CHEMICAL REVIEWS

REVIEW

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Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions

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1. INTRODUCTION

In chemistry, a nucleophile is a molecule or ion with a lone pair of electrons. It donates both bonding electrons to its reaction partner (the electrophile) when forming a chemical bond.[1] More accurately, a nucleophile is an electron-rich chemical reactant that is attracted by electron-deficient compounds. According to this concept, anions such as Cl^- or compounds with a lone pair of electrons such as amines and alcohols are nucleophiles. In practice, organometallic reagents and hydrocarbons are all nucleophiles, as the C−M bonds of organometallic reagents and the C−H bonds of hydrocarbons tend to donate both of their bonding electrons to electrophiles when forming a chemical bond. Organometallic reagents are widely used in chemical synthesis, and hydrocarbons are found in nature.[2,3] Most electrophiles, such as the widely used organohalides, are directly or indirectly prepared from their corresponding nucleophiles. Therefore, if only nucleophiles are used, synthetic procedures will be more efficient and waste production will be minimized. Consequently, bond formations between two nucleophiles have tremendous potential in the area of sustainable chemistry and will benefit society.

However, combining two nucleophiles together seems incredible by conventional thinking, which argues that a nucleophile can only react with an electrophile. The introduction of transition metals to organic synthesis has allowed the reaction between two nucleophiles to be realized, in particular by transition metal catalyzed oxidative coupling reactions in which oxidants are involved. Several oxidants, including O_2, H_2O_2, and some high valent metals (copper salts) and halides (iodine(III) oxidants), are used in different types of oxidative cross-coupling reactions, dependent on the type of nucleophiles in the reaction.

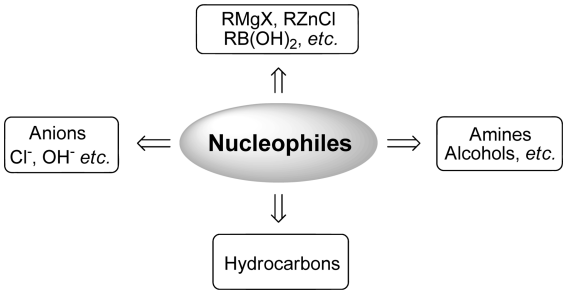
Normally, nucleophiles can be divided into four classes: MX, CM, CH, and XH (Scheme 1). In the MX group, salts such as NaI and NaF are employed as reactants to form carbon−halogen bonds. In the C−M group, a metal reagent is employed that is compatible

Special Issue: 2011 Frontiers in Transition Metal Catalyzed Reactions

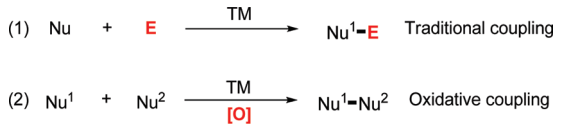
Received: November 4, 2010
Published: February 23, 2011

   dx.doi.org/10.1021/cr100379j | *Chem. Rev.* 2011, 111, 1780–1824

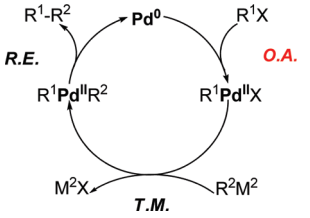
Scheme 1



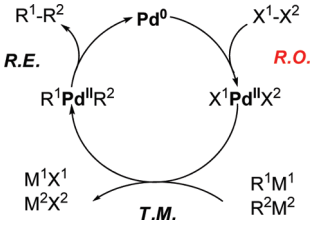
Scheme 2



Scheme 3



Scheme 4



with different kinds of functional groups, hence making transition metal catalyzed reactions accessible. For example, Grignard reactions have been well studied, for their advantages that include high activity, high selectivity, and low cost, which all provide a convenient means of predominating the performance of compounds produced. In addition, mild reaction conditions are important; under the atmosphere of molecular oxygen, it is possible to have good yields. With CH nucleophiles, oxidative cross-coupling reactions are known to occur. It is one of the most widely accepted green chemical processes, with environmentally benign byproduct such as H_2O or H_2O_2 formed when employing O_2 as the oxidant. Furthermore, various C−C bonds are formed directly from C−H and C−H bonds under oxidative conditions, thus producing larger molecules and increasing the utility of this method. The previous discussion highlights that oxidative cross-coupling reactions between two nucleophiles, especially reactions between two hydrocarbons (which are both environmentally friendly and straightforward), have great potential in the future of synthetic chemistry.

Until now, the oxidative cross-coupling reaction between two nucleophiles is a "young" field compared with traditional cross-coupling reactions. However, more and more attention is being paid to this new research topic. To the best of our knowledge, no review has ever been reported on this chemistry; therefore, we review the recent progress in the oxidative cross-coupling between two nucleophiles (Nu^1/Nu^2).

1.1. Comparison with Traditional Cross-Couplings between Nucleophiles and Electrophiles

Large amounts of coupling reactions between nucleophiles and electrophiles have been reported, and the method has become the classic model for bond constructions (Scheme 2, (1)).[4] Since transition metals were introduced into organic synthesis reactions, the coupling reactions of aryl and alkenyl electrophiles ($C(sp^2)-X$) with various nucleophiles, which cannot be achieved by traditional methods, have become possible.[5] Along with the rapid development of organometallic chemistry in the last few decades, many kinds of metal catalysts and ligands were discovered and applied in coupling reactions, leading to metal catalyzed coupling reactions becoming a "hot" research topic in chemical synthesis. Several named reactions in this field such as the Negishi, Suzuki−Miyaura, Stille, and Hiyama cross-couplings, as well as the more recently developed Buchwald−Hartwig reaction, have been explored and widely applied in industrial areas,[6] thus furthering the development of pharmaceuticals, agrochemicals, and functional materials as well as greatly enlarging the scope of organic synthesis.

The catalysts normally consist of late transition metals, such as Pd and Ni. Taking the "Pd(0)−Pd(II) catalytic cycle", for example, the widely accepted mechanism for this traditional coupling (Scheme 3) contains three main parts:[7] (1) oxidative addition of C−heteroatom bond of electrophiles R^1-X to the Pd(0) to form the intermediate $R^1-Pd(II)-X$; (2) transmetalation of nucleophiles R^2-M^1 with the Pd(II)−X bond to form intermediate $R^1-Pd(II)-R^2$; and (3) reductive elimination of intermediate $R^1-Pd(II)-R^2$ to release the coupling product R^1-R^2 and regenerate the Pd(0) species, thus completing a catalytic cycle. The electrophile in the oxidative addition step is usually an organic halide or pseudohalide. So far, this classic model has been extensively studied and widely applied in cross-coupling reactions.

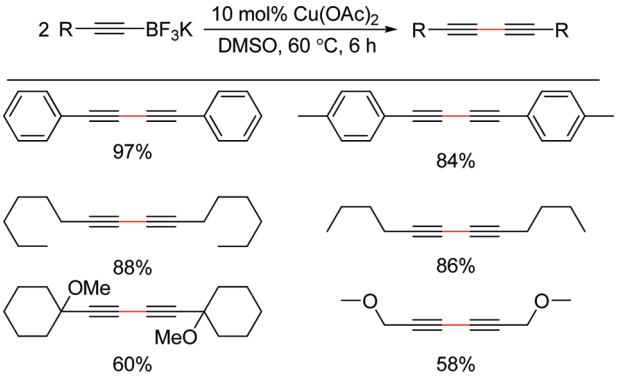
Taking the Pd(0)−Pd(II) catalytic cycle, for example, the mechanism of the oxidative cross-couplings could be illustrated as in Scheme 4.[8] This pathway starts from Pd(II) with two different leaving groups. The transmetalations of two nucleophiles R^1-M^1 and R^2-M^2 with the catalyst to form $R^1-Pd(II)-R^2$, which is followed by the reductive elimination to produce the coupling product and release the low-valent catalyst Pd(0) species. To restart the catalytic cycle, an oxidant X^1-X^2 is required to reoxidize the Pd(0) species to regenerate Pd(II).

In Scheme 3, during oxidative addition, the electrophile itself normally acts as an oxidant to oxidize the low-valent metal catalyst. Its organic group eventually becomes part of the cross-coupled product. As a result, no extra oxidant is required. In Scheme 4, the product contains two groups from two nucleophiles. The oxidant only acts as an electron acceptor to reoxidize the Pd(0) species without going into the cross-coupling product.

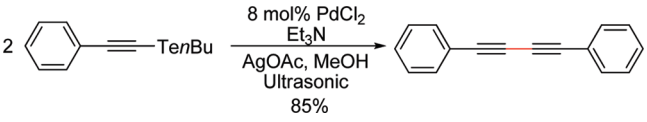
The oxidative coupling approach is also challenging. The homocoupling of the two nucleophiles and the direct reaction of the nucleophiles with the oxidant are potential side reactions. Even so, many excellent results showing high selectivity and yields have

dx.doi.org/10.1021/cr100379j |Chem. Rev. 2011, 111, 1780–1824

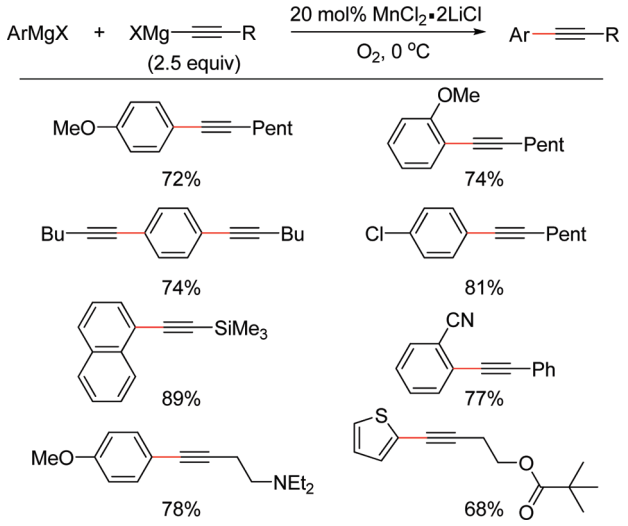
Scheme 5



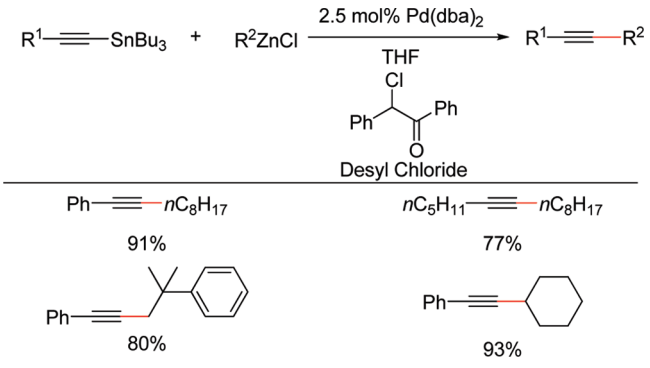
Scheme 6



Scheme 7



Scheme 8



been reported. These results will be highlighted and summarized in detail in this review. The oxidative couplings between different types of nucleophiles will be discussed. Reactions that contain two nucleophilic sites on one molecule and produce an intramolecular coupling product[9] will not be discussed in this review.

2. OXIDATIVE C−C BOND FORMATIONS BETWEEN TWO NUCLEOPHILES

2.1. Couplings between Two Organometallic Reagents as Nucleophiles

C−C bond formations are an important method in organic synthesis, and numerous methods have been developed regarding C−C bond formation and lengthening carbon chains.[10,11] Since Grignard reagents were discovered, main group organometallic derivatives with nucleophilic Csp, Csp^2, and Csp^3 atoms have been used in various C−C bond formations.[12] During the last decades, many new types of organometallic reagents have been developed, such as organozinc reagents,[13] organoboronic acids,[14] and organosilicon reagents.[15] All of these organometallic reagents are widely used in the transition metal catalyzed cross-coupling reactions with electrophiles. Meanwhile, the oxidative cross-coupling between two different organometallic reagents has also been slowly developed. The central challenge in oxidative cross-couplings is selectivity, as often homocoupling of the organometallic reagents involved occurs and the organometallic reagents can also react with oxidants. However, there are still excellent studies reported in this area.

2.1.1. Csp−M and Csp−M as Nucleophiles. Very few examples of oxidative couplings have been reported between two alkynylmetal reagents, as terminal alkynes could normally be used directly in cross-couplings, such as Sonogashira and Hay−Glaser couplings,[16,17] without the prefunctionalization of Csp−H. However, several examples have been reported.

One example was demonstrated by Stefani and co-workers in 2008,[18] in which potassium alkynyltrifluoroborates were employed as substrates in the presence of $Cu(OAc)_2$ as an efficient catalyst (Scheme 5). Symmetrical 1,3-diynes were obtained in moderate to high yields.

Alkynyltelluride reagents could also be homocoupled by using catalytic amounts of $PdCl_2$ as the catalyst under ultrasound conditions, which shows that organotellurides are also good metal reagents in coupling reactions (Scheme 6).[19]

2.1.2. Csp−M and Csp^2−M as Nucleophiles. The oxidative coupling between Csp−M^1 and Csp^2−M^2 is also understudied. The oxidation of organocuprates could be a potential route for this transformation, although a stoichiometric amount of copper salt has to be employed.[20,21] Recently, a Mn-catalyzed oxidative cross-coupling reaction between R(sp)−MgX and R(sp^2)−MgX was reported.[22] Previous studies of the homocoupling of RMgX[23] exhibited a heavy dependence of reaction rate on the nature of the organic group of RMgX. By wisely choosing the nature of different Grignard reagents, cross-couplings of the aryl Grignard reagent with alkynylmagnesium reagents to afford alkynes were achieved using oxygen as the oxidant. Functional groups such as OMe, CN, Cl, silyl, and esters are all well-tolerated, and heteroarenes are also suitable substrates (Scheme 7).

2.1.3. Csp−M and Csp^3−M as Nucleophiles. The first report on catalytic oxidative cross coupling between alkyl metal and alkynyl metal reagents was published in 2006 by Lei and coworkers, in which alkylzinc halides and alkynylstannanes were

dx.doi.org/10.1021/cr100379j |Chem. Rev. 2011, 111, 1780–1824

used as two nucleophiles and desyl chloride was applied as an oxidant (Scheme 8).[24] The desired $Csp-Csp^3$ cross-coupled products were produced with high selectivity and yields in the presence of $Pd(dba)_2$ without an extra ligand. Further studies showed that dibenzylidene acetone (DBA) acting as a π-acidic olefin ligand enhanced the reductive elimination step,[25,26] explaining the tolerance of β-hydrides on the alkyl groups. Further application of the reaction conditions showed that secondary alkylzinc halides could also be introduced and afforded the desired products in high yields.[27] Investigation of the reaction mechanism showed that the reaction involved double transmetalations of the two nucleophiles with the catalyst center followed by reductive elimination to produce the desired cross-coupling products. The authors showed that the Csp^3-Csp^3 homocoupling of alkylzinc reagent is very slow and the homocoupling of alkynylstannane did not occur separately under the standard conditions (Scheme 9). In addition, in situ IR studies indicated that the alkylzinc reagent transmetalated with the Pd−enolate bond and the alkynylstannanes reagent transmetalated with the Pd−Cl bond selectively. However, questions still remained as to which transmetalation was first.

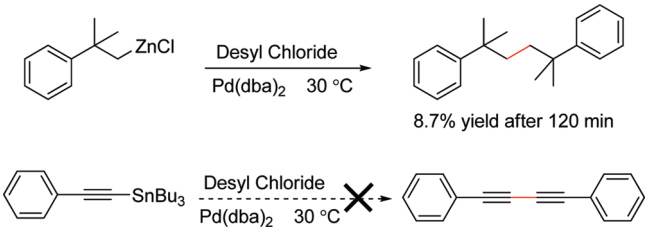
2.1.4. Csp^2-M and Csp^2-M as Nucleophiles. Biaryl compounds are significant building blocks for materials and pharmaceuticals. Hence, research into Csp^2-Csp^2 bond formations have been well investigated during the past several decades.[28] However, very few studies on the oxidative cross-couplings between two different aryl metal reagents are reported. Most of this research focuses on the coupling of aryl metal reagents with the C−H bonds of arenes and will be discussed later in more detail. Most of the reactions between two aryl metal reagents are oxidative homocouplings. This may be due to the similar reactivity of the different aryl metal reagents, and hence it is not easy to control the selectivity.

Lipshutz and co-workers reported the first oxidative cross-coupling reaction between two different aryl metal reagents to form unsymmetrical biaryls albeit in the presence of stoichiometric amounts of CuCN with oxygen as the oxidant at low temperature.[29] This early attempt encouraged others to use the oxidative coupling protocol for the synthesis of biaryl compounds. Recently, Hirao and co-workers reported an oxovanadium-catalyzed oxidative unsymmetrical biaryl synthesis from organoborates using oxygen as the oxidant (Scheme 10).[30] $VO(OEt)Cl_2$ was used as the catalyst for this transformation. Although only low yields and poor selectivities were obtained, this novel bond-formation method provides another possible route for the synthesis of unsymmetric biaryls. A similar protocol was later applied on the $Csp-Csp^2$ bond formations.[31]

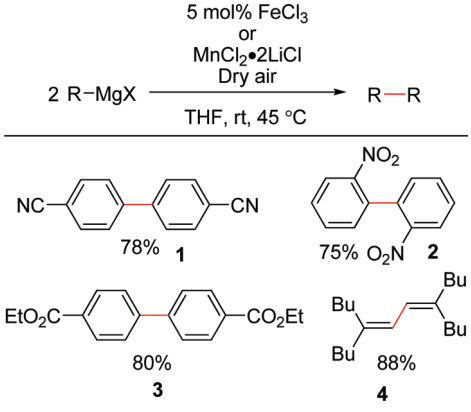
In cross-coupling reactions, attempts are made to avoid unwanted homocoupled biaryls. However, several studies focusing on the details of oxidative homocouplings of aryl metal reagents have also been reported, as symmetrical biaryls could be easily obtained via this protocol. Most of the employed nucleophiles are arylmagnesium,[32−37] arylboron,[38−46] or even arylstannanes.[47] Both organic oxidants such as α-halocarbonyl compounds,[46] 1,2-dihaloethane,[33] and 2,2,6,6,-tetramethylpiperidine-1-oxyl (TEMPO)[38] and inorganic oxidants such as Ag_2O and O_2[40,41] were used in different reaction systems. Even transition-metal-free oxidative homocoupling of arylmagnesium was also developed.[48] Among these developments, a key result was reported by Cahiez et al. in 2007, in which atmospheric oxygen was employed as an oxidant and iron or Mn was used as an efficient catalyst (Scheme 11).[23] Various aryl magnesium reagents were homocoupled in good to high yields. Functional groups such as nitrile (**1**), nitro (**2**), and ester (**3**) were well-tolerated. β-Mono- and β,β-disubstituted alkenyl Grignard reagents also afforded the corresponding conjugated dienes (**4**) smoothly, and the coupling is highly stereoselective.

2.1.5. Csp^2-M and Csp^3-M as Nucleophiles. Inspired by success of the oxidative cross-coupling between alkynylstannanes and alkylzinc reagents in 2006,[24] another combination was developed later by the same group. Arylzinc reagents and alkylindium reagents were screened as two ideal nucleophiles with desyl chloride as the oxidant.[49] The reaction proceeded smoothly at 60 °C, selectively giving the cross-coupled products

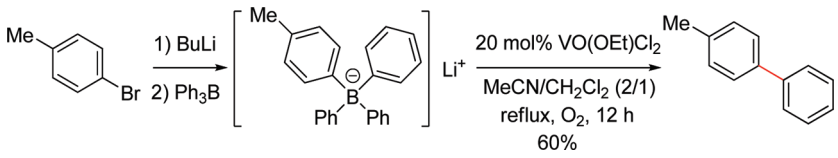
Scheme 9



Scheme 11



Scheme 10



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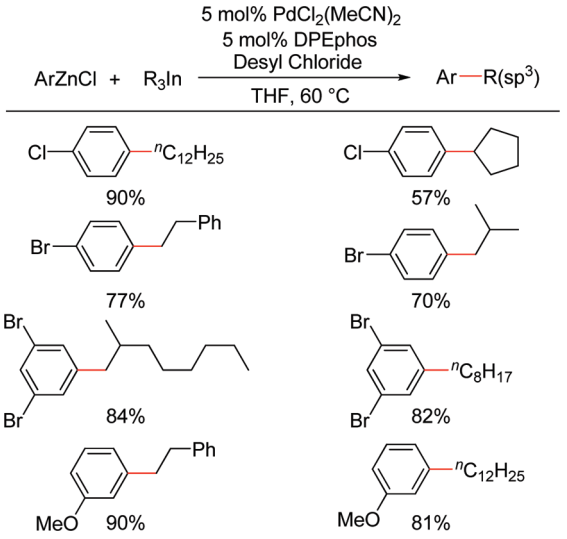
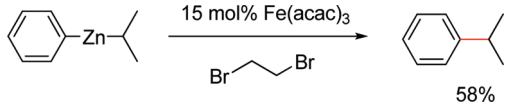
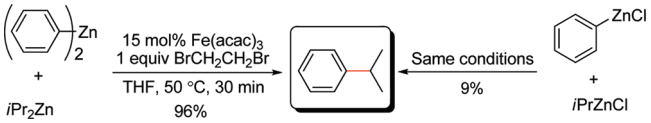
Scheme 12



Scheme 13



Scheme 14

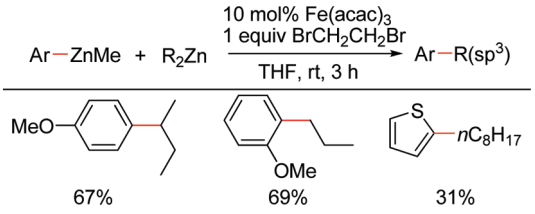


in the presence of 5 mol % of $PdCl_2(MeCN)_2$ and DPEphos (bis(2-diphenylphosphinophenyl)ether) (Scheme 12).

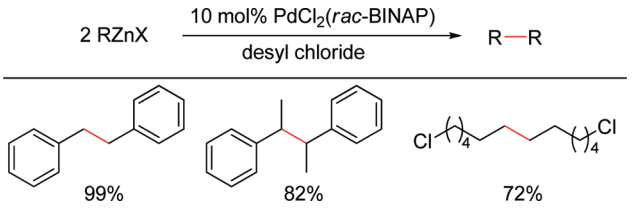
Kinetic factors were studied and a mechanism was proposed based on the Pd-catalyzed double transmetalations followed by reductive elimination to afford the final product. In this case, arylzinc reagents were proved to transmetalate with the Pd−Cl bond and alkylindium reagents were proved to transmetalate with the Pd−enolate bond; thus, high selectivity was obtained to give the cross-coupled product.

Later, Cahiez et al. reported another example in the presence of a Fe(III) catalyst.[50] Unsymmetric alkyl−aryl zinc reagents were found to undergo formal reductive elimination reactions to form the alkylarenes by employing catalytic amounts of Fe(acac)$_3$ in the presence of 1,2-dibromoethane as the oxidant (Scheme 13). The author also showed that only one phenyl group and one isopropyl group were transferred, and the desired cross-coupling product was obtained in 96% yield when diphenylzinc and diisopropylzinc were coupled together, and only 9% of the cross-coupling product was afforded when phenyl- and isopropylzinc chloride were employed as substrates (Scheme 14). Because only one-half of the diorganozinc can be transferred in this reaction, an inexpensive and nontransferable group was used. The authors first tried Me_3SiCH_2 as the nontransferable group. Although phenyl and isopropyl groups transferred selectively from $PhZnCH_2SiMe_3$ and $iPrZnCH_2SiMe_3$, a low yield (54%) of the desired product was obtained. After considerable efforts, the authors found that the methyl group is a better nontransferable group than Me_3SiCH_2 and gives the cross-coupling product in a satisfactory yield with other diorganozinc reagents (Scheme 15).

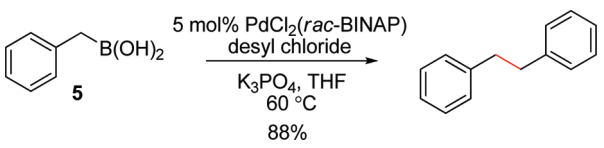
Scheme 15



Scheme 16



Scheme 17



2.1.6. Csp^3−M and Csp^3−M as Nucleophiles. One catalytic procedure based on the oxidative coupling between two alkyl metal reagents has been demonstrated by Lei and Zhang, in which the homocouplings of benzylic zinc reagents were investigated in the presence of a palladium catalyst (Scheme 16).[51] α-Halocarbonyl compounds were used as oxidants. Benzylic boronic acid (**5**) could also be involved as substrates (Scheme 17).

2.2. Oxidative Couplings between Hydrocarbons and Organometallic Reagents

The oxidative couplings between two organometallic reagents are considered as nongreen processes, as the starting materials have to be fully functionalized with C−M bonds. Taking the place of one of the C−M bonds with a C−H bond is a greener design and makes the cross-coupling cleaner. Although the C−H groups of hydrocarbons tend to donate their bonding electrons during a chemical reaction, it is not easy to activate them by a traditional manner. Many research groups have put their efforts on the C−H activation of hydrocarbons and achieved considerable results.[52,53] Some of them are trying to replace R−M reagents with R−H to couple with a proper electrophile R′−X in the traditional coupling methodology.[54,55] As this type of reaction is not an oxidative cross-coupling between two nucleophiles, it will not be discussed in this review. Several reviews have focused on the C−H

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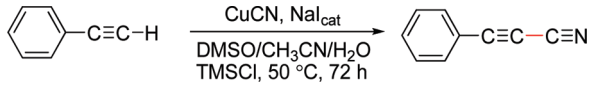
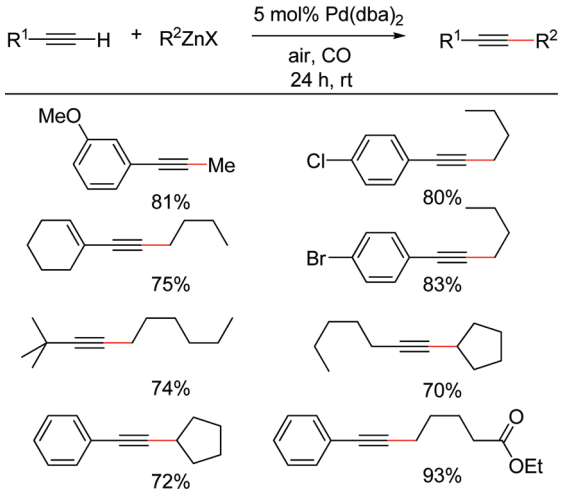
Scheme 18



Scheme 19

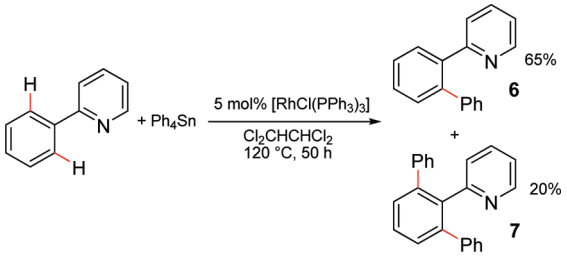


activations of various hydrocarbons and have highlighted the success of research in this area.[56−59] Some chemists also introduce C−H activation into recently developed oxidative cross-coupling reactions with another nucleophile, which could be either a organometallic reagent or another hydrocarbon.[57,60] These studies will be summarized individually in this review.

2.2.1. Csp−H (Terminal Alkynes) and Organometal Reagents as Nucleophiles. The Csp−H bonds of terminal alkynes are one of the most active C−H bonds in organic molecules, so their activation is easy to achieve, and terminal alkynes are normally directly used in C−C bond formations.[16] Most oxidative couplings involving them as nucleophiles normally occur with another C−H nucleophile and will be discussed later. The couplings between Csp−H and organometallic reagents are rare. The cyanation of terminal alkynes with cuprous cyanide is an example (Scheme 18).[61−64] The use of dimethylsulfoxide (DMSO) with CH_3CN as the cosolvent is critically important in this cyanation process. Homocouplings can be minimized to <4% when the volume ratio of DMSO and CH_3CN is 3 to 1. Meanwhile, increasing the amount of CH_3CN in the reaction can further minimize the homocouplings with a sacrifice in the yield of the desired product. Catalytic amounts of sodium iodide were found to facilitate and accelerate the oxidative cyanation process, and no cyanation reaction occurred in the absence of either TMSCl or H_2O.

Another example is the alkylation of terminal alkynes with alkylzinc reagents reported by Lei and co-workers in the presence of $Pd(dba)_2$ catalyst.[65] By comparing with DBA, a well-known π-acidic ligand,[25] CO was found to act as a π-acidic ligand in this aerobic oxidative coupling reaction, which facilitated reductive elimination in transition-metal-mediated reactions. Air or oxygen was used as oxidants, and the reaction proceeded smoothly at room temperature. As shown in Scheme 19, both electron-rich and electron-poor alkynes afforded good to excellent yields and high selectivity of the cross-coupling product. Secondary alkylzinc reagents also worked very well. Reactive functional groups such as Br and esters could be well tolerated. Kinetic studies of this reaction and the homocoupling of alkyne and alkylzinc reagent showed that the reductive elimination of C(sp)−C(sp^3) is faster than that of both C(sp)−C(sp) and C(sp^3)−C(sp^3). This affords the kinetic superiority for the selectivity of cross-coupling products. Another factor for this excellent selectivity is the low concentration of alkynylzinc reagents generated in situ from the reaction of alkylzinc reagents with terminal alkynes.

Scheme 20



2.2.2. Csp^2−H (Arenes or Alkenes) and Organometal Reagents as Nucleophiles. Direct use of arenes or alkenes as nucleophiles in oxidative cross-coupling reactions is challenging and becoming a hot topic in recent years, as it precludes the need to be prefunctionalized as aryl metal reagents, which is both a time-consuming and an economically inefficient process.[3] However, for the monosubstituted arenes, regioselectivity is problematic. Up to now, the application of directing groups is still the best means to tune the reactivity and control the regioselectivity.[56] The contribution in this area will be highlighted according to the differences between organometallic reagents used in the oxidative couplings with arenes. Because most of the oxidative cross-couplings between alkenes and organometallic reagents are called oxidative Heck reactions and have been well summarized in a recent review,[66] the details will not be outlined in this paper.

2.2.2.1. Organostannane Reagents. The first transition metal catalyzed oxidative direct coupling of arenes with an aryl metal reagent was reported by Oi et al. in 1998.[67] It is the arylation of an arene with a directing group pyridyl on the ortho-position with arylstannanes as the coupling partner in the presence of the Wilkinson catalyst (Scheme 20). Pd, Ir, Pt, and Ru catalysts were found to be ineffective in this coupling reaction. The solvent has an obvious effect on this coupling reaction, in which chlorinated alkanes such as $CHCl_3$, 1,2-dichloroethane, and 1,1,1-trichloroethane as solvents could significantly increase the yields of the coupling products. 1,1,2,2-Tetrachloroethane exhibited a dramatic effect, giving the monoarylated (**6**) and diarylated (**7**) products in good yields of 65% and 20%, respectively. The authors did not give any proposed mechanism or reasons for why chlorinated alkanes increased the yield of the coupling product. However, we can speculate that the chlorinated alkanes also act as an oxidant in this coupling reaction.[68]

Several years later, Yu and co-workers reported another oxidative cross-coupling between directing group containing arenes and alkylstannane reagents.[69] Stoichiometric experiments showed that benzoquinone could accelerate the reductive elimination of Csp^2−Csp^3 bond formation (Scheme 21). For the catalytic reaction, a proper oxidant has to be employed. After considerable screening, the author found that 1 equiv of

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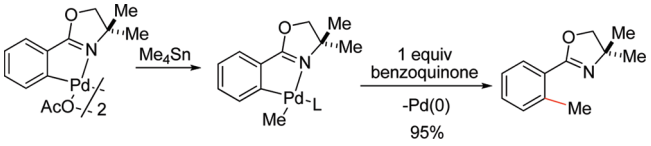
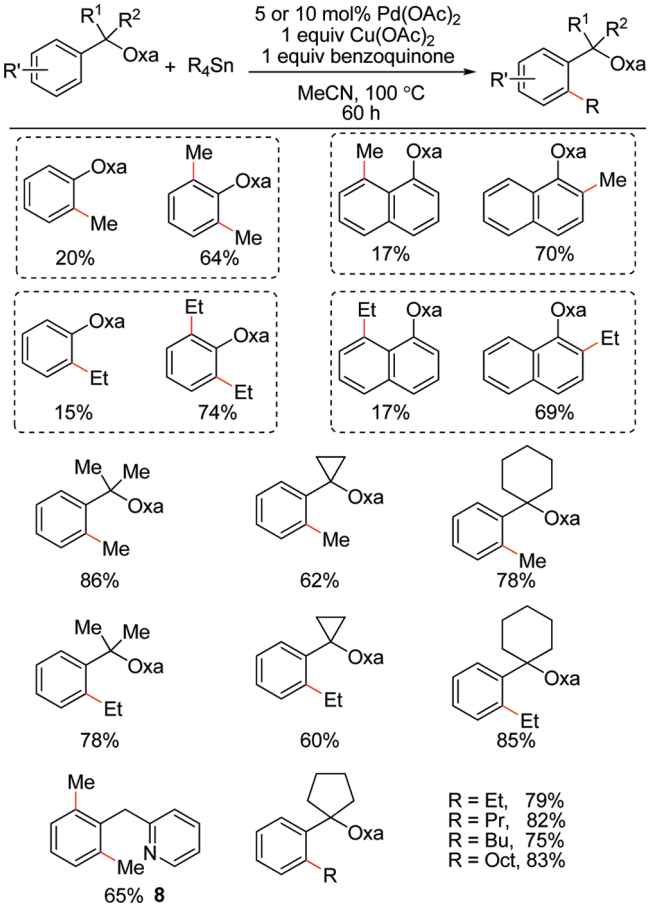
Scheme 21



Scheme 22



$Cu(OAc)_2$ combined with 1 equiv of benzoquinone under air afforded the mainly dialkylated products. By introducing one carbon atom between the aryl ring and the σ-chelating group, the desired monomethylation product was obtained (Scheme 22). The author speculated that the presence of 1 equiv of benzoquinone was essential for the C−H activation to occur with this type of substrate. Since the formation of a cyclic trinuclear mixed metal acetate $[Cu_2Pd(OAc)_6]$ was previously reported,[70] it is possible that benzoquinone prevented the formation of this complex, which is not reactive for substrates. Because of the fast reductive elimination, long-chain alkylstannanes containing β-hydrides (Et_4Sn, Pr_4Sn) were effective. Other pyridine-ring-containing substrates also worked well and afforded dimethylation of the product (**8**).

2.2.2.2. Organoboron Reagents. Organoboron reagents, especially boronic acids, have been widely applied in organic synthesis as a particularly attractive class of reagents because of their availability, stability, nontoxicity, and ease of handling.[14] Many efforts have been put into the coupling reactions involving organoboron reagents as nucleophiles.[71] The first oxidative coupling reaction between arene and organoboron was reported by Kakiuchi et al. in 2003,[72] in which aromatic ketones and arylboronates were employed. Other organoboron reagents such as arylboronic acids, arylboronic acid anhydrides, and sodium tetraphenylborate were ineffective in this coupling reaction.[73] One equiv of ketone offered the corresponding arylation product in 47% yield, while the use of 2 equiv of ketone improved the product yield to 89% (Scheme 23). NMR experiment and GC-MS results showed that the trialkoxyborane of **9** was formed during the coupling reaction, which suggested that one-half of the aryl ketone acted as the oxidant.

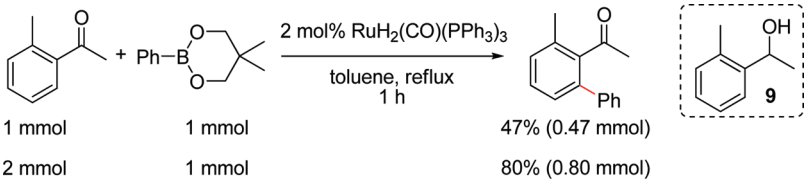
Later, Yu and co-workers reported a palladium-catalyzed oxidative cross-coupling of pyridine-directed arenes with both methylboroxine and alkylboronic acids.[74] The combination of $Pd(OAc)_2$, $Cu(OAc)_2$, and benzoquinone provided a promising solution to the reaction of C−H with methylboroxine (**10**) (Scheme 24); even the pyrazole-directed phenyl could afford the methylation product, albeit in lower yields. The electronic effects of the substitution groups were not obvious since both electron-rich and -deficient groups offered the desired product in moderate yields. Under the same reaction conditions, alkylboronic acids failed to give any cross-coupling products. The problem was solved by changing $Cu(OAc)_2$ with Ag_2O and CH_2Cl_2 solvent with *tert*-amyl alcohol (Scheme 25). Ag_2O was deduced to play a dual role as both an efficient promoter for the transmetalation and a co-oxidant with benzoquinone, which is crucial to the reductive elimination step.

Then, they changed the arene from a pyridine-directed phenyl to simple benzoic acids.[75] On the basis of their previous studies, a Pd^{II}/Pd^0 catalysis cycle most likely occurred. The benzoic acids without the sodium counterion are not reactive. Because of the enhancement of the transmetalation step for Suzuki coupling reactions, K_2HPO_4 was screened as a suitable base to increase the yield of the desired product and it also led to the in situ formation of carboxylates (**11**), so benzoic acids instead of sodium carboxylates were used directly as substrates (Scheme 26).

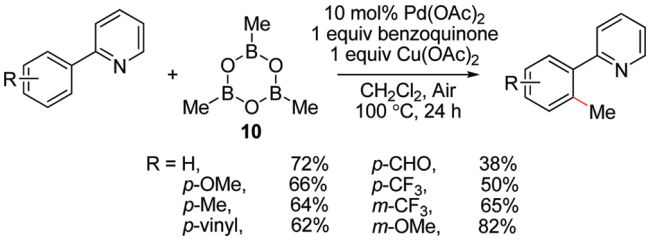
As this arylation protocol was limited to only several benzoic acids and poor yields were obtained with electron-deficient arenes, an improved procedure was later developed by the same group, in which the Ag_2CO_3 oxidant was replaced by 20 atm of air or O_2 and aryltrifluoroborates were used as coupling partners (Scheme 27).[76] This new protocol overcame the low yields for electron-deficient substituted arenes and afforded the corresponding coupling product in good to high yields. It is also effective for aryl acetic acids, which could bear α-hydrogens in the substrates (Scheme 28). Phenylacetic acid proceeded smoothly to afford a diarylated product. The presence of α-substituents provides sufficient steric hindrance to induce monoselectivity. The presence of an Ag^+ oxidant, which was essential to their previous work, was shown to lead to a complete loss of reactivity.

Shi et al. reported another oxidative cross-coupling between Csp^2−H nucleophiles and arylboronic acids, in which an acetamido moiety was used as a directing group on the arene substrates (Scheme 29).[77] After screening, they found that $Pd(OAc)_2$ combined with $Cu(OTf)_2$ as an oxidant with Ag_2O as the additive could afford the desired cross-coupling product in satisfactory yields. The Ag_2O may work as either a co-oxidant, base, or both. Two possible pathways were proposed (Scheme 30). One possibility is the initiation by electrophilic attack of the Pd^{II} center to

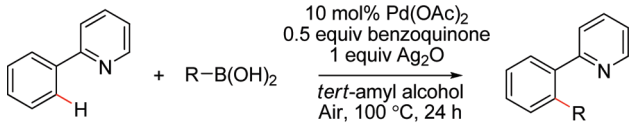
Scheme 23



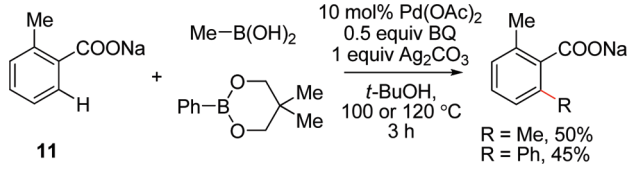
Scheme 24



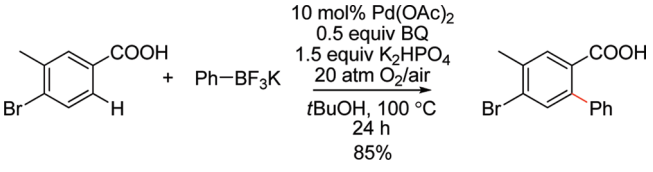
Scheme 25



Scheme 26



Scheme 27



the aromatic ring with the assistance of the acetamido group, followed by the transmetalation with arylboronic acid and reductive elimination to offer the expected coupling product (Scheme 30, path A). The other is the transmetalation of the boronic acid with Pd^{II} salts first to initially form an arylated Pd^{II} species, which attacks in an electrophilic manner to the aromatic ring to form a diaryl palladium species, which then underwent reductive elimination to give the final product (Scheme 30, path B). Further investigation showed that the cleavage of C−H bond was involved in the rate-determining step (intramolecular isotopic effect: $K_{H/D}$ = 2.3). Stoichiometric experiments showed that $Pd(OAc)_2$ should react with acetanilide to cleave the C−H bond first; otherwise, no cross-coupling product formed. So path A was believed to be a favorable possibility. Another similar procedure was later reported by the same group using *O*-methyl oximes and arylboronic acids as coupling partners.[78] The oxidative couplings of other directing group containing arenes with arylboronic acids were also reported during the progress of this protocol.[79,80]

The above reactions describe the oxidative cross-couplings between directing groups containing arenes and organoboron reagents. The direct oxidative cross-coupling between simple arenes with arylboronic acids has also been reported in recent years. An early procedure was disclosed by Shi and co-workers in which palladium acetate was applied as the efficient catalyst.[81] Mesitylene and phenylboronic acid were tested in the model reaction. After considerable optimization, they obtained the ideal conditions for this transformation by using 5.0 mol % of $Pd(OAc)_2$ and 1.0 equiv of $Cu(OAc)_2$ as a co-oxidant under an O_2 atmosphere. Various simple arenes and heteroarenes were oxidatively coupled with arylboronic acids under the optimized conditions. In general, electron-rich arenes bearing methyl substitutents showed good reactivity, and the corresponding coupling products were obtained in good yields. Electron-rich (**12**) and methoxy-substituted (**13**) polyarenes were also favorable for this transformation (Scheme 31). In the presence of a stoichiometric amount of transition metal salts such as iron and manganese salts, arylboronic acids could also be coupled with aromatic compounds (benzene, thiophene, and furan) to afford biaryl compounds.[82−84]

Oxidative coupling of heteroarenes with phenylboronic acid showed high regioselectivity on the 2-position of 2,3-benzothiophene, 2,3-benzofuran, and *N*-heterocycles, such as pyrroles and indoles, affording good to high yields (Scheme 32). C−Cl and free N−H bond were well tolerated in the reaction progress. However, the acetyl-protected indole only offered the coupling product in a very low yield, as electron-deficient groups disfavored the electrophilic attack of Pd(II) to the arene rings.

Nickel catalyst has also been applied in the oxidative cross-coupling between heteroarenes and arylboronic acids in recent times by Miura and co-workers.[85] Benzoxazoles, 1,3,4-oxadiazoles, and oxazoles are also suitable substrates to oxidatively couple with arylboronic acids in the presence of NiBr as the catalyst and 2,2′-bipyridine or 1,10-phenanthroline as the ligand under aerobic conditions. The combination of 2,2′-bipyridine with K_3PO_4, which was effective for benzoxazoles and 1,3,4-oxadiazoles, was sluggish for the transformation of oxazoles. The replacement of 2,2′-bipyridine and K_3PO_4 with 1,10-phenanthroline and NaO*t*Bu resolved this problem and afforded the desired products in moderate yields (Scheme 33).

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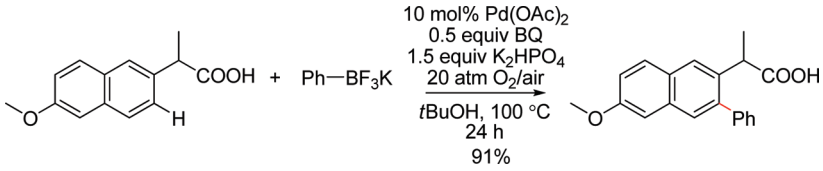
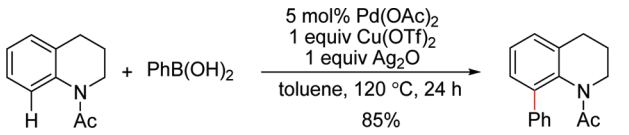
Scheme 28



Scheme 29



2.2.2.3. Organosilicon Reagents. Organosilicon reagents are another class of important organometallic compounds used in cross-coupling reactions. The palladium-catalyzed Hiyama reactions have been widely investigated in the past decades. However, oxidative couplings involving organosilicon reagents as nucleophiles are rare. Shi and co-workers reported an example in 2007, in which acetanilide and trialkoxyarylsilanes (**14**) were oxidatively cross-coupled through *ortho*-C−H activations of acetanilide (Scheme 34).[86] Acetamindo was used as a directing group. Using 5 mol % of $Pd(OAc)_2$ as the catalyst, 2 equiv of $Cu(OTf)_2$ as the oxidant, and 2 equiv of AgF as a fluoride source, the coupling reaction proceeded at 110 °C in dioxane. The author proposed that AgF not only acted as a simple fluoride source but also served as a co-oxidant to oxidize the Pd(0) species back to Pd(II) to restart the catalytic cycle. Different trialkoxyarylsilanes were tested; both (trimethoxy)phenylsilane and triethoxy(phenyl)silane showed good efficiency in this coupling reaction, yet phenyl silanol was less efficient. Different protecting groups were also tested. Benzoyl- and formyl-protected aniline offered the desired product with low efficiency. Other groups (tosyl, acetacetyl, and trifluoroacetyl, Boc) as well as *N*-alkylated and free anilines did not work for this transformation.

Later, Loh and co-workers demonstrated another similar result by using cyclic enamides (**15**) instead of acetanilide (Scheme 35).[87] $Pd(OAc)_2$ and AgF were still the best combination, yet $Cu(OTf)_2$ was not necessary for this transformation. A similar catalytic cycle to that of path A in scheme 30 was proposed.

Miura and co-workers later described a nickel-catalyzed oxidative coupling of heteroarenes with arylsilanes and one alkenylsilane.[88] It was found that 10 mol % of $NiBr_2 \cdot$ diglyme and 10 mol % bpy (2,2′-bipyridine) combined with 3.0 equiv of CsF and 2.0 equiv of CuF_2 were necessary for this transformation. A variety of heteroarenes were tested, such as benzoxazole (**16**), 2-phenyl-1,3,4-oxadiazole (**17**), 5-phenyloxazole (**18**), *N*-methylbenzimidazole (**19**), and benzothiazole (**20**). They all afforded the corresponding coupling products in moderate to high yields (Scheme 36). One alkenylsilane (**21**) was coupled with benzoxazole in 70% yield and was obtained with an *E*/*Z* value of 26:74 (Scheme 37). In this study, coupling to indole substrates was not undertaken. Hence, another report, focusing on the oxidative cross-coupling between indole and arylsiloxane, was later demonstrated by Zhang and co-workers in the presence of $Pd(OAc)_2$ as the catalyst and Ag_2O as the oxidant.[89] Tetrabutylammonium fluoride (TBAF) was employed as a fluoride source to activate the organosilanes. Still, the transformation shows high regioselectivity on the 2-position of the indole ring (Scheme 38). Electron-rich indoles (**22**) are more reactive than the electron-deficient ones (**23**), indicating the electrophilic substitution mechanism.

2.2.2.4. Organozinc Reagents. Nakamura et al. have demonstrated in several reports the iron-catalyzed oxidative cross-couplings between Csp^2−H and organozinc reagents.[90] They first reported this work in 2008 by using a directing group containing aromatic rings with the in situ formed diarylzinc reagent from arylmagnesium bromide and 1/2 equiv of $ZnCl_2 \cdot$ TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine).[91] The ligand, 1,10-phenanthroline, showed a high efficiency to accelerate this transformation. The oxidation state of iron and its counteranion had a minor effect on the catalytic activity: $FeCl_2$, $FeCl_3$, and $Fe(acac)_3$ showed almost the same efficiency. 1,2-Dichloro-2-methylpropane was used as an efficient oxidant. The author also noted that Ph_2Zn reagents prepared from phenyllithium are ineffective, indicating the different nature of zinc reagents arising from different preparation methods.[92] Pyridyl benzene afforded the monoarylated product (**6**) in 82% yield along with 12% of the diarylation product (**7**) (Scheme 39), whereas α-benzoquinoline offered the arylation product quantitatively (Scheme 40).

Then, they changed the substrates to an aryl imine by using similar conditions, in which 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) was used as the ligand instead of 1,10-phenanthroline.[93] A variety of aryl imines derived from acetophenones were tested in this oxidative coupling reaction. They exhibited good functional group tolerance, that is, C−Br, C−Cl, and C−OTf are well tolerated (Scheme 41). The electron-deficient group −CN did not affect the efficiency and afforded the corresponding products in high yields. One of the substrates (**24**) was later introduced to a further functionalization with Suzuki−Miyaura coupling (Scheme 42).

Then the Fe-catalyzed system was applied to alkenes. In this case, 1-bromo-2-chloroethane was used as an oxidant instead of 1,2-dichloro-2-methylpropane.[94] 2-Pyridyldimethylvinylsilane (**25**) was employed as a substrate, in which the pyridine group acted as a directing group to achieve complete regioselectivity and stereoselectivity. Even the phenylmagnesium reagent is reactive and offers the coupling product in 70% yield (Scheme 43).

2.2.3. Csp^3−H (Alkanes) and Organometal Reagents as Nucleophiles. Csp^3−H bonds of alkanes are the most inert bonds among hydrocarbons. Although several research groups have demonstrated the direct functionalization of C−H bonds in alkanes (borylation of alkanes),[95] it is still a challenging task to employ Csp^3−H bonds directly in cross-coupling reactions. Normally, they are activated directly by being adjacent to heteroatoms or directing groups. Most of the research in this area focuses on organoboron reagents, although the oxidative coupling of Csp^3−H with other organometallic reagents has been reported.

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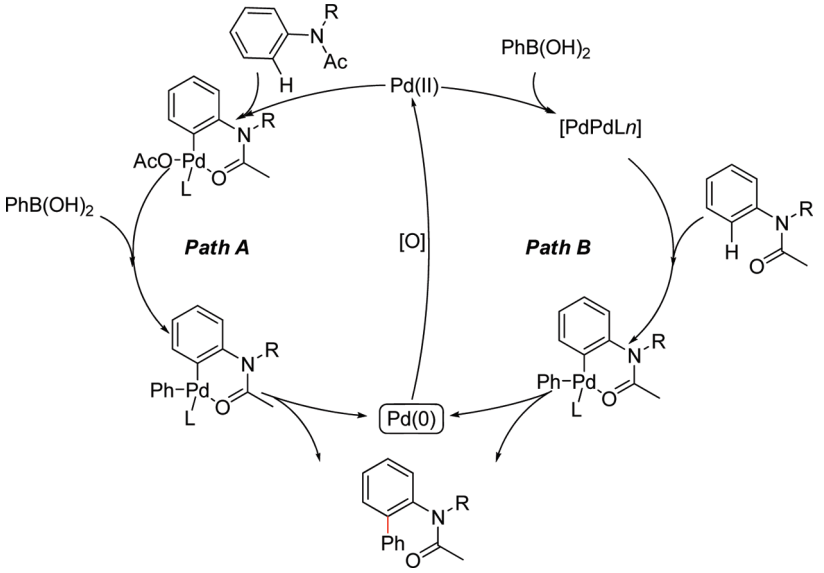
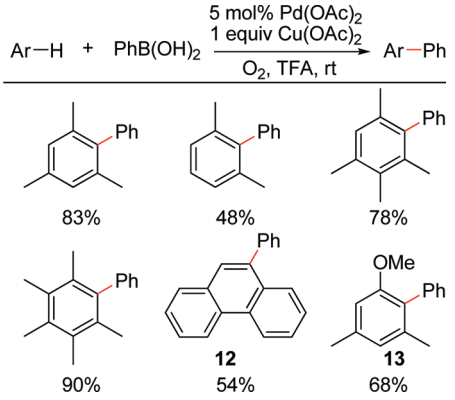
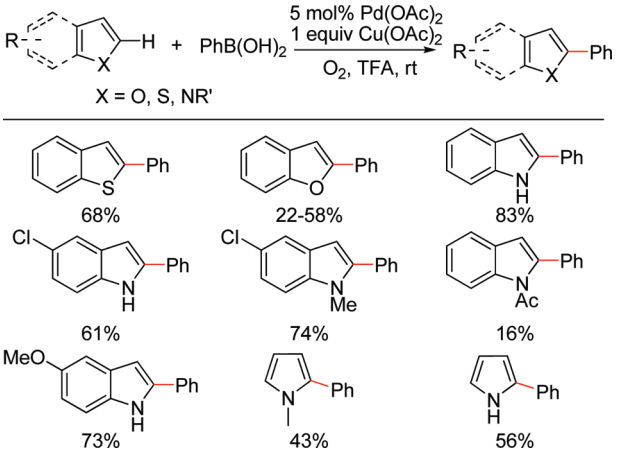
Scheme 30



Scheme 31



Scheme 32



2.2.3.1. Cyanide Ion. Although cyanide salts are not organometallic compounds, the oxidative cyanation of a Csp^3—H will form a C—C bond, and such chemistry will be summarized in this section (Scheme 44).

Murahashi et al. reported an oxidative cross-coupling between methyl groups adjacent to tertiary amines and sodium cyanide.[96] In this transformation, $RuCl_3 \cdot nH_2O$ was used as a catalyst under 1 atm pressure of O_2. *N*,*N*-dimethylaniline (**26**) was converted to *N*-methyl-*N*-phenylaminoacetonitrile (**27**) smoothly in 88% yield. About 3% yield of *N*-methylaniline (**28**) and a trace amount of *N*-methylformanilide (**29**) were observed in the reaction (Scheme 45). The coupling products, α-aminonitriles, can be readily converted into amino acids.[97,98] For example, alkaline hydrolysis of *N*-methyl-*N*-phenylaminoacetonitrile (**27**) gave *N*-methyl-*N*-phenylglycine in 87% yield (**30**). Furthermore, the α-aminonitriles thus obtained can be converted into unsymmetrical 1,2-diamines, which are important as ligands and precursors of biologically active compounds. Typically, treatment of *N*-methyl-*N*-phenylaminoacetonitrile (**27**) with lithium aluminum hydride gave *N*-methyl-*N*-phenylethylenediamine (**31**) in 92% yield (Scheme 46).

The preliminary mechanism of this transformation was then explored. The intramolecular deuterium isotope effects indicated that electron transfer from the amine to ruthenium would take place as the initial step. Molecular oxygen (1 mol) is consumed for each oxidation of 2 mol of *N*,*N*-dimethylaniline under the standard conditions, which indicated that one molecular oxygen was used for the formation of two iminium ion intermediates, which are trapped with cyanide to give the corresponding α-aminonitriles. The authors proposed a possible mechanism for this transformation as follows (Scheme 47): the coordination of a ruthenium species **32** to a tertiary amine **33** gives **34**. β-Hydride elimination results in the formation of an [iminium ion]—ruthenium hydride complex **35**. The ruthenium hydride species **35** undergoes reaction with molecular oxygen to form an [iminium ion]—Ru^nOOH complex **36**. Subsequent reaction of the [iminium ion]—Ru^nOOH complex **36** with HCN, which is generated from NaCN and acetic acid under the conditions used, gives α-aminonitrile **37**, H_2O, and a Ru^{n+2}=O species **38**, which reacts with another tertiary amine, **33**, to give the

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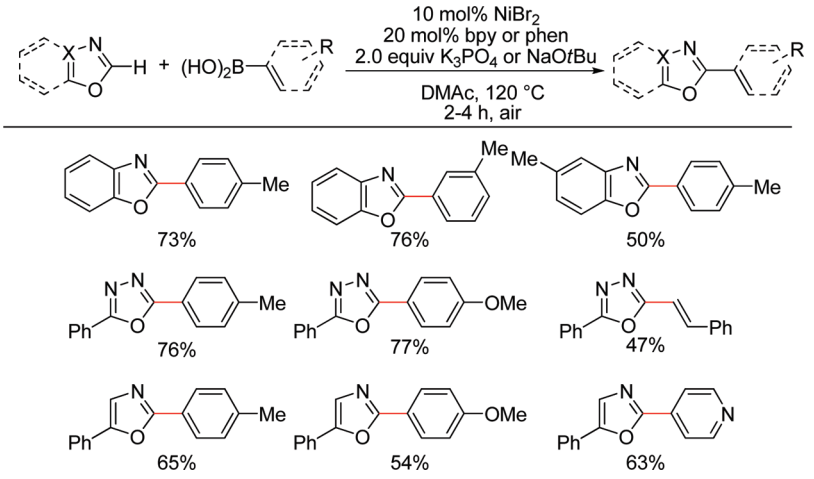
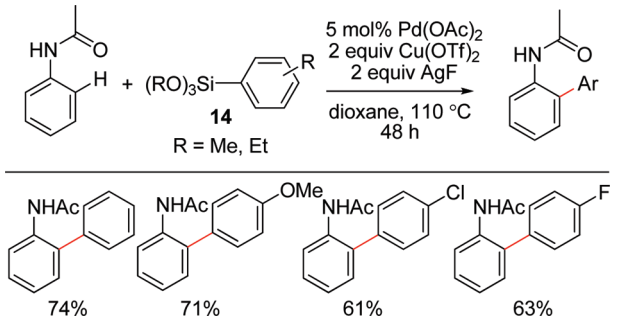
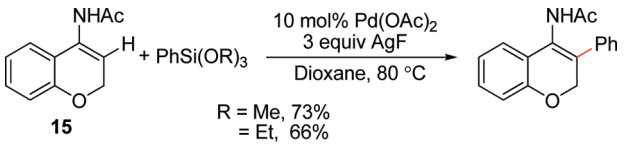
Scheme 33



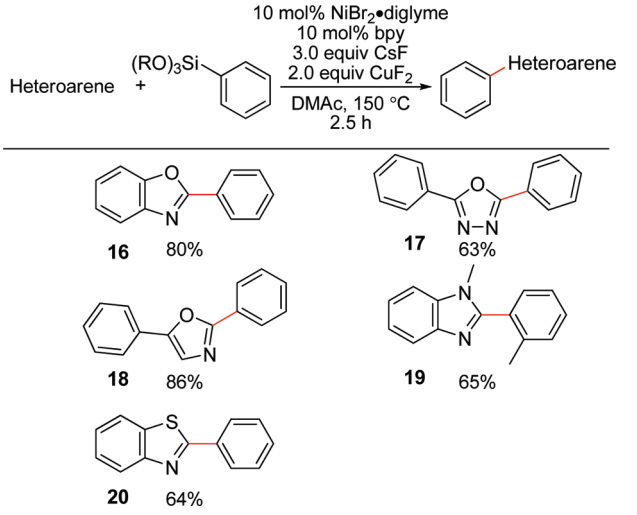
Scheme 34



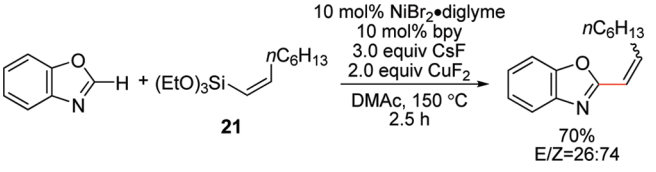
Scheme 35



Scheme 36



Scheme 37



iminium ion intermediate **39** by electron transfer and subsequent hydrogen transfer. The iminium ion intermediate **39** can be trapped with cyanide to afford α-aminonitrile **37**, and a ruthenium species **32**, to complete the catalytic cycle.

Later, they reported another similar ruthenium-catalyzed oxidative cyanation of tertiary amines with sodium cyanide by using H_2O_2 as the oxidant.[99] Details of the developments with this cyanation reaction, as well as substrate scope and mechanism, are reported by the same group in 2008.[100]

Sain and co-workers demonstrated a vanadium-based catalyst, which catalyzed oxidative cyanation of tertiary amines with sodium cyanide in the presence of molecular oxygen as the oxidant.[101] The oxidative cross-coupling products were formed in high yields within 1.5−3 h (Scheme 48). Iminium ion was also proposed as the key intermediate in this transformation.

Sodium cyanide is highly toxic and dangerous to handle, which restricts its application. Han and Ofial reported an iron-catalyzed oxidative cyanation by using trimethylsilyl cyanide as the cyano source, which is much less toxic in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 49).[102] This transformation did not need the addition of an extra ligand, and both $FeCl_2$ and $FeCl_3$ showed similar efficiencies. Notably, the reaction proceeded smoothly even at room

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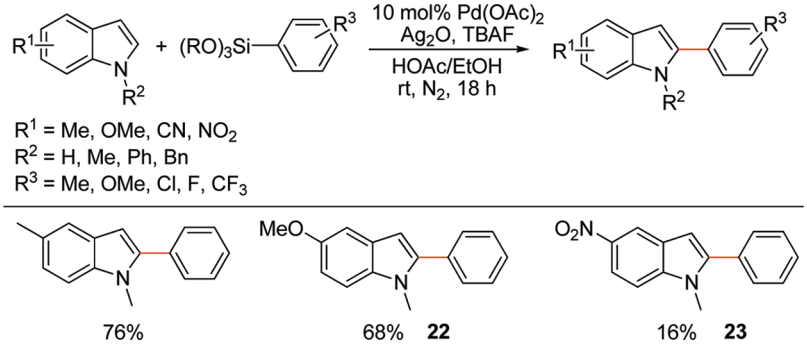
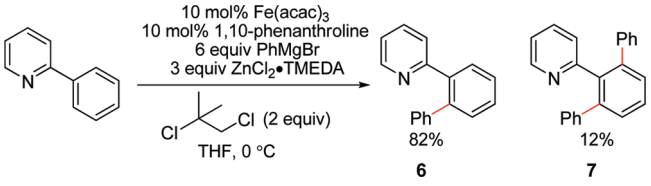
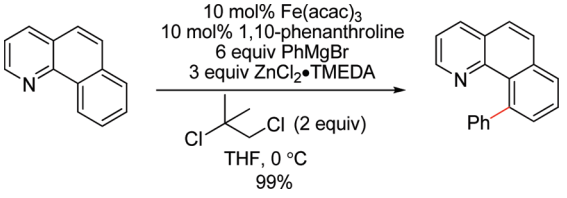
Scheme 38



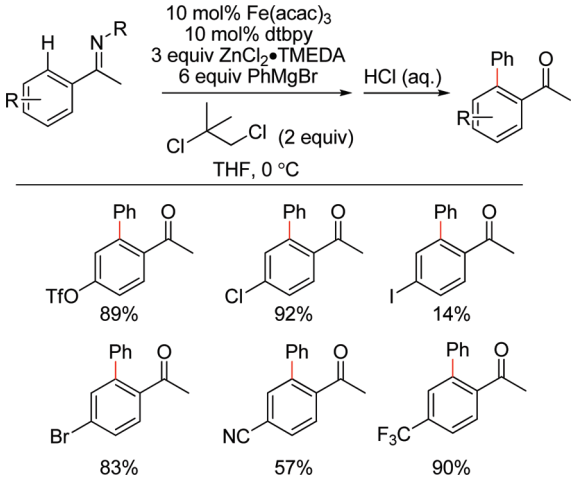
Scheme 39



Scheme 40



Scheme 41



temperature. Dicyanation products such as **40** were achieved by controlling the amount of trimethylsilyl cyanide.

2.2.3.2. Organoboron Reagents. Inspired by the ruthenium -atalyzed *ortho*-arylation of aromatic ketones discovered by Kakiuchi, Chatani, and co-workers,[72] Sames and co-workers demonstrated an sp^3 C−H bond arylation with arylboronate ester directed by an amidine protecting group.[103] The reaction proceeded smoothly at 150 °C by using 3.3 mol % of $Ru_3(CO)_{12}$ as the catalyst and pinacolone as the oxidant. Both electron-donating and electron-withdrawing substituents such as CF_3 (**41**) and OMe (**42**) attached to the arylboronates could afford the coupling products in 76% and 70% yields, respectively. The protected six-membered piperidine ring (**43**) could also undergo arylation to give the coupling product, albeit in a low yield. Other protecting groups such as pyridine (**44**) and pyrimidine (**45**) were effective for this coupling reaction and afforded the desired products (Scheme 50).

The amidine-protecting group could be easily removed from the coupling products in the presence of hydrazine and acid, offering α-aryl pyrrolidines directly. These processes can be accelerated by microwave irradiation (Scheme 51).

At the same time, Yu and co-workers reported a palladium-catalyzed oxidative cross-coupling of Csp^3−H with methylboroxine and alkylboronic acids using pyridine as a directing group.[74] Normally, organoboron reagents are used under basic conditions. However, this transformation was carried out in acetic acid solution. The combination of 10 mol % $Pd(OAc)_2$, 2 equiv of benzoquinone, and 2 equiv of $Cu(OAc)_2$ in acetic acid under O_2 provided a promising solution to the oxidative coupling between pyridine-directed Csp^3−H and methylboroxine (Scheme 52).

However, this protocol is only suitable for methylboroxine; other alkylboroxines fail to give the desired products. Then the authors turned to alkylboronic acids and finally achieved significant results. Instead of $Cu(OAc)_2$, Ag_2O was used in this case, which was speculated to play a dual role as an efficient promoter for the transmetalation and as a co-oxidant with benzoquinone (Scheme 53).

Later on, they changed the substrates to aliphatic acids. The β-C−H bonds were oxidatively coupled with the phenylboronate ester, yet the substrate scope was limited and only 6 examples were reported in low yields (20−38%) (Scheme 54).[104]

Encouraged by this preliminary research on the coupling of β-C−H of aliphatic acids, they continued to explore the β-C−H of methyl hydroxamic acids to couple with organoboronic acids.[105] The standard conditions for the oxidative cross-coupling of Csp^3−H with phenylboronic acids were 0.5 equiv of benzoquinone, 2 equiv of Ag_2O, 2 equiv of K_2CO_3, and 10 mol % of $Pd(OAc)_2$ in *t*BuOH at 70 °C for 18 h. Seven examples were presented, and moderate to

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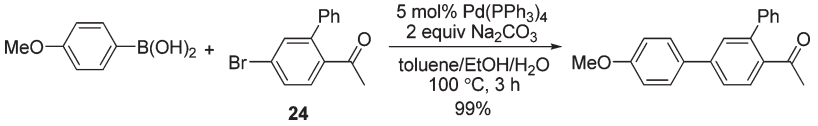
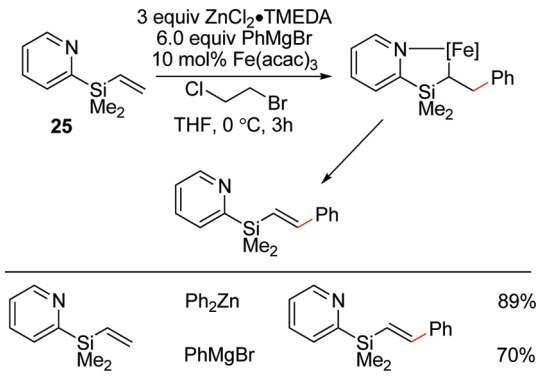
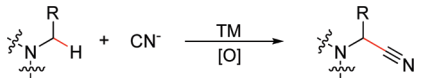
Scheme 42



Scheme 43



Scheme 44



high yields were obtained (Scheme 55). The presence of K_2CO_3 was essential for this coupling; other bases were ineffective. However, this standard procedure was not suitable for alkylboronic acids. By changing the solvent to 2,2,5,5-tetramethylTHF, the coupling of Csp^3−H with alkylboronic acids proceeded smoothly (Scheme 56). The Ag_2O oxidant could be replaced by a high pressure of O_2 (20 atm of air and 20 atm of N_2) in both cases.

Baslé and Li demonstrated a copper-catalyzed protocol between arylboronic acids and Csp^3−H adjacent to a nitrogen atom. CuBr was used as the catalyst and T-HYDRO (70 wt % of *t*-butyl hydroperoxide in water) was the suitable oxidant.[106] Water is critical for this transformation. In the absence of water, only 15% of the desired product was observed, and a small amount of water was shown to dramatically increase the yield. However, a large amount of water was detrimental. By using 20 mol % CuBr as a catalyst and 1.6 equiv of T-HYDRO as the oxidant, the coupling of phenylboronic acid and *N*-phenyltetrahydroisoquinolines offered the desired product in 90% NMR yield (Scheme 57). A stoichiometric amount of T-HYDRO could be decreased to 20 mol % in the presence of molecular O_2, affording the coupling product in 80% NMR yield (Scheme 58).

Then, they employed the copper catalyst and the *tert*-butyl hydroperoxide oxidant into the oxidative α-functionalization of peptides and glycine derivatives with arylboronic acids.[107] The transformation proceeded smoothly in 1,2-dichloroethane at 100 °C. Nonchlorinated solvents afforded the coupling products in low yields. Electron-donating groups substituted onto arylboronic acids favored this coupling reaction; however, electron-withdrawing groups were ineffective. The coupling reaction did not proceed at all when *N*-PMP (*p*-methoxyphenyl) glycine amides have no hydrogen on the amide nitrogen or an *N*-PMP glycine ester was used. Other protecting groups, such as Boc, Benzyl, and Ts, did not give any desired product. Simple dipeptides and tripeptides also proceeded in the coupling very well and afforded a similar phenomenon as shown with glycine amides (Scheme 59).

A preliminary mechanism was proposed (Scheme 60). First, CuBr/TBHP initiated an oxidative dehydrogenation of the α-amino group of glycine amide (**46**) to give an imino amide (**47**), which will then undergo tautomerization to afford the iminol form (**48**). Then the hydroxyl group of the iminol coordinates with phenylboronic acid followed by the delivery of a phenyl group to the imine bond (**49**). The final hydrolysis affords the desired product (**50**). A stepwise reaction was demonstrated to support this mechanism (Scheme 61). The oxidation of a *N*-PMP dipeptide (**51**) by CuBr/TBHP affords the corresponding imine (**52**), which undergoes the reaction with phenylboronic acid smoothly to afford the desired product **53** in dichloroethane (DCE) in the absence of CuBr.

2.3. Oxidative Couplings between Two Hydrocarbons

The best choice for oxidative couplings is to use two hydrocarbons to replace both of the organometallic reagents, as both starting materials do not need to be prefunctionalized, which adds costly multiple chemical steps and increases the amount of waste.[108] In the interests of green and sustainable chemistry, more and more chemists are trying to put their efforts into this challenging area. Various transition metals (both noble and cheap metals) are applied, and a large catalog of oxidants (both organic and inorganic) is employed. The use of O_2 as the oxidant, which is considered as the greenest and most environmentally benign protocol, is still under investigation.

2.3.1. Csp−H and Csp−H as Nucleophiles. The oxidative coupling of two terminal alkynes is old chemistry. Glaser pioneered a Cu−salt mediated oxidative homocoupling of terminal alkynes in 1869, which was later named as Glaser coupling (Scheme 62). Moreover, the Glaser coupling and related modified methods are still widely applied in the synthesis of conjugated diynes in modern chemistry. Its development and application have been well summarized in a recent review.[16]

Recently, Pd-catalyzed oxidative homocouplings of terminal alkynes by using copper as cocatalyst have been reported.[109−116] Other metals, such as Ni and Fe, have also been used as a cocatalyst, but copper is still essential.[117−126] Molecular oxygen is the main oxidant used in those protocols.[121] However, other oxidants, such as α-halocarbonyl compounds[112] and I_2,[116] have also been reported (Scheme 63).

The oxidative cross-coupling of different alkynes could be achieved by an excess of one of the two alkynes. One protocol was demonstrated by Lei and co-workers.[127] The catalyst was $NiCl_2 \cdot 6H_2O$ in the presence of CuI as cocatalyst by employing

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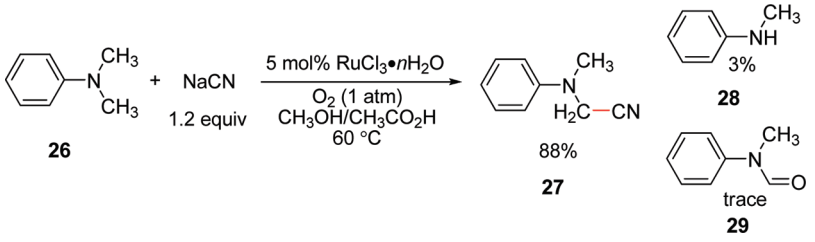
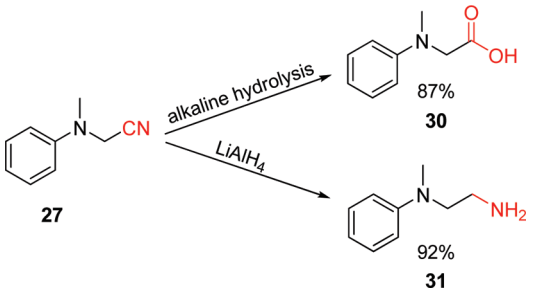
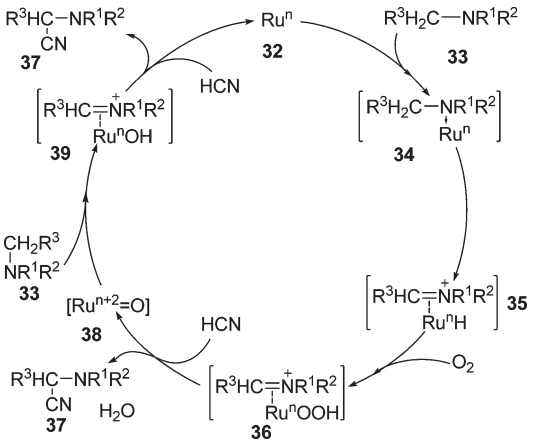
Scheme 45



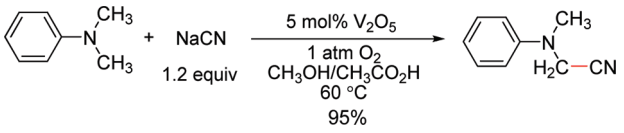
Scheme 46



Scheme 47

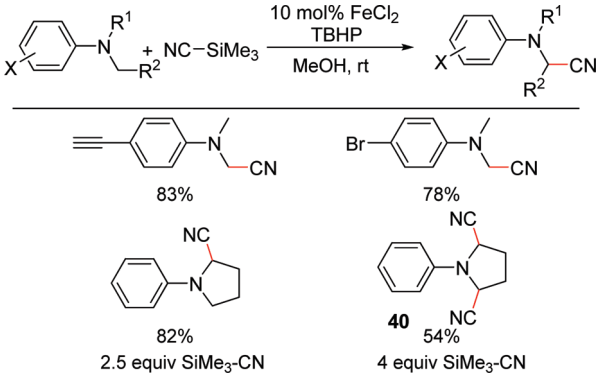


Scheme 48

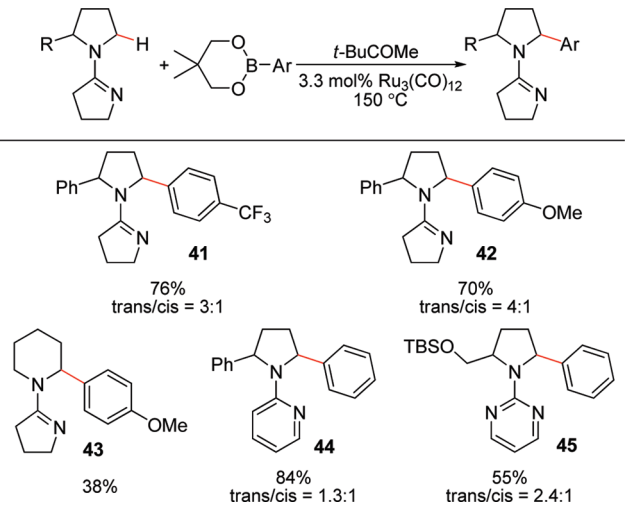


O_2 as the oxidant. The unsymmetric diynes could be obtained selectively by using an excess of one of the terminal alkynes. The kinetic profile of the homocoupling of phenylacetylene showed that the formation of the homocoupling product was accompanied by the consumption of an equal molar amount of O_2, indicating that H_2O_2 might be formed during the transformation (Scheme 64).

Scheme 49



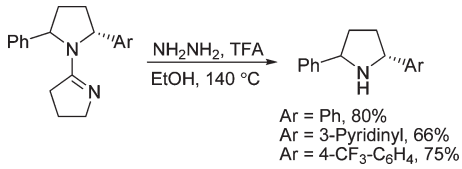
Scheme 50



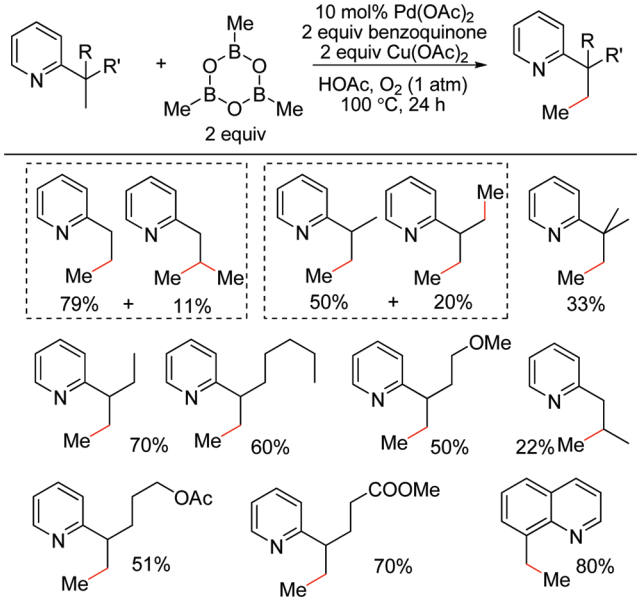
2.3.2. Csp−H and Csp^2−H as Nucleophiles. The C−C bond formations between sp carbon and sp^2 carbon produce arylacetylenes and enynes, which are important buiding blocks for pharmaceutical chemistry and functional materials. Traditionally, Pd/Cu-catalyzed Sonogashira couplings between aryl halides and alkynes are the most efficient method for constructing Csp−Csp^2 bonds.[17] Normally, aryl halides are synthesized by the halogenation of their corresponding arenes. However, the relatively cheap aryl chloride is unreactive due to the problem of its oxidative addition to a Pd(0) species. The direct coupling of arenes with alkynes without the prehalogenation would be both a green and economical process.

dx.doi.org/10.1021/cr100379j |Chem. Rev. 2011, 111, 1780–1824

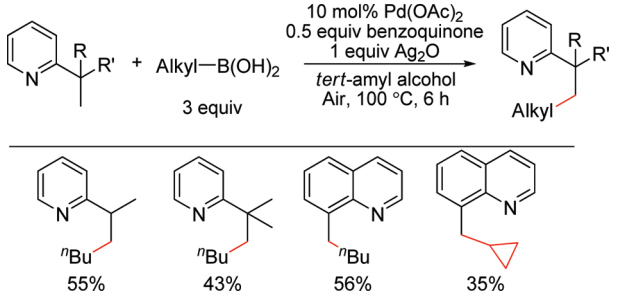
Scheme 51



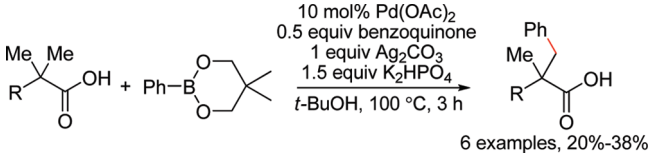
Scheme 52



Scheme 53

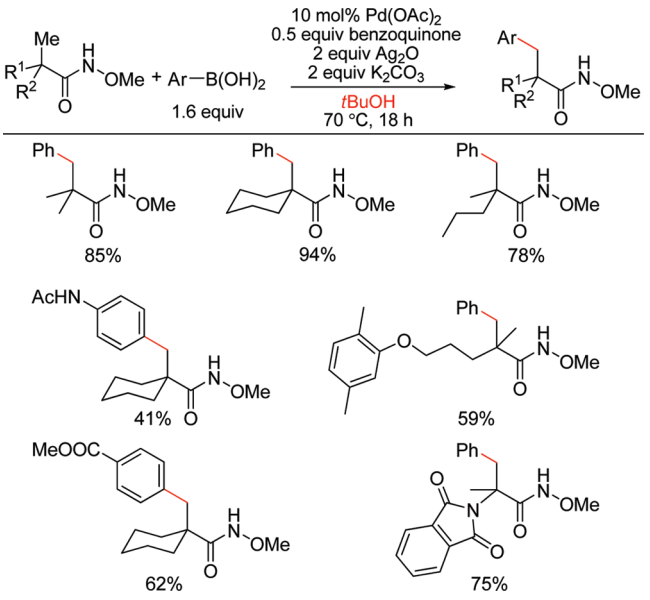


Scheme 54

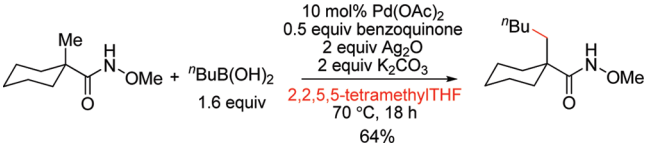


Fuchita et al. pioneered the coupling between arenes and alkynes during their research on the synthesis and reactivity of

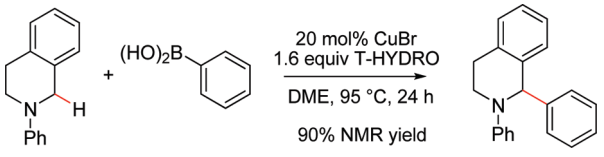
Scheme 55



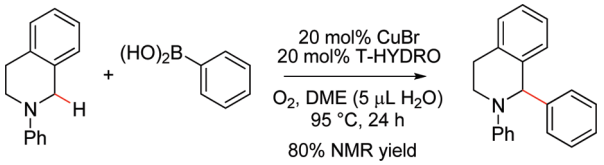
Scheme 56



Scheme 57



Scheme 58



arylgold(III) complexes.[128] The reaction of gold(III) chloride $[AuCl_3]_2$ with simple arene **54** affords the C−H cleavage of an arylAu(III) dimer complex (**55**). 2,6-Lutidine is used as a stabilizing ligand, and the arylAu(III) is isolated as a mononuclear complex (**56**). Treatment of the isolated complex with phenylacetylene offers the $Csp-Csp^2$ coupling product (**57**). The overall reaction is an Au(III)-mediated oxidative coupling of arenes with phenylacetylene (Scheme 65). Although quantitative amounts of

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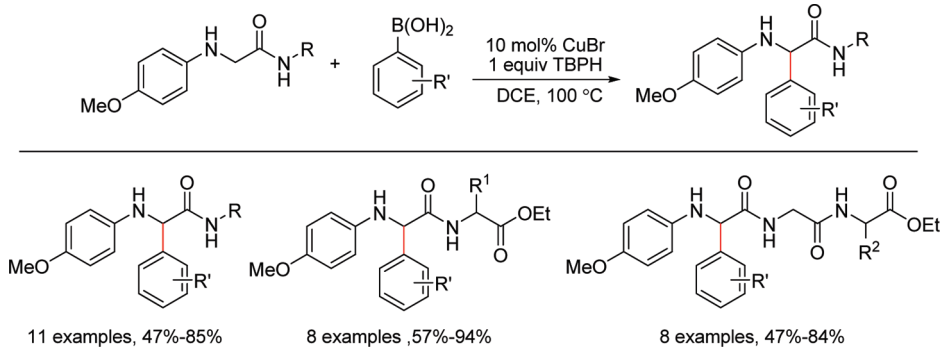
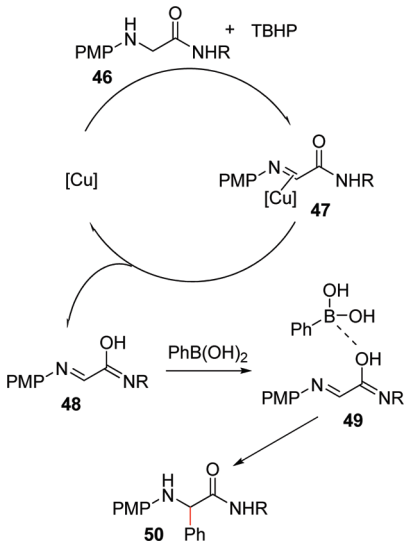
Scheme 59



Scheme 60



$AuCl_3$ have to be involved, this transformation provides a possibility for this type of coupling reaction in a catalytic version.

Haro and Nevado realized gold-catalyzed oxidative cross-couplings between arenes and alkynes by using 5 mol % Ph_3PAuCl as the catalyst in the presence of 1.5 equiv of $PhI(OAc)_2$ and 1 equiv of $NaHCO_3$ as an efficient oxidant and additive, respectively.[129] Electron-rich arenes and electron-deficient alkynes are suitable partners for this transformation. Phenylacetylene offered the coupling product in low yields due to the increased homocoupling of the alkyne. Electron-rich heteroaromatic rings, such as pyrrole and indole, also participated very well. Both 2- and 3-positions were functionalized for pyrrole (**58**), yet the functionalization of indole only took place on the 3-position together with some acetoxy derivative (**59**) (Scheme 66). The functionalization could also occur on both the chromene and the phenyl ring (**60**).

NMR experiments showed that the formation of gold(I)−acetylide was involved in the first step of the catalytic reaction. Kinetic studies exhibited the first-order relationship to both alkyne and arene substrates. Isotope effects indicated that neither the Csp−H nor the Csp^2−H bond breaking was involved in the rate-determining step of this ethynylation reaction. Two possible mechanisms were proposed, starting with the formation of the gold(I)−acetylide complex **61** and followed by the oxidation with $PhI(OAc)_2$ to give a gold(III)−alkynyl intermediate **62**. The electrophilic aromatic substitution of an arene with intermediate **62** affords complex **63**. Finally, upon reductive elimination, the new Csp^2−Csp bond is formed and the alkynylated products **64** are obtained. Alternatively, the reaction of **61** with $PhI(OAc)_2$ could afford an electrophilic alkynyl−iodonium complex **65**. A gold-mediated addition of the aromatic ring to the triple bond in **65** affords a vinyl gold intermediate **66**, which upon β-elimination would deliver the arylated alkynes **64** (Scheme 67).

As the same group member of gold in periodic table, copper also exhibits a high reactivity toward this transformation. A recent example was demonstrated based on the oxidative coupling between electron-deficient arenes and terminal alkynes by using $CuCl_2$ as the catalyst together with 1,10-phenanthroline as ligand.[130] Three equiv of *t*BuOLi facilitated the cross-coupling product, yet weak bases such as K_3PO_4 and $NaHCO_3$ were effective for the homocoupling of alkynes. O_2 was used as a terminal oxidant with 15 mol % of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the co-oxidant. The more electron-deficient arene affords the better yield (the comparison between **67** and **68**) (Scheme 68).

Palladium and nickel catalysts are widely applied in coupling reactions. They can also effect the oxidative Csp−Csp^2 bond-formation reaction. However, only one example has been demonstrated by using nickel as a catalyst.[131] Heteroarenes such as benzoxazole (**69**), 5-aryloxazole (**70**), and benzothiazole (**71**) are all proper substrates to oxidatively couple with terminal alkynes in moderate yields. A strong base *t*BuOLi has to be required to deprotonate both heteroarenes and terminal alkynes. O_2 was used as the oxidant, which made this protocol economic and green. The silyl group allows for the further transformation of the coupling products (Scheme 69).

Another example using a palladium catalyst was demonstrated by Li and co-workers. Terminal alkynes and 3-substitued indoles were employed as suitable coupling partners, perhaps because of the nonsimplex selectivity on both the 2- and 3-positions.[132] K_2PdCl_4 without an extra ligand was used as the catalyst, and O_2 was used as the terminal oxidant. A buffer system composed of 20 mol % Cs_2CO_3 and 200 mol % pivalic acid in DMSO was applied for this transformation. To suppress the homocoupling of alkynes, a slow addition technique was also applied to this system (Scheme 70).

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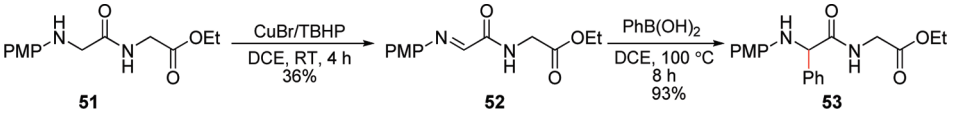
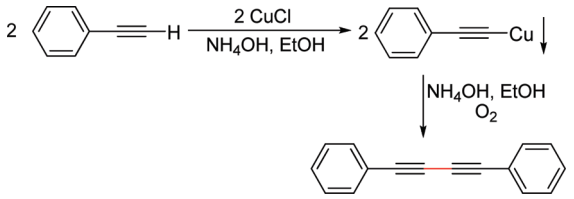
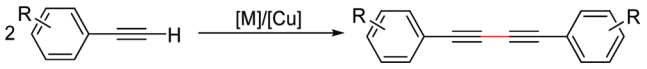
Scheme 61



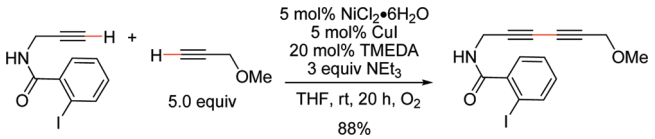
Scheme 62



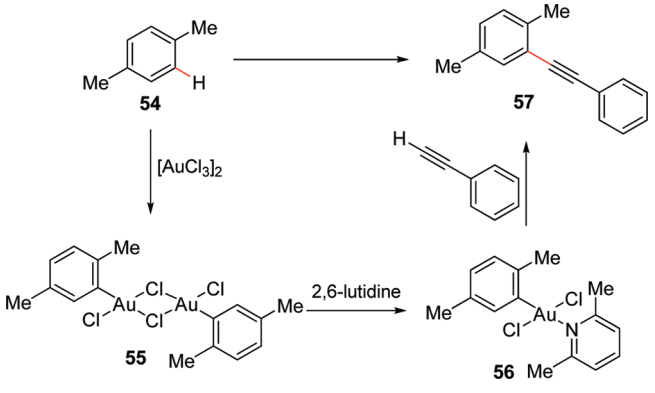
Scheme 63



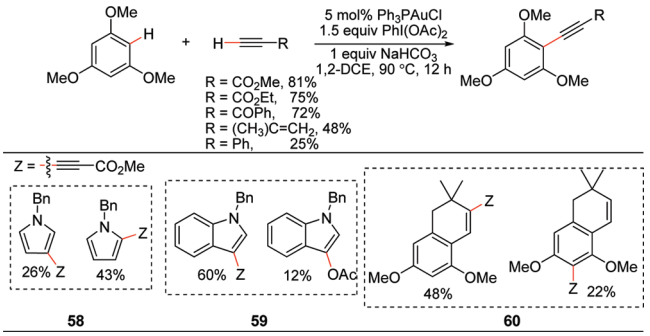
Scheme 64



Scheme 65



Scheme 66



The author also gave a tentative mechanism for this palladium-catalyzed oxidative coupling reaction (Scheme 71). First, the in situ formed $Pd^{II}(PivO)_2$ reacts with phenylacetylene to form alkynyl-palladium species **72**. Second, the electrophilic attack of intermediate **72** at the C2-position of indole generates intermediate **73**, which will be deprotonated by CsOPiv to afford intermediate **74**. Reductive elimination of intermediate **74** produces the alkynylated product **75** and Pd^0, which will be reoxidized to Pd^{II} in the presence of O_2 and PivOH. Alternatively, the reaction may start with palladation of the indole derivatives. Subsequent generation of a similar intermediate **74** and its reductive elimination results in the oxidative coupling product.

2.3.3. Csp−H and Csp^3−H as Nucleophiles. These kinds of reactions refer to the oxidative coupling between terminal alkynes and alkanes. Similar to the coupling of Csp^3−H with organometallic reagents, the sp^3 carbon normally has to be adjacent to a heteroatom such as nitrogen. The first report about the oxidative cross-coupling of terminal alkynes with alkanes was demonstrated by Miura and co-workers, in which the sp^3 carbon of alkane was adjacent to a tertiary amine. Using $CuCl_2/O_2$ and terminal alkynes, they managed to obtain the corresponding products of oxidative C−C cross-coupling, *N*-methyl-*N*-propargylanilines, albeit in low yields (27−43%) (Scheme 72).[133]

Li and Li recently reported similar results but in higher yields and efficiencies.[134] Screening of different reaction conditions showed that 5 mol % CuBr was effective for this transformation and 1 equiv of *tert*-butyl hydroperoxide was a proper oxidant. The methyl group of *N*,*N*-dimethylaniline could oxidatively couple with phenylacetylene smoothly under the standard condition to afford the desired product **76**; however, the methylene group of *N*-phenylpiperidine was less reactive and gave the coupling product in 12% yield (**77**) (Scheme 73). Benzyldimethylamine proceeded mainly on the methyl group selectively, albeit in a low yield (**78**). Cyclic amine tetrahydroisoquinoline can be selectively converted into the corresponding alkynylation compound in 74% isolated yield (**79**). After this discovery, several results based on different oxidants and catalysts were successively reported.[135−137] A catalytic asymmetric version of this oxidative Csp−Csp^3 bond formation was also realized by introducing a chiral ligand **80** (Scheme 74).[138]

Normally, the tertiary amine has to be aryl-substituted so as to improve the efficiency of the reaction, and aliphatic tertiary amines are found to be less effective substrates. By employing CuI as a catalyst and diethyl azodicarboxylate as the oxidant, Xu and Li realized the oxidative coupling of unactivated aliphatic tertiary methylamines with terminal alkynes in high yields (Scheme 75).[139] However, when *N*,*N*-dimethylaniline was used

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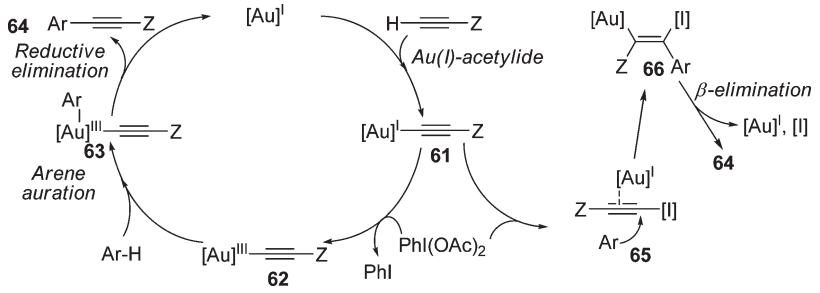
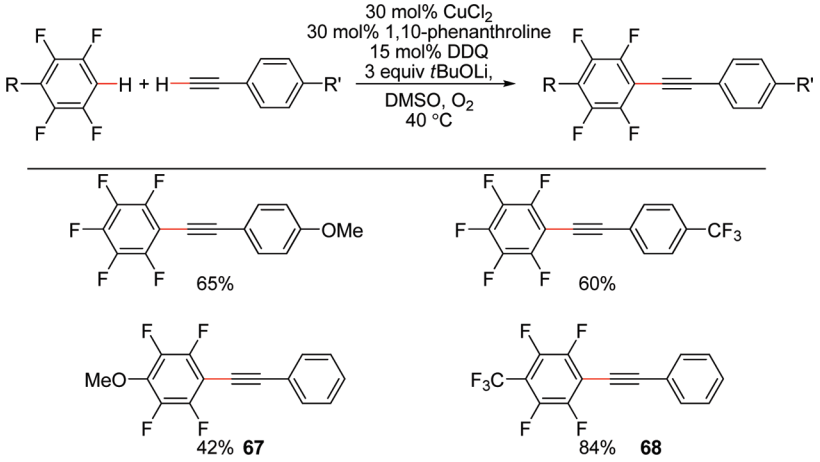
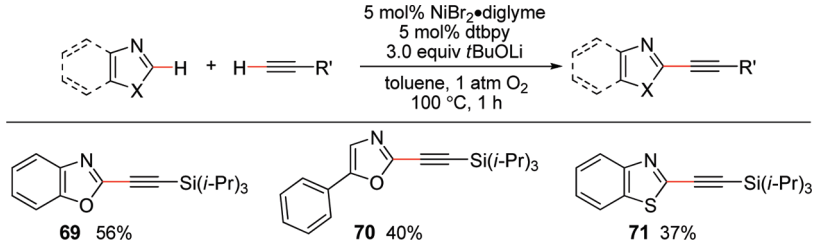
Scheme 67



Scheme 68



Scheme 69



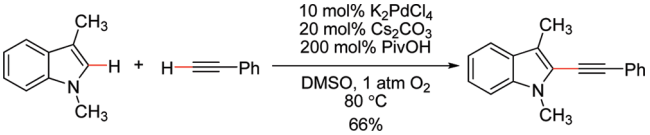
as the substrate, no desired cross-coupling product was observed and only the adduct of diethylazodicarboxylate (DEAD) with *N*, *N*-dimethylaniline was isolated (Scheme 76).

According to the observation, the author gave a tentative mechanism in Scheme 77. First, DEAD and aliphatic tertiary methylamine **81** undergo a nucleophilic addition reaction and form a 1:1 adduct **82**, which could be in equilibrium with **83** by an intramolecular hydrogen transfer. Then adduct **82** cleaves to form an ion pair consisting of 1H-DEAD **84** and iminium cation **85**. The nitrogen anion of **84** further abstracts hydrogen from the terminal alkyne with itself being transformed into 2H-DEAD in the presence of the copper catalyst, and the terminal alkyne is transformed into copper alkynylide. A further addition of the in situ generated copper alkynylide on **85** gives the desired product **87** and liberates the copper catalyst to complete the catalytic cycle. When the R^2 or R^3 is a phenyl group, the reaction proceeds to form the adduct product **86** preferably.

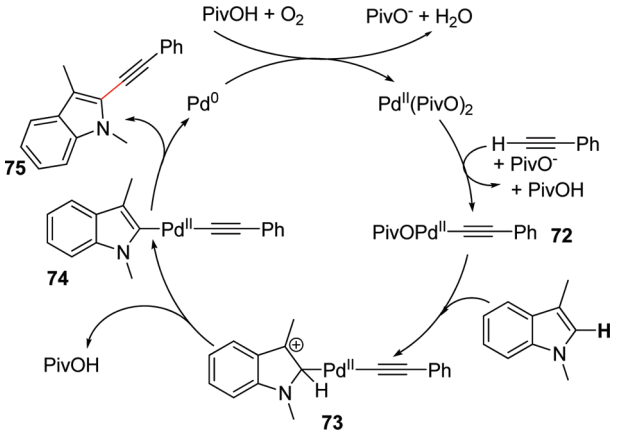
Secondary amines that contain NH groups could also be used as substrates. An oxidative cross-coupling of glycine derivatives with terminal alkynes was demonstrated. Still, Li and co-workers used CuBr as the catalyst and TBHP as the oxidant. *p*-Methoxyphenyl was a suitable protecting group.[107,140] The reaction could proceed at room temperature in dichloromethane in good yields. The R^1 group is vital to this transformation, as the OEt group prevents the reaction (**90**) and the phenyl group leads to a complex unidentified mixture of products (**91**). Amide groups ensure the coupling products smoothly (**88** and **89**) (Scheme 78). By elevating the temperature to 70 °C in dichloroethane, the protocol proceeded

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

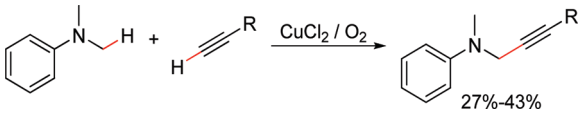
Scheme 70



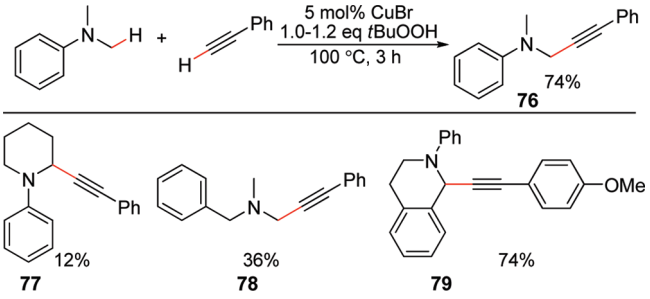
Scheme 71



Scheme 72



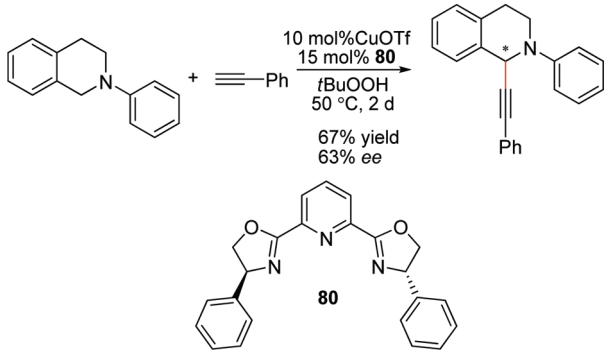
Scheme 73



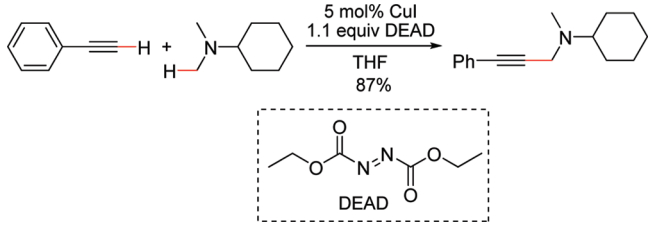
well by using a peptide as the substrate and afforded the coupling product in a 63% yield (Scheme 79). This method provides a superior tool for the functionalization of glycine derivatives.

2.3.4. Csp^2−H and Csp^2−H as Nucleophiles. Direct Csp^2−Csp^2 bond formations through oxidative C−H functionalizations were pioneered by Moritani, Fujiwara, and co-workers in 1967.[141,142] Simple benzene and styrene were used in their systems in the presence of palladium chloride (Scheme 80).[142] They showed that acetic acid was essential to this transformation and silver salts could reduce the catalytic loading of palladium. These original attempts guided the subsequent research in

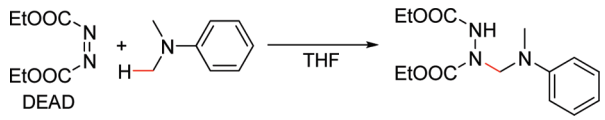
Scheme 74



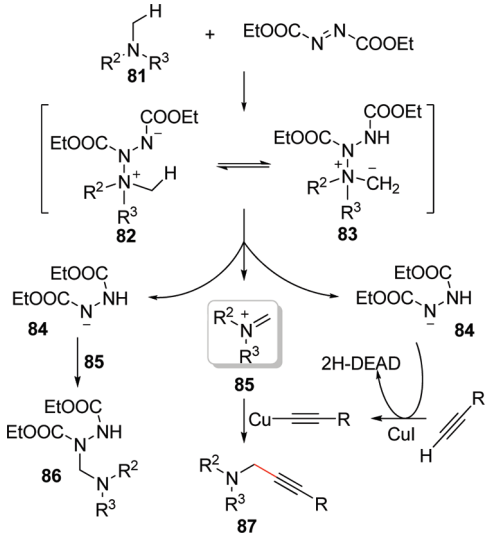
Scheme 75



Scheme 76



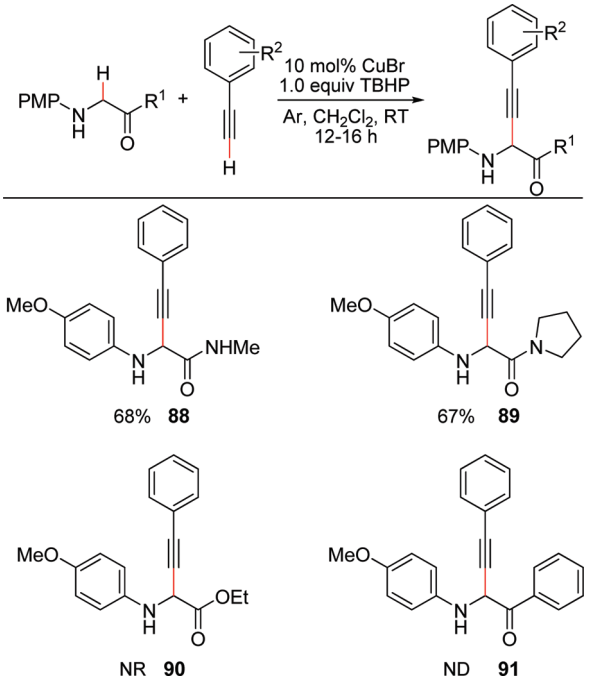
Scheme 77



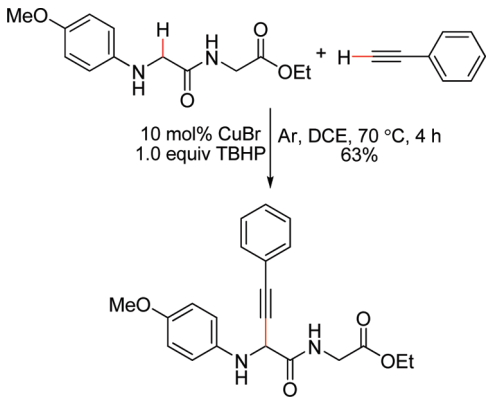
the following several decades; even in very recent years, the acidic system is still the major approach for direct arene C−H

dx.doi.org/10.1021/cr100379j |Chem. Rev. 2011, 111, 1780–1824

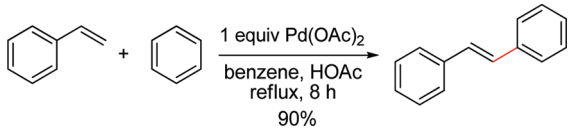
Scheme 78



Scheme 79



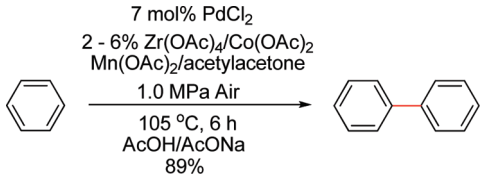
Scheme 80



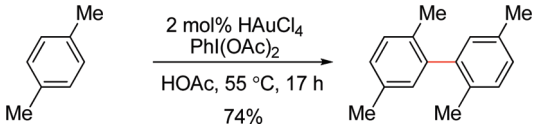
functionalizations and silver salts are still popular in modern academic research in this hot area.[53]

2.3.4.1. Couplings between Arenes. van Helden and Verberg first described an oxidative homocoupling of benzene in the presence of stoichiometric amounts of $PdCl_2$ and sodium acetate in acetic acid as the solvent to afford biphenyl.[143] After that, metals such as Hg(II),[144] Tl(III),[145] Fe(III),[146] or Cu(II)[147] and palladium catalysts

Scheme 81



Scheme 82



such as $Pd(OAc)_2$, $Pd(acac)_2$, and Pd(ETDA) (EDTA = ethylenediaminetetraacetic acid) have been employed in various conditions at high oxygen pressures and temperatures for this homocoupling reaction in a catalytic manner.[148−155] Recently, protocols for this homocoupling under aerobic oxidation have also been described in the presence of $PdCl_2$ catalyst, cocatalyst ($Zr(OAc)_4$/$Co(OAc)_2$/$Mn(OAc)_2$/acetylacetone), and AcOH/AcONa as the solvent (Scheme 81).[156,157] The authors suggested that a peroxocobalt(III) species, Co(III)−OO−Co(III),[158] could be generated in this system, although the exact role of each metallic salt was unclear. Reaction of Pd(0) with this species could give a Pd(II)−peroxo complex. In this way, it is possible to regenerate the active palladium catalyst with a faster rate than the rate of aggregation of Pd(0) to form palladium black. Gold could also be an efficient catalyst for the direct oxidative homocoupling of unactivated arenes in the presence of $PhI(OAc)_2$ as the oxidant (Scheme 82).[159,160]

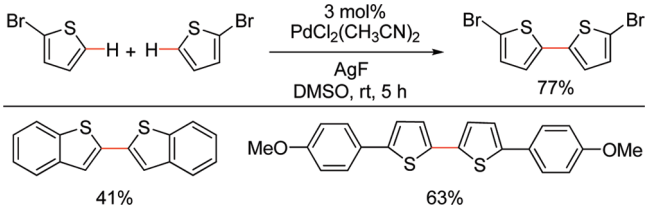
Several isomers could be obtained when monosubstituted arenes are applied;[161,162] even electron-deficient arenes such as benzoates and pyridines could be homocoupled in the presence of palladium catalyst.[163,164] Although the oxidative homocouplings of heteroarenes had earlier been developed,[162] the catalytic manner of this transformation in a low catalyst loading has just been described recently.[165] With 3 mol % of $PdCl_2(CH_3CN)_2$ as the catalyst and silver fluoride as the oxidant, the oxidative homocoupling of substituted thiophenes, benzothiophenes, and thiazoles were successfully achieved in moderate to good yields. Silver salt was essential for this reaction; other metal salts such as copper did not afford the coupling product at all (Scheme 83).

Later, the oxidative homocoupling of various azoles was realized by using a copper salt as the catalyst under aerobic conditions.[166,167] Do and Daugulis reported a deprotonative homocoupling of acidic arenes in the presence of a number of first-row transition metal salts.[168,169] Under the atmosphere of oxygen, nickel, manganese, cobalt, and iron chlorides were all effective for this transformation under strongly basic conditions (Scheme 84).

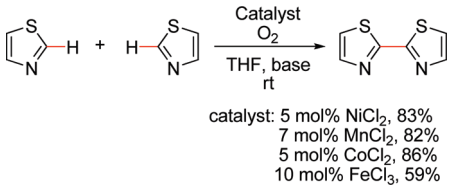
In contrast to the symmetric homocouplings, the unsymmetric homocouplings of indoles were illustrated based on their C2- and C3-positions.[170] $Pd(OAc)_2$ (5 mol %) and 1.5 equiv of monohydrated $Cu(OAc)_2$ were the optimum catalyst and oxidant in DMSO, respectively. Indoles bearing electron-rich to slightly

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

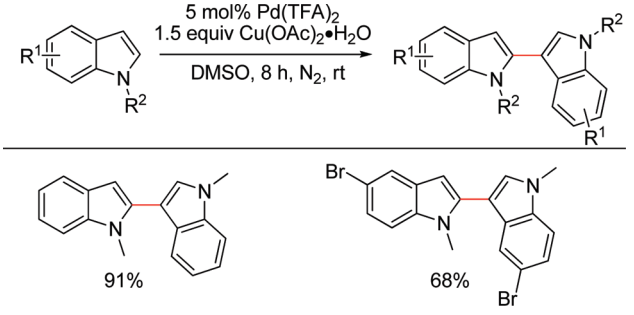
Scheme 83



Scheme 84



Scheme 85



electron-poor substituents were converted to 2,3′-biindolyls in moderate to high yields at room temperature (Scheme 85).

Arenes could also be homocoupled regioselectively directed by a pyridyl group in the presence of 5 mol % of $Pd(OAc)_2$ as the catalyst and 2 equiv of oxone as the oxidant.[171,172] The reactions proceeded at room temperature and were compatible with diverse functionalities, including aryl halides (**93** and **94**) and thiophenes (**95**). Mechanistic investigations suggested that the transformations proceeded via a mechanism involving two different pyridine-directed C−H activations at Pd(II) and Pd(IV) centers (Scheme 86). The same transformations were accomplished later by employing ruthenium as the catalyst and $FeCl_3$ as the oxidant.[172,173] Triazole-directed arenes used in regioselectively oxidative homocouplings have also been described.[172]

Another type of arene homocoupling is the well-known oxidative dimerization of phenols and naphthols, which is one of the oldest aryl−aryl bond formations (Scheme 87).[108] Many useful protocols have been developed for this purpose, especially for the enantioselective oxidative couplings of 2-naphthols.[174,175] Attention is still paid to developing greener and more efficient approaches for this transformation. Transition metals such as copper and iron are widely applied, and molecular oxygen is studied to be used as an oxidant. Cross-couplings have also been carried out in the presence of two different substituted 2-naphthols. The reaction details will not be listed in this paper.

Theoretically, by mixing two different arenes in one reaction pot under the homocoupling conditions, the oxidative cross-couplings can be achieved. However, the selectivity is problematic as both homo- and cross-coupling products can be obtained. By adjusting the substrate's properties and introducing directing groups, the cross-coupling product can be obtained in high selectivity. The first attempt was demonstrated by Lu and co-workers in 2006 with two different arenes as substrates (Scheme 88).[176] The selectivities for the cross-coupling products are good to excellent in spite of the low yields. These results are a new dawn for the cross-coupling of two different arenes.

Later on in 2007, a groundbreaking result regarding the palladium-catalyzed oxidative cross-coupling between benzene and indoles in high selectivity and yields was reported by Stuart and Fagnou.[177] A $Pd(TFA)_2$ catalyst and a $Cu(OAc)_2$ oxidant combined with a pyridine additive promoted these transformations properly (Scheme 89). The authors speculated that the pyridine additive performed as a palladium stabilizer to slow the formation of palladium black. The indole nitrogen substitutent is vital to this coupling. Free N−H indole was not reactive at all, whereas *N*-methylindole produced self-dimerization predominantly. In contrast, *N*-acetylindole gave more desired cross-coupling products. Interestingly, replacing $Cu(OAc)_2$ with AgOAc produced an inversion in regioselectivity favoring the C2 positions.[178] Reaction optimization showed that the removal of the pyridine additive and the change of *N*-acetyl with *N*-pivaloyl resulted in complete conversion and high selectivity (Scheme 90).

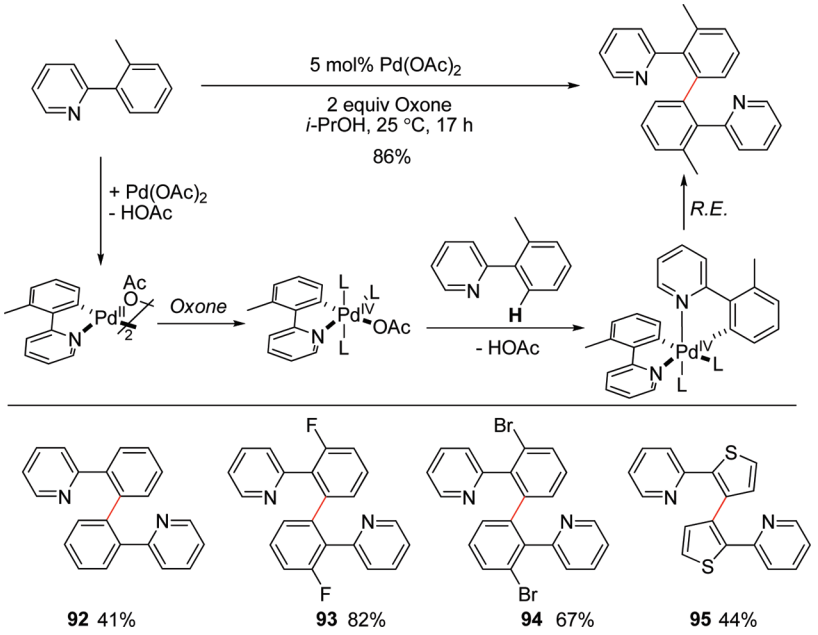
Almost at the same time, Deboef and co-workers demonstrated a palladium-catalyzed oxidative coupling of benzene with benzofuran in the presence of a catalytic amount of heteropolymolybdovanadic acid $H_4PMo_{11}VO_{40}$ (HPMV) together with O_2 as the terminal oxidant (Scheme 91).[179] The coupling regioselectively took place at the 2-position of benzofuran in 98% yield. In situ monitoring of the reaction process exhibited that biphenyl only formed after the consumption of benzofuran. Extended reaction times caused the formation of the 2,3-diarylated product, albeit in low yields. The same oxidant-controlled regioselectivity in the oxidative arylation of *N*-acetylindoles was observed by this group.[180]

Recently, palladium-catalyzed oxidative cross-couplings between two different heteroarenes have also been explored. A variety of thiophenes and furans were cross-coupled regioselectively at their 2-positions with several *N*-heteroaromatic substrates such as xanthines and azoles (Scheme 92). Density functional theory (DFT) calculation were undertaken for the coupling between *N*-methylimidazole and thiophene, suggesting that the abstraction of hydrogen from thiophene should first take place in the reaction system, yet the second C−H metalation toward homocoupling product is unfavorable compared to the metalation toward cross-coupling so as to give the desired product.[181] Perfluoroarenes were later applied to couple with benzene and heteroarenes such as thiophenes, furans, and indoles by Wei and Su (Scheme 93) and Zhang and co-workers (Scheme 94), respectively.[182,183] The direct arylation of pyridine *N*-oxides with unactivated arenes was also described (Scheme 95).[184]

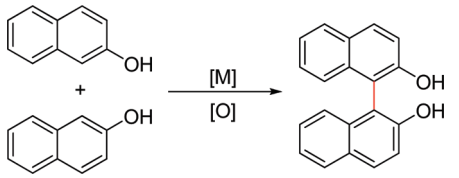
To accomplish the regioselective oxidative coupling of monosubstituted phenyl rings, directing groups are required. In 2007,

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

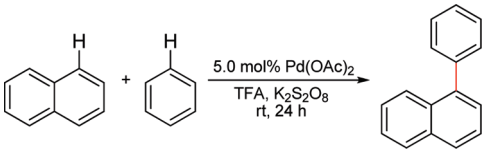
Scheme 86



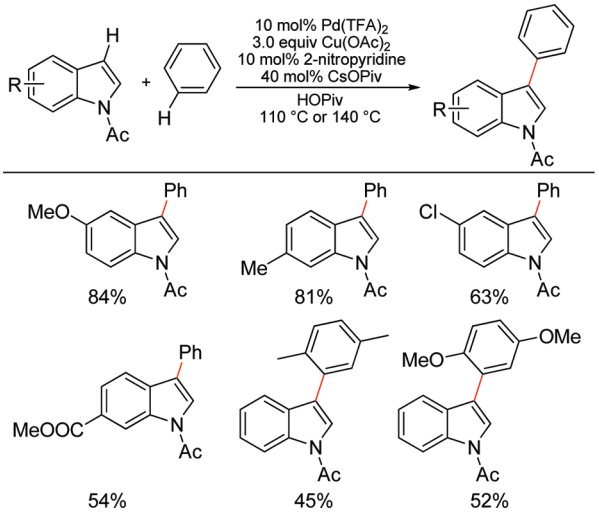
Scheme 87



Scheme 88



Scheme 89



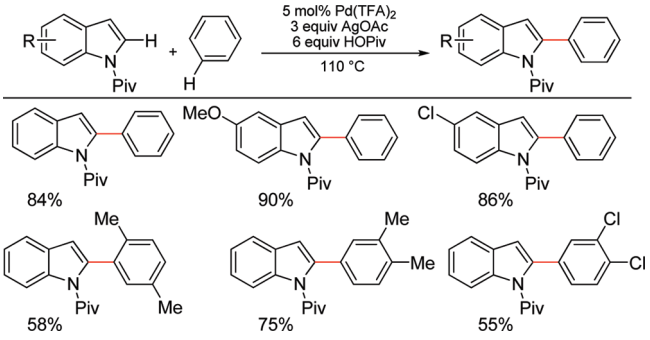
Hull and Sanford first demonstrated a palladium-catalyzed regioselectively oxidative cross-coupling of benzoquinoline with benzene.[185] Because of the coordination of the nitrogen atom of benzoquinoline to the palladium catalyst, the coupling occurred selectively on the C(10) position in a high yield. Using 0.5 equiv of benzoquinone (BQ) together with 2 equiv of Ag_2CO_3 was found to be effective for this transformation (Scheme 96). The addition of a DMSO additive could slow the catalyst decomposition/Pd^0 aggregation and thus enhance the reaction yield. The preliminary mechanistic study showed that the reaction followed a Pd^0/Pd^{II} catalytic cycle and benzoquinone was an efficient promoter for this transformation.[186] The oxazoline group was also shown to direct the oxidative arylation of ferrocene with benzene in the presence of a stoichiometric amount of $Pd(OAc)_2$.[187]

Arenes containing an acetamido, a well-known directing group, were introduced to oxidatively couple with other arenes by Shi and co-workers in 2008.[188] In the presence of $Cu(OTf)_2$ as the co-oxidant and O_2 as the terminal oxidant, palladium could catalyze this transformation with high regioselectivity at the ortho-position of the arene controlled by the acetamido directing group (Scheme 97). Other amido groups, such as NHPv, have also been reported by Buchwald and co-workers, in which a DMSO additive was also effective to prevent palladium black formation.[189]

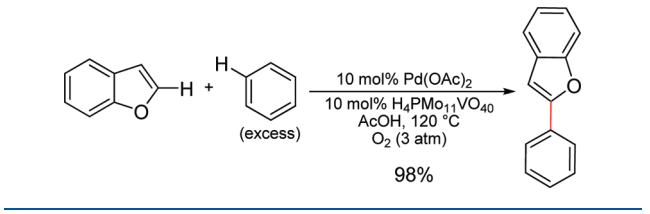
O-Carbamate directed *ortho*-arylation with simple arenes using sodium persulfate as oxidant was recently developed.[190] Both trifluoroacetyl (TFA) and sodium persulfate were found to be critical in achieving high efficiency for the transformation. Excellent reaction efficiencies and regioselectivities were observed with a range of

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

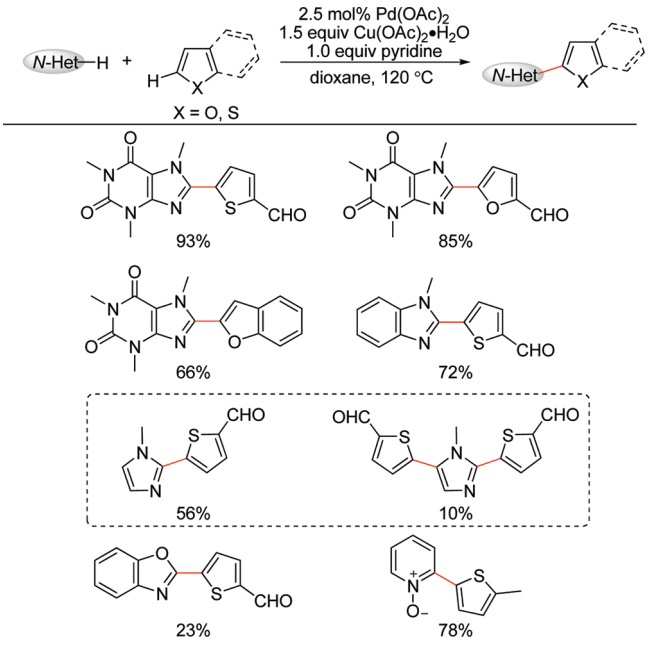
Scheme 90



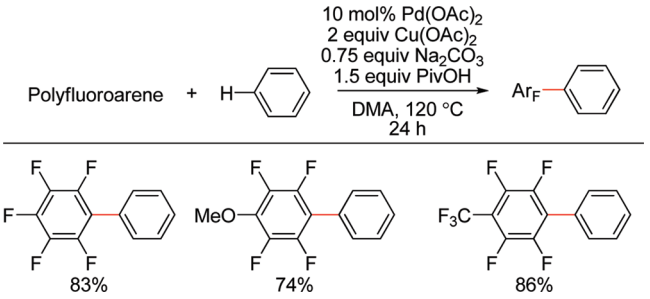
Scheme 91



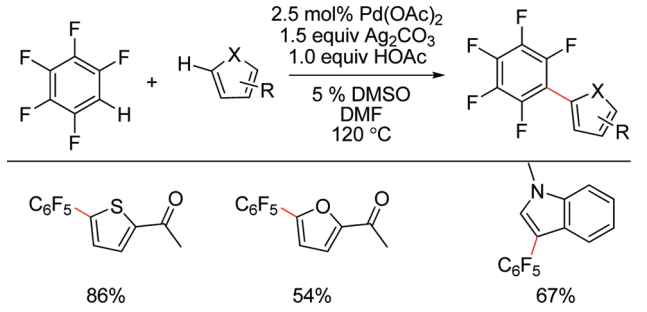
Scheme 92



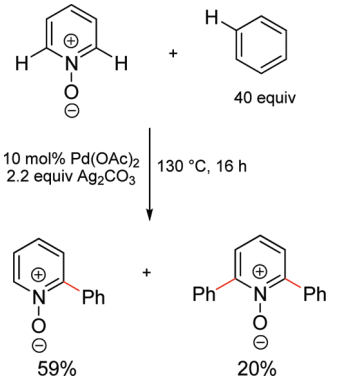
Scheme 93



Scheme 94



Scheme 95



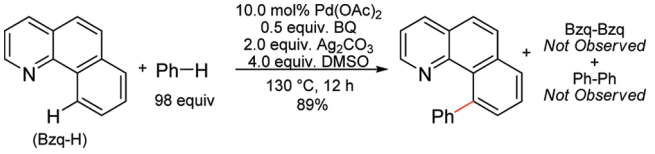
electron-rich (**98**), electron-neutral (**97**), and electron-deficient arenes (**96**); minimal homocoupling of either component was observed (Scheme 98). When two reactive C−H bonds are present on the *O*-phenylcarbamate, selective diarylation can be achieved via quadruple C−H bond functionalization.

Mechanistic studies exhibited that the use of *O*-carbamates as the directing group assisted the catalytic oxidative cross-coupling of two C−H bonds. Treatment of *m*-tolyl dimethylcarbamate (**99**) with $Pd(OAc)_2$ in the presence of TFA afforded a palladacycle characterized by NMR and X-ray crystallography (Scheme 99), which showed that it was a bimetallic palladium species **100** containing a weak Pd−Pd interaction. TFA was essential for the success of this cyclopalladation. Arylation of this Pd(II) complex with neat benzene was demonstrated in the absence of external oxidant and/or additives, which afforded the desired product **101** quantitatively. Rate comparison of various arenes with the palladacycle showed that electron-rich arenes enhanced the reaction rate; thus, the authors speculated a mechanism whereby two C−H bond activations occur via cyclopalladation and electrophilic metalation, respectively, within a Pd^0/Pd^{II} catalytic cycle.

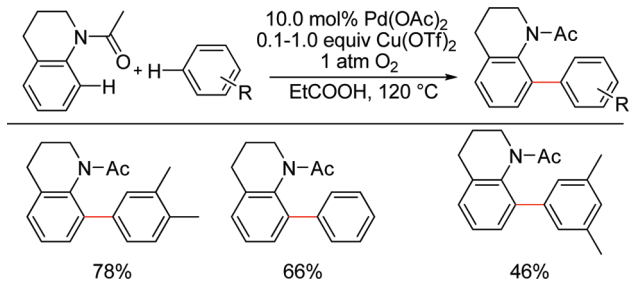
2.3.4.2. Couplings between Arenes and Alkenes. After pioneering the oxidative coupling between benzene and styrene,[141,191−193]

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

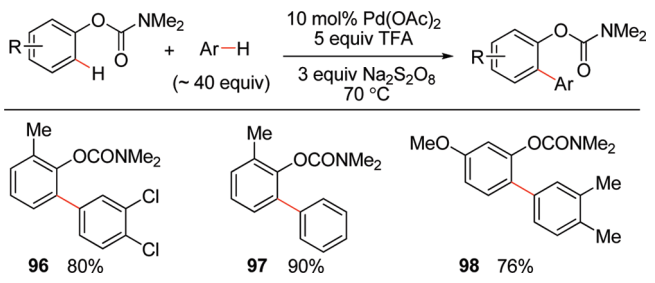
Scheme 96



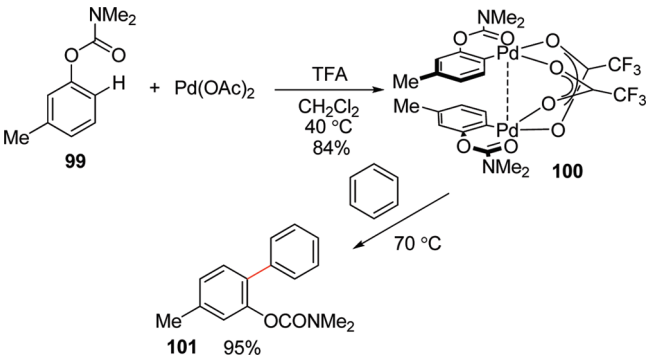
Scheme 97



Scheme 98

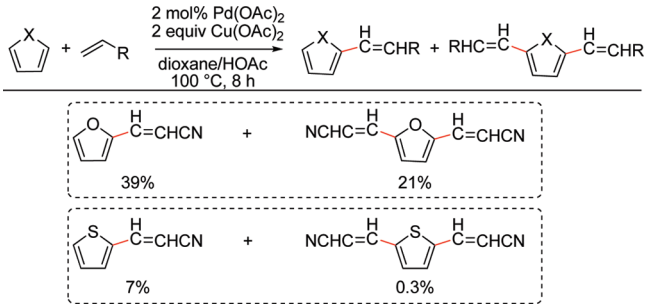


Scheme 99

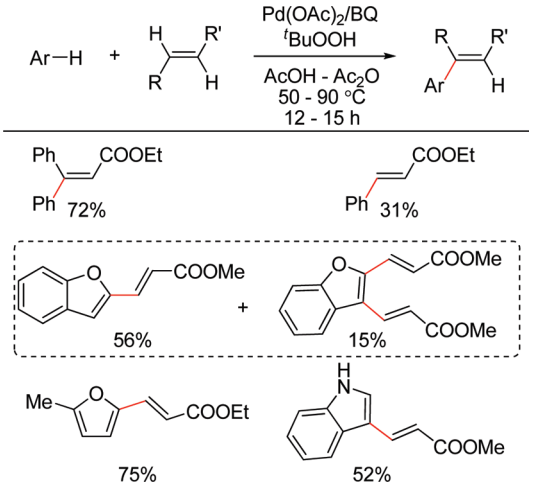


Fujiwara and co-workers continuously unfolded the essence of this palladium chemistry with catalytic amounts of palladium acetate.[194] Furthermore, they demonstrated this reaction with various heteroarenes such as furan and thiophene (Scheme 100).[195−197] Later on, Itahara and co-workers introduced pyrrole and indole into this type of oxidative cross-coupling.[162,198−200] Even quinones and uracils could be directly arylated or alkenylated in the presence of a palladium catalyst.[201,202] However, these early results normally required

Scheme 100



Scheme 101

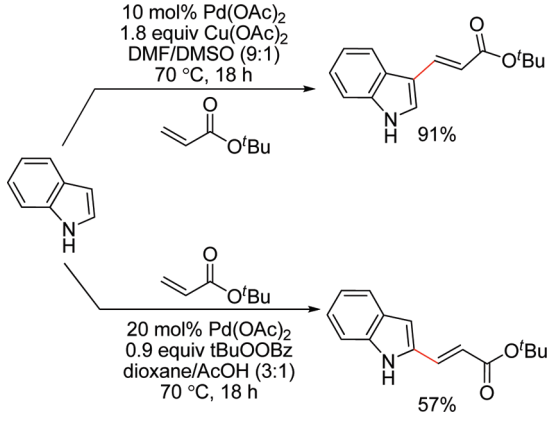


quantitative amounts of palladium catalyst and afforded low yields. In 1999, Fujiwara and co-workers reported an efficient oxidative cross-coupling of arenes with olefins in the presence of 1 mol % $Pd(OAc)_2$ and 10 mol % benzoquinone as the catalyst and *tert*-butyl hydroperoxide as the oxidant.[203] The catalytic system was especially active for the coupling of heteroarenes such as furans and indole with activated olefins with high regio- and stereoselectivity, predominantly giving *trans*-olefins (Scheme 101).

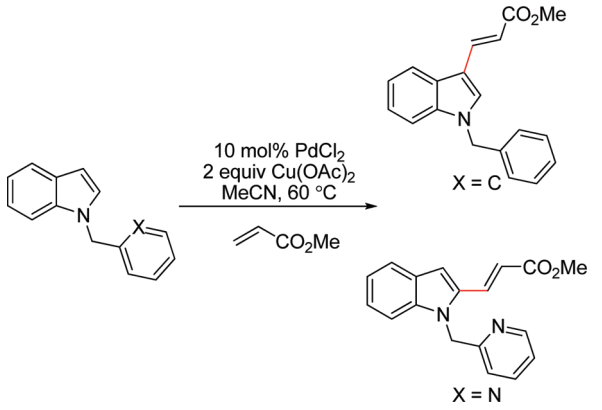
In the interests of green chemistry, more and more attention is paid to the replacement of heavy metal oxidants with molecular oxygen.[204−209] However, the regioselectivity for the alkenylation of monosubstituted phenyl rings is still problematic.[210,211] Normally, the oxidative cross-couplings take place at the 2- and 5-positions of five-membered heteroarenes and at the 3-position for indoles. Nevertheless, a palladium-catalyzed alkenylation of free (NH) indole can selectively take place at the C2-position by a solvent-controlled process.[212] Gaunt and co-workers discovered that indole was oxidatively coupled with *n*-butyl acrylate selectively at the C3-position when the reaction was carried out in polar solvents such as DMSO and dimethylformamide (DMF). However, using the nonpolar solvent dioxane together with AcOH as a cosolvent showed that alkylation proceeded selectively at the C2-position (Scheme 102). The authors speculated that acidic conditions slowed down the deprotonation of the first palladation of the indole species and allowed the migration of the C3−PdX bond to the C2-position, resulting in the formation of C2 alkenylation products. This

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 102



Scheme 103

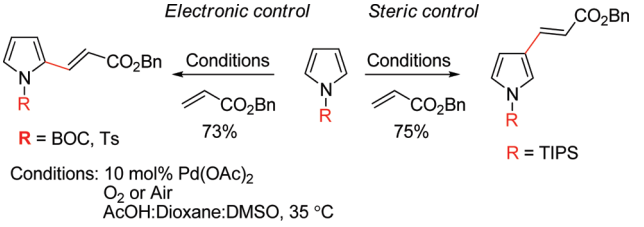


regiospecific selectivity could also be achieved by installing a directing group on the indole nitrogen, such as 2-pyridylmethyl group.[213] By replacing the directing group with a nondirecting group such as benzyl, the regioselectivity on C2 disappeared and the reaction selectively occurred on C3-position (Scheme 103).

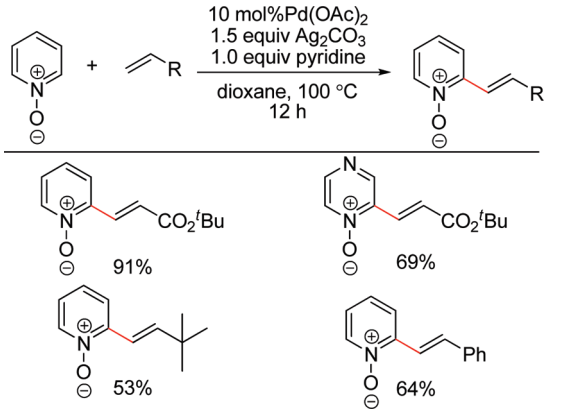
In 2006, the same group demonstrated an *N*-substitutent controlled regioselectively oxidative alkenylation of pyrroles under aerobic conditions.[214] Electron-withdrawing *N*-protecting groups such as *N*-Boc and *N*-Ts reduced the reactivity of pyrrole and yielded the C2 alkenylation products selectively in good yields, while the sterically hindered *N*-TIPS group shielded the C2-position and afforded the C3 alkenylation products with high selectivity under the same reaction conditions (Scheme 104).

Electron-deficient heteroarenes, such as pyridine *N*-oxides, have also been used as suitable substrates in oxidative cross-coupling with alkenes. These transformations performed selectively at the 2-position of pyridine *N*-oxides in the presence of $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant.[215] Unlike most other C−H activation processes, this reaction proceeded under basic conditions with 1 equiv of pyridine as the additive. Both electron-deficient and aliphatic alkenes worked well with moderate to high yields (Scheme 105). Other types of *N*-oxides derived from pyrazine and pyridazine were also applied. This approach serves as an appealing platform toward 2-functionalized pyridines.

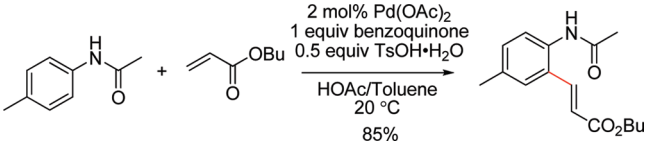
Scheme 104



Scheme 105



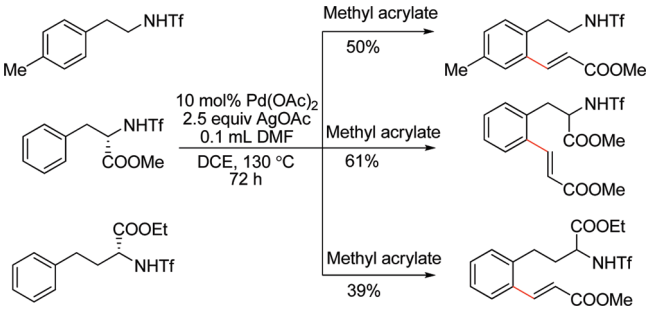
Scheme 106



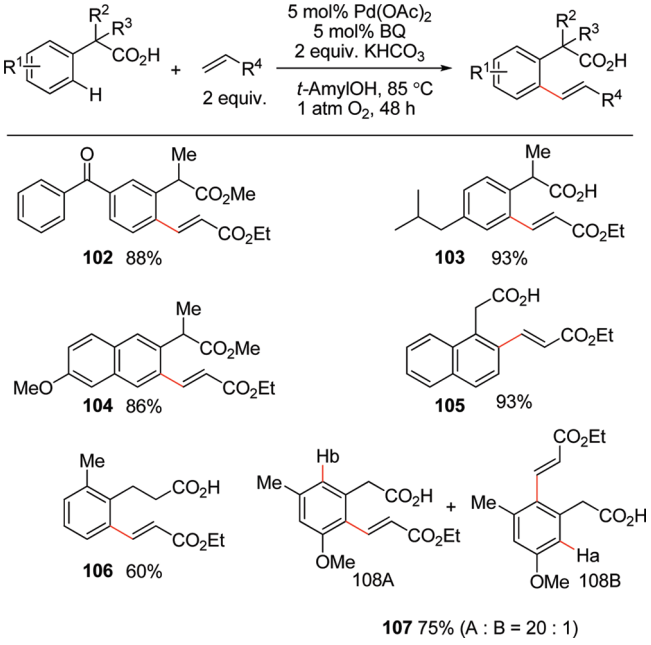
For the alkenylation of substituted phenyl rings, a directing group is a versatile means to achieve high regioselectivity. An acetomido group is still very popular in this oxidative coupling reaction. van Leeuwen and co-workers first introduced this type of substrate to cross-couple with electron-deficient alkenes under oxidation conditions (Scheme 106).[216] Only the ortho-substituted isomer was observed, indicating the importance of the directing effect of the amido group. With $Pd(OAc)_2$ as the catalyst and benzoquinone as the oxidant, the transformation proceeded smoothly in the presence of a TsOH additive even at room temperature. Benzoquinone was still speculated as an effective ligand to stabilize the different Pd species present during the catalytic cycle. Electron-rich arenes reacted significantly faster, indicating an electrophilic palladation process. They also measured the kinetic isotope effect, which showed that the C−H cleavage of arenes was rate-limiting. Later, halogenated acetanilides were introduced as substrates by Prasad and co-workers under similar reaction conditions.[217] Replacement of benzoquinone with O_2 together with a catalytic amount of $Cu(OAc)_2$ as the oxidant and acetone as the solvent also exhibited efficiency

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 107



Scheme 108

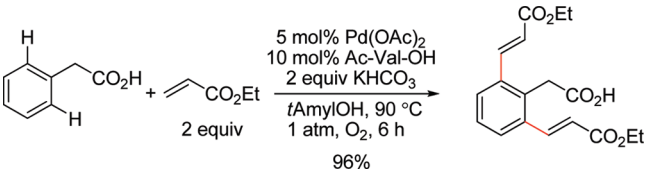


for this transformation and were demonstrated separately by Brown and co-workers and Liu and co-workers.[218,219] With a cationic palladium catalyst, this type of reaction could even proceed in water.[220] Other metals, such as rhodium, have also been employed as efficient catalysts in very recent times.[221,222]

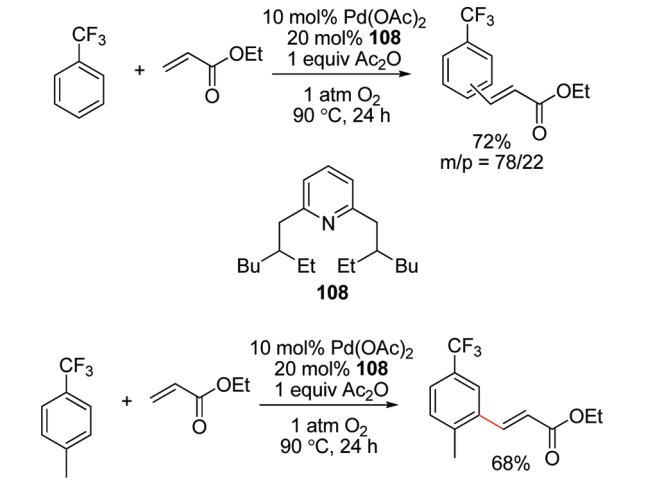
Yu and co-workers developed several other protocols for the oxidative alkenylation of substituted phenyl rings with triflamido and carboxyl groups as the directing group. Highly regioselective alkenylation of protected 2-phenylethylamines at the ortho-position of the substitutent were realized in the presence of a triflamido directing group.[223] A range of substrates such as 3-phenylpropylamines could be subjected to these reaction conditions (Scheme 107).

When phenylacetic acids were subjected to the oxidative cross-couplings with olefins, the reaction also proceeded smoothly and regioselectively in the presence of palladium catalyst and benzoquinone ligand.[224] Several drug substrates, including ketoprofen (**102**), ibuprofen (**103**), and naproxen (**104**), were found to be compatible with this protocol and afforded the *ortho*-olefination products in high yields (Scheme 108). Interestingly, a ligand-enabled reactivity

Scheme 109



Scheme 110

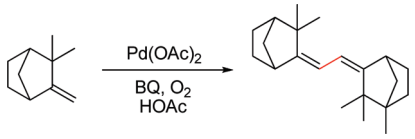


and selectivity were observed when 3-arylpropionic acids (**106**) and multiply substituted phenylacetic acids were examined as substrates. With mono-*N*-protected amino acids as ligands, the yield of the desired product was increased dramatically from 8% to 60%. The positional selectivity for Ha and Hb of 3-methyl-5-methoxy-phenylacetic acid (**107**) was also improved, albeit with lower efficiency. A sequential dialkenylation protocol was later developed using a screened amino acid ligand Ac-Val-OH in this palladium-catalyzed transformation (Scheme 109).[225] Further mechanistic studies of the ligand effect on the substrate scope, reaction rate, and catalyst turnover showed that the observed rate increases as a result of acceleration in the C−H cleavage step. These studies also suggest that a change in the mechanism of C−H cleavage from electrophilic palladation to proton abstraction occurs.[226]

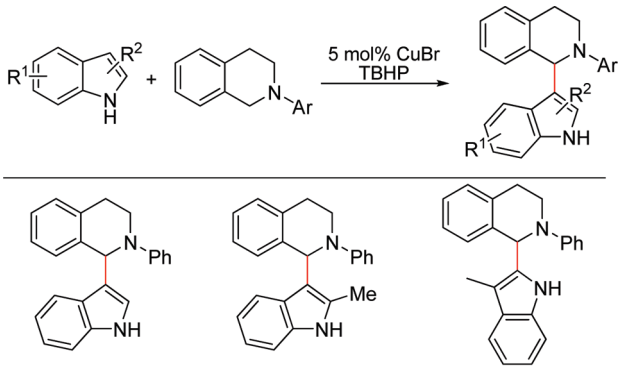
Most of the arenes employed in the oxidative C−H olefinations are electron-rich, as the electronic palladation process is the main pathway for those transformations. One report based on electron-deficient arenes was demonstrated recently by Yu and co-workers.[227] The oxidative olefination took place selectively at the meta- and para-positions of the monosubstituted arenes, and the meta-isomer is the major product with 2,6-dialkylpyridine **108** as the ligand. The detailed origin of this special ligand still remained unclear, but the loss of the reactivity at the ortho-position could be attributed to a steric influence from this ligand. An electrophilic substitution ($S_{Ar}E$) at the meta-position appears to be a plausible explanation for the meta-selectivity over para-selectivity, because the oxidative olefination of *para*-methyltrifluoromethylbenzene selectively occurred at the ortho-position of the methyl group (Scheme 110).

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 111



Scheme 112

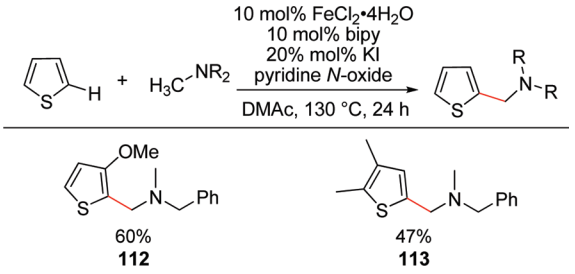


2.3.4.3. Couplings between Alkenes. Compared with the oxidative coupling between arenes and alkenes, the examples of the oxidative couplings between alkenes are rare. The oxidative homocoupling of camphene was demonstrated in several reports in the presence of a $Pd(OAc)_2$ catalyst. $LiNO_3$ or BQ together with O_2 were applied as efficient oxidants. This transformation was very convenient for the intermediate synthesis of natural products (Scheme 111).[228,229]

2.3.5. Csp^2−H and Csp^3−H as nucleophiles. Normally, the Csp^2−H of aromatic arenes is less active than the Csp−H of terminal alkynes. Even so, the oxidative coupling between Csp^2−H and Csp^3−H was achieved by using a similar protocol as the coupling between Csp−H and Csp^3−H. Indole was first used as a substrate to couple with alkyl groups adjacent to tertiary amines (Scheme 112).[230] The reaction took place selectively on the C3-position of indoles when both C2 and C3 are unsubstituted (**109**). When the C3-position of indole was substituted, the reaction proceeded smoothly at the C2-position (**111**).[231] The tetrahydroisoquinoline could be replaced by dipeptides and tripeptides to give the desired α-functionalization products in good yields.[107] Iron catalysts are also effective for the oxidative coupling of indole with tertiary amines; moreover, other heteroaromatic arenes such as thiophene (**112**)[232] (Scheme 113) and pyrroles (**114**)[137] (Scheme 114) are also suitable for the iron-catalyzed systems. 2-Naphthol could also be introduced in this type of transformation, while $CuBr_2$ was more efficient than CuBr and offered the cross-coupling product in a 72% NMR yield together with 11% of a 1,1′-bi-2-naphthol (BINOL) byproduct (Scheme 115).[231]

Combining with the Morita−Baylis−Hillman (MBH) reaction, electron-deficient alkenes could be used in this oxidative dehydrogenative coupling by adding an organocatalyst (Scheme 116).[231] Acrylonitrile was used to couple with tetrahydroisoquinoline in the presence of 10 mol % 1,4-diaza[2.2.2]bicyclooctane (DABCO) and 5 mol % CuBr as the catalyst and TBHP as the oxidant.

Scheme 113



Allylic sp^3 C−H bonds that are not adjacent to nitrogen were later developed to react with indoles under oxidative conditions.[233] $PdCl_2$ was found to be the most efficient catalyst together with DDQ as the oxidant, which is a well-known oxidation reagent in organic synthesis.[234] The C3-position of indole is still the active site and participates in the reaction (Scheme 117).

Recently, an oxidative coupling between arene and unactivated cycloalkanes was developed.[235] Ruthenium was found to be superior to other metal catalysts, such as Fe, Co, Ir, Ni, and Pd, in this transformation. *tert*-Butyl peroxide proved to be the best oxidant, and cycloalkanes were used as both the reactant and the solvent. With a pyridyl group as a directing group, the reaction occurred exclusively on the non-nitrogen atom containing aromatic rings, leading to both mono- (**117**) and bisalkylation products (**118**) (Scheme 118).

By switching the ruthenium catalyst to a scandium salt, a Lewis acid, the reaction proceeded selectively on the nitrogen atom-containing aromatic rings and displayed a preference for the CH bond adjacent to the nitrogen atom (Scheme 119).[236] The oxidative coupling between 2-phenylpyridine and cyclooctane selectively occurred at the 6-position in a 52% yield without any observation of the alkylation on the phenyl ring (**121**).

2.3.6. Csp^3−H and Csp^3−H as Nucleophiles. Traditional methods for Csp^3−Csp^3 bond construction are more commonly known as the S_N2 reaction.[237] However, in the S_N2 reaction, both starting materials need to be prefunctionalized. The direct coupling between two sp^3 C−H bonds leading to a Csp^3−Csp^3 bond is appealing yet also very challenging. Many efforts have been put into this field in recent five years. Li and co-workers have developed a general oxidative dehydrogenative coupling (CDC) reaction between two CH bonds, in which the C−H of sp^3 carbons is widely applied.[238] Because several reviews have been published to summarize the achievements in this area and most of the transformations share similar reaction conditions, detailed discussion of each example will not be reported and instead the details are listed in Scheme 120.

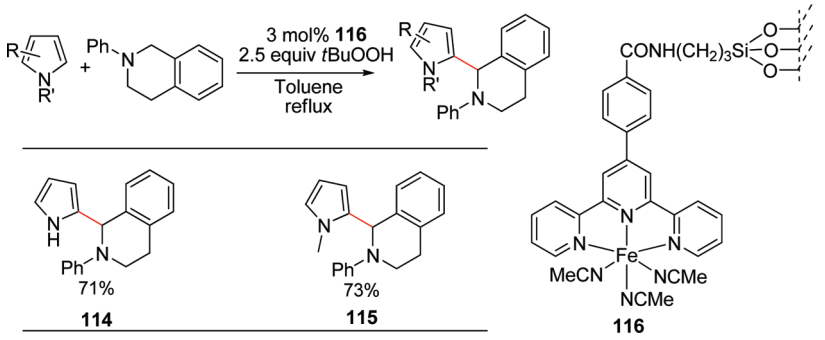
3. OXIDATIVE C−X BOND FORMATIONS BETWEEN TWO NUCLEOPHILES

3.1. C−M and X−H as Nucleophiles

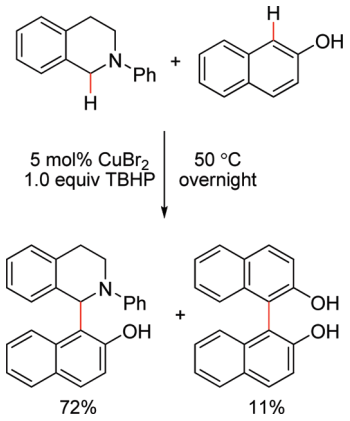
Transition metal catalyzed oxidative coupling of organic boronic acid (silane, stannane) derivatives and heteroatom nucleophiles is a highly useful method for the formation of

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

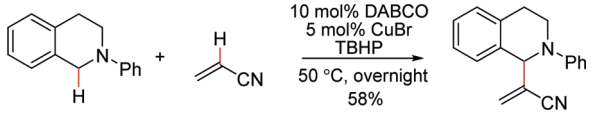
Scheme 114



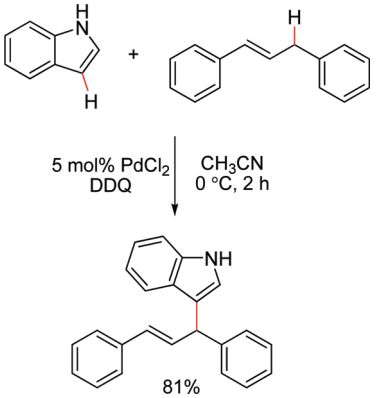
Scheme 115



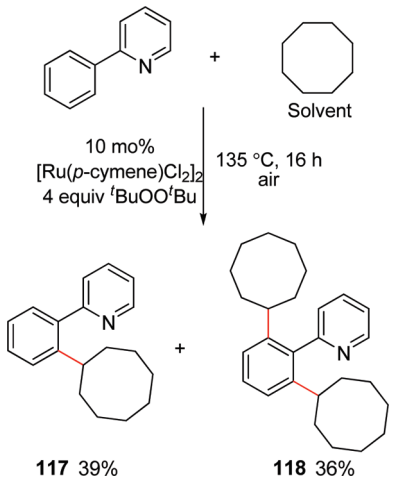
Scheme 116



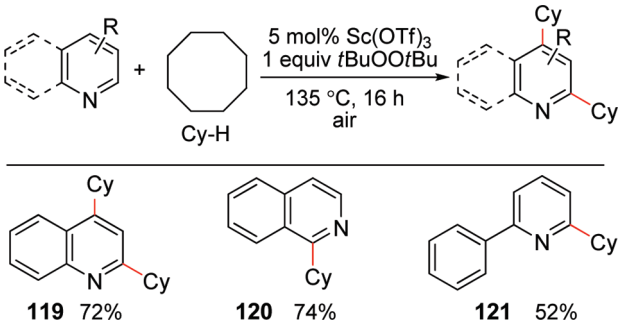
Scheme 117



Scheme 118



Scheme 119

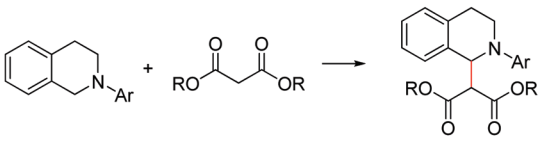
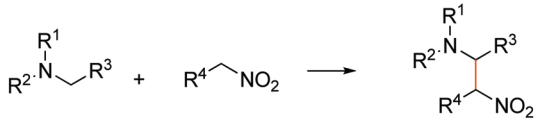
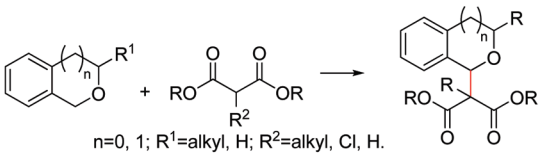
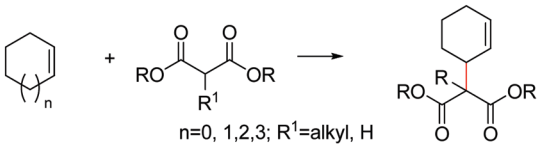
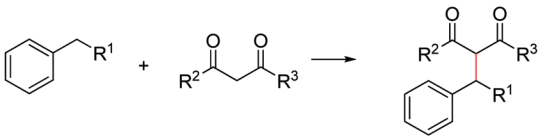
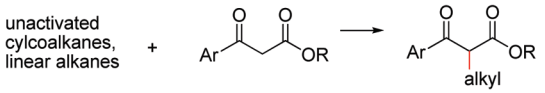
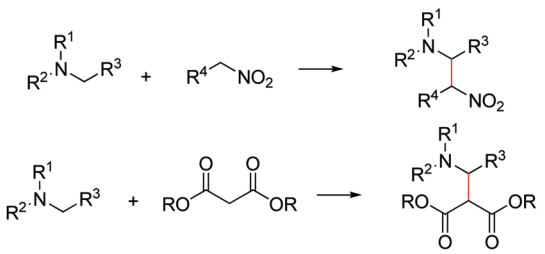
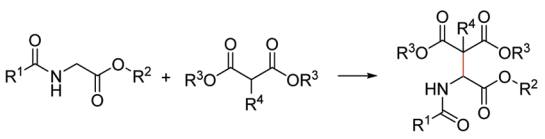
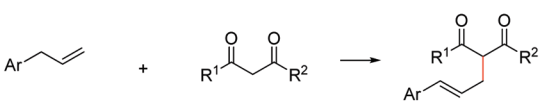


aryl−heteroatom bonds (Scheme 121). Pioneered by Chan et al., Evans et al., and Lam et al. in 1998,[253−255] these reactions typically employ milder reaction conditions than the analogous Ullmann−Goldberg reactions, and their applications have expanded significantly since the initial reports. Recently, this transformation has been reviewed in detail;[256−259] therefore, it will not be discussed in this review.

Despite remarkable development, the relevant reaction mechanism is still unknown and has never been the focus of systematic investigation. Very recently, mechanistic studies by Stahl's group on copper-catalyzed aerobic oxidative coupling

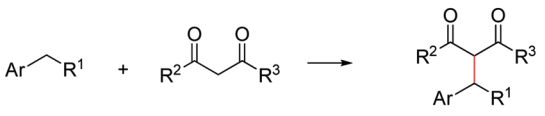
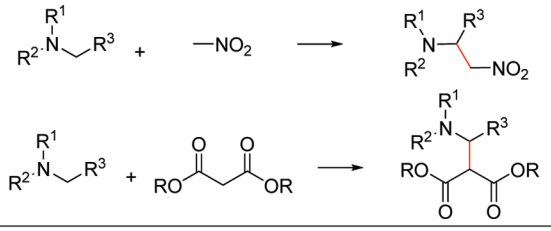
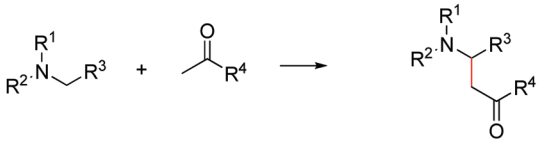
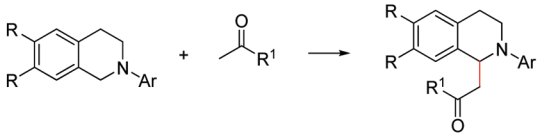
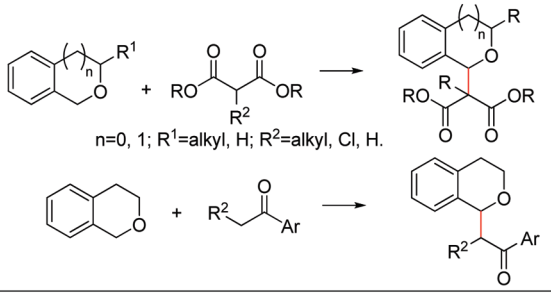
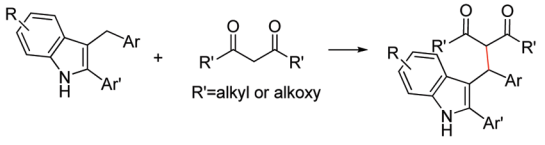
dx.doi.org/10.1021/cr100379j |Chem. Rev. 2011, 111, 1780–1824

Scheme 120

Year	Authors	Reaction formula	Reaction conditions	Ref
2005	C. Li *et al.*		5 mol% CuBr, TBHP, r.t.	231,239
2005	C. Li *et al.*		5 mol% CuBr, TBHP, r.t.	231,240
2006	C. Li *et al.*	 n=0, 1; R^1=alkyl, H; R^2=alkyl, Cl, H.	5 mol% $InBr_3$, 5 mol% $Cu(OTf)_2$, DDQ, r.t.	241
2006	C. Li *et al.*	 n=0, 1,2,3; R^1=alkyl, H	2.5 mol% CuBr, 10 mol% $CoCl_2$, TBHP, r.t.	242
2006	C. Li *et al.*		20 mol% $FeCl_2$, 10 mol% DABCO, TBHP, 80 °C	243
2007	C. Li *et al.*		20 mol% $FeCl_2.4H_2O$, TBHP, 100 °C	244
2007	C. Li *et al.*		5 mol% CuBr, O_2, 60 °C	245
2008	C. Li *et al.*		2 equiv $Cu(OAc)_2$, 20 mol% Cs_2CO_3 di(2-pyridyl)ketone, 60 °C	140
2008	Z. Shi *et al.*		10 mol% [Pd], BQ, O_2, 60 °C	246

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 120. Continued

Year	Authors	Reaction formula	Reaction conditions	Ref
2008	D. A. Powell *et al.*		20 mol% $Cu(ClO_4)_2$, 5 mol% bathophenanthroline, *t*BuOOBz, 60 °C	247
2009	J. Xiang *et al.*		2.5 mol% $RuCl_3$, O_2, 55 °C	248
2009	Z. Tan, C. Guo, *et al.*		5 mol% CuI, O_2, 80 °C	249
2009	M. Klussmann *et al.*		10 mol% $VO(acac)_2$, 10 mol% proline, TBHP, r.t.	250
2009	C. Li. *et al.*	 n=0, 1; R^1=alkyl, H; R^2=alkyl, Cl, H.	5 mol% $InCl_3$, 5 mol% $Cu(OTf)_2$, 20 mol% *N*-hydroxyphthalimide, O_2, 55-75 °C	251
2010	L. Gong *et al.*	 R'=alkyl or alkoxy	10 mol% $Cu(OTf)_2$, 12 mol% ligand, DDQ, -10-0 °C	252

revealed that this reaction proceeded via an "oxidase"-style mechanism (Scheme 122).[260] Kinetic and spectroscopic studies exhibit that transmetalation of the aryl group from boron to Cu(II) is the turnover-limiting step and reoxidation of the reduced catalyst by O_2 is rapid. Further mechanistic analysis implicates the involvement of an aryl−copper(III) intermediate that undergoes facile C−O bond formation.

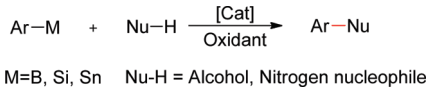
3.2. C−H and X−M as Nucleophiles

3.2.1. C−Halogen Bond Formations. Halogenated organic compounds play a very important role in chemistry; they are essential in organic synthesis as starting compounds and synthetic intermediates and as designer molecules for material science, industrial chemicals, and bioactive compounds.[261]

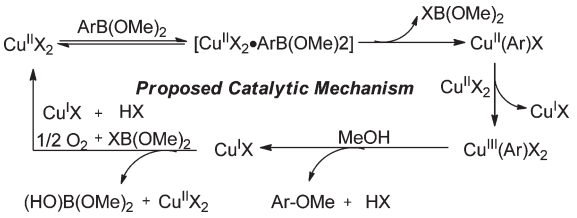
Vanadium catalysts have been widely employed in the oxidative halogenation with H_2O_2, among which the two main catalysts are NH_4VO_3 and V_2O_5.[262−267] Ammonium vanadate (V) could be an effective catalyst for oxidative halogenations of various phenols and anisoles. The reaction is performed with 30% aqueous H_2O_2 as oxidant and potassium halides as halo resource (Scheme 123).

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

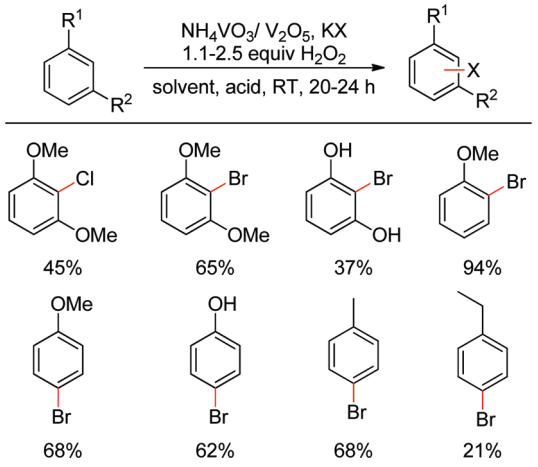
Scheme 121



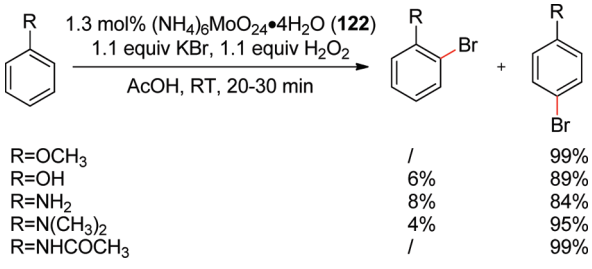
Scheme 122



Scheme 123



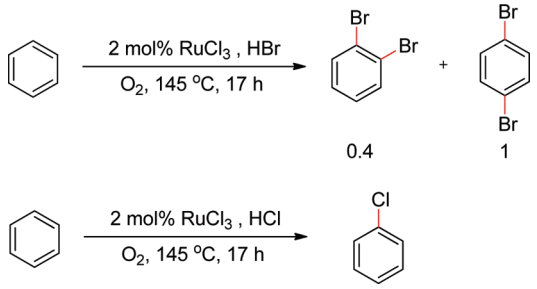
Scheme 124



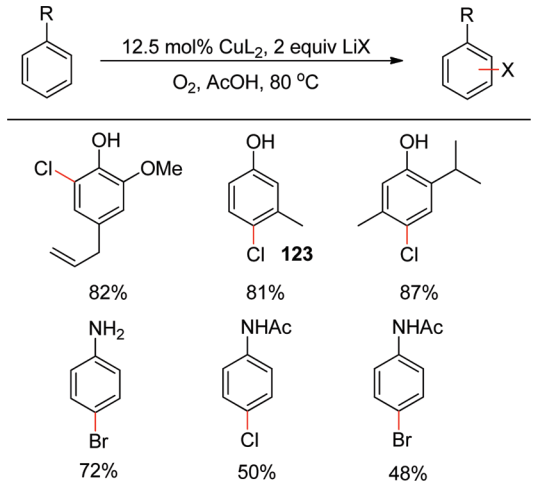
Polystyrene-bound vanadium and molybdenum complexes have been also prepared enabling the recovery of catalyst, and the catalytic potential of these complexes for the oxidative bromination of salicylic aldehyde was reported.[268,269]

Molybdenum(VI) complexes are a further class of catalysts for oxidative halogenation with H_2O_2.[270−272] Using AcOH as a reaction medium, ammonium molybdate (**122**)-catalyzed oxidative bromination of phenols, anilines, and their derivatives in high yields was demonstrated (Scheme 124).

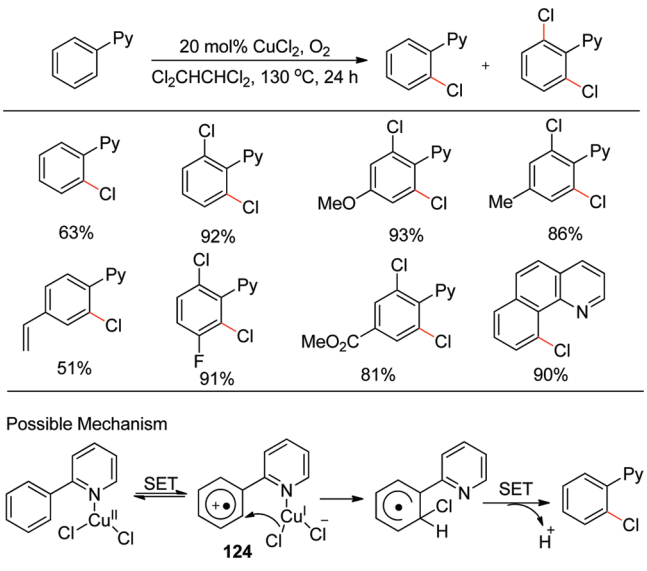
Scheme 125



Scheme 126



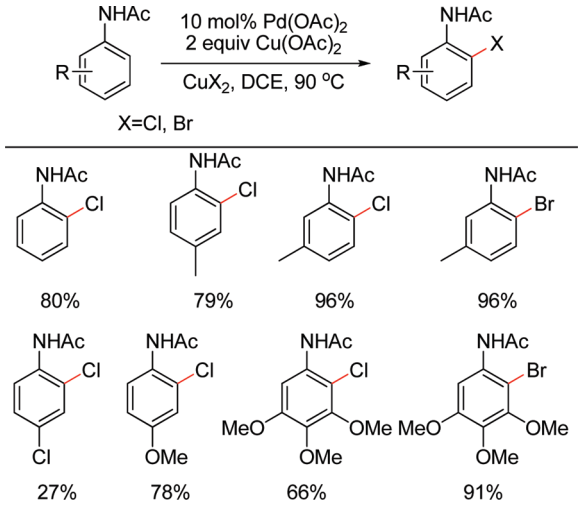
Scheme 127



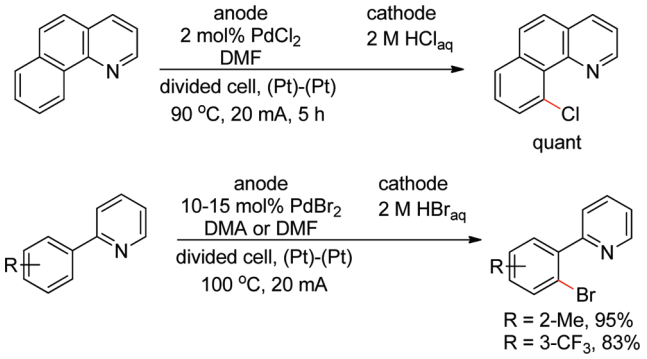
$RuCl_3$ was also found to be effective for aerobic bromination and chlorination with concentrated HBr or HCl, respectively, and O_2 in an aqueous/organic biphasic system in an atmosphere of pure oxygen at 1 atm (Scheme 125).[273]

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 128



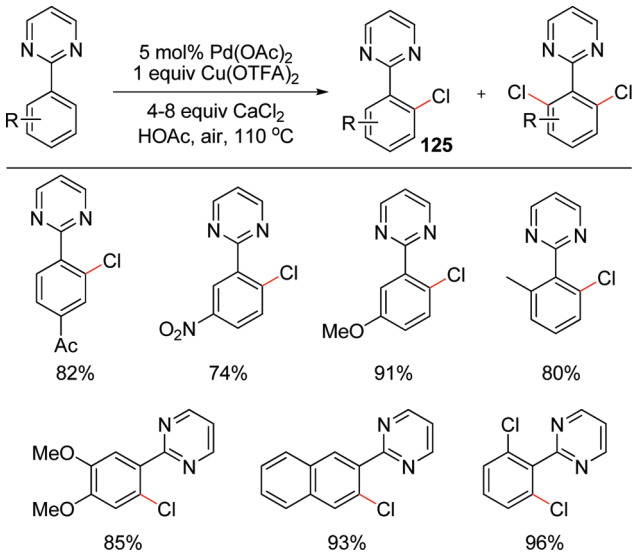
Scheme 129



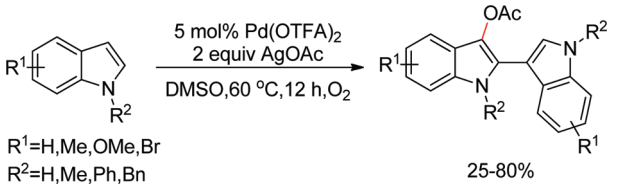
Copper salts are the most studied metal catalysts for aerobic oxidative halogenation.[274−277] It was demonstrated that $CuCl_2$ is able to catalyze the chlorination and bromination of various phenols and anilines (Scheme 126). The reaction of 3-methylphenol with 2 equiv of LiCl in the presence of O_2 and 12.5 mol % $CuCl_2$ in acetic acid at 80 °C resulted in 81% yield of 4-chloro-3-methylphenol (**123**). Analogously, the oxidative bromination was performed with LiBr and a catalytic amount of $Cu(OAc)_2$.

Cu(II)-catalyzed aerobic halogenation of aryl C−H bonds was developed by Yu and co-workers. (Scheme 127).[278] ortho-Selectivity was observed with a wide range of 2-arylpyridine substrates, and both mono- and difunctionalizations were achieved by tuning the reaction conditions. In this case, the source of the halogen atoms was the solvent. A radical-cation pathway was proposed in which a single-electron transfer (SET) from the aryl ring to the coordinated Cu(II) center to give the cation radical intermediate is the rate-limiting step. The observed ortho-selectivity is explained by an intramolecular anion transfer from a nitrogen-bound Cu(I) complex (**124**).

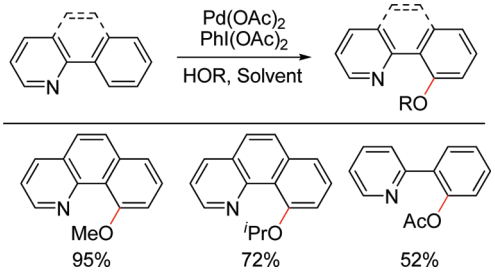
Scheme 130



Scheme 131



Scheme 132

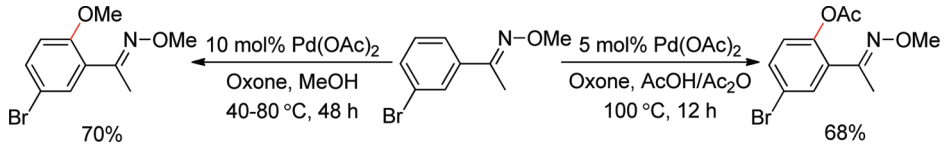


Shi and co-workers also developed a highly regioselective C−H halogenation of acetanilides to produce *ortho*-haloacetanilides catalyzed by $Pd(OAc)_2$ and $Cu(OAc)_2$ with CuX_2 as the halogen source (Scheme 128).[279]

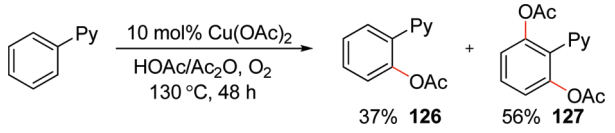
A new strategy for aromatic C−H halogenation by means of electrochemical oxidation has been described by Kakiuchi et al. (Scheme 129).[280] A combination of palladium-catalyzed aromatic C−H bond cleavage and halogenation with electrochemically generated halonium ions enables highly efficient, selective halogenations of aromatic compounds in a green-sustainable manner.

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

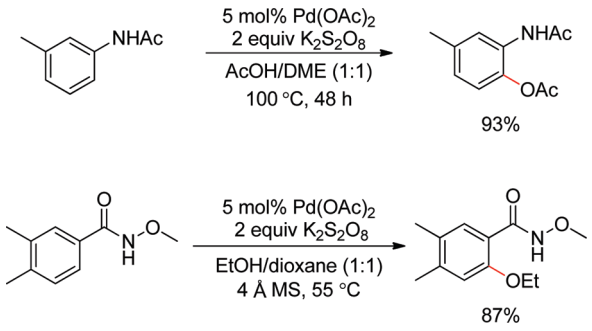
Scheme 133



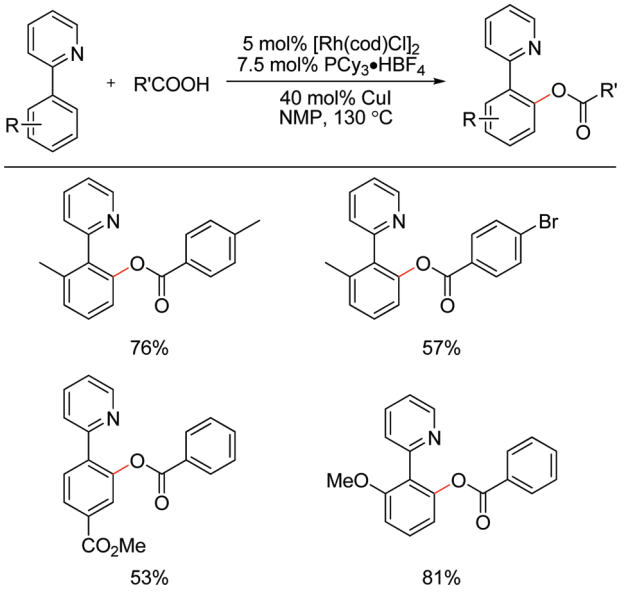
Scheme 134



Scheme 135

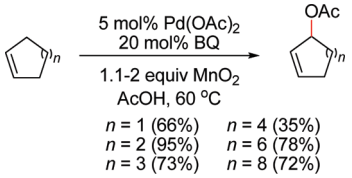


Scheme 136

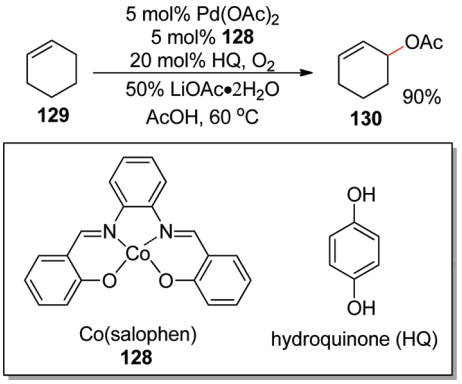


Recently, a wide variety of *ortho*-halogenated arylpyrimidines were prepared with high monoselectivity (**125**) and functional-group tolerance by using calcium halides as crucial halogenating agents and cupric trifluoroacetate as oxidant in the presence of air (Scheme 130).[281]

Scheme 137



Scheme 138



3.2.2. C–O Bond Formations. Zhang and co-workers developed a one-pot approach to C3-position acetoxylated biindolyls realized via palladium catalysis by the use of AgOAc under oxygen atmosphere as oxidants (Scheme 131).[170] Notably, the reaction tolerates the bromide substituent on indoles.

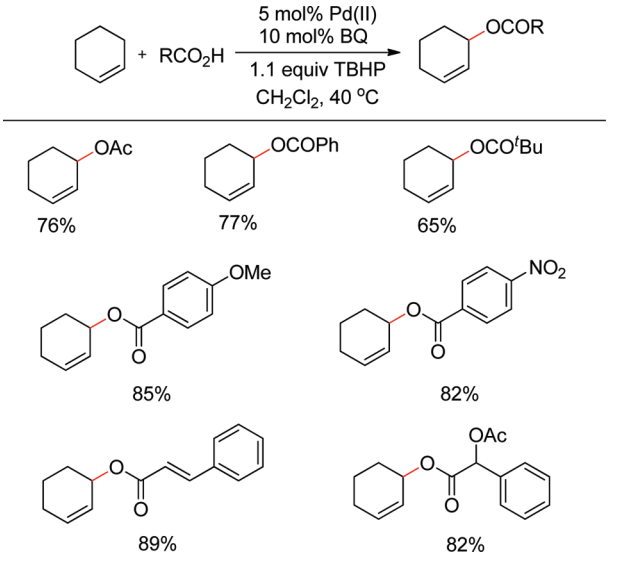
3.3. C–H and X–H as Nucleophiles

3.3.1. C–O Bond Formations. *3.3.1.1. Csp^2–H as Nucleophiles.* In 2004, Sanford and co-workers described a new and highly practical Pd(II)-catalyzed method for the regio- and chemoselective oxidative functionalization of arenes and alkanes (Scheme 132).[282] Carbon–hydrogen bonds of substrates that contain a variety of directing groups (e.g., pyridine, azobenzene, pyrazole, and imine derivatives) were selectively transformed into esters and ethers under mild conditions. Reaction of benzoquinoline with $PhI(OAc)_2$/ $Pd(OAc)_2$ in alcohol solvents produced a range of alkyl–aryl ethers in good yields.

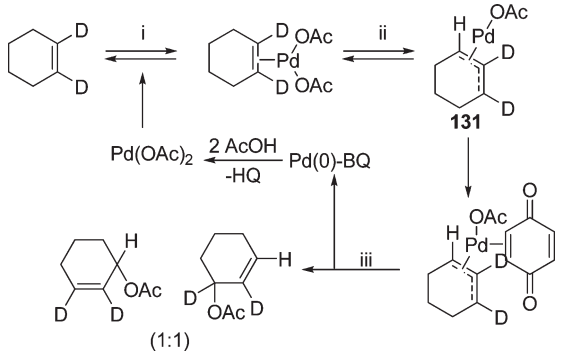
The application of peroxide-based oxidants in the $Pd(OAc)_2$-catalyzed acetoxylation and etherification of arene and alkane C–H bonds was also disclosed by Sanford and co-workers (Scheme 133).[283] Oxone in acetic acid and/or methanol proved

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

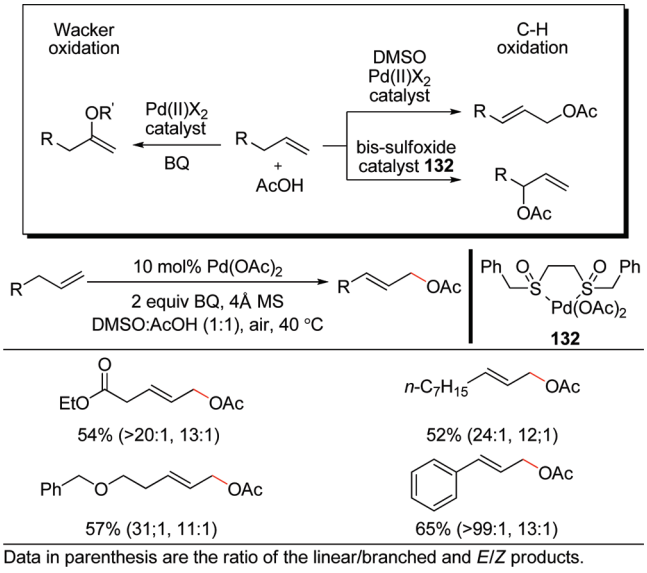
Scheme 139



Scheme 140

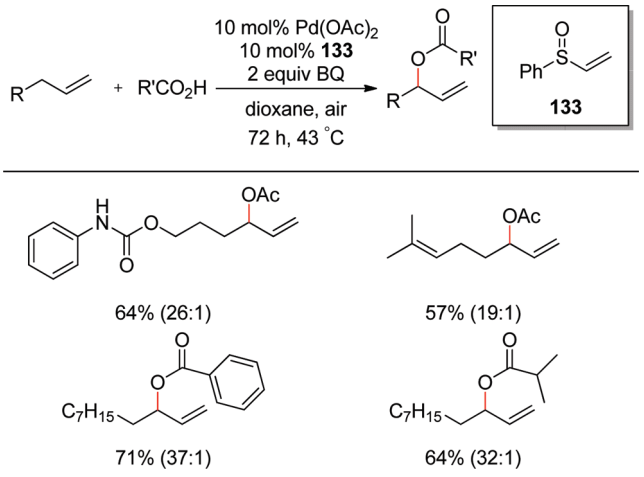


Scheme 141



Data in parenthesis are the ratio of the linear/branched and *E*/*Z* products.

Scheme 142



to be particularly effective, and these transformations were applied to a wide variety of substrates.

Cu(II)-catalyzed acetoxylation of aryl C−H bonds was then developed by Yu and co-workers. (Scheme 134).[278] ortho-Selectivity was observed when 2-phenylpyridine was employed as substrate and both mono- and difunctionalizations (**126** and **127**) were achieved. Use of O_2 as a stoichiometric oxidant proved to be a significant advantage over Pd-catalyzed C−H functionalization reactions developed before.

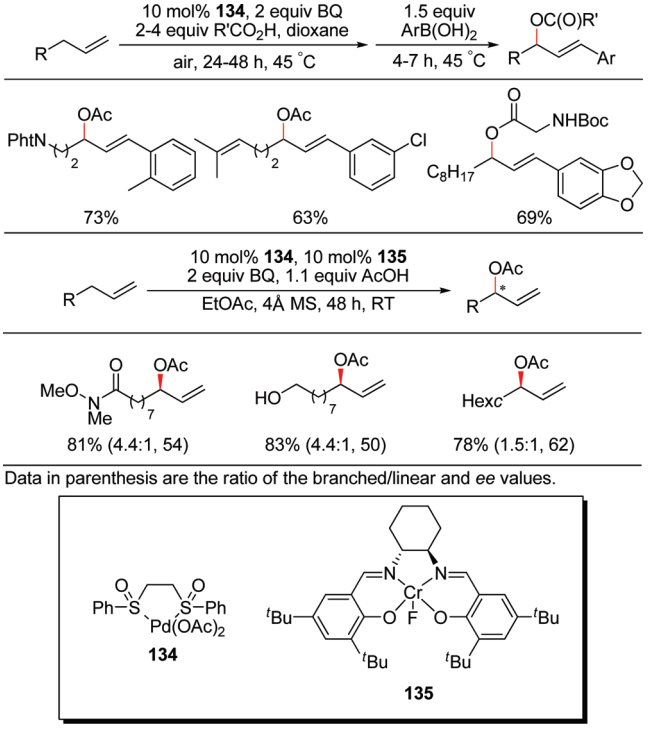
Direct *ortho*-acetoxylation of anilides and *ortho*-alkoxylation of *N*-methoxybenzamides through a $Pd(OAc)_2$-catalyzed C−H bond activation process were achieved (Scheme 135).[284,285] Using $K_2S_2O_8$ as oxidant, the amido group and CONHOMe group functionalized as directing group converted aromatic sp^2 C−H bonds into C−O bonds in high regioselectivity, respectively.

Recently, Cheng and co-workers described a rhodium-catalyzed *ortho*-benzoxylation of the sp^2 C−H bond with carboxylic acids.[286] The procedure provides the benzoyloxylated products in moderate to good yields, in which methoxycarboyl, formyl, bromo, chloro, and nitro groups can be well tolerated (Scheme 136). Importantly, no external oxidant was required for the transformation. Furthermore, they reported the acyloxylation of the benzylic sp^3 C−H bond through a chelation-assisted palladium catalysis, which employed $PhI(OAc)_2$ as a stoichiometric oxidant.[287]

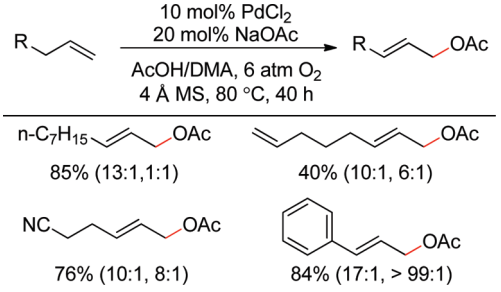
3.3.1.2. Csp^3−H as Nucleophiles. Early in the 1990s, Heumann, Åkermark, and co-workers have demonstrated the $Pd(OAc)_2$/BQ/MnO_2 system to be a useful tool for the allylic acetoxylation of olefins (Scheme 137).[288−290] Unsubstituted cycloalkenes gave good to excellent yields of allylic acetates. Reactions for substituted cycloalkenes and linear alkenes afforded good yields with several isomeric acetates. This catalytic system also worked efficiently for the acyloxylation of alkenes and cycloalkenes.[291,292]

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 143



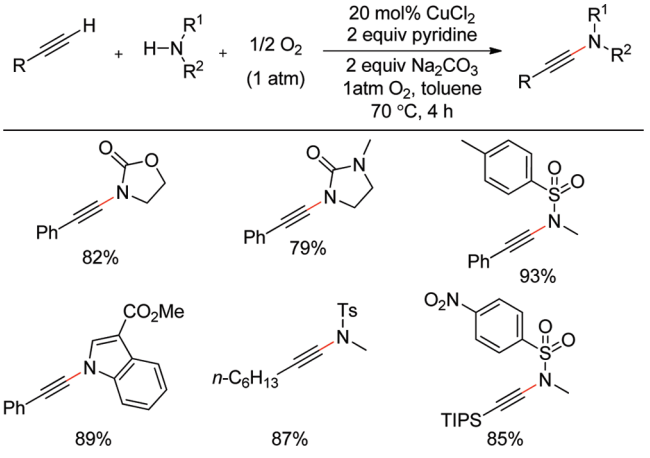
Scheme 144



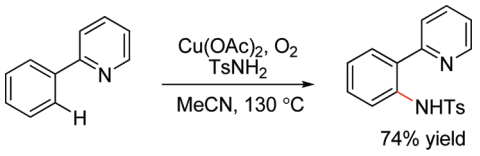
Palladium-catalyzed aerobic allylic oxidation of cyclic olefins with the aid of a metal macrocycle−quinone system has been developed by Bäckvall et al. (Scheme 138).[293] This transformation involves a multistep electron transfer with three catalysts ($Pd(OAc)_2$, hydroquinone, metal macrocycle). Employing this aerobic three-component catalytic system with Co(salophen) (**128**) as oxygen-activating catalyst, cyclohexene (**129**) is quantitatively oxidized to 3-acetoxycyclohexene (**130**). Later on, other metal−macrocycle oxygen-activating catalysts or heteropolyacid were also employed for aerobic allylic acetoxylation reactions.[294−296]

Utilizing CH_2Cl_2 as solvent and employing the desired carboxylic acid as a reagent, allylic acyloxylation was achieved with Pd(II) as catalyst and BQ as cocatalyst in the presence of hydrogen peroxide or TBHP as oxidant (Scheme 139).[297] Other catalytic systems such as $Pd(OAc)_2$−BQ−H_2O_2 and $PdCl_2$−

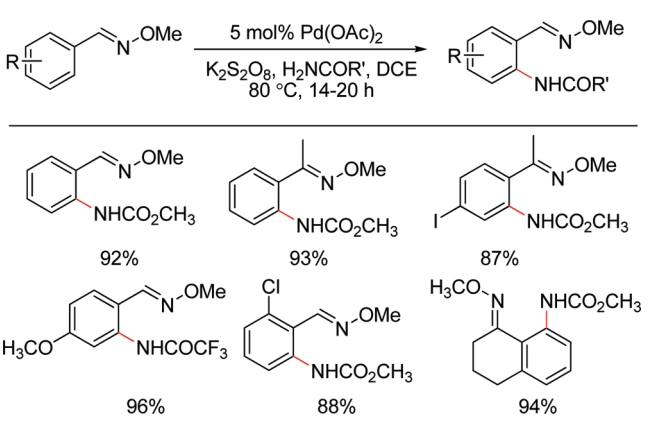
Scheme 145



Scheme 146



Scheme 147



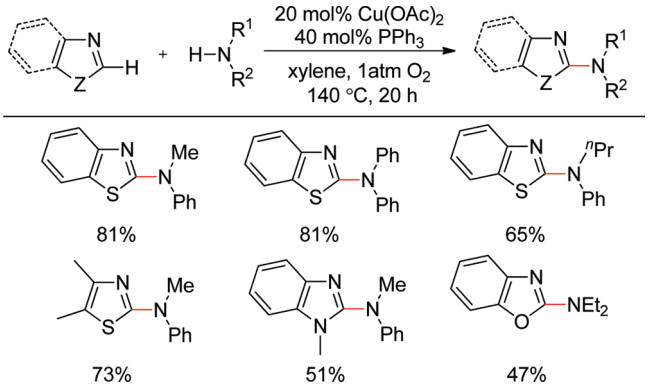
$AgOAc-TeO_2$−TBHP were also reported for allylic acetoxylation of olefins.[298−304]

Using 1,2-dideuterated cyclohexene as substrate, the mechanism of quinone-based allylic acetoxylation of cyclic alkenes was studied (Scheme 140).[305−307] After activation of the olefin by coordination to the metal (step i), removal of an allylic hydrogen leads to a (σ-allyl) palladium intermediate **131** (step ii). A BQ molecule coordinates the latter and undergoes nucleophilic attack by the acetate at either allyl terminus to give the allylic acetate and Pd(0) (step iii).

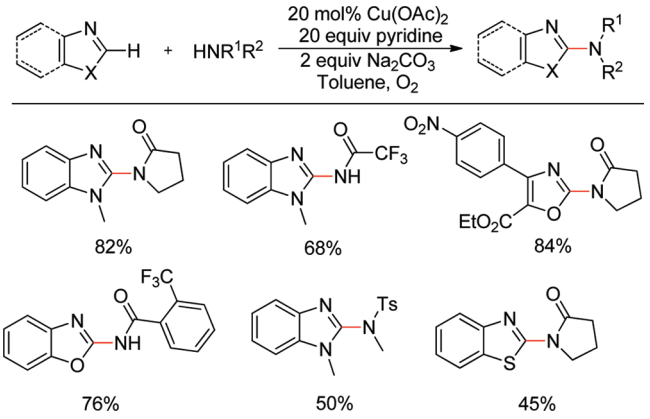
In 2004, Chen and White reported an allylic acetoxylation of terminal alkenes using PdX_2 as catalyst and BQ as oxidant in a DMSO/AcOH (1:1) solution, which was compatible

dx.doi.org/10.1021/cr100379j |Chem. Rev. 2011, 111, 1780–1824

Scheme 148



Scheme 149



with a wide range of functionality (e.g., amides, carbamates, esters, and ethers) (Scheme 141).[308] Addition of DMSO was found to be critical for promoting the C−H oxidation pathway, with AcOH alone or in combination with a diverse range of dielectric media, leading to mixtures favoring Wacker-type oxidation products. To explore the role of DMSO as a ligand, the bis-sulfoxide $Pd(OAc)_2$ complex **132** was formed and found to be an effective C−H oxidation catalyst in the absence of DMSO. Moreover, catalyst effects a reversal of regioselectivity, favoring the formation of branched allylic acetates.

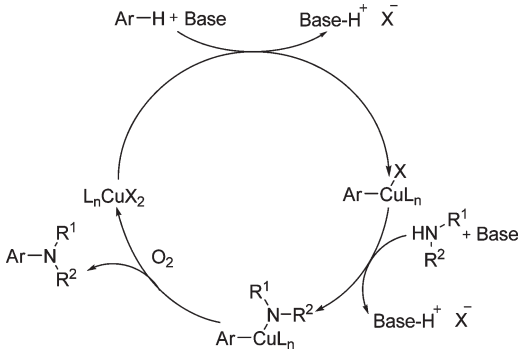
After that, they discovered a highly chemo- and regioselective Pd(II)-catalyzed allylic oxidation of α-olefins[309] to furnish branched allylic esters that proceeds via a novel serial ligand catalysis mechanism in which two different ligands (vinyl sulfoxide **133** and BQ) interact sequentially with the metal to promote distinct steps of the catalytic cycle (Scheme 142).

Further, a sequential allylic C−H oxidation/vinylic C−H arylation catalyzed by $Pd(OAc)_2$/bis-sulfoxide **134** was disclosed, in which α-olefin hydrocarbons were converted to *E*-arylated allylic esters with high regio- and *E*/*Z* selectivities (Scheme 143).[310] Recently, an enantioselective allylic C−H oxidation of terminal olefins was also reported using a heterobimetallic Pd^{II}/bis(sulfoxide) (**134**)/CrIII(salen) (**135**) system (Scheme 143).[311]

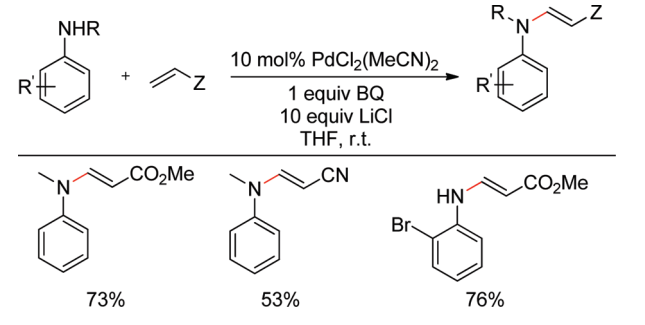
Kaneda and co-workers also described the regioselective acetoxylation of terminal alkenes to linear allylic acetates using molecular oxygen as oxidant, in which a combination of palladium dichloride and *N*,*N*-dimethylacetamide (DMA) constituted a highly efficient and reusable catalytic system (Scheme 144).[312] Addition of *n*-heptane to the reaction mixture upon completion of the reaction followed by decantation of the *n*-heptane phase containing the oxidized products allows the active Pd species in the residual DMA solution to be recycled.

3.3.2. C−N Bond Formations. *3.3.2.1. Csp−H Nucleophiles.* Stahl and co-workers have recently developed a copper-catalyzed direct aerobic oxidative amidation of terminal alkynes for the preparation of ynamides (Scheme 145).[313] Various nitrogen nucleophiles, including cyclic carbamates, amides, and ureas, and *N*-alkyl-arylsulfonamides and indoles were coupled with terminal alkynes.

Scheme 150



Scheme 151

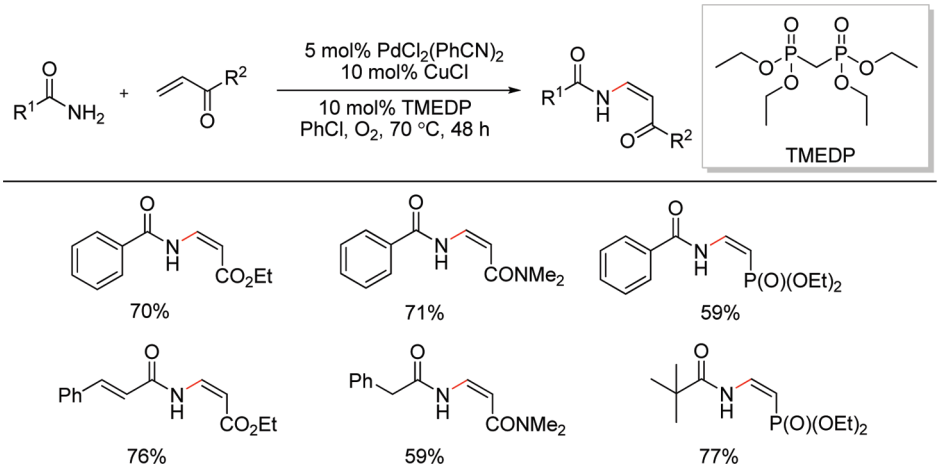


3.3.2.2. Csp²−H as Nucleophiles. 3.3.2.2.1. Arenes. The pioneering development of a simple copper-catalyzed C−H amination was reported by Yu and co-workers,[278,314] using $Cu(OAc)_2/O_2$ to effect the pyridine-directed functionalization of a Csp^2−H bond with a variety of anionic nucleophiles, including halogens, cyanide, alcohols, and sulfonamides (Scheme 146).

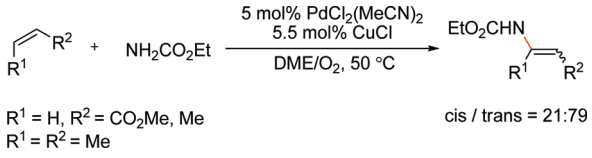
After that, Che and co-workers described the $Pd(OAc)_2$-catalyzed intermolecular amidation reactions of unactivated sp^2 and sp^3 C−H bonds using primary amides and potassium persulfate (Scheme 147).[315] The substrates containing a pendent

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

Scheme 152



Scheme 153



oxime or pyridine group were amidated with excellent chemo- and regioselectivities.

Mori and co-workers detailed the use of $Cu(OAc)_2$ for the direct amination of benzothiazole with *N*-methylaniline under mild reaction conditions (Scheme 148).[316] Amination of azoles takes place at the 2-position with several amines in the presence of 1 atm O_2.

Wang and Schreiber recently developed closely related reaction conditions for the amidation of various heterocyclic compounds (Scheme 149).[317] The optimized conditions also use 20 mol % $Cu(OAc)_2$ with pyridine and Na_2CO_3.

The mechanism proposed by both Mori and Schreiber is directly analogous to that proposed by Stahl for the amidation of alkynes: formation of organocopper intermediate by deprotonation, coordination of the nucleophile, and then reductive elimination with the catalyst regenerated by molecular oxygen (Scheme 150).

3.3.2.2.2. Alkenes. Bozell and Hegedus first disclosed the intermolecular reactions of substituted anilines with electron-deficient olefins to produce vinylogous arylamino ketones, esters, and nitriles (Scheme 151).[318] Interaction of conjugated enones with palladium was particularly sensitive to substitution, since the reaction was restricted to enones lacking α- and *β*-substitution.

An efficient procedure for the preparation of enamides has been developed involving the reaction of primary amides with conjugate olefins (Scheme 152).[319] The preference for the formation of *Z*-enamides is presumably due to the presence of an intramolecular hydrogen bond between the amido proton and the carbonyl oxygen.

The addition of urethane to alkenes such as methyl acrylate by means of the catalytic system $PdCl_2(MeCN)_2/CuCl/O_2$ yielded olefinic carbamates (Scheme 153).[320]

Hosokawa and co-workers discovered the amidation of electron-deficient alkenes with cyclic carbamates or lactams affording the corresponding *N*-substituted compounds (Scheme 154).[321] $PdCl_2(MeCN)_2$ and CuCl were used as catalyst under 1 atm of O_2, and carbamates were more reactive than lactams.

Stahl and co-workers achieved the direct amidation of *p*-substituted styrenes with oxazolidinone using $PdCl_2(MeCN)_2$ and $CuCl_2$ as catalysts under 1 atm of O_2 (Scheme 155).[322] Addition of NEt_3 led to complete regioselectivity with the exclusive formation of the Markovnikov product. Relevant experiments confirmed that this regioselectivity arises from a Bronsted base effect. Therefore, the use of previously deprotonated oxazolidinone resulted in the formation of the Markovnikov product even in the absence of an external base.

The reaction was also applied to unactivated alkenes (Scheme 156).[323,324] Catalyzed by $Pd(OAc)_2$, cycloalkenes and acyclic alkenes reacted well with phthalimide, giving corresponding nitrogenated compounds in benzonitrile under oxygen atmosphere. Nonacidic NH groups including morpholine, piperidine, and anilines were unreactive under the same conditions.

3.3.2.3. Csp^3—H as nucleophiles. The first significant progress in this direction arose from the studies of Che and co-workers (Scheme 157).[325,326] They demonstrated the high capacity of ruthenium and manganese porphyrin complexes to catalyze the amidation of benzylic and allylic C—H bonds. By employing manganese *meso*-tetrakis(pentafluorophenyl)-porphyrins **136**, the amidations can be effected by directly using NH_2R as amidating reagents.

A copper-catalyzed amidation of allylic and benzylic C—H bonds with both primary and secondary sulfonamides was also described (Scheme 158).[327] The reaction is applicable to the coupling of a diverse set of hydrocarbon species with aryl, heteroaryl, and alkyl sulfonamides and is tolerant of a variety of functional groups.

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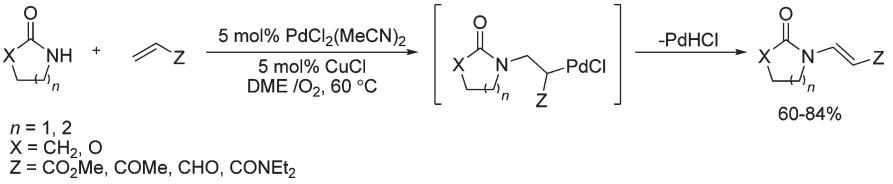
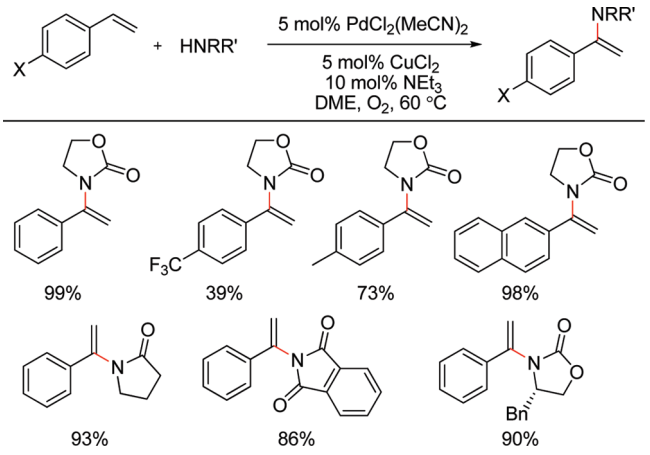
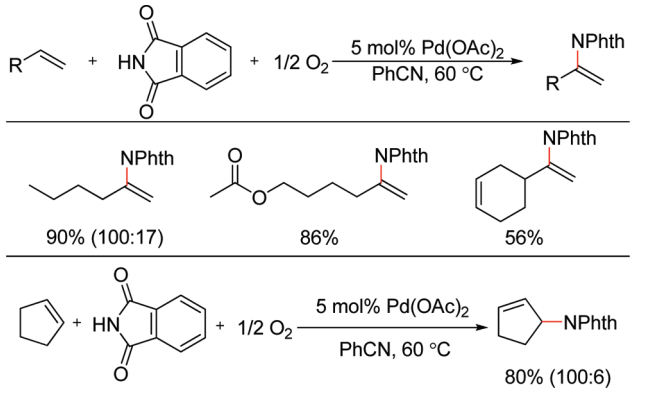
Scheme 154



Scheme 155



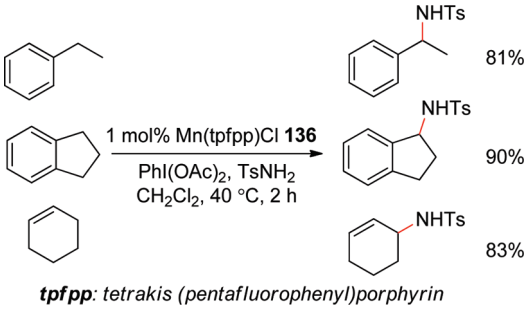
Scheme 156



Fu and co-workers have developed a novel copper-catalyzed amidation of unactivated sp^3 C−H bonds adjacent to a nitrogen atom by using an inexpensive catalyst-oxidant (CuBr/*t*BuOOH) system under mild conditions (Scheme 159).[328] The dephenylation was first found for *N*-benzylaniline **137**, and the new class of products provided diverse structures for pharmaceuticals and combinatorial chemistry.

Intermolecular C−H amination of benzylic and 3° C−H bonds catalyzed by $Rh_2(esp)_2$ (**138**) was described by Fiori and Du Bois.[329] The transformation displays high chemoselectivity for benzylic C−H oxidation (Scheme 160).

Scheme 157



In 2006, Müeller and co-workers have discovered a highly efficient intermolecular C−H amination procedure catalyzed by a chiral rhodium catalyst **139** (Scheme 161).[330] This reaction occurs with good to excellent diastereoselectivities, particularly at secondary benzylic positions, and can be applied with equal success to the synthesis of both isomers of the resulting amine. A similar intermolecular regioselective C−H amination was achieved through the same rhodium(II) catalyst (Scheme 161).[331] Good to excellent yields and excellent diastereoselectivities can be obtained with a stoichiometric amount of benzylic and allylic substrates as well as alkanes.

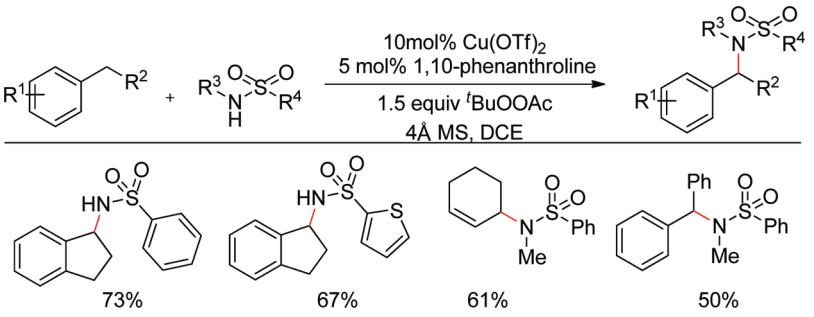
Lately, Fu and co-workers have developed a general and efficient method for copper-catalyzed amidation of saturated C−H bonds under mild conditions,[332] and the used substrates include benzylic reagents, the *N*,*N*-dimethylaniline derivatives, the free carboxamides, and sulfonamides (Scheme 162). The protocol uses inexpensive and readily available CuBr/*N*-halosuccinimide (NBS or NCS) as the catalyst/oxidant, providing practical applications for synthesis of various amides via C−H activation.

3.3.2.4. Allylic C−H as Nucleophiles. Reed and White reported the first heterobimetallic Pd(II) sulfoxide/(salen)Cr(III)Cl-catalyzed intermolecular linear allylic C−H amination (Scheme 163).[333] This reaction directly converts densely functionalized α-olefin substrates to linear (*E*)-allylic carbamates with good yields and outstanding regio- and stereoselectivities (>20:1). Chiral bis-homoallylic and homoallylic oxygen, nitrogen, and carbon substituted α-olefins undergo allylic C−H amination with good yields, excellent selectivities, and no erosion in enantiomeric purity.

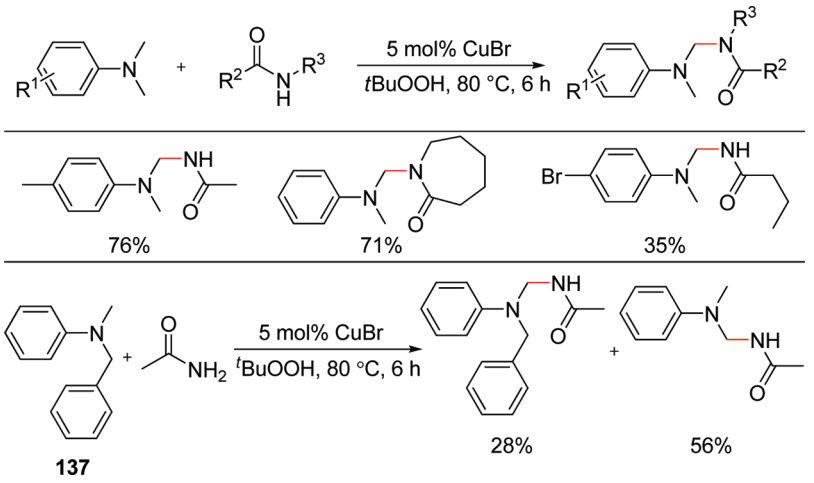
Palladium-mediated intermolecular aerobic oxidative allylic amination was later developed by Liu et al. to synthesize linear (*E*)-allylimides with high regioselectivity (Scheme 164).[334] The proposed mechanism involves an allylic C−H activation with

dx.doi.org/10.1021/cr100379j |*Chem. Rev.* 2011, 111, 1780–1824

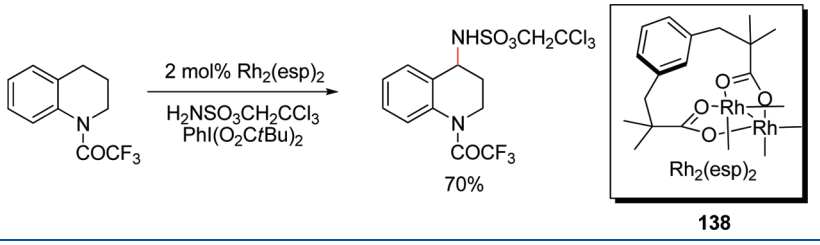
Scheme 158



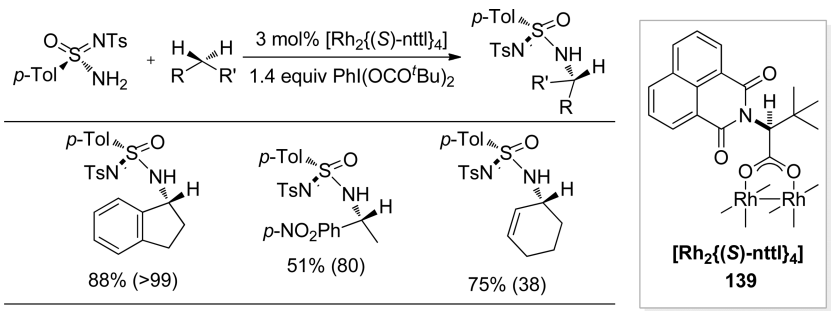
Scheme 159



Scheme 160



Scheme 161



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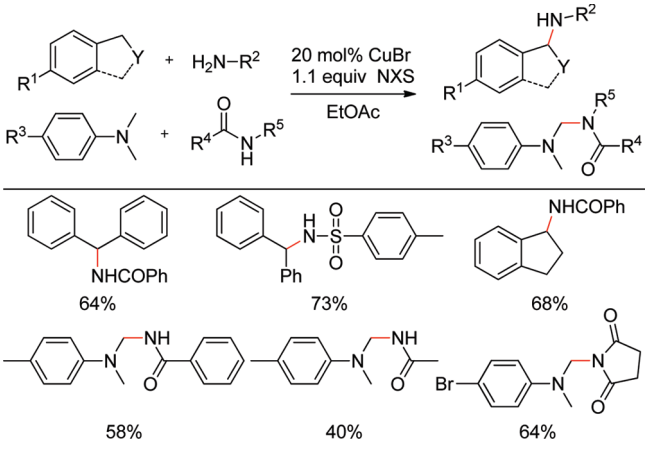
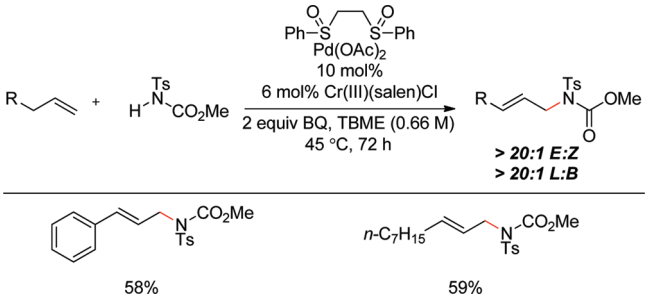
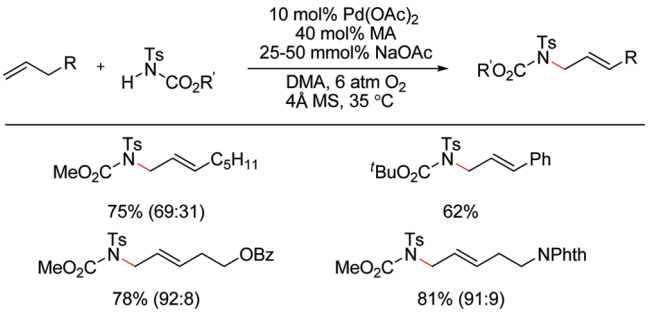
Scheme 162



Scheme 163



Scheme 164

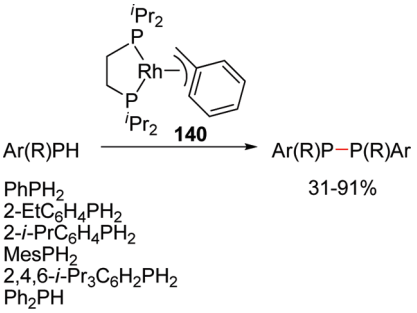


subsequent nitrogen nucleophile substitution. The catalytic system allows efficient dioxygen-coupled turnover without additional cocatalysts.

4. OXIDATIVE X−X BOND FORMATIONS BETWEEN TWO NUCLEOPHILES

Few examples were reported as to X−X bond formation. In 2006, Han and Tilley reported dehydrogenation couplings of phosphines catalyzed by rhodium complex **140** (Scheme 165).[335] Efficient dehydrogenation couplings of 2-$EtC_6H_4PH_2$, 2-$iPrC_6H_4PH_2$, and 2,4,6-$iPr_3C_6H_2PH_2$ were observed. Complex **140** also catalyzes the cross-coupling of Ph_2PH with PhSH (to Ph_2P−SPh).

Scheme 165



5. CONCLUSIONS

Oxidative couplings between two nucleophiles have been extensively studied in recent years. Various bond formations were achieved in the presence of transition metal catalysts, among which palladium played a central role. Organometallic reagents are still popular to oxidatively couple with other nucleophiles. Moreover, due to green chemistry, much attention has been paid to realize bond formations between two hydrocarbons in the presence of molecular oxygen, the greenest oxidant. However, challenges still remain. The essential of oxidative couplings is selectivity for cross-coupling products. To achieve this goal, various directing groups and an excess of one nucleophile partner have to be used, which restricts the substrate scope and potential applicability. Reaction conditions are still not mild. In spite of those drawbacks, the advantages of oxidative couplings will be realized step by step and further exciting developments are expected.

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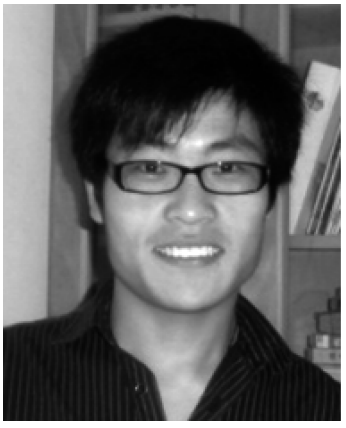
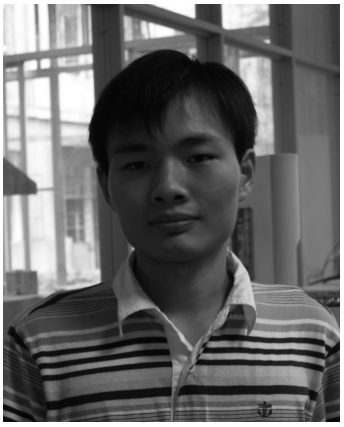


Chao Liu received his Bachelor's degree (2007) from Wuhan University, China. He joined Prof. Aiwen Lei's group in 2006 and started his Ph.D. in 2007. He spent one year from October 2008 to October 2009 as an exchange Ph.D. student under the supervision of Prof. Todd B. Marder at Durham University, U.K., funded by the China Scholarship Council. He is currently a

4th year Ph.D. student in Prof. Aiwen Lei's group and focuses on palladium-catalyzed coupling reactions.

Hua Zhang was born in 1987 and received his Bachelor's Degree of Science in 2008 from Wuhan University, under the supervisor of Prof. Aiwen Lei. He has joined Prof. Lei's group since 2007, and is currently a 3rd year Ph.D. student. His research focuses on the transition metal catalyzed oxidative coupling reactions.



Wei Shi was born in 1985 and received his Bachelor's Degree of Science in 2006 from Wuhan University, under the supervision of Prof. Aiwen Lei. He has joined Prof. Lei's group since 2005 and is currently a 5th year Ph.D. student. His research interest focuses on the transition metal catalyzed cross-coupling reactions and their applications in materials science.

Aiwen Lei received his Bachelor's degree (1995) from Huaibei Normal University, Huaibei, P. R. China, and obtained his Ph.D (2000) whilst supervised by Prof. Xiyan Lu at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (CAS). He then moved to Pennsylvania State University, U.S.A., and worked with Prof. Xumu Zhang as a postdoctoral fellow. He joined Stanford University (2003), working with Prof. James P. Collman as a research associate. He then became a full professor (2005) at College of Chemistry and Molecular Sciences, Wuhan University, China. His research focuses on novel approaches and understanding toward bond formations.

ACKNOWLEDGMENT

We gratefully acknowledge support from the National Natural Science Foundation of China (21025206, 20832003, 20972118, and 20772093) and the "973" Project from the MOST of China (2011CB808600). We also thank the support from "the Fundamental Research Funds for the Central Universities" and Program for New Century Excellent Talents in University (NCET).

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