Synthesis F. Zhang et al. Short Review

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

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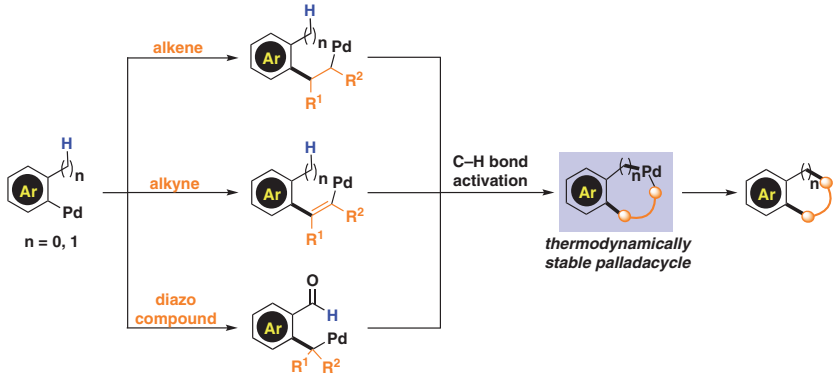
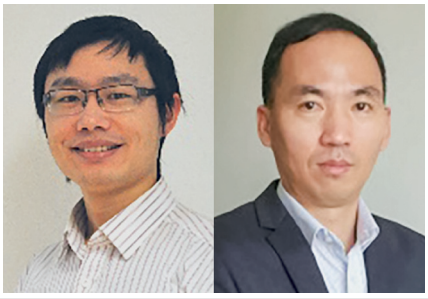


Dedicated to the 60th anniversary of the Fujian Institute of Research on the Structure of Matter

Received: 05.06.2020
Accepted after revision: 04.08.2020
Published online: 22.09.2020
DOI: 10.1055/s-0040-1707268; Art ID: ss-2020-m0310-sr

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.

Key words palladium catalysis, bridging C–H activation, alkenes, alkynes, diazo compounds, migratory insertion



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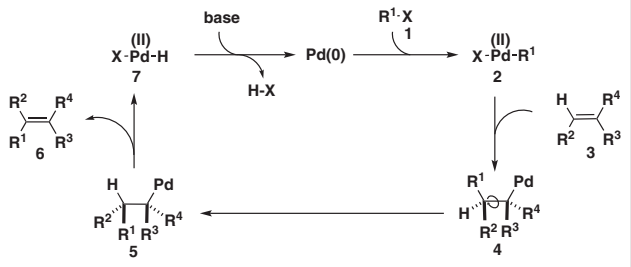
1 Introduction

Transition-metal-catalyzed direct inert C–H bond functionalization has been recognized as a concise method to construct molecules with diverse functionalities from read-

ily accessible chemicals.[1] Mechanistically, among established reaction modes, directing-group-enabled C–H bond activation through the formation of a thermodynamically stable metallacycle has gained much attention.[2] 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,[3] 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[4] and alkenes[5] is a prominent example of alkene bridging C–H activation. Related work on these topics has already been discussed in recent reviews.[6]

2 Palladium-Catalyzed Alkene Bridging C–H Activation



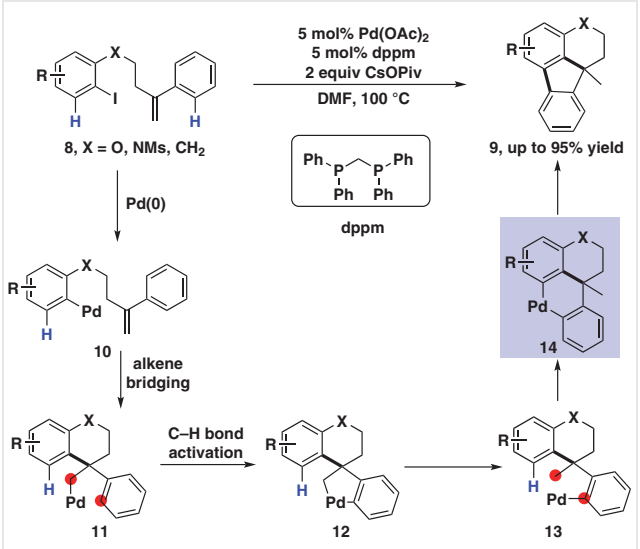
Scheme 1 Simplified mechanism for the palladium-catalyzed Heck reaction

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 **1** 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 **7**. 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.[7] 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

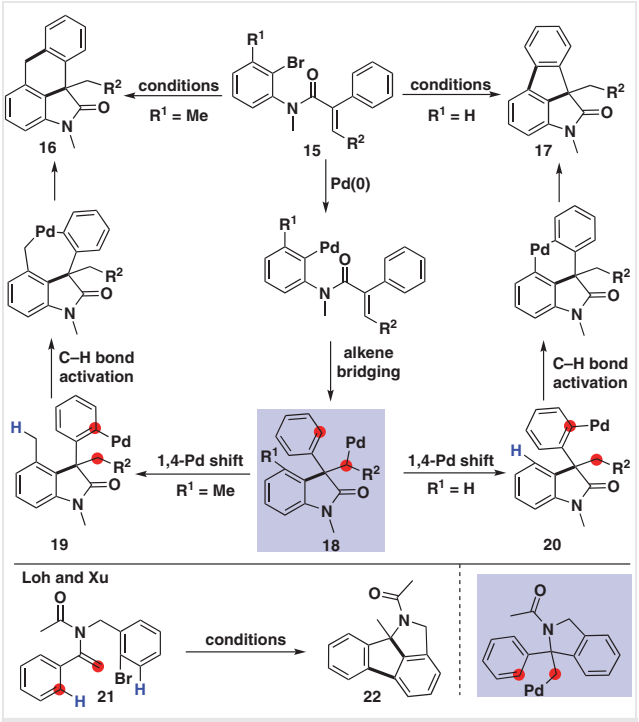
By employing bifunctional compounds **8** as reactants, Larock and co-workers achieved the synthesis of fused polycyclic compounds **9** (Scheme 2).[8] From a mechanistic viewpoint, intramolecular migratory insertion of the C–C double bond in intermediate **10** can be considered as the alkene bridging process (**10** → **11**), which is crucial for the following 1,4-palladium translocation[9] 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.



Scheme 2 Larock's 1,4-palladium shift initiated by intramolecular alkene bridging C–H activation

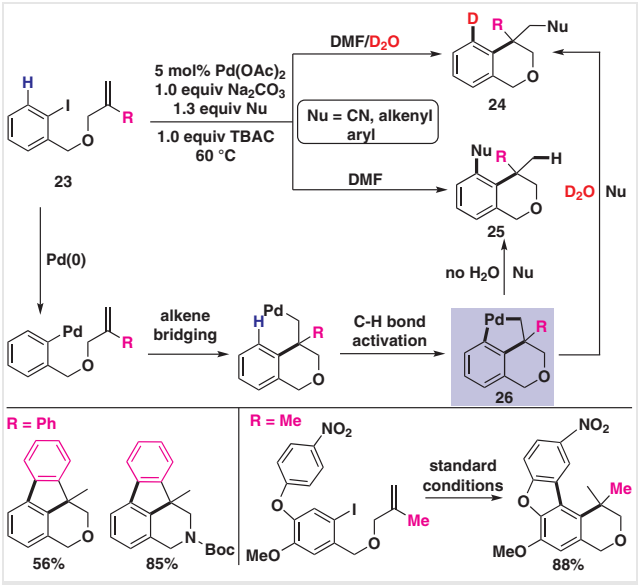
According to a similar principle, several transformations based on alkene migratory insertion via a 1,4-palladium shift/intramolecular C–H bond functionalization were reported recently. For example, Zhu and co-workers have applied this strategy for fused oxindole synthesis.[10] As de-

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.[11] They found that the regioselectivity could be altered by the substituents on the double bond.



Scheme 3 Palladium-catalyzed synthesis of fused oxoindoles through an intramolecular alkene bridging 1,4-Pd shift and C–H bond arylation

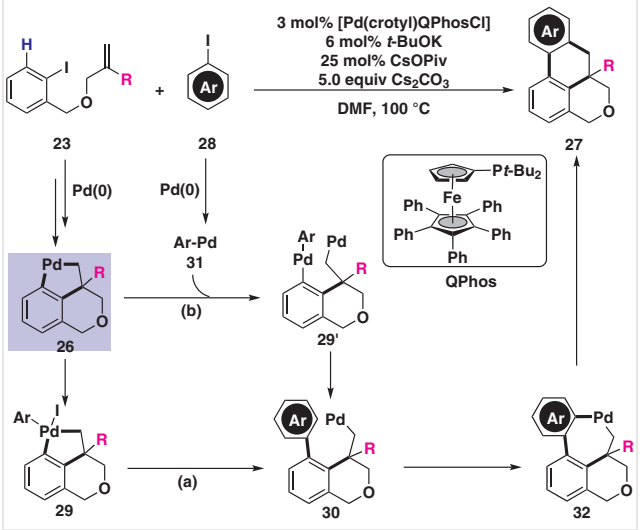
The five-membered palladacycle generated through intramolecular alkene bridging C–H activation could be trapped by a range of external reagents under appropriate conditions. In 2010, Jia and co-workers reported a water-controlled regioselective alkene bridging C–H functionalization.[12] According to 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 $K_4[Fe(CN)_6]\cdot 3H_2O$, styrene, methyl acrylate, unactivated ole-



Scheme 4 Water-controlled palladium-catalyzed regioselective alkene bridging C–H bond functionalization

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).[13] Compared with Jia's work,[12] they found that five-membered palladacycle **26**

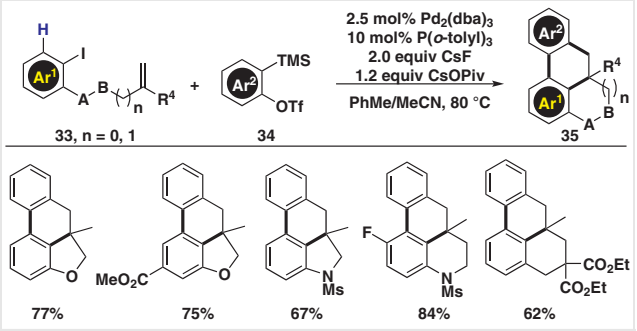


Scheme 5 Palladium-catalyzed synthesis of fused biaryl compounds through intramolecular alkene bridging C–H activation

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**.

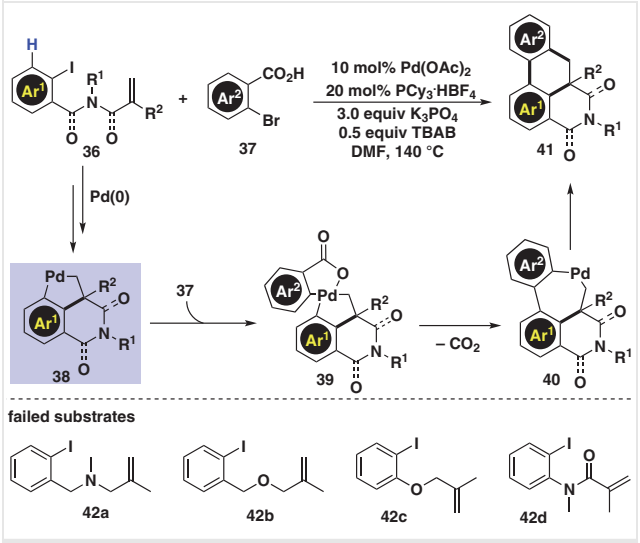
According to the results they obtained, two plausible pathways were proposed. For path a, oxidative addition of palladacycle **26** to aryl iodide **28** might give the palladium(IV) intermediate **29**, which upon aryl–aryl reductive elimination could generate intermediate **30**. As an alternative 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)Cl_2] as the precatalyst.[14] Yang and Liang have applied this strategy for oxindole synthesis, and two aryl groups derived from **28** were incorporated in the final products.[15] In their subsequent study, Lautens and co-workers found that intermediate **26** could be trapped by Me_6Si_2 or Me_6Ge_2, thus disilylation or digermanylation of **23** could be easily realized.[16a] Shortly after this study, Liang and Yang reported a palladium-catalyzed domino Heck-disilylation and borylation of alkene-tethered 2-(2-halophenyl)-1*H*-indoles.[16b]

Yao[17] and Lautens[18] 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.



Scheme 6 Palladium-catalyzed intramolecular alkene bridging C–H activation and aryne insertion

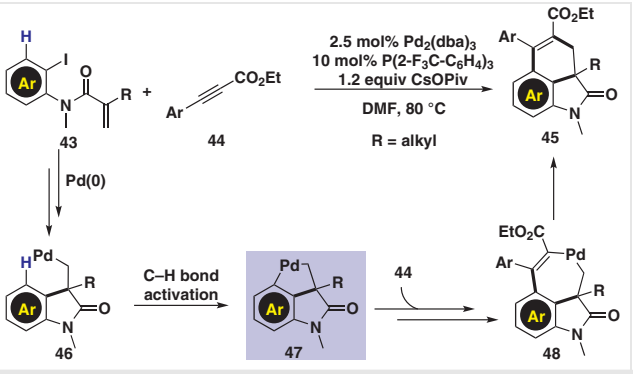
Very recently, Yang and Liang reported a new method for the synthesis of fused isoquinolinediones and isoquinolinones through a cascade reaction of compounds **36** with 2-bromobenzoic acid (**37**) (Scheme 7, top).[19] Mechanistically, a Heck-type cyclization of **36** in presence of a suitable palladium 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.



Scheme 7 Palladium-catalyzed intramolecular alkene bridging C–H activation and decarboxylation

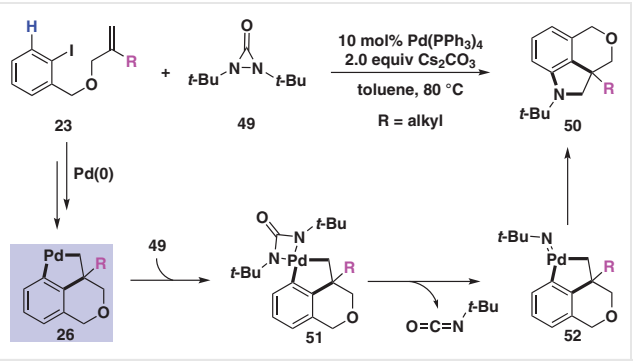
In their subsequent studies, Lautens and co-workers described a regioselective insertion of an unsymmetrical alkyne into the five-membered palladacycle **47**. The utilization of a phosphine ligand, P(2-F_3C-C_6H_4)$_3$, with the right balance of both electronic and steric characters was critical to achieve high efficiency. By contrast, the reaction using the electron-neutral ligand PPh_3 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(sp^2)–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).[20] For the reactant **43**, an alkyl group was always situated at the α-position relative to the carbonyl group (R = alkyl).

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

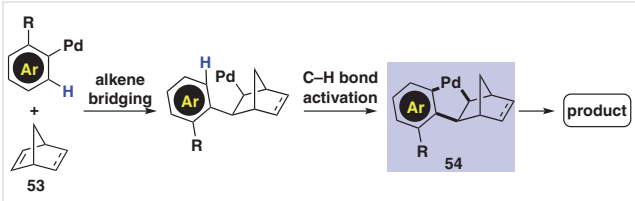
In 2014, Shi and co-workers found that the palladacycle **26** could react with di-*tert*-butyldiaziridinone (**49**) to form a spiro palladium(IV) intermediate **51**. After releasing one equivalent of *tert*-butyl isocyanate, indolines **50** bearing a *tert*-butyl group could be obtained (Scheme 9).[22] 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 = 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

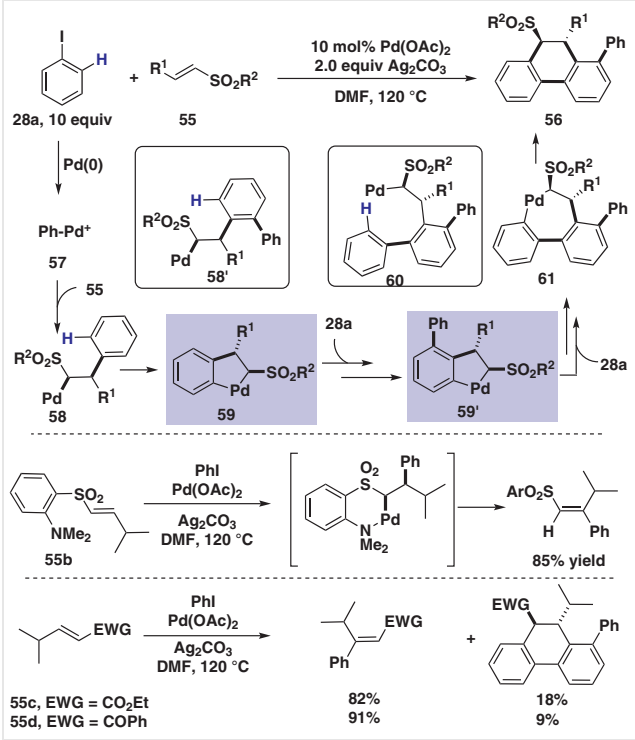
2.2 Intermolecular Reactions

The main obstacle in developing palladium-catalyzed intermolecular alkene bridging C–H activation lies in the facile β-hydride elimination to form substituted olefins. As mentioned previously, when a *syn*-β-hydrogen atom is not available, the σ-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

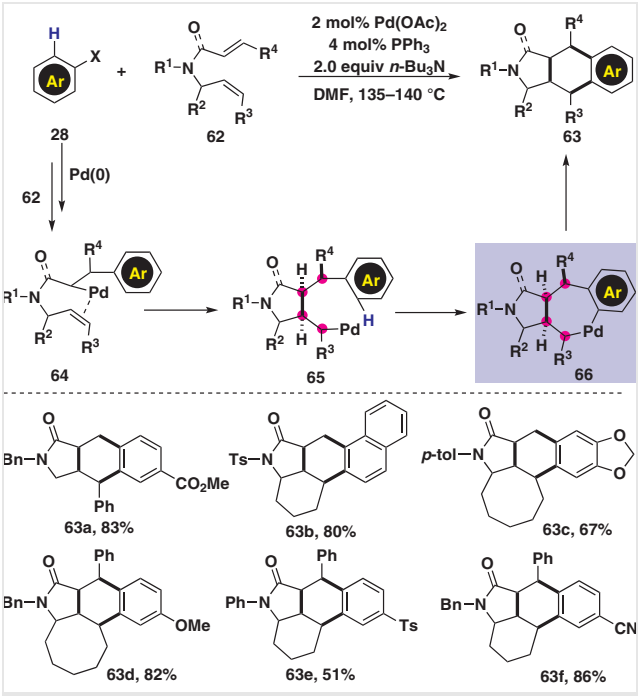
In 2001, Carretero and co-workers discovered the first palladium-catalyzed cascade arylation of an acyclic alkene when they tested the activity of β-substituted vinylsulfone **55** with phenyl iodide (**28a**), (Scheme 11, top).[23] According to their systematic examination of the reaction conditions, they found that the utilization of Ag_2CO_3 as the base, a sulfone-containing α,β-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

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 Ag_2CO_3 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 σ-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(sp^2)–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).[24] 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 protecting groups (R^1), substituents on the alkene termini (R^3 and R^4) 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.

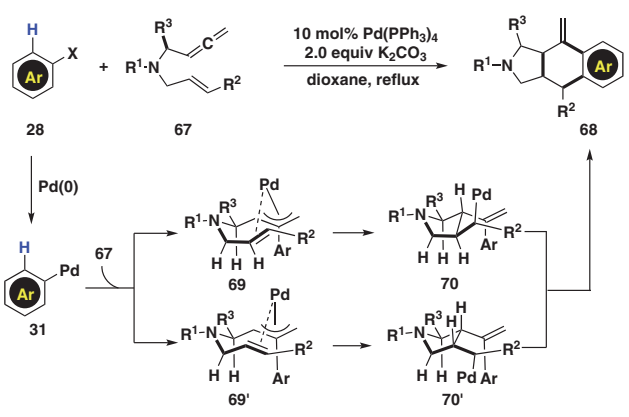


Scheme 12 Palladium-catalyzed intermolecular alkene bridging C–H activation using 1,6-dienes as the bridging reagents

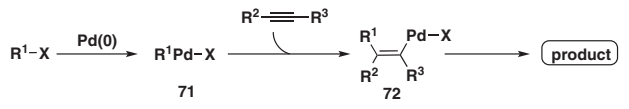
In 2005, Ohno and Tanaka demonstrated that enallenes could participate in palladium-catalyzed bridging C–H bond arylation reactions. They found that different (hetero)-aryl halides **28** could participate in the cascade cyclization reaction with substituted enallenes **67**, and that the presence of a substituent on the alkene terminus (R^2) 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).[25]

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.



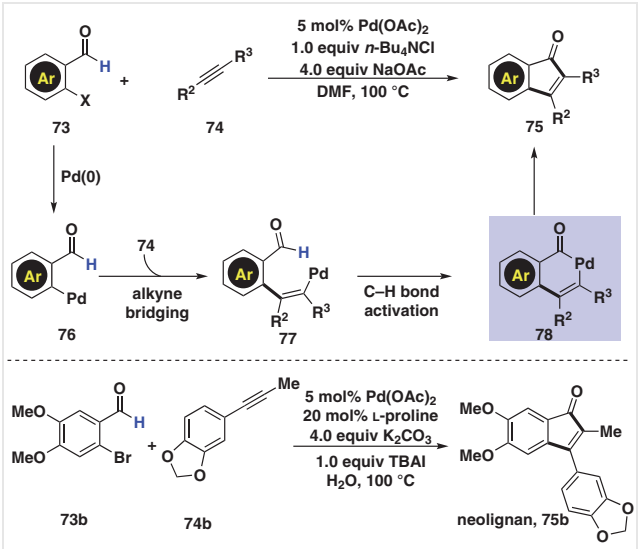
Scheme 13 Palladium-catalyzed intermolecular alkene bridging C–H activation using enallenes as the bridging reagents



Scheme 14 The *syn* carbopalladation of alkynes

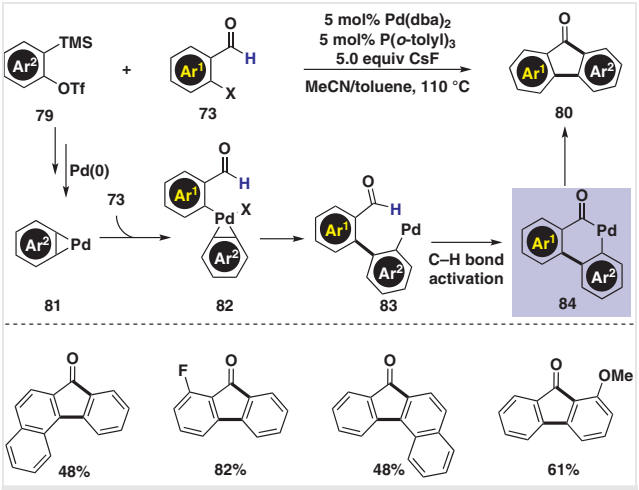
3.1 Intermolecular Reactions

In 1989, Heck reported the preparation of 2,3-diphenylindenone via a palladium-catalyzed coupling of *o*-iodobenzaldehyde with diphenylacetylene.[26] Following this report, Larock and co-workers re-examined this reaction and expanded the scope to produce a broader range of indenone derivatives **75** (Scheme 15).[27] 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 **73** to generate aryl palladium(II) intermediate **76**, which could further react with alkyne **74** to accomplish the alkyne bridging process and produce intermediate **77**. Intramolecular C–H bond palladation of the aldehyde moiety would furnish a six-membered palladacycle **78**. Reductive elimination of **78** then affords substituted indenones **75** (Scheme 15, top). This process was highly regioselective for alkynes 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 (Scheme 15, bottom).[28]



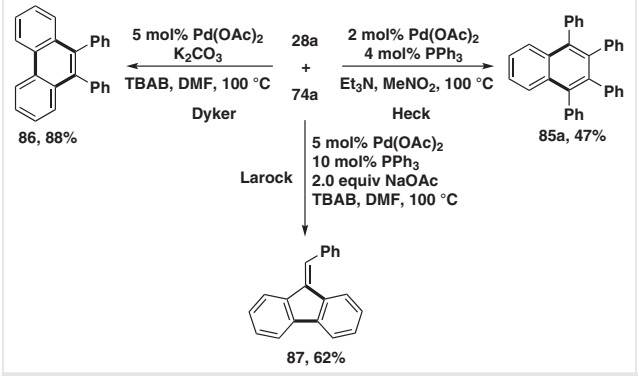
Scheme 15 Palladium-catalyzed intermolecular alkyne bridging C–H activation for indenone synthesis

In addition to alkynes, arynes are also competent bridging reagents that participate in Pd-catalyzed annulations. Larock and co-workers reported a Pd-catalyzed annulation of arynes with *o*-haloarenecarboxaldehydes **73** to provided fluoren-9-ones **80** in good yields.[29] 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 **82**. 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 **84**. However, the authors could not rule out a pathway in which the Pd(0) catalyst inserts directly into the C–X bond of aryl halide **73** to form intermediate **76** (see Scheme 15), which then undergoes carbopalladation of the aryne to give rise to **83**. Reductive elimination of **84** would give fluoren-9-ones **80**. Interestingly, the reaction of 3-methoxybenzyne exhibited very high regioselectivity, and 1-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**.



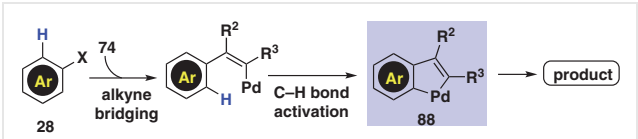
Scheme 16 Palladium-catalyzed intermolecular alkyne bridging C–H activation using an aryne as the bridging reagent

Sakakibara,[30] Heck[26] and Miura[31] have reported reactions on the palladium-catalyzed annulation of simple aryl halides with internal alkynes to give tetrasubstituted naphthalenes **85**. Interestingly, the chemoselectivities could be altered by slightly modifying the reaction conditions (Scheme 17). Accordingly, Heck and co-workers found that the reaction of phenyl iodide **28a** with diphenylacetylene **74a** using a catalyst generated from $Pd(OAc)_2$ and PPh_3 in nitromethane could give 1,2,3,4-tetraphenylnaphthalene (**85a**) in 47% yield. By contrast, Dyker and co-workers found that the major product could be switched to 9,10-diphenylphenanthrene (**86**) by using simple $Pd(OAc)_2$ as the catalyst and DMF as the solvent.[32] More intriguingly, in 2000, Larock and co-workers reported that the annulation of aryl iodide **28a** and diphenylacetylene **74a** provided fluorene **87** under similar conditions, albeit using NaOAc as the additive.[33]



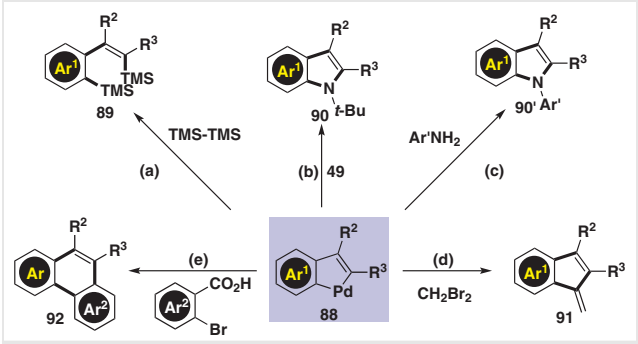
Scheme 17 Divergent syntheses of carbocyclic products through palladium-catalyzed intermolecular alkyne bridging C–H activation

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).



Scheme 18 Palladium-catalyzed intermolecular alkyne bridging C–H activation for the formation of a five-membered palladacycle

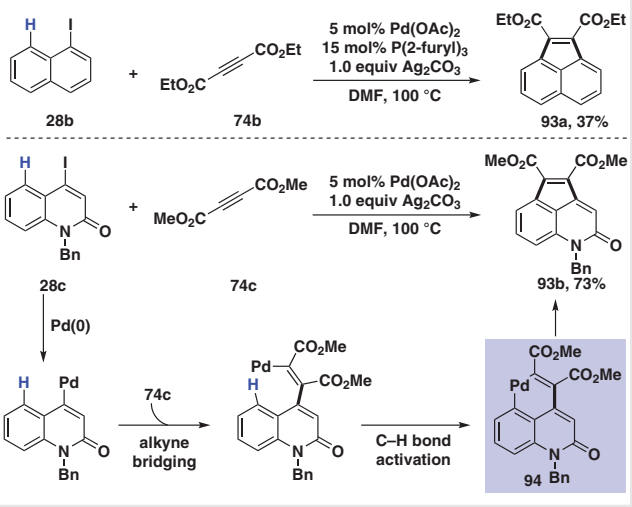
Hexamethyldisilane is commercially available and has been widely employed as a trimethylsilyl source in organosilicon chemistry. Zhang and co-workers reported that the addition of hexamethyldisilane into palladacyclic species **88** could afford a range of vinylsilanes **89** (Scheme 19, a).[34] The 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).[35] More recently, Habibi and Jafarpour used simple and readily accessible anilines as nitrogen sources to react with palladacycle **88**, giving *N*-aryl-substituted indoles **90′** in a highly efficient manner (Scheme 19, c).[36] By using CH_2Br_2 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).[37] 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).[38]



Scheme 19 Trapping palladacycle **88** with different electrophiles

In 2003, during an exploration on the palladium-catalyzed reactions of aryl iodides 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).[31] 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

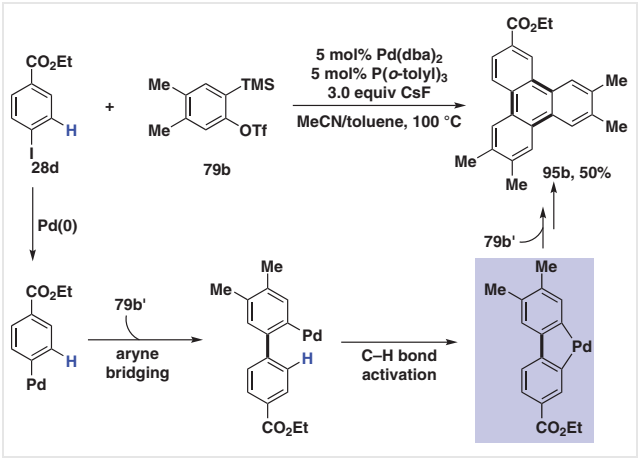
slow addition of the activated alkyne **74c** could suppress the formation of the [2+2+2] annulation product effectively without adding phosphine ligands.[39] In analogy to the aforementioned work, alkyne **74c** acted as a bridging reagent to facilitate formation of the six-membered palladacycle **94** via an intramolecular C–H bond activation. Reductive elimination of **94** then afforded product **93b** (Scheme 20, bottom).



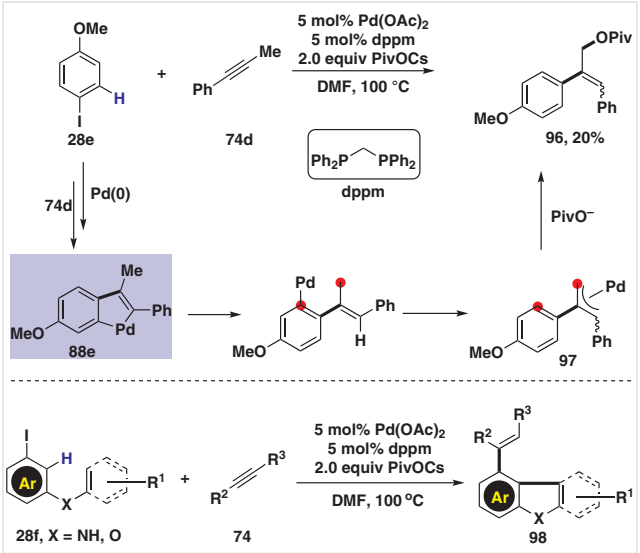
Scheme 20 Palladium-catalyzed intermolecular alkyne bridging C–H activation by using an activated internal alkyne as the bridging reagent

During their studies on the palladium-catalyzed annulation of arynes with 2-halobiaryls,[40] Larock and co-workers discovered that the reaction of ethyl 4-iodobenzoate (**28d**) with two equivalents of the aryne **79b′**, derived from 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**79b**), gave the corresponding substituted triphenylene **95b** in 50% yield. As depicted in Scheme 21, this reaction probably proceeds through an aryne-bridging C–H activation pathway.[41]

As consequence of studies in the area of through space 1,4-palladium shifts,[33] Larock and co-workers have demonstrated a consecutive vinylic to aryl to allylic palladium migration via alkyne bridging C–H activation.[42] 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 η_3-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).[43]



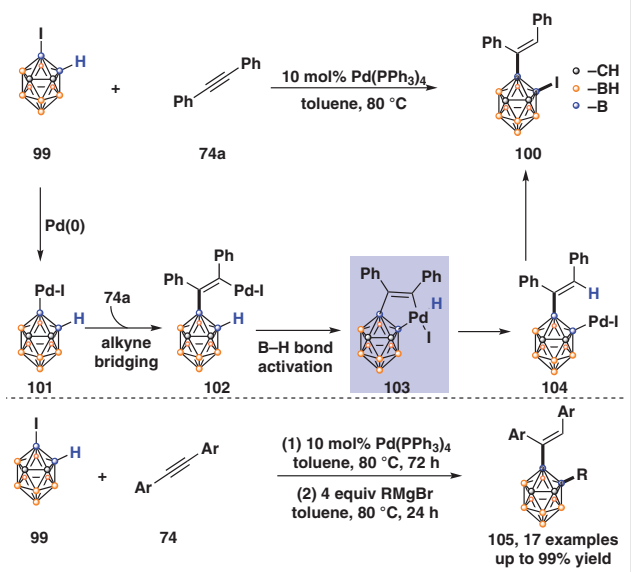
Scheme 21 Palladium-catalyzed aryne bridging C–H activation for triphenylene synthesis



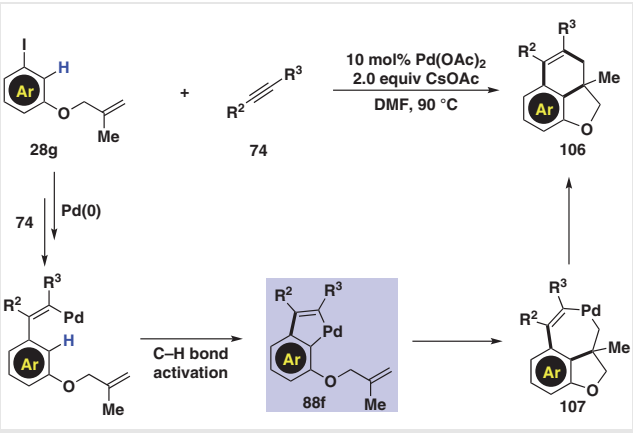
Scheme 22 An alkyne bridging 1,4-palladium shift strategy

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).[44] Accordingly, the *syn* insertion of alkyne **74a** into intermediate **101** could facilitate B–H bond activation to furnish palladacycle **103**. The transformation from **102** → **103** → **104** can be considered as a 1,4-palladium shift process. Reductive elimination of **104** could then complete the difunctionalization of **99**. Interestingly, product **100** could be trapped in situ by addition of a Grignard reagent. Thus dicarbofunctionalization of **99** 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 alkynes **74**. The tethered alkenyl moiety in aryl iodide **28g** could insert into the tran-



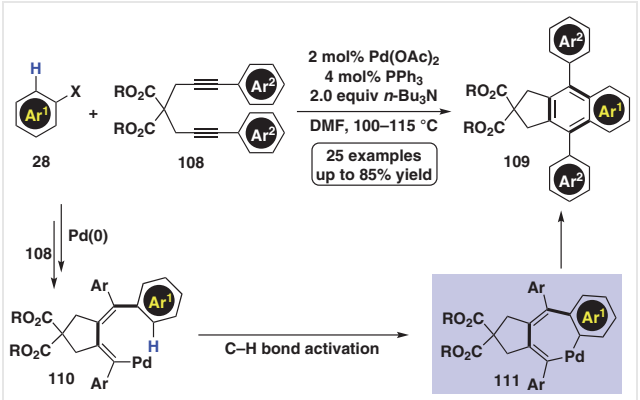
Scheme 23 Palladium-catalyzed bifunctionalization of 3-iodo-*o*-carborane through intermolecular alkyne bridging B–H activation



Scheme 24 A cascade reaction through palladium-catalyzed intermolecular alkyne bridging C–H activation and intramolecular alkene insertion

sient five-membered palladacycle **88f**, which was generated through alkyne bridging C–H activation. Reductive elimination of the resulting seven-membered palladacycle **107** resulted in the fused polycyclic products **106** (Scheme 24). Kinetic isotope effect (KIE, K_H/K_D = 2.3) experiments indicated that cleavage of the C(sp^2)–H bond might be involved in the rate-determining step.[45]

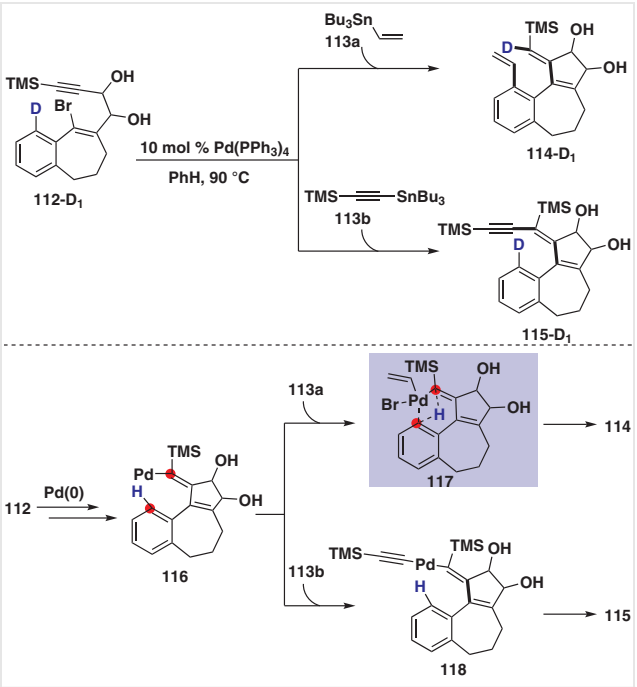
Akin to simple internal alkynes, 1,6-diynes **108** could also serve as bridging reagents to promote proximal inert C–H bond activation. In 2010, Hu and co-workers reported an efficient protocol for the preparation of polysubstituted aromatics **109**. Mechanistically, two-fold *syn* migratory insertion of palladium(II) species **31** could complete the diyne bridging process to give the vinyl palladium(II) species **110**. Intramolecular C–H bond activation could afford a seven-membered palladacycle **111**, 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]



Scheme 25 Palladium-catalyzed alkyne bridging C–H activation using 1,6-diynes as the bridging reagents

3.2 Intramolecular Reactions

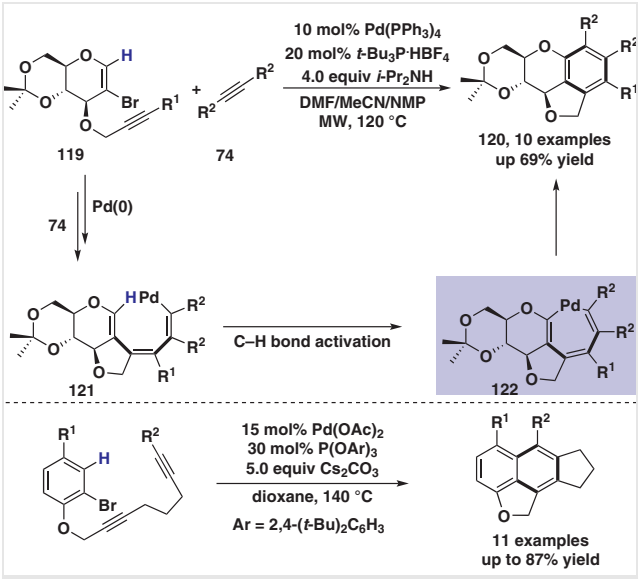
The introduction of a tethered alkyne moiety into organic halides can greatly enhance the structural complexity of the corresponding products. For example, in 2005, Suffert and Bour reported a tin-reagent-dependent palladium-catalyzed cascade reaction, in which an intramolecular alkyne bridging C(sp^2)–H bond heteroarylation, allylation and vinylation were observed.[47] To understand the mechanism, the authors prepared deuterium labeled diol **112-D_1**. 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. In contrast, when an alkynyl tin reagent was employed, the alkynylation took place at the vinyl position, with the deuterium atom retained on the phenyl ring (Scheme 26, top).



Scheme 26 Palladium-catalyzed intramolecular alkyne bridging C–H activation/Stille cross-coupling

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]



Scheme 27 Palladium-catalyzed cascade reaction for benzene annulation via intramolecular alkyne bridging C–H bond activation

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**), *o*-bromophenols **123b**, *p*-bromophenols **123c**, ethyl 2-(4-bromonaphthalen-1-yl)acetate (**123d**) and benzoyl O-substituted hydroxylamine **123e**.[51]

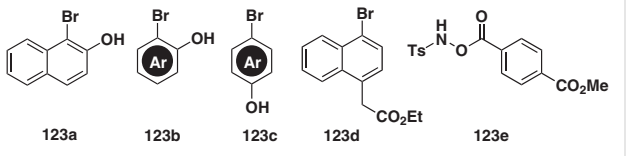
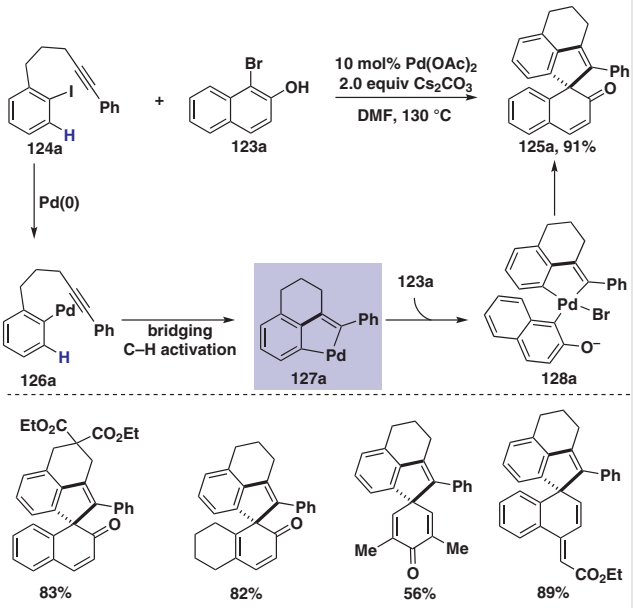


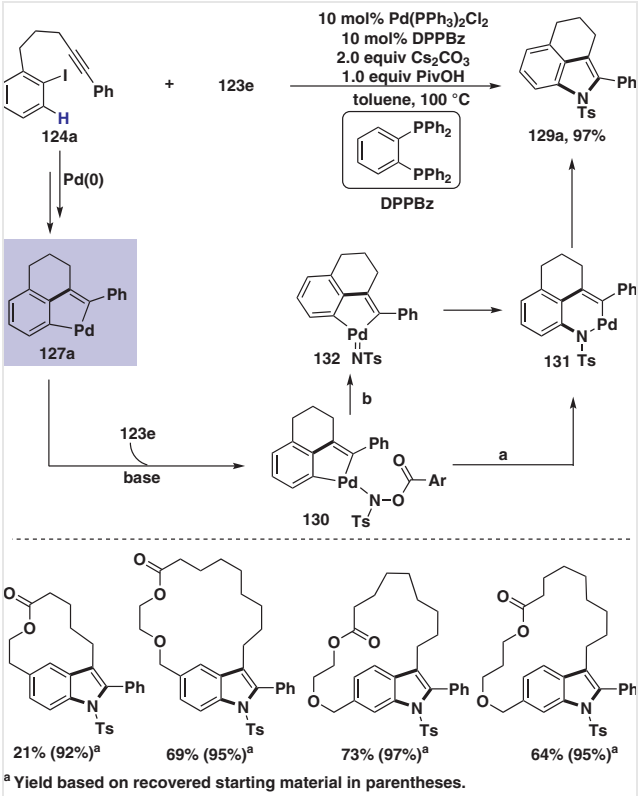
Figure 1 Structures of bifunctional reagents **123**



Scheme 28 Synthesis of spirocyclic products **125** through palladium-catalyzed intramolecular alkyne bridging C–H activation

For the palladium-catalyzed reactions of aryl iodides **124** with alkynes **123a–d**, dearomatization of **123** to form a range of spiro products **125** was observed.[51a] This reaction was operationally simple, and required no external ligands, while exhibiting broad substrate scope (53 examples). The products **125** were obtained in moderate to excellent yields (48–92%). Herein we take the reaction of **124a** with **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 **124a**. Intramolecular *syn* carbopalladation of the resulting intermediate **126a** produced a vinyl palladium(II) species. The key intermediate **127a** was formed by intramolecular C–H palladation. At this stage, additional oxidative addition of **127a** to **123a** would generate the palladium(IV) species **128a**. Finally, a two-fold reductive elimination of **128a** involving dearomatization of the naphthalene ring would eventually give the final spiro product **125a** (Scheme 28).

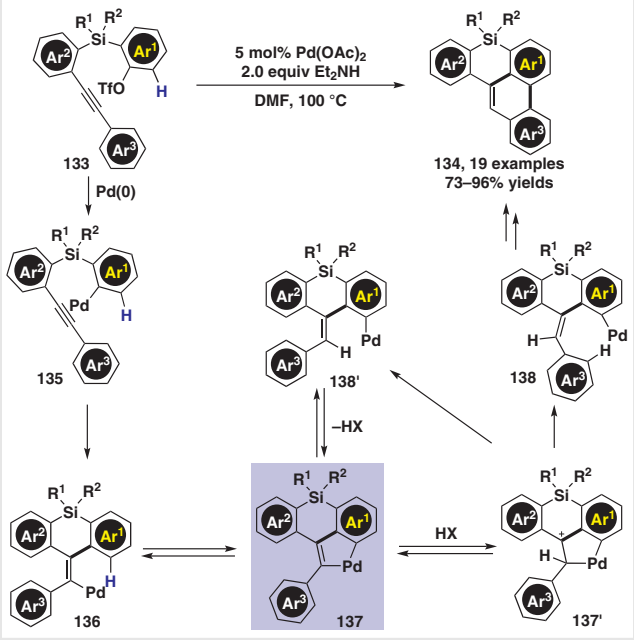
In their subsequent study, Luan and co-workers identified that hydroxylamine derivative **123e** could act as an excellent bifunctional nitrogen source in the reaction with transient palladacycle **127**, providing a rapid access to diverse tricyclic indole scaffolds.[51b] Based on their comprehensive mechanistic studies, two plausible reaction pathways were proposed. Coordination of deprotonated **123e** to the electrophilic palladium intermediate **127a** could furnish another five-membered palladacycle **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 **131**. Alternatively, the formation of a putative Pd-nitrene species **132** was also equally reasonable to explain the reaction outcome. Migratory insertion of the aryl moiety could furnish intermediate **131** as well (pathway b). Reductive elimination of **131** would afford tricyclic indole **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 alkynyl 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 **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*-butyldiaziridinone **49** as the amination reagent.[52]



Scheme 29 Synthesis of tricyclic indoles **129** through palladium-catalyzed intramolecular alkyne bridging C–H activation

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.[53] Specifically, oxidative addition of **133** to the active palladium(0) catalyst could provide palladium(II) intermediate **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^1). 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**.

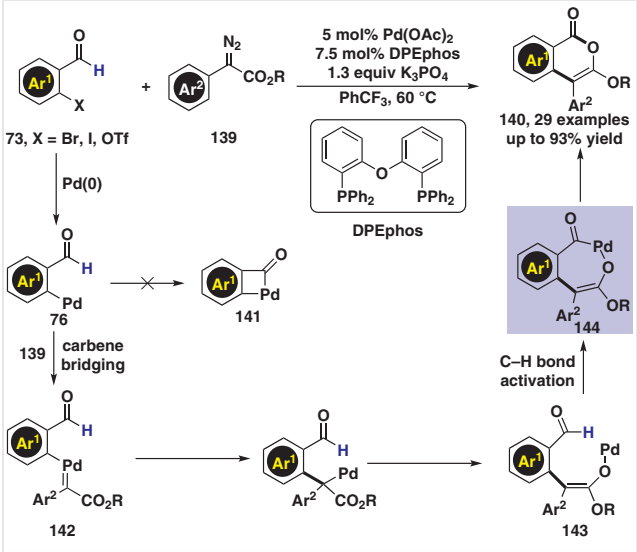


Scheme 30 Benzophenanthroline synthesis via intramolecular alkyne bridging C–H activation and a 1,4-palladium shift

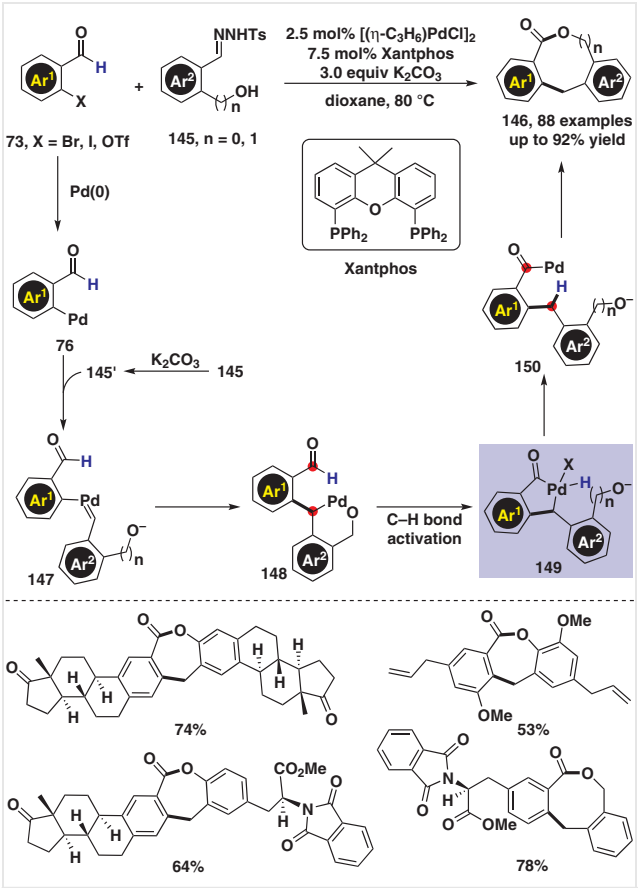
4 Palladium-Catalyzed Carbene Bridging C–H Activation

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.[1e,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 carbenes[56] 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.



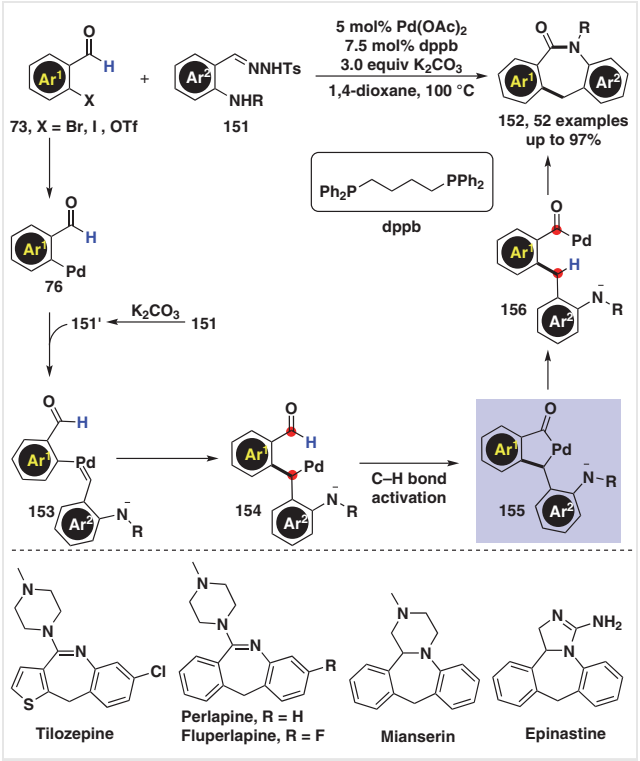
Scheme 31 Palladium-catalyzed isocoumarin synthesis via carbene bridging C–H bond activation



Scheme 32 Palladium-catalyzed medium-sized lactone synthesis via carbene bridging C–H bond activation

Encouraged by the aforementioned work, Huang and co-workers applied their CBA strategy for the synthesis of seven- and eight-membered lactones.[60] 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**.

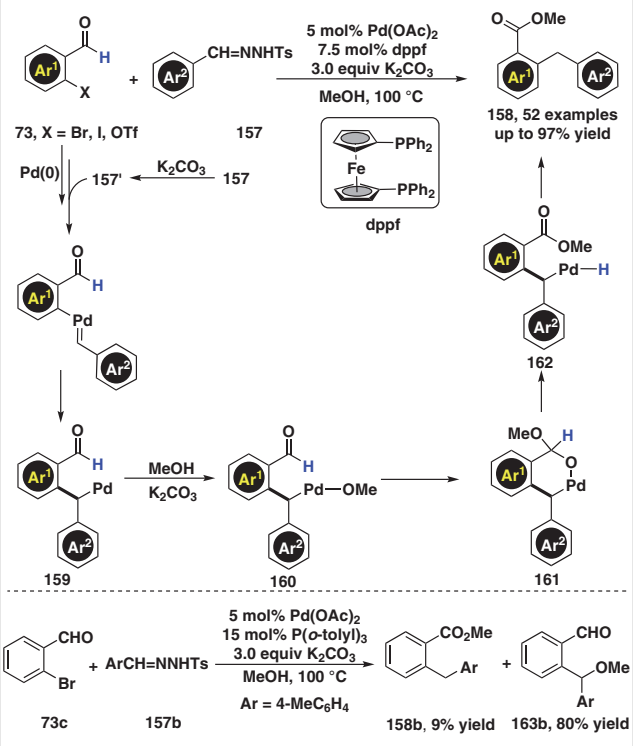
Tricyclic ring systems possessing a dibenzo structure joined to a seven-membered heterocyclic ring often show important biological activities. However, a brief survey of the literature revealed that a modular approach to such compounds based on an efficient intermolecular reaction of readily available 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).[61] 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.



Scheme 33 Palladium-catalyzed synthesis of dibenzo-fused ε-lactams via carbene bridging C–H bond activation

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-benzoylbenzoates **158**.[62] 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.[63] 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.



Scheme 34 Palladium-catalyzed three-component coupling reaction of *o*-bromobenzaldehydes, *N*-tosylhydrazones, and methanol

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.

Funding Information

We are grateful for financial support from the National Natural Science Foundation of China (NSFC) (Grant Nos. 21402197, 21871259, and 21901244), the Hundred Talents Program, and the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000).

References

(1) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (d) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (f) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (g) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (i) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (j) Zhu, R. Y.; Farmer, M. E.; Chen, Y. Q.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578. (k) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787. (l) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864. (m) Newton, C. G.; Wang, S. G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908.

(2) (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70. (f) Baudoin, O. *Acc. Chem. Res.* **2017**, *50*, 1114. (g) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Q. *Chem. Rev.* **2017**, *117*, 8754.

(3) (a) McNally, A.; Haffemayer, B.; Collins, B. S.; Gaunt, M. J. *Nature* **2014**, *510*, 129. (b) He, C.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15840. (c) Smalley, A. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 10632. (d) Willcox, D.; Chappell, B. G.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 851. (e) He, C.; Gaunt, M. J. *Chem. Sci.* **2017**, *8*, 3586. (f) Hogg, K. F.; Trowbridge, A.; Alvarez-Pérez, A.; Gaunt, M. J. *Chem. Sci.* **2017**, *8*, 8198. (g) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 1412. (h) Wen, J.; Wang, D.; Qian, J.; Wang, D.; Zhu, C.; Zhao, Y.; Shi, Z. *Angew. Chem. Int. Ed.* **2019**, *58*, 2078. (i) Su, B.; Bunescu, A.; Qiu, Y.; Zuend, S. J.; Ernst, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2020**, *142*, 7912.

(4) (a) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990. (b) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (c) Jiao, L.; Bach, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 6080. (d) Sui, X.; Zhu, R.; Li, G.; Ma, X.; Gu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 9318. (e) Zhao, K.; Xu, S.; Pan, C.; Sui, X.; Gu, Z. *Org. Lett.* **2016**, *18*, 3782. (f) Li, R.; Zhou, Y.; Xu, X.; Dong, G. *J. Am. Chem. Soc.* **2019**, *141*, 18958.

(5) (a) Wang, J.; Dong, Z.; Yang, C.; Dong, G. *Nat. Chem.* **2019**, *11*, 1106. (b) Wu, Z.; Fatuzzo, N.; Dong, G. *J. Am. Chem. Soc.* **2020**, *142*, 2715.
(6) (a) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (b) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (c) Gu, Z.; Sui, X.; Zhu, R. *Synlett* **2013**, *24*, 2023. (d) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, *7*, 863. (e) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389. (f) Kim, D. S.; Park, W. J.; Jun, C. H. *Chem. Rev.* **2017**, *117*, 8977. (g) Gandeepan, P.; Ackermann, L. *Chem* **2018**, *4*, 199. (h) Cheng, H. G.; Chen, S.; Chen, R.; Zhou, Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 5832. (i) Wang, J.; Dong, G. *Chem. Rev.* **2019**, *119*, 7478.
(7) (a) Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Adv. Synth. Catal.* **2011**, *353*, 809. (b) Mehta, V. P.; García-López, J.-A. *ChemCatChem* **2017**, *9*, 1149. (c) Ping, Y.; Li, Y.; Zhu, J.; Kong, W. *Angew. Chem. Int. Ed.* **2019**, *58*, 1562.
(8) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460.
(9) (a) Ma, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2005**, *44*, 7512. (b) Shi, F.; Larock, R. C. *Top. Curr. Chem.* **2010**, *292*, 123. (c) Rahim, A.; Feng, J.; Gu, Z. *Chin. J. Chem.* **2019**, *37*, 929.
(10) (a) Piou, T.; Bunescu, A.; Wang, Q.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12385. (b) Bunescu, A.; Piou, T.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 334.
(11) Wang, M.; Zhang, X.; Zhuang, Y. X.; Xu, Y. H.; Loh, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 1341.
(12) Lu, Z.; Hu, C.; Guo, J.; Li, J.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *12*, 480.
(13) Sickert, M.; Weinstabl, H.; Peters, B.; Hou, X.; Lautens, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 5147.
(14) He, H.-Y.; Wang, W.; Yu, X.-J.; Huang, J.; Jian, L.; Fu, H.-Y.; Zheng, X.-L.; Chen, H.; Li, R.-X. *Eur. J. Org. Chem.* **2016**, 5616.
(15) Luo, X.; Xu, Y.; Xiao, G.; Liu, W.; Qian, C.; Deng, G.; Song, J.; Liang, Y.; Yang, C. *Org. Lett.* **2018**, *20*, 2997.
(16) (a) Wollenburg, M.; Bajohr, J.; Marchese, A. D.; Whyte, A.; Glorius, F.; Lautens, M. *Org. Lett.* **2020**, *22*, 3679. (b) Lu, H.; Yang, X.; Zhou, L.; Li, W.; Deng, G.; Yang, Y.; Liang, Y. *Org. Chem. Front.* **2020**, *7*, 2016.
(17) Yao, T.; He, D. *Org. Lett.* **2017**, *19*, 842.
(18) Yoon, H.; Lossouarn, A.; Landau, F.; Lautens, M. *Org. Lett.* **2016**, *18*, 6324.
(19) Luo, X.; Zhou, L.; Lu, H.; Deng, G.; Liang, Y.; Yang, C.; Yang, Y. *Org. Lett.* **2019**, *21*, 9960.
(20) Rodriguez, J. F.; Marchese, A. D.; Lautens, M. *Org. Lett.* **2018**, *20*, 4367.
(21) Yoon, H.; Rolz, M.; Landau, F.; Lautens, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 10920.
(22) Zheng, H.; Zhu, Y.; Shi, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 11280.
(23) (a) Mauleón, P.; Alonso, I.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2001**, 40 , 1291. (b) Mauleon, P.; Nunez, A. A.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2003**, *9*, 1511. (c) Alonso, I.; Alcami, M.; Mauleon, P.; Carretero, J. C. *Chem. Eur. J.* **2006**, *12*, 4576.
(24) (a) Hu, Y.; Song, F.; Wu, F.; Cheng, D.; Wang, S. *Chem. Eur. J.* **2008**, *14*, 3110. (b) Hu, Y.; Yu, C.; Ren, D.; Hu, Q.; Zhang, L.; Cheng, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 5448. (c) Hu, Y.; Ouyang, Y.; Qu, Y.; Hu, Q.; Yao, H. *Chem. Commun.* **2009**, 4575. (d) Hu, Y.; Qu, Y.; Wu, F.; Gui, J.; Wei, Y.; Hu, Q.; Wang, S. *Chem. Asian J.* **2010**, *5*, 309. (e) Hu, Y.; Ren, D.; Zhang, L.; Lin, X.; Wan, J. *Eur. J. Org. Chem.* **2010**, 4454.
(25) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J.* **2005**, *11*, 3728.
(26) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550.
(27) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.
(28) Ramesh, K.; Satyanarayana, G. *Eur. J. Org. Chem.* **2018**, *2018*, 4135.
(29) (a) Zhang, X.; Larock, R. C. *Org. Lett.* **2005**, *7*, 3973. (b) Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6679.
(30) Sakakibara, T.; Tanaka, Y.; Yamasaki, S.-i. *Chem. Lett.* **1986**, *15*, 797.
(31) Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 6836.
(32) (a) Dyker, G. *J. Org. Chem.* **1993**, *58*, 234. (b) Dyker, G.; Kellner, A. *Tetrahedron Lett.* **1994**, *35*, 7633.
(33) (a) Tian, Q.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3329. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372.
(34) Zhou, B.; Lu, A.; Shao, C.; Liang, X.; Zhang, Y. *Chem. Commun.* **2018**, *54*, 10598.
(35) Zhou, B.; Wu, Z.; Ma, D.; Ji, X.; Zhang, Y. *Org. Lett.* **2018**, *20*, 6440.
(36) Jafarpour, F.; Ghasemi, M.; Mohaghegh, F.; Asgari, S.; Habibi, A. *Org. Lett.* **2019**, *21*, 10143.
(37) Zhou, B.; Wu, Z.; Qi, W. X.; Sun, X. L.; Zhang, Y. H. *Adv. Synth. Catal.* **2018**, *360*, 4480.
(38) Yang, Y.; Zhou, L.; Yang, X.; Luo, X.; Deng, G.; Yang, Y.; Liang, Y. *Synthesis* **2020**, *52*, 1223.
(39) Yamamoto, Y.; Jiang, J.; Yasui, T. *Chem. Eur. J.* **2020**, *26*, 3749.
(40) (a) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223. (c) Liu, Z.; Larock, R. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 2535.
(41) Jayanth, T. T.; Cheng, C. H. *Chem. Commun.* **2006**, 894.
(42) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1873.
(43) (a) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701. (b) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340.
(44) Ge, Y.; Zhang, J.; Qiu, Z.; Xie, Z. *Angew. Chem. Int. Ed.* **2020**, *59*, 4851.
(45) Guo, S.; Li, P.; Guan, Z.; Cai, L.; Chen, S.; Lin, A.; Yao, H. *Org. Lett.* **2019**, *21*, 921.
(46) (a) Hu, Y.; Yao, H.; Sun, Y.; Wan, J.; Lin, X.; Zhu, T. *Chem. Eur. J.* **2010**, *16*, 7635. (b) Hu, Y.; Zhu, T.; Mu, X.; Zhao, Q.; Yu, T.; Wen, L.; Zhang, Y.; Wu, M.; Zhang, H. *Tetrahedron* **2012**, *68*, 311.
(47) Bour, C.; Suffert, J. *Org. Lett.* **2005**, *7*, 653.
(48) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171.
(49) Leibeling, M.; Milde, B.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem. Eur. J.* **2011**, *17*, 9888.
(50) Leibeling, M.; Pawliczek, M.; Kratzert, D.; Stalke, D.; Werz, D. B. *Org. Lett.* **2012**, *14*, 346.
(51) (a) Zuo, Z.; Wang, J.; Liu, J.; Wang, Y.; Luan, X. *Angew. Chem. Int. Ed.* **2020**, *59*, 653. (b) Fan, L.; Hao, J.; Yu, J.; Ma, X.; Liu, J.; Luan, X. *J. Am. Chem. Soc.* **2020**, *142*, 6698.
(52) Cheng, C.; Zuo, X.; Tu, D.; Wan, B.; Zhang, Y. *Org. Lett.* **2020**, *22*, 4985.
(53) Tsuda, T.; Kawakami, Y.; Choi, S. M.; Shintani, R. *Angew. Chem. Int. Ed.* **2020**, *59*, 8057.
(54) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Zhang, Z. H.; Wang, J. B. *Tetrahedron* **2008**, *64*, 6577. (f) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (g) Liu, L.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 506. (h) Cheng, Q. Q.; Deng, Y.; Lankelma, M.; Doyle, M. P. *Chem. Soc. Rev.* **2017**, *46*, 5425. (i) Zhu, D.; Chen, L.; Fan, H.; Yao, Q.; Zhu, S. *Chem. Soc. Rev.* **2020**, *49*, 908.

(55) (a) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (b) Xiang, Y. Y.; Wang, C.; Ding, Q. P.; Peng, Y. Y. *Adv. Synth. Catal.* **2019**, *361*, 919.

(56) (a) Zhang, Y.; Wang, J. B. *Eur. J. Org. Chem.* **2011**, 1015. (b) Zhang, Z.; Zhang, Y.; Wang, J. *ACS Catal.* **2011**, *1*, 1621. (c) Barluenga, J.; Valdes, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. (d) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (e) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (f) Xia, Y.; Wang, J. *Chem. Soc. Rev.* **2017**, *46*, 2306. (g) Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810. (h) Xia, Y.; Wang, J. *J. Am. Chem. Soc.* **2020**, *142*, 10592.

(57) Xu, S.; Chen, R.; Fu, Z.; Zhou, Q.; Zhang, Y.; Wang, J. *ACS Catal.* **2017**, *7*, 1993.

(58) Yu, Y.; Lu, Q.; Chen, G.; Li, C.; Huang, X. *Angew. Chem. Int. Ed.* **2018**, *57*, 319.

(59) Yan, C.; Yu, Y. H.; Peng, B.; Huang, X. L. *Eur. J. Org. Chem.* **2020**, 723.

(60) Yu, Y.; Chakraborty, P.; Song, J.; Zhu, L.; Li, C.; Huang, X. *Nat. Commun.* **2020**, *11*, 461.

(61) Yu, Y.; Ma, L.; Xia, J.; Xin, L.; Zhu, L.; Huang, X. *Angew. Chem. Int. Ed.* **2020**, *59*, in press; DOI: 10.1002/anie.202007799.

(62) Zhu, L.; Ren, X.; Yu, Y.; Ou, P.; Wang, Z. X.; Huang, X. *Org. Lett.* **2020**, *22*, 2087.

(63) Ren, X.; Zhu, L.; Yu, Y.; Wang, Z. X.; Huang, X. *Org. Lett.* **2020**, *22*, 3251.