CHEMICAL REVIEWS

Review

Cite This: *Chem. Rev.* 2019, 119, 7478–7528

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Palladium/Norbornene Cooperative Catalysis

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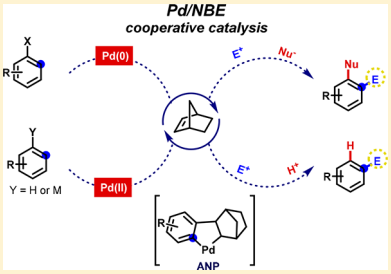
ABSTRACT: Palladium/norbornene cooperative catalysis has emerged as a distinct approach to construct polyfunctionalized arenes from readily available starting materials. This Review provides a comprehensive overview of this field, including the early stoichiometric investigations, catalytic reaction developments, as well as the applications in the syntheses of bioactive compounds and polymers. The section of catalytic reactions is divided into two parts according to the reaction initiation mode: Pd(0)-initiated reactions and Pd(II)-initiated reactions.



CONTENTS

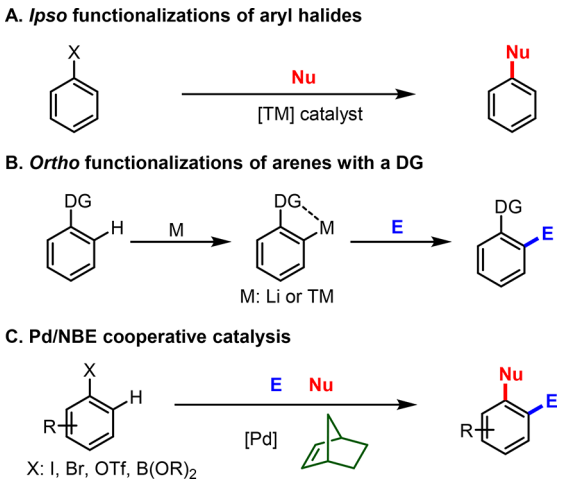
1. INTRODUCTION

Polysubstituted aromatics are ubiquitously found in pharmaceuticals and agrochemicals. In particular, benzene and pyridine represent the **most** frequently used ring systems from small molecule drugs.[1] During the past decades, cross-coupling and nucleophilic aromatic substitutions (S_NAr) clearly have become indispensable tools for preparing functionalized arenes from readily available aryl halides (haloarenes), and have been widely used in drug discovery and development.[2,3] In a typical cross-coupling[4] or S_NAr reaction,[5] a halogen substituent (X, or other leaving group) is replaced by a nucleophile at arene *ipso* position, which can be catalyzed by a transition metal (TM) such as palladium (Scheme 1A). While these reactions, particularly with the advancement of novel ligands and catalysts, can be highly efficient, the position of a newly introduced functional group (FG) is mainly dictated by the position of the halogen substituent. Hence, these arene-functionalization approaches largely rely on the availability of the corresponding aryl electrophiles (ArX).

Received: February 1, 2019
Published: April 25, 2019

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478–7528

Scheme 1. Pd/NBE Catalysis: Merge of *Ipso* and *Ortho* Functionalizations



Besides using ArX as substrates, arene functionalization has also been frequently realized through substituting a less reactive C−H bond. Classical electrophilic aromatic substitution (EAS) is practical for electron-rich arenes; however, its site-selectivity is normally controlled by the inherent electronic bias of substrates.[6] Recently, *ortho* metalation approaches, mediated by either stoichiometric organometallics (e.g., organolithium)[7] or catalytic TMs,[8,9] enabled broadly useful *ortho* C−H functionalization methods, which require assistance of a directing group (DG) (Scheme 1B). While examples of direct metalation at other positions of arenes with and without a DG have been reported,[10−13] more general approaches remain to be uncovered.

Complementary to the aforementioned approaches, the palladium/norbornene (Pd/NBE) cooperative catalysis, also known as Catellani-type reactions, merge the merits of cross-coupling and *ortho* metalation, two powerful organic reactions, into one single transformation. The Pd/NBE chemistry, originally discovered by Catellani, allows simultaneous functionalization of both *ortho* and *ipso* positions of simple aryl halides (Scheme 1C). A nucleophile is coupled at the *ipso* position like cross-coupling reactions, while an electrophile is introduced at the *ortho* position, analogous to the *ortho* metalation approaches. Thus, the Pd/NBE catalysis holds the potential to introduce unusual strategies that can streamline synthesis of complex polysubstituted aromatic compounds. Beyond using aryl iodides as substrates, new advances on Pd(II)-initiated processes have emerged recently, which allow for site-selective functionalization of indoles, *meta*-C−H functionalization of arenes with *ortho* DGs and use of arylboron species as substrates.

This Review article was inspired by several excellent reviews and accounts in the field of Pd/NBE catalysis,[14−22] and here will provide a comprehensive summary up to January 2019. It is structured in the following way: beginning with the section of early stoichiometric reactions, we will provide the historical background and describe the key studies of each step in the catalytic cycle. We will then discuss the development of catalytic reactions, including the classical Pd(0)-initiated reactions and the more recent Pd(II)-initiated reactions. Finally, the synthetic applications on preparing bioactive molecules and polymers will be summarized. This Review is focused on reactions using NBE as the cocatalyst, therefore catalytic reactions using NBE as stoichiometric reactants will not be included unless closely related.

2. STOICHIOMETRIC REACTIONS

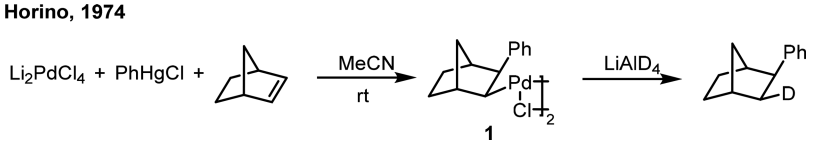
2.1. Formation of Aryl-Norbornyl-Palladacycle (ANP) Intermediate

In a regular Mizoroki−Heck reaction, oxidative addition of an aryl halide to Pd(0) followed by olefin migratory insertion (e.g., ethylene) results in an alkyl-Pd(II) intermediate that would undergo fast β-hydrogen elimination to form styrene-type products.[23,24] However, using a rigid olefin, such as NBE, instead could lead to a different scenario. For example, in 1974 Horino and co-workers isolated complex (**1**) from NBE migratory insertion into the Pd−Ph bond (Scheme 2).[25] Through further reduction by $LiAlD_4$, the deuterium-labeled product confirmed the *exo cis* migratory addition process, which was the reason for a difficult β-hydrogen elimination step.

In 1982, Catellani and Chiusoli examined the reaction between bromobenzene and NBE using $Pd(PPh_3)_4$ as the catalyst (Scheme 3).[26] In the presence of potassium acetate, a cyclic compound (**2**) containing two molecules of NBE was isolated, in which the *ortho* C−H bond of the arene was activated. Later, when potassium *tert*-butoxide was used instead, a different product **3** containing only one molecule of NBE, but two molecules of arenes, was formed.[27] To explain the formation of these *ortho* functionalized arene products, an aryl-norbornyl-palladacycle (ANP) (**4**) was proposed to be the intermediate, which is formed via *ortho* palladation of Horino's intermediate (**1**). Bases seemed to play an important role in the reactivity of ANP. In the presence of potassium phenoxide, however, reductive elimination from the same intermediate **4** to norbornyl benzocyclobutene **5** occurred, along with an elimination product (**6**).[28] It is interesting to note that, when using the sodium salt of di-*tert*-butyl-*p*-cresol, **5** was selectively formed in 85% yield.

To probe the presence of the ANP intermediate, Catellani and Chiusoli prepared complex **7** with 1 equiv of phenanthroline ligand (Scheme 4).[29] The addition of potassium phenoxide led to complex **8**, which was fully characterized by ^{1}H NMR and confirmed by its reaction with $NaBD_4$. In 1992, Catellani and Chiusoli further examined the arene substituent effect on the rate of the palladacycle formation step.[30] They found that complex **10** was stable below −50 °C but would undergo cyclometalation to form **11** at −30 °C. Half conversion of **10** to **11** occurred in approximately 10, 100, and 240 min for R = OMe, H, NO_2, respectively. Based on this trend, they proposed

Scheme 2. Migratory Insertion of NBE into the Pd−Ph Bond



DOI: 10.1021/acs.chemrev.9b00079
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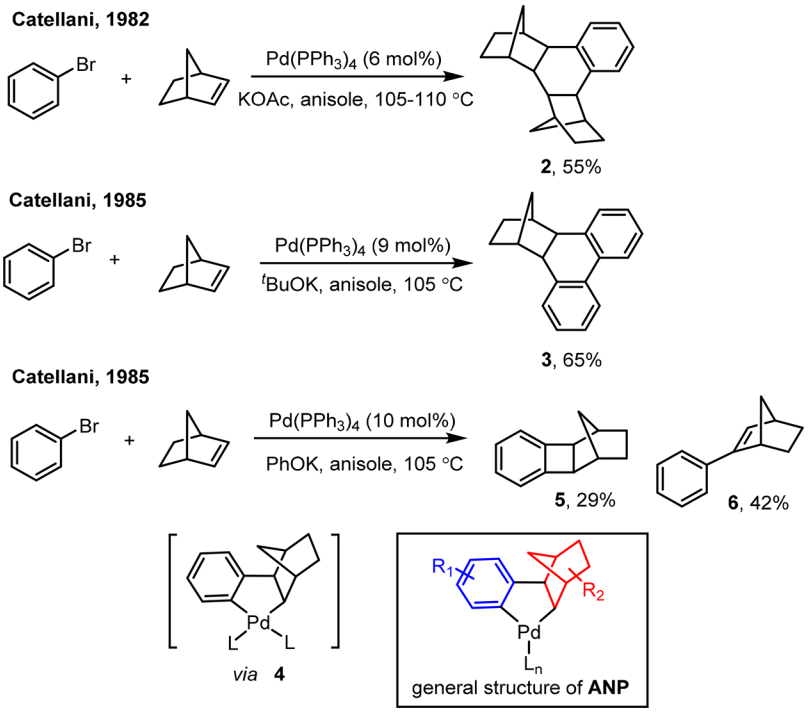
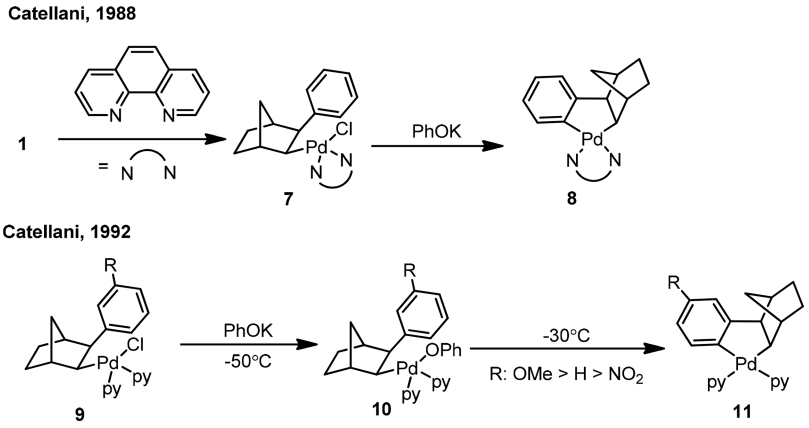
Scheme 3. Pd-Catalyzed Interrupted Heck Reaction of Phenyl Bromide with NBE



Scheme 4. Stoichiometric Studies on the Cyclopalladation Step

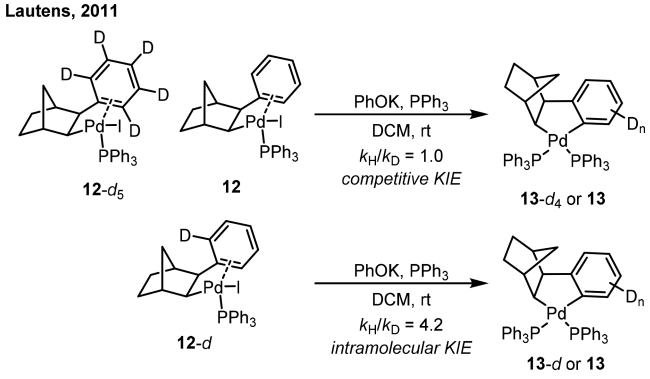


electrophilic aromatic substitution via a Wheland-type intermediate. However, more recent computational studies[31−33] indicated that the palladation step during the ANP formation can also proceed through a concerted metalation−deprotonation (CMD) mechanism, particularly in catalytic reactions.

In 2011, Lautens and co-workers measured the kinetic isotopic effect (KIE) for the C−H metalation step (Scheme 5).[34] The competition intermolecular KIE of **12** was determined to be 1.0, while the intramolecular KIE was found to be 4.2. The absence of a KIE in the intermolecular case suggested that ligand exchange with phenoxide could be rate-determining; the intramolecular KIE of 4.2 was consistent with a CMD mechanism.

The structure of the migratory insertion product prior to palladacycle formation was also studied (Scheme 6). The Cheng group obtained a crystal structure of compound **14**, prepared from the reaction between iodobenzene and norbornadiene.[35] They found that the phenyl group was weakly bound to the palladium center in a η^2 fashion, as the distance of Pd−C_{ipso} and

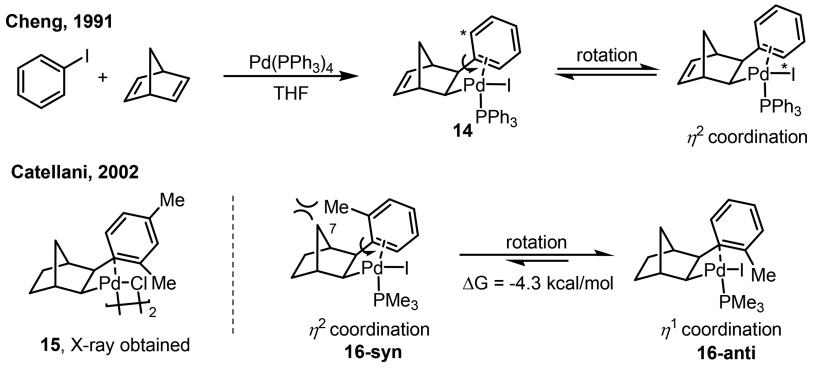
Scheme 5. Kinetic Isotopic Effect on the Cyclopalladation Step in Stoichiometric Studies



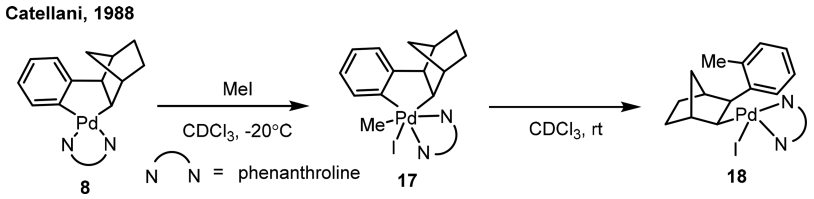
Pd−C_{ortho} bonds were 2.43 and 2.59 Å, respectively. Interestingly, addition of excess ligands (e.g., PPh_3, dppe, pyridine) did not replace the η^2-coordinated arene. Presumably,

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

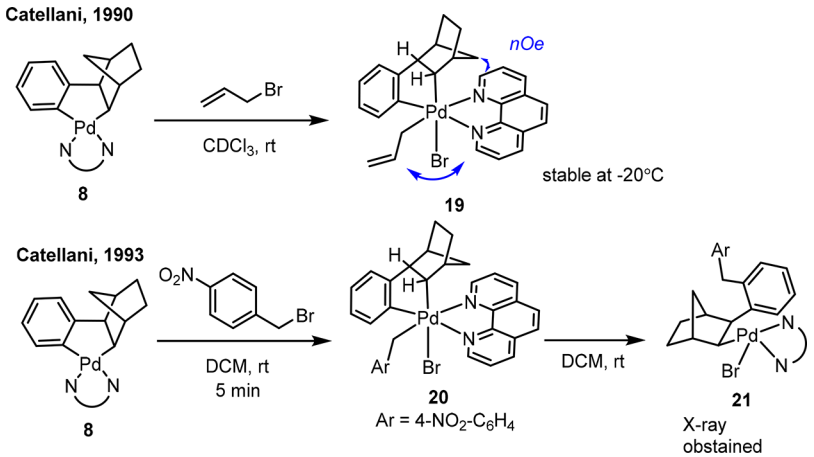
Scheme 6. Formation of Intramolecular η^2-Arene Palladium Species



Scheme 7. Stoichiometric Reaction between ANP and Methyl Iodide



Scheme 8. Stoichiometric Reaction between ANP and Allyl/Benzyl Bromides



the rigid skeleton of norbornadiene and the suitable *cis* arrangement of the phenyl ring and the palladium center contributed to the stabilization of the η^2 interaction. The rotation of the aryl ring about the C−C bond was found to be rapid on the NMR time scale at 40 °C, but slow at the low temperature (−40 °C). Such a η^2 interaction could play a role in the further C−H metalation step since it brings the palladium closer to the *ortho* C−H bond.

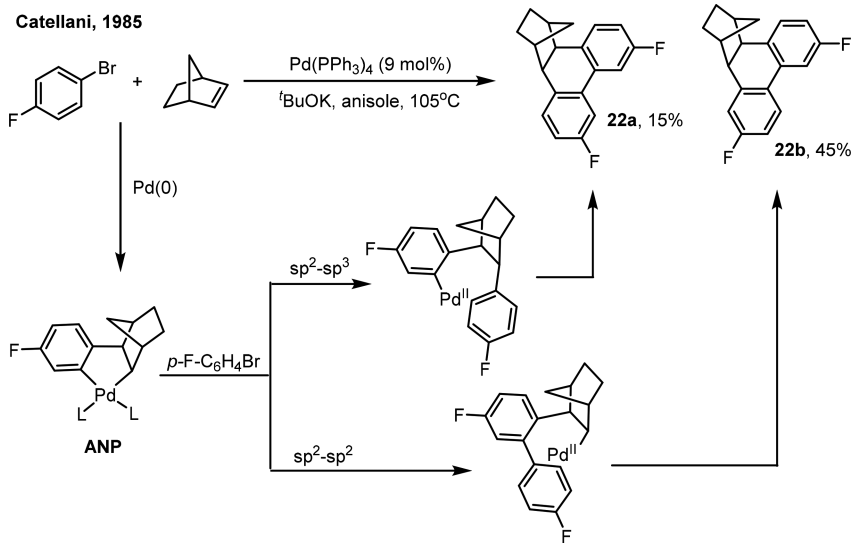
Catellani later synthesized and characterized a series of dichloro-bridged arylbicycloheptylpalladium complexes with different substituents on the aryl ring.[36] Among these complexes, the structure of *ortho* and *para* substituted complex **15** was characterized by X-ray crystallography. In addition, the rotation barrier for the *ortho* unsubstituted complex was determined by NMR to be ∼17 kcal/mol. Interestingly, when an *ortho* methyl group was present in the complex, the palladium center favored a η^1 interaction with the *ipso* carbon, according to both the NMR study and the X-ray structure. Further DFT calculation showed that the methyl substituent in complex **16** prefers *anti* relationship with respect to the C7 methylene due to steric repulsion, which would push the palladium to have a η^1 interaction with the *ipso* carbon instead of a η^2 interaction. Consequently, the η^1 coordination mode likely puts the palladium in a suitable position for the β-carbon elimination reaction to extrude NBE.

2.2. Reaction with Electrophiles

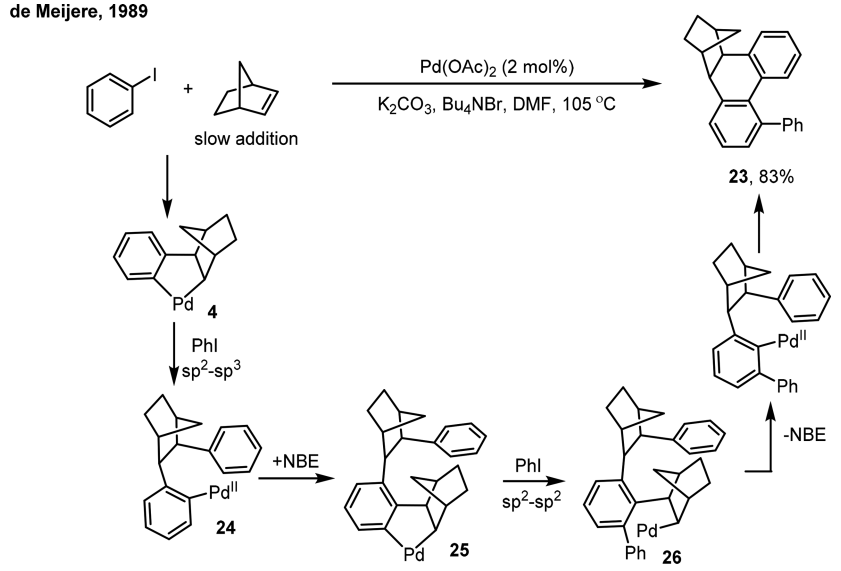
The reactivity of the ANP intermediate with alkyl and aryl halides was then studied mainly by Catellani. As mentioned earlier, Catellani found that the reaction of bromobenzene and NBE gave product **3** in the presence of $Pd(PPh_3)_4$ and KO^{t}Bu (*vide supra*, Scheme 3). It was anticipated that oxidative addition of bromobenzene to ANP was involved in the catalytic cycle. To further probe the intermediacy of a Pd(IV) species, Catellani found that complex **17** was formed upon addition of methyl iodide to the ANP complex **8** at −20 °C (Scheme 7).[29] Complex **17** is stable at −20 °C, but would undergo reductive elimination to give **18** when the reaction was slowly warmed to room temperature. It is interesting to note that the methyl group exclusively migrated to the aromatic ring instead of the norbornyl group. Later, the Cheng group found that the

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 9. Unselective Reaction between *Para*-Substituted Aryl Bromides with NBE



Scheme 10. Reaction between Iodobenzene with NBE under Jeffery's Conditions



analogous *ortho* methylation reaction using norbornadiene can also take place smoothly.[37]

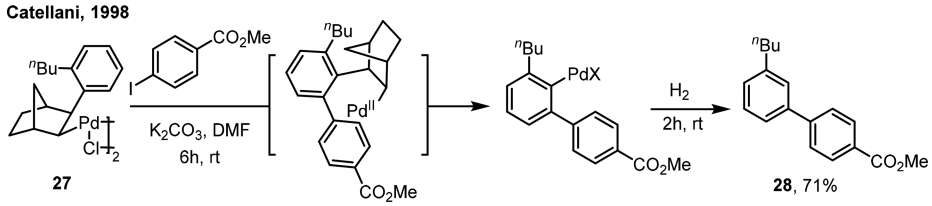
To elucidate the stereochemistry of the Pd(IV) complex formed, Catellani and Mann studied complex **19**, prepared from the reaction with of ANP **8** with allyl bromide (Scheme 8).[38] The nuclear Overhauser effects (NOE) were consistent with the stereochemistry drawn. Using *p*-nitrobenzyl bromide instead of allyl bromide, Catellani was able to isolate a similar Pd(IV) complex **20**, which underwent further reductive elimination to give complex **21**.[39] It was proposed that, in such a model reaction, an initial rearrangement of ligands took place to put the aryl and benzyl groups at axial−equatorial, rather than equatorial *cis* positions (thus avoiding the need for an unlikely N−Pd−N widening), presumably by temporary dissociation of the bromide ligand. The relative stereochemistry of the oxidative addition step was later determined by the Lautens group in a catalytic reaction using an enantioenriched secondary alkyl halide (*vide infra*, Scheme 49).[40] Since the product showed a net inversion of stereochemistry, the S_N2 mechanism for the oxidative addition step was determined to be in accordance with the experiments.

The reaction of ANP with aryl halides is more complicated based on studies of the catalytic reactions (Scheme 9). First, unlike the reaction with alkyl halides, the corresponding Pd(IV) complex from oxidative addition of ANP with aryl halides has not yet been observed. Second, the reaction outcomes depended on the substitution pattern in aryl halides: the reaction was unselective if an *ortho*-unsubstituted aryl halide was used. For example, when 1-bromo-4-fluorobenzene was allowed to react with NBE, two regioisomeric products were formed in a 1:3 ratio.[27] The two products derived from aryl migration to either the norbornyl or the aryl site of ANP followed by ring closure. For example, compound **22a** was formed through an initial $C(sp^2)-C(sp^3)$ bond formation while **22b** was derived from an initial $C(sp^2)-C(sp^2)$ bond formation.

Interestingly, the de Meijere group found that under Jeffery's conditions, the reaction between iodobenzene and NBE gave a different product **23** (Scheme 10).[41−43] Later, Catellani and Motti proposed that the reaction of iodobenzene with the initial

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 11. Discovery of the "*Ortho* Effect"



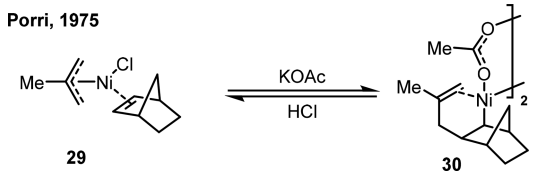
ANP intermediate (**4**) took place via $C(sp^2)-C(sp^3)$ bond formation to afford **24**.[44] Further migratory insertion of NBE and cyclopalladation resulted in new ANP **25**. Interestingly, this time, the reaction of iodobenzene with ANP **25** occurred via $C(sp^2)-C(sp^2)$ bond formation to afford **26**. Further NBE extrusion and C−H annulation gave product **23**. Nevertheless, it was interesting to note that the first and second *ortho* arylation proceeded through different selectivity.

An important discovery made by Catellani was that, when aryl halides with *ortho* substituents (e.g., the *n*-butyl group in **27**) were used as the substrates, arylation could occur selectively at the arene site (Scheme 11).[44] Due to the presence of two *ortho* groups, the NBE moiety was then spontaneously extruded, and the final biphenyl product **28** was obtained by hydrogenolysis. In contrast, *ortho* unsubstituted substrates, such as *meta* or *para* substituted aryl halides, gave a mixture of products with arylation at aryl or norbornyl sites. Hence, Catellani attributed such a behavior to the steric effect caused by the presence of the *ortho* groups, which was later termed the "*ortho* effect". Such an effect could also explain why intermediate **25** underwent the second arylation selectively through $C(sp^2)-C(sp^2)$ bond formation in the aforementioned de Meijere's case (Scheme 10).

2.3. NBE Extrusion

One of the most distinctive properties of NBE is its ability for reversible migratory insertion. Such a transformation was first discovered in a nickel system. In 1975, Porri and co-workers observed that NBE can reversibly insert into the Ni−allyl bond by switching the anionic ligands (Scheme 12).[45] Acetate anions

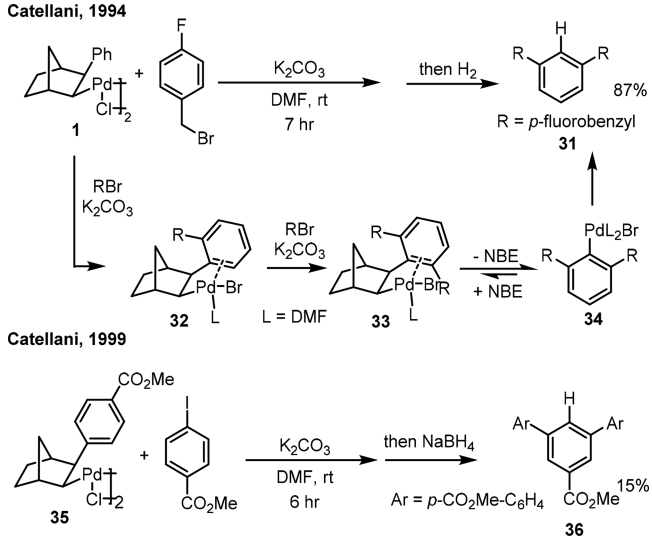
Scheme 12. Reversible Insertion of Nickel−Allyl Bond into NBE



favored the NBE insertion product while halide anions favored the NBE extrusion product. One explanation is that the equilibrium exists in solution and different *trans* effect of the anionic ligands would shift the equilibrium.

In 1994, a seminal work by Catellani and Fagnola showed that complex **1** can react with *p*-fluorobenzylbromide under basic conditions to first give *ortho* alkylated complex **32**, which can then undergo another *ortho* alkylation to afford complex **33** (Scheme 13).[46] At this moment, NBE extrusion happened spontaneously to give an aryl-palladium complex (**34**). It was proposed that the NBE extrusion was driven by steric hindrance around the arene, and it could only happen after both *ortho* positions were substituted. Clearly, the NBE extrusion is not limited to *ortho* alkylation reactions (*vide supra*, Scheme 11). As

Scheme 13. NBE Extrusion after Double *Ortho* Functionalizations



discussed above, after selective aromatic C−H arylation of *ortho*-substituted complex **27**, NBE extrusion occurred to afford product **28** after hydrogenolysis. It is interesting to note that a higher yield could be obtained if NBE was continuously removed by vacuum, suggesting an equilibrium of NBE insertion and extrusion. NBE extrusion could also take place after double *ortho* arylation (**36**), albeit in a lower yield due to the aforementioned "*ortho* effect".

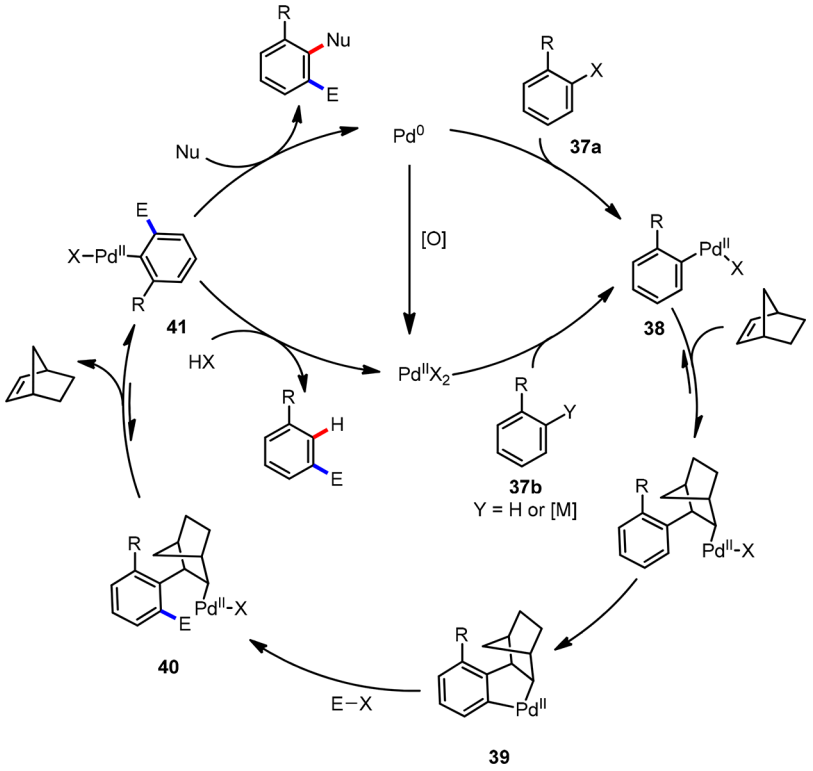
3. CATALYTIC REACTIONS

3.1. General Considerations

3.1.1. General Catalytic Cycle. Prior to the discussion of catalytic reactions, the general reaction mechanism is described first in this section. Based on the early studies of stoichiometric reactions (Section 2), the standard catalytic cycle typically contains four different stages (Scheme 14). The reaction is initiated by forming aryl-Pd(II) species **38** through either oxidative addition of ArX to Pd(0), C−H palladation, or transmetalation of an aryl nucleophile to Pd(II). Intermediate **38** then undergoes migratory insertion of NBE followed by C−H metalation to form the key ANP species **39**. While ANP is a Pd(II) complex, it is quite electron-rich due to the two σ-donating carbon ligands. Thus, ANP **39** can further react with an external electrophile to introduce a functional group at the *ortho* position. In the last stage, the resulting intermediate **40** undergoes β-carbon elimination to extrude NBE, followed by termination to regenerate either the Pd(0) or Pd(II) catalyst. In this section, we classify the catalytic reactions according to the initial stage of the catalytic cycle (i.e., how intermediate **38** is formed). The first type is initiated by Pd(0) through oxidative addition into aryl halides or triflates while the second type is

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 14. General Catalytic Cycle for Pd/NBE Catalysis

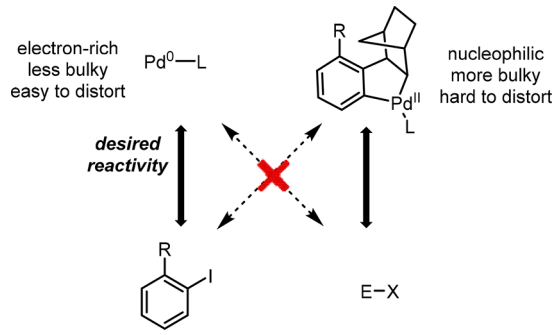


initiated by Pd(II) through N−H activation of indoles, C−H activation of arenes, or transmetalation with aryl nucleophiles. Recent variations on the classical Catellani reactions are closely related to these general processes, which include (1) enabling new pathways for generating aryl-Pd(II) species **38**, (2) designing new electrophiles to selectively intercept ANP, and (3) designing new NBEs and ligands for selectivity/reactivity control.

Based on the general catalytic cycle in the Pd(0)-initiated reactions, one may assume that a plethora of transformations could be developed simply by switching different nucleophiles and electrophiles. However, the complexity of the Pd/NBE cooperative catalysis lies on the coexistence of various electrophiles and nucleophiles in a single reaction vessel. The success of this complex reaction depends on a number of *selective and sequential* reactions between different pairs of electrophiles and nucleophiles, which are modulated through different oxidation states of intermediates and subtle differences in electronic and steric effects among the different species. The early investigations of the Catellani reaction revealed that a variety of nucleophiles can be coupled with intermediate **41** in the termination step, which largely paralleled classical cross-coupling reactions.[14−19] Generally, the reactivity of terminating nucleophiles needs to be carefully tuned, so that a premature termination with intermediate **38** would not happen. In many cases, the use of a masked nucleophile that can slowly generate the real nucleophile is preferable. On the other hand, the introduction of electrophiles at the *ortho* position seemed to be more challenging and quite limited. The key to develop new *ortho* functionalization is to enable selective reactions with the Pd(0) catalyst and the ANP intermediate **39**: the electrophile employed should selectively oxidize the ANP intermediate instead of the Pd(0) catalyst, while the aryl halide substrate must selectively react with the Pd(0) instead of ANP.

Such selectivity could be made possible through differentiating the reactivity between ANP and the Pd(0) species (Scheme 15). We hypothesize that ANP is nucleophilic based on

Scheme 15. Selectivity Issue for Oxidative Addition of Pd(0) versus ANP



Catellani's earlier works (*vide supra*, Schemes 7 and 8), but it is more sterically crowded and thus harder to undergo geometrical distortion. In contrast, Pd(0) is more flexible toward geometrical distortion. Therefore, aryl iodides containing a weak C−I bond should selectively react with Pd(0) under distortion control, and the electron-rich Pd(0) interacts with iodoarene's π^* orbital through back-donation.[47] In contrast, a hard, more electrophilic external electrophile would tend to react with ANP. In addition, a coordinating moiety on the electrophile would help oxidative addition with ANP as the Pd(II) center is anticipated to be more Lewis acidic. For comparison, ANP would have a hard time to react with aryl iodides with *ortho* substituents due to its steric encumbrance. It should be noted that different electrophiles might interact with ANP in different ways and subtle changes on the additives might also affect reaction selectivity.

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

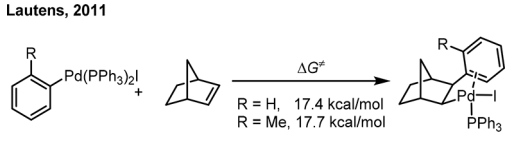
On the other hand, the Pd(II)-initiated reactions face a different type of challenge. The competition between aryl halide substrates and external electrophiles does not exist in this system, thus the scope of external electrophiles can be expected to be broader than the Pd(0)-initiated reactions. However, due to the use of aryl nucleophiles **37b** as the substrates, their direct competing reactions with electrophiles become a notable issue, e.g., indole *N*-alkylation, directed *ortho* functionalization, and protodeboronation (*vide infra*). Other additional challenges will be discussed in the section 3.3.

Another interesting yet still challenging aspect is the control of enantioselectivity in the Pd/NBE catalysis. For asymmetric induction through *ipso* functionalization, the ligand effect in principle should parallel classical cross-coupling reactions. However, the difficulty could come from compatibility of chiral phosphine ligands in the Pd/NBE catalysis as many bidentate phosphines were found not suitable for these reactions. For asymmetric induction through *ortho* functionalization, the situation is more complicated. If a chiral phosphine ligand is used, at least two potential diastereomers of ANP could be formed considering the stereocenters introduced by NBE. Thus, a potential solution is to use chiral NBEs instead of chiral phosphine ligands (*vide infra*, Schemes 52 and 116). Since different oxidation states are involved in the catalytic cycle, it becomes hard to judge whether the phosphine ligand is bound to Pd all time, which could be another challenge for asymmetric induction.

3.1.2. Why Is NBE Unique? One intriguing aspect of the Pd/NBE catalysis is the reason that NBE is unique as a cocatalyst. Besides an olefin that is unable to undergo β-hydrogen elimination after X−Pd−Ar insertion, NBE has a strained, rigid, but not too sterically hindered [2.2.1] bicyclic scaffold, which allows for fast migratory insertion, convenient *ortho* C−H palladation, and reversible β-carbon elimination.

First, the migratory insertion rate of NBE is fast, thus suppressing the undesired direct *ipso* coupling of **37a** with terminating nucleophiles in the Pd(0)-initiated reactions and undesired direct reaction of **37b** (Scheme 14) with electrophiles in the Pd(II)-initiated reactions. Lautens measured the activation barrier for NBE migratory insertion rate using PPh_3 as the ligand,[34] which was found to be 17−18 kcal/mol for aryl palladium(II) species described in Scheme 16. The exceptionally high reactivity of NBE toward addition reactions can be explained from both thermodynamic and kinetic viewpoints. Thermodynamically, NBE has strain energy of 21.6 kcal/mol, while that of norbornane is 16.6 kcal/mol.[48] The heat of hydrogenation was measured to be about 6 kcal/mol higher than that of cyclohexene,[49] which is roughly the difference of ring strain between NBE and norbornane. Kinetically, the addition of NBE is accelerated because it is easier to distort this strained (predistorted) olefin to a pyramidalized transition state geometry (Figure 1). The alkene moiety in NBE is pyramidalized (instead of flat), resulting from mixing of the 2s orbital of the alkene carbon and the 2p orbital of the π bond.[50,51] The out-of-plane bending angle (defined as the C—C═C—H dihedral angle) for NBE and norbornadiene is 7° and 2−4°, respectively.[52]

Scheme 16. Measurement of the Migratory Insertion Barriers into NBE



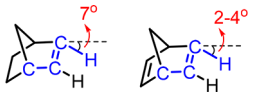
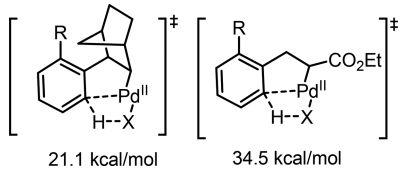


Figure 1. Out-of-Plane Bending Angles for NBE and norbornadiene.

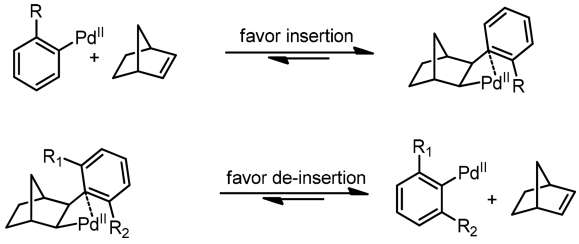
Second, the rigid structure of NBE would reduce the distance between Pd and the arene *ortho* C−H bond after migratory insertion,[36] thereby facilitating the C−H metalation step. The DFT calculation by Bi and co-workers showed that, when cesium carbonate was used as the base, the C−H metalation from such a NBE-directed species required an energy barrier of 21.1 kcal/mol, while the corresponding transition state derived from a flexible olefin (e.g., acrylate) exhibited a significantly higher barrier (Scheme 17).[53]

Scheme 17. Activation Barrier of NBE or Acrylate Directed C−H Metalation



Finally, perhaps the most distinct feature for NBE is its facile β-carbon elimination reaction when both *ortho* positions are substituted. Presumably, the β-carbon elimination is kinetically facilitated by the η^1 interaction between the palladium center and the *ipso* carbon, benefiting from the rigid structure of NBE. The NBE insertion and extrusion might be viewed as an equilibrium. While mono *ortho* substituted aryl palladium species favors NBE insertion, the two *ortho* substituents change the position of the equilibrium (Scheme 18). It should be pointed out that other reaction parameters, such as ligands and additives, could also have an influence on the equilibrium.

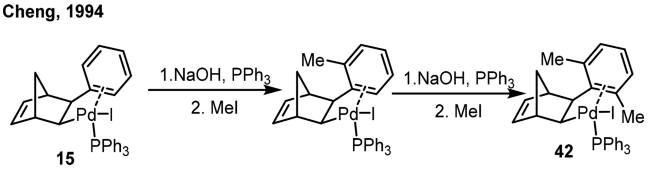
Scheme 18. Equilibrium of NBE Insertion/Extrusion



It would be most informative to compare NBE with other potential "surrogates". Norbornadiene seems to be a potential candidate, which has ring strain energy of 32.4 kcal/mol, making migratory insertion less reversible. In a stoichiometric study, Cheng employed complex **15** for C−H metalation and *ortho* methylation twice to give complex **42** with two *ortho* methyl groups (Scheme 19).[37] However, norbornadiene extrusion did not take place spontaneously, which is in sharp contrast with the NBE case.[46] Hence, in the catalytic reactions, use of

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 19. Absence of Norbornadiene Extrusion in Stoichiometric Reactions



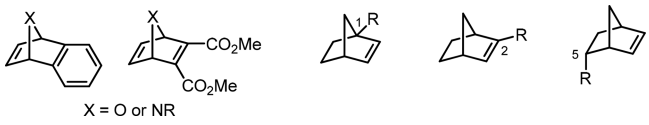
norbornadiene generally gives lower yields compared to NBE if norbornadiene extrusion is required in the reaction.

Acyclic olefins usually contain available β-hydrogens; however, palladacycle formation could still be favored over β-hydrogen elimination if a proper alkene is used (Scheme 20). For example, α,β-unsaturated sulfone **43** with a large isopropyl group can effectively slow down β-hydrogen elimination.[54] The palladacycle formation and *ortho* arylation reaction took place selectively. However, after double *ortho* arylation, alkene extrusion did not occur; instead, another aromatic C−H activation followed by reductive elimination led to the final product. In addition, Lautens reported that, when a 1,1-disubstituted olefin was tethered to an aryl iodide (**44**), a similar *ortho* arylation took place to form a polycyclic ring.[55]

The 7-oxa or aza-[2.2.1]bicyclic alkenes could be possible options (Scheme 21). Migratory insertion, ANP formation, and oxidative addition are expected to have similar barriers. However, achieving β-carbon elimination and meanwhile suppressing β-oxygen/nitrogen elimination turned out to be challenging. However, if extrusion of 7-oxa/aza[2.2.1]bicyclic alkenes is not required in the catalytic cycle, successful examples have been reported where these bicyclic alkenes were incorporated in the final products.[56] Yet, to the best of our knowledge, no example has been reported for using these alkenes as cocatalysts in the Catellani-type reactions, although an interesting Rh-catalyzed C−H amidation using 7-oxa[2.2.1]-bicyclic alkenes was reported.[57]

Due to these distinct features of NBE, the successful modification usually maintains its original skeleton. Currently, the effective variations are at the C1, C2, or C5 positions (Scheme 21). By and large, the reactivity of the C5-substituted NBEs is close to (yet sometimes slightly different from) simple unsubstituted NBE. The C1-substituted NBEs would inhibit C−H metalation, but promote β-carbon elimination, and thus they were developed for addressing the "*ortho* constraint" (*vide infra*, see Section 3.2.7). The C2-substituted NBEs are valuable in preventing side reactions, e.g., minimizing the undesired C−C reductive elimination from ANP to give norbornyl benzocyclobutene side-products. More detailed discussions will be provided in the following subsections.

Scheme 21. Structures of Alternative Substituted NBEs



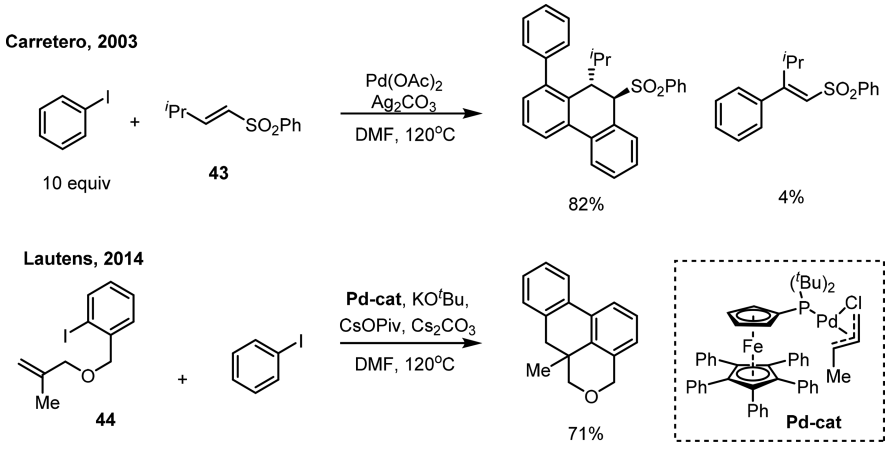
3.2. Catalytic Reactions Initiated by Pd(0)

To date, various types of *ortho*/*ipso* difunctionalizations have been reported. The discovery time for each type of transformations is summarized in Table 1. The following subsections are arranged based on catalytic reactions involving different *ortho* functionalizations.

3.2.1. *Ortho* Alkylation of Aryl Iodides. *3.2.1.1. Intermolecular Couplings.* Based on their prior stoichiometric studies (*vide supra*, Scheme 13), Catellani and co-workers reported the first catalytic example of a Pd/NBE system in 1997, in which acrylates were added as the termination reagents to regenerate Pd(0) (Scheme 22).[58] In this seminal work, alkyl iodides were used as the electrophile, which introduced alkyl groups at both of the *ortho* positions: iodobenzene and *para*-substituted aryl iodides were employed as the substrates, affording bis-*ortho* alkylated products. The optimized reaction conditions employed complex **1** as the catalyst, and the reaction proceeded at room temperature. While each step in the catalytic cycle was known conceptually at that time, it is remarkable that such a selective and catalytic process can be established. In particular, Pd(0) can selectively react with the aryl iodide instead of the alkyl iodide, while ANP can selectively react with the alkyl iodide instead of the aryl iodide.

To obtain products with two different *ortho* alkyl groups, Catellani and Cugini then used *ortho*-substituted aryl iodides as the substrates (Scheme 23).[59] In this case, $Pd(OAc)_2$ was found to be a better precatalyst, and potassium acetate was added to facilitate NBE insertion[60] and/or C−H palladation. The major side reaction was the direct reductive elimination from ANP to give the norbornyl benzocyclobutene derivative. Increasing the bulkiness of the *ortho* substituent led to lower conversion of substrates and formation of a greater amount of the norbornyl

Scheme 20. Acyclic Olefin Mediated *Ortho* Arylation



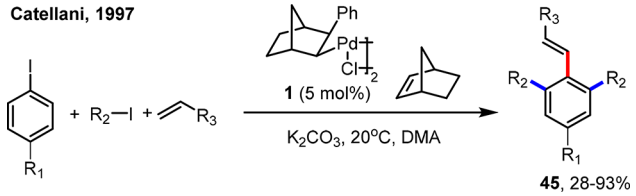
DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Table 1. Summary of Discovery Time of *Ortho*/*Ipso* Difunctionalizations of Aryl Iodides

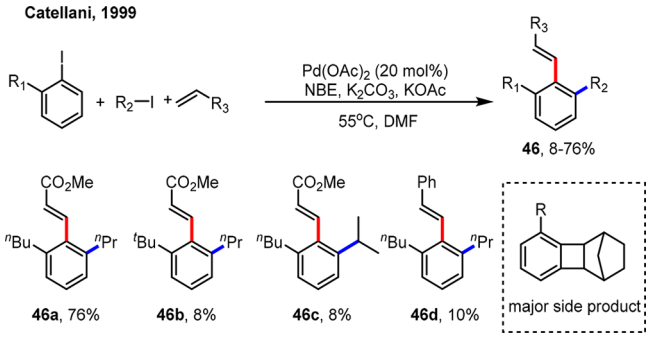
ipso	*ortho*[a]				
	alkylation	arylation	amination	acylation	alkoxycarbonylation
Heck	**1997**[58]	2003[138]	2014[180]	**2015**[191−193]	**2016**[204]
Suzuki	2000[74]	2003[140]	2014[182]	**2015**[191,193]	
alkyne annulation	2008[109]	**2001**[137]			
Sonogashira	2004[76]		2015[77,78]	2018[197]	
C−N coupling	2007[107]	2004[161]	2018[189]		
sp^2 C−H activation	2005[87]	2009[142]		2018[198]	
hydrogenation	2005[81]	2005[141]	**2013**[179]	**2015**[193]	**2016**[204]
cyanation	2007[72]	2007[72]	2016[184,185]	2016[196]	
enolate coupling	2016[92]	2009[90,91]	2017[186]		
1,2-addition		2009[91]			
C−O coupling	2018[131]	2012[153]			
carbene coupling	2014[86]		2014[183]		
borylation			2015[187]	2019[202]	
thiolation				2016[200]	
sp^3 C−H activation			2018[190]		

[a]The year in which the type of the ortho functionalization was first discovered in bold.

Scheme 22. First Catalytic Example in the Pd/NBE Catalysis



Scheme 23. *Ortho* Alkylation/*Ipso* Heck Reaction of Aryl Iodides

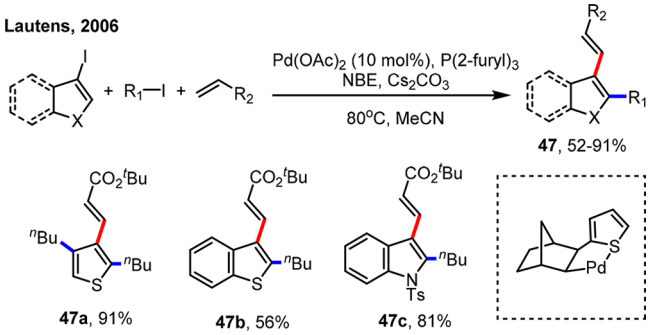


benzocyclobutene side product, which suggests that reductive elimination from ANP could be promoted by bulky *ortho* substituents. Low reactivity was observed (**46c**) when secondary alkyl halides were used, which indicated that the ANP intermediate could be sensitive to sterics of the electrophile. In addition, styrene was less reactive as a terminating olefin (**46d**).

While these initial discoveries by Catellani are mechanistically interesting and synthetically appealing, it is noteworthy that an important change in conditions that have made the reaction practical and widely useful was reported by Lautens in 2000 (*vide infra*, Scheme 42).[61] The introduction of phosphine ligands (e.g., PPh_3 and P(2-furyl)$_3$), as well as the use of Cs_2CO_3 as base and CH_3CN as solvent, has greatly improved the generality of the reaction. Since then, this new set of conditions has been widely adopted in the Pd(0)-initiated catalytic reactions.

Using such conditions, in 2006, Lautens expanded the substrate scope to hetereoaryl iodides (Scheme 24).[62] This

Scheme 24. Expansion of the *Ortho* Alkylation/*Ipso* Heck Reaction of Heteroaryl Iodides



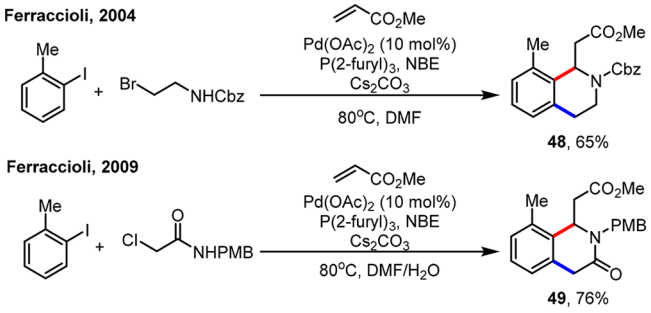
was the first time that 5-membered heterocycles were demonstrated to work in the Pd/NBE catalysis. Thiophene (**47a**), benzothiophene (**47b**), and *N*-protected indole (**47c**) were shown to be suitable heterocyclic cores in haloarene substrates, though 2-iodothiophene was not effective. The choice of the protecting group in the indole substrate (**47c**) was also important, as use of the methyl protecting group only gave the direct Heck product. Free primary alcohol[63] and alkyl bromide[64] were tolerated under modified reaction conditions.

Functionalized alkyl halides can also be successfully coupled. For example, Ferraccioli's group showed that when alkyl halides containing a nitrogen nucleophile were used, further aza-Michael reactions could take place to give tetrahydroisoquinoline **48** (Scheme 25).[65,66] When the reaction was stopped early, the major product was the uncyclized Heck product. Additional KO^{t}Bu was needed for forming the seven-membered ring. Later, the same group used 2-chloroamides to access isoquinolin-3-one **49** in a similar fashion.[67]

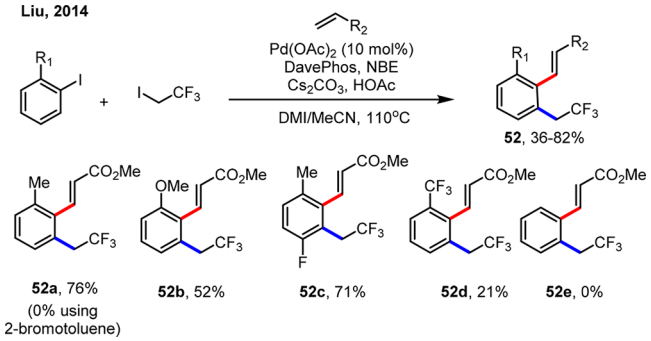
In 2014, the Liu group reported the *ortho* trifluoroethylation via the Pd/NBE catalysis (Scheme 26).[68] Electron-rich DavePhos was employed as the ligand to facilitate oxidative addition with CF_3CH_2I, which was assumed to be the rate-limiting step in this transformation. In a competition experiment, CF_3CH_2I was found much less reactive than isobutyl

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 25. *Ortho* Alkylation/*Ipso* Heck/Aza-Michael Cascade of Aryl Iodides



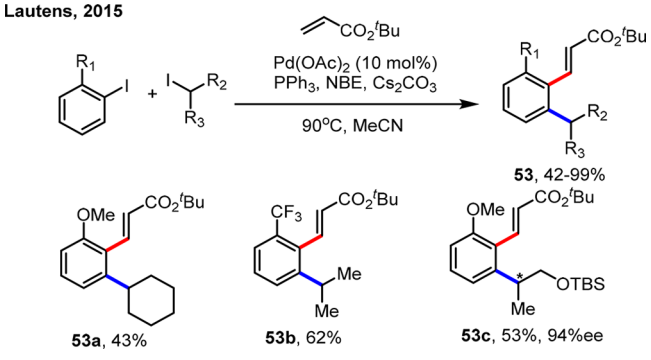
Scheme 26. *Ortho* Trifluoroethylation/*Ipso* Heck Reaction of Aryl Iodides



iodide but more reactive than neopentyl iodide. The reaction exhibited a broad substrate scope for both aryl iodides and olefins. Reactions of electron-neutral or -rich substrates proceeded smoothly, but strongly electron-withdrawing substituents, such as the trifluoromethyl group (**52d**), were detrimental to this reaction. In addition, 2-bromotoluene and simple iodobenzene (**52e**) were not suitable substrates.

In 2015, conditions that can effectively couple sterically hindered secondary alkyl iodides intermolecularly were reported by Lautens, which were previously problematic electrophiles (Scheme 27).[69] This reaction was most effective when *tert*-butyl acrylate was employed as the termination reagent, and both alkyl iodides and acrylates were used in excess. A variety of electron-rich and -deficient aryl iodides and acyclic and cyclic secondary alkyl iodides were suitable substrates. A chiral alkyl iodide (**53c**) was successfully coupled without significant loss of stereochemical information when MeCN was used as solvent.

Scheme 27. Employing Secondary Alkyl Halides in the Pd/NBE catalysis



To incorporate a functionalized one-carbon alkyl unit into the *ortho* position, the Gu group used iodomethylsilane **54** as the electrophile (Scheme 28).[70] The silyl moiety in the alkylated product **55** could be converted to other functional groups, e.g., an alcohol (**56**).

The introduction of a methyl group could have a profound impact on the biological activity of a drug candidate.[71] Besides Lauten's first use of methyl iodide in the *ipso* cyanation reaction (*vide infra*, Scheme 37),[72] another example was reported by Wilson on a pyridine substrate in 2016 (Scheme 29).[73]

Besides the Heck quench at the *ipso* position, other types of cross-coupling reactions could also be employed as the terminating steps. In 2000, Catellani reported the first example of the *ortho* alkylation/*ipso* Suzuki−Miyaura reaction (Scheme 30).[74] The reaction proceeded under mild reaction conditions using alkyl bromides as the alkylating reagent. When iodobenzene was used, the *ortho* dialkylation product **58a** was observed. Note that isopropyl bromide (**58d**) was successfully coupled in this case, though an extended time (144 h) was required. *Ortho*-substituted arylboronic acids gave low reactivity under the optimized conditions.

Recently, Gu and co-workers reported an enantioselective synthesis of biaryl atropisomers using the *ortho* alkylation/*ipso* Suzuki−Miyaura reaction (Scheme 31).[75] The key was to use a specific P−N ligand containing both axial and center chirality. The *ortho*-substituted arylboronic acids were successfully coupled, and the aldehyde moiety could be further transformed to other functional groups.

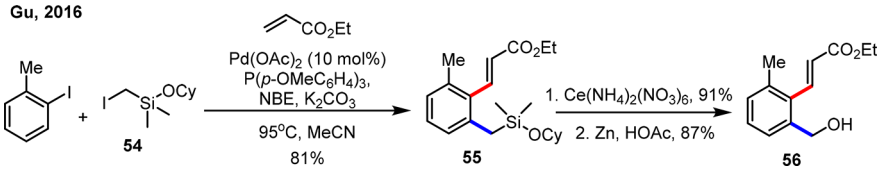
The Sonogashira coupling has also been employed as the termination step. In 2004, Catellani reported the first *ortho* alkylation-*ipso*-Sonogashira reaction (Scheme 32).[76] However, high reactivity of terminal alkynes made it susceptible to generate multiple intermediates and consequently give various side products. For example, the direct Sonogashira coupling could compete with NBE insertion to give alkyne **61a**; the alkyne could also intercept the aryl-norbornyl palladium intermediate after the NBE insertion step to give **61b** as the side-product. Catellani found that the selectivity was improved when replacing K_2CO_3 with KOAc, probably owing to a more favorable NBE insertion or faster metalation to give the ANP intermediate. In addition, slow addition of both terminal alkynes and alkyl bromides suppressed side-reactions by maintaining a low concentration of reactive alkynes.

If a masked alkyne is used instead, the terminal alkyne would be generated slowly during the reaction, thereby maintaining a low concentration, which would avoid the slow addition operation. Based on their own[77] and Chen's[78] work on the *ortho* amination/*ipso* Sonogashira reaction, the Gu group employed 1,1-dimethyl-2-alkynyol **62a** as the masked alkyne reagent to slowly release terminal alkynes through the loss of acetone (Scheme 33).[79] Interestingly, when aryl propiolic acid **62b** was used, the esterification became the major side reaction. Both alkyl- and aryl-substituted alkynes were suitable coupling partners.

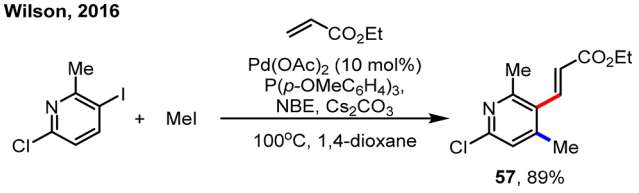
Although efficient, masked alkynes are usually synthesized from the corresponding terminal alkynes. Thus, it is still attractive to directly use terminal alkynes. Shortly after Gu's work, Zhou found the acetylide anion could be maintained at a low concentration through carefully tuning the reaction conditions. As a consequence, good yields were obtained without slow addition of reagents (Scheme 34).[80] Alkyl iodides, bromides, and chlorides were used in the reaction and a secondary alkyl iodide (**64b**) was successfully coupled. Other

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

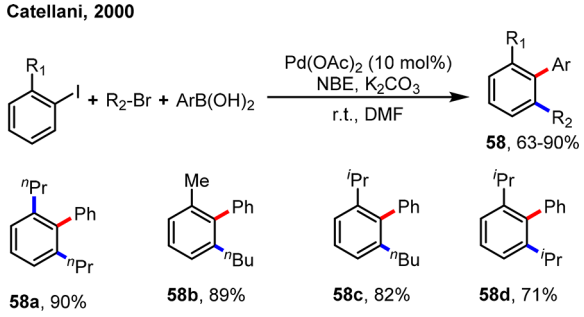
Scheme 28. *Ortho* Silylmethylation/*Ipso* Heck Reaction of Aryl Iodides



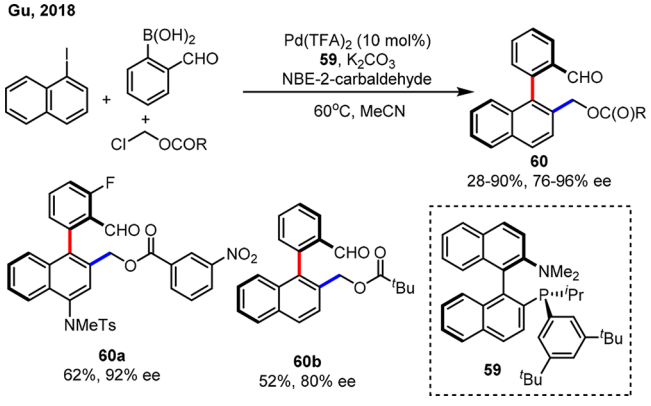
Scheme 29. *Ortho* Methylation/*Ipso* Heck Reaction of Aryl Iodides



Scheme 30. *Ortho* Alkylation/*Ipso* Suzuki−Miyaura Reaction of Aryl Iodides



Scheme 31. Asymmetric *Ortho* Alkylation/*Ipso* Suzuki−Miyaura Reaction of Aryl Iodides



types of alkynes (**64c** and **64d**) were also suitable under a modified condition.

Perhaps the simplest *ipso*-functionalization is hydrogenation, a transformation that would lead to *meta*-substituted arenes. As early as in 1994, the stoichiometric *ipso*-hydrogenation was achieved by blowing hydrogen gas into the system.[46] However, use of hydrogen gas is nonselective; therefore, a process that can slowly release hydride is preferable in the catalytic version. As an unexpected discovery, Wilhelm and Lautens found that *ipso* hydrogenation reaction could be achieved using alkyl boronic acids, e.g., ^{i}PrB(OH)$_2$, as the terminating reagents (Scheme 35).[81] It was proposed that, after transmetalation of ^{i}PrB(OH)$_2$, *β*-hydrogen elimination took place instead of alkyl-aryl reductive elimination. Subsequent control experiments showed that the *ipso* hydrogenation products could be obtained without adding ^{i}PrB(OH)$_2$ in some cases, and further deuterium study showed that alkyl halides could serve as an alternative hydride source (*vide infra*, Scheme 36). The substrate scope was later expanded to 3-iodothiophene by the same group.[62]

When exploring the *ortho* benzylation reaction using benzyl chlorides, Martins and Lautens found that *ipso* hydrogenation products could be obtained without adding ^{i}PrB(OH)$_2$ (Scheme 36).[82] Deuterium labeling studies showed that multiple pathways could lead to the hydrogenation product: 56% of deuterium incorporation (**68a**) came from benzyl chloride. Interestingly, 7% of deuterium incorporation (**68b**) came from aryl iodide, presumably through protodepalladation of the final aryl-Pd(II) intermediate. Control experiments further showed the importance of iodide anion in the reduction process, and it was thus proposed that the benzyl carbonate **69**, originated from *in situ* formed benzyl iodide, released benzyl alcohol through decarboxylation, which served as the real reductant.

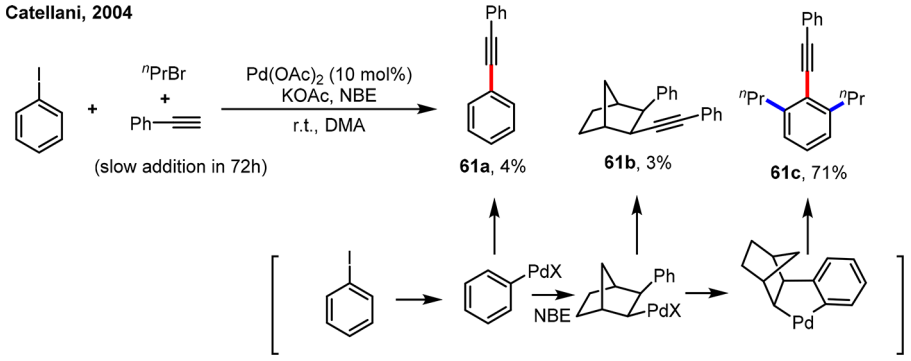
Ipso cyanation has been achieved using metal cyanides as the nucleophile in the *ortho* alkylation reaction.[83] The nature of metal cyanides was found to be critical:[72] the less reactive potassium hexacyanoferrate was more effective than zinc cyanide by maintaining a low concentration of cyanide anion (Scheme 37). A variety of alkyl halides have been used, including methyl iodide (**70b**). Interestingly, alkyl chloride could also be coupled when more electron-rich PBu$_3$ was used. Under the optimized conditions, *α*-chloroamides (**70c**), *α*-chloroesters, and benzyl chlorides (**70d**) all afforded the desired products.

Diazo compounds are known to serve as a surrogate for vinyl nucleophiles through carbene insertion followed by *β*-hydrogen elimination.[84] They can be slowly generated from *N*-tosylhydrazones[85] through the base-mediated Bamford−Stevens reaction, and are therefore suitable for the termination step in the Pd/NBE catalysis. In 2014, the Liang group reported the *ipso* vinylation/*ortho* alkylation using *N*-tosylhydrazones as the nucleophile (Scheme 38).[86] The base employed was important, as it was needed for both the C−H metalation and diazo species generation steps. During Liang's study, Cs_2CO_3 was found to be more effective than LiO^{t}Bu. Addition of water improved the yield, though the reason remains unknown. In addition, a one-pot procedure that directly used aromatic ketones without isolation of *N*-tosylhydrazones has also been developed.

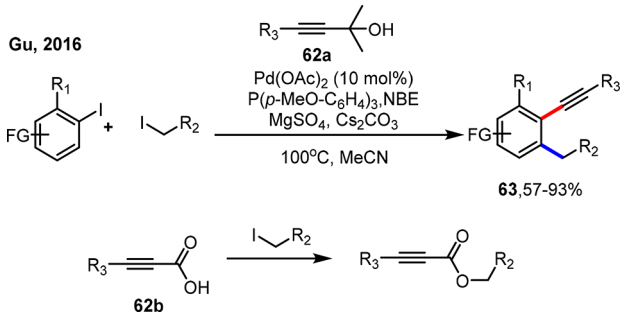
Direct coupling of heteroarenes at the *ipso* position provides a straightforward way to form aryl−heteroaryl bonds. Although the intramolecular *ipso*-heteroarylation was developed by Lautens in 2005,[87] its intermolecular counterpart was not developed until 2015. Zhou and co-workers found that, when using NaOH as the base, the relatively acidic protons in various five-membered heteroarenes could be reversibly removed, thereby slowly generating real nucleophiles (Scheme 39).[88] As a result, different heteroarenes, such as benzoxazoles (**72a**), oxazoles (**72b**), and electron-deficient thiophenes (**72c**), could be coupled at the *ipso* position. Fast H/D exchange at the acidic

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

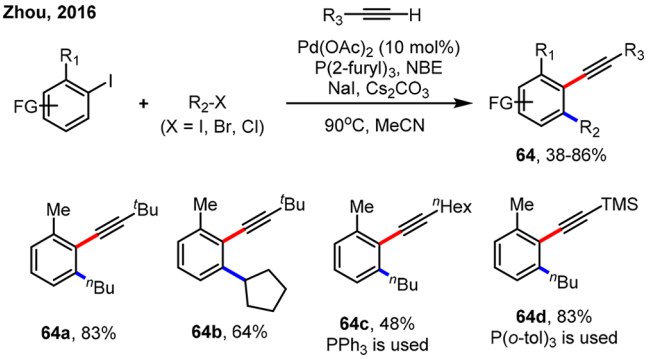
Scheme 32. *Ortho* Alkylation/*Ipso* Sonogashira Reaction of Aryl Iodides



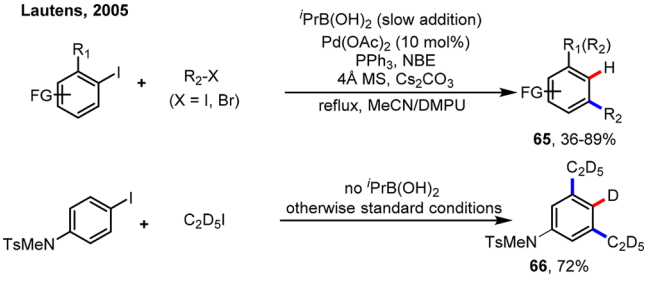
Scheme 33. *Ortho* Alkylation/*Ipso* Sonogashira Reaction of Aryl Iodides Using Masked Alkynes



Scheme 34. *Ortho* Alkylation/*Ipso* Sonogashira Reaction of Aryl Iodides Using Unprotected Alkynes

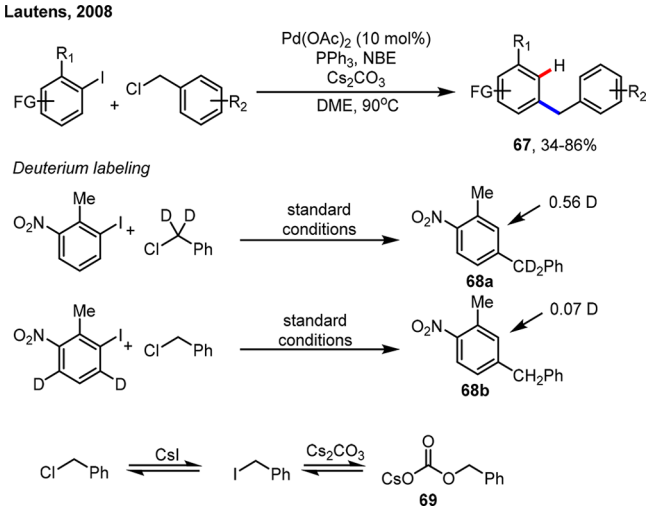


Scheme 35. *Ortho* Alkylation/*Ipso* Hydrogenation Reaction of Aryl Iodides

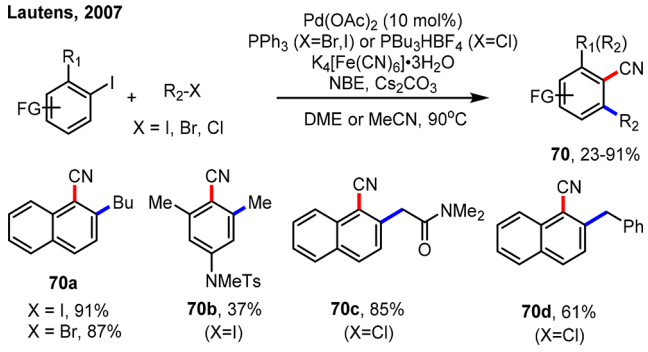


C−H bonds in heteroarenes was observed in the presence of NaOH alone. *Meta*-substituted aryl iodides afforded a NBE-containing side-product (**72d**), probably due to a challenging β-carbon elimination step.

Scheme 36. *Ortho* Benzylation/*Ipso* Hydrogenation Reaction of Aryl Iodides



Scheme 37. *Ortho* Alkylation/*Ipso* Cyanation Reaction of Aryl Iodides



Enolates have been established as viable cross-coupling partners to achieve the α-arylation of carbonyl compounds and nitriles.[89] The Lautens and Catellani groups concurrently demonstrated the use of enolate coupling as the termination step in the *ortho* arylation reactions in 2009.[90,91] In 2016, the Zhou group reported the first *ortho* alkylation/*ipso* enolate coupling reaction (Scheme 40).[92] The key, again, was to use NaOH as the base. This suppressed unproductive side reactions such as ketone α-alkylation and self-aldol condensation. Secondary alkyl iodides (**73b**) could be coupled, albeit in a lower yield. In addition, tetraline product (**73c**) could be formed using 1-bromo-3-chloropropane through an intramolecular cyclization.

DOI: 10.1021/acs.chemrev.9b00079
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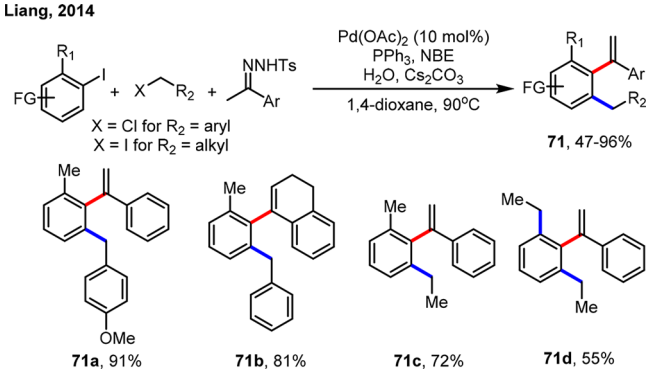
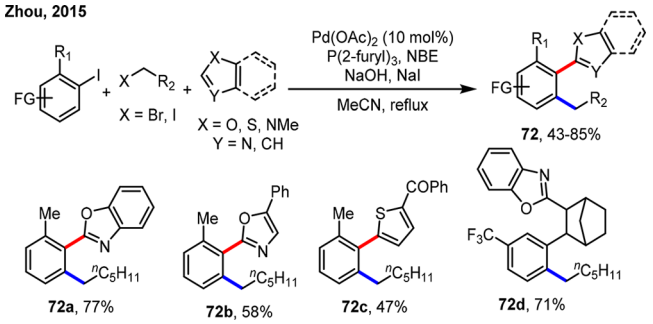
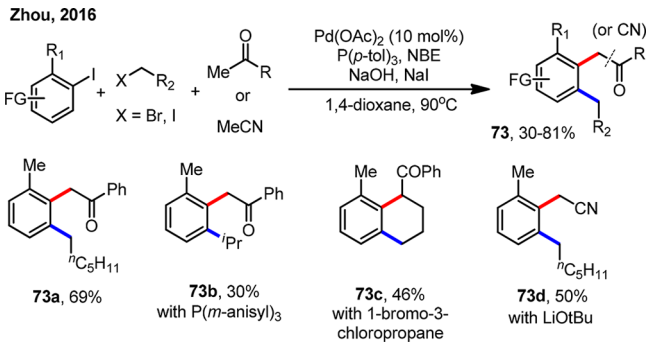
Scheme 38. *Ortho* Alkylation/*Ipso* Carbene Insertion Reaction of Aryl Iodides



Scheme 39. *Ortho* Alkylation/*Ipso* Direct Arylation Reaction of Aryl Iodides



Scheme 40. *Ortho* Alkylation/*Ipso* Enolate Coupling Reaction of Aryl Iodides

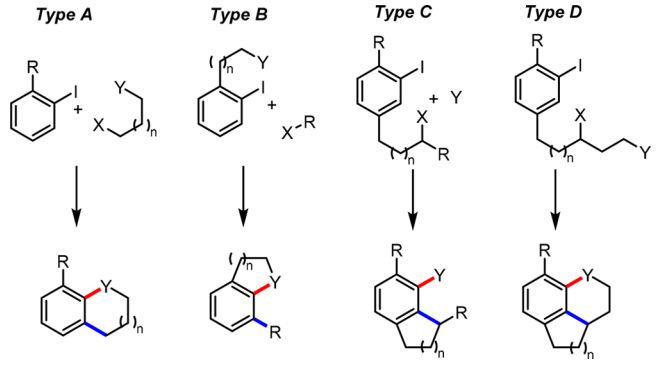


Besides ketones, acetonitrile can also be coupled using LiO^{t}Bu as the base (**73d**), possibly due to a higher pK_a of the α protons in nitriles compared to ketones.

3.2.1.2. Intramolecular Couplings. As a three-component coupling reaction, the Pd/NBE catalysis can give cyclized products if at least two of the coupling partners are linked together (Scheme 41). Generally, there are four types of intramolecular couplings, depending on how these three components are tethered. Type A involves tethering the alkylation reagent with the termination nucleophile; Type B involves tethering aryl iodides with the termination nucleophile; Type C involves tethering aryl iodides with the alkylation reagent; Type D involves tethering aryl iodides with both the alkylation reagent and the termination nucleophile.

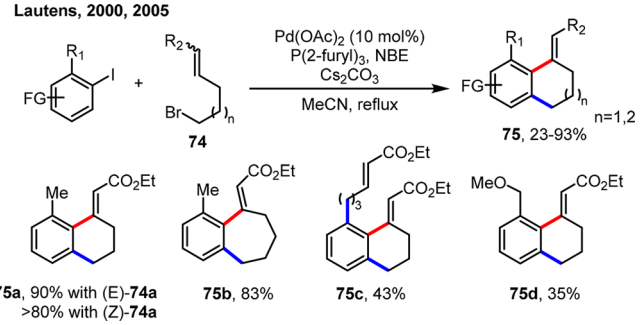
In the first type of intramolecular couplings (Type A), the *ipso* termination could be considered favored as the nucleophile would react intramolecularly after the *ortho* alkylation has

Scheme 41. Four Types of Intramolecular Couplings



occurred. Foreseeing the potential of constructing fused carbocycles, the Lautens group reported the first Pd/NBE-catalyzed annulation reaction using olefin-tethered alkyl halides in 2000 (Scheme 42).[61,93] This was also the first time that a

Scheme 42. *Ortho* Alkylation/*Ipso* Intramolecular Heck Coupling Reaction of Aryl Iodides



phosphine ligand was used in the Pd/NBE catalysis, which greatly improved the generality and reproducibility of the reaction. They also found that Cs_2CO_3 was superior to K_2CO_3. These changes in conditions have been widely adopted by the community in the development of other types of transformations. Regarding the substrate scope, both six- and seven-membered rings could be formed. Simple iodobenzene led to *o*,*o*′-dialkylated products (**75c**). Aryl iodides bearing *ortho*-chelating groups were generally poor substrates (**75d**), partially due to a competing self-dimerization reaction (*vide infra*, Scheme 57). Alkyl bromide **74** was more efficient than the corresponding iodide, and both *Z* and *E* enoates of **74a** could afford the same product **75a**. Unfortunately, aryl bromides and triflates were not suitable coupling partners in this reaction. Variations on the linkers and substitutions were later investigated by the same group.[94,95]

In 2018, Zhou and co-workers utilized the redox-relay Heck reaction as the termination step to access tetrahydronapthalene (**76a**−**c**) and indane (**76d**) scaffolds (Scheme 43).[96,97] Preliminary studies of the asymmetric version was also described using a chiral phosphoramidite as the ligand, though the enantioselectivity and yield were moderate. The utility was demonstrated in a 4-step synthesis of (±)-eptazocine (see section 4.1).

Tethering alkyl halides with heteroarenes provides an opportunity construct fused heterocycles through *ipso* arylation (Scheme 44). Various hetereoarenes, including indole,[87,98,99] pyrrole,[100] pyrazole,[100] imidazole,[101] thiophene,[102,103] furan,[102]

DOI: 10.1021/acs.chemrev.9b00079
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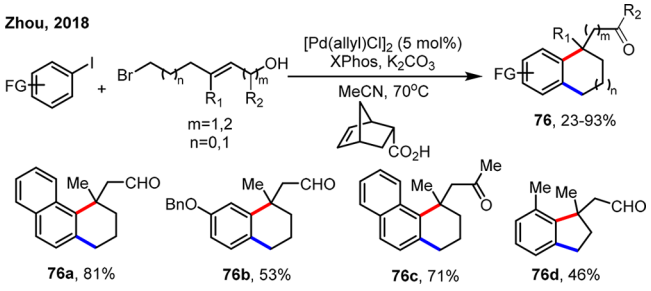
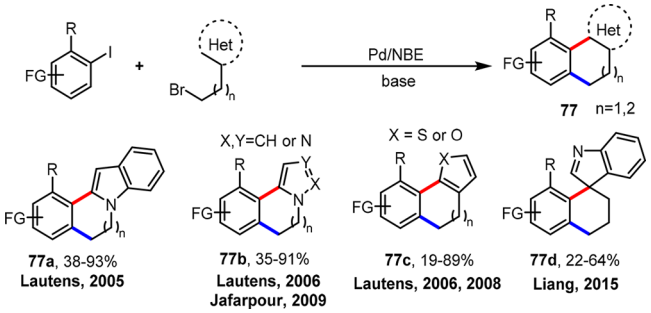
Scheme 43. Synthesis of Tetrahydronapthalenes or Indanes via *Ortho* Alkylation/*Ipso* Redox-Relay Heck Coupling Reaction of Aryl Iodides



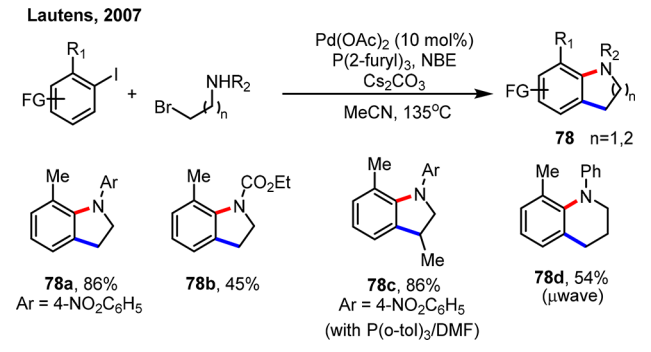
Scheme 44. Representative Examples of *Ortho* Alkylation/*Ipso* Intramolecular Direct Arylation Reaction of Aryl Iodides



benzothiophene,[102,103] azaindole,[104] indazole,[105] and triazole[105] have been successfully coupled. Interestingly, when the C3-tethered unprotected indole was used, a spirocyclic indoline (**77d**) was formed via a dearomative cyclization reaction.[106]

The intramolecular Buchwald–Hartwig amination was also demonstrated as a suitable termination step by Lautens.[107] Since bromoalkyl amines tend to self-cyclize under basic conditions, the protecting groups on the nitrogen were thus important. Although Boc, Bz, and Ts groups led to decomposition or aziridination, aryl (**78a**) and carbamates (**78b**) were suitable protecting groups (Scheme 45). Unexpectedly, 3-nitro-2-

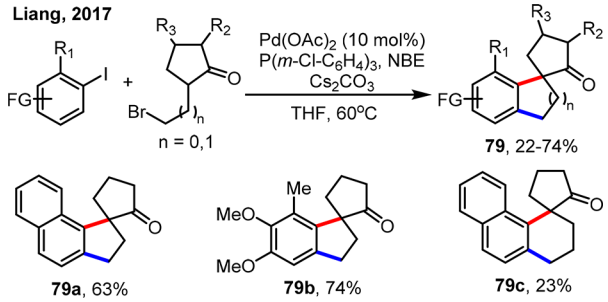
Scheme 45. *Ortho* Alkylation/*Ipso* Intramolecular C–N Coupling Reaction of Aryl Iodides



methyliodobenzene produced the corresponding indole as the product, possibly due to further dehydrogenation reaction. A secondary bromoalkylamine (**78c**) and bromopropylamine (**78d**) could also be coupled.

Although enolate coupling was demonstrated to be an effective termination step,[90−92] tertiary α-carbons of ketones cannot be coupled intermolecularly due to their low reactivity. In 2017, the Liang group showed that such ketones could be successfully coupled in an intramolecular fashion via Type A cyclization to construct spiral structures (Scheme 46).[108]

Scheme 46. *Ortho* Alkylation/*Ipso* Intramolecular Enolate Coupling Reaction of Aryl Iodides



When alkyne-tethered alkyl halides were used, a complex catalytic cycle could take place, which may provide a variety of poly fused ring systems (Scheme 47). A common vinyl palladium intermediate **80** would be formed through carbopalladation of the alkyne. When R_1 is a heteroaryl group (such as pyrrole[109,110] or indole[110]) or R_3 is an aryl/heteroaryl group,[111] intermediate **80** could be terminated via intramolecular C–H annulation (**81a–c**). The Luan group recently reported that indole and arene dearomatization could also be used as the termination step (**81d,e**),[112,113] whereas the intermolecular alkyne annulation could also be achieved. Otherwise (when neither R^1 or R^3 is an aryl group), further NBE insertion with **80** and annulation on the adjacent aromatic ring would occur (**81f**).[114] Interestingly, chiral helical alkenes could be accessed when enantiopure bromoalkyl aryl alkynes were used (**81g**).[115]

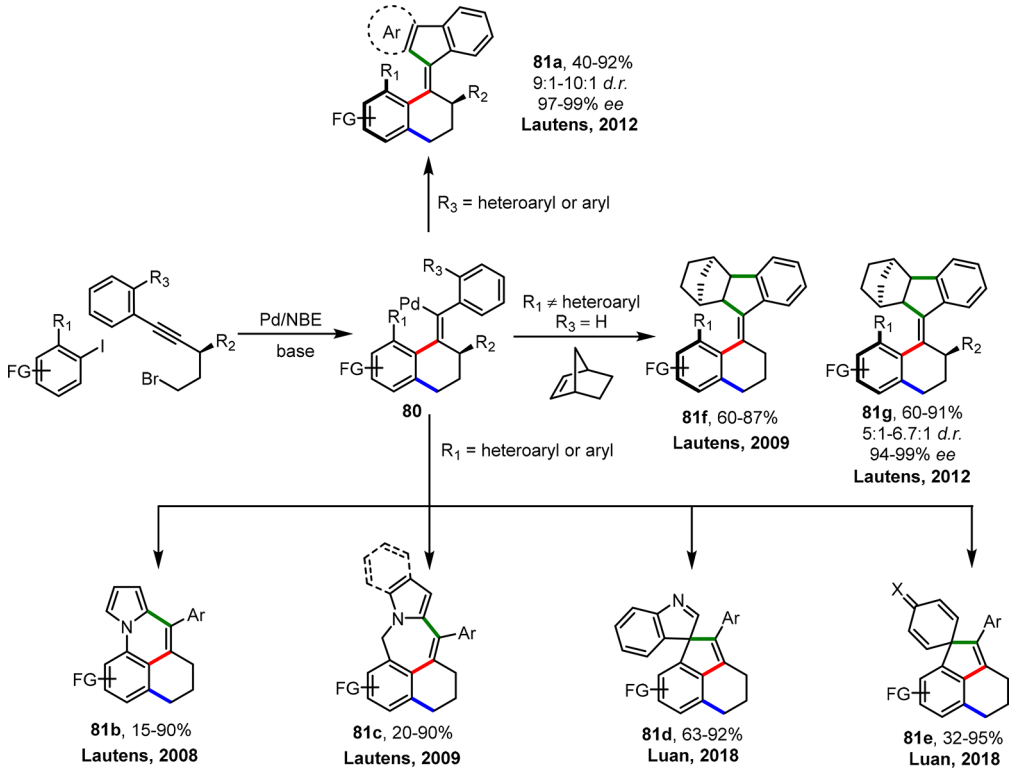
To date, there are only two examples of Type B cyclization, which employed Heck reaction[116] and Buchwald–Hartwig amination,[117] respectively, as the termination steps to construct fused bicyclic structures (Scheme 48).

In Type C or Type D annulations, the alkylation reagent is tethered intramolecularly with aryl iodide substrates. The Lautens group reported the intramolecular *ortho* alkylation and intermolecular *ipso* Heck reaction (Scheme 49).[118] The substrate scope was later extended to secondary alkyl halides, other types of linkers, and different ring sizes.[40,119−122] Notably, the Lautens group studied the reaction with enantioenriched substrates and found that the annulation proceeded with an overall inversion of the stereocenter (**84f**) originating from the secondary alkyl halide.[40] Considering that reductive elimination typically proceeds with retention of stereochemistry, this result suggests that oxidative addition of the secondary alkyl halide to ANP undergoes a S_N2-like pathway. Interestingly, if the termination nucleophile is attached to the aryl halide, fused tricyclic structures could be formed (**84b**).[123] Besides *ipso* Heck coupling, *ipso* cyanation[83] and vinylation via carbene insertion[86,124] have been established with aryl iodides and bromides under the intramolecular type-C reaction mode. Recently, the Liang group utilized a Pd/Cu cocatalyst system to synthesize polyfluoroarene-substituted benzofuran and benzopyran derivatives,[125] where a polyflouoroaryl copper species was believed to be the key intermediate.[126]

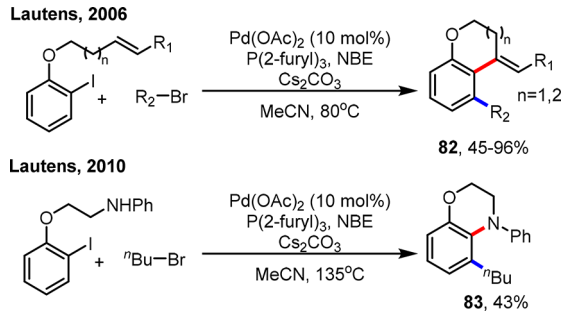
In Type D intramolecular couplings, tricyclic products have been formed via either Heck or direct arylation as the termination step (Scheme 50).[40,120]

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478–7528

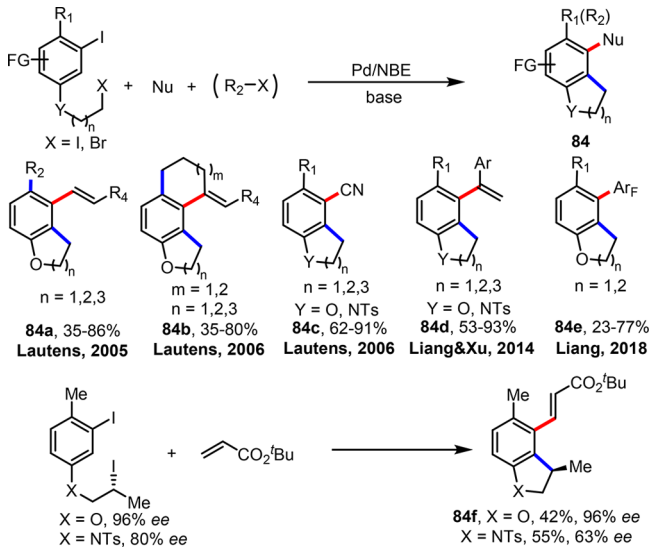
Scheme 47. *Ortho* Alkylation of Aryl Iodides Followed by Alkyne Insertion



Scheme 48. Synthesis of Bicyclic Structures by Type B Intermolecular Couplings



Scheme 49. Synthesis of Bicyclic Structures by Type C Intermolecular Couplings



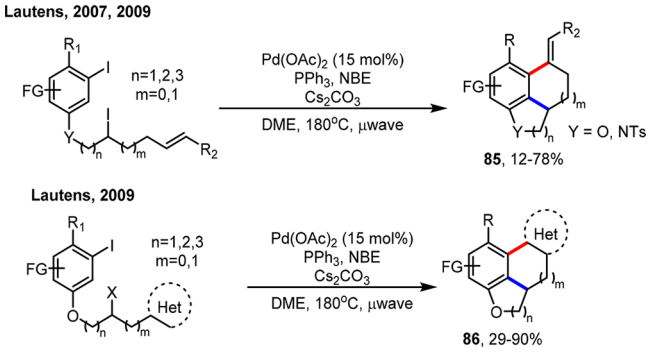
3.2.1.3. Epoxides, Azirines, and Aziridines as Alkylation Reagents. The previous subsections focus on *ortho* alkylation using alkyl halides. Alternative alkylation reagents that have been reported in the Pd/NBE catalysis include azirines, epoxides, or aziridines. These sterically less hindered and hard electrophiles are expected to selectively react with ANP rather than Pd(0) and can provide oxygen or nitrogen-containing heterocycles as products. Another advantage of using epoxides or aziridines for annulation reactions is that the termination nucleophiles are automatically "masked" by default, therefore minimizing direct *ipso* termination side reactions.

In 2010, the Lautens group reported the first annulation reaction using 2*H*-azirines for indole synthesis (Scheme 51).[127] During their initial studies, they focused on the use of bifunctional α-haloimines for enabling the *ortho* alkylation/*ipso* *N*-arylation. Though effective, preparation of these α-haloimines was not trivial, leading them to explore 2*H*-azirines as an α-haloimine equivalent. Regarding the *ortho* alkylation step, it was proposed that the C−N oxidative addition to the ANP intermediate took place to give a Pd(IV) intermediate, followed by C−C reductive elimination.[128] Due to the high reactivity of 2*H*-azirines (with a strain energy of 44−48 kcal/mol), some side reactions were also observed, such as dimerization of 2*H*-azirines and the further [3 + 2] reaction with the product to give polycyclic dihydroimidazoles.

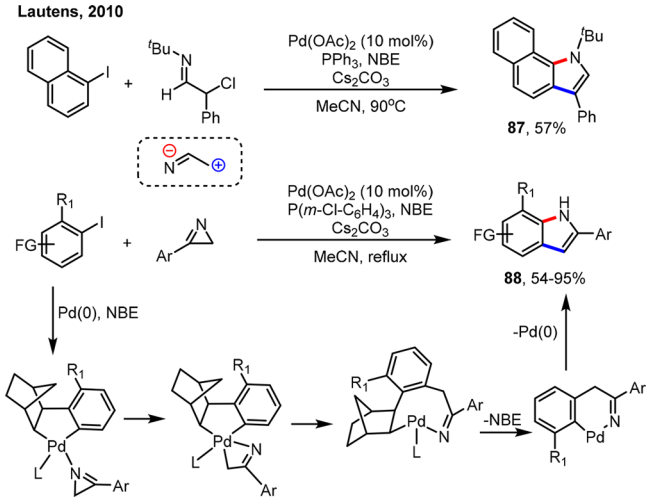
The use of abundant but less reactive epoxides[129,130] in the Pd/NBE-catalyzed reactions was not reported until 2017. The Dong group developed an annulation between aryl iodides and epoxides to form 2,3-dihydrobenzofurans (Scheme 52).[131] A polar aprotic solvent, DMF, was used, likely facilitating a S_N2 type ring opening of epoxides. Sterically hindered Buchwald ligands were employed to circumvent undesired β-hydrogen

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 50. Synthesis of Tricyclic Structures by Type D Intermolecular Coupling



Scheme 51. Synthesis of Indoles by *Ortho* Alkylation of Aryl Iodides Using 2*H*-Azirines



elimination from intermediate **93** and facilitate the C−O bond formation step. Simple NBE provided the desired product but suffered from the multiple-NBE insertion pathway, the use of a bulky C2-substituted NBE **89** that is less reactive toward insertion suppressed such a side reaction. When an enantiopure epoxide was used, the enantiopure product was obtained with stereoretention (**90c**). Later, the catalytic asymmetric reaction via kinetic resolution of racemic epoxides with chiral NBE cocatalysts was explored by the same group.[132] While the enantioselectivity was moderate (**90d**), it represents one of the first examples of chiral NBE-promoted asymmetric reactions in the Pd/NBE catalysis (for a chiral NBE-promoted asymmetric *meta* functionalization via a Pd(II)-initiated pathway, see Scheme 116). The synthetic utility of this method was demonstrated in the 4-step synthesis of insecticide fufenozide (see section 4.1).

In 2018, Zhou and co-workers independently reported the *ortho* alkylation/*ipso* Heck using epoxides as the electrophile (Scheme 53).[133] Similarly, polar NMP as the solvent was essential for this reaction to produce the desired product. A novel C5-carboxylate-substituted NBE **94** (50 mol %) was used as both the cocatalyst and the base, which could also be conveniently removed after the reaction. In addition, through tethering the epoxide with an olefin, the intramolecular Heck termination led to a macrocycle (**95b**). Moreover, a one-pot *oxa*-Michael addition could be carried out under basic conditions to furnish the isochroman scaffold (**96c**). Such conditions were later applied to the synthesis of 2,3-dihydrobenzofurans.[134]

Analogous to epoxides, the Liang group developed an *ortho* alkylation method using aziridines to afford indolines in 2018 (Scheme 54).[135] P(*m*-ClC_6H_4)$_3$ was chosen as the optimal ligand and nonpolar toluene was used as the solvent. Interestingly, *ortho*-unsubstituted and electron-deficient aryl iodides could still give the desired products (**97b**), but simple iodobenzene was still not a suitable substrate. It is likely that the use of a bifunctional reagent might help the NBE extrusion step in the case of *meta*-substituted electron-deficient aryl iodides. For 1-alkyl aziridines, the C−N bond cleavage took place at the less sterically hindered site (**97c**); for 1-aryl aziridines, the C−N bond cleavage preferred to occur at the weaker benzylic position (**97d**). The difference of the regioselectivity could be explained by the relative easiness for the S_N2 reactions. To further support the S_N2 mechanism for ring opening, inversion of stereochemistry was observed at the benzylic position. In addition, their model stoichiometric reactions proved that NBE extrusion occurred from an 8-membered palladacycle to give a 6-membered palladacycle.

Later, Zhou and co-workers achieved the *ortho* alkylation/*ipso* Heck reaction followed by aza-Michael addition using aziridines as the alkylation reagent to synthesize tetrahydroisoquinolines (Scheme 55).[136] Excellent diastereoselectivity was observed during the 1,4-addition step (**99b,c**). Improved regioselectivity control was achieved with respect to 1-aryl aziridine substrates (**99c**).

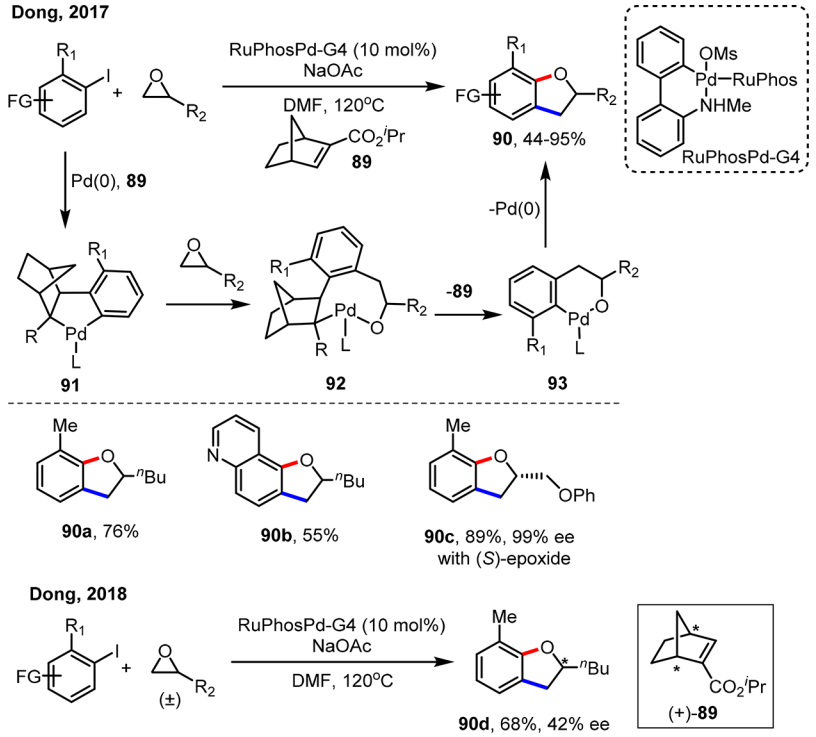
3.2.2. *Ortho* Arylation of Aryl Iodides. *3.2.2.1. Intermolecular Couplings.* Besides alkyl-type electrophiles, the second class of electrophiles employed in the Pd/NBE catalysis are aryl halides. As discussed in the stoichiometric reactions section (*vide supra*, Scheme 9), the use of aryl halides as external electrophiles often led to more complicated outcomes, but the finding of the "*ortho* effect" was the key for selective aryl−aryl couplings. The Catellani group reported the first catalytic *ortho* arylation in 2001 using internal alkynes as the termination reagents (Scheme 56).[137] A range of phenanthrene products (**100**) were obtained using diaryl alkynes. When the *ortho* substituent on aryl iodides was large, such as a *tert*-butyl group, no product was observed (**100b**). Alkylaryl alkynes gave a mixture of regioisomers (**100c**) together with some allene products; in contrast, dialkylacetylenes predominately gave the allene product (**100d**).

Analogous to the *ortho* alkylation reactions, olefins could be employed as the termination reagents (Scheme 57). In 2003, Catellani reported the first example of *ortho* arylation/*ipso* Heck using electron-poor, -rich, and -neutral olefins.[138] Interestingly, *ortho* carbomethoxy-substituted aryl iodide gave the best yield (**101b**), likely due to its faster reaction with ANP. The reaction gave poor yields when a small *ortho* substituent was present (**101c**). Later, the same group demonstrated the first use of redox-relay Heck reaction as the termination step (**102**).[139]

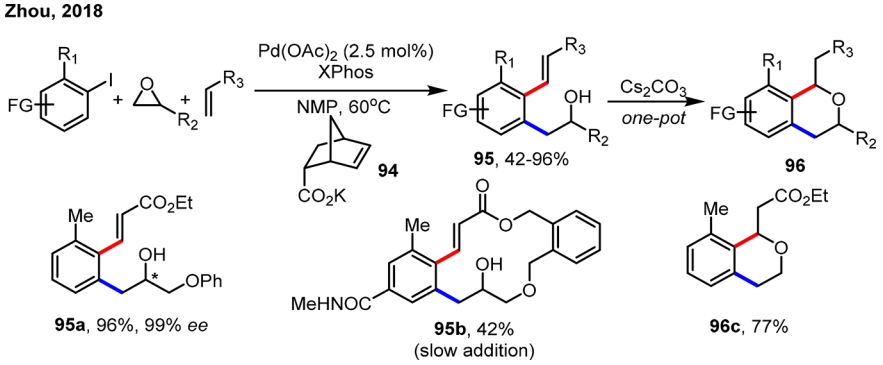
Like the *ortho* alkylation cases, other types of cross-coupling reactions have been employed to functionalize the *ipso* position. For example, the Suzuki−Miyaura termination[140] with arylboronic acids was achieved in the *ortho* arylation reaction (**103a**), affording *o*-terphenyl products (Scheme 58). While the *ipso* hydrogenation was achieved previously in the stoichiometric reactions,[46] the use of dihydrogen gas led to a nonselective outcome in the catalytic reactions. Catellani therefore screened different hydrogen-transfer reagents and found that benzyl alcohol gave the best result (**103b**).[141] In 2009, the same group

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

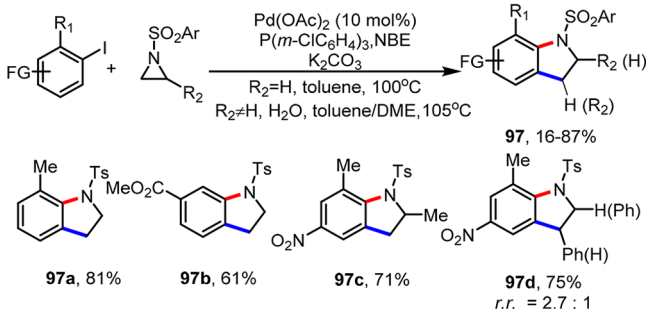
Scheme 52. Synthesis of 2,3-Dihydrobenzofurans by *Ortho* Alkylation of Aryl Iodides Using Epoxides



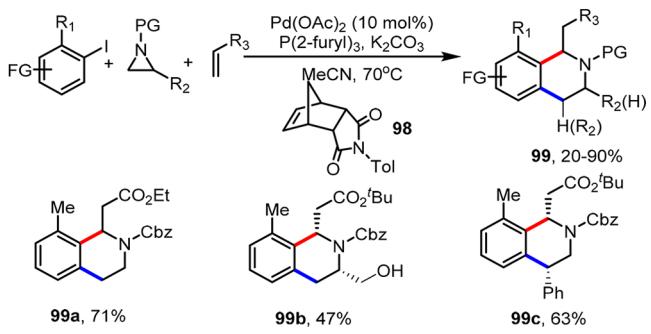
Scheme 53. Synthesis of Isochromans by *Ortho* Alkylation of Aryl Iodides Using Epoxides



Scheme 54. Synthesis of Indolines by *Ortho* Alkylation of Aryl Iodides Using Aziridines



Scheme 55. Synthesis of Tetrahydroisoquinolines by *Ortho* Alkylation of Aryl Iodides Using Aziridines

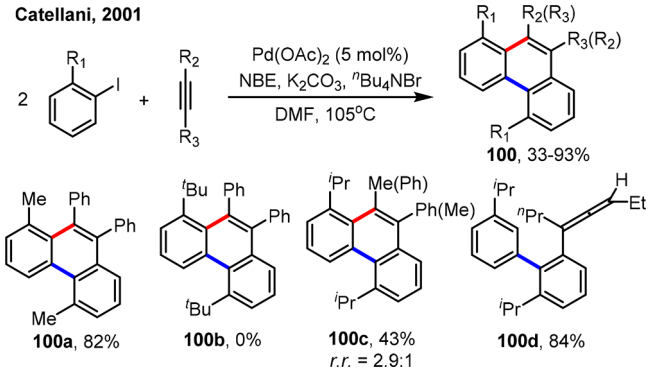


reported one of the first examples of using enolate coupling as the termination step (**103c**),[90] where the combination of 10% KOPh with K_2CO_3 was essential to maintain a suitable range of enolate concentration. They also reported using direct arylation as the termination step to afford teraryls (**103d**).[142]

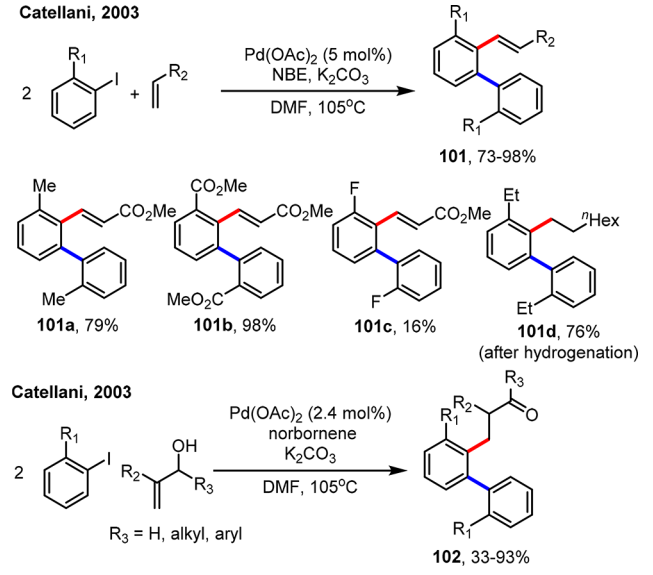
The previous *ortho* arylation examples involved the homocoupling of aryl iodide substrates. It would be highly desirable if cross-couplings between two different aryl halides could be achieved; however, this would be more challenging

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

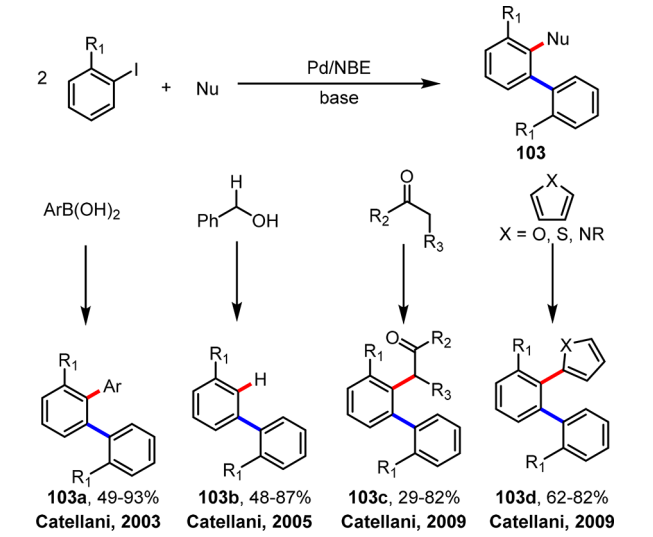
Scheme 56. Synthesis of Phenanthrenes from *Ortho*-Substituted Aryl Iodides and Internal Alkynes



Scheme 57. Homo *Ortho* Arylation/*Ipso* Heck reaction of Aryl Iodides



Scheme 58. Homo *Ortho* Arylation/*Ipso* Functionalizations of Aryl Iodides



because one aryl halide needs to selectively react with Pd(0) and the other has to selectively react with ANP. For example, the reaction between *o*-iodotoluene and *o*-iodoethylbenzene gave all four possible products with low selectivity.[143] Catellani and co-workers found that, when replacing *o*-iodoethylbenzene with methyl *o*-iodobenzoate **104a**, only three products were observed (Scheme 59).[143] The predominance of the homocoupling product **105c** suggested that methyl *o*-iodobenzoate is highly reactive to both Pd(0) and ANP. Interestingly, when the less reactive methyl *o*-bromobenzoate was used instead, the reaction selectively afforded **105b** as the sole product.

Although the exact reason remains to be uncovered, such selectivity could be tentatively explained as follows (Scheme 60). Compared to a C−I bond, a C−Br bond is shorter and stronger; thus, it generally requires more distortion in the transition state of oxidative addition. Thus, oxidative addition of aryl iodides with Pd(0) is favored by the low distortion energy, likely due to a more flexible Pd(0) complex and a weaker C−I bond. On the other hand, the Pd(II) center in ANP is considered to be more Lewis acidic and more rigid than the softer Pd(0) species; thus through chelation[144] with the ester moiety, ANP would selectively react with aryl bromide **104b** rather than the less coordinative 2-iodotoluene. It should be noted that these explanations still require further experimental and/or computational support, and caution must be taken when considering these simplified explanations since other factors like ligands and anions might also be crucial for achieving the desired selectivity.

During their exploration of the reaction scope, Catellani and co-workers found that the "*ortho* effect" only required the aryl iodide to bear an *ortho* substituent, while an *ortho* group on the aryl bromide was not necessary (Scheme 61). Since electron-withdrawing or *ortho* chelating groups on haloarenes would increase their reactivity toward ANP, it is better to use electron-donating and nonchelating *ortho* substituents on the aryl iodide substrate to avoid their reactions with ANP. One exception is the *ortho*-CF_3 substituted aryl iodide: the steric hindrance and noncoordinative nature of the CF_3 moiety reduced its reactivity with ANP (**106c**, **106d**). On the other hand, electron-withdrawing (**106e**) or *ortho* chelating groups (**106f**) on the aryl bromide part is preferable. Both electron-rich and -poor olefins could be coupled at the *ipso* position. Recently, gaseous ethylene was also successfully employed as the termination agent by Della Ca' and Noël using the flow technique.[145]

When an *ortho* heteroatom group is present in the aryl bromide part, it could act as not only a chelating group, but also a nucleophile to react with the enoate moiety formed at the *ipso* position (Scheme 62). An *oxa*-Michael reaction took place to give 6*H*-dibenzopyrans (**107a**) when *o*-bromophenol was used.[146] The corresponding *m*-bromophenol or *p*-bromophenol did not react, showcasing the importance for *ortho* chelation when using electron-rich aryl bromides. The enantioselective version was later developed by Zhou and Catallani using a cinchona alkaloid as a cocatalyst.[147] Similarly, *o*-bromoarenesulfonylanilines afforded phenanthridine (**107b**) via a subsequent *aza*-Michael reaction.[148] When trifluoroacetyl-protected 2-bromoanilines were used, hydrolytic cleavage of the trifluoroacetyl protecting group, followed by a retro-Mannich reaction, gave the phenanthridine product (**107c**).[149] Methyl vinyl ketone was found to be an excellent termination reagent to promote the retro-Mannich reaction. In a similar manner, the reaction with bromobenzylamine provided dibenzo[*c*,*e*]azepines and their imine analogues (**107d**).[150]

Other types of termination reactions have also been developed for cross-aryl couplings (Scheme 63). Cyanation

DOI: 10.1021/acs.chemrev.9b00079
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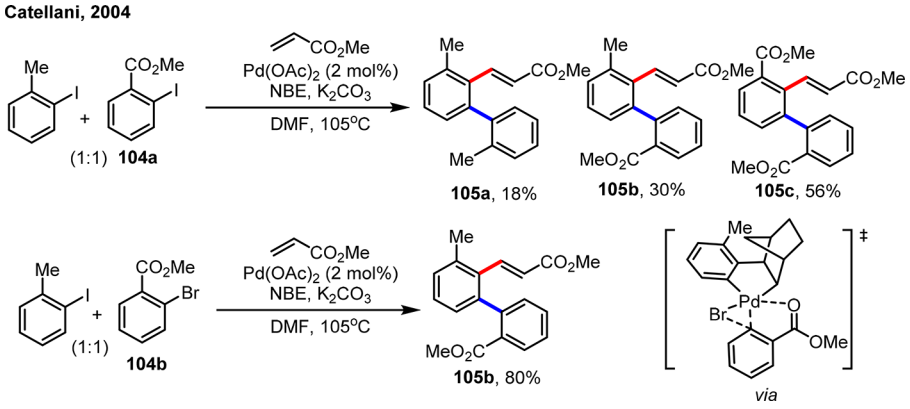
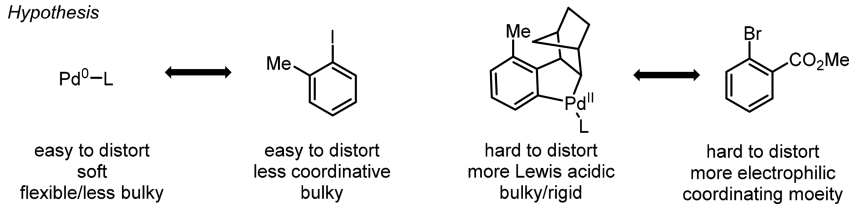
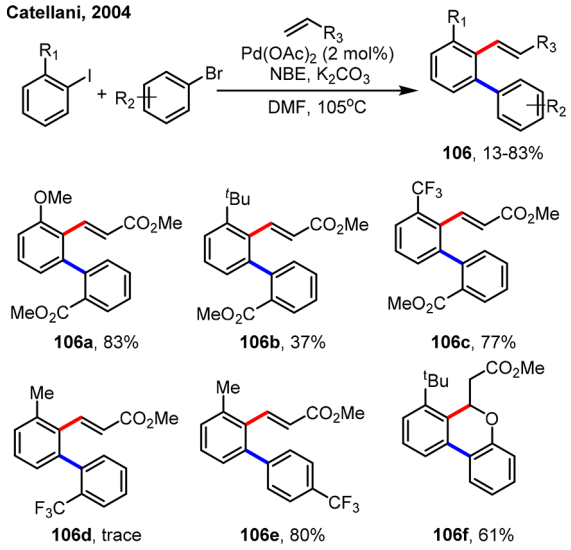
Scheme 59. Selectivity Problems in Cross *Ortho* Arylation



Scheme 60. Tentative Explanations on the Observed Selectivity



Scheme 61. Cross *Ortho* Arylation/*Ipso* Heck of Aryl Iodides



with $K_4[Fe(CN)_6]\cdot 3H_2O$ was achieved by Lautens under microwave conditions to give aromatic nitrile products (**108a**).[72] The same group later found that *ipso* hydrogenation (**108b**) could be achieved using 1,2-dimethoxyethane (DME) as the solvent and the reductant.[151] Their deuterium labeling study unambiguously confirmed that the hydride source was the methylene hydrogen from DME. Catellani and co-workers reported the Suzuki–Miyaura quench with arylboronic acids (**108c**).[152] Interestingly, the arylation selectivity could be improved when diethyl maleate was added as the ligand. If *o*-bromobenzyl alcohol was used, *ipso* hydrogenation occurred through transfer hydrogenation of the benzyl alcohol moiety,[153] which gave *o*-biaryl carbaldeydes (**108d**) as the products.

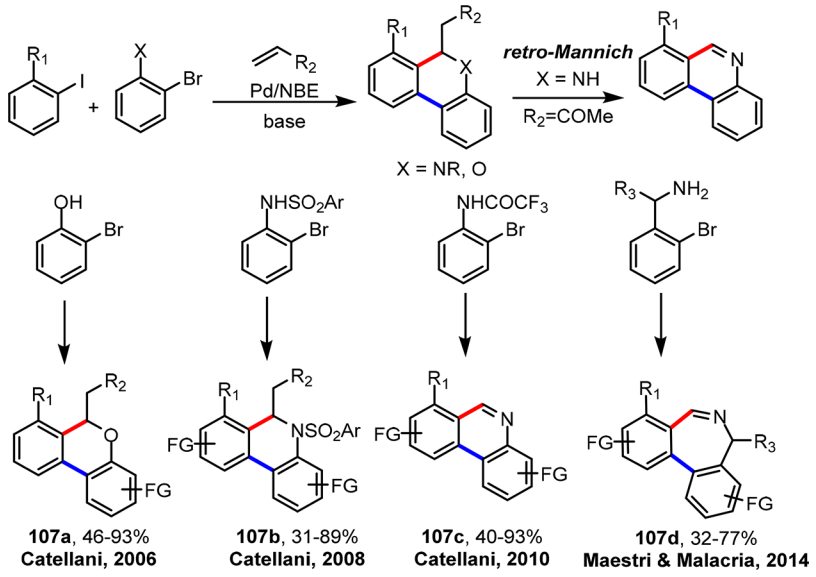
When the carboxyl group was used as the chelating group, a further decarboxylation reaction could occur to give intermediate **109**, which serves as the common intermediate for further functionalization (Scheme 64). In 2017, Kwong and Lin reported a net π-extension reaction of aryl halides using 2-halobenzoic acids and norbornadiene to afford product **110**.[154] The products were formed through reductive elimination from a **109**-like intermediate, followed by a retro-Diels–Alder reaction. In 2018, Kwong and Fu group extended this reaction by adding alkynes to achieve a regioselective aromatic π-extension reaction (**111**).[155] Instead of reductive elimination, in this case, **109** underwent NBE extrusion and alkyne insertion/annulation. In the same year, Yang and Liang reported that **109** could undergo another arylation with 2-bromobenzoic acid, followed by norbornene extrusion, another decarboxylation, and reductive elimination to give triphenylenes **112** as products.[156]

3.2.2.2. The "Ortho Effect" in Ortho Arylation Reactions. As discussed in section 2.2, the outcome of the reaction between ANP and the haloarene electrophile depends on the substituent pattern of the ANP aryl ring. If the ANP intermediate is derived from an aryl iodide with an *ortho* substituent, selective aryl–aryl bond formation (rather than aryl–norbornyl bond formation) would occur.[44] Otherwise, the arylation would be unselective. Such a phenomenon was termed by Catellani as the "*ortho* effect". While the "*ortho* effect" successfully helped the development of the *ortho* arylation reactions, its origin remained unknown for a long time.

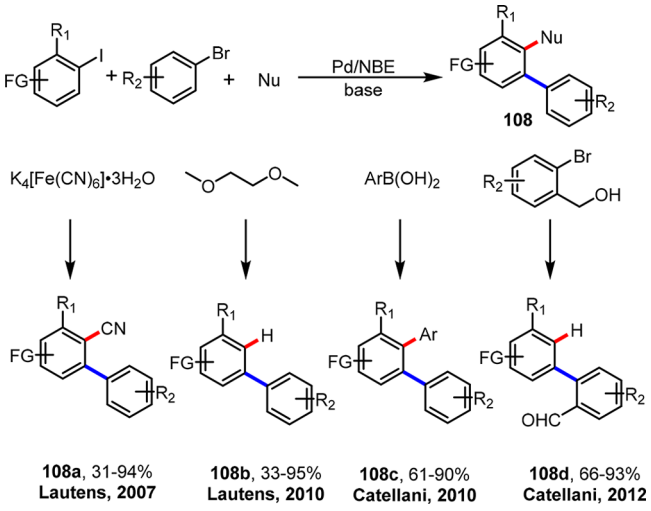
To date, two possible pathways have been proposed for the reaction of ANP with the haloarene electrophile. The first one involves a Pd(IV) pathway, where ANP directly undergoes oxidative addition with haloarene. The intermediacy of Pd(IV) has been directly observed with alkyl electrophiles,[38] however not in with aryl electrophiles. In a related case, Vicente reported isolation of a Pd(IV) complex by oxidative addition of 2-iodobenzoic acid to a Pd(II) complex,[144] proving the feasibility of such a process. The alternative pathway involves a transmetalation process, where oxidative addition of the haloarene electrophile with a separate Pd(0) species forms an aryl-Pd(II) species, followed by dinuclear transmetalation between the aryl-Pd(II) species and ANP. Such a pathway has

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478–7528

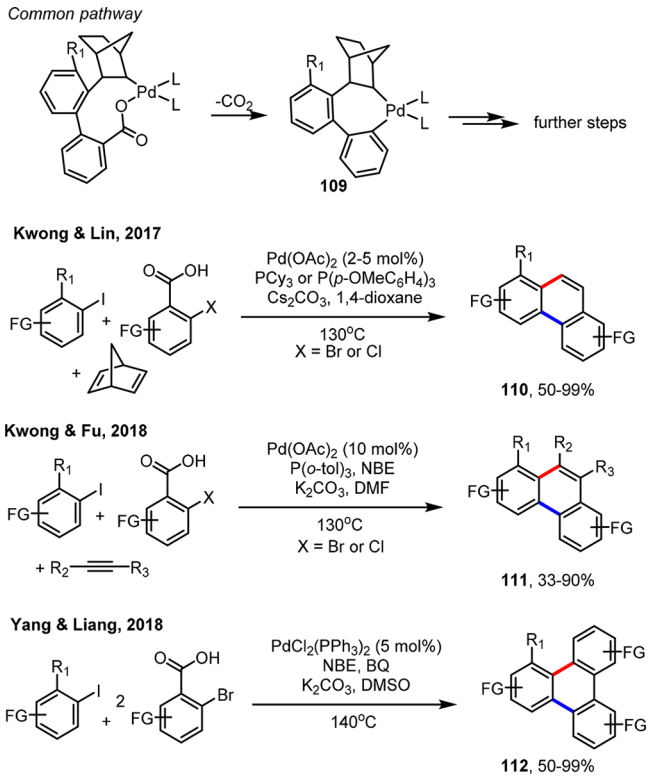
Scheme 62. Cross *Ortho* Arylation/*Ipso* Heck Followed by Michael Reaction



Scheme 63. Cross *Ortho* Arylation/*Ipso* Functionalizations of Aryl Iodides



Scheme 64. π-Extension Reaction Using 2-Halobenzoic Acids



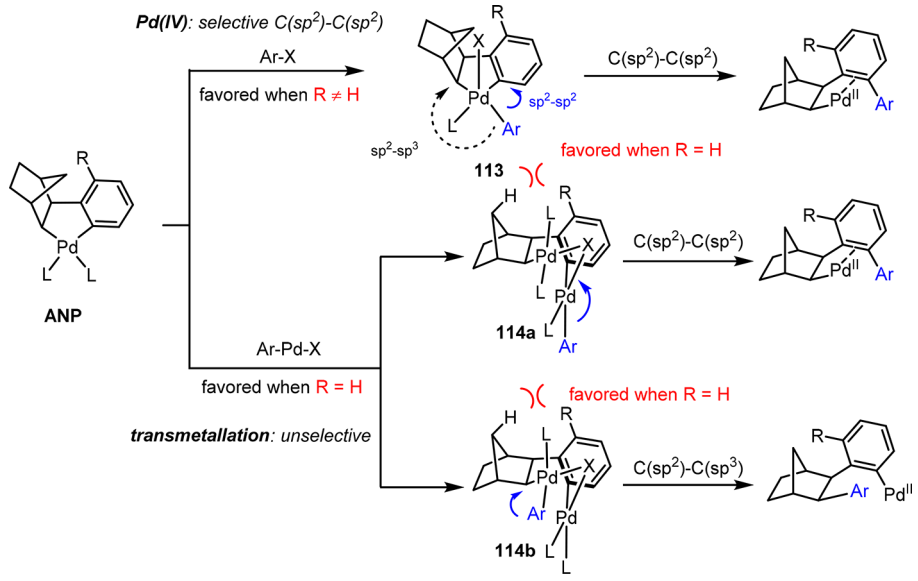
been supported by DFT calculation on a simplified system by Cardens and Echavarren.[157]

In 2011, Catellani, Deret, and Malacria performed the DFT calculation using M06 hybrid functional to study the origin of the "*ortho* effect" (Scheme 65).[158] First, they found that both pathways could dominate depending on the substituent pattern on the aryl moiety in ANP. Without the *ortho* substituent, the transmetalation pathway is favored over the Pd(IV) pathway by 8−10 kcal/mol for different substrates, in agreement with the Echavarren's finding. In contrast, the Pd(IV) pathway becomes the preferred pathway when an *ortho* substituent is present in the aryl moiety of ANP by 1−7 kcal/mol. The steric clash between the *ortho* substituent and NBE (**114a** and **114b**) greatly increases the barrier for the transmetalation pathway, while the Pd(IV) pathway remains with a similar barrier. Second, they found that, for the *ortho*-unsubstituted ANP, the energy difference between the two coupling modes, i.e., $C(sp^2)-C(sp^2)$ or $C(sp^2)-C(sp^3)$, in the transmetalation pathway is small (1.5−2.0 kcal/mol), rendering an unselective arylation. In contrast, the reductive elimination step from the Pd(IV) intermediate **113** is highly selective, favoring the $C(sp^2)-C(sp^2)$ coupling by 4−12 kcal/mol over the $C(sp^2)-C(sp^3)$ coupling.

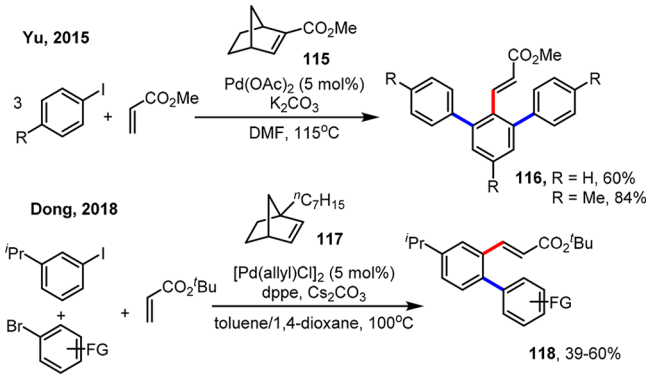
Although understanding the *ortho* effect allows choosing appropriate substrates for successful reactions, it is still highly desirable to use common *ortho*-unsubstituted aryl iodides as substrates for selective cross couplings. In 2015, the Yu group found that 2-carbomethoxy-substituted NBE **115** could afford a "normal" bis *ortho* arylation product of iodobenzene rather than the NBE-containing product (Scheme 66).[159] It is likely that the undesired $C(sp^2)-C(sp^3)$ coupling was inhibited due to the steric repulsion of the carbomethoxy substituent on NBE **115**. In

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 65. DFT Calculations on the Origin of the "*Ortho* Effect"



Scheme 66. Overcoming *Ortho* Effect with Substituted NBEs

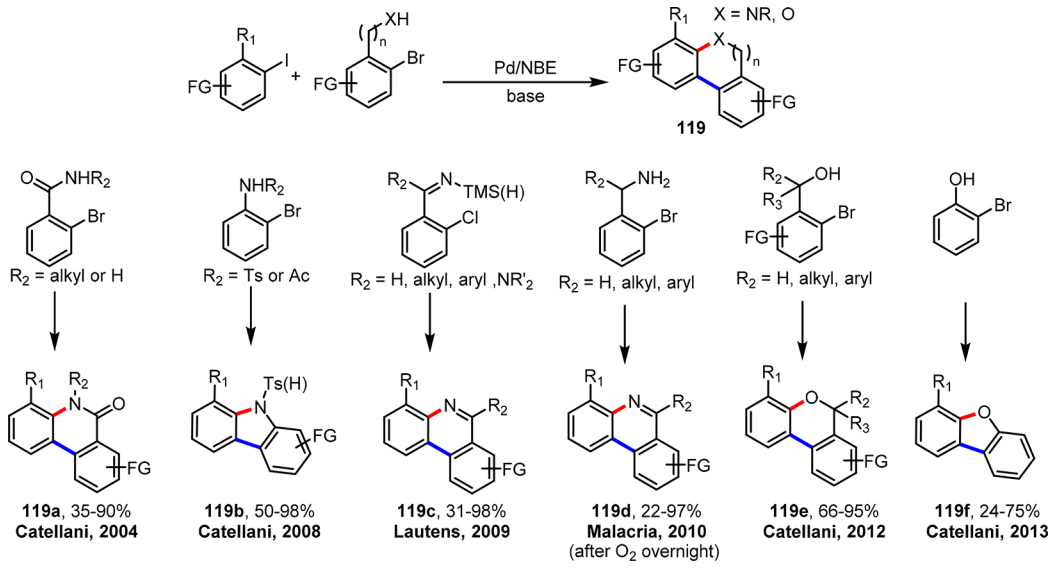


this case, both *ortho* positions were arylated to form a self-trimer structure. Very recently, the Dong group employed bridgehead-substituted NBE **117** to achieve mono-*ortho* arylation of *ortho*-unsubstituted aryl iodides via cross couplings.[160] Presumably, the presence of the bridgehead substituent on NBE not only inhibited the undesired arylation on the NBE part but also promoted the NBE extrusion (for a detailed discussion, see section 3.2.7).

3.2.2.3. Intramolecular Couplings. Since the cross *ortho* arylation between an aryl iodide and an aryl bromide requires an *ortho* chelating group on the aryl bromide, the chelating moiety could be conveniently used as the termination agent. Such intramolecular couplings could be viewed as a Type A annulation (*vide supra*, Scheme 41). However, caution should be taken in these types of transformations, since an alternative pathway involving *ipso* coupling, followed by oxidative addition into ArBr and C−H annulation could potentially give the same product in the absence of NBE.

The first example of such a transformation was reported by Catellani, in which the *ortho* amide group served both as a chelating group and a nucleophile for the *ipso* termination

Scheme 67. Synthesis of Fused Rings via *Ortho*-Arylation *Ipso*-C−N or C−O Coupling



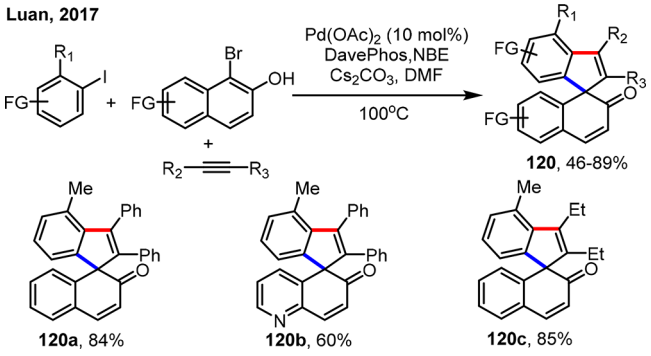
DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

(Scheme 67).[161] A range of 6-phenanthridinones (**119a**) was afforded in moderate to excellent yields. Notably, this was also the first time when the Buchwald−Hartwig amination was employed as the termination step. Surprisingly, in the absence of NBE, self-dimerization of *o*-bromoarylcarboxamide took place to give condensed pyridones.[162] Similarly, *o*-bromo-*N*-tosylaniline afforded carbazole products (**119b**). Interestingly, when acetamide was used instead of sulfonamide, deprotected carbazole products were observed, and carbazomycin A was synthesized using this method (see section 4.1).[163]

Lautens employed *o*-chloro-*N*-silylimines to achieve *ipso* C−N coupling and provide phenanthridine products (**119c**).[164] *N*-Silylimines are more stable than the corresponding unprotected imines and the silyl group was cleaved under the reaction conditions.[165] Interestingly, the reaction scope was broad, as *N*-silylketimine, *N*-silylamidines, and even *N*-unsubstituted ketimines were all suitable substrates. To avoid using unstable imines, Malacria synthesized phenanthridines (**119d**) from benzyamines and aryl iodides.[166] Subsequent oxidation using dioxygen provided the aromatic products. Control experiments showed no product formation when NBE was omitted, ruling out the alternative pathway involving amination of the aryl iodide followed by intramolecular ring closure. Assoanine and pratosine were later synthesized using this method (see section 4.1).[167] Besides *ipso* C−N coupling, *ipso* C−O coupling has also been developed. In 2012, Catellani reported the first example of such transformations in the synthesis of dibenzopyrans (**119e**) using *o*-bromobenzyl alcohols as the coupling partner.[153] In this case, no additional phosphine ligand was added, but a tertiary alcohol had to be used to avoid *β*-hydrogen elimination. Similarly, the use of *o*-bromophenol provided dibenzofurans (**119f**).[168]

Due to the difficulty of the C−O bond reductive elimination using *o*-bromophenols, the intermediate after NBE extrusion could be trapped for further functionalization. In 2017, the Luan group successfully intercepted such an intermediate through alkyne insertion and dearomatization to achieve a [2+2+1] spiroannulation using 1-bromo-2-naphthol and an internal alkyne (Scheme 68).[169]

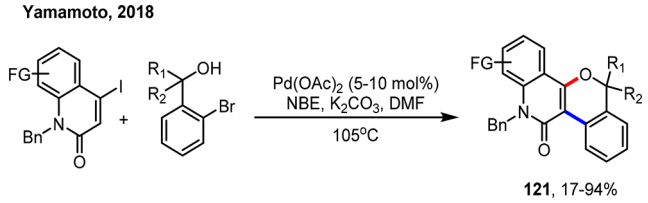
Scheme 68. Dearomatizing [2+2+1] Annulation of Bromonaphthols with Aryl Iodides and Alkynes



In 2018, Yamamoto reported an annulation with 4-iodo-2-quinolones via *ortho* arylation/*ipso* C−O coupling (Scheme 69).[170] The presence of NBE was found to be essential for this reaction. DFT calculations showed the importance of the amide group serving as a directing moiety in the CMD step.

It is important to note that, although the chelating group in the aryl bromide part could lower the barrier for the oxidative addition with ANP, it might increase the barrier and change the regioselectivity in the subsequent reductive elimination step.[171] Discovered by Malacria and Lacôte, the reaction of 2-iodotoluene and 2-bromophenylacetamide gave a NBE-containing dihydrophenanthrene product (**122a**) (Scheme 70).[172] This product came from the arylation at the norbornyl site, which was abnormal when considering the *ortho* effect. Interestingly, the addition of excess water switched the selectivity back to the normal aryl−aryl coupling product **122b**, albeit followed by a dearomatization step. According to their DFT studies, the Pd(IV) pathway was still favored over the transmetalation pathway, in accordance with the *ortho* effect. However, the presence of the chelating group forced a distorted octahedral geometry in the Pd(IV) intermediate **123**, which subtly changed the reductive elimination selectivity. With the addition of water, the chelation could be partially released, restoring the normal selectivity. The nature of the primary amide chelating group also plays an important role, as other chelating groups did not show such an effect.

Scheme 69. *Ortho* Arylation/*Ipso* C−O Coupling of 4-Iodo-2-Quinolones



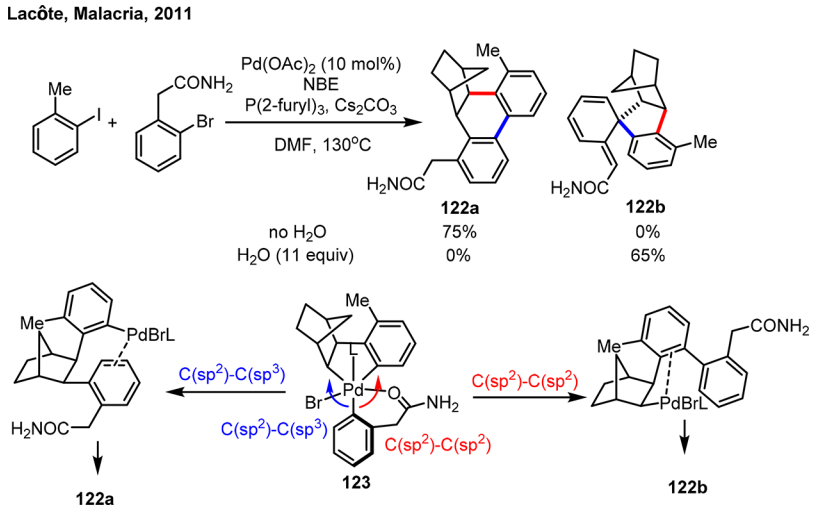
Another unusual example is the use of 2-bromoaniline (Scheme 71). The unexpected $C(sp^2)-C(sp^3)$ coupling followed by *ortho* C−N coupling gave NBE-containing products **124**, even though *ortho* substituted aryl iodides were used.[173] Such a transformation became synthetically useful when norbornadiene was used instead of NBE, so that the product (**124**) could be further transformed into dibenzoazepines (**125**) via a retro-Diels−Alder reaction. *Ortho*-unsubstituted aryl iodides reacted similarly. These results are in sharp contrast with the case of aforementioned *N*-protected 2-bromoanilines (**119b**). The DFT calculation showed that the electron-rich aniline ring is nucleophilic and nicely matched the LUMO around the norbornyl $C(sp^3)$ position; in contrast, the protected aniline is less electron-rich; thus it provided the normal aryl−aryl coupling product.

Very recently, the Chen group reported the *ortho* arylation of iodoarenes using 2-bromo-NH-sulfoximines as the arylation reagent (Scheme 72).[174] When *ortho*-substituted aryl iodides were used, the expected *ortho* arylation, followed by *ipso* C−N coupling, afforded cyclic sulfoximines (**128a**). In contrast, when *meta*-substituted aryl iodides were used, NBE-containing products (**128b**) were obtained instead, resulting from the $C(sp^2)-C(sp^3)$ coupling. These results could be nicely explained by the *ortho* effect, where the transmetalation pathway took place when *ortho* unsubstituted aryl iodides were used.

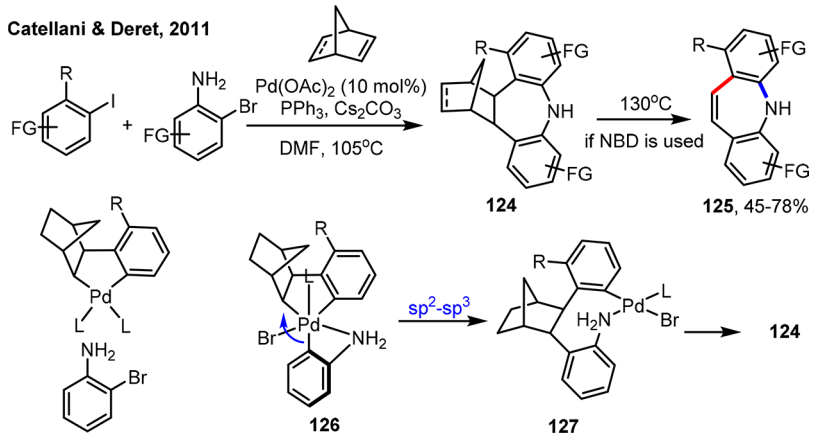
Ketone, ester, and aldehyde-derived aryl bromides can also serve as bifunctional reagents (Scheme 73). The aryl-Pd(II) intermediates are usually considered to be electrophilic especially in the C−C cross-coupling reactions; however, sometimes they could also show nucleophilic characteristics when interacting with carbon−heteroatom multiple bonds.[175] Lautens first showed such dual reactivity in the Pd/NBE catalysis using 2′-chloroaceteophenone as a reagent.[91] Using

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

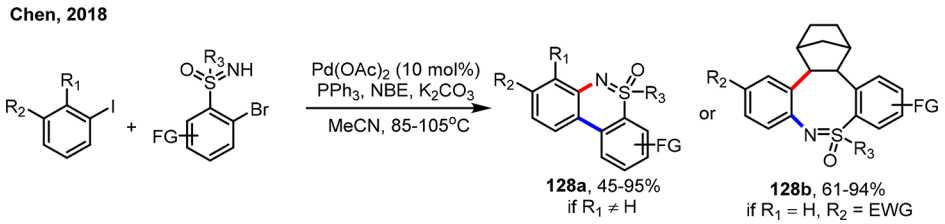
Scheme 70. Switching Regioselectivity for Reductive Elimination by Chelation



Scheme 71. Formation of Dibenzoazepine Derivatives by *Ortho* Arylation of Aryl Iodides with *o*-Bromoanilines



Scheme 72. Divergent Preparation of Heterocyclic Sulfoximines



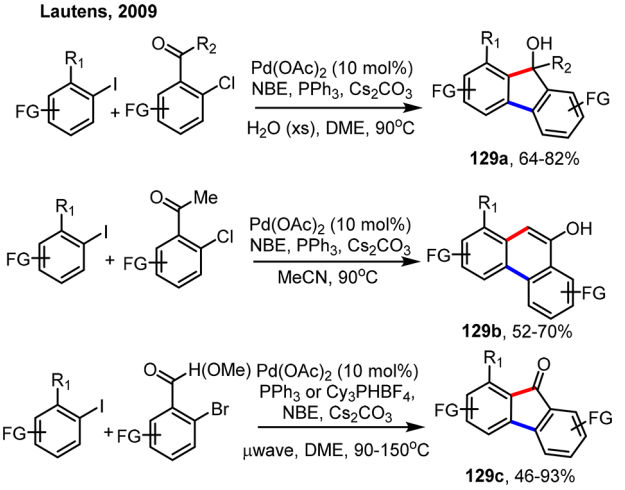
DME as the solvent with excess water, *ipso* 1,2-addition occurred to give 9*H*-fluoren-9-ol **129a**. It is likely that water acted as a proton source and DME behaved as a reductant. In contrast, in anhydrous acetonitrile, phenanthren-9-ol **129b** was obtained as a result of the *ipso* enolate coupling. Besides ketones, 1,2-addition to esters, aldehydes, and *N*-sulfinyl imines as the termination step has also been demonstrated (**129c**).

Although most intermolecular couplings involving *ortho* arylation belong to Type A, a few examples of Type B annulation have also been reported (Scheme 74). The first example was described by Lautens in 2010, where phenoxazines and dihydrodibenzoxazepines were obtained through the *ortho* arylation/*ipso* C−N coupling (**130**).[117] In 2013, the Gu group applied the *ortho* arylation/*ipso* intramolecular Heck reaction with iodopyrroles in the total synthesis of rhazinal (see section 4.1).[176] In 2017, the Luan group used alkyne-tethered aryl iodides as substrates, which enabled an intramolecular alkyne insertion and dearomatization (**131**) for constructing the cores of polyketide natural products, dalesconols A and B.[169]

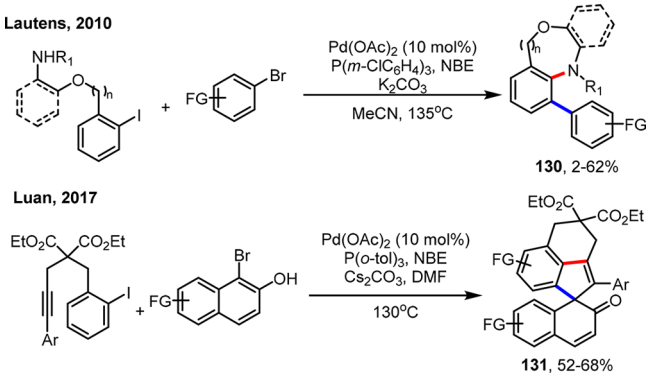
3.2.3. *Ortho* Amination of Aryl Iodides. Despite the early discovery of *ortho* alkylation (1997) and arylation (2001), the introduction of heteroatoms at the arene *ortho* position in the Pd/NBE catalysis was not reported until 2013. The Dong group found that *O*-benzoylhydroxylamines[177,178] can serve as an excellent external electrophile to trap ANP, which led to the development of *ortho* amination reactions (Scheme 75).[179] The electrophilic nitrogen moiety in *O*-benzoylhydroxylamines is expected to have a strong interaction with the nucleophilic ANP, and the benzoate part might act as both a leaving group and a chelating moiety. For comparison, *N*-chloroamines only gave a complex mixture. Isopropanol was employed as the reductant to deliver hydrogen at the *ipso* positions, and the deuterium

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

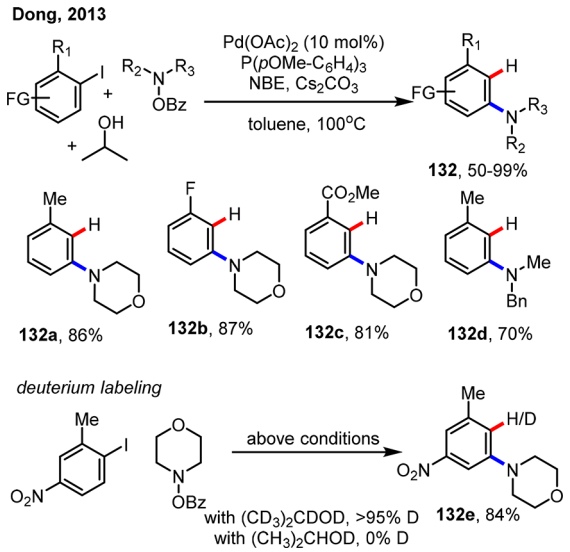
Scheme 73. *Ortho* Arylation/Intramolecular *Ipso* 1,2-Addition of Aryl Iodides



Scheme 74. Type B Intramolecular Coupling in *Ortho* Arylation of Aryl Iodides



Scheme 75. *Ortho* Amination/*Ipso* Hydrogenation of Aryl Iodides



labeling study confirmed the hydride transfer mechanism. The three reactants were used in near equimolar ratio with only 25 mol % of NBE. The scope of aryl iodides is also quite broad: some traditionally challenging substrates could be successfully coupled. For example, 1-fluoro-2-iodobenzene (**132b**) that was known to have difficulties in the β-carbon elimination step[143] due to the small size of fluorine can work in the *ortho* amination reaction. Methyl 2-iodobenzoate usually afforded self-arylation dimer in other cases,[143] and its success (**132c**) shows that *O*-benzoylhydroxylamines are more reactive and/or selective toward ANP. Acyclic secondary *O*-benzoylhydroxylamines could be coupled (**132d**) but primary *O*-benzoylhydroxylamines were not suitable. When aryl iodides with *para* substituents or small *meta* substituents were used, *ortho*/*ortho'* bisamination took place, similar to the *ortho* alkylation chemistry.

Subsequently (2014−2018), other types of *ortho* amination reactions with different *ipso* terminations have been developed (Scheme 76). For example, Heck coupling with electron-deficient[180] or -rich[181] olefins (**133a**, **133f**), Suzuki−Miyaura coupling with arylboronic esters (**133b**)[182] or methyl boronic acids (**133i**),[73] carbene coupling (**133c**),[183] Sonogashira coupling (**133d**, **133e**),[77,78] cyanation (**133g**, **133h**),[184,185] and enolate coupling (**133j**)[186] have been successfully demonstrated at the *ipso* position using the similar strategies developed in the aforementioned *ortho* alkylation/arylation reactions.

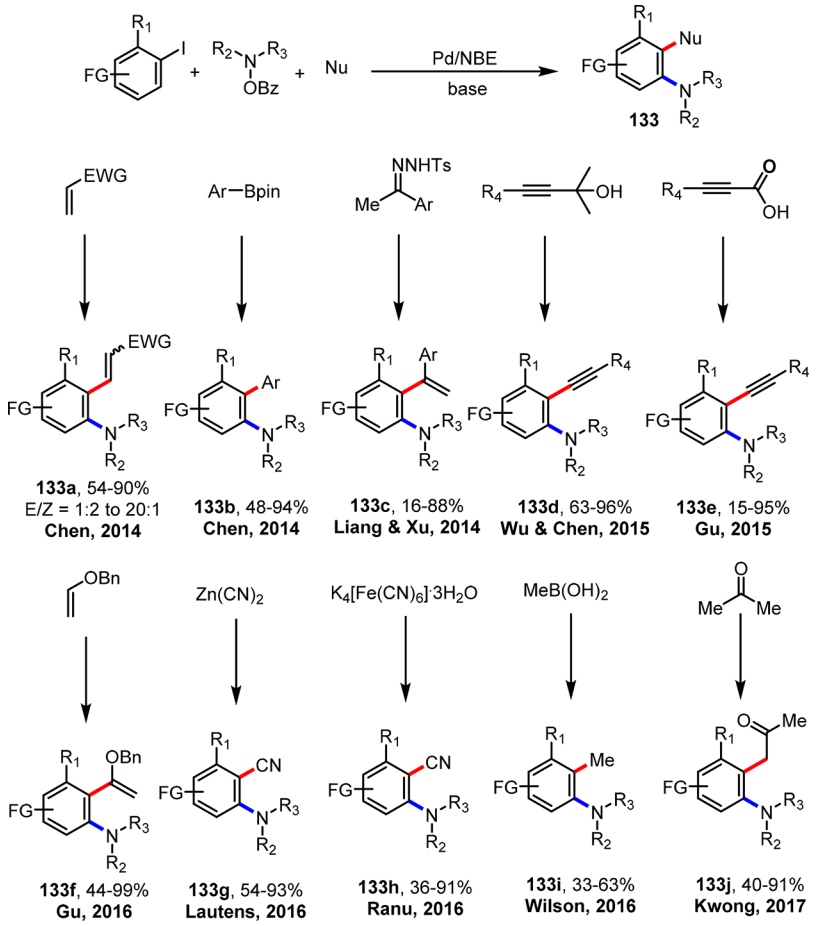
Interestingly, the Ritter group reported the first example of the *ipso* borylation reaction using bis(pinacolato)diboron as the termination reagent (Scheme 77).[187] The merit of such a transformation was demonstrated in the diverse and convenient derivatizations of the formed B(pin) moiety. For example, the C−B bond can be converted into C−N (**134b**), C−Cl, C−Br (**134c**), and C−I and C−OH (**134d**) bonds, which are hard to access via direct terminations. The major side reaction was the *ipso* hydrogenation, and the reductant was the HBpin generated in the reaction. The synthetic utility was demonstrated in the modular syntheses of Abilify and Flunixin (see section 4.1).

Besides intermolecular reactions, Type B intramolecular couplings have also been reported based on *ortho* amination (Scheme 78). Using phenol-tethered aryl iodides, the Luan group developed an intercepted *ortho* amination terminated by phenol dearomatization,[188] in which norbornadiene was incorporated into the product (**135**). In 2018, Lautens reported the first example of the Pd/NBE-catalyzed intermolecular *ipso* amidation reaction (**136**).[189] The key was the use of $Pd(PPh_3)_4$ as the catalyst, preventing intermolecular *ipso* termination; in contrast, the use of RuPhos gave the direct *ipso* termination side products (no *ortho* amination). Very recently, the Liang group developed the first *ipso* termination using intramolecular sp^3 C−H activation (**137**).[190] The use of catalytic pivalic acid was important to lower the activation barrier for palladation of unactivated aliphatic C−H bonds, as shown by their DFT calculations.

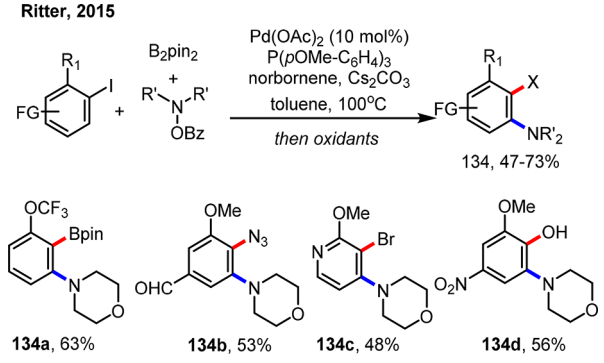
3.2.4. *Ortho* Acylation of Aryl Iodides. Aromatic ketones are widely found in pharmaceuticals, agrochemicals, organic electrons, and polymers; thus, it is attractive to develop efficient and site-selective methods for arene acylation. In 2015, the Liang,[191] Gu,[192] and Dong[193] groups concurrently reported the Pd/NBE-catalyzed *ortho* acylation reaction of aryl iodides (Scheme 79). The work by Liang and Gu focused on using the Heck reaction to functionalize the *ipso* position. Symmetrical acyl anhydrides were used by Liang, and *in situ* generated acyl anhydrides from acyl chlorides were used by Gu. Good functional group tolerance was observed for both cases. In addition, both aromatic and aliphatic acyl electrophiles were compatible, although α-nonbranched aliphatic anhydrides usually gave reduced yields (**139c**).

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

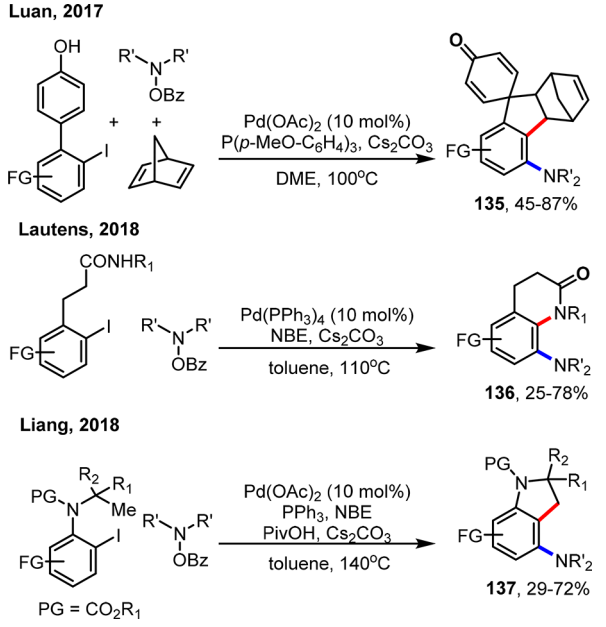
Scheme 76. *Ortho* Amination/*Ipso* Functionalizations of Aryl Iodides



Scheme 77. *Ortho* Amination/*Ipso* Borylation and Derivatization of Aryl Iodides



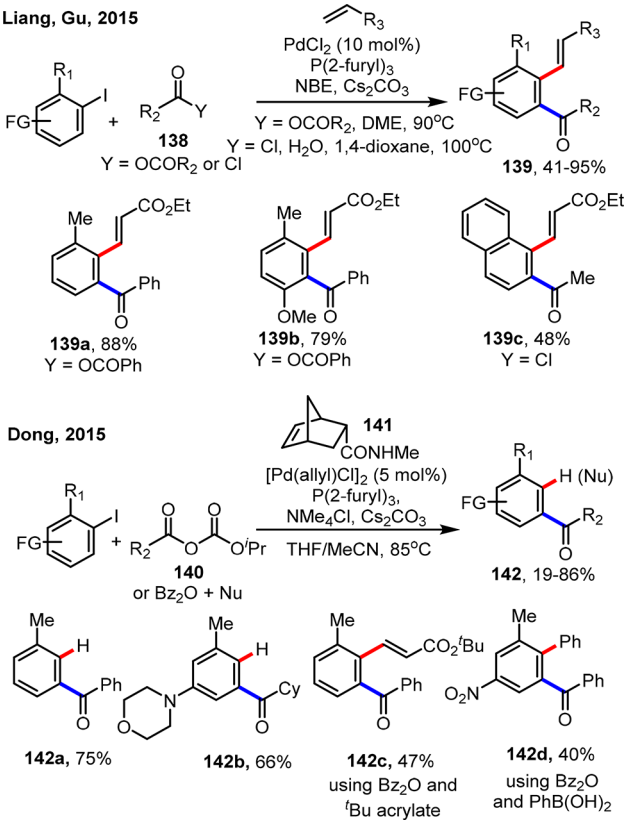
Scheme 78. Type B Intramolecular Couplings in *Ortho* Amination



The Dong group developed an *ortho* acylation/*ipso* hydrogenation method, in which a bifunctional mixed anhydride was designed to provide the acyl electrophile and slowly release isopropanol reductant. The acyl−O bond was selectively cleaved instead of the carboxyl−O bond, probably owing to the higher electrophilicity of the former. An amide-substituted NBE (**141**) was found to be more effective than simple NBE. Both electron-rich and deficient (hetero)aryl iodides were suitable substrates. *Para*-substituted aryl iodides gave bis-*ortho* acylation along with a tandem cyclization product. Aryl (**142a**), heteroaryl, and alkyl (**142b**) carboxylic anhydrides were suitable substrates. While the scope was focused on *ipso* hydrogenation, *ipso* Heck (**142c**) and Suzuki−Miyaura (**142d**) couplings were also demonstrated as single examples. The synthetic utility of the *ortho* acylation/*ipso* hydrogenation method was demonstrated in the synthesis of ketoprofen (see section 4.1).

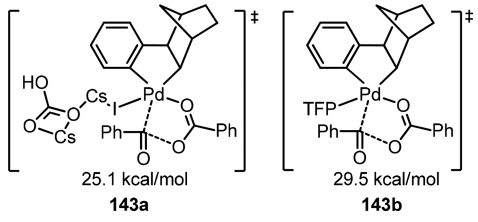
DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 79. Initial Reports of *Ortho* Acylation Reaction



Similar to the *N*-benzoyloxyamines, the electrophilic acyl moiety should also have strong interactions with ANP; in addition, the carboxylate leaving group could further decrease the oxidative addition barrier through chelating effects. DFT calculations have been performed to understand the reaction between benzoic anhydride and ANP,[53] which was found to be the rate-determining step (Scheme 80). The benzoate leaving

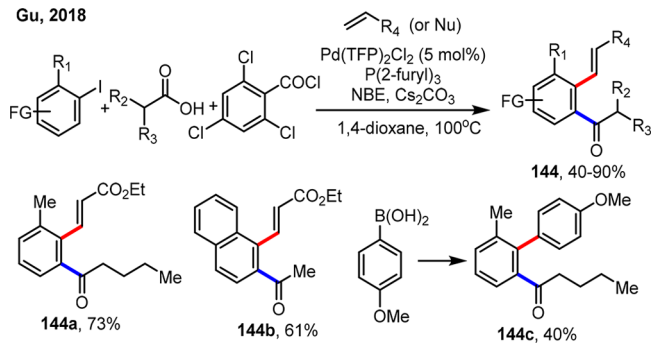
Scheme 80. DFT Calculations on the Reaction of ANP with Anhydrides



group acts as a chelating group and the C−O bond is cleaved via a five-membered transition state (**143a**). Interestingly, the iodide ligated transition state was found to be more reactive than the P(2-furyl)$_3$-ligated (**143b**) one. In addition, oxidative addition of the P(2-furyl)$_3$-ligated Pd(0) with aryl iodides was more favorable than with anhydrides by 10 kcal/mol.

Very recently, the Gu group utilized the *in situ* generated mixed-anhydrides to successfully expand the scope of the acyl moieties that can be installed (Scheme 81).[194] The Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) was added to convert carboxylic acids to mixed anhydrides during the reaction. Notably, α-nonbranched aliphatic anhydrides can be smoothly coupled, possibly due to an increased electrophilicity. Pivalic

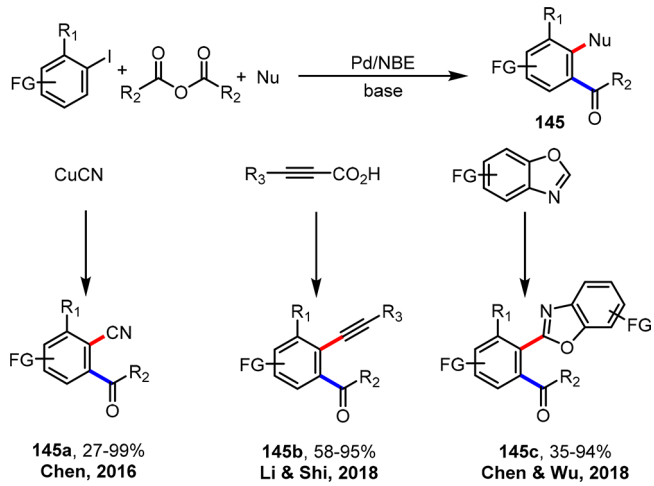
Scheme 81. Expanding Scope of *Ortho* Acylation of Aryl Iodides Using Mixed Anhydride



acid cannot be coupled using this protocol, likely owing to the bulkiness of the anhydride reagent.

Besides Heck,[191,192] Suzuki−Miyaura,[191,193,195] and hydrogenation[193] quenches in the *ortho* acylation, other termination reactions have also been developed for *ipso* functionalization (Scheme 82). For example, *ipso* cyanation[196] of *ortho*-

Scheme 82. Different *ipso* Functionalizations in *ortho* Acylation Reaction

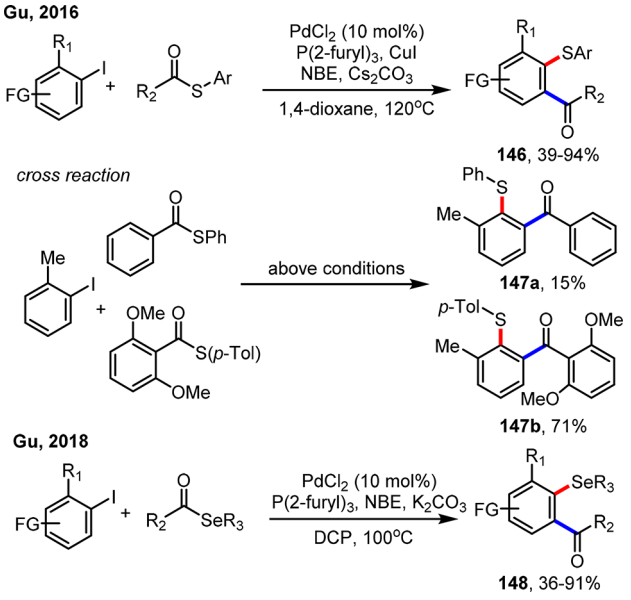


substituted aryl iodides was achieved by Chen using CuCN as the cyanide source (**145a**). Other transformations like Sonogashira coupling (**145b**)[197] and direct heteroarylation (**145c**)[198] have also been realized with the *ortho* acylation chemistry.

In addition to the use of anhydrides as the acylating reagent, thioesters were also found to be suitable electrophiles. Based on studies of the Liebeskind−Srogl reaction,[199] the Gu group first demonstrated the use of thioesters in the Pd/NBE-catalyzed *ortho* acylation/*ipso* thiolation reaction in 2016 (Scheme 83).[200] The addition of CuI dramatically improved the yield from 10% to 85% with 1-iodonaphthalene. The Cu(I) salt was proposed to serve as a C(O)−S bond activator, and its exact role remains to be disclosed. Thioesters derived from aromatic, heteroaromatic, and aliphatic acids can all be coupled. A reaction using two different thioesters in one pot did not give cross-products (**147**). In 2018, the same group reported the related *ortho* acylation/*ipso* selenation reaction (**148**) using acyl selenides.[201] In this case, CuI was found to be detrimental to the reaction.

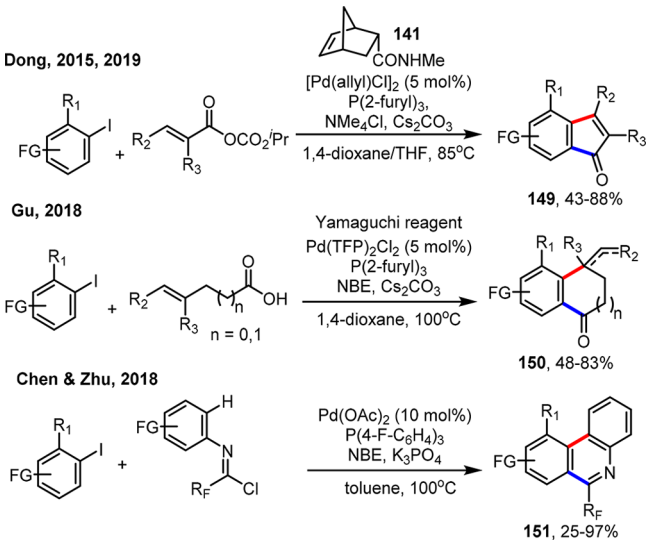
DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 83. *Ortho* Acylation/*Ipso* Thiolation and Selenation Reaction of Aryl Iodides



Besides intermolecular reactions, Type A intramolecular couplings have also been reported (Scheme 84). In 2015, the

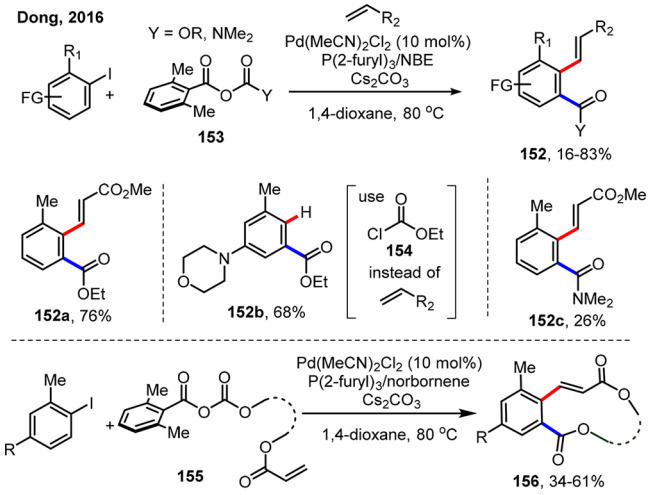
Scheme 84. *Ipso* Intermolecular Couplings in *Ortho* Acylation Reaction



Dong group found the acrylic acid-derived anhydride provided indenone products (**149**) likely through an *ortho* acylation/*ipso* intermolecular Heck annulation.[193] The scope of this transformation was later expanded to various other α,β-unsaturated acid anhydrides,[202] and the reaction was applied in the syntheses of pauciflorol F and acredinone A (see section 4.1). Employing the *in situ* generated mixed anhydride strategy, the Gu group also reported the *ipso* intermolecular Heck using carboxylic acid-tethered olefins,[194] forming five- and six-membered rings (**150**). Highly electrophilic fluorinated imidoyl chlorides were used by Chen and Zhu as a new type of electrophiles, and subsequent intermolecular *ipso* C(sp^2)−H activation afforded the phenanthridine products (**151**).[203]

3.2.5. *Ortho* Alkoxycarbonylation and Aminocarbonylation of Aryl Iodides. Aryl carboxylic acid derivatives are not only commonly found in biologically important molecules, but also serve as a versatile C1 unit to access other types of functional groups, e.g., CHO, CH_2OH, CN, etc. In 2016, the first example of an *ortho* alkoxycarbonylation reaction was realized using a modified mixed anhydride by the Dong group (Scheme 85).[204] By taking advantage of the fact that ANP is

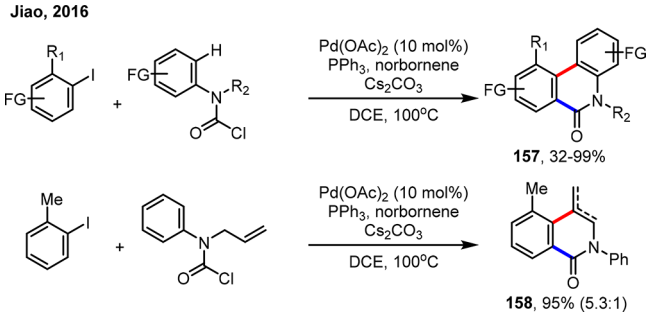
Scheme 85. *Ortho* Alkoxylcarbonylation Reaction of Aryl Iodides and Its Extension



sensitive to the sterics of the electrophile, selective cleavage of the less bulky C(carboxyl)−O bonds was achieved with 2,6-dimethylbenzoate-derived anhydrides (**153**). A Heck reaction was used as the *ipso* termination. Preliminary results on *ortho* alkoxycarbonylation/*ipso* hydrogenation (**152b**) and *ortho* aminocarbonylation/*ipso* Heck reactions (**152c**) were also achieved by similar strategies. When tethering the anhydride with an olefin, macrolactone products were formed in moderate to good yields, which represents a Type A annulation.

In 2016, Jiao and co-workers reported the *ortho* aminocarbonylation/*ipso* C(sp^2)−H activation reaction using aryl carbamic chlorides as the electrophiles (Scheme 86).[33]

Scheme 86. *Ortho* Aminocarbonylation/*Ipso* Intramolecular Coupling Reactions



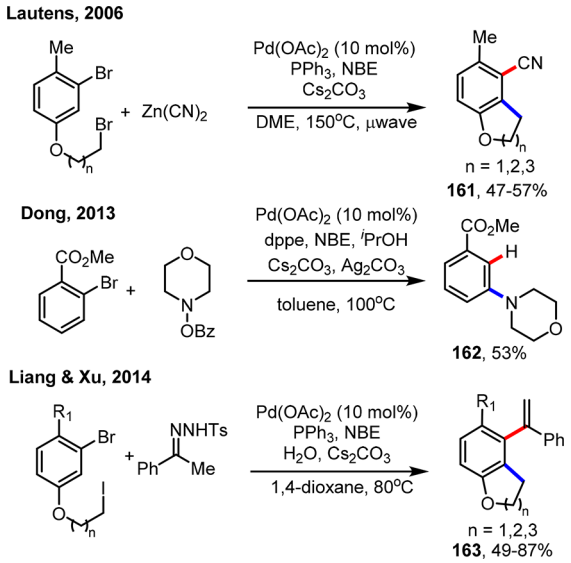
Phenanthridinones were formed as the major products. When one substituent on the nitrogen is an allyl group, an *ipso* Heck reaction was favored to afford lactams **158**. Subsequent KIE, Hammett plot, and computational studies suggested that the rate-limiting step was the oxidative addition of ANP with aryl carbamic chlorides.

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

3.2.6. *Ortho* Functionalizations of Aryl Bromides and Triflates. From the viewpoint of practicality, aryl bromides are usually cheaper and more accessible than the corresponding aryl iodides. However, in contrast to the wide use of aryl bromides in cross-coupling reactions, aryl iodides are dominatingly used in the Pd/NBE chemistry. Such a constraint could be attributed to the slower oxidative addition of Pd(0) with aryl bromides or triflates, which makes external electrophiles more competitive for oxidation with Pd(0).

In the case of *ortho* alkylation reactions, two Type C intramolecular couplings (**161** and **163**) have been reported using aryl bromides as substrates (Scheme 87).[83,124] The

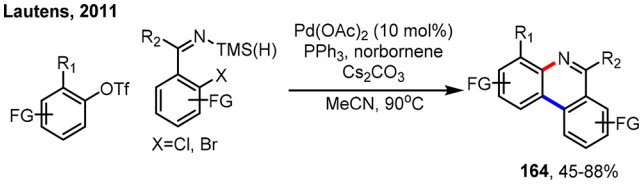
Scheme 87. *Ortho* Alkylation/Type C Intramolecular Couplings of Aryl Bromides



efficiencies were generally lower than the corresponding aryl iodides. Another special example was reported in the case of the *ortho* amination reaction (**162**), where the use of Ag_2CO_3 as the additive and dppe as the ligand were important for the success of the reaction.[179]

Using aryl bromides or triflates in *ortho* arylation appears to be harder due to the selectivity issue in the initial oxidative addition of Pd(0). In 2011, Lautens and co-workers demonstrated the first example of using aryl triflates in the *ortho* arylation/*ipso* C–N coupling (Scheme 88) and applied this reaction in the

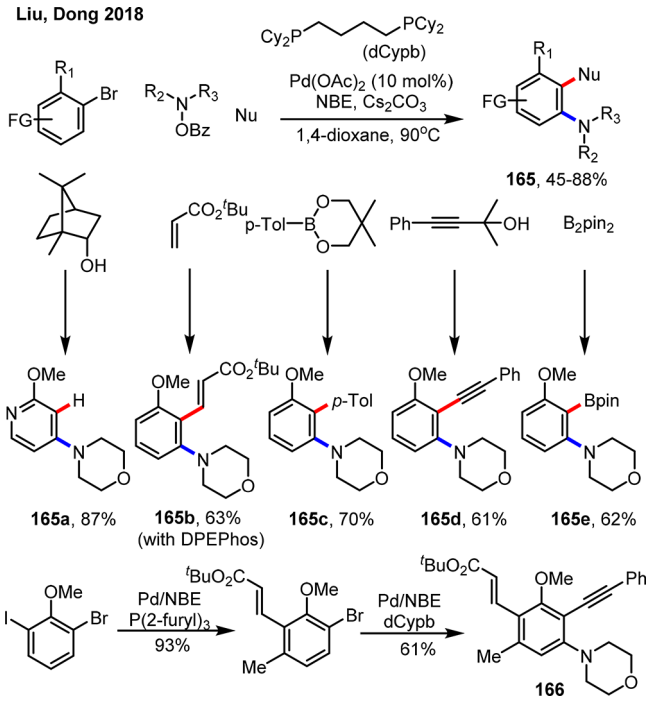
Scheme 88. *Ortho* Arylation of Aryl Triflates



synthesis nitidine and NK109 (see section 4.1).[205] Remarkable selectivity was observed in this reaction, though the exact reason is unclear. In a similar endeavor, Maestri and Malacria reported their synthesis of this class of products through coupling of aryl triflates with bromobenzylamines.[206]

In 2018, the Liu and Dong groups systematically studied the use of aryl bromides in the Pd/NBE catalysis, particularly in the intermolecular settings (Scheme 89).[207] Bidentate phosphines with a flexible backbone (e.g., dCypb and DPEPhos) were found

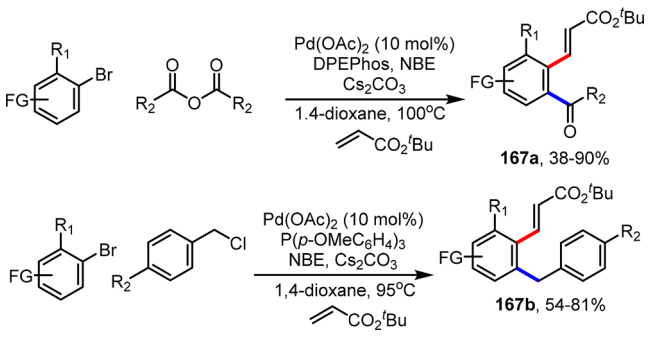
Scheme 89. *Ortho* Amination of Aryl Bromides



to generally give higher yields. The DFT study suggested that the use of flexible bidentate ligands not only accelerated the oxidative addition into aryl bromides, but also facilitated the NBE extrusion step. Different *ipso* termination reactions, including hydrogenation (**165a**), borylation (**165e**), Heck (**165b**), Suzuki–Miyaura (**165c**), and Sonogashira (**165d**) couplings, have been demonstrated to be effective with various aryl and heteroaryl bromides. The availability of this method allowed for two consecutive Pd/NBE-catalyzed difunctionalizations to construct penta-substituted aromatic compounds (**166**). Other *ortho* functionalizations, such as acylation (**167a**) and alkylation (**167b**), have also been achieved using aryl bromides as substrates (Scheme 90).

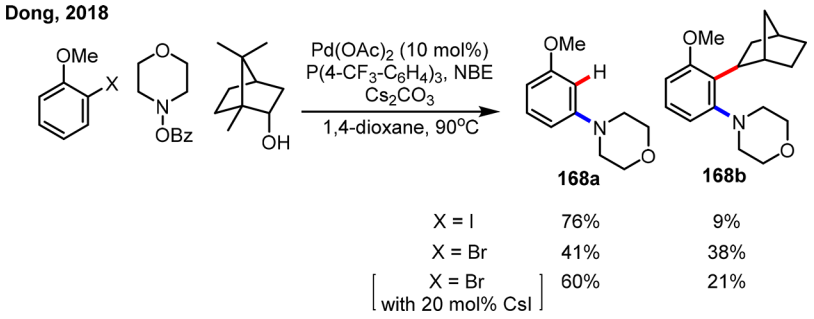
Beside the difficulty in achieving selective oxidative addition of Pd(0) with aryl bromides, the steps after *ortho* functionalizations could also be affected due to the presence of different halide anions. It was found that the ratio between products **168a** and **168b** depended on the halogen substitution of the substrate (Scheme 91).[207] The aryl bromide gave more premature

Scheme 90. Other *Ortho* Functionalizations of Aryl Bromides



DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478–7528

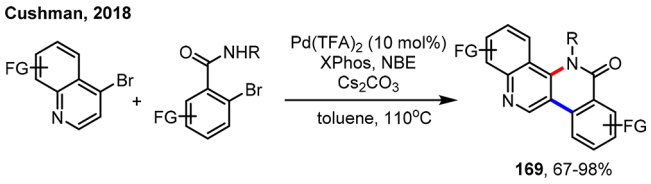
Scheme 91. Halide Effect in the Pd/NBE Catalysis



termination product (**168b**) than the aryl iodide. Interestingly, the addition of 20 mol % CsI improved the selectivity for the desired product (**168a**), which indicated that the halide anion might influence the steps after the *ortho* amination with ANP. Later, the Della Ca' group also observed that the presence of potassium iodide was crucial for improving the yield with aryl bromides.[208]

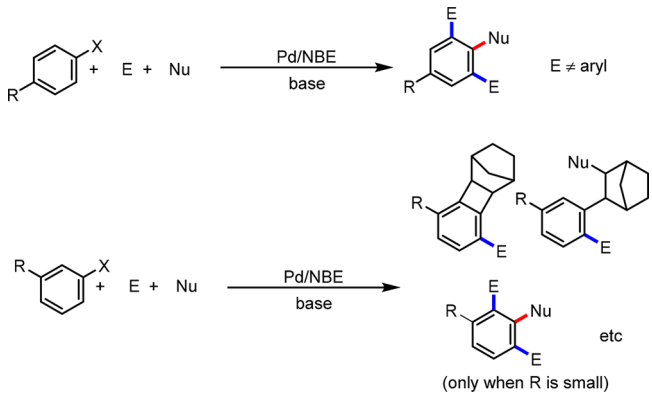
Very recently, Cushman disclosed the synthesis of benzo[1,6]naphthyridinones from 4-bromoquinolines (Scheme 92).[209] Less than 2% of the product was obtained in the absence of NBE, suggesting that this reaction went through an *ortho* arylation pathway. Interestingly, although two aryl bromides were used, the self-dimerization of *o*-bromobenzamides did not take place.

Scheme 92. Synthesis of Benzo[1,6]naphthyridinones from 4-Bromoquinolines



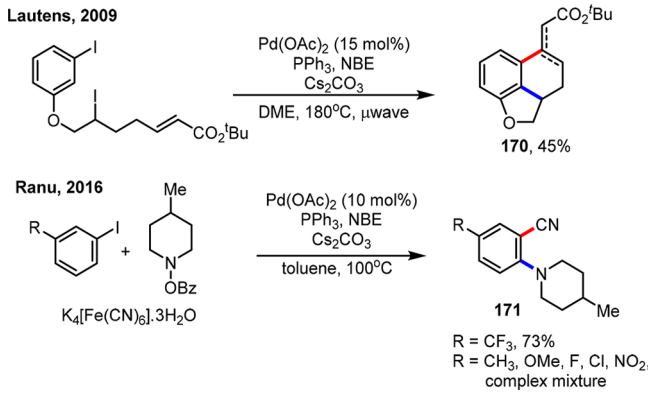
3.2.7. The "*Ortho* Constraint" and Development of Bridgehead-Substituted NBEs. One long-standing limitation in the Pd/NBE catalysis is the requirement of an *ortho* substituent in aryl halide substrates in order to achieve mono *ortho* functionalization. Generally, if *ortho* unsubstituted aryl iodides are employed, mono *ortho* functionalized products cannot be obtained, but instead, either NBE-containing side-products or bis-functionalized products would be formed (Scheme 93). This phenomenon is termed as the "*ortho* constraint".[160] To be more specific, if *para*-substituted aryl iodides were used, bis-*ortho*-functionalized products were usually the major products for the *ortho* alkylation,[58] amination,[179] acylation,[193] and alkoxycarbonylation reactions.[204] As a special case, the *ortho* arylation reactions would be more complicated due to the aforementioned selectivity problem on Ar−Ar vs Ar−norbornyl couplings, also known as the "*ortho* effect" (*vide supra*, section 3.2.2.2). As for the *meta* substituted aryl iodides, if the *meta* substituent is small (e.g., a methoxy group), bis-*ortho*-functionalized products could sometimes be observed.[81] In other cases, NBE-containing side-product(s) caused by unsuccessful β-carbon elimination were usually formed.[88,160] The origin of such an "*ortho* constraint" is closely related to the aforementioned early finding by Catellani that the NBE extrusion only occurred easily when both *ortho* substituents were present.[46]

Scheme 93. "*Ortho* Constraint" in the Pd/NBE Catalysis



Yet, there were still some special cases when such an "*ortho* constraint" was not obeyed (Scheme 94). The first example was reported in 2009,[120] where Lautens successfully employed *ortho*-unsubstituted aryl iodides in a Type D intramolecular reaction (**170**). This experiment showed that, under certain reaction conditions, NBE extrusion could occur with only one *ortho* substituent present. NBE extrusion could be described as a thermodynamically unfavorable but kinetically feasible process; thus, the equilibrium could be shifted if a facile intramolecular termination step is present. For the same reason, the use of bifunctional reagents also led to the success in two other special cases (*vide supra*, **76b** and **97b** in Schemes 43 and 54, respectively).[96,135] However, the success of this approach is largely relied on the structure of bifunctional reagents, and in many other cases, bifunctional reagents could not afford the desired products for *ortho*-unsubstituted aryl iodides. For

Scheme 94. Violation of the "*Ortho* Constraint" in Special Cases

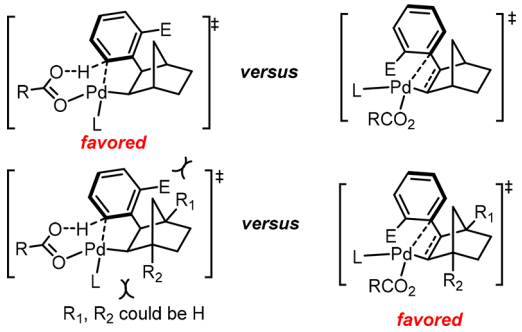


DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

intermolecular *ipso* couplings, Ranu and co-workers reported a single example of using *meta*-CF_3-substituted iodobenzene in a successful *ortho* amination reaction (**171**).[185] In contrast, other *meta* substituents gave a mixture of products. It is noteworthy that such *meta*-CF_3-substituted aryl halides were not always successful in other Pd/NBE-catalyzed transformations.[204,207]

The cause for the "*ortho* constraint" is attributed to a facile second C−H metalation instead of *β*-carbon elimination. Aiming to develop a general catalyst-controlled approach to address the "*ortho* constraint", the Dong group in 2018 designed and synthesized a class of bridgehead-substituted NBEs (Scheme 95).[160] The hypothesis was that, by installing proper group(s) at C1 bridgehead position(s), the steric repulsion between R_1 and E and/or between R_2 and L would destabilize the transition state for the second C−H metalation and meanwhile the *β*-carbon elimination can be promoted through controlling the orientation of the aryl group to form the η^1 complex.

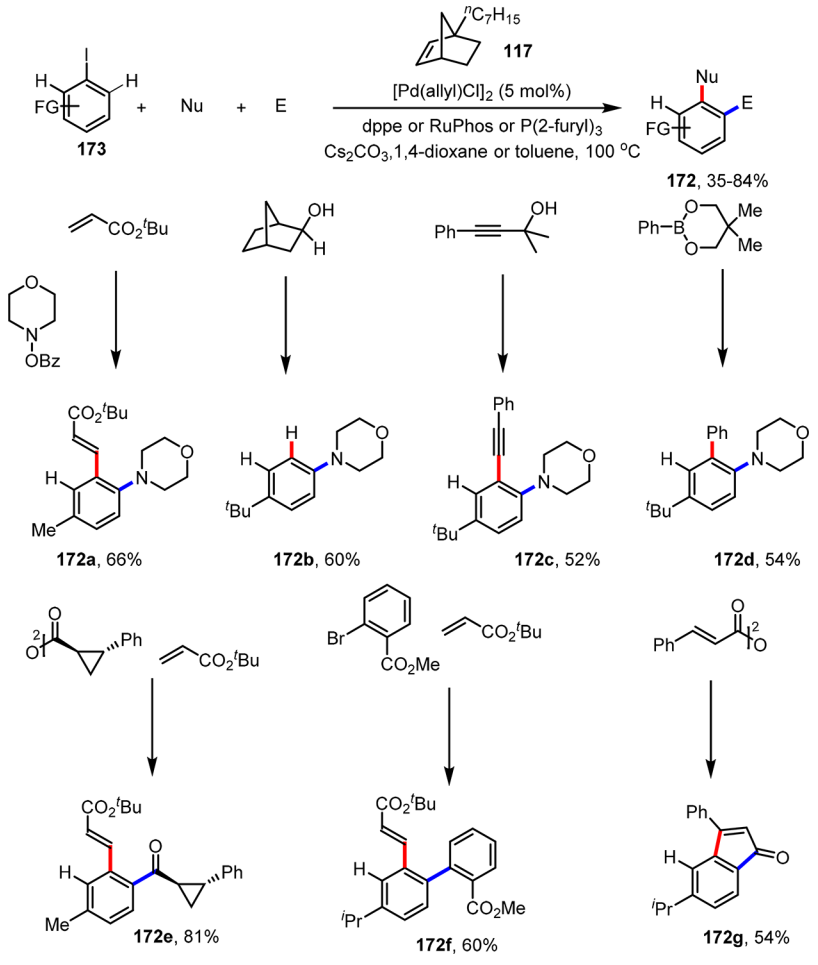
Scheme 95. Controlling Relative Rates for C−H Metalation versus *β*-Carbon Elimination Using Modified NBEs



Alkyl C1-substituted NBE **117** was found to be most selective and reactive. A range of *ortho*-unsubstituted aryl iodides, previously problematic substrates, can now be employed to provide mono *ortho*-functionalized products effectively. Such bridgehead-substituted NBEs proved to be general in various *ortho*/*ipso* bis-functionalizations (Scheme 96). Different *ipso* terminations, like Heck coupling (**172a**), hydrogenation (**172b**), Sonogashira coupling (**172c**), and Suzuki−Miyaura coupling (**172d**), can be employed. Besides *ortho* amination, *ortho* acylation (**172e**) and arylation (**172f**) can also be achieved. The same group also used such C1-substituted NBE **117** for the annulation reaction to synthesize indenone (**172g**), where the simple NBE failed to deliver the desired product.[202]

Para-substituted aryl iodides and simple iodobenzene are more challenging substrates to give mono *ortho* functionalization due to a fast second C−H metalation step. In this case, the double bridgehead-substituted NBE afforded the desired products in high mono/di-selectivity (Scheme 97). The DFT calculation supports the effect of the presence of bridgehead substituents in NBE in retarding the second C−H metalation step while promoting the *β*-carbon elimination step. Mono *ortho*

Scheme 96. Mono *Ortho* Functionalization of Aryl Iodides without *Ortho* Substituents



DOI: 10.1021/acs.chemrev.9b00079
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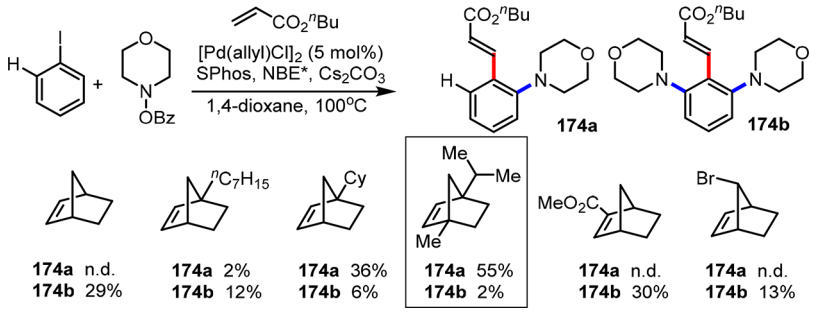
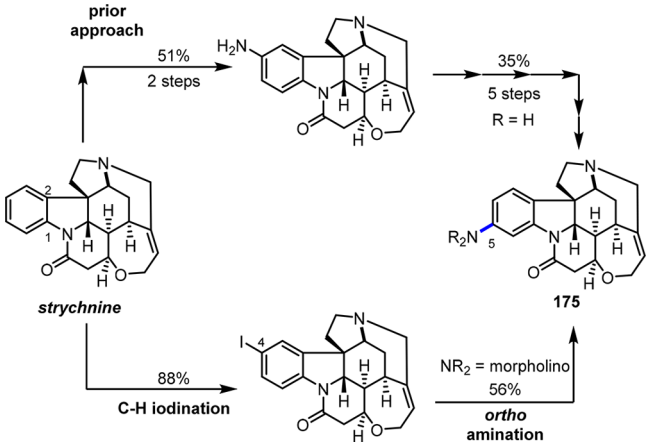
Scheme 97. Mono *Ortho* Functionalization of Iodobenzene



functionalization of *para*-substituted aryl iodides with electron-donating or withdrawing groups (EDGs or EWGs) has also been demonstrated.

The synthetic utility of this method was illustrated in the arene functionalization at the site complementary to the EAS reactions. A sequence of electrophilic iodination followed by *ortho* functionalization allowed for installing FGs at positions *para* to EWGs or *meta* to EDGs. For example, site-selective amination of strychnine at the C5 position was achieved in two steps (**175**), while the conventional approach required a seven-step sequence (Scheme 98).[210]

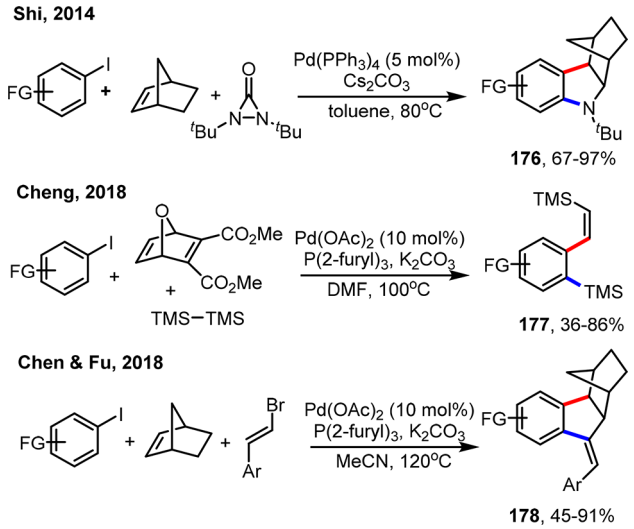
Scheme 98. Complementary Functionalization of Strychnine



3.2.8. Other Types of *Ortho* Functionalizations. Sometimes even though the external electrophile could selectively react with the ANP intermediate, NBE might still get stuck into the product when the side-reaction pathways are faster than the desired β-carbon elimination reaction. In these cases, NBE functions as a reactant instead of a catalyst. In addition, since NBE is not extruded during the reaction, the *ortho* substituent of aryl halides is generally not required. Though strictly speaking these reactions do not fall into the category of the Pd/NBE cooperative catalysis, they are still discussed here due to the relevance of the reaction pathways.

In 2014, Shi and co-workers reported an *ortho* amination reaction using diaziridinones as the external electrophile (Scheme 99).[211] In their proposed mechanism, the ANP intermediate undergoes oxidative addition with diaziridinones, which subsequently releases *tert*-butyl isocyanate (^{t}BuNCO) to form the indoline structure (**176**). If norbornadiene was used instead, the products could be further transformed into indoles through a retro-Diels–Alder reaction. Later, it was shown that the use of anilines or ureas could lead to similar products.[212]

Scheme 99. Other Types of *Ortho* Functionalizations of Aryl Iodides



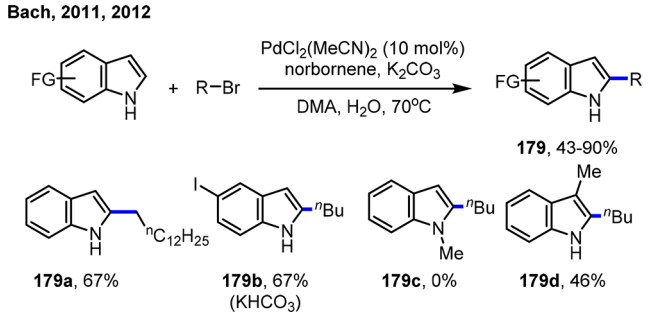
Recently, disilanes was also found to be able to intercept the ANP intermediate by the Zhang,[213] Cheng,[56,214] and Liang[215] groups. Due to the facile C–Si reductive elimination, NBE-containing bis-silylated products were obtained. Interestingly, if 2,3-dicarbomethoxy-7-oxanorbornadiene was used instead of NBE, retro-Diels–Alder reaction occurred to give **177** as the final products. When vinyl bromides were utilized as the electrophiles, an intramolecular Heck reaction instead of NBE extrusion led to products **178**, after the *ortho* alkenylation step.[216]

3.3. Catalytic Reactions Initiated by Pd(II)

3.3.1. N–H Bond Activation-Initiated 2-Functionalization of Indoles. In 2011, Jiao and Bach reported a Pd/NBE-catalyzed C2-alkylation of unprotected indoles with alkyl bromides, which represents the first Pd(II)-initiated Pd/NBE-catalyzed reaction (Scheme 100).[217] The reaction is highly regioselective and unprotected indoles were used directly as substrates. Addition of water greatly enhanced the reaction rate. The major side reactions were base-mediated formation of *N*- or 3-alkylindoles; thus, a weaker base, e.g., K_2CO_3, was found to be more effective than Cs_2CO_3. $KHCO_3$ could also be used when more acidic indoles were employed as substrates (**179b**). The reaction was sensitive to steric hindrance of the alkyl bromides, and secondary alkyl bromides did not react. Aryl bromides and aryl iodides (**179b**) were tolerated because Pd(0) was in principle not involved. The *N*-methylindole failed to give any product (**179c**), while 3-methylindole exhibited moderate

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478–7528

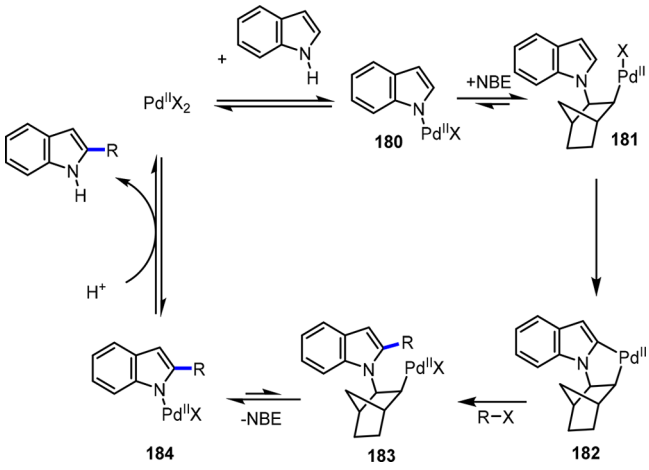
Scheme 100. 2-Alkylation of Indoles via Pd/NBE Catalysis



reactivity (**179d**).[218] This method has been successfully applied in various natural product syntheses (see section 4.1).

Regarding the proposed catalytic cycle, the reaction is initiated by Pd(II)-mediated N−H activation of indole, followed by NBE insertion and C2-palladation to give the key pallacycle intermediate (**182**) (Scheme 101).[218] Oxidative addition of **182**

Scheme 101. Catalytic Cycle for 2-Alkylation of Indoles

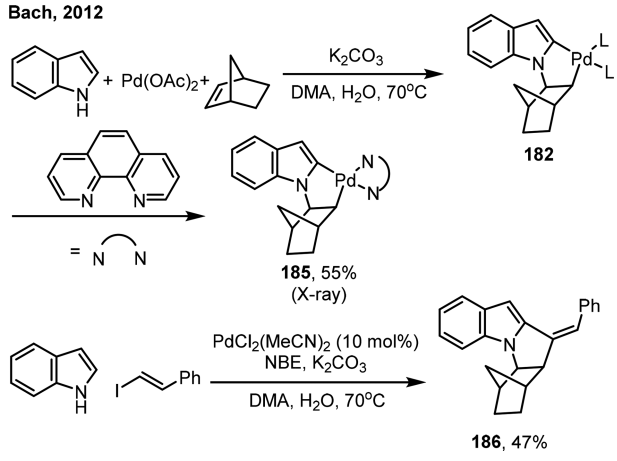


with alkyl bromide, followed by reductive elimination and NBE extrusion, would afford intermediate **184**, which then undergoes protodepalladation to afford the 2-alkylindole product and regenerate the Pd(II) catalyst. The structure of such a five-membered palladacycle was unambiguously prepared and characterized by single crystal X-ray crystallography (Scheme 102). In addition, such a structure could be trapped using *β*-iodostryene as the electrophile (**186**) (*vide supra*, Scheme 99).

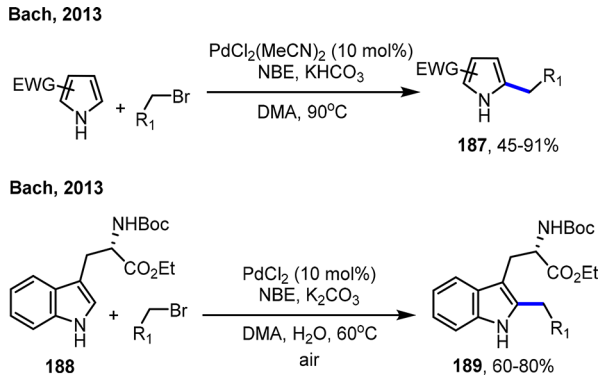
In 2013, Bach developed the 2-alkylation of electron-deficient pyrroles (Scheme 103).[219] Given that pyrroles are generally more electron-rich and less acidic than indoles, electron-withdrawing substituents were necessary for this reaction. In this case, addition of water did not significantly affect the yield. They further achieved C2 alkylation of Boc-protected tryptophan (**189**).[220] The presence of air seemed to be advantageous in this case as it prevented reduction of Pd(II) to Pd(0).

Besides alkylation, one example using iodobenzene as the external electrophile was reported by Bach for C2-arylation of indoles (Scheme 104).[217] In 2017, Jiang and Xue further extended the substrate scope for this reaction.[221] Iodobenzene gave a higher yield than bromobenzene, and chlorobenzene was unreactive. Unlike the Pd(0)-initiated cross arylation reactions, electron-deficient aryl electrophiles were not required, although

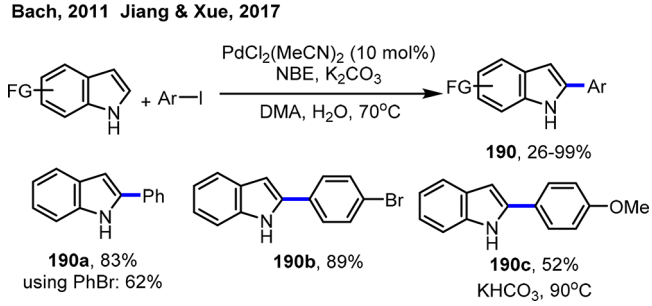
Scheme 102. Evidence for the Formation of the *N*-NBE Type Palladacycle



Scheme 103. Reaction Extension to 2-Alkylation of Pyrroles and Indoles



Scheme 104. 2-Arylation of Indoles via the Pd/NBE Catalysis



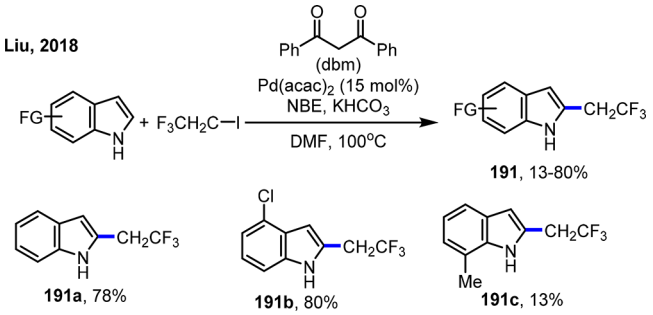
they would generally give higher yields than the more electron-rich ones.

In 2018, the Liu group reported a related C2 trifluoroethylation of indoles owing to the interest of 2-trifluoroethylindole moieties in medicinal chemistry (Scheme 105).[222] Dibenzoylmethane (dbm) was found to be the most effective ligand. The reaction tolerated different substitutions in the indole ring (**191a,b**), but having a substitution at the C7 position (**191c**) or an EWG at the C3 position significantly reduced the reactivity. The utility of this transformation was demonstrated in the late-stage trifluoroethylation of some bioactive molecules.

3.3.2. C−H Bond Activation-Initiated *Meta* Functionalization of Arenes Using a Directing Group. *3.3.2.1. Meta-Arylation and Alkylation of Arenes.* As described

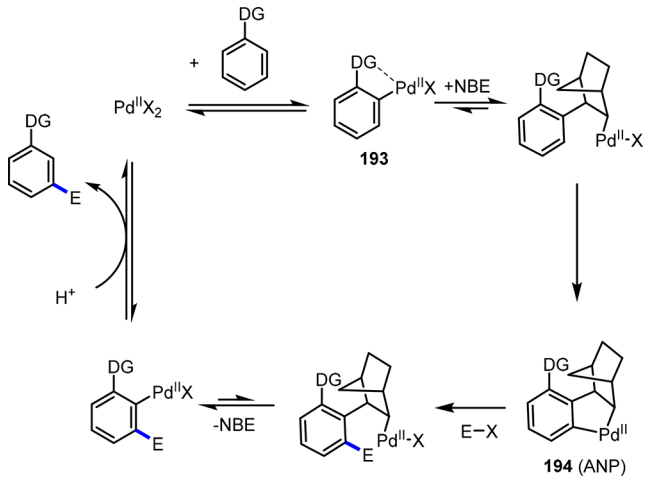
DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 105. 2-Trifluoroethylation of Indoles via Pd/NBE Catalysis



in the general catalytic cycle (Scheme 14), the aryl-Pd(II) intermediate (**38**) can not only be generated from oxidative addition with ArX but also come from a directed *ortho* palladation process, which is present in numerous Pd-catalyzed *ortho*-functionalizations of arenes. In 2015, the Yu[223] and Dong[224] groups independently reported the Pd/NBE-catalyzed *meta*-selective arene C−H activation reactions using *ortho*-DGs (Scheme 106). In this transformation, NBE relays the palladium

Scheme 106. General Reaction Pathway for the *Meta*-Functionalization of Arenes Using *Ortho*-DGs

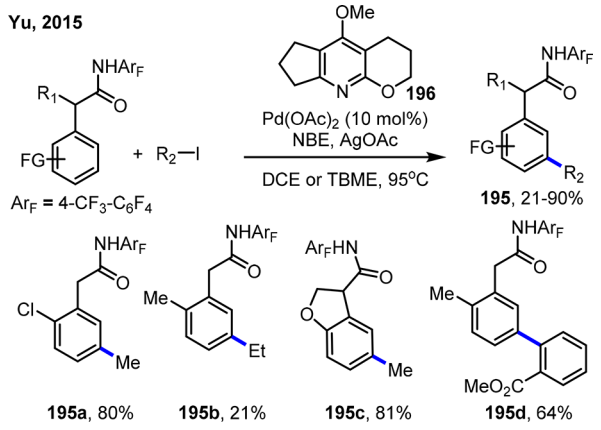


from the initial *ortho* position to the *meta* position; upon *meta* functionalization with an electrophile and NBE extrusion via *β*-carbon elimination, the resulting aryl-Pd(II) species undergoes protodepalladation (the reverse process of *ortho* palladation) to generate the Pd(II) catalyst. Based on such a catalytic cycle, the nature of the *ortho* DG is expected to play a critical role because it needs to be strong enough to direct *ortho* palladation but not too strong to inhibit NBE insertion and protodepalladation.

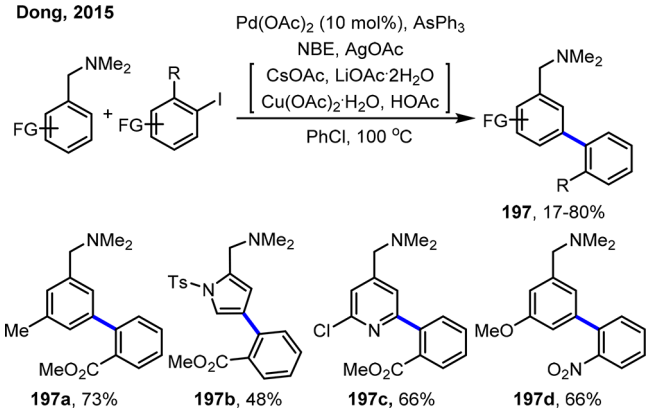
In 2015, Yu and co-workers reported the *meta*-selective C−H alkylation and arylation using an amide DG (Scheme 107).[223] The pyridine-type ligand **196** was found most efficient. Different alkyl halides without *β*-hydrogens could be smoothly coupled, such as methyl iodide (**195a**), ethyl iodoacetate and benzyl bromides. Ethyl iodide gave a low yield (**195b**). *Meta*-methylation of dihydrobenzofurans was also effective (**195c**). A *meta* arylation method was also successfully developed using electron-deficient aryl iodides with an *ortho* chelating group (**195d**) or multiple electron-withdrawing groups.

Concurrently, the Dong group developed the *meta* arylation of *N*,*N*-dialkyl benzyl amines (Scheme 108).[224] Under mildly

Scheme 107. *Meta*-Alkylation/Arylation of Phenylacetic-Acid-Derived Amides



Scheme 108. *Meta*-Arylation of Simple Tertiary Benzyl Amines

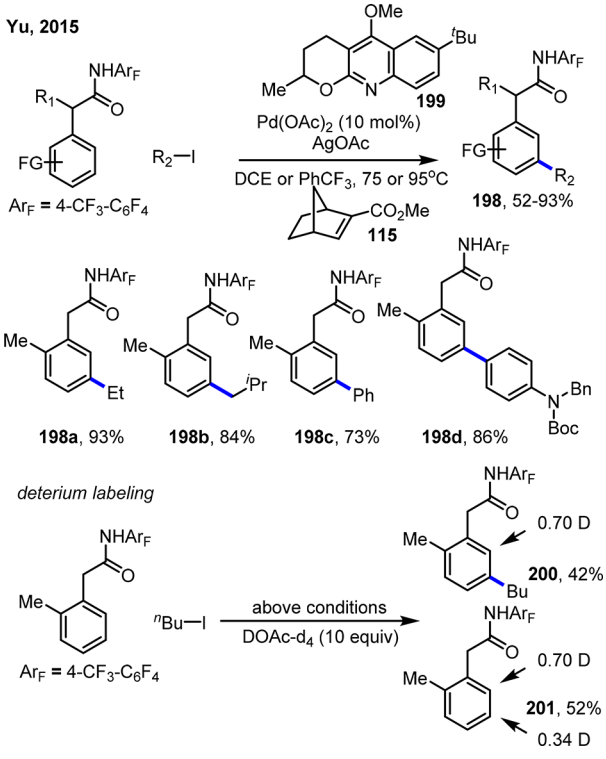


acidic conditions, the dimethylamine moiety can direct reversible *ortho* metalation; such a DG could be easily installed and transformed into other FGs, such as benzyl chloride or aldehyde. $AsPh_3$ was used as the ligand along with a "cocktail" of acetate salts. Heteroarene substrates, such as pyrrole **197b** and pyridine **197c**, were also amenable to this transformation. *Ortho* chelating groups were needed in the aryl iodide part to facilitate the oxidative addition with ANP.

Alkyl halides with *β*-hydrogens and aryl iodides without *ortho* coordinating groups were problematic electrophiles because reductive elimination from the ANP intermediate to form the norbornyl benzocyclobutene would become the major competitive pathway. To address the scope limitation, the Yu group found 2-carbomethoxy-substituted NBE **115** could effectively suppress formation of the benzocyclobutene side-product (Scheme 109).[159] Together with an elaborated quinoline ligand **199**, alkyl halides with *β*-hydrogens (**198a** and **198b**) and regular aryl iodides without *ortho* coordinating groups (**198c** and **198d**) were successfully coupled. Yet, the extension to heterocycles was unsuccessful under these conditions. When the reaction was performed in the presence of 10 equiv of deuterated acetic acids, the observed 70% D-incorporation at the *ortho* position is consistent with the protodepalladation pathway. Interestingly, both *ortho* and *meta* positions were deuterated in the recovered starting material, indicating the reversibility of the *meta*-C−H activation step.

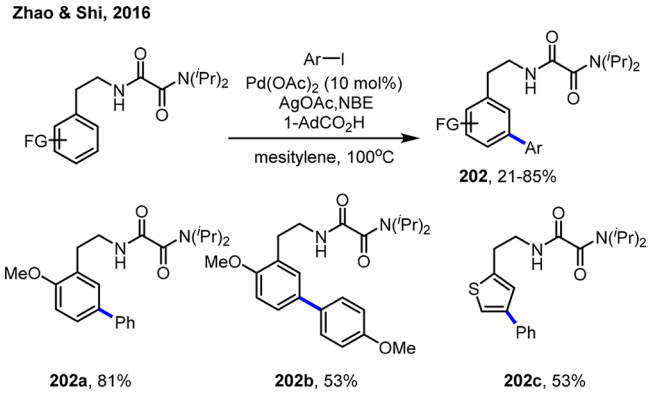
DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 109. Expanding Scope of *Meta*-Alkylation/Arylation with a Modified NBE



In 2016, Zhao and Shi reported an interesting *meta* arylation of oxalyl amide-protected *β*-arylethylamines (Scheme 110).[225]

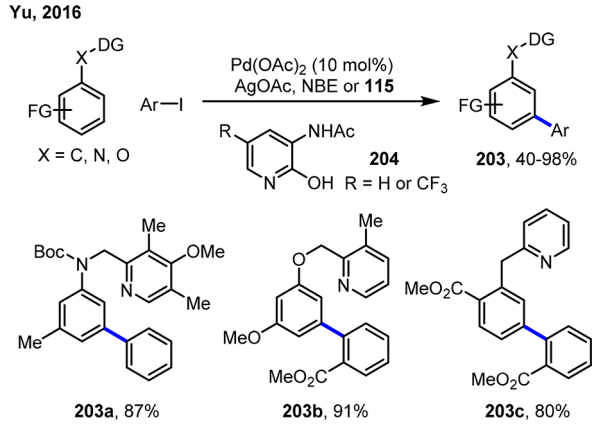
Scheme 110. *Meta*-Arylation of Oxalyl Amide-Protected *β*-Arylethylamines



It was demonstrated that aryl iodides without *ortho* chelating groups could be coupled with regular NBE. Remarkably, electron-rich aryl iodides could also be coupled (**202b**), albeit in a moderate yield. *Meta*-arylation of thiophenes (**202c**) was also successful. Although the exact reason is unclear, the unique DG employed here and/or the absence of ancillary ligands might play a key role in promoting the desired arylation instead of forming the benzocyclobutene side-product.

To expand the types of DGs that can be employed, the Yu group developed a versatile 3-acetylamino-2-hydroxypyridine class of ligands (**204**) to achieve *meta* arylation of a wide range of substrates, including aniline, phenol, and 2-benzyl heterocycle derivatives (Scheme 111).[226] These DGs allowed for forming 6- or 7-membered palladacycles. The utility was demonstrated in

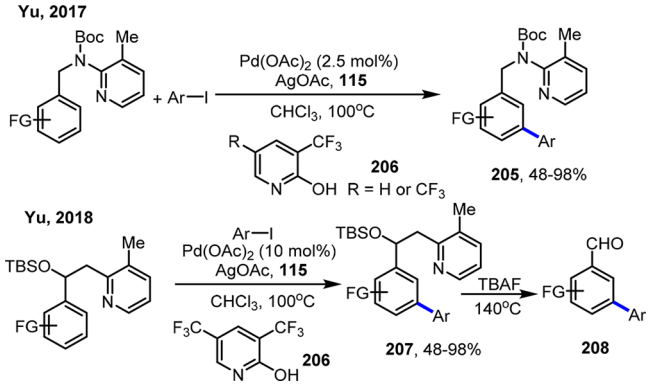
Scheme 111. *Meta*-Arylation of Anilines, Phenols, and Heterocycles with Pyridine-Type DGs



the *meta* arylation of a lenalidomide-derived substrate. In addition, silver-free conditions were also established using CsOAc in place of AgOAc in *t*-Amyl−OH.

The Yu group further found that electron-deficient 2-pyridone **206** can effectively promote *meta* C−H arylation with pyridine-based DGs (Scheme 112),[227,228] which likely

Scheme 112. *Meta*-Arylation of Benzylamines and Protected Aldehydes with Pyridine-Type DGs



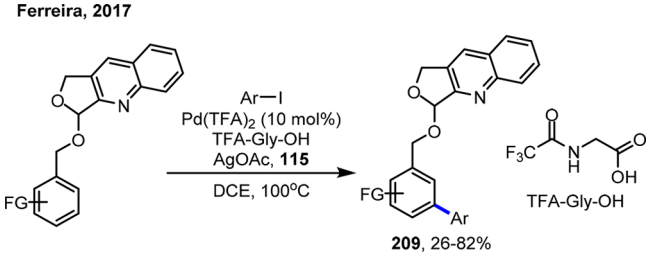
served as an efficient X-ligand to promote the CMD process.[229] The ring size of the initially formed palladacycle was found to be crucial for the success of this reaction: while 6- or 7-membered palladacycles could engage in the following steps under these conditions, 5-membered palladacycles were found to be too stable to react. This represents a difference from Dong's benzylamine system (*vide supra*, Scheme 108).

In 2017, Ferreira and co-workers used quinoline-derived DGs to realize *meta* C−H arylation of masked benzyl alcohols with 2-carbomethoxy-substituted NBE **115** (Scheme 113).[230] Different from Yu's system, TFA-Gly-OH performed better than the 2-pyridione-type ligands. Notably, the DG can be easily cleaved under acidic conditions to generate free benzyl alcohols.

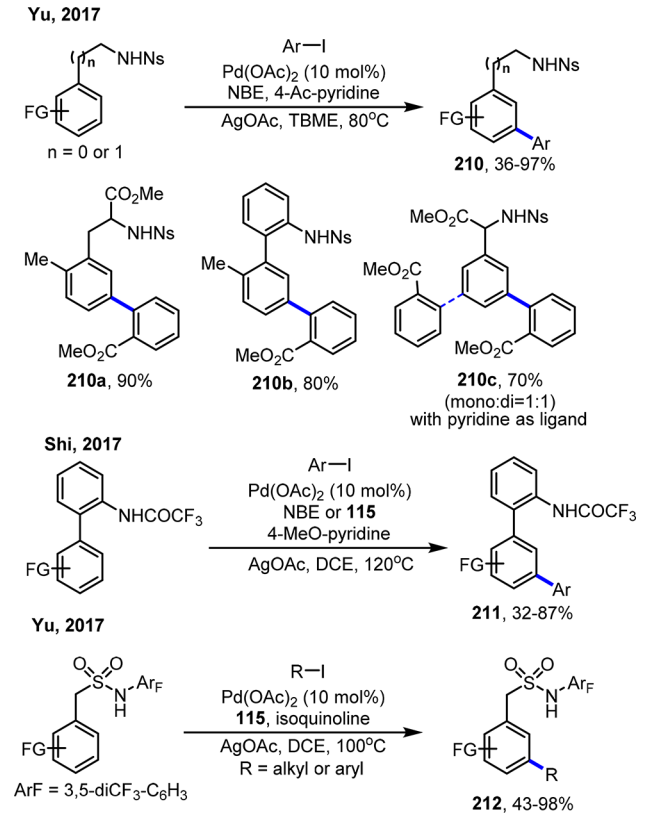
In 2017, Yu and co-workers found that nosyl-protected amines can serve as excellent DGs (Scheme 114).[231] 4-Acetylpyridine was identified to be the optimal ligand, and simple NBE was used in a catalytic amount. Nosyl-protected phenethylamines (**210a**), 2-aryl anilines (**210b**), and benzylamines (**210c**) were all suitable substrates. Similar to the Zhao and Shi's case (*vide supra*, Scheme 110), aryl iodides without *ortho* chelating groups could be coupled but less effectively. In

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 113. *Meta*-Arylation of Benzyl Alcohol with Quinoline-Type DG



Scheme 114. *Meta*-Arylations with the Amide-Type DG

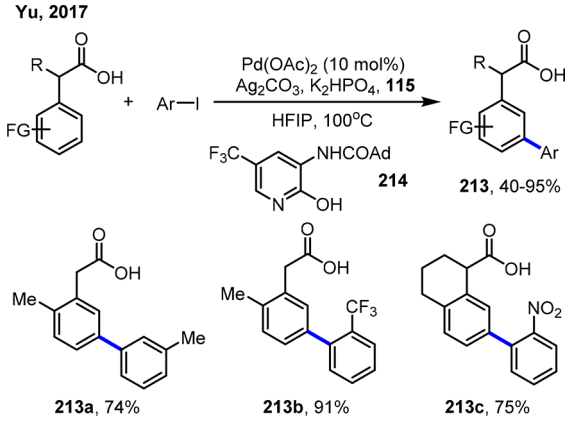


addition, aryl bromides with *ortho* chelating groups could be used. *Meta* C−H alkylation of nosyl-protected benzylamines was later reported by Ding and co-workers.[232] Almost simultaneously, Shi reported *meta*-arylation using trifluoroacetyl-protected 2-aryl anilines as the DG with 4-methoxypyridine as the ligand and 2-carbomethoxy-substituted NBE **115** as the cocatalyst (**211**).[233] Later in 2017, Yu described the use of benzylsulfonamides as the DG in the Pd/NBE-catalyzed *meta* C−H arylation and alkylation with isoquinoline as the ligand.[234] A broad range of alkyl and aryl iodides as electrophiles has been demonstrated.

In the same year, the use of carboxylic acids as the DG in the *meta* C−H arylation was reported by the Yu group (Scheme 115).[235] Substituted 2-pyridone **214** proved to be the best ligand, which was found to accelerate the *ortho* C−H activation step. Note that noncoordinating *ortho* substituents in the aryl iodides were compatible in this transformation (**213b**).

In 2018, Yu reported the first example of enantioselective *meta* C−H arylation and alkylation using a chiral NBE cocatalyst (Scheme 116).[236] With diarylmethylamines as the model

Scheme 115. *Meta*-Arylations of Phenylacetic Acids



substrate, chiral phosphoric acid (*R*)-BNDHP (1,1′-binaphthyl-2,2′-diyl hydrogen phosphate) was used as an additive. Control experiments suggested that chiral NBE (+)-**115** was responsible for the chiral induction while the chiral acid has a minor beneficial effect. A broad aryl iodide scope (**215a** and **215b**) and good FG tolerance (**215c** and **215d**) were observed. Asymmetric *meta* C−H arylation and alkylation of nosyl-protected homobenzylamines were also achieved (**216**), through either desymmetrization or kinetic resolution. Parallel KIEs were measured to be 1.03 and 1.33 for *ortho* and *meta* C−H bonds, respectively, indicating that neither C−H bond cleavage was the rate-determining step. The reaction rate was first order on [Ar−I], indicating that the reaction of ANP with aryl iodides was likely the rate-determining step.

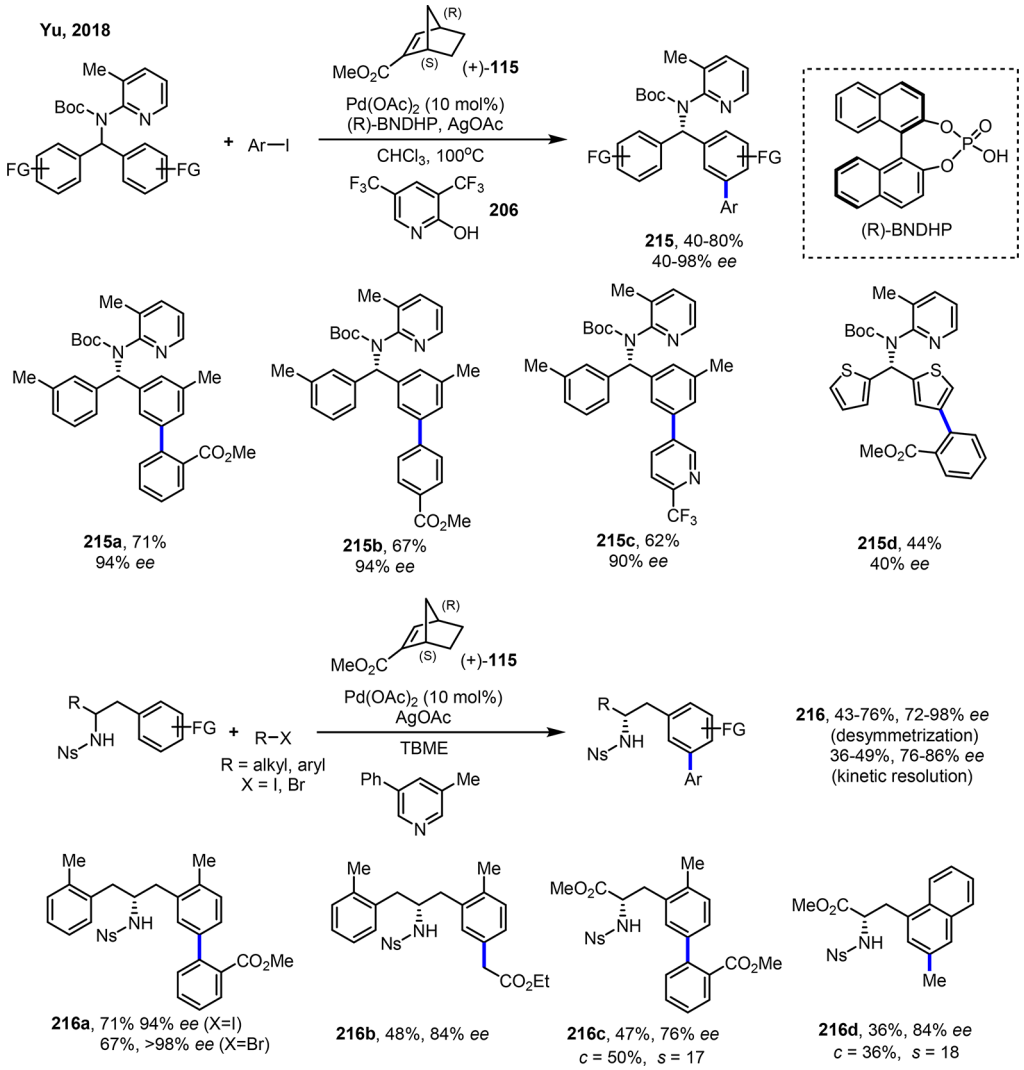
3.3.2.2. Meta-Amination, Alkynylation, and Chlorination of Arenes. Besides arylation and alkylation, other types of *meta* functionalizations have also been demonstrated. In 2016, Yu and co-workers achieved *meta* amination of aniline and phenol derivatives by using *O*-benzoylhydroxylamines as the electrophile (Scheme 117).[237] The synthetic utility was demonstrated in the synthesis of 3-fluoro-5-morpholinoaniline, which was the synthetic intermediate of a BRAF inhibitor. In 2017, a single example of *meta* amination of a benzyl amine derivative was reported using similar conditions.[227]

Since the reaction is not initiated by a Pd(0)-mediated process, there is less limitation on using stronger electrophiles. Though alkynyl bromides and aryl chlorosulfates have not been used as electrophiles in the Pd(0)-initiated Pd/NBE catalysis, the corresponding *meta* alkynylation and chlorination have been successfully demonstrated by Yu and co-workers (Scheme 118).[238,239] The *meta* alkynylation required bulky silyl-protected alkynyl bromides, while alkyl or aryl alkynyl bromides were not effective. For the *meta* chlorination, the use of less electrophilic aryl chlorosulfates was important, while *N*-chlorosuccinimide (NCS) only gave *ortho* chlorination products. In 2017, a single example of *meta* chlorination of a benzyl amine derivative was reported under similar conditions.[227]

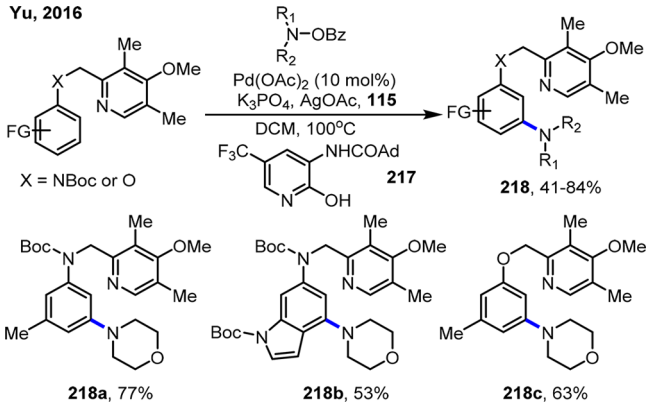
3.3.3. Transmetalation-Initiated *Ortho* Functionalization of Arylboron Species. Besides oxidative addition of aryl halides to Pd(0) and directed C−H activation of arenes, another way to generate the aryl-Pd(II) species (**38**) in the general catalytic cycle (*vide supra*, Scheme 14) is through a transmetalation process from aryl nucleophiles to Pd(II) (Scheme 119). In 2018, Zhang[240] and Zhou[241] independently reported the Pd/NBE-catalyzed *ortho* alkylation/*ipso* Heck reaction using arylboron species as substrates (Scheme 120). In Zhang's

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

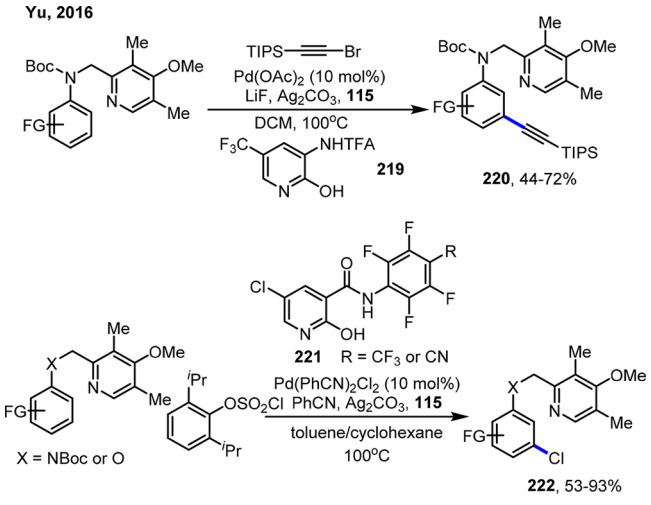
Scheme 116. Enantioselective Remote *Meta* C−H Arylation and Alkylation of (Homo)Benzylamines with Pyridine-Type DGs



Scheme 117. *Meta*-Amination of Anilines and Phenols with Pyridine-Type DGs



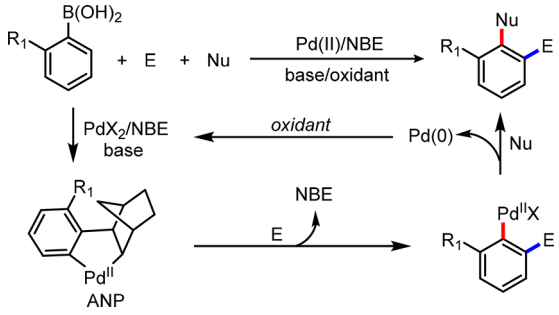
Scheme 118. *Meta*-Alkynylation and Chlorination with Pyridine-Type DGs



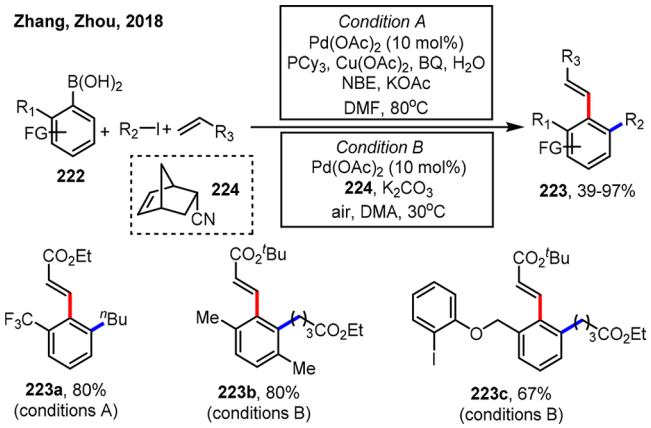
reactions, arylboronic acids were used and the Pd(0) generated from the Heck termination was oxidized back to Pd(II) using $Cu(OAc)_2$ as the stoichiometric oxidant. Zhou and co-workers employed a phosphine ligand-free open-flask condition, in which air was used as the terminal oxidant to regenerate Pd(II) from Pd(0). Thus, both systems need stoichiometric bases during the termination step. In Zhou's reaction, 5-NBE-2-carbonitrile **224** was identified to be more effective than simple NBE; both arylboronic acids and pinacol boronates were

DOI: 10.1021/acs.chemrev.9b00079
Chem. Rev. 2019, 119, 7478−7528

Scheme 119. Transmetalation-Initiated Pd/NBE Catalysis



Scheme 120. Oxidative *Ortho* Alkylation/*Ipso* Heck Reaction of Arylboronic Acids

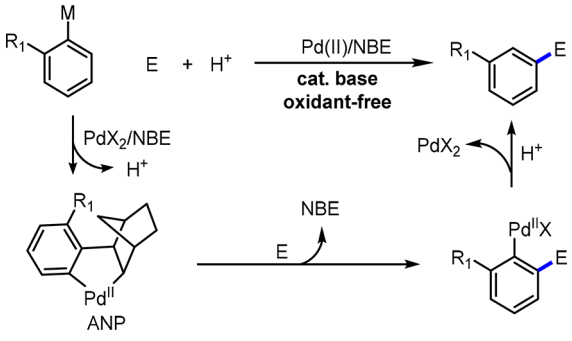


suitable substrates. Similar to the aforementioned C−H activation-initiated processes, aryl iodides were also tolerated in the transmetalation-based reactions. In both systems, arylboronic acids without *ortho* substituents gave bis-alkylation products.

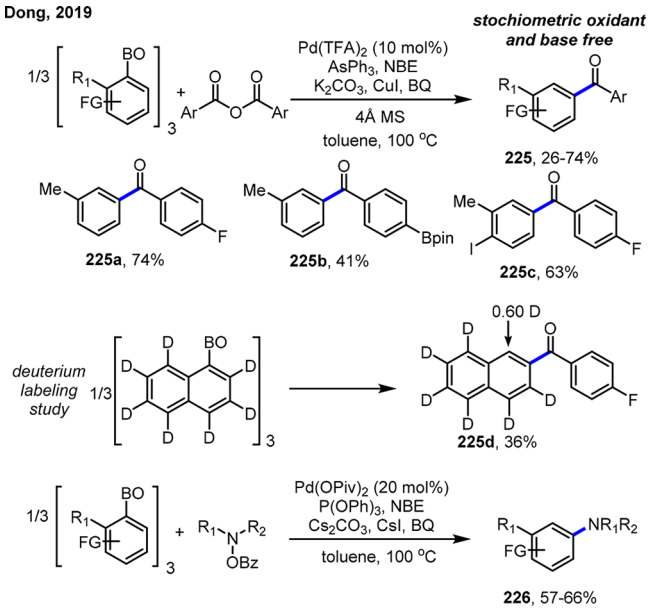
In the transmetalation-initiated process, one could imagine that, instead of terminating the aryl-Pd(II) species with an nucleophile (or an olefin) and then reforming the Pd(II) catalyst through oxidizing the resulting Pd(0) intermediate, an alternative pathway involves direct protonation of the aryl-Pd(II) species for catalyst regeneration (Scheme 121). This would prevent using stoichiometric oxidants, and further avoid stoichiometric bases, which leads to a redox-neutral *ortho* functionalization of aryl nucleophiles.

Very recently, the Dong group developed a Pd/NBE-catalyzed *ortho* functionalization of aryl boroxines (Scheme 122).[242] Different from Zhang and Zhou's conditions, this reaction is terminated via protodepalladation, therefore not

Scheme 121. Redox-Neutral *Ortho* Functionalizations of Aryl Nucleophiles



Scheme 122. Redox-Neutral *Ortho* Functionalizations of Aryl Boroxines



requiring stoichiometric external oxidants or bases. Both *ortho* acylation and amination have been demonstrated using carboxylic acid anhydrides and *O*-benzoylhydroxylamines as electrophiles, respectively. For the *ortho* acylation reaction, arsine-type ligands, i.e., $AsPh_3$, were found to be most effective, likely through promoting both the transmetalation and protodepalladation steps. Notably, both arylboronic esters (**225b**) and aryl iodides (**225c**) were tolerated. Further deuterium labeling studies were consistent with the *ipso* protodepalladation pathway. For the *ortho* amination with aryl boroxines, phosphite-type ligands, such as $P(OPh)_3$, were most efficient. The major side reaction in these redox-neutral transformations was the reductive elimination of the ANP intermediate to form benzocyclobutenes.

4. SYNTHETIC APPLICATIONS

4.1. Applications in Synthesis of Bioactive Compounds

The Pd/NBE cooperative catalysis has been widely utilized in the synthesis of biologically important compounds, including natural products, drugs, and agrochemicals. In particular, the *ortho*/*ipso* bisfunctionalziations of aryl halides are highly powerful for preparing polysubstituted arenes in a site-selective and step-economical manner. In this section, these examples are summarized according to the type of the key transformations used in the syntheses.

4.1.1. Synthesis using *Ortho* Alkylation Reactions. In 2013, Lautens and co-workers reported the enantioselective total synthesis of (+)-linoxepin (Scheme 123).[243,244] Using the *ortho* alkylation/*ipso* Heck reaction, the tetrasubstituted arene core was efficiently constructed in a convergent way. Oxidative cleavage of the olefin to an aldehyde followed by intramolecular aldol condensation afforded **228**, which was subjected to the Mizoroki−Heck reaction to furnish the synthesis of (+)-linoxepin (**229**).

DOI: 10.1021/acs.chemrev.9b00079
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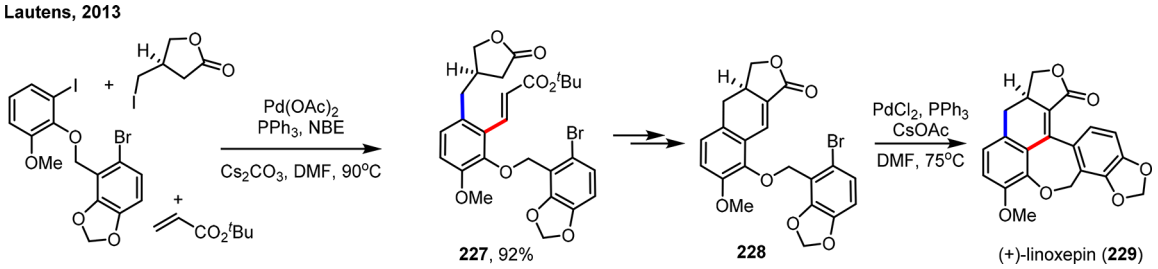
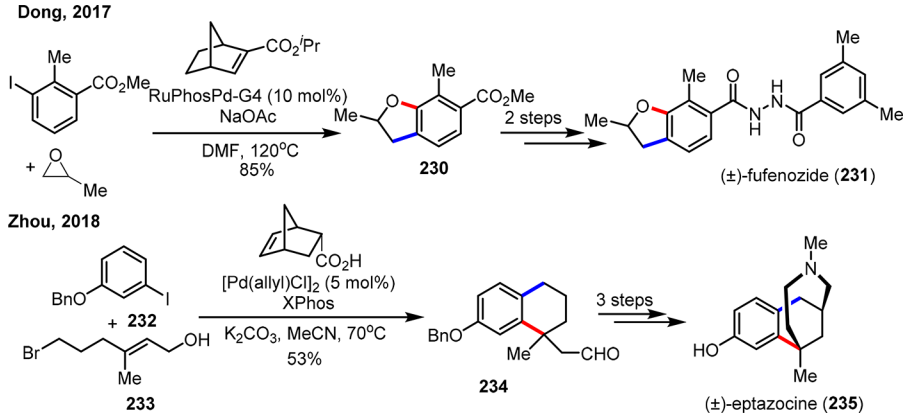
Scheme 123. Total Synthesis of (+)-Linoxepin



Scheme 124. Synthesis of (±)-Fufenozide and (±)-Eptazocine

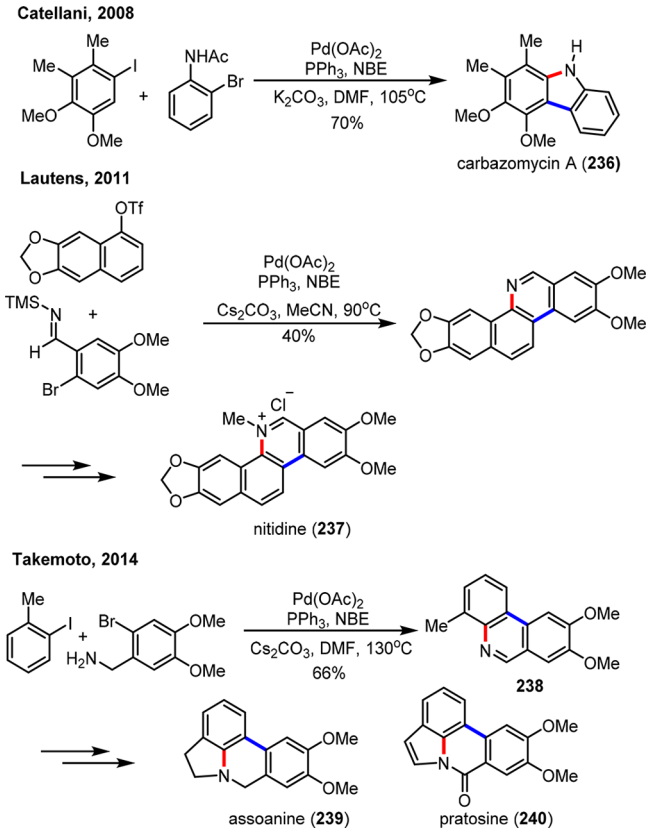


Fused ring structures can be efficiently generated using Type A bifunctional alkylation reagents. In 2017, the Dong group applied the annulation reaction with epoxides in the synthesis of insecticide fufenozide (Scheme 124).[131] Dihydrobenzofuran **230** was efficiently constructed through the direct coupling between the aryl iodide and propylene oxide. Subsequent hydrolysis and amide condensation provided fufenozide (**231**) in three total steps. Later, Zhou and co-workers applied their *ortho* alkylation/*ipso* Heck annulation in a concise synthesis of eptazocine, which is a benzomorphan-type analgesic drug.[96] The reaction of aryl iodide **232** with bromo-allyl alcohol **233** afforded aldehyde **234** in 53% yield, which was transformed into eptazocine (**235**) in three steps.

4.1.2. Synthesis Using *Ortho* Arylation Reactions. Likewise, *ortho* arylation with Type A bifunctional reagents provides a quick access to poly fused aromatic rings. In 2008, Catellani reported direct synthesis of antibiotics carbazomycin A (**236**) through *ortho* arylation/*ipso* amination using *o*-bromo-*N*-acetylaniline as the reactant (Scheme 125).[163] Later, Lautens achieved formal synthesis of benzo[c]phenanthridine alkaloids, nitidine (**237**) and NK109, taking advantage of the *ortho* arylation/*ipso* amination with aryl triflates.[205] In 2014, assoanine and pratosine were synthesized from a common intermediate **238** by Takemoto, utilizing a similar *ortho* arylation/*ipso* amination reaction.[167]

On the other hand, *ortho* arylation with Type B bifunctional reagents leads to a different type of fused ring systems. In 2013, Gu and co-workers employed the *ortho* arylation/*ipso* Heck reaction in the total synthesis of rhazinal (**242**). 1-Bromo-2-nitrobenzene was found to be an effective aryl electrophile, and the EWG in the pyrrole ring was essential in this Pd/NBE-catalyzed reaction. The resulting key intermediate **241** was transformed into rhazinal in three steps (Scheme 126).[176] Later, the same group achieved the enantioselective version of the

Scheme 125. Synthesis of Carbazomycin A, Nitidine, Assoanine, and Pratosine



synthesis using chiral ligand **243**,[245] which featured the first catalytic asymmetric example in the Pd/NBE catalysis. Total

DOI: 10.1021/acs.chemrev.9b00079
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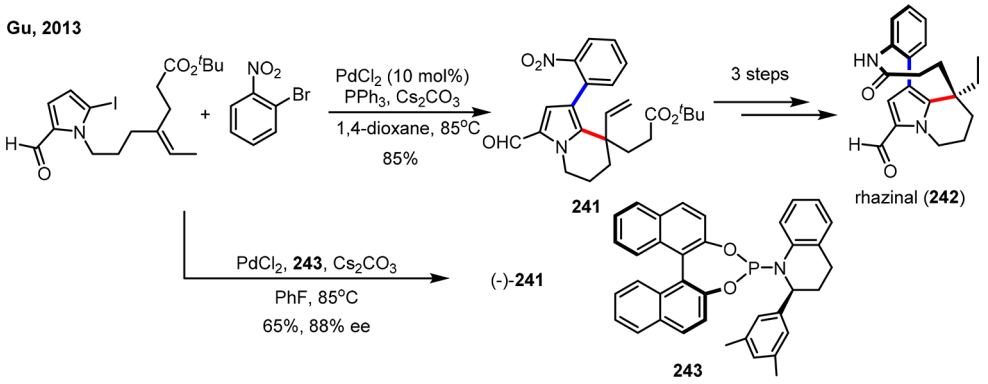
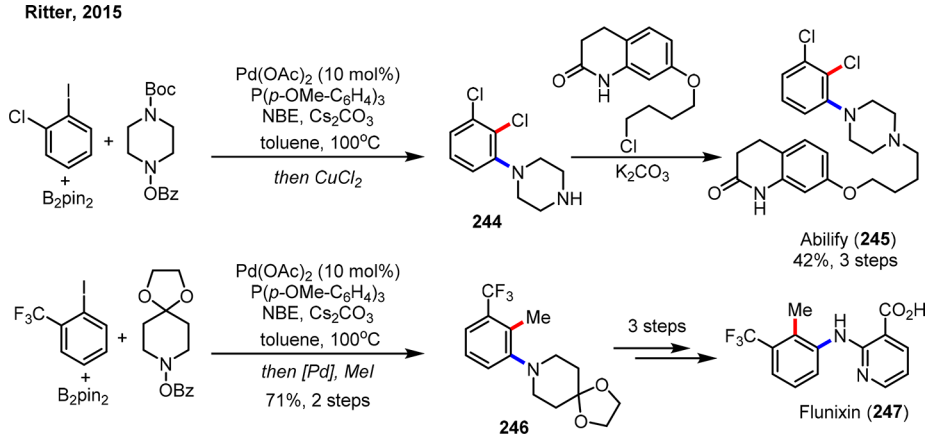
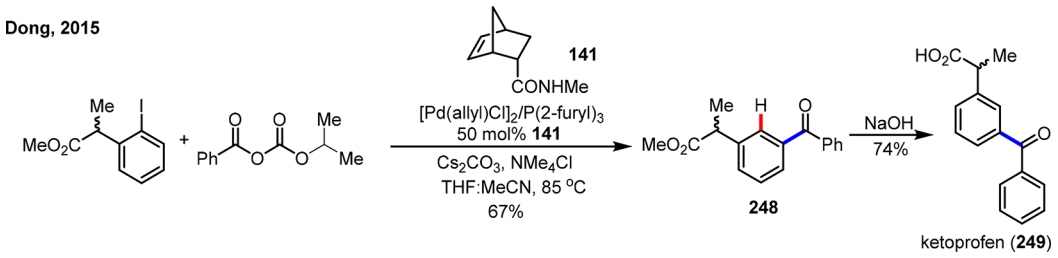
Scheme 126. Total Synthesis of (+)-Rhazinal



Scheme 127. Syntheses of Abilify and Flunixin



Scheme 128. Formal Synthesis of Ketoprofen



syntheses of related alkaloids, (+)-rhazinilam and (+)-kopsiyunnanine C1−3, have also been achieved.

4.1.3. Synthesis Using *Ortho* Amination Reactions. In 2015, Ritter demonstrated that the *ortho* amination/*ipso* borylation reaction could be used to quickly assemble the antipsychotic drug, Abilify (**245**), and the anti-inflammatory drug, Flunixin (**247**) (Scheme 127).[187] The key arylboronic ester intermediates generated via the Pd/NBE catalysis were conveniently converted to other FGs, such as chloride in the synthesis of Abilify and a methyl group in the synthesis of Flunixin.

4.1.4. Synthesis Using *Ortho* Acylation Reactions. In 2015, the Dong group applied the *ortho* acylation/*ipso* hydrogenation in a concise synthesis of ketoprofen (**249**) (Scheme 128),[193] which is a nonsteroidal anti-inflammatory drug for relieving arthritis-related inflammatory pains or severe toothaches. This method shows an advantage of preparing *meta*-substituted aryl ketones.

In addition, utilizing an intramolecular Heck termination has also been employed recently by the same group in the syntheses of indanone-type natural products (Scheme 129).[202] For example, pauciflorol F (**261**) were synthesized in five steps. They also reported the first total synthesis of acredinone A (**266**), which represents the first nonpeptidic natural product that can inhibit the voltage-gated potassium channel. The synthesis features two Pd/NBE-catalyzed *ortho* acylation reactions for constructing the two penta-substituted arene fragments. To be specific, the *ortho* acylation/*ipso* Heck annulation of aryl iodide **252** led to indenone **254**, and the *ortho* acylation/*ipso* borylation of aryl iodide **253** afforded intermediate **255**. The fragments **254** and **255** were ultimately coupled through the Suzuki−Miyaura reaction, followed by deprotection to give acredinone A (**256**) in eight steps in the longest linear sequence.

4.1.5. Synthesis Using 2-Alkylation of Indoles. Due to the biological importance of the indole moiety, Bach's 2-alkylation of indoles has been applied in a number of total

DOI: 10.1021/acs.chemrev.9b00079
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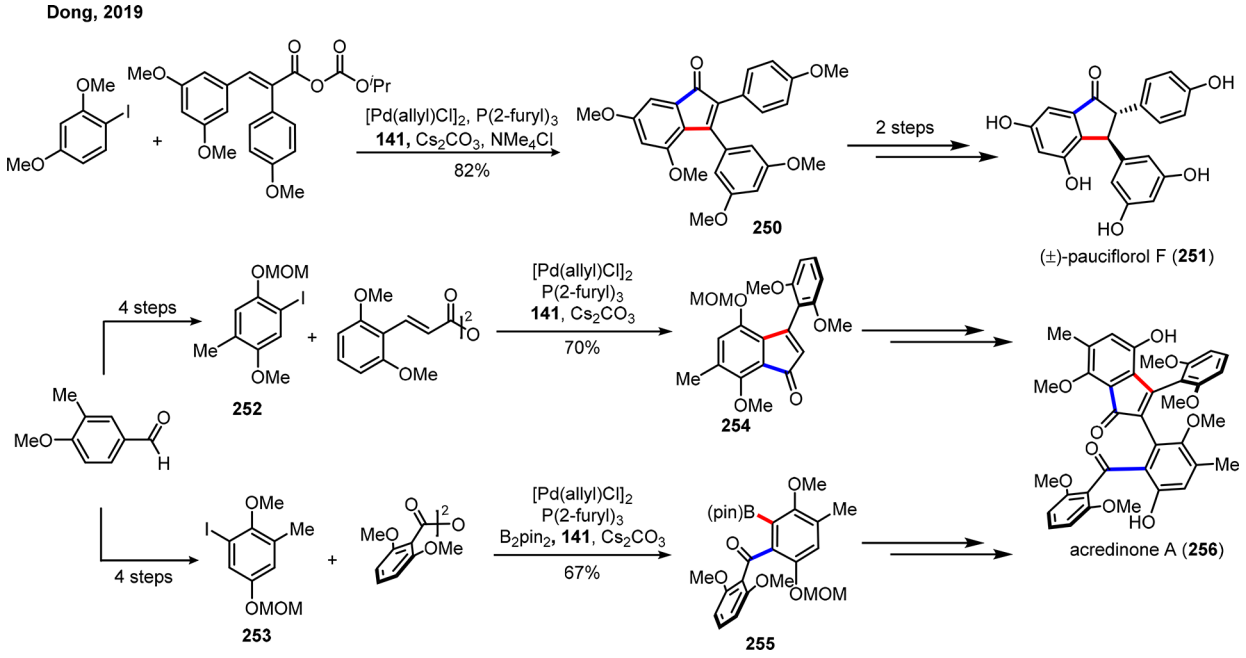
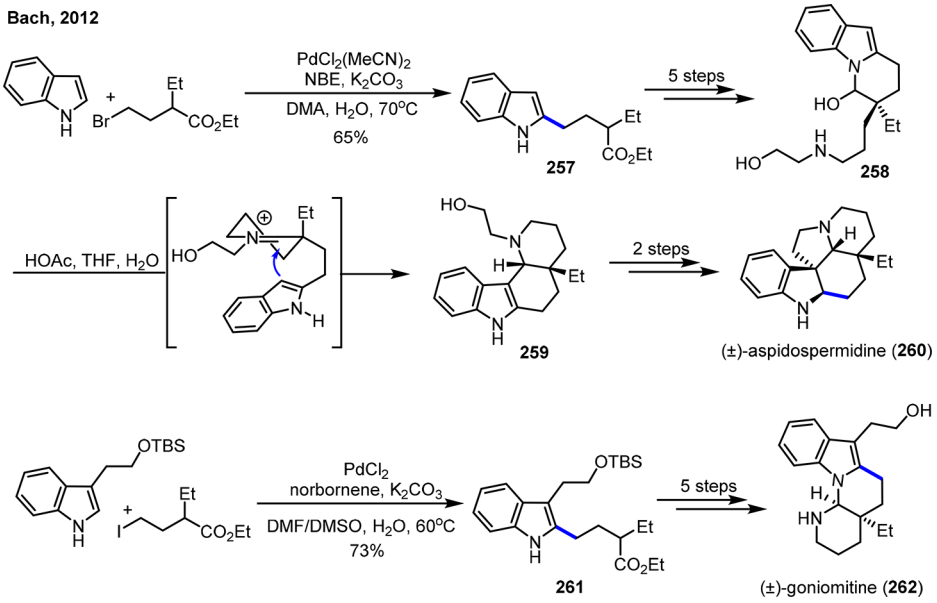
Scheme 129. Syntheses of Pauciflorol F and Acredinone A



Scheme 130. Total Syntheses of (±)-Aspidospermidine and (±)-Goniomitine



syntheses of indole alkaloids. In 2012, Jiao and Bach reported the total syntheses of (±)-aspidospermidine and (±)-goniomitine (Scheme 130).[218] In both cases, 2-alkylation of indoles was carried out at an early stage of the synthesis, demonstrating the practicability of this method. The intermediate **257** was further converted to **258** in five steps. Upon treatment with acids, annulation of **258** resulted in tetracycle **259**, which was further transformed to (±)-aspidospermidine (**260**). Similarly, total synthesis of (±)-goniomitine started from 2-alkylation of TBS-protected tryptophol. An improved catalytic condition was identified for the synthesis of indole **261** in order to accommodate the C3-substitution. Ultimately, (±)-goniomitine (**262**) was synthesized in five steps from intermediate **261**.

Subsequently, this 2-alkylation method has been frequently adopted in the total synthesis of other indole alkaloids. For example, Mukai,[246] Yang,[247] and Qin[248] successfully employed such an approach in the total syntheses of (+)-kopsihainanine A (**263**), (−)-aspidophylline A (**264**), and (+)-strictamine (**265**), respectively (Scheme 131). In addition, this method has also been used in the synthesis of certain pharmaceutical intermediates.[249−251]

4.2. Applications in Polymer Chemistry

Besides in bioactive compounds, polysubstituted arenes are also commonly found in organic polymers. Thus, the Pd/NBE catalysis is expected to be useful in preparing aromatic polymers due to its capability to construct multiple bonds simultaneously in one single transformation.

Reductive elimination of ANP to form norbornyl benzocyclobutenes is a common side reaction in the Pd/NBE

DOI: 10.1021/acs.chemrev.9b00079
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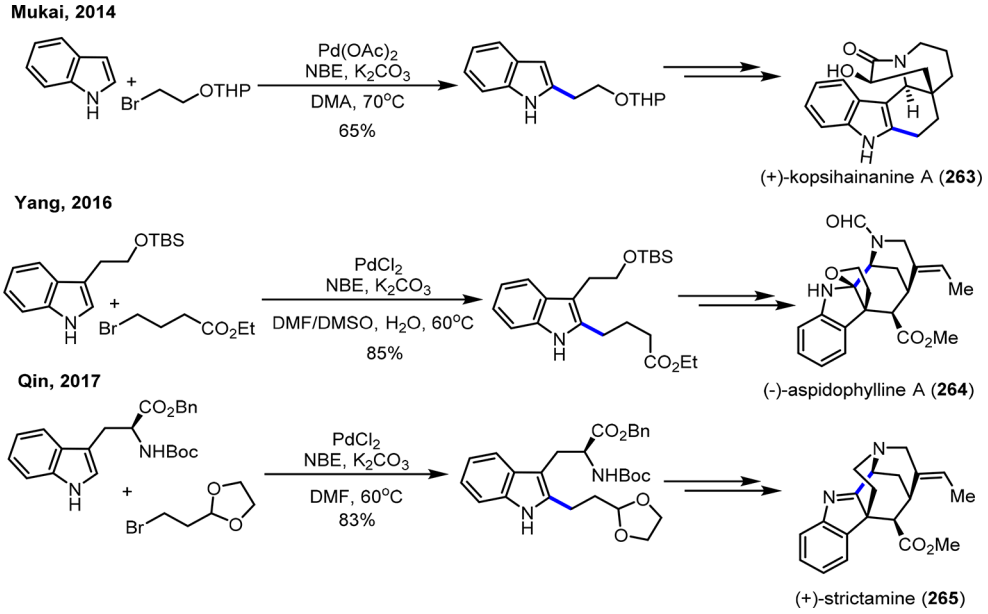
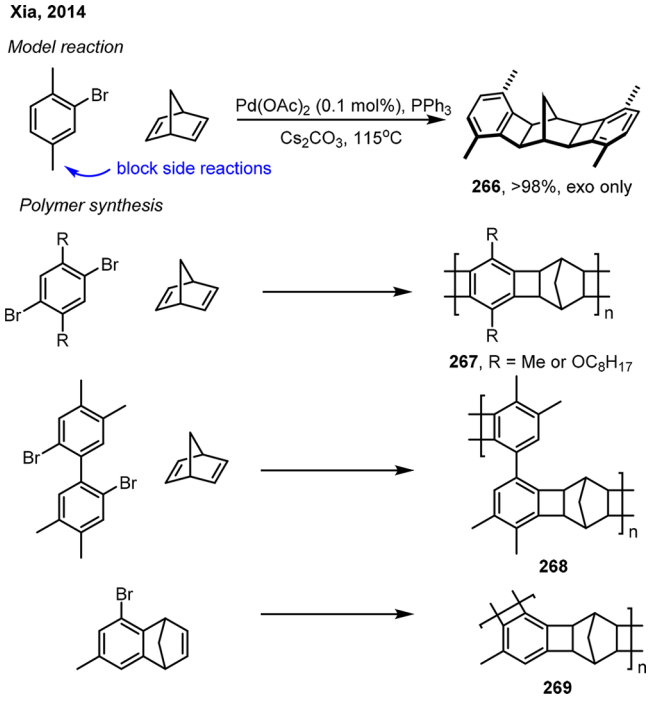
Scheme 131. Total Syntheses of (+)-Kopsihainanine A, (−)-Aspidophylline A, and (+)-Strictamine



catalysis.[28,252,253] However, the Xia group nicely took advantage of this unique arene/NBE annulation reaction and applied it in the synthesis of a new class of ladder polymers (Scheme 132).[254]

Scheme 132. Synthesis of Ladder Polymers Using Catalytic Arene-NBE Annulation



Both aryl bromides and triflates could be used as monomers to couple with norbornadienes. They found C1 and C4 substitutions in aryl bromides to be important for the efficiency of the annulation reaction. Besides the beneficial effect of the *ortho* substituent, the additional *meta* substituent suppressed side reactions, such as *ortho* arylation and NBE multi-insertion. The model study of 2,5-dimethyl-bromobenzene with norbornadiene gave >98% yield with excellent *exo* selectivity, which showed that this method was suitable for polymer synthesis. Polymers with a backbone in a bowing-ribbon conformation (**267**) can be conveniently synthesized from disubstituted *p*-dibromobenzenes and norbornadiene. Use of the biphenyl monomer afforded the polymer with a certain degree of bending freedom (**268**) due to the presence of the restricted yet rotatable biphenyl bond. Besides AA- and BB-type monomers, AB-type monomers could also be used (**269**). Ladder polymers with high molecular weights (10−50 kDa) can be obtained. These polymers exhibited excellent thermal stability, high carbonization yields, and large intrinsic porosity. Later, the same group demonstrated that spirocyclic motif could be introduced into the polymer backbone[255] and different FGs could be introduced into the side chains.[256] Besides using norbornadienes, benzooxanorbornadienes can also be used to construct polycyclic conjugated hydrocarbons using the same annulation reaction followed by aromatization.[257−260]

In the aforementioned polymerizations, norbornadiene was used as the monomer instead of a cocatalyst. In 2018, Yoon and Dong reported the first Pd/NBE-catalyzed polymerization, which simplified the synthesis of certain classes of functional aromatic polymers (Scheme 133).[261] Based on the *ortho* amination/*ipso* Sonogashira coupling, an A_2B_2C-type multicomponent polymerization was developed to prepare various amine-functionalized arylacetylene-containing polymers (**270**). Compared to the conventional "pre-functionalization" or "post-functionalization" approaches, this "*in situ* functionalization" strategy allows for simultaneously constructing polymer backbones and installing side chains in one catalytic cycle. Thus, this method provides a rapid and modular preparation of various amine-substituted polymers from readily available monomers. For the AA diaryl iodide monomers, both flexible and rigid linkers could be used. For the diacetylene BB monomers, both electron-rich and -poor linkers were compatible in the polymerization process. Simply through changing the amine C monomer, a range of pendant-functionalized aromatic polymers were prepared. For example, the polymer containing the ferrocene moiety showed redox response from the cyclic voltammogram (**270a**), and the polymer containing a

DOI: 10.1021/acs.chemrev.9b00079
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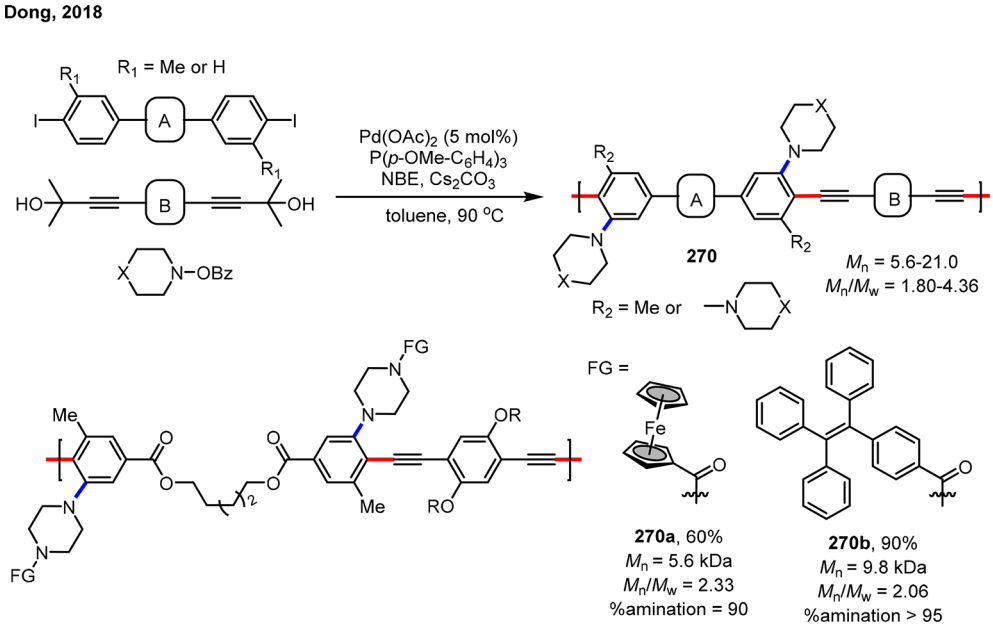
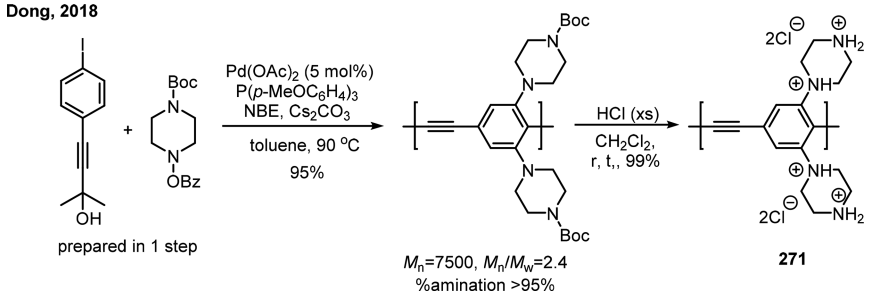
Scheme 133. Multicomponent "*In Situ* Functionalization" Polymerization by Palladium/NBE Catalysis



Scheme 134. Synthesis of the Water-Soluble PPE with *Meta* Side Chains



tetraphenylethylene motif displayed solid-state photoluminescence (**270b**).

Very recently, the same group disclosed a three-step preparation of highly water-soluble poly(*para*-phenylene ethynylene)s (PPEs) via the Pd/NBE-catalyzed AB-C-type polymerization (Scheme 134).[262] Instead of using the AA- and BB-type monomers, an AB-type alkyne-substituted aryl iodide monomer was employed, in which two piperazine *meta* side chains were concurrently installed with the construction of the PPE backbone. Upon removal of the *N*-Boc-protecting group, the polymer was found to be highly water-soluble since the piperazine side chains can be doubly protonated (**271**) under aqueous acidic conditions. Interestingly, these PPEs with *meta* side chains were found less aggregated and more soluble with higher fluorescent quantum yields compared to the corresponding PPEs with *para* side chains.

5. CONCLUSION AND OUTLOOK

Since Catellani's seminal discovery in 1997 and opening of the synthetic potential by Catellani and Lautens, the field of the Pd/NBE cooperative catalysis has expanded enormously to a number of dimensions, including new method development, natural product synthesis, and polymer chemistry. Particularly over the past decade, several new directions have been found, which have significantly increased the synthetic utilities of these methods. For example, the discovery of new classes of electrophiles allows for a variety of new *ortho* functionalizations, which extends the scope of the aromatic products that can be accessed. The design of new reaction pathways enables various Pd(II)-initiated reactions, including 2-alkylation of indoles, *meta* functionalization of arenes with *ortho* DGs, and *ortho* functionalization of arylboron species. The development of new types of substituted NBEs can overcome certain limitations in these reactions, particularly regarding the substrate scope and selectivity. In addition, an increasing number of applications have appeared in streamlined syntheses of complex target molecules and functional polymers due to the efficiency of *ipso*/*ortho* difunctionalization introduced by this unique approach. Thus, this field is now in a rapidly growing stage.

Despite the myriad recent advances, several limitations remain to be addressed in the future, in order to further improve the practicality and versatility of these methods. For example, compared to the widely adopted cross-coupling reactions, the scope of the electrophiles in the Pd/NBE catalysis is still much narrower and mainly based on carbon electrophiles. Hence, enabling broad C–X (X ≠ C) bond formation at the *ortho* position in the Pd(0)-initiated reactions would be highly desirable for extending the reaction scope. The solution to this problem could come from careful design of the external electrophiles and/or new NBE cocatalysts. In addition, better understanding the reaction of ANP with electrophiles should offer useful insights for reaction design, which could be achieved

DOI: 10.1021/acs.chemrev.9b00079
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through a combination of experimental and computational studies. Moreover, it could be exciting to discover new classes of substrates beyond arenes or heteroarenes in the Pd/NBE catalysis, which may lead to new transformations that are difficult to achieve via conventional approaches. Regarding the Pd(II)-initiated *meta* C−H functionalization of arenes, the direction has clearly been moving to the use of common FGs (e.g., aldehydes, ketones, alcohols) as DGs. One promising solution could be the use of catalytic directing templates, along with more enabling ligands and/or NBE cocatalysts. Besides using *ortho*-DGs, one could imagine that the use of a *meta*-DG, pioneered by Yu[263−265] and others, could afford *para*-substituted products. Finally, another underexplored direction could be the use of undirected arene C−H activation to initiate the Pd/NBE catalysis, in which the judicious choice of ligands/NBE cocatalysts would be important for the desired selectivity and reactivity.

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Notes

The authors declare no competing financial interest.

Biographies

Jianchun Wang was born in Taizhou, China. He received his B.S. degree in chemistry from Peking University in 2014, where he carried out undergraduate research of olefin polymerization in the laboratory of Professor Yuguo Ma. In the same year, he joined Professor Guangbin Dong's research lab at the University of Texas at Austin, and he moved to University of Chicago with Professor Dong in 2016. He is currently pursuing his Ph.D. with a focus on Pd/NBE cooperative catalysis.

Guangbin Dong received his B.S. degree from Peking University and completed his Ph.D. degree in chemistry from Stanford University with Professor Barry M. Trost, where he was a Larry Yung Stanford Graduate fellow. In 2009, he began to research with Professor Robert H. Grubbs at California Institute of Technology, as a Camille and Henry Dreyfus Environmental Chemistry Fellow. In 2011, he joined the department of chemistry and biochemistry at the University of Texas at Austin as an assistant professor and a CPRIT Scholar. Since 2016, he has been a Professor of Chemistry at the University of Chicago. His research interests lie in the development of powerful chemical tools for addressing questions of biological importance.

ACKNOWLEDGMENTS

We thank University of Chicago and NIGMS (1R01GM124414-01A1) for research support. Dr. Zhao Wu, Mr. Renhe Li, Mr. Alexander Rago, and Mr. Ki-Young Yoon are acknowledged for checking the manuscript.

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