Double C–H Activation for the C–C Bond Formation Reactions

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Abstract: Background: Among the numerous bond-forming patterns, C–C bond formation is one of the most useful tools for building molecules for the chemical industry as well as life sciences. Recently, one of the most challenging topics is the study of the direct coupling reactions via multiple C–H bond cleavage/activation processes. A number of excellent reviews on modern C–H direct functionalization have been reported by Bergman, Bercaw, Yu and others in recent years. Among the large number of available methodologies, Pd-catalyzed reactions and hypervalent iodine reagent mediated reactions represent the most popular metal and non-metal involved transformations. However, the comprehensive summary of the comparison of metal and non-metal mediated transformations is still not available.

Objective: The review focuses on comparing these two types of reactions (Pd-catalyzed reactions and hypervalent iodine reagent mediated reactions) based on the ways of forming new C–C bonds, as well as the scope and limitations on the demonstration of their synthetic applications.

Conclusion: Comparing the Pd-catalyzed strategies and hypervalent iodine reagent mediated methodologies for the direct C–C bond formation from activation of C–H bonds, we clearly noticed that both strategies are powerful tools for directly obtaining the corresponding products. On one hand, the hypervalent iodine reagents mediated reactions are normally under mild conditions and give the molecular diversity without the presence of transition-metal, while the Pd-catalyzed approaches have a broader scope for the wide synthetic applications. On the other hand, unlike Pd-catalyzed C–C bond formation reactions, the study towards hypervalent iodine reagent mediated methodology mainly focused on the stoichiometric amount of hypervalent iodine reagent, while few catalytic reactions have been reported. Meanwhile, hypervalent iodine strategy has been proved to be more efficient in intramolecular medium-ring construction, while there are less successful examples on C(sp2)-C(sp3) bond formation. In summary, we have demonstrated a number of selected approaches for the formation of a new C–C bond under the utilization of Pd-catalyzed reaction conditions or hyperiodine reagents. The direct activations of sp2 or sp3 hybridized C–H bonds are believed to be important strategies for the future molecular design as well as useful chemical entity synthesis.

Keywords: C–H activation, C–C bond formation, Pd-catalyzed, hypervalent iodine, polycyclic system construction, inter-, intra-molecular coupling.

1. INTRODUCTION

Since Pauling published the “BIBLE” on molecular bonding theory in 1939, the molecular design via new bond formation strategy has become an important research area in organic chemistry [1].

Typically, the chemical bonds include C–H, C–X and C–C bonds. Among the numerous bond-forming patterns, C–C bond formation is one of the most useful tools for building molecules for the chemical industry as well as life sciences [2].

Mechanistically, the formation of C–C bond can be realized by the reaction of two carbon synthons as demonstrated in Fig. (1).

C–C bond formation can be designed as the reaction of an electrophile 2 and a nucleophile 3 as shown in Fig. (1 path A). Alternatively, the C–C bond could also be facilitated via diradical reactions as described in Fig. (1 path B).

Recently, one of the most challenging topics is the study of the direct coupling reactions via multiple C–H bond cleavage/activation processes. A number of excellent reviews on modern C–H direct functionalization have been reported by Bergman, Bercaw, Yu and others in recent years [3].
Among the large number of available methodologies, Pd-catalyzed reactions and hypervalent iodine reagent mediated reactions represent the most popular metal and non-metal involved transformations. However, the comprehensive summary of the comparison of metal and non-metal mediated transformations is still not available. In this review, we are focusing on comparing these two types of reactions based on the ways of forming new C–C bonds, as well as the scope and limitations on the demonstration of their synthetic applications. With regard to the large variety of available research, the Cross Dehydrogenative Coupling (CDC) reaction, Heck type of direct alkenylation and other reactions involved alkynes and aldehydes are not included in this review.

2. ANNULATION REACTIONS FORMED BY INTRAMOLECULAR C–C COUPLING

Heterocyclic compounds, as the basic skeleton of many natural products and pharmaceutical compounds with physiological activity, are a very important class of organic synthetic intermediates. In particular, compounds containing structures such as pyrrole, furan, thiophene and carbazole have unique synergistic physiological and pharmacological activities, and thus studies on their syntheses are highly valuable. Intramolecular C–C coupling is an efficient method of atomic economy to build heterocyclic compounds.

2.1. Pd-catalyzed Annulation Reactions

The syntheses of biaryl motifs have been widely utilized in medicinal chemistry, agrochemical and material sciences [4]. More recently, transition metal catalyzed multi C–H bond activation has been systematically studied (Scheme 1).

Early in 1970s, Itatani reported Pd(II)-catalyzed intramolecular C(sp²)–C(sp²) coupling reactions of biphenyl ether, but only obtained dibenzofurans 10 of a low yield under harsh conditions [5]. Using Pd(II) and 10 mol% Pd(TFA)₂, AgOAc, K₂CO₃, PivOH, 130 °C, 24 h [9].

With the development of green chemistry, strategies using oxygen (O₂) or even air as the oxidant to complete the oxidative coupling reaction have also received wide attention. In the presence of Pd(OAc)₂ and K₂CO₃ in PivOH, Fagnou utilized green oxidant (air) to achieve the intramolecular coupling of N,N-diarylamine compounds and obtained a series of carbazole derivatives in good to excellent yields. It is worth noting several natural products such as Murrayafoline A 12, Clausenine 13 and Mukonine 14 were prepared in relatively high yields [7] (Scheme 2). In addition, microwave assisted reaction could reduce reaction time (60 minutes) for carbazole synthesis [8].

The synthesis of heterocycles with sulfur atoms are also realized via the ring closure. Benzothiophene 16 and other potential semi-conductive derivatives were also successfully synthesized through Pd(II)-mediated oxidative coupling reactions [9] (Scheme 2).

A one-pot procedure using Buchwald-Hartwig cross-coupling protocol for the reaction of aryl triflates 17 with aniline derivatives
followed by an intramolecular oxidative arylation was utilized to synthesize carbazoles \[21 - 23\] \[10\] (Scheme 3).

Even for the synthesis of strained heterocycle, indolo[3,2-\(jk\)]carbazole \[25\] was isolated in 70\% yield under Pd-catalyzed conditions \[11\] (Scheme 4).

The methodology for the construction of furan rings with pyridine oxides was also disclosed. In 2015, Wang developed an efficient oxidative cyclization to the straightforward synthesis of benzo\(furo[3,2-b]\)pyridine-1-oxides \[27\] with high regio-selectivity via Pd-catalyzed intramolecular dual C-H activation. The resulting products could be deoxygenated easily to the corresponding benzo\(furo[3,2-b]\)pyridines \[28\] in excellent yield \[12\] (Scheme 5).

Up to now, there are limited examples for the intramolecular C(sp\(^2\))-C(sp\(^2\)) bond formations. In 2008, Fagnou and co-workers reported the intramolecular C-C coupling of arenes and unactivated alkane under air \[13\]. Many functional groups, including carbonyls, esters and spirocycles, were well tolerated under these conditions (Scheme 6). Differentially substituted amides can achieve very high...
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Baudoin’s lab focused on the cyclization of thiophene-cyclopentanes compounds and compared C(sp<sup>3</sup>)–H/C(sp<sup>2</sup>)–H and C(sp<sup>3</sup>)–H/C(sp<sup>2</sup>)–X (X = leaving group) types reactions directly [14]. They managed to achieve the cyclization of thiophene-cyclopentanes 35 by Pd(II)-catalyzed dehydrogenative C(sp<sup>2</sup>)–H/C(sp<sup>3</sup>)–H coupling from 36. However, this reaction showed lower efficiency comparing to C(sp<sup>3</sup>)–H/C(sp<sup>2</sup>)–X types reactions. Moreover, the chemo- and diastereoselectivity of C(sp<sup>2</sup>)–H/C(sp<sup>3</sup>)–H coupling seems particularly good (Scheme 7).

Among six-membered ring construction, Pd-catalyzed strategy has been proved to be efficient for both carbocycle and heterocycle. For instance, Dong and co-workers used Pd(OAc)<sub>2</sub> as the catalyst and Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as the oxidant to facilitate an intramolecular oxidative coupling reaction [15] (Scheme 8).


Scheme 7. C–H activation for cyclopentane ring formation.

Scheme 8. Synthesis of N-methylcrinasiadine.

N-methylcrinasiadine 38, a natural product could be synthesized under these conditions in 30% yield. In the following year, in order to better understand the mechanism, Dong isolated and characterized the dimeric Pd complexes 39 via analogous stoichiometric cyclopalladation reaction of the corresponding N-methyl-N-phenyl-benzamide. The complex could be transformed to the desired product 40 under similar reaction conditions. However, the reaction mechanism varies greatly depending on the directing groups as well as the oxidants [16] (Scheme 9). Similarly, the construction of the C–C bond between imidazoles and simple benzene rings via the intramolecular oxidative coupling catalyzed by PdCl<sub>2</sub> was also reported [17]. Activation of the acidic C–H bond between two nitrogen atoms followed by the oxidative addition of benzene facilitates the produce of desired tricycle 42 in excellent 96% yield (Scheme 10).
One of the most challenging coupling reactions is that direct coupling of C(sp³)–C(sp³) bonds in a selective manner. Shi and co-workers published Pd-catalyzed both intra- and inter-direct allylic alkylation of alkenes [18]. This method was based on the Tsuji-Trost alkylation, which provided new pathways for the construction of ring system. As described in Scheme 11, ketones 44 and 47 were produced by the formation of new allylic C(sp³)–C(sp³) bonds.

Compared with five and six-membered ring, Pd-catalyzed medium-ring construction is rarely studied. Greaney accomplished seven- and eight-membered ring system via Pd-catalyzed intramolecular oxidative C–H coupling of indoles and simple arenes [19]. A number of representative functional groups, especially aldehydes, were proven to be tolerated in the reactions (Scheme 12).
2.2. Annulation Reactions Involving Hypervalent Iodine Reagents

Similar to Pd-involved intramolecular oxidative coupling reactions, hypervalent iodine reagents, such as phenyliodine diacetate (PIDA) or phenyliodine bis trifluoroacetate (PIFA), were broadly employed as the oxidant for C–C annulation reactions. Palladium-catalyzed methods are usually easier to form five- or six-membered heterocycles, while the hypervalent iodine-mediated strategies are more effective and feasible for the construction of middle rings such as seven- or eight-membered rings.

In 2008, Zhang’s group reported that in the presence of CuSO$_4$ and DMAP, compound 51 reacted with iodobenzene acetate to obtain spiro product 52. However, in the absence of copper salts, 51 could be oxidized to cyclohexadienone, and then went through Michael addition reaction under basic conditions to give intermediate 50, then the aromatic rearrangement reaction took place under the catalytic action of p-toluensulphonic acid, resulting in the formation of polysubstituted cerium oxide 53. And product 53 could undergo a few simple steps to obtain the natural product horsfiline [20] (Scheme 13).

Lombardo and co-workers used 2.0 equivalents of PIFA for the oxidative coupling of aryl tethered phenol 55 to give a tetracycle spirodienone 56 albeit the yield is rather low, which could then be transformed into a pentacyclic natural product 6a-epipretazettine 57 [21]. Propylene oxide was used as co-oxidant during the processes (Scheme 14).

Kita reported the first effective iodoarene-catalyzed C–C bond forming reactions to generate a series of tricyclic azepines [22]. The active hypervalent iodine(III) species were rapidly generated in situ at low temperatures and then catalyzed the C–C intramolecular coupling. This new catalytic system supplied a wide range of substrates and functional availabilities sufficient to be used in the key synthetic process of producing high yields of biologically important Amaryllidaceae alkaloids (Scheme 15).

HPAs as the Brønsted acid to activate PIFA, showed a different coupling pathway to BF$_3$·Et$_2$O involved reactions. Base on the methoxy substituted biaryl substrates, the combination of PIFA and BF$_3$·Et$_2$O led to the normal coupled biaryl compound 63, while the spirodienone 62 was the only product from the same substrate in the
presence of HPAs instead of BF$_3$.Et$_2$O [23]. The application of this novel method was the most distinct for the non-phenolic coupling of the benzyl tetrahydroisoquinolines 64 to build up the morphinandienone-type alkaloid skeletons [24], which are the important precursors for many pharmaceutical useful compounds [25] (Scheme 16).

Scheme 16. HPA-mediated coupling reactions.

In 2001, Kita provided a convenient PIFA-mediated synthesis of benzannulated and spirobenzannulated compounds 68, which was conducted through an intramolecular substitution reaction of phenol ether derivatives 67 [26]. The reaction was carried out at -40 °C and the products 69 and 70 were obtained in good yields (Scheme 17).
3. INTERMOLECULAR C–C HOMOCOUPING

Apart from intramolecular coupling, intermolecular C–C bond formation could produce more diverse molecules, which are more practical for chemistry synthesis.

3.1. Pd-catalyzed C–C Homocoupling Reactions

In recent years, it has been found that by introducing more effective cocatalysts into the reactions system, Pd-catalyzed strategies can achieve the homocoupling of benzene and its derivatives under mild conditions. And the homocoupling reactions of various heterocyclic aromatic compounds have also made significant progress.

3.1.1. Pd-catalyzed Homocoupling of Arenes

In 2000, by using PdCl₂ as the catalyst, tetrahexyl-ammonium chloride (THAC), NaOAc and chlorobenzene as additives, and AcOH as a solvent, Sasson reported homocoupling of benzene, yields of coupling biphenyl products were 35% to 50% [27] (Scheme 18).

When there is no addition of chlorobenzene to the reaction system, only a trace amount of biphenyl was obtained; when chlorobenzene was used as the only substrate, the reaction could not proceed. Based on this, the possible reaction mechanism was proposed (Scheme 19): Benzene was oxidatively homocoupled to give biphenyl under the catalysis of Pd(II), at the same time, Pd(II) was converted to Pd(0); chlorobenzene could reconvert Pd(0) to Pd(II) and at the same time, conduct its homocoupling, so that the synergy of the two processes together accomplished the catalysis cycle of Pd(II)-Pd(0)-Pd(II).

Later, using benzene as the only aromatic substrate to achieve the biphenyl was reported by Yamaji. In the presence of high pressure of O₂ and cocatalyst MoO₂(acac)₂, they obtained a high yield of biphenyl. The homo-coupling products 73 showed good selectivity over the oxidized product 76 and acetylated arene 77 [28] (Scheme 20).

By the introduction of weak coordinates, Greaney and co-workers developed Pd(II)-catalyzed oxidative homo-coupling of phenylacetamides. Substoichiometric amount of Cu(II) salt was used as the oxidant and O₂ served as the co-oxidant, affording symmetrical 2, 2-disubstituted amide biaryl 79 in 87% yield [29] (Scheme 21).

Beraw and co-workers synthesized a cationic complex, [(a-diimine)Pd(CH₃)(H₂O)][BF₄]²⁻, which was then utilized for the direct activation of electron deficient arenes at room temperature [30]. During the regioselectivity studies with respect to trifluorotoluene, they found that electron-deficient sites are less favoured for the coupling, which resulted in the meta-selectivity due to the steric and electronic effects (Scheme 22-A). Later, by using Pd(OAc)₂ as the catalyst, similar results were obtained but with slightly higher meta-selectivity compared with Beraw’s discoveries [31] (Scheme 22-B).

In the presence of Pd(OAc)₂ catalyst and oxone oxidant, Sanford and coworkers achieved a highly selective ortho-coupling product of 82 [32] (Scheme 23).

Substrate expansion tests showed that the presence of pyridine ring could greatly increase the regioselectivity of the reaction. The reason might be that the nitrogen atom on the pyridine ring acted as...
Scheme 19. Proposed mechanism process.

\[
Pd^{2+} + 2C_6H_6 \rightarrow C_6H_5 + Pd^0 
\]
71

\[
Pd^{2+} + C_6H_6 + C_6H_3Cl \rightarrow C_6H_5 + Pd^0 
\]
71 72

\[
Pd^{2+} + C_6H_3Cl + C_6H_3Cl \rightarrow C_6H_5Cl + Pd^0 
\]
72 72 75

\[
Pd^0 + 2C_6H_3Cl \rightarrow C_6H_5 + Pd^{2+} 
\]
72 73

Scheme 20. Synthesis of biphenyl.

\[
Pd(OAc)_2, MoO_2(acac)_2, AcOH, O_2 (10 atm), 130 \, ^\circ C, \, 4 \, h \rightarrow \]
71

\[
\text{Biphenyl} + \text{Biphenyl} \rightarrow 88\% 
\]
73

\[
\text{Biphenyl} + \text{Biphenyl} \rightarrow 6\% 
\]
76

\[
\text{Biphenyl} \rightarrow 6\% 
\]
77


\[
\text{Biphenyl} + \text{Biphenyl} \rightarrow 87\% 
\]
79
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Scheme 23. Homo-coupling of pyridine directed benzenes and mechanism study.

In 2017, a convenient and efficient method has been developed by Mao for the construction of seven-membered N-heterocycle through Pd(II)-catalyzed direct homo-coupling reaction of benzamides and subsequent intramolecular condensation reaction in one pot. By using the simplest amide CONH$_2$ as a directing group, the Pd-catalyzed homocoupling was realized via ortho-selective double C–H bond activation to afford 89, and the subsequent intramolecular condensation reaction proceeded smoothly to generate 88 in 83% yield [33] (Scheme 24).
3.1.2. Pd-catalyzed homocoupling of Heterocycles

Mori and co-workers reported the Pd-catalyzed C–H homocoupling of thiophenes [34]. Even the hexamer 92, octamer 93 of thiophenes could be obtained in reasonable yields (Scheme 25).

When AgF was replaced by other silver reagents (such as AgOTf, Ag₂CO₃, Ag₂O, etc.), the reaction could not proceed smoothly. They speculated that AgF acted as an appropriate oxidant during the conversion from Pd(0) to palladium(II). And other oxidants (such as CuCl₂, Cu(OAc)₂) could not result in the coupling products as well.

Homo-coupling of heterocycles for the synthesis of biindolizines through C–H activation was also developed [35]. As shown in Scheme 26, although there were no directing groups in these compounds, coupling reactions could still be conducted via ortho-arylation in excellent yields. In the presence of Cu(OAc)₂ and K₂CO₃, a mixture of indolizine 94, 5 mol% of Pd(OAc)₂ in DMF

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Scheme 24. Direct homo-coupling of benzamides.


Scheme 26. Coupling of indolizines.
was stirred at 60°C, then biaryl 95 was isolated in an excellent 99% yield.

3.2. C–C homocoupling Reactions Involving Hypervalent Iodine

Hypervalent iodine reagents as a class of easily prepared, mildly-selective, high-selectivity organic reagents are now extensively used in modern organic synthesis. Various hypervalent iodine mediated homocoupling reactions have been well established.

3.2.1. Hypervalent Iodine Mediated Homocoupling of Arenes

In review of previous studies, preparative methods for alkyllarene dimers have been limited to metal-catalyzed coupling reactions such as, Suzuki, Heck, Stille, and Negishi reactions via halogenated or other functionalized alkylarenes. Kita reported a PIFA mediated C–C formation for the synthesis of biaryls. In the presence of active iodine reagent-PIFA, the oxidative biaryl homocoupling of electron-rich aromatic compounds generated the biphenyl and binaphthyl dimer in high yields [36] (Scheme 27).

Scheme 27. Naphthalene homo-coupling.

Subsequently, the combination of catalytic amounts of PIFA with 0.125 equivalent of m-CPBA and BF$_3$.Et$_2$O in CH$_2$Cl$_2$ at -40°C to room temperature, the homocoupling product 4-bromoveratrole 100 was isolated in 59% yield [37] (Scheme 28).

Scheme 28. Biaryl homo-coupling of electron-rich aromatic compounds.

3.2.2. Hypervalent Iodine Mediated Homocoupling of Heterocycles

A series of hypervalent iodine reagent-promoted reactions of heterocycle were also established, especially for the syntheses of thiophenes, pyroles, indoles and electron-rich heterocycles dimer.

Similarly, it is important to note that intermolecular coupling of N-substituted pyrroles would predominantly facilitate $\alpha$,$\beta'$-bipyrrroles over $\alpha$-$\alpha'$-bipyrrrole, while the $1H$-pyrrrole mainly gave the $\alpha$-$\alpha'$-bipyrrrole. Among various substituents, benzyl group showed the best $\alpha$,$\beta'$-bipyrrroles selectivities (Scheme 30).

In another hypervalent iodine-mediated homocoupling strategy [39], the direct oxidative coupling of 3-alkylthiophenes seemed to be difficult to comply with single selective manner, and the corresponding $\alpha$-free bithiophenes 107 [head to tail (H-T) dimer] and 108 [head to head (H-H) dimer] were obtained from 3-hexylthiophene. The forming dimers of 3-alkyl- thiophenes, 107 or
are likely to be further oxidized and reacted at the free γ/γ2-positions due to their lower oxidation potentials than the initial monomers (Scheme 31).

A broadly applicable oxidative strategy that proceeds via iodonium intermediates was put forward, which showed unique reactivities at the 5-position [40]. This methodology provided metal-free intermolecular unsymmetrical oxidative coupling to form H-T dimers regiospecific (Scheme 32).

Actually, similar approaches for convenient and efficient syntheses of bipyrroles were developed. The dimerization of two pyroles was promoted by hypervalent iodine reagents for the access of bispyrroles. Using 2.0 equivalents of TMSBr relative to PIFA, the desired coupling reaction could be finished within 1 h, affording the α,α'-bipyrroles 113-116 in good yields (60-78%) [41]. Interestingly, only regiospecific product α,α'-bipyrroles were observed (Scheme 33).

It is worth mentioning that: during the reaction, it is not necessary to protect the amine group in pyrrole, which greatly reduces the steps of coupling reaction of nitrogen-containing heterocyclic aromatic compounds and enhances the practicality of the reaction. When other Lewis acids (such as BF3·Et2O, TMSOTf, TMSCl, etc.) were used instead of TMSBr, the reaction could not proceed smoothly.

The possible reaction mechanism is shown in Scheme 34. PIFA directs pyrrole single electron transfer (SET) to form cationic radical, and then synergizes with another pyrrole to complete the dehydrogen process to achieve the coupling. Through ion exchange of PIFA with Br- (from TMSBr), I–Br bond was formed in hypervalent iodide, which can activate hypervalent iodide, thus effectively improving the activity of the reaction substrate.

When the reaction was applied to 3-methylindole coupling reaction, dihydroindole and bisindole were isolated in a 29:74 ratio (Scheme 35). And the isolated indoline could not transfer to the bisindole under the reaction conditions.

4. INTERMOLECULAR C–C CROSS-COUPLING REACTIONS

While chemists are exploring mild conditions to achieve catalytic homocoupling of aromatic compounds, cross-coupling reac-
tions of different aromatic compounds are also being developed. The cross-coupling reaction of aromatic compounds has a wide variety of practical applications, but the cross-coupling reactions that were explored in the early stage are often accompanied by the formation of homocoupling products. As we mentioned, one of the challenges in the cross-coupling reaction is the control of reaction chemoselectivity to avoid the formation of statistical mixtures. Recent years, a large number of highly selective cross-coupling reactions have been realized. Here we mainly demonstrate the efficient cross-coupling reactions involving Pd catalysts and hypervalent iodine reagents.

### 4.1. Pd Catalyzed Cross-coupling Reactions

In 2006, Lu reported a Pd(II)-catalyzed cross-coupling of aryl compounds [42]. In the presence of Pd catalyst and K$_2$S$_2$O$_8$ oxidant, the mixture of benzene and naphthalene in TFA was stirred at room temperature for 24h to get the corresponding cross coupled hydrocarbon 125. Changing the amount of solvent could significantly affect the proportion of the homocoupling product biphenyl. When the amount of solvent was reduced to an appropriate level, the proportion of cross-coupling reactions could be significantly increased. Under mild conditions, the cross-coupling reactions showed excellent selectivity comparing to homo-coupling products albeit with slightly low yield (32%) (Scheme 36).

Catalytic cross-coupling of unactivated arenes with heterocycles had never been reported until Fagnou developed a Pd catalyzed cross-coupling of N-acetylindoles and benzenes. Selected examples are shown in Scheme 37, indole 128 and pyrrole 129 were prepared successfully in high yield with good regioselectivity [43].

Compared with the nonfluorinated counterparts, perfluoroarenes served as an aryl template could significantly reduce the HOMO and LUMO energy gap [44]. Zhang used perfluorooarenes as the “special arene” to realize the synthesis of thiophenes, indoles and other electron-rich heterocycles [45].

Instead of the heterocycles, Su and co-workers developed a coupling approach of simple arenes and polyfluoroarenes [46]. Similarly, Shi expanded the substrate scope of arenes and polyfl-
uoroarenes [47]. Interestingly, under these conditions, polyfluoro-
pyridine 138 was also isolated in 79% yield (Scheme 38c).

Chang applied the N-oxide under Pd catalyzed intermolecular
oxidative coupling reactions for the introduction of aromatic sub-
stituent at the e-position [48]. Substrate expansion tests showed that
the N-O bond in the pyridine nitrogen oxide can guide its ortho-
arylation, and when two ortho-positions are not substituted, the
corresponding double-arylation product was the main product, es-
pecially for the aromatic substrates with electron-withdrawing
groups (Scheme 39).

As another example, You and co-workers realized the direct
arylation method of ferrocenyloxazolines in the presence of stoichiometric equivalent of Pd catalyst [49]. The presence of ox-
zoline ring could guide the introduction of phenyl in the ortho posi-
tion, and ferrocene 145 could be prepared in 70% yield (Scheme 40).
In 2008, Buchwald reported a Pd-catalyzed ortho- arylation of anilides, the effect of the amino group caused the reaction to occur selectively in the ortho position [50]. Soon after, You modified the procedure of this cross-coupling of aniline with simple aromatics and used (NH₄)₂S₂O₈ instead of O₂ as the oxidant [51]. The reaction could proceed at room temperature under mild conditions and obtain a good yield of the coupling products (Scheme 41).

Dong reported an ortho-arylation of O-iPr carbamates using Na₂S₂O₈ as the common oxidant in 2010 [52]. Based on the mechanism, they proposed two C–H bond activations occurred via cyclopalladation and electrophilic metalation, respectively, within a Pd(0/II) catalytic cycle. Later, they successfully used substrates of arenes bearing a cyclic directing group such as anilide 153 for the synthesis of ortho-arylated biarene 154 in a gram-scale [53] (Scheme 42).

As a novel strategy, Han and Wang have developed a palladium-catalyzed diarylation of coumarins 155 by using diaryliodonium salts 156 in the synthesis of 4, 5-benzocoumarin derivatives 157. This method features simultaneous C–I and vicinal C–H bond activations of diaryliodonium salts via palladium catalyzed strategy [54] (Scheme 43).

The formation of C(sp²)–C(sp³) bond was rarely reported, Pi-hko described the synthesis of β-ketoesters and indoles which could be realized under mild conditions with Pd(II) catalyst. Subsequently, electron-rich arenes were also examined and three-component domino reactions (3CR) involved Pd-catalyzed oxidative coupling of β-ketoesters, indoles, and aryl boronates were then developed [55] (Scheme 44).

More recently, Kozlowski developed the intermolecular C(sp$^3$)–C(sp$^3$) cross coupling of phenylglycineazlactone 173 and toluene 174 induced by stoichiometric amount of Pd(OAc)$_2$. After the reaction mixture was heated at 90 °C for 24 h, the benzyl lactone 175 was obtained in a good yield of 83% [56]. (Scheme 45) The C–C bond formation was achieved by selective C/g1H activation of the benzylic position of toluene, and $m$-xylene was highly effective, mesitylene proceeded in only 14% yield. They thought the reason was the steric effect of three alkyls of mesitylene, which hinder the coordination of the Pd to the π-system and failed to initiate C–H activation.

4.2. Cross-coupling Reactions Involving Hypervalent Iodine

Hypervalent iodide mediated cross-coupling reactions of the aromatic compounds have advantages of mild conditions (the reaction proceeds smoothly at room temperature), no need of transition metals, high yield, high regioselectivity, wide range of the substrates scope, and no polymerization in the product. The highly selective cross-coupling reactions overcome the disadvantage that in order to avoid the occurrence of homocoupling reaction, one of the inexpensive and readily available reactants must be greatly excessive and provide a series of valuable reference strategies.

In 2008, Kita and co-workers firstly reported a novel direct oxidative cross coupling of naphthalenes and mesitylenes [57]. This was the first successful example of selective transition-metal-free cross coupling of unfunctionalized arenes via single electron transfer (SET) processes (Scheme 46).

Subsequently, they have also reported the intermolecular C–H cross coupling of aromatic ethers 179 and 180 or 168 [58]. The key point of the reaction is the utilization of the perfluorinated PIFAs, which provided higher conversion and better selectivity compared with the traditional synthesis of biaryls using PIFA or PIDA. (Scheme 47).

In 2007, the group of Canesi used stoichiometric amounts of PIDA to achieve an oxidative C–C coupling of $para$-substituted anilides with thiophene. Different functional groups, such as aliphatic alcohols, aryl chlorides, and aryl bromides are tolerated under these reaction conditions. (Scheme 48) Under the conditions, substituted thiophenes 184 were obtained in 58-84% yields [59].

The reaction mechanism is shown in the Scheme 49, the amine group participates in the arylation process, resulting in the reaction occurs selectively in the ortho position. In addition, when the amine group on the aromatic ring is changed to a hydroxyl group, due to
**Scheme 44.** Oxidative coupling of electron-rich arenas.

**Scheme 45.** Benzylic coupling reactions.

**Scheme 46.** Oxidative coupling of mesitylene and naphthalenes.
Scheme 47. Oxidative coupling of substituted naphthalene with electron-rich arenas.

Scheme 48. Directed functionalization for the introduction of heterocycles.

Scheme 49. Proposed mechanism process.

the greater electronegativity of oxygen than that of nitrogen, the yield will be significantly decreased.

Organocatalytic intermolecular oxidative biaryl cross coupling provides potential strategies for developing greener synthetic methods of the valuable biaryl motifs. The direct synthesis of diarylbiodonium(III) salts in fluoroalcohol media was reported in 2009 [60]. Firstly thiophene afforded the corresponding α-thienyl-iodonium(III) salt, then in the presence of sequential addition of 1-methoxynaphthalene and TMSBr, resulting in the cross-coupling biaryl in excellent yield (Scheme 50) [61].

The electron-rich heteroaromatic compounds could selectively react at the 2-position with the iodine oxidant Phl(OH)OTs firstly, to form the stable iodonium(III) salts. The process rapidly occurred with the aid of fluoroalcohol as the solvent. These OTs compounds were usually inert toward the neutral aromatic nucleophiles. However, they could be activated by TMSBr in hexafluoroisopropanol (HFIP) to form iodonium(III) bromide salts intermediates, which underwent though further nucleophilic reaction to provide the biaryl products (Scheme 51).

Kita stated the synthesis of phenyl ethers, and in this reaction, the oxidation ability (through single-electron-transfer (SET) process) of PIFA resulted in the corresponding aromatic cation radicals [62]. Since then, hypervalent iodine(III) has been utilized as a selective and efficient SET oxidizing agent that enables a variety of direct C–H functionalizations of electron-rich arenes under mild conditions. Later they reported hypervalent iodine induced C(sp2)/ C(sp3) formation by para-substituted phenol ethers reacting with a variety of nucleophiles.

Cation radicals [ArH⁺] played a crucial role in the reaction, as reactive intermediates generated by SET from the charge-transfer (CT) complex of phenol ethers with PIFA. This was the first exam-
CONCLUSION

Comparing the Pd-catalyzed strategies and hypervalent iodine reagent mediated methodologies for the direct C–C bond formation from activation of C–H bonds, we clearly noticed that both strategies are powerful tools for directly obtaining the corresponding products. On one hand, the hypervalent iodine reagents mediated reactions are normally under mild conditions and give the molecular diversity without the presence of transition-metal, while the Pd-catalyzed approaches have a broader scope for the wide synthetic applications. On the other hand, unlike Pd-catalyzed C–C bond formation reactions, the study towards hypervalent iodine reagent mediated methodology mainly focused on the stoichiometric amount of hypervalent iodine reagent, while few catalytic reactions have been reported. Meanwhile, hypervalent iodine strategy has been proved to be more efficient in intramolecular medium-ring construction, while there are less successful examples on C(sp³)–C(sp³) bond formation.

In summary, we have demonstrated a number of selected approaches for the formation of a new C–C bond under the utilization of Pd-catalyzed reaction conditions or hyperiodine reagents. The direct activations of sp² or sp³ hybridized C–H bonds are believed to be important strategies for the future molecular design as well as useful chemical entity synthesis.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.
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