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Perspective

Modern Palladium-Catalyzed Transformations Involving C−H Activation and Subsequent Annulation

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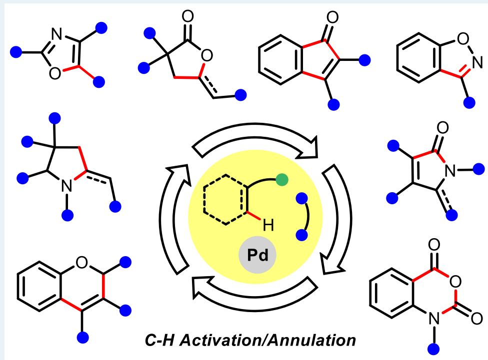
ABSTRACT: The metal-catalyzed "cascade C−H activation/annulation" is a highly promising approach to the construction of aromatic and heteroaromatic compounds. In this context, Pd-complexes play a crucial role whereby molecules bearing a directing group can be activated with high catalytic efficiency. These reactions will expand the synthetic potential of Pd-catalyzed C−H activation and subsequent aromatic and aliphatic C−C bond formation. Described herein is an outline of the recent advances in this research subject.



KEYWORDS: *palladium, C−H activation, annulation, coupling, aromatics, heterocycles*

1. INTRODUCTION

Palladium (Pd) has played a key role in innovating organic transformations over the years. In 1803, this rare metal was discovered by English chemist William Hyde Wollaston.[1] Since then, palladium has been used extensively for a wide range of applications, particularly as a catalyst, because of its high catalytic activity and exquisite selectivity. The importance of palladium in organic synthesis has increased over the years, and its applications include various coupling reactions,[2] for example, cross-dehydrogenative couplings (CDC),[3] oxidative couplings,[4] allylations,[5] and many other processes, such as catalytic hydrogenations[6] and C−H functionalizations.[7] One of the most significant advancements of Pd-catalyzed reactions is C−H functionalization,[8−10] and recently, many articles have been published on "cascade C−H activation/annulation" for the synthesis of bioactive organic molecules.[11−13] Furthermore, the construction of aromatic and heteroaromatic compounds using Pd-catalysis remains at the forefront of research efforts.

Aromatics and heteroaromatics are scaffolds present in functional molecules ranging from nucleic acids, pharmaceuticals, and biomass materials to natural and synthetic dyes.[14] In fact, more than 85% of all biologically active compounds contain at least one heterocyclic moiety, and around 59% of US FDA-approved drugs contain a nitrogen heterocycle,[15] which proves the importance of heterocycles and their design and synthesis. Increasing demands for the efficient construction of heterocycles can be met by modern advances in C−H functionalization and annulation reactions. These methods allow rapid access to a wide variety of functionalized heterocycles. More specifically, Pd-catalyzed C−H functionalization and annulation by intramolecular carbo−heteroatom bond formation could be used to fulfill these purposes. Despite the importance of this research field from both chemical and biological perspectives, there is no pertinent review published in the literature, which prompts us to provide an overview of recent advancements in Pd-catalyzed C−H activation/annulation reactions.

In this Perspective, covering examples published since 1998, are summarized state of the art Pd-catalyzed reactions of C−H activation/annulation and the associated mechanisms that justify the observed products (Figure 1). The reactions of arenes bearing a directing group for activating a $C(sp^2)$−H or $C(sp^3)$−H bond have been systematically presented, which are mainly organized following the functionality of coupling partners such as alkenes, allenes, alkynes, arynes, arenes, aryl halides, arylamines, aryl aldehydes, aryl carboxylic acids, cyclic/acyclic β-dicarbonyl compounds, isocyanates, peracids, aryl/benzyl nitriles, aryl isonitriles, and carbon monoxide. For clarity, coordination geometries at the palladium complex are not explicitly shown in some of the mechanisms.

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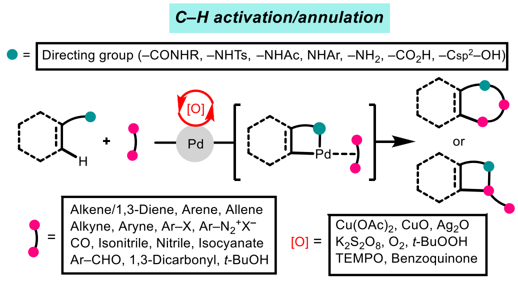
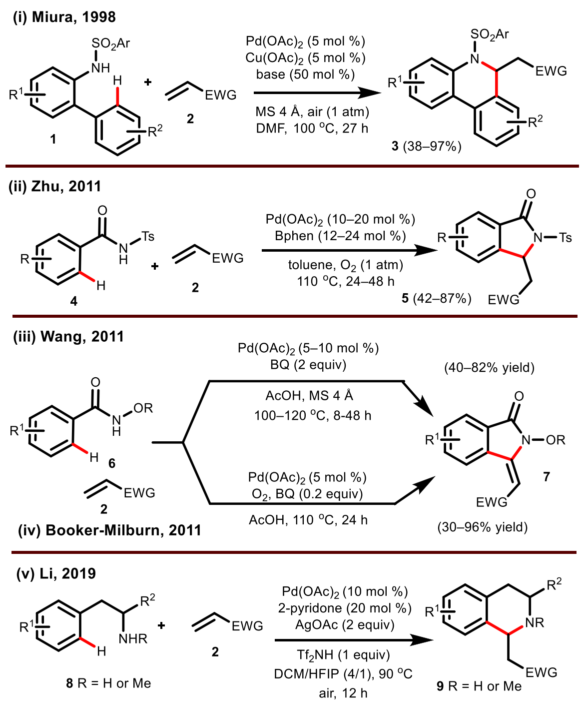


Figure 1. Pd-catalyzed C−H activation/annulation cascade.

2. DISCUSSION

2.1. Pd-Catalyzed C−H Activation/Annulation with Alkenes and Allenes. Pd-catalyzed $C(sp^2)-H/C(sp^3)-H$ alkenylation of free *N*H-containing or *N*-substituted substrates with alkenes followed by subsequent annulation has been amply documented. In 1998, the Miura group reported the reaction between *N*-(2′-phenylphenyl)benzene-sulfonamides **1** and acrylate **2** to generate 5,6-dihydro-5-(benzenesulfonyl)-phenanthridine-6-acetate derivatives **3** wherein the functionalization of a C−H bond was achieved with $Pd(OAc)_2$ and $Cu(OAc)_2$ (Scheme 1i).[16] Subsequently, several groups

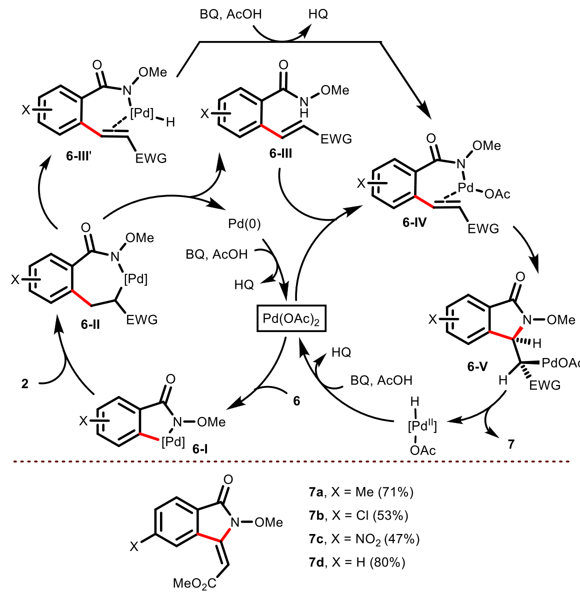
Scheme 1. C−H Activation/Annulation with Acrylate



reported slightly modified protocols to construct heterocycles **5** and **7** relying on imide and amide as a directing group, respectively (Scheme 1ii−v).[17−20] Despite the similarity between these three protocols, more oxidized isoindolinone *E*-isomer product **7** was obtained with an electron-rich amide directing group.[18] Recently, Li and co-workers reported a Pd(II)-catalyzed $C(sp^2)-H$ olefination of simple free primary and secondary amines **8** to access tetrahydroquinolines **9** (Scheme 1v).[20] In contrast with earlier reports[21] that are limited to only α-disubstituted amines, this protocol does not require any substituent on the α-position of the amino group. Most notably, the protocol is suitable for the synthesis of tetrahydroqionolines in biologically active molecules such as baclofen and phenylalanine ester.

The formation of product **7** (Scheme 2) is proposed to proceed via C−H activation of benzamide **6** with $Pd(OAc)_2$ to

Scheme 2. Mechanism of $C(sp^2)-H$ Activation/Intramolecular Oxidative Amidation for Isoindolinone Synthesis



form palladacycle **6-I** followed by olefin insertion to generate a seven-membered palladacycle **6-II**. β-Hydride elimination followed by reductive elimination from **6-II** generates an *ortho*-olefinated product **6-III**, which re-enters the second catalytic cycle to furnish intermediate **6-IV**. Alternatively, after the β-hydride elimination, the resulting amido-Pd−H complex **6-III′** can be directly oxidized to generate the same intermediate **6-VI**. Subsequent *syn*-amino palladation and stereospecific β-hydride elimination from **6-V** leads to the observed products **7a**−**7d**. The reactions of substrates bearing an electron-withdrawing group afforded relatively low yield.[18]

The groups of Yu, Sanford, Gemmeren, and Maiti, also explored the cascade reactions of Pd-catalyzed $C(sp^3)-H$ activation/annulation (Scheme 3i,v).[22−28] Compared with the activation and annulation with $C(sp^2)-H$ bonds, the corresponding transformation of $C(sp^3)-H$ bonds remained unexplored until Yu's report in 2010 (Scheme 3i).[22] In 2014, the same group reported the β-$C(sp^3)-H$ olefination of alanine-derived amides using a tricyclic quinoline ligand.[23] Later, the Sanford group explored the $C(sp^3)-H$ bond activation/annulation reaction of 2-alkylated pyridines **12** to generate *N*-heterocyclic salts **13** relying on Pd/polyoxometalate-catalyst and aerobic oxidation (Scheme 3ii).[24] This method provides not only a convenient route to 6,5-*N*-fused bicycles but also access to functionalized alkene products. In 2018, the Yu group reported the Pd(II)-catalyzed olefination of $C(sp^3)-H$ bonds of free carboxylic acids **14** to form γ-lactones (Scheme 3iii).[25] A new thioether-based bidentate ligand, acetyl-protected aminoethyl phenyl thioether, successfully promoted β-$C(sp^3)-H$ olefination of a broad range of free carboxylic acids. The same group extended this protocol to the synthesis of δ-lactones using aliphatic carboxylic acids and

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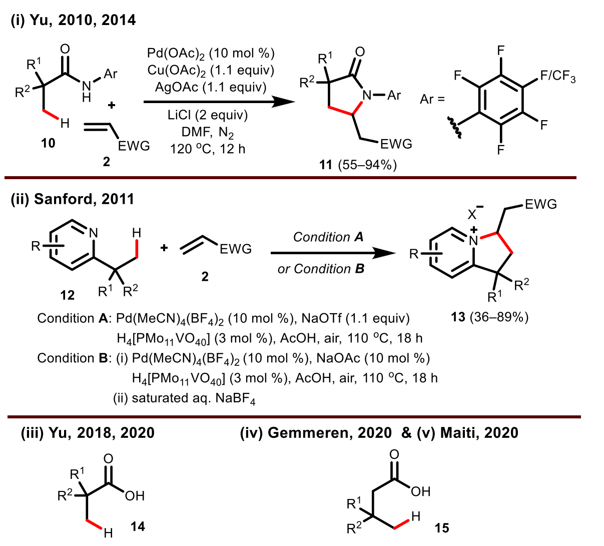
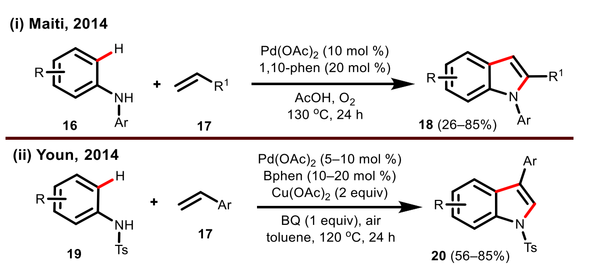
Scheme 3. Pd-Catalyzed C(sp^3)−H Activation/Annulations



2-methyl benzoic acids as substrates using Ac-Phe-OH as a ligand to provide lactone products in good yields.[26] The groups of Gemmeren and Maiti independently developed similar approaches for the synthesis of δ-lactones using *N*-Ac-Val-OH or *N*-Ac-Ala-OH as a ligand (Scheme 3iv,v).[27,28] In these reactions, carboxylic acids bearing alkyl and aryl groups and olefins bearing electron-withdrawing groups, such as ketone, nitrile, sulfone, or diethyl phosphonate could be employed. In addition, olefins bearing other functionalities such as hydroxymethyl group were also successfully utilized.

The groups of Maiti and Youn reported regiodivergent indole synthesis using monosubstituted olefin (Scheme 4i,ii).[29,30] In 2014, Maiti observed a regioselective Pd-catalyzed

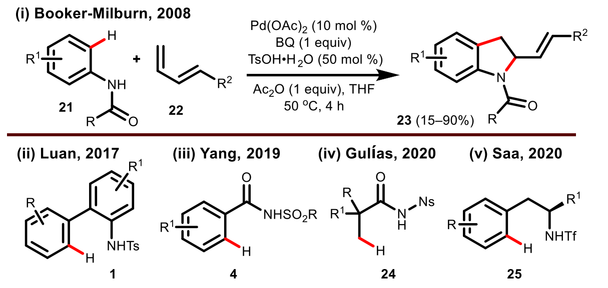
Scheme 4. C−H Activation/Annulation with Alkene



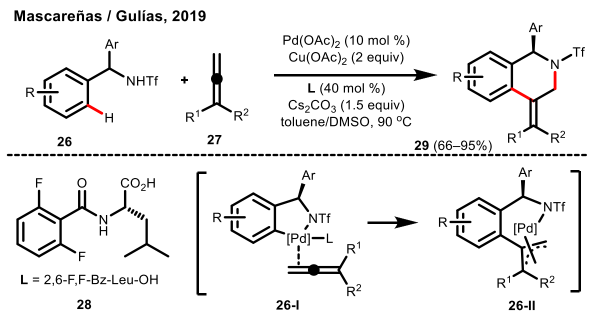
reaction of diarylamines **16** and alkene **17** to generate 2-substituted indole **18** (Scheme 4i).[29] On the contrary, under slightly different conditions, Youn observed the Pd-catalyzed reaction of Ts-anilines **19** and styrene derivatives afforded 3-arylindoles **20** (Scheme 4ii).[30] This regioselective and robust reaction protocol provided diverse 3-arylindoles from commercially available starting materials with good functional group tolerance.

Conjugated dienes and allenes were found to be viable alkene counterparts in Pd-catalyzed C(sp^2)−H activation and cyclization approach for the construction of benzo-fused nitrogen heterocycles (Schemes 5 and 6). The unique reactivity of 1,3-diene **22** in combination with various reactants bearing a different directing group (**21**, **1**, **4**, **24**, and **25**) smoothly afforded the corresponding heterocycles.[31−35]

Scheme 5. C−H Activation/Annulation with 1,3-Diene



Scheme 6. C−H Activation/Annulation with Allene



The Mascareñas group reported asymmetric ring construction from diarylmethylamide **26** and allene **27** using a leucine-derived chiral ligand **28** (Scheme 6).[36] The authors proposed that desymmetrization via C(sp^2)−H activation leads to allene-coordinated palladacycle **26-I**, which undergoes allene migratory insertion to form π-allyl-Pd complex **26-II** as the penultimate intermediate. In the final step, the regioselective C−N bond formation at the less-substituted carbon of the π-allyl-Pd complex provides the observed product **29**.

2.2. Pd-Catalyzed C−H Activation/Annulation with Alkynes.

Alkynes have been extensively utilized as coupling partners in Pd-catalyzed C−H activation/annulation reactions to construct multisubstituted aromatic and heteroaromatic compounds. In 2010, Wu reported chemo- and regioselective 1:2 coupling of aniline derivative **19** with alkyne **30** to generate highly substituted naphthalene derivatives **31** (Scheme 7i).[37] In 2011, Li developed a ligand-free and eco-friendly method involving the coupling of *N*-aryl-2-aminopyridines **32** with alkyne **30** to form *N*-(2-pyridyl)indoles **33** using an inexpensive palladium complex $Pd(MeCN)_2Cl_2$ (Scheme 7ii), which is found to be superior to Rh-catalyzed transformation.[38] In 2014, Guan reported an oxidative coupling between enamides **34** and alkynes **30** to form pyrrole derivatives **35** (Scheme 7iii).[39] Zeng further developed this protocol by employing pyridyl functionalized ketoimines **36** instead of enamides (Scheme 7iv).[40] The pyridyl moiety serves as an efficient directing group for the synthesis of highly functionalized pyrrole derivatives **37**. Following the earlier success, Zeng developed a one-pot Pd-catalyzed domino reaction to construct cyclopentaquinolines **39** from *ortho*-vinylaniline derivative **38** along with two molecules of alkyne counterparts (Scheme 7v).[41]

The features of this transformation include the formation of four σ-bonds and an aromatization-driven 1,2-alkyl shift. Recently, Gogoi reported on a Pd-catalyzed vinylic geminal double C(sp^2)−H activation of *ortho*-vinylaniline derivative **40**

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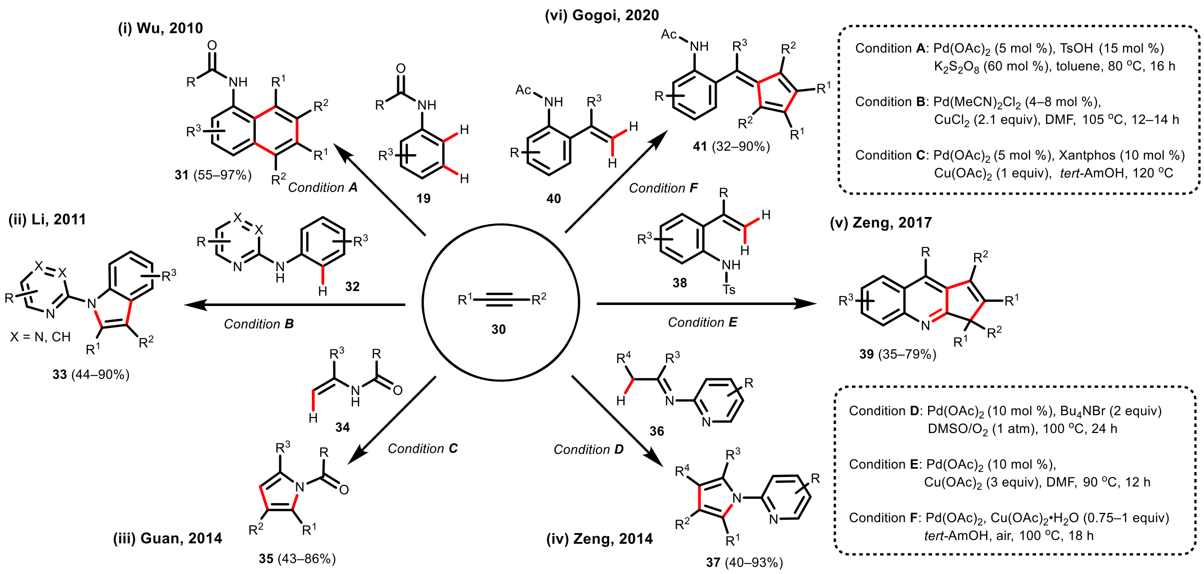
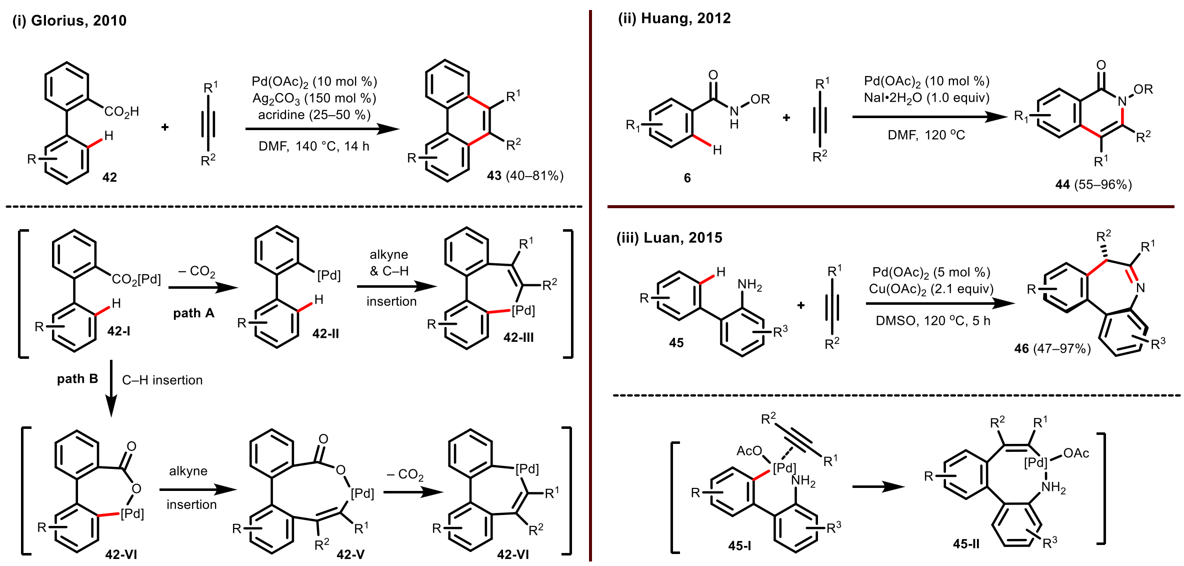
Scheme 7. Pd-Catalyzed C−H Activation/Annulation with One or Two Molecules of Alkyne for the Synthesis of Multi-substituted Aromatic and Heteroaromatic Compounds



Scheme 8. C−H Activation/Annulations with Alkyne



to generate pentafulvenes **41** (Scheme 7vi).[42] Mechanistically, this transformation involves an initial C(sp^2)−H activation, two consecutive migratory insertions of alkynes, and an intramolecular Heck-type cyclization to complete the formation of the pentafulvene moiety.

The Glorius group took advantage of a carboxylic acid as a directing group, which also undergoes decarboxylative Pd-insertion into C(sp^2)−CO_2H bond. Thus, under Pd(II)-catalyzed conditions, 2-phenyl benzoic acids **42** and alkyne generated phenanthrenes (Scheme 8i).[43] This protocol is appealing because of its potential use for the synthesis of polyaromatic hydrocarbons, which are of great interest in the material science field. In terms of reaction mechanism, there are two plausible pathways proposed depending on the time of the decarboxylation event. In the pathway A, Pd-carboxylate **42-I** undergoes decarboxylation to **42-II** followed by alkyne insertion to generate a penultimate intermediate **42-III**, a reductive elimination of which leads to product **43**. In the pathway B, the C−H insertion by **42-I** generates **42-IV**, which undergoes alkyne insertion to form **42-V** followed by decarboxylation to **42-IV**, and subsequent reductive elimination will lead to product **43**.

In 2012, Huang reported a unique Pd-catalyzed annulation reactions involving C(sp^2)−H bond activation in benzamides **6** followed by migratory insertion with an alkyne to furnish *N*-alkoxy isoquinolinones **44** (Scheme 8ii).[44] In 2015, Luan developed a C(sp^2)−H bond activation/annulation of *ortho*-arylanilines **45** and alkyne (Scheme 8iii),[45] which provided diastereomerically pure atropisomers of dibenzo[*b*,*d*]azepines **46**. This reaction is assumed to proceed through the formation of a key intermediate **45-I**, which is the consequence of C(sp^2)−H activation followed by alkyne coordination. Migratory insertion of the coordinated alkyne into the C−Pd bond in **45-I** would generate azapalladacyclooctatriene **45-II**,

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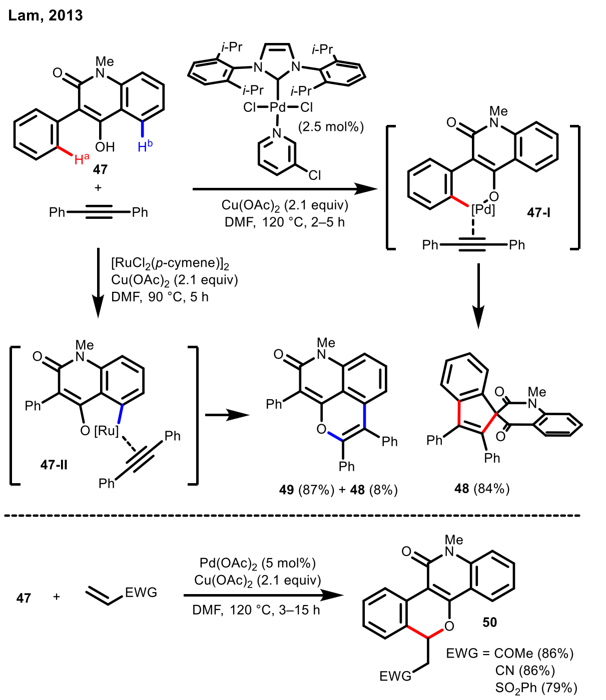
which will undergo reductive elimination to form an enamine moiety. A diastereoselective tautomerization of the enamine would set the configuration of the R^2 substituent, which is controlled by the axial chirality of the biphenyl scaffold.

Lam reported an efficient spirocyclization that involves chemoselective C−H activation/annulation (Scheme 9).[46]

Scheme 9. Selectivity in C−H Activation/Annulations

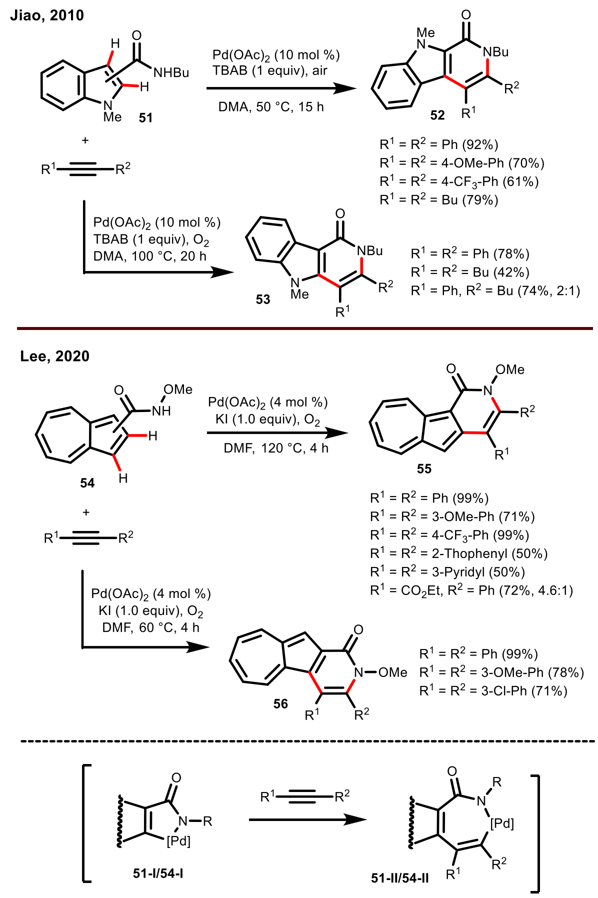


When 3-aryl-4-hydroxylquinolin-2-one **47** and alkyne were treated with a Pd-*N*-heterocyclic carbene complex, spiroindene **48** was generated in good yield, and benzopyran **49** was not observed. This is the consequence of preferential activation of H^a over H^b, forming six-membered palladacycle **47-I** instead of five-membered palladacycle **47-II**. In stark contrast, switching the Pd-catalyst to a ruthenium complex $RuCl_2$(*p*-cymene)$]_2$, benzopyran **49** (87%) was obtained predominantly along with a minor amount of spiroindene **48** (8%). This result indicated that a ruthenium complex prefers to activate H^b over H^a to form a five-membered metallacycle **47-II**. The reaction with a rhodium complex $[RhCp^*Cl_2]_2$ also provided predominantly **49** (79%) over **48** (13%) but with slightly reduced selectivity. The reaction of alkenes with $Pd(OAc)_2$ provided annulation product **50** via a Heck-type coupling followed by Michael addition.

The groups of Jiao and Lee independently developed protocols for the preparation of pyridinones employing the Pd-catalyzed C(sp^2)−H activation/annulation (Scheme 10).[47,48] Under slightly different conditions, indole carboxamide **53** and alkyne efficiently participated in C(sp^2)−H activation/annulation to generate isomeric pyridinones **52** and **53**. Similarly, *N*-methyloxyazulene carboxamide **54** provided isomeric pyridinones **55** and **56**.

Mechanistically, the activation of C(sp^2)−H bonds on five-membered rings is effective as those on six-membered rings to form palladacycle **51-I**/**54-I**. Migratory insertion of an alkyne molecule to form penultimate intermediate **51-II**/**54-II**, which upon reductive elimination leads to pyridinones fused with indole and azulene.

Scheme 10. C−H Activation/Annulation on the Five-Membered Ring of Indole and Azulene Carboxamides



In 2013, Cheng and Gandeepan devised a method for a palladium-catalyzed *ortho* C−H activation of allylarenes **57** in the presence of internal alkynes to form substituted naphthalenes **58** (Scheme 11).[49] The mechanism involves the initial formation of an electrophilic $[Pd(TFA)]^+$ species, which coordinates with the C−C double bond and the aryl group to form intermediate **57-I**. Subsequent formation of Pd(II) σ-aryl complex **57-II** through cyclometalation followed by alkyne insertion leads to **57-III**. Ring closure to generate **57-IV** via *syn*-addition followed by syn-β-hydride elimination generates **57-V** and a regenerated Pd-catalyst, and final isomerization of the benzylidene moiety yields naphthalene product **58**. A variety of diarylalkynes with electron-withdrawing and electron-donating substituents as well as aliphatic alkynes react well to form substituted naphthalenes. Reactions involving unsymmetrical alkynes are suitable although resulting in regioisomeric products. Generally, C−H activation occurred at a less hindered *ortho* position whenever meta position is substituted and environmentally friendly oxidant O_2 can be used in the reaction.

Wang further expands the scope of the C−H activation/annulation strategy by employing ferrocenyl carboxamide **59** for the synthesis of ferrocene-fused pyridinones **60** (Scheme 12i).[50] While this reaction proceeds through palladacycle **59-I**, the parent ferrocene **61** can be activated to form ferrocenyl Pd-complex **61-I** under relatively mild conditions, which

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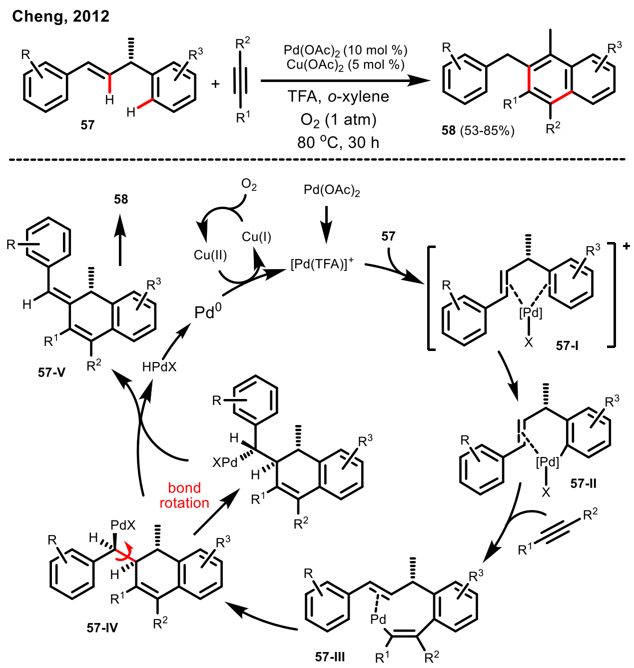
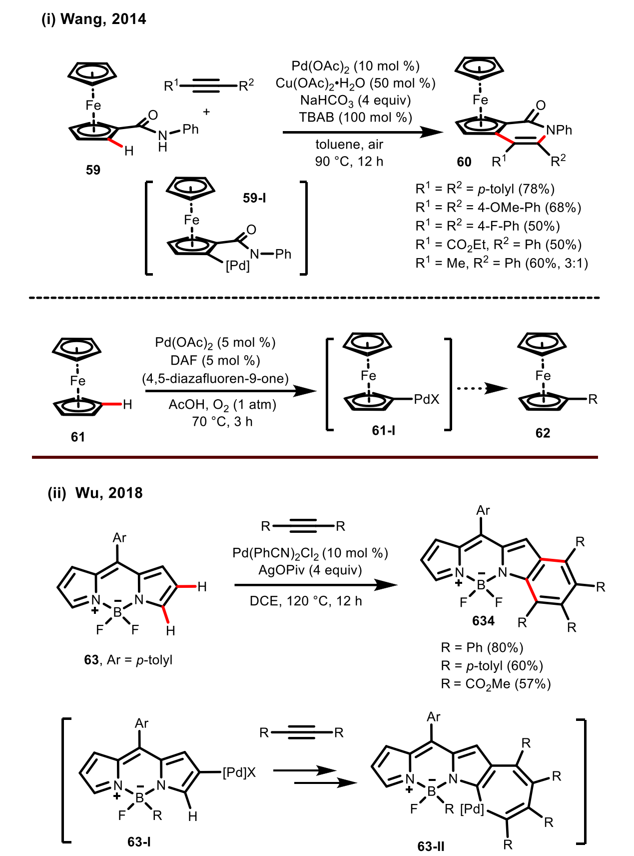
Scheme 11. C−H Activation/Annulation of Allylarenes with Alkynes



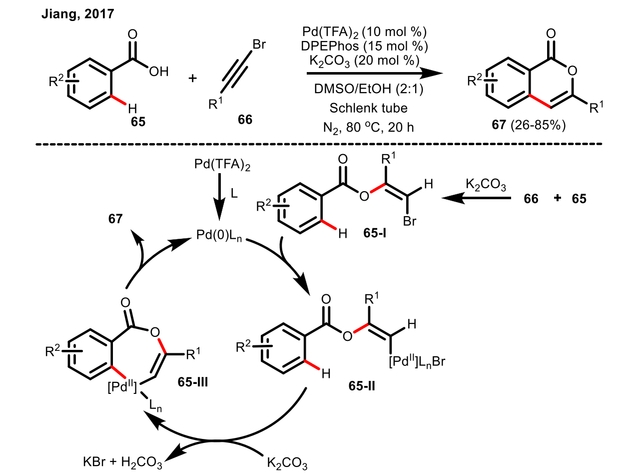
Scheme 12. C−H Functionalization of Electron-Rich Five-Membered Aromatic Systems



participates in dehydrogenative coupling reactions to form product **62**.[51] Wu took advantage of C−H activation/annulation of BODIPY **63** to construct unsymmetrical benzo[*b*]-fused BODIPY derivatives **64** (Scheme 12ii).[52] The actual mechanism for the formation of a key intermediate **63-I** is most likely an electrophilic aromatic substitution between an electron-rich pyrrole moiety and Pd(II). Once formed, **63-I** undergoes two consecutive migratory insertions with alkyne followed by intramolecular electrophilic aromatic substitution (formal C−H activation) to generate **63-II**, which upon reductive elimination provides the observed product **64**. However, the construction of four-membered ring systems remains underdeveloped as compared with five- and six-membered rings.

The Jiang group developed a protocol to access 3-substituted isocoumarins via Pd-catalyzed annulation using benzoic acids **65** and bromoalkynes **66** (Scheme 13).[53]

Scheme 13. C−H Activation/Annulation of Benzoic Acids with Bromoalkynes



Mechanistically, initial *cis*-nucleophilic addition of benzoic acid and bromoalkynes gives intermediate **65-I**. Oxidative addition to generate intermediate **65-II** followed by formal *ortho*-C(sp^2)−H activation forming putative palladacycle **65-III** and subsequent reductive elimination affords 3-substituted coumarin **67**.

2.3. Pd-Catalyzed C−H Activation/Annulation with Carbon Monoxide.

The past decade has witnessed rapid developments in the Pd-catalyzed carbonylation of C−H bonds with CO. Using this C−H activation/annulation approach, various heterocyclic motifs with four- to seven-membered rings have been synthesized. Gaunt reported on the construction of β-lactam **69** by activating a C(sp^3)−H bond (Scheme 14).[54] This reaction shows high efficiency, site selectivity, and functional group tolerance with a broad range of substrates. The C−H bond activation occurs selectively with primary over secondary or tertiary C−H bonds to deliver products **69**. Even the C(sp^2)−H bond near a nitrogen-directing group in **69c** does not compete with the primary C−H bond activation. Additives, such as bulky carboxylic acid, benzoquinone, and an amine ligand, were found to be crucial for high yield. The bulky carboxylic acid helps for the formation of a sterically biased Pd-anhydride **68-I**, which steers selective amine attack to generate carbamoyl-Pd intermediate **68-II**, minimizing the unproductive carboxamide formation and Pd-reduction. The kinetic isotope effect suggests that the conversion of **68-I** to **68-II** is irreversible, while the C−H bond activation with **68-II** occurs reversibly through concerted

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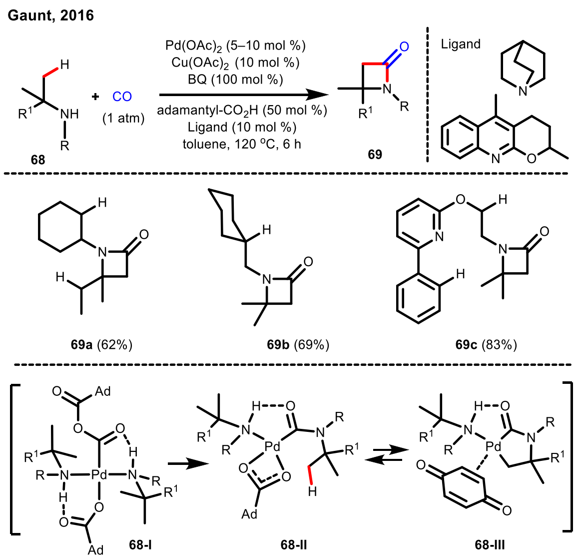
Scheme 14. C−H Activation/Annulation with Carbon Monoxide to Form Four-Membered Rings

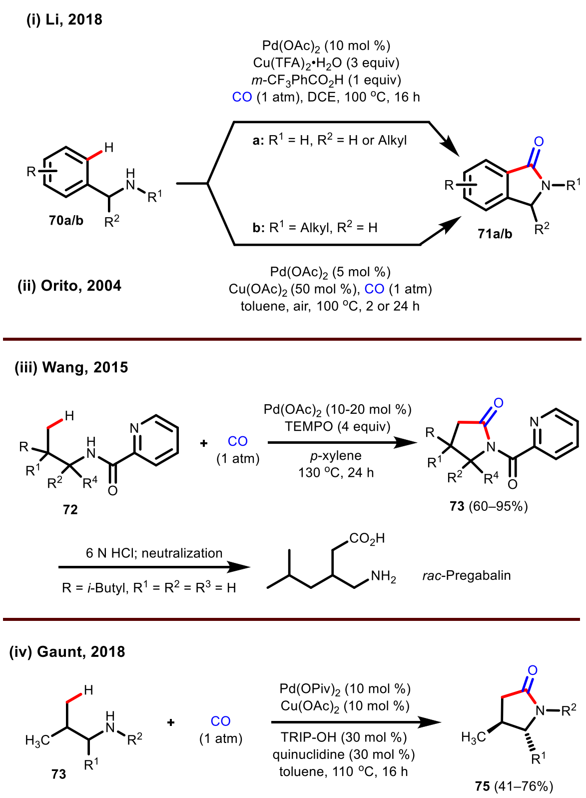


metalation deprotonation to form cyclopalladation intermediate **68-III**. While benzoquinone promotes the reductive elimination of **68-III** to the final product and Pd(0), the amine ligand such as quinoline derivative or quinuclidine may stabilize Pd(0) species before oxidation by preventing aggregation.

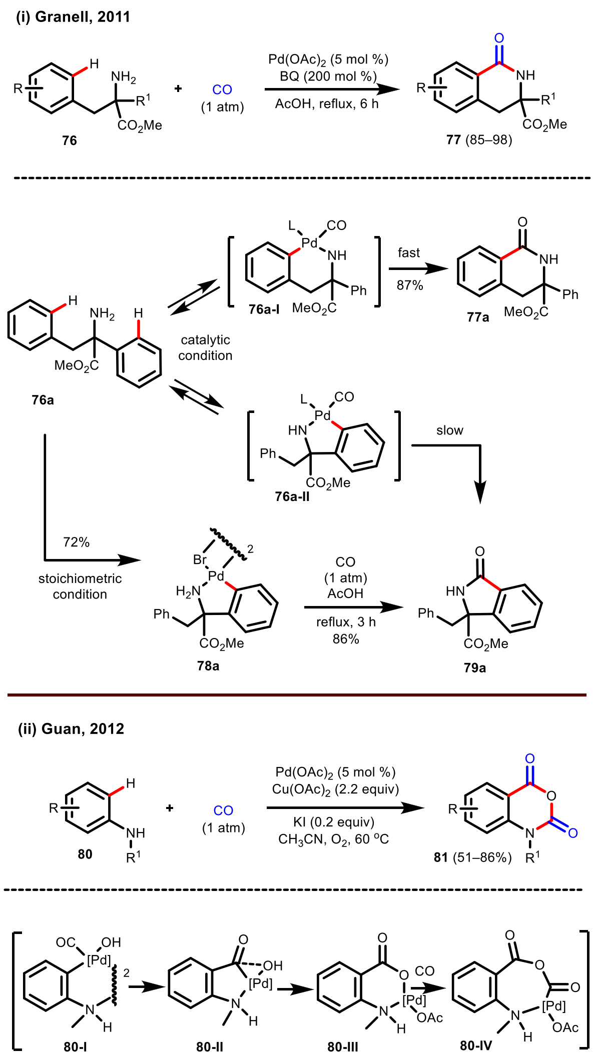
The groups of Li,[55] Orito,[56] Wang,[57] and Gaunt[58] explored the C−H activation/annulation strategy to construct five-membered ring systems (Scheme 15). While Li developed an efficient protocol for C(sp^2)−H carbonylation with primary amine **70a** to generate benzolactam **71a** (Scheme 15i),[55] Orito employed secondary amine **70b** to generate benzolactam **71b** (Scheme 15ii).[56] The C(sp^2)−H carbonylation involving a nitrogen directing group to form γ-lactams was found to be equally efficient. Wang used 2-pyridylcarboxamides **72** containing one or more β-alkyl branches to generate the corresponding γ-lactams **73** in good yields, one of which can be hydrolyzed to provide *rac*-pregabalin (Scheme 15iii).[57] Gaunt investigated the C(sp^3)−H carbonylation with unprotected secondary aliphatic amines **74** for the construction of *trans*-4,5-disubstituted pyrrolidinones **75** (Scheme 15iv).[58]

The construction of six-membered rings via C−H activation/annulation utilizing carbon monoxide has been actively explored. Garcia developed a Pd-catalyzed carbonylation protocol using aromatic α-amino esters **76** and CO to generate benzolactams **77** (Scheme 16i).[59] Under catalytic conditions, a strong preference to form six-membered lactam **77a** compared with five-membered lactam **79a** was observed, which is the opposite trend to that of Orito.[56] However, the corresponding stoichiometric reaction led to the selective formation of a dimeric five-membered azapalladacycle **78a**,

Scheme 15. C−H Activation/Annulation with CO to Form Five-Membered Rings



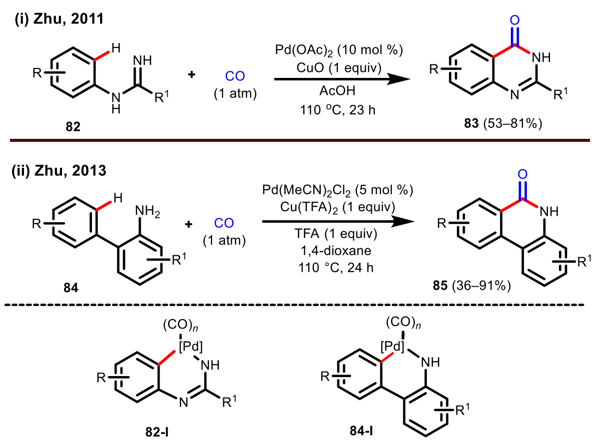
Scheme 16. Selectivity in C−H Carbonylation to Form Six-Membered Rings



which provided **79a** upon treatment with CO. To justify this dichotomy, it was proposed that while the formation of azapalladacycles **76a-I** and **76a-II** is in equilibrium, the rate of CO insertion into the former is faster, leading to selective formation **77a**. Guan reported a regioselective Pd-catalyzed C−H bond carbonylation of *N*-alkyl anilines **80** to form isatoic anhydrides **81** (Scheme 16ii).[60] This reaction proceeds through the formation of an eight-membered dimeric Pd-complex **80-I**, which was confirmed by X-ray diffraction analysis, and its conversion to the observed product **81** (R = H, R^1 = Me) by resubjecting it to the same reaction conditions. Thus, it was proposed that **80-I** undergoes CO migratory insertion to generate **80-II**, which rearranges to **80-III** followed by another CO insertion to form the penultimate intermediate **80-IV**, and the final reductive elimination will lead to the product.

Zhu employed *N*-arylamidines **82** to construct quinazolin-4(3*H*)-ones **83** via the Pd-catalyzed intramolecular C−H carboxamidation where CuO was used as an oxidant (Scheme 17i).[61] The geometrical constraints of an aniline moiety similar

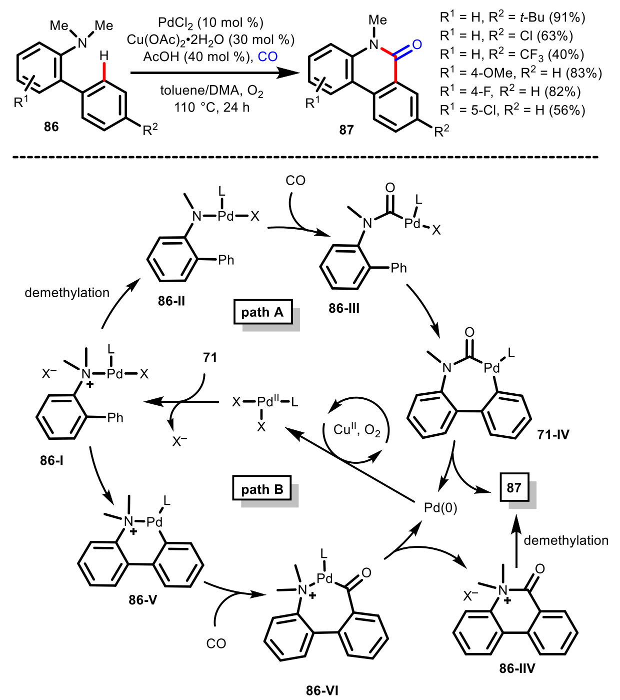
Scheme 17. C−H Activation/Annulation to Form Six-Membered Rings with Amidine/Aniline as a Directing Group



to that of an amidine group in *ortho*-phenylanilines **82** allow efficient aminocarbonylation to form (*N*H)-phenanthridinones **85** (Scheme 17ii).[62] In these reactions, it is believed that the C−H activation by the nitrogen-bound palladium species readily forms putative palladacycle intermediates **82-I** and **84-I**. On the basis of the structural similarity, this carbonylation reaction was further extended to *N*-aryl-2-aminopyridines, which generate 11*H*-pyrido[2,1*b*]-quinazolin-11-ones as the product.[63]

Lei further expanded these C−H bond carbonylations to *N*-dealkylative carbonylation of biphenyl-2-dimethylamine **86** to form phenanthridinones **87** (Scheme 18).[64] This reaction is tolerant with a range of substituents on both aryl moieties to generate the products in moderate to good yield. In terms of the mode of demethylation, there are two plausible pathways. The pathway A involves demethylation from Pd-complex **86-I** to generate intermediate **86-II**, which undergoes CO insertion into the *N*-Pd bond to form intermediate **86-III**. The subsequent C−H bond activation to generate a seven-membered palladacycle **86-IV** followed by reductive elimination delivered product **87** and Pd(0), which is reoxidized to Pd(II) by copper(II) and O_2. In the pathway B, Pd-complex

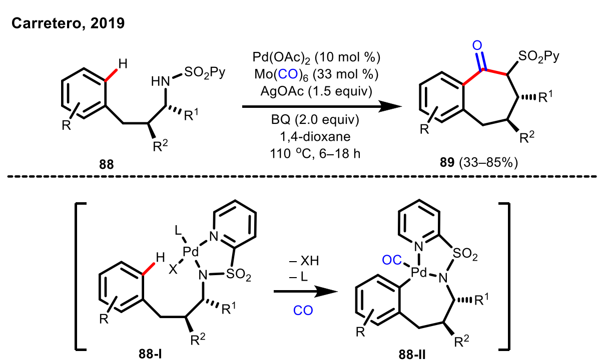
Scheme 18. Mechanism for C−N Activation/Annulation



86-I undergoes C−H bond activation to form a six-membered palladacycle **86-V** followed by CO insertion to form **86-VI**. Subsequent reductive elimination will generate acylammonium salt **86-VII**, which undergoes demethylation to deliver the final product **87**. A foreseeable difficulty in path A is associated with the activation of a relatively remote C−H bond in **86-III** to form favorable seven-membered palladacycle **86-VI**. On the contrary, path B involves the C−H activation in **86-I** to form a six-membered palladacycle **86-V**, which seems to be kinetically more reasonable.

Despite the plethora of C−H activation/annulation to form five- and six-membered rings, the corresponding seven-membered or larger ring formation is rare. This discrepancy stems from the entropically difficult C−H activation via a nine-membered ring transition state. To overcome the difficulty, Carretero employed a robust pyridyl sulfonamide (*N*-SO_2Py)-based directing group to promote an efficient remote C(sp^2)−H carbonylation with substrate **88** to form benzo[*c*]azepin-1-ones **89** (Scheme 19).[65] Electron-donating substituents at the

Scheme 19. C−H Activation/Annulation with CO to Form Seven-Membered Rings



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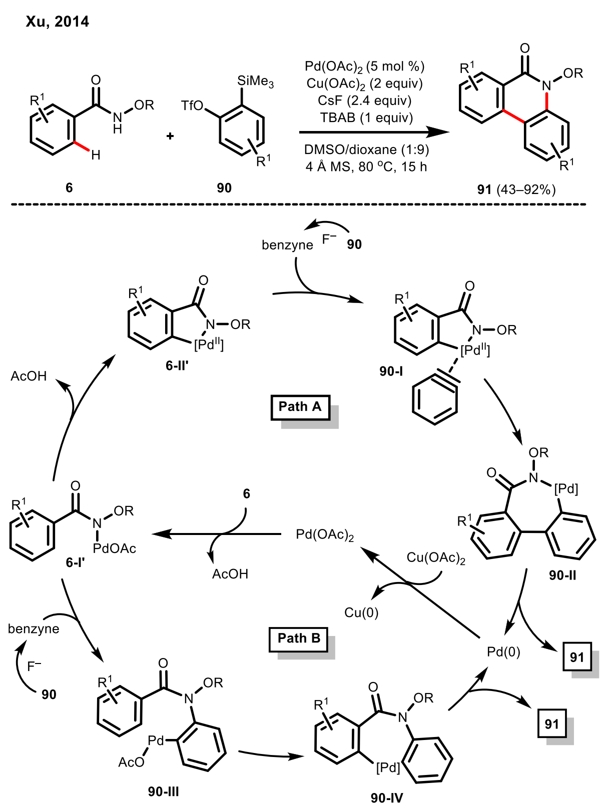
meta or *para* position of the aromatic ring give products in good yields, but an electron-withdrawing substituent lowers the yield and produces a mixture of benzoazepinone and γ-lactam. This suggests that the cleavage of the C−H bond in Pd-chelate **88-I** to form a palladacycle **88-II** should involve an electrophilic aromatic substitution mechanism instead of a σ-bond metathesis process.[66]

2.4. Pd-Catalyzed C−H Activation/Annulation with Other Coupling Partners.

The versatility of Pd-catalyzed C−H activation/annulation has attracted many researchers to explore its potential for the synthesis of various compounds. By tuning the reaction conditions with different oxidants, various coupling partners of different oxidation levels such as arynes, aryl halides, aryldiazonium salts, and arenes could be employed in these reactions.

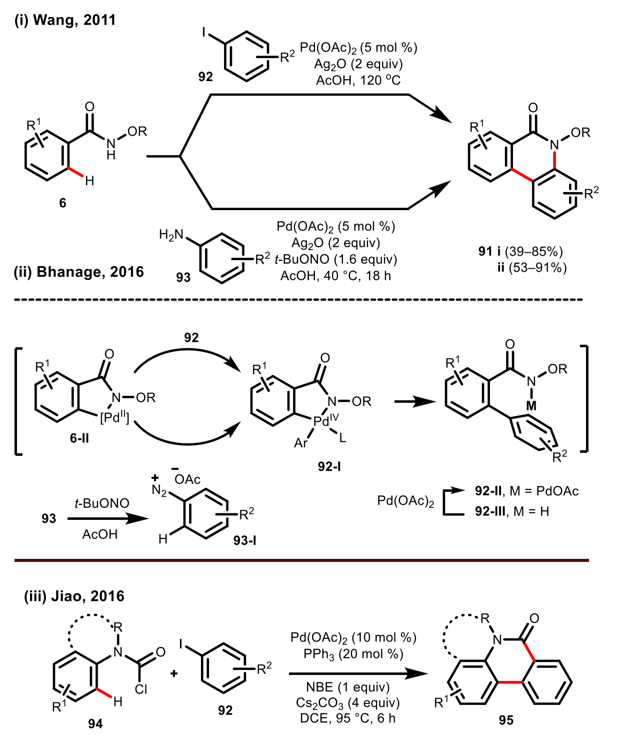
In 2014, Xu reported on the Pd-catalyzed annulation of benzamides **6** with arynes generated from precursor **90** to construct phenanthridinones **91** (Scheme 20).[67] Depending on the timing of the C−H activation and aryne insertion, there are two possible mechanistic pathways for the sequence of forming C−C and C−N bonds. In Path A, the initially formed amidopalladium species **6-I′** undergoes C−H activation to form palladacycle **6-II′** followed by aryne insertion to form seven-membered palladacycle **90-II** via Pd-aryne complex **90-I**. However, Path B involves aryne insertion with **6-I** to form intermediate **90-III**, which undergoes C−H activation to generate an isomeric seven-membered palladacycle **90-IV**.

Scheme 20. Plausible Mechanism of Pd-Catalyzed C−H Activation/Annulation with Aryne



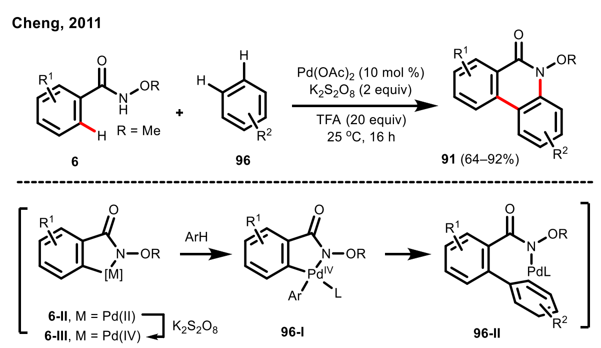
The C−H activation/annulation approach to form phenanthridinone **91** relying on arynes could be further extended to aryl halides and aryl diazonium salts (Scheme 21).[68,69] While Wang employed aryl iodide, Bhanage used an aryl diazonium salt that is in situ generated from the precursor aniline and *tert*-butyl nitrite. In terms of the reaction mechanism, these two coupling partners play an identical role to be engaged in the oxidative addition with palladacycle **6-II**, generating a putative Pd(IV)-aryl complex **92-I**. The reductive elimination in **92-I** can form amidopalladium species **92-II**, which undergoes C−N bond formation to deliver **91**. Alternatively, the corresponding protonated form **92-III** is generated and it reacts with $Pd(OAc)_2$ to regenerate **92-II**. The Jiao group reported a protocol utilizing aryl carbamic chlorides **94** instead of benzamides **6** and iodobenzenes **92** to synthesize phenanthridinone **95** via Pd-catalyzed dual C−H activation (Scheme 21iii).[70] The protocol has a wide substrate scope including heterocyclic coupling partners that are useful to access valuable bioactive phenanthridinone scaffolds.

Scheme 21. C−H Activation/Annulation with Aryl Halides



Under conditions with a suitable oxidant, arenes can be a functional equivalent of aryne or alkyl halide in the Pd-catalyzed C−H activation/annulation (Scheme 22).[71] Cheng employed potassium persulfate ($K_2S_2O_8$) as an oxidant to form phenanthridinones **91** from benzamide **6** and arene **96**. A

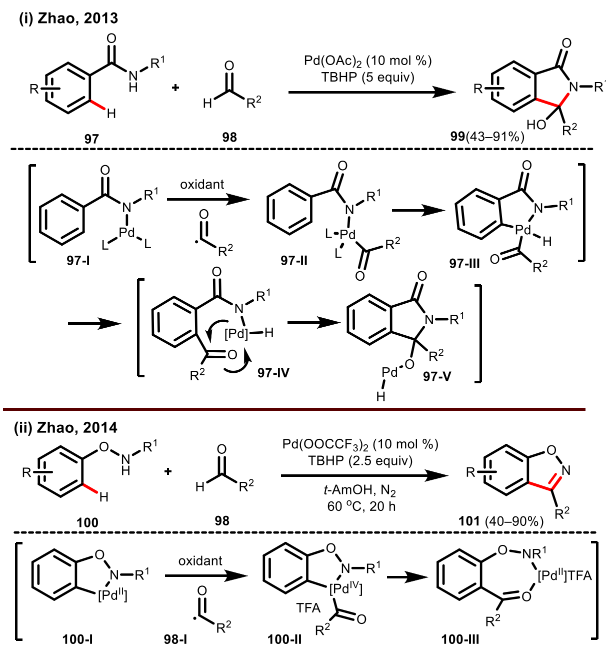
Scheme 22. C−H Activation/Annulation with Arenes



putative mechanism involves oxidation of the initially formed Pd(II) complex **6-II** to the corresponding Pd(IV) species **6-III** followed by a formal C−H activation of the arene, most likely via electrophilic aromatic substitution, to form intermediate **96-I**. The subsequent formation of a C−C bond via reductive elimination in **96-I** followed by C−N bond formation with intermediate **96-II** delivers the final product **91**. The aldehyde can serve as a one-carbon component in the C−H activation/annulation to constitute a formal [4 + 1] annulation.

In 2013, Zhao described the palladium-catalyzed transformation involving benzamide **97** and aldehydes **98** to access the hydroxy isoindolone compounds **99** (Scheme 23i).[72] The

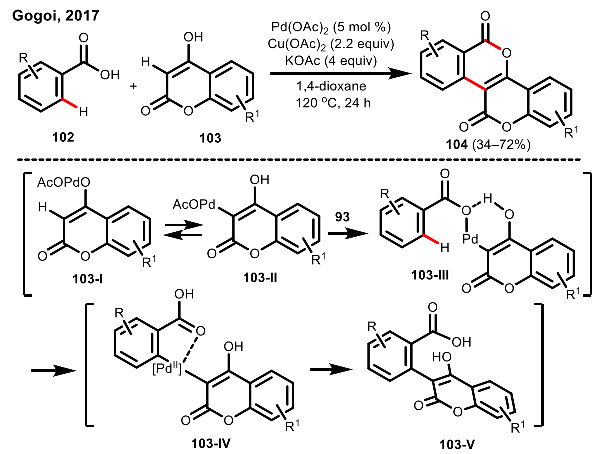
Scheme 23. C−H Activation/Annulation with Aldehydes



proposed mechanism involves the addition reaction between **97-I** and aldehyde radical to form intermediate **97-II**. Subsequent C−H bond activation to form **97-III** and its reductive elimination forms **97-IV**. Cyclization via forming C−N bond to **97-V** and subsequent reductive elimination affords the hydroxy isoindolone **99**. Zhao reported the Pd-catalyzed reaction between phenoxyacetamides **100** and aldehydes **98** to afford 1,2-benzisoxazoles **101** (Scheme 23ii).[73] The key mechanistic steps involve the formation of Pd(IV) intermediate **100-II** from palladacycle **100-I** and formyl radical **98-I** and oxidant. Subsequent reductive elimination to form **100-III** followed by deacetylative condensation generates the benzisooxazole.

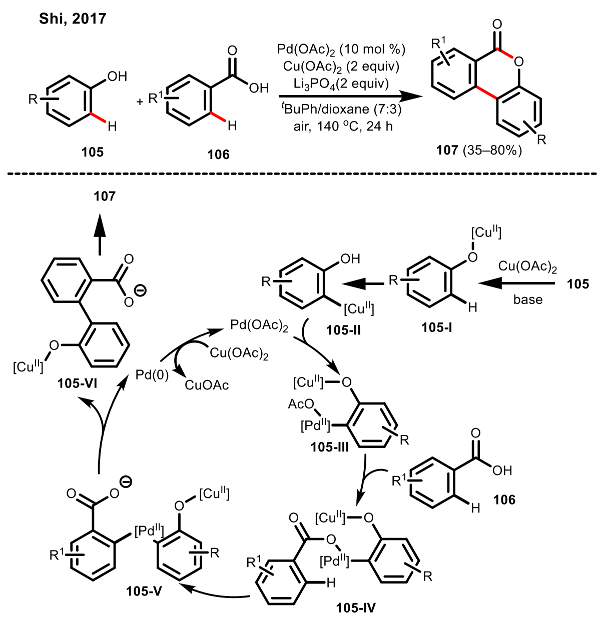
Gogoi developed the C−H activation/annulation with benzoic acids **102** and 4-hydroxycoumarin **103** to generate highly fluorescent biscoumarin **104** (Scheme 24).[74] It was proposed that the ligand exchange with $Pd(OAc)_2$ with 4-hydroxycoumarin generates vinylogous acid complex **103-I**, which rearranges to C-bound Pd-complex **103-II**. The second ligand exchange with benzoic acid **102** leads to intermediate **103-III**, which undergoes C−H activation to generate intermediate **103-IV**. The final product **104** will be generated from reductive elimination of **103-IV** followed by lactonization of **103-V**.

Scheme 24. C−H Activation/Annulation of Aryl Carboxylic Acid and 4-Hydroxycoumarin



The Shi group exploited the Pd-catalyzed C−H activation/annulation strategy to synthesize dibenzopyranone **107** (Scheme 25).[75] The protocol features good functional group

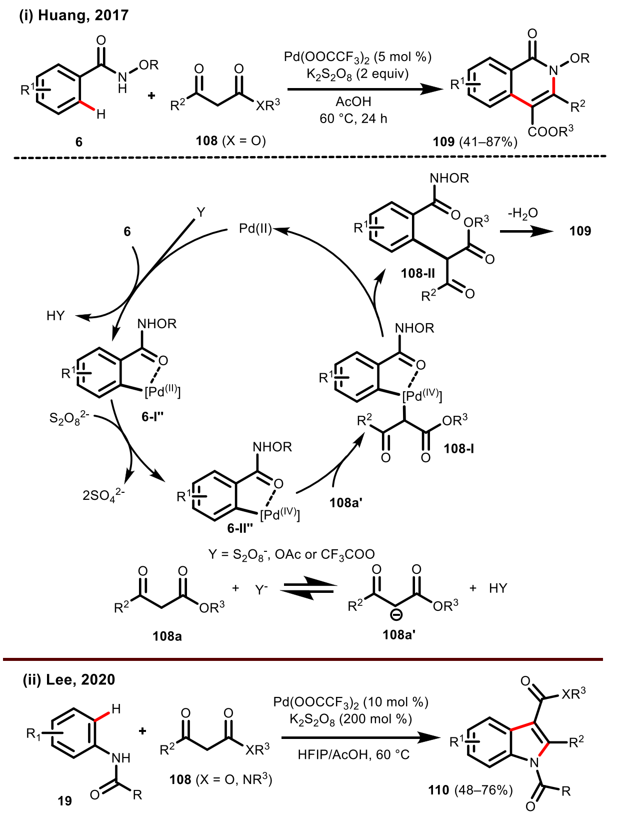
Scheme 25. C−H Activation/Annulation of Phenols and Benzoic Acids



compatibility and wide substrate scope. The oxidant $Cu(OAc)_2$ plays a dual role in the reaction, as an oxidant and as a stabilizer for the palladium catalyst. The catalytic process starts by forming Pd-phenol complex **105-III** from the corresponding organocopper species **105-II**. After ligand exchange with benzoate, the resulting complex **105-IV** promotes C−H activation forming **105-V** followed by reductive elimination generates **105-VI**. Finally, spontaneous lactonization of **105-VI** leads to dibenzopyranone **107**.

In 2017, Xu and Huang reported a Pd-catalyzed cascade dehydrogenative cross-coupling/annulation reaction involving *N*-alkoxybenzamides **6** and *β*-ketoesters **108** to furnish isoquinolinone derivatives **109** (Scheme 26i).[76] The observed kinetic isotope effect suggests that the rate-determining step is the α-C(sp^2)−H functionalization. A plausible reaction

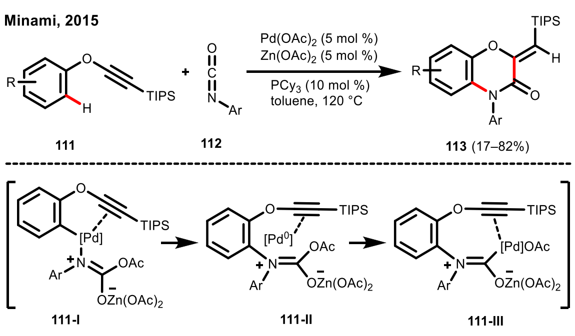
Scheme 26. C−H Activation/Annulation of β-Ketocarbonyl Compounds



mechanism involves the initial carbonyl-directed activation of α-C(sp^2)−H bond of benzamide **6** by Pd(II) to form a five-membered palladacycle **6-I″**. Oxidation of Pd(II) to Pd(IV) by $K_2S_2O_8$ to form **6-II″**, which reacts with acetoacetate anion **108a′** to form Pd(IV) intermediate **108-I** followed by reductive elimination yielding C−H functionalized intermediate **108-II** and regenerated Pd(II) catalyst. Finally, an intramolecular condensation of **108-II** affords the isoquinolinones. Alternatively, Lee employed anilides **19** instead of *N*-alkoxybenzamides **6** to synthesize *N*-acylindoles **110** (Scheme 26ii).[77] It also involves formation of six-memebered palladacyclic intermediate in contrast to the aforementioned protocol.

In 2015, Minami explored the Pd-catalyzed cyclization of alkynyl aryl ethers **111** and isocyanates **112** to afford solid-state luminescence 2-methylidene-2*H*-1,4-benzoxazin-3(4*H*)-ones **113** (Scheme 27).[78] This reaction is proposed to proceed via

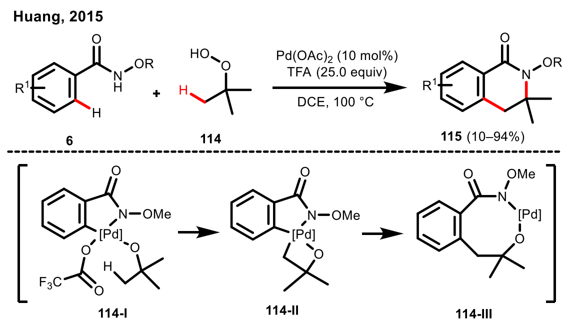
Scheme 27. C−H Activation/Annulation with Isocyanates



forming C−H activated complex **111-I**. After reductive elimination, the Pd(0) complex **111-II** undergoes oxidative addition to form **111-III** followed by cyclization and protonation to deliver product **113** and Pd(II). This reaction is redox neutral, and thus, an external oxidant is not needed.

Huang explored the Pd-catalyzed double C−H activation/annulation reaction between benzamides **6** and *tert*-butyl hydroperoxide **114**, where the peroxide is an oxidant and an isobutylene equivalent as well (Scheme 28).[79] This reaction

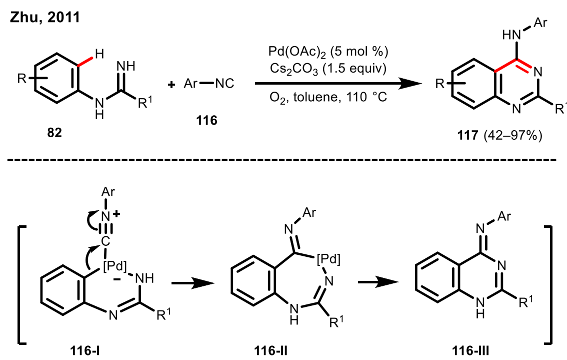
Scheme 28. C−H Activation/Annulation with Peroxide



proceeds through a putative intermediate **114-I**, which undergoes C−H activation to form palladaoxetane **114-II** followed by reductive elimination to generate **114-III**. The final step involves the extrusion of an oxo-Pd species with concomitant formation of the C−N bond in product **115**.

In 2011, Zhu developed the Pd-catalyzed intramolecular C−H amidination of *N*-arylamidines **82** with isonitriles **116** to synthesize 4-aminoquinazolines **117** (Scheme 29).[80] The aryl C−H amidination occurs via isonitrile insertion with intermediate **116-I** to form **116-II** followed by reductive elimination and tautomerization of **116-III**.

Scheme 29. C−H Activation/Annulation with Aryl Isonitriles



In 2018, Liao explored the construction of β-carbolines **120** through the Pd-catalyzed C−H activation of indole derivative **106**. Formation of intermediate **118-I** followed by nitrile **119** insertion to form an adduct **118-II** followed by its cylocondensation leads to **120** (Scheme 30).[81] γ-Carbolines **121** could be synthesized in the same manner starting from the isomer of **118**.

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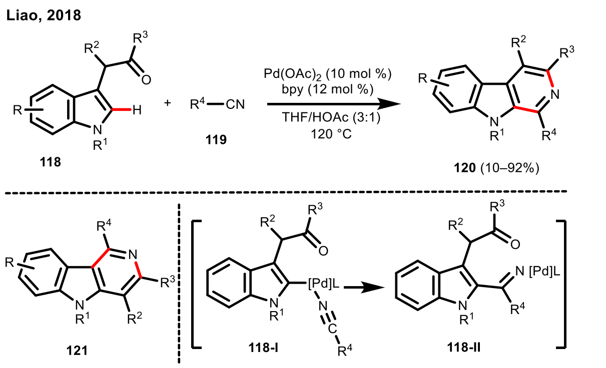
Scheme 30. C−H Activation/Annulation with Aryl/Benzylic Nitriles



3. CONCLUSION

Pd-catalyzed C−H activation/annulation reactions have demonstrated the capacity to form a variety of chemical structures of interesting properties. These compounds range from polyaromatics and carbocycles to various heterocycles. Compounds bearing seven-membered heterocyclic moieties, such as diazepines and dibenzoazepines, have been easily accessed, and benzo[*b*]-fused BODIPYs have also been prepared. The C−H activation mainly relies on the proximity between the C−H bond to be activated and the Pd-complex ligated to a directing group. Alkynes are versatile counterparts for annulation with the organopalladium intermediates, whereas alkenes are relatively limited to sterically unhindered and electronically activated ones such as acrylate and styrene derivatives. Tuning the reaction variables including Pd-complex, ligand, oxidant, solvent, temperature, and reaction time is needed to improve the efficiency and chemo/regioselectivities. Specifically, regioselectivity control is difficult to achieve when terminal alkyne or alkenes are used. New strategies to manage these regioselectivity hurdles will be exciting achievements in the future. Carbon monoxide has been extensively exploited in the C−H activation/annulation to form mainly lactams with ring sizes between four and seven. Arenes, aryl halides, arylamines, aryl aldehydes, β-ketocarbonyl compounds, isocyanates, peracids, aryl/benzyl nitriles, and aryl isonitriles have shown their characteristic reactivities as annulation counterparts Reactions controlled by DGs with these coupling partners, as opposed to alkenes, allenes, alkyne, and carbon monoxide, are scarcely reported. In-depth exploration of these new coupling reactions will be an engaging topic in the future. Despite the abundance of reports in the literature on Pd-catalyzed C−H activation/annulation, the existing examples mainly focuse on cascade C−C/C−C, C−C/C−O, or C−C/C−N bond formation. Thus, the cascade C−C/C−S bond formation would be an interesting extension. Additionally, the Pd-catalyzed C−H activation/annulation would have significant impact on modifying natural products and pharmaceutically important compounds. The representative examples of Pd-catalyzed C−H activation/annulation summarized herein clearly show that this powerful tandem ring-forming strategy already demonstrated the utility in chemical synthesis and expected to be further developed as invaluable tools for various chemical transformations in the future. We believe that this Perspective will be an up-to-date report of an important research topic in the field of catalysis.

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Notes

The authors declare no competing financial interest.

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