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Chemical Oxidative C—C Bond Formation

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1.1 Introduction

Efficient and selective C—C bond formation has been one of the longstanding central topics in synthetic organic chemistry because it is the indispensable methodology for the construction of organic skeletons. In general, an overall redox-neutral process using a carbon electrophile and a carbon nucleophile is employed owing to preferable polarity of two coupling fragments (Scheme 1.1a). On the other hand, the C—C bond-forming reaction with two different nucleophiles in the presence of suitable chemical oxidants (chemical oxidative C—C bond formation) can provide a good alternative to the above overall redox-neutral process particularly when the corresponding carbon electrophile is difficult to prepare (Scheme 1.1b). Moreover, the ultimate direct C—C bond-forming reaction of two simple C—H fragments without any stoichiometric preactivations (e.g. halogenation and metalation) is also theoretically possible. Additionally, the oxidative strategy often enables otherwise challenging C—C bond formations with uniquely high chemo-, regio-, and stereoselectivity. Such complementary features have prompted synthetic chemists to develop numerous strategies for the oxidative C—C bond formation. In this chapter, the recently developed oxidative C—C bond formations are categorized according to the carbon hybridization state of the coupling fragments, and their scope, limitations, and mechanisms are briefly summarized.

1.2 Oxidative Aryl–Alkenyl Bond Formation

Since the aryl–alkenyl π-conjugation frequently occurs in many pharmaceuticals, biologically active compounds, and functional materials, the aromatic C_{sp^2}–alkenyl C_{sp^2} bond formation has been widely explored by many synthetic chemists. The most famous and standard approach is the Mizoroki–Heck reaction with aryl halides and alkenes, in conjunction with a suitable palladium catalyst and base [1, 2]. This

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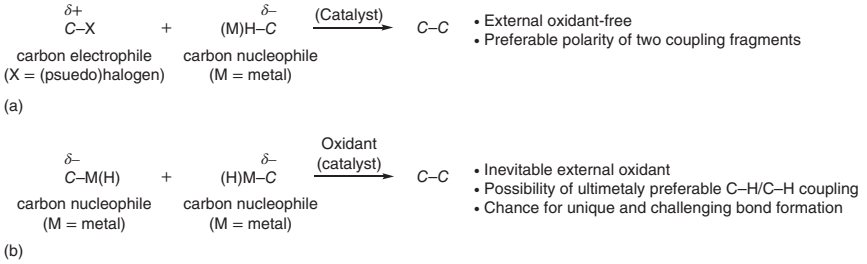
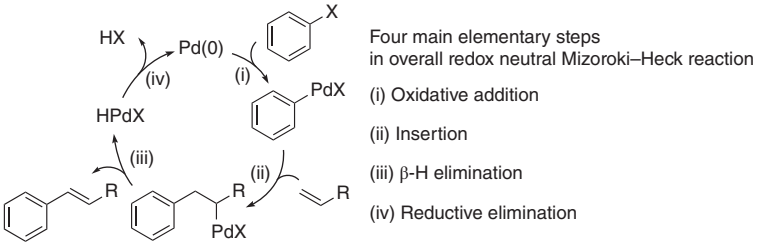


Scheme 1.1 Overall redox-neutral C−C bond formation (a) vs. oxidative C−C bond formation (b).

reaction is the overall redox-neutral process containing oxidative addition and reductive elimination in the catalytic cycle (Scheme 1.2). Although numerous efforts for development of palladium catalysts and their supporting ligands have allowed various aryl halides, including unactivated aryl chlorides, to be adopted, the alkene fragments are still largely limited to electronically activated α,β-unsaturated carbonyls and styrenes. Moreover, the preparation of the corresponding aryl halides from the parent arenes (stoichiometric halogenation) is an additional drawback to be addressed. The chemical oxidative coupling approach can be a good solution to the above problems inherent in the classical Mizoroki–Heck reaction. In this section, the oxidative Mizoroki–Heck reaction with arylmetal reagents as aromatic C_{sp^2} fragments and direct aromatic C_{sp^2}–alkenyl C_{sp^2} coupling (Fujiwara–Moritani reaction) are mainly presented.

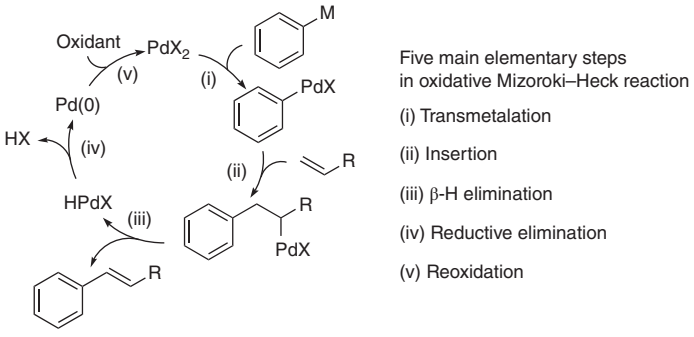


Scheme 1.2 General mechanism of palladium-catalyzed overall redox-neutral Mizoroki–Heck reaction of aryl halides with alkenes.

1.2.1 Oxidative Mizoroki–Heck Reaction with Arylmetal Reagents

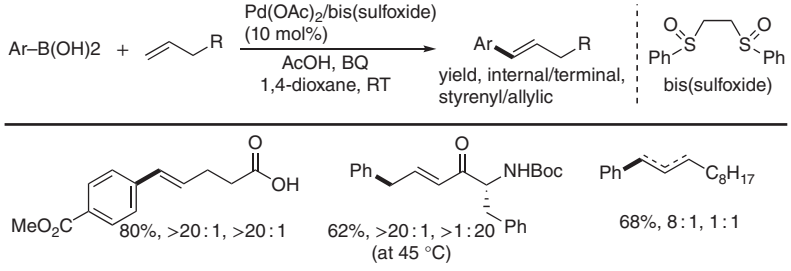
As mentioned in the above introduction part, the redox-neutral Mizoroki–Heck reaction still suffers from the relatively narrow scope of alkenes. The oxidative Mizoroki–Heck reaction can address the problem probably because of the formation of more reactive, coordinately unsaturated arylpalladium species through transmetalation between PdX_2 and arylmetal reagents rather than the oxidative addition of aryl halides (Scheme 1.3).

In 2008, White and coworkers reported the $Pd(OAc)_2$/bis(sulfoxide) catalyst for the oxidative Mizoroki–Heck reaction with arylboronic acids [3]. In the presence



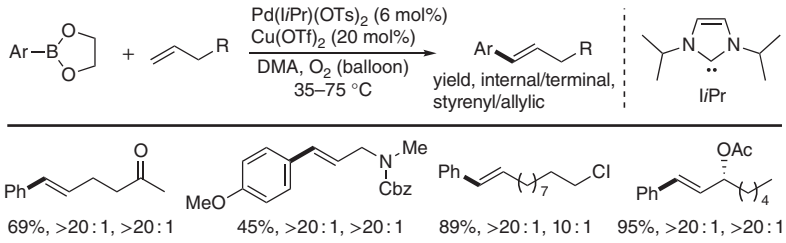
Scheme 1.3 General mechanism of palladium-catalyzed oxidative Mizoroki–Heck reaction of arylmetal reagents with alkenes.

of a benzoquinone (BQ) terminal oxidant, unactivated aliphatic terminal alkenes undergo the Mizoroki–Heck-type arylation (Scheme 1.4). Milder reaction conditions are compatible with somewhat labile point chirality derived from α-amino acids as well as functional groups such as a free carboxylic acid. The regioselectivity (internal/terminal) is also well controlled in most cases, but the olefinic position of product (styrenyl/allylic) is highly dependent on the substrate structure and its control still remains a challenging task. A related Pd(I*i*Pr)$(OTs)_2$ catalysis was reported by Sigman and Werner in 2010 (Scheme 1.5): the beneficial point is the use of molecular oxygen as an terminal oxidant, where $Cu(OTf)_2$ is added as a co-oxidant [4]. Also in this case, the reaction proceeds without erosion-of-point chirality. Particularly notable is the high styrenyl/allylic selectivity as well as internal/terminal selectivity in almost all cases.



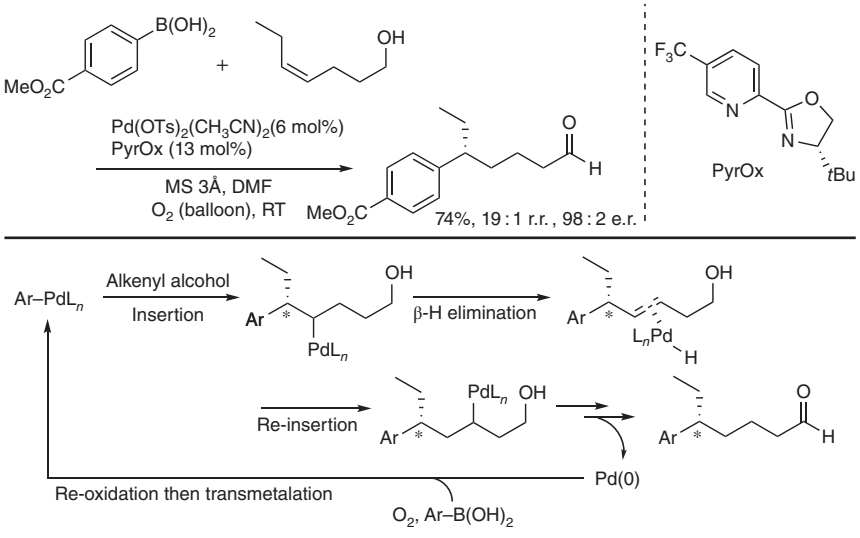
Scheme 1.4 Pd$(OAc)_2$/bis(sulfoxide)-catalyzed oxidative Mizoroki–Heck reaction of unactivated terminal alkenes. BQ = benzoquinone.

While not aryl–alkenyl bond formation, the group of Sigman subsequently developed the enantioselective oxidative Mizoroki–Heck reaction of internal alkenyl alcohols by using the chiral pyridine-oxazoline hybrid ligand, PyrOx (Scheme 1.6) [5]. The key to success is the redox-relay process: the alkene is migrated toward the alcohol via an iterative β-H elimination and insertion, and finally converted to the carbonyl functionality by the formal oxidation event. As a result, the regioselective and enantioselective remote arylation of carbonyl compound is possible. This



Scheme 1.5 Pd(I*i*Pr)(OTs)-catalyzed oxidative Mizoroki–Heck reaction of unactivated terminal alkenes. Ts = *p*-toluenesulfonyl, Tf = trifluoromethanesulfonyl.

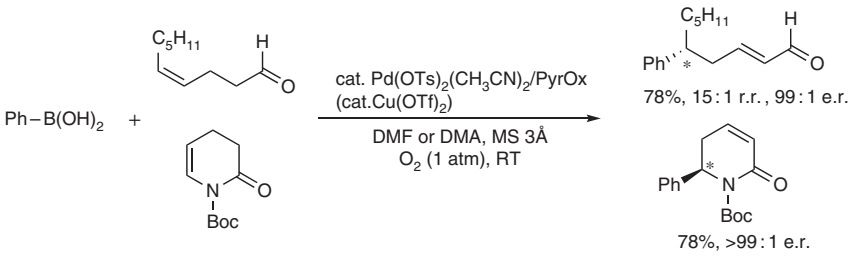
strategy is also applicable to alkenyl aldehydes and enelactams to deliver the remotely arylated enantioenriched α,β-unsaturated aldehydes and α,β-unsaturated δ-lactams, respectively (Scheme 1.7) [6].



Scheme 1.6 Palladium-catalyzed enantioselective redox-relay oxidative Mizoroki–Heck reaction of internal alkenyl alcohols and its redox-relay mechanism. Source: Modified from Mei et al. [5].

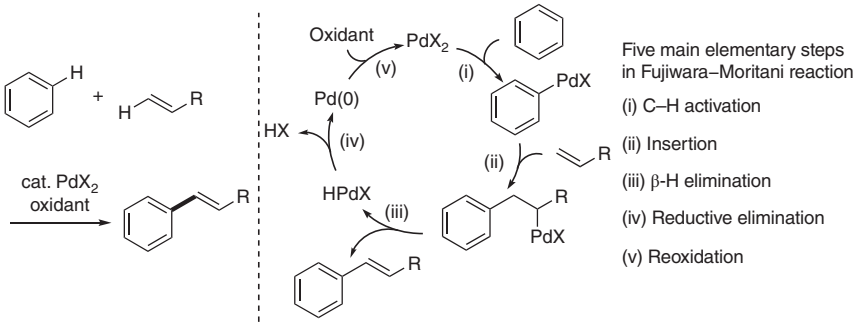
1.2.2 Direct Oxidative Mizoroki–Heck Reaction with Arene C–Hs (Fujiwara–Moritani Reaction)

One of the biggest drawbacks in the above Mizoroki–Heck reaction with aryl halides or aryl boronic acids is their tedious preparation from the parent simple arenes. In 1969, Fujiwara et al. reported seminal work on the palladium-catalyzed coupling reaction of simple arenes and alkenes, in the presence of $Cu(OAc)_2$ or AgOAc terminal oxidant, to form the corresponding alkenylarenes directly (Scheme 1.8) [7]. This protocol received significant attention from the viewpoint of organic synthesis because the arene C–H and alkene C–H are directly cross-coupled without any preactivation steps of both starting substrates. Since then, such a



Scheme 1.7 Palladium-catalyzed enantioselective redox-relay oxidative Mizoroki–Heck reaction of alkenyl aldehydes and enelactams. Source: Modified from Zhang et al. [6a], Yuan and Sigman [6b].

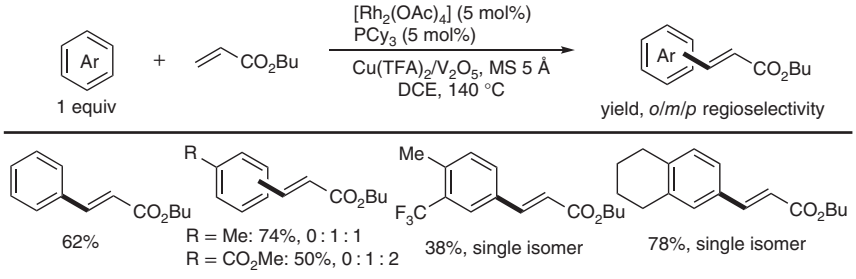
transition-metal-promoted "C–H activation" strategy has greatly and rapidly progressed by efforts of many research groups, and the Fujiwara–Moritani reaction is now a powerful synthetic tool for the construction of aryl–alkenyl π-conjugation. However, the disadvantage of early studies on the Fujiwara–Moritani reaction is the inevitable use of excess arene substrates (in many cases solvent amount).



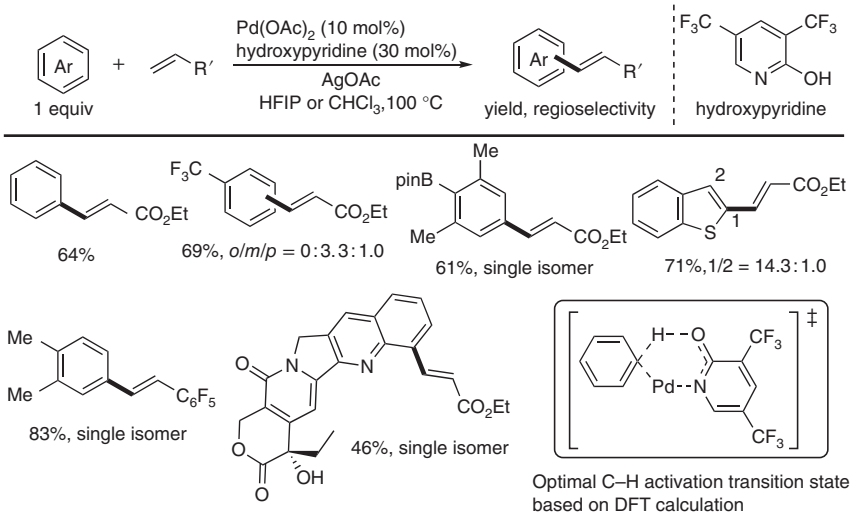
Scheme 1.8 General reaction scheme and mechanism of palladium-catalyzed Fujiwara–Moritani reaction. Source: Modified from Fujiwara et al. [7a], Jia et al. [7b].

In this context, Yu and coworkers reported the Fujiwara–Moritani reaction with the simple arene as the limiting reagent (1.0 equiv) under Rh(II)/PCy_3/Cu(TFA)$_2$/V_2O_5 oxidative catalysis (Scheme 1.9) [8]. Although the exact role of PCy_3 ligand as well as copper and vanadium combined oxidation system still remains to be elucidated, the reaction proceeds smoothly even in the presence of 1 equiv of simple arenes. More recently, the same research group developed the well-defined and robust Pd(OAc)$_2$/hydroxypyridine catalyst for the reaction with much broader simple arenes, including benzene derivatives, heteroaromatics, and even more challenging complex drug-like molecules (Scheme 1.10) [9]. Also in this case, the arene substrate works well even at 1 equiv loading. The well-designed hydroxypyridine ligand is key to success, and its pivotal role in the C–H activation step of otherwise unreactive simple arene is also uncovered by computational studies with density functional theory (DFT) calculation. Although the alkene coupling partners are still limited to electronically activated acrylates and styrenes, the above

work successfully overcomes the big issue in the conventional Fujiwara–Moritani reaction.



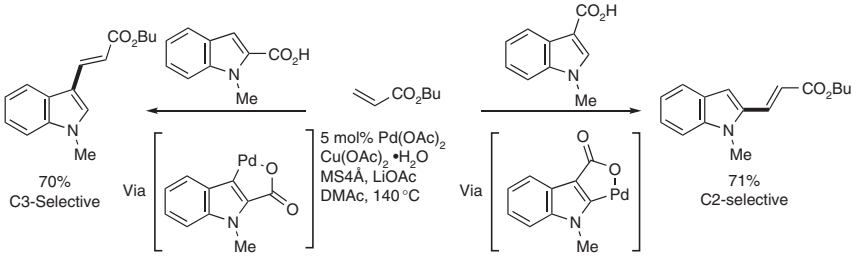
Scheme 1.9 Rhodium(II)-catalyzed Fujiwara–Moritani reaction of simple arenes as limiting reagents. DCE = 1,2-dichloroethane. Source: Modified from Vora et al. [8].



Scheme 1.10 Palladium/hydroxypyridine-catalyzed Fujiwara–Moritani reaction of simple arenes as limiting reagents and proposed transition state based on DFT calculation. HFIP = 1,1,1,3,3,3-hexafluoroisopropyl alcohol. Source: Modified from Wang et al. [9].

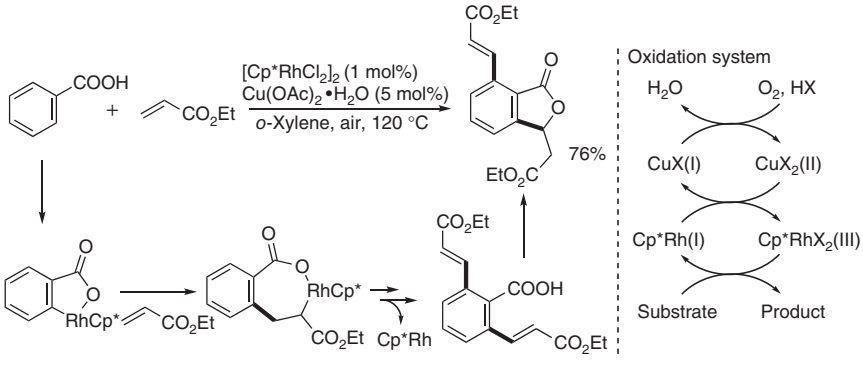
Additional inherent problem of the Fujiwara–Moritani reaction is the regioselectivity: for example, when the mono-substituted arene is employed, there are three possible reaction sites, namely ortho, meta, and para C–Hs, and its control is also of great importance in chemical synthesis. A good solution of such a regioselective issue is the introduction of coordinating functional group (directing group): a suitable functional group coordinates to the metal center to promote the C–H activation at the proximal ortho position. The formed five- or six-membered metalacycle intermediate undergoes the insertion reaction with the alkene substrate, eventually leading to the ortho-alkenylated product with high regioselectivity. Since Murai's et al. milestone work on the ruthenium-catalyzed ortho-alkylation of ketones [10],

numerous research groups joined this field to develop various directing groups containing nitrogen, oxygen, sulfur, phosphorus, and even less polar C—C π-bond [11]. A representative example of indole carboxylic acids is shown in Scheme 1.11. In this case, the carboxyl group works as a unique "traceless" ortho-directing group: 2- and 3-indole carboxylic acids react with the acrylate with concomitant decarboxylation under palladium catalysis to furnish 3- and 2-alkenylated indoles, regioselectively [12].



Scheme 1.11 Carboxylic-acid-directed ortho-selective Fujiwara–Moritani reaction of indole carboxylic acids with concomitant decarboxylation.

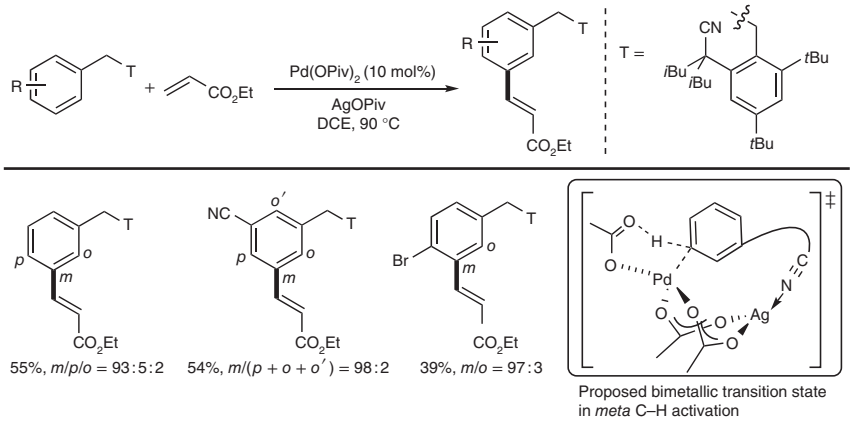
In addition to the palladium salts, Cp*Rh(III) catalysts also show high performance in the directed Fujiwara–Moritani reaction. In 2007, Satoh and coworkers reported the pioneering work on the Cp*Rh(III)-catalyzed ortho-selective alkenylation of benzoic acids with acrylates (Scheme 1.12) [13]. The initially formed alkenylated product spontaneously undergoes intramolecular Michael-type addition of carboxylic acid directing group to form the observed lactone derivative. Additional beneficial point of the Cp*Rh(III) catalysis is the reoxidation system: the most environmentally benign atmospheric molecular oxygen works as a terminal oxidant in the presence of a catalytic amount of internal oxidant, $Cu(OAc)_2 \cdot H_2O$. Thus, the formed byproduct is only nontoxic water. Since then, more and more



Scheme 1.12 Cp*Rh(III)-catalyzed ortho-selective Fujiwara–Moritani reaction of benzoic acids with acrylates. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl. Source: Modified from Ueura et al. [13].

oxidative coupling reactions between aromatic compounds and alkenes or alkynes have been explosively developed under the Rh(III)/Cu(II) or related Rh(III)/Ag(I) oxidative catalysis [14].

The directed meta- or para-alkenylation is much more challenging than the ortho-alkenylation because of formation of kinetically less favored medium- and large-sized metalacycle intermediate. However, some seminal works recently appeared. In 2012, Yu and coworkers elegantly designed the nitrile-based, U-shaped template to direct the meta-selective Fujiwara–Moritani reaction under Pd/Ag catalysis (Scheme 1.13) [15]. Owing to the end-on coordinating nature of nitrile, the relatively large and unique Pd/Ag bimetallic metalacycle is formed as the key intermediate, which is supported by computational studies in the follow-up article [16]. This work prompted several researchers to develop the related directing groups for the meta-C–H alkenylation of various aromatic compounds, but all of them still rely on the nitrile functionality [17]. The same strategy is also effective for the rhodium-catalyzed meta-C–H alkenylation (Scheme 1.14) [18].

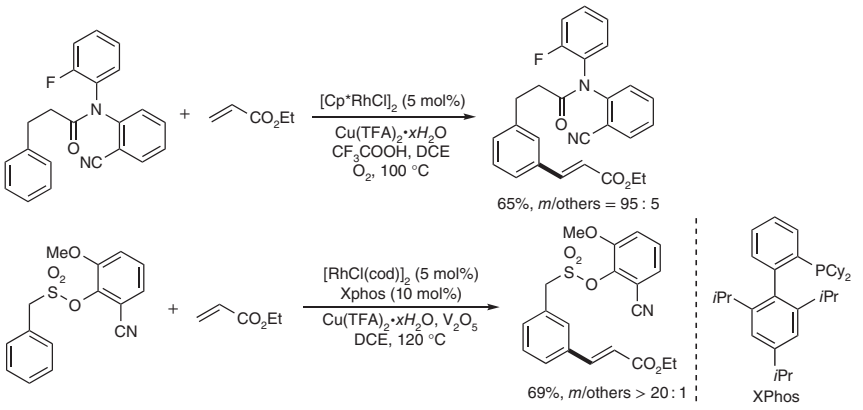


Scheme 1.13 Palladium/silver-catalyzed meta-selective Fujiwara–Moritani reaction assisted by nitrile-based U-shaped template and proposed bimetallic transition state in C–H activation. Piv = *tert*-butylcarbonyl. Source: Modified from Leow et al. [15].

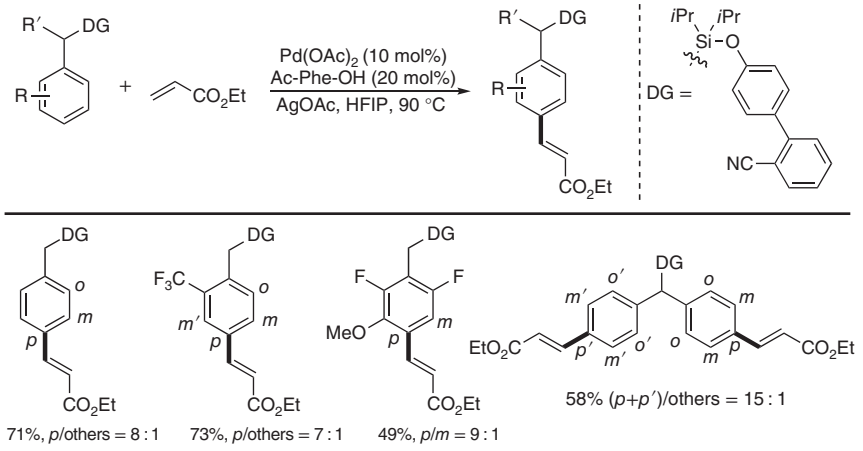
In 2015, Maiti and coworkers developed a similar nitrile-based D-shaped template for the para-selective Fujiwara–Moritani reaction (Scheme 1.15) [19]. The biggest feature is the long biphenyl template ligated with flexible Si tether of sp^3 hybridization. Additionally, the positive Thorpe–Ingold effect is successfully promoted by two bulky isopropyl groups on Si. In the presence of a $Pd(OAc)_2$ catalyst and amino acid ligand, Ac-Phe-OH, a variety of benzene derivatives undergo the alkenylation selectively at the para position beyond their innate electronic biases.

1.3 Oxidative Aryl–Aryl Bond Formation

Due to the ubiquity of biaryl structure in biologically active compounds, natural products, pharmaceutical targets, and organic functional materials, the aromatic

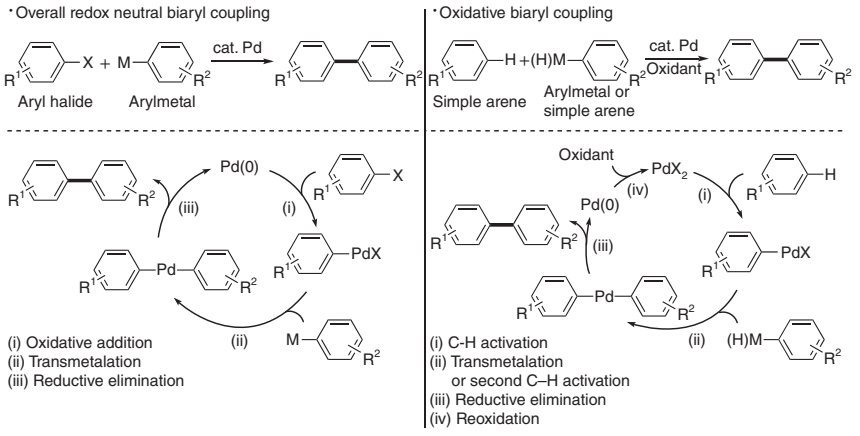


Scheme 1.14 Rhodium-catalyzed meta-selective Fujiwara–Moritani reaction assisted by nitrile-based U-shaped template. Source: Modified from Xu et al. [18a], Bera et al. [18b].



Scheme 1.15 Palladium-catalyzed para-selective Fujiwara–Moritani reaction assisted by nitrile-based D-shaped template. Ac-Phe-OH = *N*-acetylphenylalanine. Source: Modified from Bag et al. [19a], Patra et al. [19b].

$C_{sp}{}^2$–aromatic $C_{sp}{}^2$ bond-forming reaction is always one of the hot research topics in synthetic organic chemistry. The Nobel Prize–winning palladium-catalyzed overall redox-neutral cross-coupling reaction of aryl halides with arylmetal reagents is now the most powerful and reliable approach to the above biaryl linkage (Scheme 1.16, left). On the other hand, the oxidative aryl–aryl bond-forming reaction can replace the aryl halide electrophiles with the simple and readily accessible arenes (C–H/C–M cross-coupling; Scheme 1.16, right). Such an oxidative coupling protocol often enables the challenging biaryl coupling under the redox-neutral conditions. Moreover, an ideal oxidative cross-coupling of two simple arenes (C–H/C–H cross-coupling) is potentially possible. In this section, the recent advances in the above two types of oxidative biaryl coupling are demonstrated.



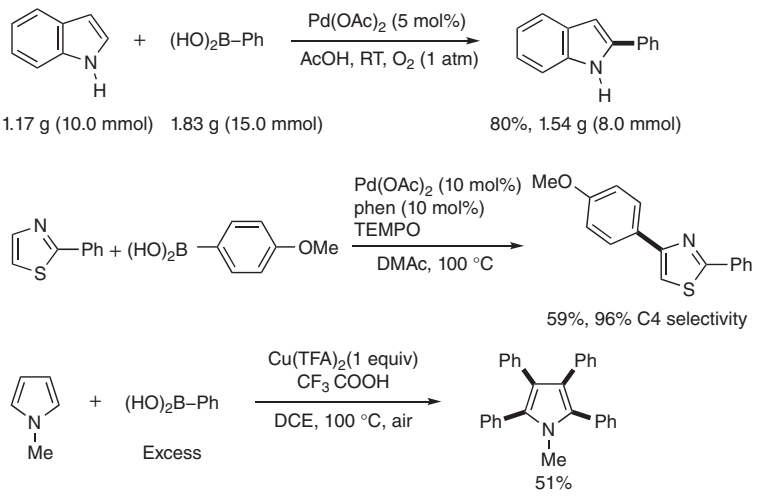
Scheme 1.16 General mechanisms of overall redox-neutral biaryl cross-coupling of aryl halide and arylmetal (left) and oxidative biaryl cross-coupling of simple arene and arylmetal or another simple arene (right).

1.3.1 Oxidative C–H/C–M Biaryl Cross-Coupling

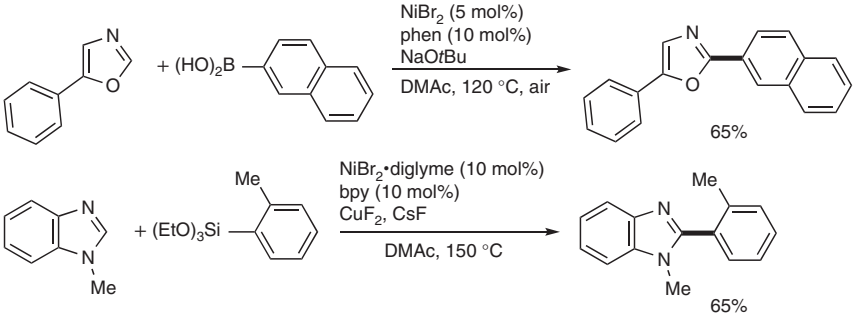
Electron-rich heterocycles such as indole, thiazole, and pyrrole relatively easily participate in the oxidative biaryl cross-coupling reaction with arylmetals (Scheme 1.17). In the case of indole, the simple $Pd(OAc)_2$-catalyzed C–H arylation with phenylboronic acid often proceeds even at room temperature by using the molecular oxygen as the sole oxidant [20]. Owing to its experimental simplicity, the reaction is also easily scaled up to a gram quantity. The thiazole is also arylated in the presence of a $Pd(OAc)_2$/1,10-phenanthroline (phen) catalyst and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) oxidant [21]. The additional unique feature is the otherwise challenging C4 selectivity. Although generally less reactive, the abundant first-row transition metals also promote similar reactions. For example, $Cu(TFA)_2$ mediates the multiple oxidative arylation of pyrrole with excess phenylboronic acid to form the tetraphenylpyrrole in one shot [22].

The 1,3-azoles have relatively acidic C–Hs at the C2 position, and thus they are more reactive under somewhat basic conditions. The oxazole and imidazole are directly arylated selectively at the C2 position under cost-effective nickel catalysis (Scheme 1.18) [23]. Notably, in the latter case, the less reactive arylsilane also works well as the arylation reagent.

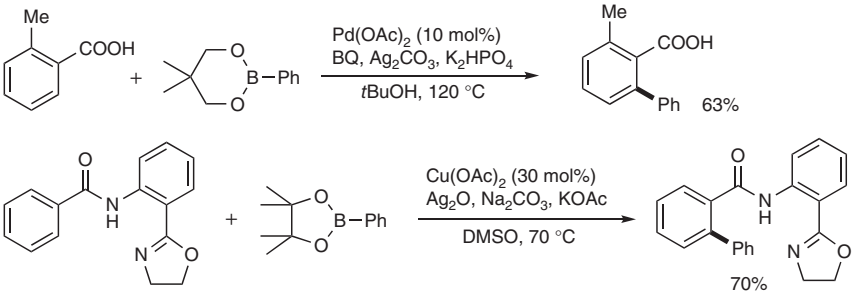
The benzene derivatives are less reactive than heteroarenes mentioned above, and the suitable coordinating functional groups, namely directing groups, are generally essential for obtaining satisfactory reactivity as well as control of regioselectivity (Scheme 1.19). Similar to the Fujiwara–Moritani reaction (Schemes 1.11 and 1.12), the carboxyl group is the effective ortho-directing group under oxidative Pd(II)/BQ catalysis to deliver the corresponding arylated product in a good yield [24]. With the assistance of well-designed N,N-bidentately coordinating group, the abundant copper salt also catalyzes the C–H arylation with the arylboronate in the presence of Ag_2O oxidant [25].



Scheme 1.17 Oxidative C–H/C–M biaryl coupling of electron-rich indole, thiazole, and pyrrole.

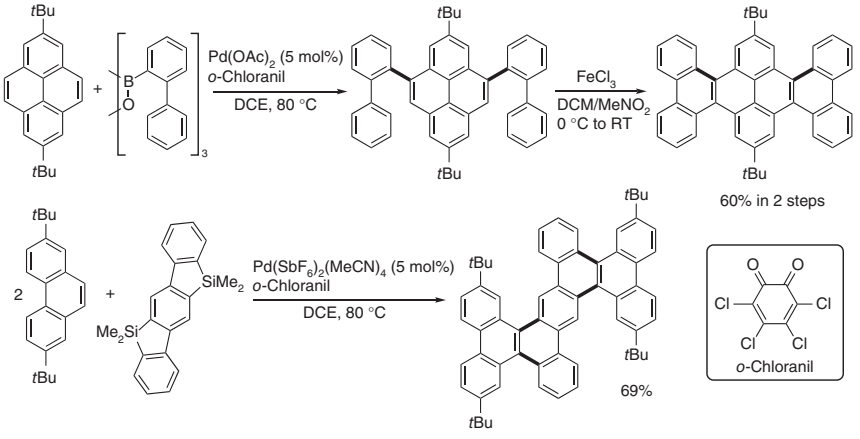


Scheme 1.18 Nickel-catalyzed oxidative C–H/C–M biaryl coupling of relatively acidic C2 C–Hs of 1,3-azoles. bpy = 2,2′-bipyridyl. Source: Modified from Hachiya et al. [23].



Scheme 1.19 Oxidative C–H/C–M biaryl coupling of benzene derivatives with assistance of directing groups.

Exceptionally, the highly fused benzene derivatives show a remarkably high reactivity under the oxidative C–H arylation conditions because of their lower aromaticity, i.e. alkene-like reactivity (Scheme 1.20). In 2011, Itami and coworkers reported the Pd(II)/*o*-chloranil oxidative catalyst for the C–H arylation of pyrene derivatives with arylboroxines [26]. The reaction is apparently unique to the higher-fused aromatics but of great interest in the bottom-up synthesis of π-extended polyaromatic hydrocarbons (PAHs), which have received tremendous attention in the field of material science. Actually, application to the rapid and concise synthesis of extended PAHs was demonstrated by the C–H arylation/Scholl reaction sequence. Subsequently, the same catalyst system was successfully applied to the K-region-selective one-shot π-extension with the dibenzosiloles [27]. The *o*-chloranil is the key of catalysis, and its multitask nature as the ligand, oxidant, and base was recently uncovered by computational studies with DFT calculation.

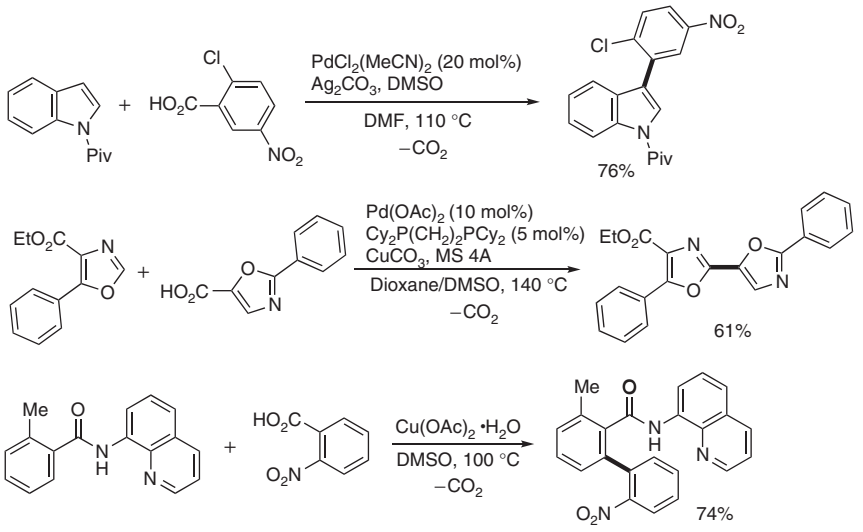


Scheme 1.20 Pd/*o*-chloranil-catalyzed oxidative C–H/C–M biaryl coupling of higher fused benzene derivatives. DCM = dichloromethane.

As mentioned in Schemes 1.17–1.20, the air-stable and easy-to-handle arylboronic acids and arylsilanes are frequently employed as the arylmetals in the oxidative C–H/C–M biaryl coupling reaction. Although still limited in scope, more readily available benzoic acids can also couple with some arene C–Hs, via decarboxylation, to afford the corresponding biaryls under appropriate oxidative conditions (Scheme 1.21). The decarboxylative C–H arylation of indole and oxazole derivatives efficiently occurs in the presence of Pd(II)/Ag(I) or Cu(II) oxidative catalysts [28]. The copper salt alone also mediates a similar reaction of benzamide substrate that bears the suitable 8-aminoquinoline-based N,N-bidentate coordination [29].

1.3.2 Oxidative C–H/C–H Biaryl Cross-Coupling

The direct oxidative coupling of two different arenes via dual C—H bond cleavage is the most attractive and ideal approach to the biaryl structure from the viewpoint of

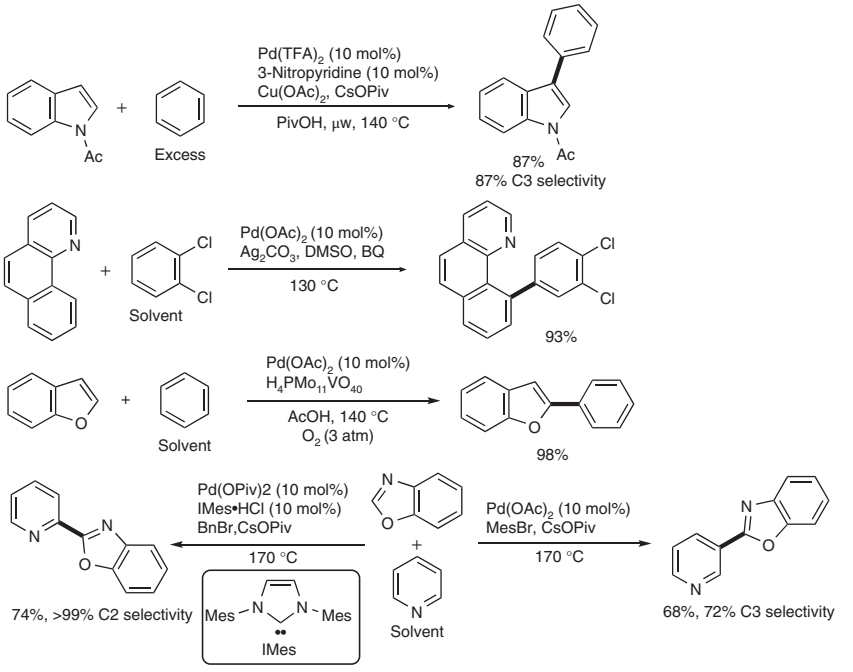


Scheme 1.21 Oxidative biaryl coupling via decarboxylative C–H arylation.

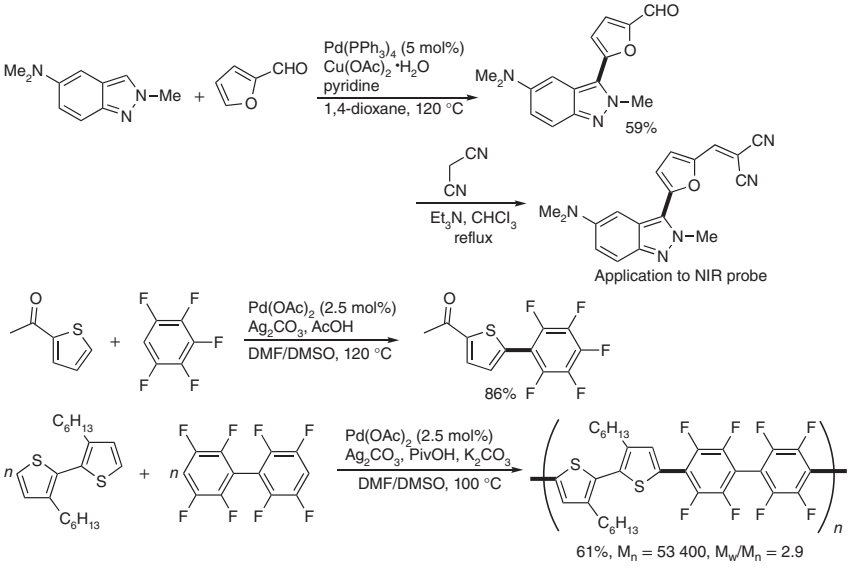
atom and step economy because the preactivation step of both starting substrates can be skipped. The biggest challenge is chemoselectivity for the desired cross-coupling product over the homo-coupling byproducts. The first breakthrough was reported by Fagnou and coworker in 2007: the oxidative $Pd(TFA)_2$/3-nitropyridine/$Cu(OAc)_2$ system promotes the highly selective C–H/C–H biaryl coupling of indole and simple benzene to form the C3-arylated indole selectively (Scheme 1.22). The undesired homo-coupling products from both indole and benzene are not detected at all, and the selectivity switching is thus perfectly operated in the first and second C–H activation steps. Subsequently, related oxidative couplings of benzofurans and arylpyridines were reported. Recently, the direct coupling of benzoxazole with electron-deficient pyridines was also achieved under Pd(II)/organic bromide oxidative catalysis, where the C2/C3 regioselectivity was controlled by the judicious choice of organic halide oxidant. However, all procedures rely on excess of simple benzene derivatives (c. 30 equiv to solvent amount), which still remains to be improved [30].

By replacing the simple benzenes with more reactive heteroarenes or suitably functionalized arenes such as indazole, furan, and polyfluoroarene, the loading can be dramatically decreased to the practical amount (~3.0 equiv) (Scheme 1.23). The former reaction is applied to the discovery of photostable near-infrared (NIR) probe for mitochondria. In the latter case, the highly selective cross-dehydrogenative polycondensation of bithiophene and octafluoronaphthalene is possible to form the corresponding polymer with a good yield, molecular weight, and M_w/M_n [31]. Thus, the C–H/C–H biaryl coupling now provides an opportunity to develop new biaryl-based functional materials, which are otherwise difficult to access by the conventional methods.

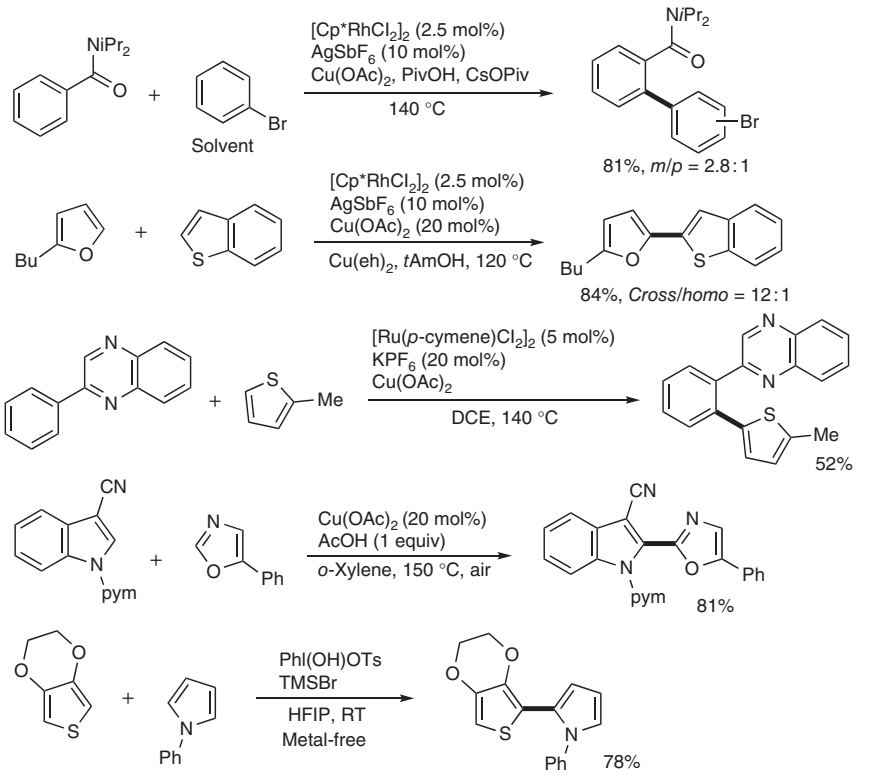
In addition to the palladium, other transition metals also promote the direct biaryl coupling (Scheme 1.24). The Cp*Rh(III) complex catalyzes the C–H/C–H



Scheme 1.22 Oxidative C–H/C–H biaryl coupling with simple benzene and pyridine substrates. Mes = 2,4,6-trimethylphenyl.



Scheme 1.23 Oxidative C–H/C–H biaryl coupling with relatively activated heteroarenes or functionalized arenes. M_n = the number average of molecular weight; M_w = the weight average of molecular weight.



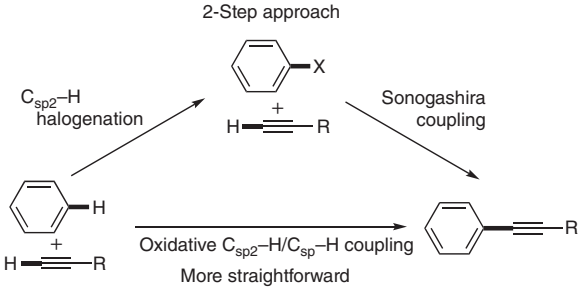
Scheme 1.24 Oxidative C–H/C–H biaryl couplings promoted by transition metals other than palladium or I(III) reagents. pym = 2-pyrimidyl.

coupling of benzamides with a solvent amount of bromobenzene in preference to the conceivably more reactive aryl C—Br bond of bromobenzene. Additionally, the same catalyst couples simple furans with thiophenes chemoselectively even in the absence of any directing groups [32]. The less expensive Ru(*p*-cymene)Cl_2 is also efficient for the direct coupling of arylpyridines and thiophenes [33]. The direct coupling between *N*-pyrimidylindoles and 1,3-azoles proceeds in the presence of $Cu(OAc)_2$ catalyst alone. In this case, the molecular oxygen works as the terminal oxidant, thus providing an environmentally benign process with H_2O as the sole byproduct [34]. Furthermore, metal-free coupling between thiophenes and pyrroles can also be achieved by using a well-defined hypervalent-iodine(III) reagent [35]. The stepwise addition of thiophene followed by pyrrole is essential, but the reaction occurs even at room temperature with high cross-coupling selectivity.

1.4 Oxidative Aryl–Alkynyl Bond Formation

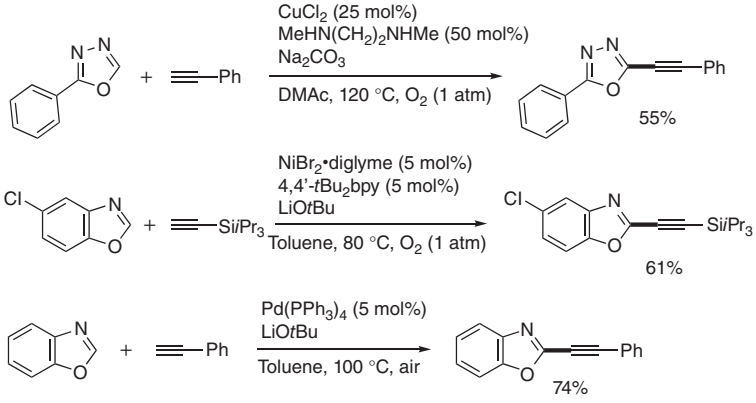
Arylacetylenes are among the most fundamental and important π-conjugated systems in various areas of organic chemistry. The most powerful and reliable

approach to these molecules is the palladium/copper-cocatalyzed cross-coupling of aryl halides with terminal alkynes, also known as Sonogashira coupling (Scheme 1.25, top). Given the preparation of starting aryl halides from the parent simple arenes, the oxidative direct coupling between arenes and terminal alkynes via twofold C—H bond cleavage of both substrates is an ideal protocol (Scheme 1.25, bottom). However, the C_{sp}–H at the alkyne termini readily reacts with transition metals, and thus the biggest challenge is the selectivity control toward cross-coupling over alkyne homo-coupling under oxidative conditions.



Scheme 1.25 Approaches to arylacetylenes via aryl–alkynyl coupling.

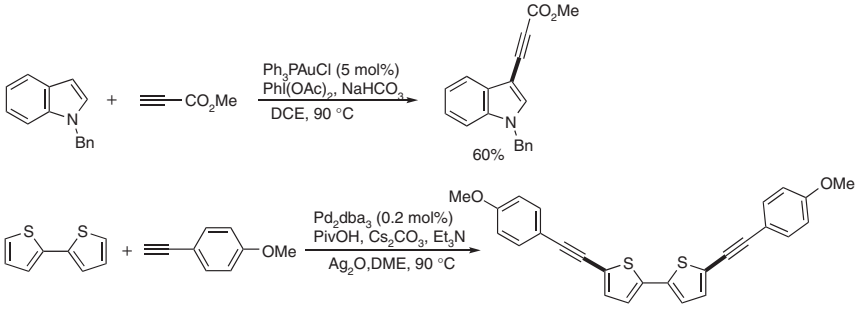
The first successful attempt of 1,3-azoles using $CuCl_2$ as a catalyst was reported by Miura and coworkers in 2010 (Scheme 1.26) [36]. Although the relatively high catalyst loading is essential, the pioneering work has stimulated further discoveries of other transition metal catalysts. These include the use of nickel [37] and palladium [38] complexes for the direct alkynylation of several acidic 1,3-azoles with the assistance of relatively strong base, LiO*t*Bu. It is noteworthy that molecular oxygen is the sole oxidant in these transformations.



Scheme 1.26 Copper-, nickel-, and palladium-catalyzed oxidative aryl–alkynyl couplings of relatively acidic 1,3-azoles. Source: Modified from Kitahara et al. [36a], Wei et al. [36b].

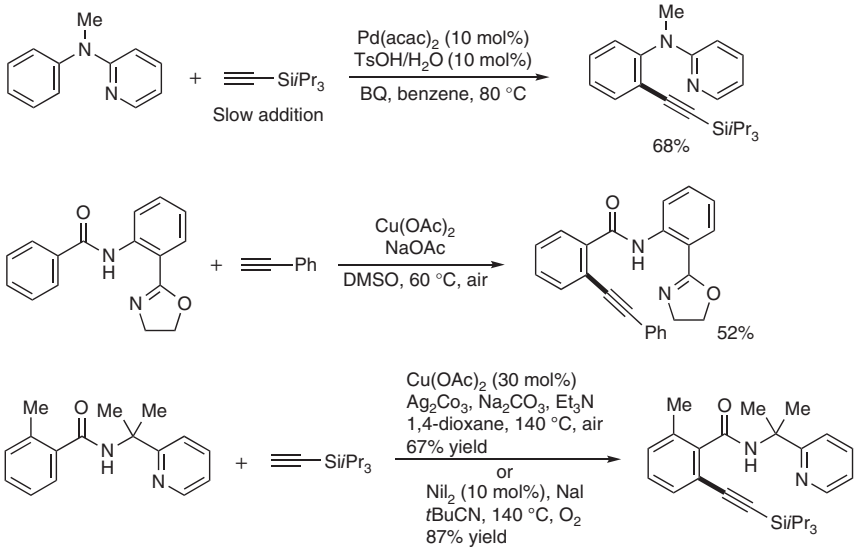
The alkynylation of electron-rich indoles and pyrroles is achieved by a Ph_3PAuCl catalyst (Scheme 1.27) [39]. However, the use of $PhI(OAc)_2$ as the oxidant is critical

for success. Subsequently, the more robust palladium-based catalyst system was reported, in which electron-rich thiophene, furan, oxazole, thiazole, and pyrazole as well as indole and pyrrole were accommodated [40].



Scheme 1.27 Gold- and palladium-catalyzed oxidative aryl–alkynyl couplings of electron-rich heteroaromatics. dba = dibenzylideneacetone. Source: Modified from de Haro et al. [39a], Jie et al. [40].

The benzene derivatives can also be employed by using suitable directing groups (Scheme 1.28). The aniline derivatives are oxidatively coupled with tri(isopropyl)silylacetylene in the presence of a $Pd(acac)_2$ catalyst and BQ terminal oxidant [41]. However, to suppress the undesired homo-coupling of terminal acetylene, the somewhat tedious slow addition technique is inevitable. The well-designed N,N-bidentately coordinating groups allow the benzoic acid derivatives to be adopted in this reaction [42]. The phenyloxazine-containing benzamides undergo

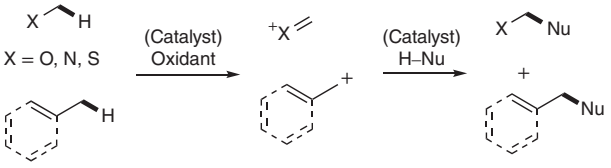


Scheme 1.28 N,N-bidentately coordinating group-promoted oxidative aryl–alkynyl couplings of benzene derivatives. acac = acetylacetonate.

the Cu(II)-mediated C–H/C–H coupling with various terminal alkynes, including alkylacetylenes and even more challenging arylacetylenes. While limited to the tri(isopropyl)silylacetylene, the $Cu(OAc)_2/Ag_2CO_3$ system promotes the oxidative coupling of benzamides derived from the 2-(pyridine-2-yl)isopropylamine. The same reaction occurs with better reaction efficiency under more environmentally benign $Ni(II)/O_2$ oxidative conditions.

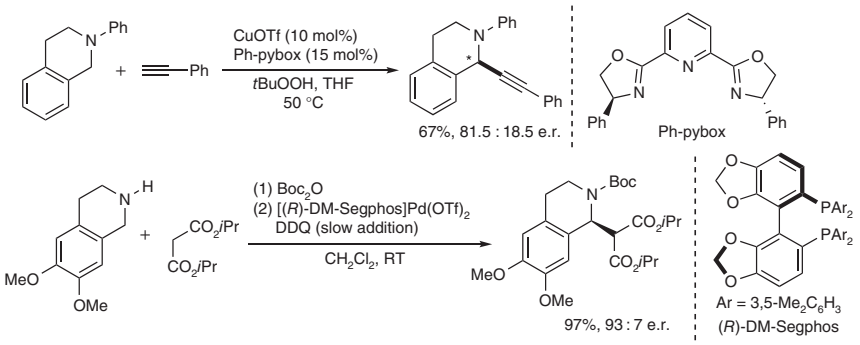
1.5 Oxidative C–C Bond Formation at $C_{sp}{}^3$ Center

The oxidative cross-coupling reaction at the saturated $C_{sp}{}^3$ center still remains a great challenge because of the lack of π bond coordination to the reactive metal catalyst. However, the $C_{sp}{}^3$—H bond adjacent to heteroatoms (e.g. O, N, S) or π-bonds (e.g. alkene and benzene) shows exceptionally high reactivity under oxidative conditions: it can be easily oxidized to the cationic intermediate by the action of electron-donating nature of proximal heteroatoms or π-bonds to readily participate in the addition reaction with external nucleophiles (Scheme 1.29). Since the stimulating work on the oxidative coupling between *N*-methylanilines and terminal alkynes was reported by Li and coworkers in 2004, such an oxidative coupling at the $C_{sp}{}^3$ center was called cross-dehydrogenative coupling (CDC) and extensively explored by many research groups. The comprehensive review article was already published [43], and selected important examples are thus presented in this section.



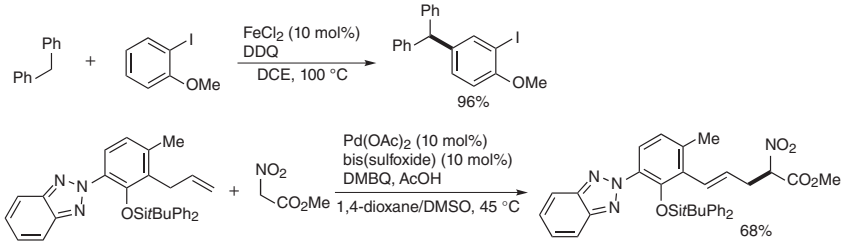
Scheme 1.29 General mechanism of cross-dehydrogenative coupling (CDC) of $C_{sp}{}^3$—H bonds adjacent to heteroatoms or π-bonds.

The tetrahydroisoquinoline is one of the most frequently employed substrates in the CDC reaction because the cationic intermediate can be doubly stabilized by proximal nitrogen atom and benzene ring. Additionally, the suitable chiral catalyst renders the reaction enantioselective (Scheme 1.30) [44]. Li developed the Cu(I)/Ph-pybox-catalyzed enantioselective CDC reaction of *N*-phenyltetrahydroisoquinoline with terminal alkynes. The enantioselectivity is still moderate (up to 87 : 13 e.r.), but the point chirality can be readily constructed from the unfunctionalized simple starting materials. In this case, *t*BuOOH works well as the oxidant. Sodeoka also reported the Pd(II)/DM-Segphos-catalyzed enantioselective coupling of *in situ*-generated *N*-Boc-tetrahydroisoquinolines and malonate nucleophiles in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) terminal oxidant. The reaction proceeds smoothly even at room temperature, and the maximum 93 : 7 enantiomeric ratio was obtained.



Scheme 1.30 Enantioselective CDC reactions of tetrahydroisoquinoline derivatives. DDQ = 2,3-dichloro-4,5-dicyanobenzoquinone. Source: Modified from Li and Li [44a], Dubs [44b].

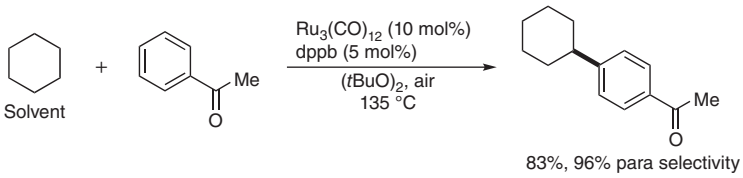
The simple benzylic position is also reactive under the typical CDC conditions (Scheme 1.31). Shi and coworkers reported the Fe(II)/DDQ catalyst system for the oxidative coupling of diarylmethane and electron-rich arenes to form the corresponding triarylmethanes directly [45]. Additionally notable is the compatibility with the otherwise reactive aryl C–I moiety. The isoelectronic allylic system is also a viable substrate and can be directly coupled with active methylene compounds in the presence of a Pd(II) catalyst and modified BQ, 2,6-dimethylbenzoquinone (DMBQ) [46]. In this case, the π-allyl palladium species is formed as the putative intermediate, and the reaction can be thus regarded as the direct oxidative Tsuji–Trost reaction.



Scheme 1.31 CDC reactions of benzyl- and allyl-type substrates.

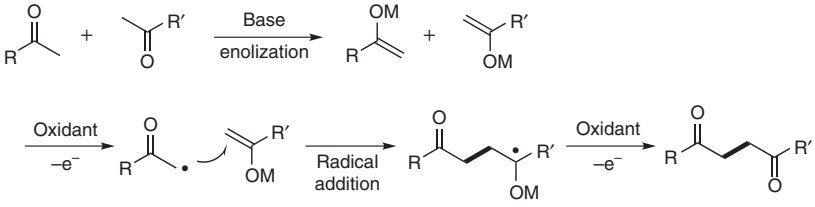
The completely unfunctionalized simple alkane also participated in the CDC reaction, although a solvent amount of alkane is inevitable (Scheme 1.32). Under the oxidative Ru/$(t\text{BuO})_2$ system, cyclohexane directly reacts with acetophenone to deliver the cross-coupling product with high para selectivity [47]. Due to the regioselective issue, almost all reported examples use the cyclic alkane as the C_{sp^3} source.

The C_{sp^3}—H bond adjacent to electron-withdrawing groups such as carbonyl is usually reluctant to be oxidized. Thus, a protocol different from the above CDC reaction is necessary for the oxidative coupling at the relatively electron-deficient C_{sp^3}



Scheme 1.32 CDC reaction of simple alkane.

center. In the case of carbonyl compounds, the generation of radical species via enolization and one-electron oxidation is the promising strategy (Scheme 1.33).

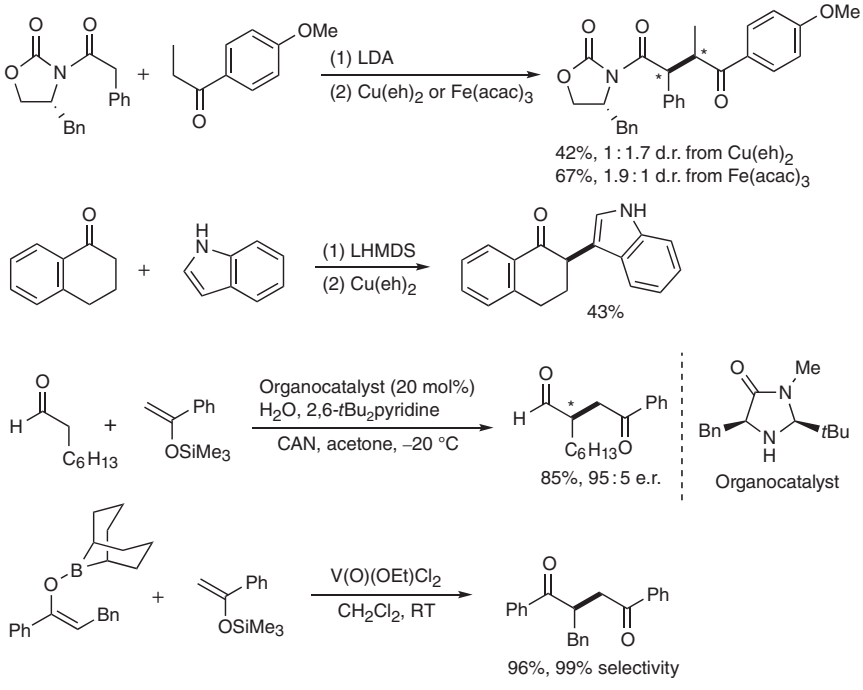


Scheme 1.33 General mechanism of oxidative coupling of two carbonyl compounds via enolization and one-electron oxidation.

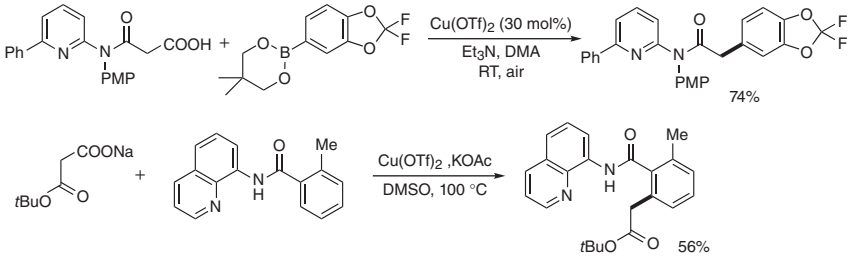
Baran and coworkers reported the $Cu(eh)_2$- or $Fe(acac)_3$-mediated oxidative cross-coupling of two different lithium enolates derived from the Evans amides and simple ketones or esters (Scheme 1.34) [48]. A similar strategy is applicable to the oxidative coupling between ketones and indoles. The enolate–enolate oxidative cross-coupling reaction can be extended to the reaction of silyl enolates and *in-situ*-generated enamines, in which the suitable chiral organocatalyst successfully induces the enantioselectivity [49]. Recently, Amaya et al. succeeded in the related V(V)-mediated highly selective oxidative coupling of boron enolates and silyl enolates despite that both enolates originate from ketones at the same oxidation level [50].

Another approach to the oxidative C—C bond formation at the position α to carbonyl is the copper-catalyzed decarboxylative oxidative coupling of malonic acid half esters with arylboronic acids (Scheme 1.35) [51]. The mild reaction conditions (at room temperature under air) are compatible with a wide range of functional groups such as halides, ethers, carbonyls, and heterocycles. The 8-aminoquinoline-derived benzamide is also a viable aryl-coupling partner under similar copper-based oxidative conditions.

The suitable directing groups allow more general and otherwise unactivated $C_{sp}{}^3$–H to be adopted in the oxidative C—C bond formation. The highly fluorinated amide, pyridine, and sulfonamide groups direct the Fujiwara–Moritani-type coupling at the $C_{sp}{}^3$–H with electron-deficient alkenes under oxidative Pd(II) catalysis (Scheme 1.36) [52]. In all cases, the initially formed alkenylated intermediates spontaneously undergo the intramolecular Michael addition to form the cyclized products, same as shown in Scheme 1.12. Notably, the second reaction uniquely



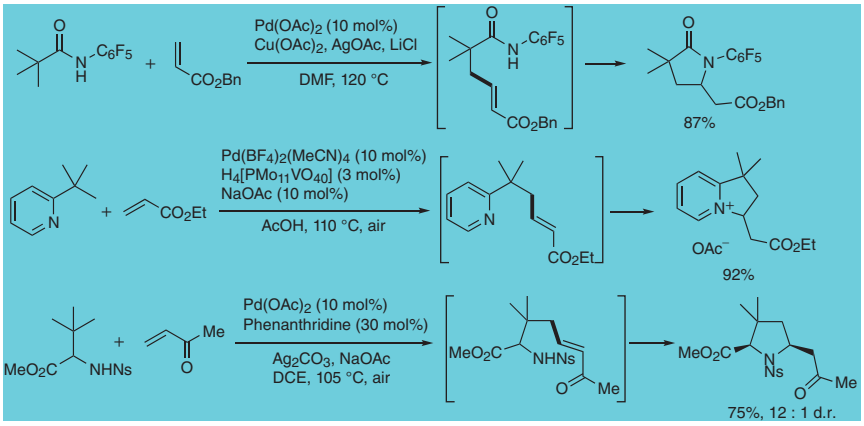
Scheme 1.34 Cu(II)-, Fe(III)-, Ce(IV)-, and V(V)-mediated oxidative cross-coupling of carbonyl compounds via enolization. eh = 2-ethylhexanoate, LHMDS = lithium hexamethyldisilazide, CAN = $(NH_4)_2Ce(NO_3)_6$. Source: Modified from DeMartino et al. [48a], Richter et al. [48b], Jang et al. [49], Amaya et al. [50].



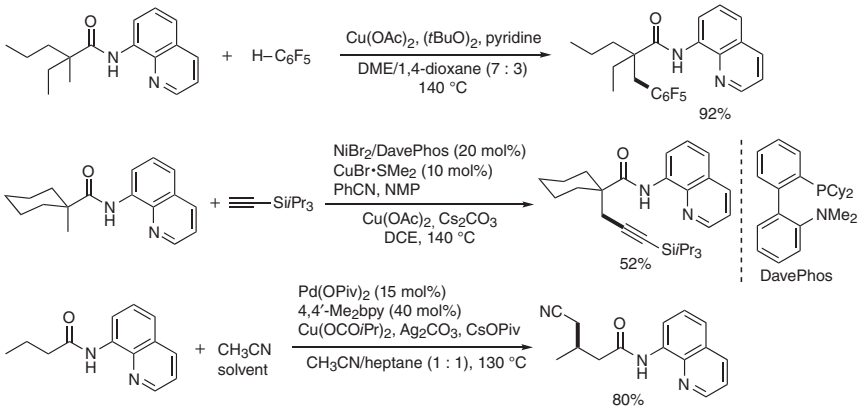
Scheme 1.35 Oxidative decarboxylative coupling of malonic acid half esters. PMP = *p*-methoxyphenyl. Source: Modified from Moon et al. [51a], Takamatsu et al. [51b].

necessitates the polyoxometalate co-oxidant, $H_4[PMo_{11}VO_{40}]$, for the acceptable catalyst turnover.

The 8-aminoquinoline-based N,N-bidentately coordinating group is also frequently employed in the oxidative couplings of unactivated C_{sp^3}–H (Scheme 1.37). Although limited to the highly electron-deficient polyfluoroarenes, the Cu(II)/$(t\text{BuO})_2$ system mediates direct C_{sp^3}–H/aromatic C_{sp^2}–H coupling [53]. The oxidative alkynylation with tri(isopropyl)silylacetylene is also possible under Ni(II)/Cu(I) cooperative catalysis [54]. Furthermore, probably the most challenging



Scheme 1.36 Directed Fujiwara–Moritani-type reaction at unactivated $C_{sp}{}^3$–H. Ns = *o*-nitrobenzenesulfonyl. Source: Modified from Wasa et al. [52a], Stowers et al. [52b], and Jiang et al. [52c].



Scheme 1.37 Bidentately coordinating group directed oxidative C–C bond formations at unactivated $C_{sp}{}^3$–H with aromatic $C_{sp}{}^2$–H, alkynyl C_{sp}–H, and aliphatic $C_{sp}{}^3$–H.

dehydrogenative $C_{sp}{}^3$–H/$C_{sp}{}^3$–H cross-coupling was recently achieved albeit with solvent amount MeCN as the coupling partner [55]. Additionally, in the last case, more sterically crowding methylene $C_{sp}{}^3$–H can be functionalized, whereas the former two reactions are restricted at the sterically most accessible methyl $C_{sp}{}^3$–H.

1.6 Conclusion

An oxidative strategy can make the C—C bond potentially more effective than the conventional overall redox process using organic halide electrophiles because the parent simple organic materials can be directly used via C–H activation. Thus, it deserves significant attention from the viewpoint of atom- and step-economies, and

more and more oxidative catalysts as well as stoichiometric conditions have been developed by synthetic chemists. Additionally, even in the case that organometallic coupling partners are still necessary, the oxidative protocol often shows the uniquely high functional group compatibility, chemoselectivity, and stereoselectivity, which are difficult to achieve under the overall redox-neutral process. The oxidative C—C bond formation is already one of the indispensable synthetic tools in chemical synthesis, but further development of oxidative catalysis and discovery/design of new chemical oxidants will improve the reaction efficiency and selectivity much more and realize the creation of complex functional molecules inaccessible by means of the redox-neutral reaction.

References

1 For seminal works: (a)Mizoroki, T., Mori, K., and Ozaki, A. (1971). Arylation of olefin with aryl iodide catalyzed by palladium. *Bull. Chem. Soc. Jpn.* 44: 581. (b) Heck, R.F. and Nolley, J.P. (1972). Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Organomet. Chem.* 37: 2320–2322.

2 Selected reviews: (a)Beletskaya, I.P. and Cheprakov, A.V. (2000). The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* 100: 3009–3066. (b) Dounay, A.B. and Overman, L.E. (2003). The asymmetric intramolecular Heck reaction in natural product total synthesis. *Chem. Rev.* 103: 2945–2964. (c) Mc Cartney, D. and Guiry, P.J. (2011). The asymmetric Heck and related reactions. *Chem. Soc. Rev.* 40: 5122–5150.

3 Delcamp, J.H., Brucks, A.P., and White, M.C. (2008). A general and highly selective chelate-controlled intermolecular oxidative Heck reaction. *J. Am. Chem. Soc.* 130: 11270–11271.

4 Werner, E.W. and Sigman, M.S. (2010). A highly selective and general palladium catalyst for the oxidative Heck reaction of electronically nonbiased olefins. *J. Am. Chem. Soc.* 132: 13981–13983.

5 Mei, T.-S., Werner, E.W., Burckle, A.J., and Sigman, M.S. (2013). Enantioselective redox-relay oxidative Heck arylations of acyclic alkenyl alcohols using boronic acids. *J. Am. Chem. Soc.* 135: 6830–6833.

6 (a) Zhang, C., Santiago, C.B., Kou, L., and Sigman, M.S. (2015). Alkenyl carbonyl derivatives in enantioselective redox relay Heck reactions: accessing α,β-unsaturated systems. *J. Am. Chem. Soc.* 137: 7290–7293. (b) Yuan, Q. and Sigman, M.S. (2018). Palladium-catalyzed enantioselective relay Heck arylation of enelactams: accessing α,β-unsaturated δ-lactams. *J. Am. Chem. Soc.* 140: 6527–6530.

7 (a) Fujiwara, Y., Moritani, I., Danno, S. et al. (1969). Aromatic substitution of olefins. VI. Arylation of olefins with palladium(II) acetate. *J. Am. Chem. Soc.* 91: 7166–7169. (b) Jia, C., Kitamura, T., and Fujiwara, Y. (2001). Catalytic functionalization of arenes and alkanes via C—H bond activation. *Acc. Chem. Res.* 34: 633–639.

8 Vora, H.U., Silvestri, A.P., Engelin, C.J., and Yu, J.-Q. (2014). Rhodium(II)-catalyzed nondirected oxidative alkenylation of arenes: arene loading at one equivalent. *Angew. Chem. Int. Ed.* 53: 2683–2686.

9 Wang, P., Verma, P., Xia, G. et al. (2017). Ligand-accelerated non-directed C–H functionalization of arenes. *Nature* 551: 489–494.

10 Murai, S., Kakiuchi, F., Sekine, S. et al. (1993). Efficient catalytic addition of aromatic carbon–hydrogen bonds to olefins. *Nature* 366: 529–531.

11 For recent comprehensive reviews: Chen, Z., Wang, B., Zhang, J. et al. (2015). Transition metal-catalyzed C—H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* 2: 1107–1295.

12 Maehara, A., Tsurugi, H., Satoh, T., and Miura, M. (2008). Regioselective C–H functionalization directed by a removable carboxyl group: palladium-catalyzed vinylation at the unusual position of indole and related heteroaromatic rings. *Org. Lett.* 10: 1159–1162.

13 Ueura, K., Satoh, T., and Miura, M. (2007). An efficient waste-free oxidative coupling via regioselective C—H bond cleavage: Rh/Cu-catalyzed reaction of benzoic acids with alkynes and acrylates under air. *Org. Lett.* 9: 1407–1409.

14 A leading review: Satoh, T. and Miura, M. (2010). Oxidative coupling of aromatic substrates with alkynes and alkenes under rhodium catalysis. *Chem. Eur. J.* 16: 11212–11222.

15 Leow, D., Li, G., Mei, T.-S., and Yu, J.-Q. (2012). Activation of remote meta-C—H bonds assisted by an end-on template. *Nature* 486: 518–522.

16 Yang, Y.-F., Cheng, G.-J., Liu, P. et al. (2014). Palladium-catalyzed *meta*-selective C—H bond activation with a nitrile-containing template: computational study on mechanism and origins of selectivity. *J. Am. Chem. Soc.* 136: 344–355.

17 (a) Li, S., Cai, L., Ji, H. et al. (2016). Pd(II)-catalysed *meta*-C–H functionalizations of benzoic acid derivatives. *Nat. Commun.* 7: 10443. (b) Modak, A., Mondal, A., Watile, R. et al. (2016). Remote *meta* C—H bond functionalization of 2-phenethylsulphonic acid and 3-phenylpropanoic acid derivatives. *Chem. Commun.* 52: 13916–13919. (c) Yang, L., Fu, L., and Li, G. (2017). Incorporation of carbon dioxide into carbamate directing groups: palladium-catalyzed *meta*-C–H olefination and acetoxylation of aniline derivatives. *Adv. Synth. Catal.* 359: 2235–2240. (d) Deng, Y. and Yu, J.-Q. (2015). Remote *meta*-C–H olefination of phenylacetic acids directed by a versatile U-shaped template. *Angew. Chem. Int. Ed.* 54: 888–891.

18 (a) Xu, H.-J., Lu, Y., Farmer, M.E. et al. (2017). Rh(III)-catalyzed *meta*-C–H olefination directed by a nitrile template. *J. Am. Chem. Soc.* 139: 2200–2203. (b) Bera, M., Agasti, S., Chowdhury, R. et al. (2017). Rhodium-catalyzed *meta*-C–H functionalization of arenes. *Angew. Chem. Int. Ed.* 56: 5272–5276.

19 (a) Bag, S., Patra, T., Modak, A. et al. (2015). Remote para-C–H functionalization of arenes by a D-shaped biphenyl template-based assembly. *J. Am. Chem. Soc.* 137: 11888–11891. (b) Patra, T., Bag, S., Kancherla, R. et al. (2016). Palladium-catalyzed directed *para* C–H functionalization of phenols. *Angew. Chem. Int. Ed.* 55: 7751–7755.

20 Yang, S.-D., Sun, C.-L., Fang, Z. et al. (2008). Palladium-catalyzed direct arylation of (hetero)arenes with aryl boronic acids. *Angew. Chem. Int. Ed.* 47: 1473–1476.

21 Kirchberg, S., Tani, S., Ueda, K. et al. (2011). Oxidative biaryl coupling of thiophenes and thiazoles with arylboronic acids through palladium catalysis: otherwise difficult C4-selective C–H arylation enabled by boronic acids. *Angew. Chem. Int. Ed.* 50: 2387–2391.

22 Ban, I., Sudo, T., Taniguchi, T., and Itami, K. (2008). Copper-mediated C—H bond arylation of arenes with arylboronic acids. *Org. Lett.* 10: 3607–3609.

23 (a) Hachiya, H., Hirano, K., Satoh, T., and Miura, M. (2010). Oxidative nickel–air catalysis in C–H arylation: direct cross-coupling of azoles with arylboronic acids using air as sole oxidant. *ChemCatChem* 2: 1403–1406. (b) Hachiya, H., Hirano, K., Satoh, T., and Miura, M. (2010). Nickel-catalyzed direct C–H arylation and alkenylation of heteroarenes with organosilicon reagents. *Angew. Chem. Int. Ed.* 49: 2202–2205.

24 Giri, R., Maugel, N., Li, J.-J. et al. (2007). Palladium-catalyzed methylation and arylation of sp^2 and sp^3 C—H bonds in simple carboxylic acids. *J. Am. Chem. Soc.* 129: 3510–3511.

25 Shang, M., Sun, S.-Z., Dai, H.-X., and Yu, J.-Q. (2014). $Cu(OAc)_2$-catalyzed coupling of aromatic C—H bonds with arylboron reagents. *Org. Lett.* 16: 5666–5669.

26 Mochida, K., Kawasumi, K., Segawa, Y., and Itami, K. (2011). Direct arylation of polycyclic aromatic hydrocarbons through palladium catalysis. *J. Am. Chem. Soc.* 133: 10716–10719.

27 (a) Ozaki, K., Kawasumi, K., Shibata, M. et al. (2015). One-shot K-region-selective annulative p-extension for nanographene synthesis and functionalization. *Nat. Commun.* 6: 6251. (b) Shibata, M., Ito, H., and Itami, K. (2018). C–H arylation of phenanthrene with trimethylphenylsilane by Pd/*o*-chloranil catalysis: computational studies on the mechanism, regioselectivity, and role of *o*-chloranil. *J. Am. Chem. Soc.* 140: 2196–2205.

28 (a) Cornella, J., Lu, P., and Larrosa, I. (2009). Intermolecular decarboxylative direct C-3 arylation of indoles with benzoic acids. *Org. Lett.* 11: 5506–5509. (b) Xie, K., Yang, Z., Zhou, X. et al. (2010). Pd-catalyzed decarboxylative arylation of thiazole, benzoxazole, and polyfluorobenzene with substituted benzoic acids. *Org. Lett.* 12: 1564–1567. (c) Zhang, F. and Greaney, M.F. (2010). Decarboxylative C–H cross-coupling of azoles. *Angew. Chem. Int. Ed.* 49: 2768–2771.

29 Takamatsu, K., Hirano, K., and Miura, M. (2017). Copper-mediated decarboxylative coupling of benzamides with *ortho*-nitrobenzoic acids by directed C–H cleavage. *Angew. Chem. Int. Ed.* 56: 5353–5357.

30 (a) Stuart, D.R. and Fagnou, K. (2007). The catalytic cross-coupling of unactivated arenes. *Science* 316: 1172–1175. (b) Hull, K.L. and Sanford, M.S. (2007). Catalytic and highly regioselective cross-coupling of aromatic C–H substrates. *J. Am. Chem. Soc.* 129: 11904–11905. (c) Dwight, T.A., Rue, N.R., Charyk, D. et al. (2007). C—C bond formation via double C–H functionalization: aerobic oxidative coupling as a method for synthesizing heterocoupled biaryls. *Org. Lett.* 9: 3137–3139. (d) Yamada, S., Murakami, K., and Itami, K. (2016).

Regiodivergent cross-dehydrogenative coupling of pyridines and benzoxazoles: discovery of organic halides as regio-switching oxidants. *Org. Lett.* 18: 2415–2418.

31 (a) Cheng, Y., Li, G., Liu, Y. et al. (2016). Unparalleled ease of access to a library of biheteroaryl fluorophores via oxidative cross-coupling reactions: discovery of photostable NIR probe for mitochondria. *J. Am. Chem. Soc.* 138: 4730–4738. (b) He, C.-Y., Fan, S., and Zhang, X. (2010). Pd-catalyzed oxidative cross-coupling of perfluoroarenes with aromatic heterocycles. *J. Am. Chem. Soc.* 132: 12850–12852. (c) Aoki, H., Saito, H., Shimoyama, Y. et al. (2018). Synthesis of conjugated polymers containing octafluorobiphenylene unit via Pd-catalyzed cross-dehydrogenative-coupling reaction. *ACS Macro Lett.* 7: 90–94.

32 (a) Wencel-Delord, J., Nimphius, C., Patureau, F.W., and Glorius, F. (2012). [Rh^{III}Cp*]-catalyzed dehydrogenative aryl–aryl bond formation. *Angew. Chem. Int. Ed.* 51: 2247–2251. (b) Kuhl, N., Hopkinson, M.N., and Glorius, F. (2012). Selective rhodium(III)-catalyzed cross-dehydrogenative coupling of furan and thiophene derivatives. *Angew. Chem. Int. Ed.* 51: 8230–8234.

33 Dong, J., Long, Z., Song, F. et al. (2013). Rhodium or ruthenium-catalyzed oxidative C–H/C–H cross-coupling: direct access to extended π-conjugated systems. *Angew. Chem. Int. Ed.* 52: 580–584.

34 Nishino, M., Hirano, K., Satoh, T., and Miura, M. (2012). Copper-mediated and copper-catalyzed cross-coupling of indoles and 1,3-azoles: double C–H activation. *Angew. Chem. Int. Ed.* 51: 6993–6997.

35 Kita, Y., Morimoto, K., Ito, M. et al. (2009). Metal-free oxidative cross-coupling of unfunctionalized aromatic compounds. *J. Am. Chem. Soc.* 131: 1668–1669.

36 (a) Kitahara, M., Hirano, K., Tsurugi, H. et al. (2010). Copper-mediated direct cross-coupling of 1,3,4-oxadiazoles and oxazoles with terminal alkynes. *Chem. Eur. J.* 16: 1772–1775. (b) Wei, Y., Zhao, H., Kan, J. et al. (2010). Copper-catalyzed direct alkynylation of electron-deficient polyfluoroarenes with terminal alkynes using O_2 as an oxidant. *J. Am. Chem. Soc.* 132: 2522–2523.

37 Matsuyama, N., Kitahara, M., Hirano, K. et al. (2010). Nickel- and copper-catalyzed direct alkynylation of azoles and polyfluoroarenes with terminal alkynes under O_2 or atmospheric conditions. *Org. Lett.* 12: 2358–2361.

38 Kim, S.H., Yoon, J., and Chang, S. (2011). Palladium-catalyzed oxidative alkynylation of heterocycles with terminal alkynes under air conditions. *Org. Lett.* 13: 1474–1477.

39 (a) de Haro, T. and Nevado, C. (2010). Gold-catalyzed ethynylation of arenes. *J. Am. Chem. Soc.* 132: 1512–1513. stoichiometric version: (b)Fuchita, Y., Utsonomiya, Y., and Yasutake, M. (2001). Synthesis and reactivity of arylgold(III) complexes from aromatic hydrocarbons *via* C—H bond activation. *J. Chem. Soc., Dalton Trans.*: 2330–2334.

40 Jie, X., Shang, Y., Hu, P., and Su, W. (2013). Palladium-catalyzed oxidative cross-coupling between heterocycles and terminal alkynes with low catalyst loading. *Angew. Chem. Int. Ed.* 52: 3630–3633.

41 Kim, S.H., Park, S.H., and Chang, S. (2012). Palladium-catalyzed oxidative alkynylation of arene C—H bond using the chelation-assisted strategy. *Tetrahedron Lett.* 68: 5162–5166.

42 (a) Shang, M., Wang, H.-L., Sun, S.-Z. et al. (2014). Cu(II)-mediated ortho C–H alkynylation of (hetero)arenes with terminal alkynes. *J. Am. Chem. Soc.* 136: 11590–11593. (b) Liu, Y.-J., Liu, Y.-H., Yin, X.-S. et al. (2015). Copper/silver-mediated direct *ortho*-ethynylation of unactivated (hetero)aryl C—H bonds with terminal alkyne. *Chem. Eur. J.* 21: 205–209. (c) Liu, Y.-H., Liu, Y.-J., Yan, S.-Y., and Shi, B.-F. (2015). Ni(II)-catalyzed dehydrative alkynylation of unactivated (hetero)aryl C—H bonds using oxygen: a user-friendly approach. *Chem. Commun.* 51: 11650–11653.

43 (a) Li, Z. and Li, C.-J. (2004). CuBr-catalyzed efficient alkynylation of sp^3 C–H bonds adjacent to a nitrogen atom. *J. Am. Chem. Soc.* 126: 11810–11811. (b) Girard, S.A., Knauber, T., and Li, C.-J. (2014). The cross-dehydrogenative coupling of C_{sp3}—H bonds: a versatile strategy for C—C bond formations. *Angew. Chem. Int. Ed.* 53: 74–100.

44 (a) Li, Z. and Li, C.-J. (2004). Catalytic enantioselective alkynylation of prochiral sp^3 C—H bonds adjacent to a nitrogen atom. *Org. Lett.* 6: 4997–4999. (b) Dubs, C., Hamashima, Y., Sasamoto, N. et al. (2008). Mechanistic studies on the catalytic asymmetric Mannich-type reaction with dihydroisoquinolines and development of oxidative Mannich-type reactions starting from tetrahydroisoquinolines. *J. Organomet. Chem.* 73: 5859–5871.

45 Li, Y.-Z., Li, B.-J., Lu, X.-Y. et al. (2009). Cross dehydrogenative arylation (CDA) of a benzylic C—H bond with arenes by iron catalysis. *Angew. Chem. Int. Ed.* 48: 3817–3820.

46 Young, A.J. and White, M.C. (2008). Catalytic intermolecular allylic C–H alkylation. *J. Am. Chem. Soc.* 130: 14090–14091.

47 Guo, X. and Li, C.-J. (2011). Ruthenium-catalyzed para-selective oxidative cross-coupling of arenes and cycloalkanes. *Org. Lett.* 13: 4977–4979.

48 (a) DeMartino, M.P., Chen, K., and Baran, P.S. (2008). Intermolecular enolate heterocoupling: scope, mechanism, and application. *J. Am. Chem. Soc.* 130: 11546–11560. (b) Richter, J.M., Whitefield, B.W., Maimone, T.J. et al. (2007). Scope and mechanism of direct indole and pyrrole couplings adjacent to carbonyl compounds: total synthesis of acremoauxin A and oxazinin 3. *J. Am. Chem. Soc.* 129: 12857–12869.

49 Jang, H.-Y., Hong, J.-B., and MacMillan, D.W.C. (2007). Enantioselective organocatalytic singly occupied molecular orbital activation: the enantioselective r-enolation of aldehydes. *J. Am. Chem. Soc.* 129: 7004–7005.

50 Amaya, T., Maegawa, Y., Masuda, T. et al. (2015). Selective intermolecular oxidative cross-coupling of enolates. *J. Am. Chem. Soc.* 137: 10072–10075.

51 (a) Moon, P.J., Yin, S., and Lundgren, R.J. (2016). Ambient decarboxylative arylation of malonate half-esters via oxidative catalysis. *J. Am. Chem. Soc.* 138: 13826–13829. (b) Takamatsu, K., Hirano, K., and Miura, M. (2018). Copper-mediated decarboxylative coupling of benzamides with potassium malonate monoesters via directed C–H cleavage. *Chem. Lett.* 47: 450–453.

52 (a) Wasa, M., Engle, K.M., and Yu, J.-Q. (2010). Pd(II)-catalyzed olefination of sp^3 C—H bonds. *J. Am. Chem. Soc.* 132: 3680–3681. (b) Stowers, K.J., Fortner, K.C., and Sanford, M.S. (2011). Aerobic Pd-catalyzed sp^3 C–H olefination: a route to both N-heterocyclic scaffolds and alkenes. *J. Am. Chem. Soc.* 133: 6541–6544. (c) Jiang, H., He, J., Liu, T., and Yu, J.-Q. (2016). Ligand-enabled γ-C(sp^3)–H olefination of amines: en route to pyrrolidines. *J. Am. Chem. Soc.* 138: 2055–2059.

53 Wu, X., Zhao, Y., and Ge, H. (2015). Pyridine-enabled copper-promoted cross dehydrogenative coupling of C(sp^2)—H and unactivated C(sp^3)—H bonds. *Chem. Sci.* 6: 5978–5983.

54 Luo, F.-X., Cao, Z.-C., Zhao, H.-W. et al. (2017). Nickel-catalyzed oxidative coupling of unactivated C(sp^3)—H bonds in aliphatic amides with terminal alkynes. *Organometallics* 36: 18–21.

55 Liu, Y., Yang, K., and Ge, H. (2016). Palladium-catalyzed ligand-promoted site-selective cyanomethylation of unactivated C(sp^3)—H bonds with acetonitrile. *Chem. Sci.* 7: 2804–2808.