular C–H bond activation. Reductive elimination of 94 then afforded product 93b (Scheme 20, bottom).

During their studies on the palladium-catalyzed annulation of arynes with 2-halobenzenes, Larock and co-workers discovered that the reaction of ethyl 4-iodobenzoate (28d) with two equivalents of the aryne 28c, derived from 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (79b), gave the corresponding substituted triphenylene 93b in 50% yield. As depicted in Scheme 21, this reaction probably proceeds through an aryne-bridging C–H activation pathway.

As consequence of studies in the area of through space 1,4-palladium shifts, Larock and co-workers have demonstrated a consecutive vinylic to aryl to allylic palladium migration via alkyne bridging C–H activation. Taking the reaction of aryl iodide 28e with internal alkyne 74d as a specific example, the first 1,4-palladium migration (vinylic → aryl) was proposed to proceed through the five-membered palladacycle 88e. The second 1,4-palladium migration (aryl → allylic) could furnish the η1,4-allyl palladium intermediate 97. Addition of a pivalate anion to 97 gave the final allylic pivalate product 96 as a mixture of E/Z isomers (Scheme 22, top). According to a report from Larock and co-workers, such an alkyne bridging 1,4-palladium shift strategy could be applied for the synthesis of substituted carbazoles, indoles, and dibenzofurans (Scheme 22, bottom).

Very recently, Xie’s group described a palladium-catalyzed highly selective bifunctionalization of 3-iodo-o-carborane (99) through alkyne bridging palladium migration (Scheme 23). Accordingly, the syn insertion of alkyne 74a into intermediate 101 could facilitate B–H bond activation to furnish palladacycle 103. The transformation from 102 to 103 could be achieved in a 1,4-palladium shift process. Reductive elimination of 104 could then complete the bifunctionalization of 99. Interestingly, product 100 could be trapped in situ by addition of a Grignard reagent. Thus dicarbosubstituted isomers 106 could be achieved in a straightforward manner.

In 2019, Yao and co-workers reported a palladium-catalyzed reaction of 1-iodo-3-[(2-methylallyl)oxy]benzene (28g) with a range of internal alkyne 74. The tethered alkyl moiety in aryl iodide 28g could insert into the tran-
Akin to simple internal alkynes, 1,6-diynes 108 could also serve as bridging reagents to promote proximal inert C–H bond activation. In 2010, Hu and co-workers reported an efficient protocol for the preparation of polysubstituted aromatics 109. Mechanistically, two-fold migratory insertion of palladium(II) species 110 could complete the diyne bridging process to give the vinyl palladium(II) species 111. Intramolecular C–H bond activation could afford a seven-membered palladacycle 112, which upon reductive elimination would furnish the final product 109. The whole process was very efficient for the formation of multiple bonds, and a broad range of polyaromatic compounds was obtained in moderate to high yields (Scheme 25).46

3.2 Intramolecular Reactions

The introduction of a tethered alkyne moiety into organic halides can greatly enhance the structural complexity of the corresponding products. For example, in 2005, Suffert and Bour reported a tin-reagent-dependent palladium-catalyzed cascade reaction, in which an intramolecular alkyne bridging C(sp2)–H bond heteroaryl ation, allylation and vinylation were observed.47 To understand the mechanism, the authors prepared deuterium labeled diol 112-D1. When a vinyl tin reagent was employed, a product was obtained in which vinylation took place at the ipso position of the deuterium atom on the phenyl ring, and in which the deuterium atom was completely transferred to the vinyl position (Scheme 26, top).
Based on this intriguing observation, a plausible mechanism was proposed (Scheme 26, bottom). The process was initiated by oxidative addition of the palladium(0) catalyst to vinyl bromide 112. Next, syn cyclocarbopalladation of the tethered triple bond would give vinyl palladium(II) species 116, a process which can be referred to as the alkyne bridging process. At this stage, the destiny of intermediate 116 was determined by the type of tin reagent involved.

When a vinyl tin reagent was used, selective hydrogen abstraction would take place followed by transmetalation with the vinyl tin reagent to give the six-membered palladacycle 117. Hence this pathway accounts for the vinylation on the phenyl ring to form 114. In contrast, when a stannylated alkyne was utilized, the selective formation of 115 was observed. The authors performed DFT calculations on the pathway to form 114, which revealed that a vinyl to aryl 1,5-palladium shift and a Pd(0)/Pd(II) redox cycle were involved in the pathway.48

Mechanistically similar to Hu’s work on alkyne bridging C–H activation,46 Werz and co-workers designed a palladium-catalyzed benzene annulation for the synthesis of chromanes and isochromanes.49 In this work, 2-bromoglycal 119, with an appropriate alkyne tether, was employed as the model substrate for reactions with a variety of symmetric internal alkynes 74. As depicted, the alkyne bridging process probably takes place via a two-fold carbopalladation pathway to give the vinyl palladium(II) species 121. Subsequent C–H bond activation could then afford a seven-membered palladacycle 122, which upon reductive elimination leads to the formation of chromane derivatives 120 (Scheme 27, top). By slight variation of the structure of the reactant, isochromane derivatives could also be prepared in a straightforward manner under the standard conditions. This strategy has also been applied for the synthesis of naphthalene derivatives by the same group (Scheme 27, bottom).50

Very recently, Luan and co-workers examined the reactivity of the five-membered palladacycle 127, (see Scheme 28), generated through intramolecular alkyne bridging C–H activation, toward several bifunctional reagents (Figure 1), including 1-bromo-2-naphthol (123a), α-bromophenols 123b, p-bromophenols 123c, ethyl 2-(4-bromonaphthalen-1-yl)acetate (123d) and benzoyl O-substituted hydroxylamine 123e.51

Figure 1 Structures of bifunctional reagents 123
membered aza-palladacycle $\text{131}$.
Alternatively, the formation of a putative Pd-nitrene species $\text{132}$ was also equally reasonable to explain the reaction outcome. Migratory insertion of the aryl moiety could furnish intermediate $\text{131}$ as well (pathway b). Reductive elimination of $\text{131}$ would afford tricyclic indole $\text{129a}$ as the final product and release the active palladium catalyst (Scheme 29, top). Again, this reaction displayed a very broad substrate scope (more than 50 examples). It is noteworthy to mention that the linker on the phenyl ring was not restricted to the ortho position with respect to the iodide moiety. Substrates with an appropriate alkenyl linker located at meta or para positions were viable reactants. This strategy has been applied for the construction of a variety of macrocycle-embedded indole derivatives $\text{129}$ (Scheme 29, bottom). Almost at the same time, Zhang and co-workers reported a similar tricyclic indole synthesis by applying a comparable strategy, but using N,N-di-tert-butylidiaziridine $\text{49}$ as the amination agent.$^{32}$

For the palladium-catalyzed reactions of aryl iodides $\text{124}$ with alkynes $\text{123a–d}$, dearomatization of $\text{123}$ to form a range of spiro products $\text{125}$ was observed.$^{31}$ This reaction was operationally simple, and required no external ligands, while exhibiting broad substrate scope (53 examples). The products $\text{125}$ were obtained in moderate to excellent yields (48–92%). Herein we take the reaction of $\text{124a}$ with $\text{123a}$ as an example to explain the mechanism based on the results obtained by Luan and co-workers. In analogy with the aforementioned alkyne bridging C–H activation, the reaction started with oxidative addition of the in situ generated palladium(0) catalyst to alkyne $\text{124a}$. Intramolecular syn carbopalladation of the resulting intermediate $\text{126a}$ produced a vinyl palladium(II) species. The key intermediate $\text{127a}$ was formed by intramolecular C–H palladation. At this stage, additional oxidative addition of $\text{127a}$ to $\text{123a}$ would generate the palladium(IV) species $\text{128a}$. Finally, a two-fold reductive elimination of $\text{128a}$ involving dearomatization of the naphthalene ring would eventually give the final spiro product $\text{125a}$ (Scheme 28).

In their subsequent study, Luan and co-workers identified that hydroxylamine derivative $\text{123e}$ could act as an excellent bifunctional nitrogen source in the reaction with transient palladacycle $\text{127}$, providing a rapid access to diverse tricyclic indole scaffolds.$^{31b}$ Based on their comprehensive mechanistic studies, two plausible reaction pathways were proposed. Coordination of deprotonated $\text{123e}$ to the electrophilic palladium intermediate $\text{127a}$ could furnish another five-membered palladacycle $\text{130}$. For pathway a, a concerted 1,2-aryl migration from the palladium atom to the nitrogen center would lead to the formation of six-membered aza-palladacycle $\text{131}$. Alternatively, the formation of a putative Pd-nitrene species $\text{132}$ was also equally reasonable to explain the reaction outcome. Migratory insertion of the aryl moiety could furnish intermediate $\text{131}$ as well (pathway b). Reductive elimination of $\text{131}$ would afford tricyclic indole $\text{129a}$ as the final product and release the active palladium catalyst (Scheme 29, top). Again, this reaction displayed a very broad substrate scope (more than 50 examples). It is noteworthy to mention that the linker on the phenyl ring was not restricted to the ortho position with respect to the iodide moiety. Substrates with an appropriate alkenyl linker located at meta or para positions were viable reactants. This strategy has been applied for the construction of a variety of macrocycle-embedded indole derivatives $\text{129}$ (Scheme 29, bottom). Almost at the same time, Zhang and co-workers reported a similar tricyclic indole synthesis by applying a comparable strategy, but using N,N-di-tert-butylidiaziridine $\text{49}$ as the amination agent.$^{32}$

Recently, Shintani and co-workers described an intramolecular alkyne bridging C–H activation via a 1,4-palladium shift with a concomitant double bond isomerization from the E-isomer to the Z-isomer.$^{33}$ Specifically, oxidative addition of $\text{133}$ to the active palladium(0) catalyst could provide palladium(II) intermediate $\text{135}$ (Scheme 30).
Migratory insertion of the tethered alkyne moiety would furnish a vinyl palladium(II) species 136, which was ready to undergo a 1,4-palladium shift to generate another aryl palladium(II) species 138 through two interconvertible five-membered palladacycles 137 and 137'. Deuterium labeling experiments indicated that the proton located at the vinyl position in 138 was derived from an external hydrogen donor other than the hydrogen atom from the aryl ring (Ar'). Additional mechanistic studies by synthesis of plausible intermediates supported the involvement of palladium(II) species 138 and its E-isomer 138'. Finally, C–H bond activation in 138 and subsequent reductive elimination of the potential seven-membered palladacycle gave the product benzophenanthroline 134.

4 Palladium-Catalyzed Carbene Bridging C–H Activation

The extrusion of dinitrogen from diazo compounds in the presence of an appropriate transition-metal catalyst has been considered as a reliable method to generate reactive metal carbene intermediates.16,54 In the past decade, studies on metal carbenes participating in inert C–H bond functionalization has attracted much attention.55 When considering the mechanistic pathway, for the majority of the developed reactions, inert C–H bond metalation takes place prior to metal carbene formation. In this section, we will focus on the recent progress made on palladium carbenes56 participated C–H bond activation with a well-defined mechanistic perspective in which the elementary step of C–H activation proceeds after palladium carbene formation.57 In other words, without formation of a carbene intermediate, the C–H activation event would not occur.

In 2018, Huang and co-workers reported a palladium-catalyzed intermolecular acylation of aryl diazoesters 139 with ortho-bromobenzaldehyde (73b).58 Inspired by the work of Heck and co-workers on indenone synthesis,26 Huang conceived a novel reaction mode for the metal carbene participated C–H bond activation. In detail, oxidative addition of the low valent palladium(0) catalyst to 73 could give the palladium(II) species 76. According to the conventional metal carbene participated reactions, C–H bond palladation would proceed first. However, due to the high strain energy, the formation of benzopalladabutenone 141 was unlikely. Hence, 76 was expected to react with aryl diazoester 139 to form the palladium carbene intermediate 142. Migratory insertion of 142 and subsequent isomerization would furnish the palladium(II) enolate 143. At this stage, C–H bond palladation with the proximal aldehyde tether would be facile, and a seven-membered palladacycle 144 could be produced. In subsequent studies of this reaction, Huang and co-workers referred to the whole process from 76 to 144 as carbene bridging C–H activation (CBA).59 Reductive elimination of 144 would give the final isocoumarin derivatives 140 (Scheme 31). Huang also performed DFT calculations to understand the reaction mechanism, which provided a reasonable energy profile that supported the CBA pathway.
Encouraged by the aforementioned work, Huang and co-workers applied their CBA strategy for the synthesis of seven- and eight-membered lactones. As demonstrated in Scheme 32, N-tosylhydrazones 145 derived from salicylaldehyde analogs were selected as the precursors of bifunctional diazo compounds to react with benzaldehydes 73. This reaction displayed very broad substrate scope. By variation of the carbene precursors 145, besides seven-membered lactones, synthetically more challenging eight-membered lactones could be prepared in a modular fashion. The employment of ortho-formyl aryl triflates as reactants was noteworthy, as formal dimerization of the salicylaldehyde analogs could be achieved. Moreover, substrates containing pharmacophoric fragments could be coupled with high efficiency. Based on deuterium experiments and DFT calculations, a CBA pathway was proposed by the authors. Akin to their previous study, the reaction involved oxidative addition and palladium carbene 147 formation. Migratory insertion of 147 could afford intermediate 148, which was setup to undergo a 1,4-palladium shift, probably through five-membered palladacycle 149, to give acyl palladium(II) species 150. Ring closure of 150 would give the final medium-sized lactones 146.

Tricyclic ring systems possessing a dibenzo structure joined to a seven-membered heterocyclic ring often show important biological activities. However, a brief survey of the literature revealed that a modular approach to such compounds based on an efficient intermolecular reaction of readily available substrates was lacking. As part of further studies on palladium carbene bridging C–H activation, Huang and co-workers developed a modular approach to construct dibenzo-fused ε-lactams 152 by using o-(pseudo)halo arylaldehydes 73 and N-tosylhydrazones 151 as reactants (Scheme 33). Again, this reaction exhibited broad substrate scope (52 examples, up to 97% isolated yield) and good functional group compatibility. Moreover, the same group have applied this protocol as a key step for the synthesis of several bioactive molecules.

Inspired by these studies, Huang and co-workers conceived that the transient palladacycle 149 might be trapped by a suitable external nucleophile. Based on this rationale, Huang has very recently reported a palladium-catalyzed three-component reaction of o-bromobenzaldehydes 73, N-tosylhydrazones 157 and methanol to give methyl 2-benzylbenzoates 158. It was found that the employment of methanol as the reaction medium was essential to achieve high yields of 158. Furthermore, according to their DFT calculations, a different mechanistic pathway was proposed. Namely, after the carbene bridging process, palladium(II)
species 159 could transmetalate with methanol to give intermediate 160. A subsequent methoxy group transfer from the palladium center to the tethered aldehyde moiety could furnish hemiacetal 161. Selective hydrogen atom migration would generate the palladium hydride species 162, which upon reductive elimination would give the desired product 158 (Scheme 34, top). More interestingly, the choice of ligand not only controlled the chemoselectivity of the whole reaction, but also altered the pathway for the formation of 158. For example, when the sterically hindered phosphine ligand P(o-tolyl)3 was employed, methyl ether 163b was obtained as the major product (80% yield, Scheme 34, bottom). According to the energetics, the minor product 158b (9% yield) was probably produced through a CBA pathway analogous to that shown in Scheme 32.

5 Conclusion and Outlook

As outlined in this short review, it is apparent that bridging C–H activation offers valuable methods to functionalize inert C–H bonds in simple molecules. The introduction of appropriate bridging reagents not only facilitates proximal C–H bond activation, but also increases the structural complexities of the products. According to the general principles of such methods, we anticipate that transition-metal catalysts other than palladium may be applicable for such transformations. On the other hand, as can be seen from the advances summarized here, only a few types of compounds are suitable as bridging reagents. Therefore, highly efficient catalytic systems remain to be developed in the future so that a wider range of feedstock chemicals can be employed as bridging reagents.

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