OXIDATIVE Csp^2–H/Csp^2–H (HETERO)ARYLATION OF AROMATIC HETEROCYCLES. AN OVERVIEW

DOI: http://dx.medra.org/10.17374/targets.2025.28.368

Ahmed El Akkaoui,[a] Nabil El Brahmi,[b] Jamal Koubachi,[c]* Saïd El Kazzouli[b]*

[a]*Laboratory of Analytical and Molecular Chemistry (LCAM), Polydisciplinary Faculty of Safi, Cadi Ayyad University, Sidi Bouzid, B.P. 4162, 46000 Safi, Morocco*

[b]*Euromed Research Center, Euromed University of Fes (UEMF), 30000 Fez, Morocco*

[c]*Polydisciplinary Faculty of Taroudant, Biotechnology, Analytical Sciences, and Quality Control Team, AMENSE Laboratory, Ibnou Zohr University, BP. 271, 83000 Taroudant, Morocco*

(e-mail: j.koubachi@uiz.ac.ma, s.elkazzouli@ueuromed.org)

Abstract. *The heteroarenes, present in a plethora of natural and pharmaceutical products, are nowadays very interesting scaffolds for drug design and discovery. The presence of multiple C–H bonds in heterocycles makes C–H activation an attractive way for their functionalization and an interesting alternative to traditional cross-coupling methods. The C–H functionalization of heteroarenes, which respects the principal of green chemistry and sustainable development, is so far the most rapid and atom-economical method for the formation of new carbon-carbon bounds as well as for the synthesis of complex (hetero)aromatic molecules. This review summarizes the recent reports achieved in the field of direct dehydrogenative C–H functionalization and discusses the recently published methods employing the oxidative coupling of heteroarenes by means of 4d and 5d transition metal catalysts (Pd, Ru, Rh, Ir). This review covers the following areas: i) cross-hydrogenative coupling between a heteroarene and an arene; and ii) Csp^2–H/Csp^2–H type coupling between two different heteroarenes (including homocoupling of heteroarenes). The paper also examines the site selectivity functionalization and highlights the most important applications of the synthesized (hetero)arylated heteroarenes. The scopes of the substrate, limitations, mechanism of the reaction, regioselectivity, and strategies for controlling these reactions are also discussed.*

Contents

1. Introduction

The formation of carbon-carbon (C–C) bonds is central to organic synthesis, in which the organometallic reagents play a key role in the form of transition metal-catalyzed cross-couplings. The necessity to develop new techniques to solve new synthetic challenges has always been a continuous process. Over the past decades, the oxidative/dehydrogenative cross-coupling (CDC) reactions have been shown as a modern tool for the construction of C–C bonds and are suitable to organic chemists for sustainable chemistry. Likewise, there are few relevant reviews that report the CDC reactions, using 3d transition metal catalysts (Co, Ni, Cu, Fe, Cr, V[1-3] or 4d and 5d metal catalysts (Ru, Rh, Ir, and Pd)[4-10] as well as oxidative coupling of Csp^3–H and Csp–H bonds.[4,11-13] It is noteworthy that the other transition-metal-catalyzed C–H functionalization method have been extensively reviewed.[14]

In continuation of our interest in developing original methods for C–H activation including direct and oxidative palladium-catalyzed (hetero)arylation[15-21] and oxidative alkenylation[22-24] of heterocyclic systems (heteroarenes), we describe in this review the recent progress in the 4d and 5d (Ru, Pd, Rh, Ir) transition metal-catalyzed Csp^2–H/Csp^2–H oxidative coupling/cross-dehydrogenative coupling (CDC) of aromatic heterocycles for C–C bond formation of heteroarenes, having significant applications, which have been reported in the last nine years (2015-2023). In the literature, the use of oxidants is frequently required to facilitate the cross-dehydrogenative coupling reaction of heteroarenes.[9]

In recent times, Pd, Ru, Rh, and Ir transition metal-catalyzed oxidative coupling approaches have appeared as polyvalent and atom economical procedures to synthesize aryl-heteroaryl, and heteroaryl-heteroaryl motifs because the Csp^2–H/Csp^2–H cross-dehydrogenative coupling eliminates the necessity for pre-functionalization of substrates and coupling partners. In addition, the oxidative coupling offers an environmentally friendly solution to cross-coupling reactions.[23,24,25-31]

The number of publications appearing on Scopus between 2000 and 2023 using various keywords as article titles is shown in Figure 1.

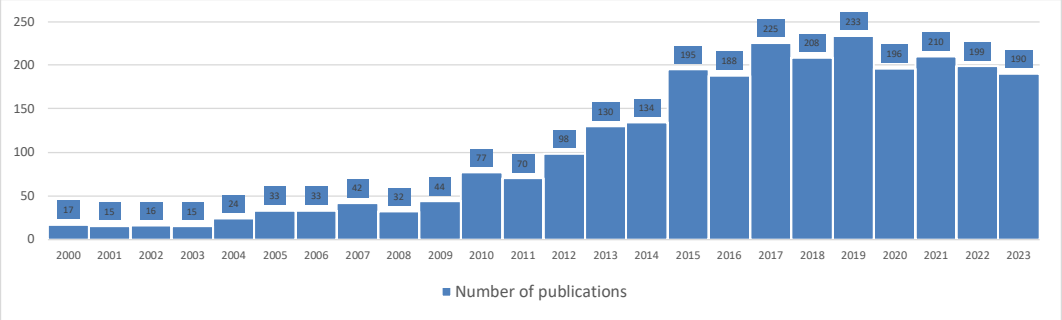
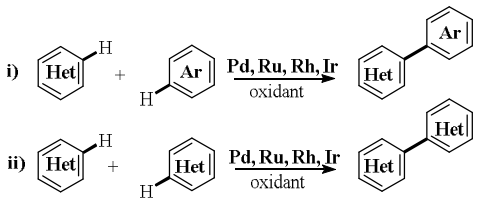


Figure 1. Number of publications from 2000 to 2023 on Scopus using the following key words as article title (oxidative direct arylation or cross-dehydrogenative couplig or dehydrogenative C–H/C–H cross-coupling or C–H/C–H cross-coupling or oxidative cross-coupling or dehydrogenative coupling or oxidative Csp^2–H/Csp^2–H arylation of aromatic heterocycles.

Scheme 1 shows a selection of recent approaches used in the C–H activation of (hetero)arenes using Csp^2–H/Csp^2–H cross-dehydrogenative coupling arylation: i) Csp^2–H/Csp^2–H cross-coupling reactions between a (hetero)arene and arenes, in which an unactivated arene is reacted with aromatic heterocycle as substrate; ii) Csp^2–H/Csp^2–H type coupling, in which two different heteroarenes react together or by cross-dehydrogenative homocoupling. The new C–C made by C–H/C–H functionalization are indicated by red bold lines in all over schemes.

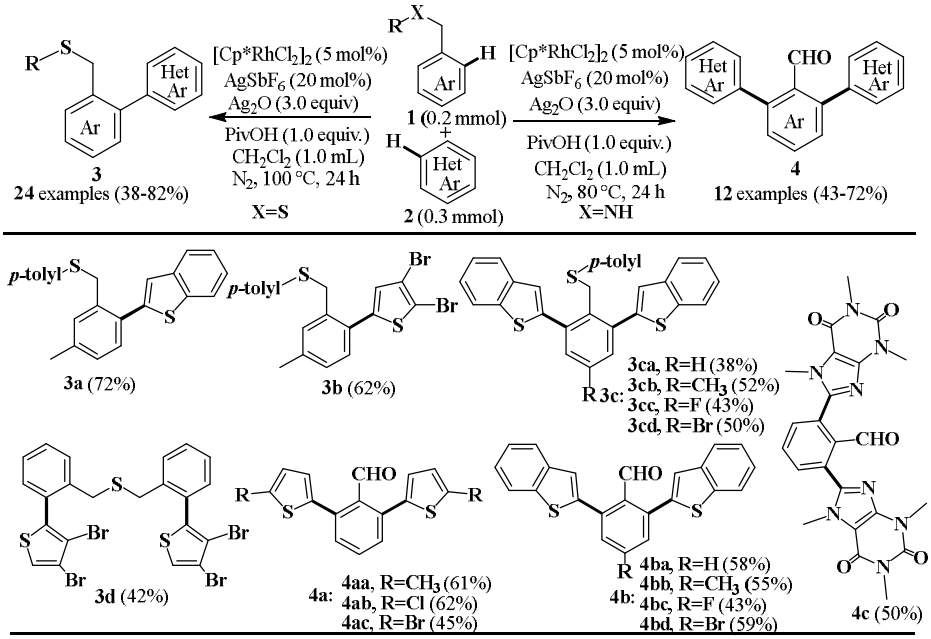


Scheme 1. Types of arylations presented in this review: i) Csp^2–H/Csp^2–H cross-coupling reactions between a (hetero)arene and arenes; ii) Csp^2–H/Csp^2–H type coupling between two different heteroarenes or by cross-dehydrogenative homocoupling.

2. Cross-dehydrogenative coupling (CDC) reactions between (hetero)arene and arene

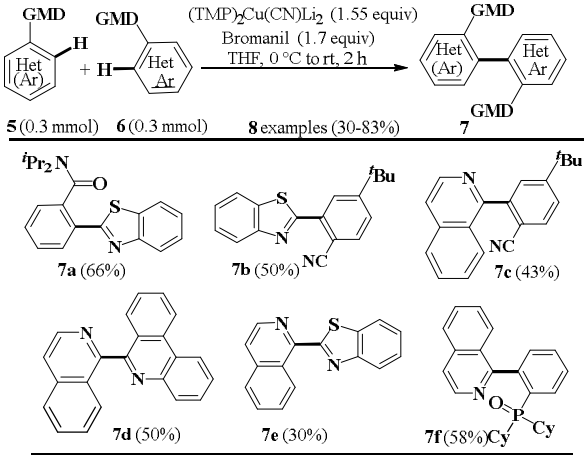
Regarding the importance of the aryl thiophene scaffolds, Yang *et al.*[32] reported an efficient synthetic method to functionalize thiophene **2** with benzylthioethers or benzylamines **1** trough C–H/C–H cross-coupling reaction catalyzed by $[RhCp^*Cl_2]_2/AgSbF_6$ system. First, the oxidative coupling between benzothiophene **2** and benzylthioethers **1** using $[RhCp^*Cl_2]_2$/ $AgSbF_6$ as the catalyst system, Ag_2O as the oxidant, and PivOH as additive in CH_2Cl_2 at 100 °C for 24 h, led to cross-coupled products in moderate to good yields. Remarkably, when the 4-methyl-, 4-bromo-, 4-fluoro-substituted benzyl(*p*-tolyl)thioether and benzyl(*p*-tolyl)sulfane were used as partners, the diheteroarylated benzylthioethers products **3c** (**3ca**, **3cb**, **3cc**, and **3cd**) were obtained in moderate yields (Scheme 2). Under the optimal conditions, the scope of benzothiophenes and thiophenes was investigated. Then, various benzothiophenes and thiophenes **2** were efficiently coupled with

(3-methylbenzyl)(*p*-tolyl)sulfane **1** to afford the cross-coupled products **3** in moderate to good yields (45-80%) (Scheme 2). In this study, the bis(3-methylbenzyl)thioether could also undergo diheteroarylation to give the corresponding product **3d** in moderate yield. Under the same optimal conditions and by decreasing the reaction temperature to 80 °C, the authors have also reported a surprising cross-coupling reaction of benzylamine derivatives **1** with benzothiophene and thiophene **2**, which gave only diheteroarylated benzaldehydes **4** as the final products (45-72%). When caffeine was used as a partner of the reaction, the *ortho*-selective C–H/C–H cross-coupling reaction gave the corresponding diheteroarylated benzaldehyde **4c** in 50% yield. To investigate the mechanism of both kinds of cross-coupling reactions, the authors have carried out deuteration and kinetic isotope effect (KIE) experiments, which showed that the mechanism of formation of diheteroarylated benzylthioethers proceeds through the coordination of the substrates to Rh(III), followed by the insertion reaction with partners. Finally, a reductive elimination occurs, providing the cross-coupled product. Concerning the preparation of diheteroarylated benzaldehydes, the mechanism involved three steps: the first is the *ortho*-C–H diheteroarylation of benzylamine **1**, then the oxidation of benzylamine to imine, and finally the hydrolysis of imine to aldehyde.



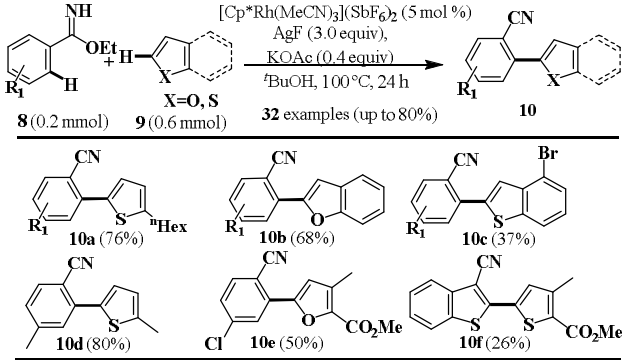
Scheme 2. Rhodium-catalyzed C−H/C−H cross-coupling of benzylthioethers and benzylamines with thiophenes.

Tezuka *et al.*[33] prepared a series of unsymmetrical biaryl structures from different arenes having a variety of directed metalation groups (DMGs) and ancillary function groups through sequential directed *ortho*-cupration and oxidation reactions. The cross-dehydrogenative coupling of benzamide (or heteroarenes) **5** with heteroarenes **6** bearing various types of DMGs was carried out using cuprate base $(TMP)_2Cu(CN)Li_2$ and bromanil oxidant (Scheme 3). The reaction goes through the formation of heteroleptic diarylcuprate as intermediate *in situ* by deprotonations of two different arenes using cuprate base. Then, an oxidative coupling gives the heterobiaryl **7** in moderate to good yields and in a highly regio- and chemoselective manner. Under these reaction conditions, the substrate scope for benzamide was expanded to include benzo[*d*]thiazole and heterobiaryls which gave their corresponding *ortho*-substituted (hetero)biaryls. In the case of (hetero)arenes with various DMGs, the scope of this transformation included also electron-deficient and electron-donating substituted arenes, benzo[*d*]thiazole and heterobiaryls.



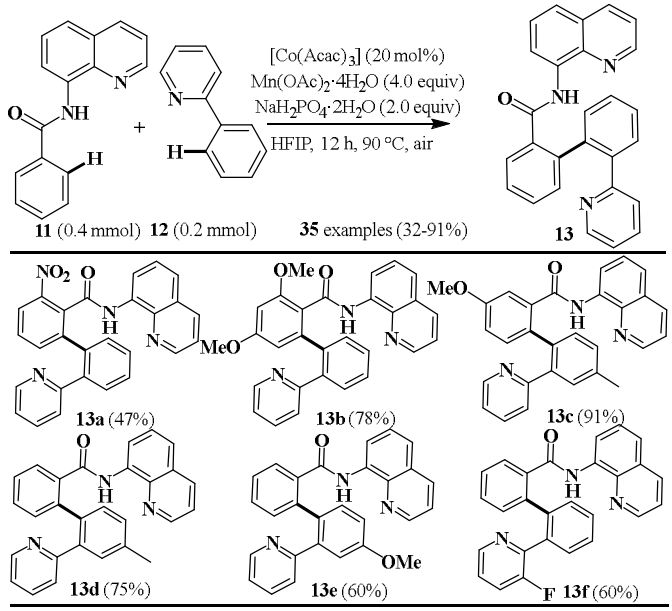
Scheme 3. Base $(TMP)_2Cu(CN)Li_2$ direct cross-coupling of C−H/C−H bonds of two arenes.

The oxidative aryation of benzimidates **8** using an heteroarenes **9** as the reaction partners in the presence of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as catalyst, AgF as oxidant and KOAc as additive in ^{t}BuOH at 100 °C for 24 h, was achieved by Wang *et al.*[34] Only biheteroaryl-2-carbonitriles **10** were obtained after *in situ* dealcoholization in moderate to good yields with a wide substrate scope which included electron-donating or electron-withdrawing groups (Scheme 4). The authors realized this reaction also in gram-scale, obtaining the arylation products in good yield.



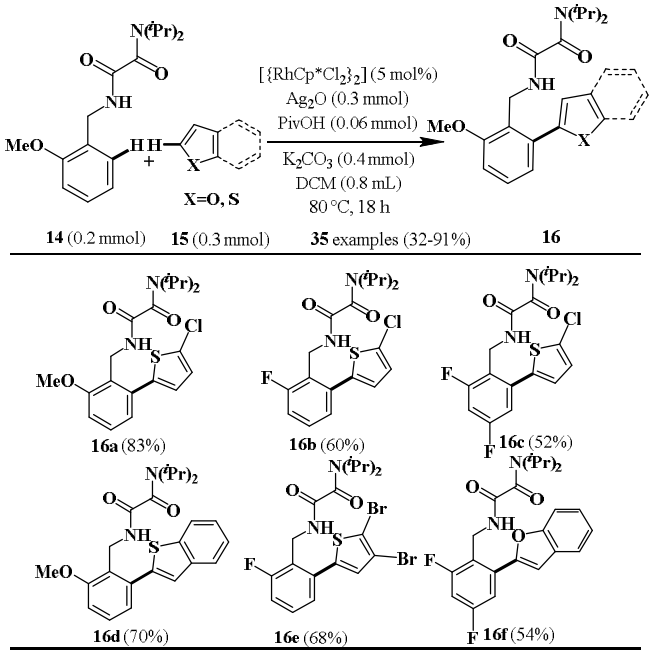
Scheme 4. Rhodium-catalyzed C–H/C–H oxidative coupling and dealcoholization reaction of benzimidates with heteroarenes.

The first example of Cp*-free cobalt-catalyzed oxidative C–H/C–H bond arylation of unactivated arenes was reported in 2016 by Du *et al.* (Scheme 5).[35] Using commercially available $[Co(acac)_3]$ as the catalyst, $Mn(OAc)_2{\cdot}4H_2O$ as the cooxidant, $NaH_2PO_4{\cdot}2H_2O$ as the base in HFIP at 90 °C for 12 h, the reaction of 8-aminoquinoline amide **11** with 2-phenylpyridine **12** gave the cross-coupling product **13a-f** in good yield (Scheme 5). The amido quinoline and the pyridyl moieties of both substrates acts as mixed directing group to mediate the intermolecular single electron transfer (SET) and concerted metalation-deprotonation (CMD) processes, respectively. This procedure was shown to be tolerant towards a variety of mono, di or trisubstituents on the bezamides such as methyl, methoxy, phenyl, halogeno, ester, nitro or trifluoromethyl affording the cross-coupling products in 47-82% yields. This system also tolerated a wide variety of substituents on the 2-arylpyridines. It should be noted that negligible homocoupled product (<5%) of **11** and no homocoupled product of **12** were observed.



Scheme 5. Cobalt-catalyzed oxidative C–H/C–H bond arylation of unactivated arenes. comma,

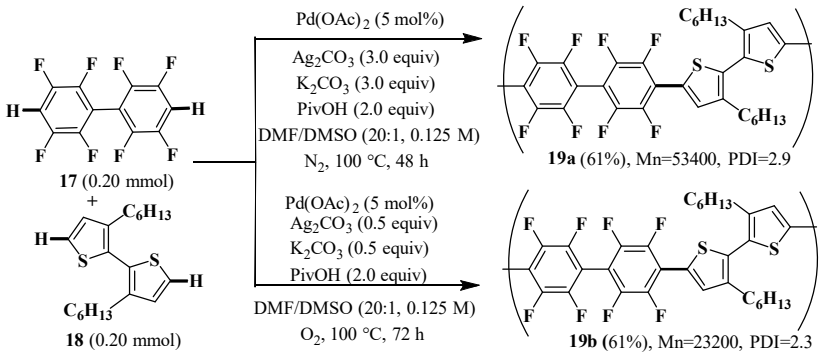
The rhodium-catalyzed *ortho*-oxidative C–H/C–H arylation of oxalyl amide-protected benzylamines **14** with different heteroarnes **15** was described by Hu and co-workers[36] in 2016 (Scheme 6).



Scheme 6. Rhodium(III)-catalyzed oxidative C−H/C−H cross-coupling of heteroarenes and masked benzylamines.

The reaction was realized in the presence of [{RhCp*Cl_2}$_2$] (Cp*=C_5Me_5), Ag_2O as the best oxidant and PivOH as additive in CH_2Cl_2 under basic medium (K_2CO_3) and under mild conditions (80 °C). With this method, a variety of *ortho*-heteroarylated benzylamine derivatives **16** were synthesized in moderate to good yields with a wide substrate scope, on the six membered ring of the benzylamine **14** including sensitive functional groups such as methyl, methoxy, cyano, bromo, fluoro, ester *etc*. This oxidative cross-coupling reaction also tolerated various thiophenes and furans **15** as partners bearing aldehyde, ketone, ester and bromo groups. Remarkably, the direct arylation gave only the diheteroarylated products in good yields, with less than 5% yield of the monoheteroarylated products **16** when *meta*-substituted **14** benzylamines have been used, but when *para*-substituted benzylamines have been used, only diheteroarylated products were detected (Scheme 6).

The direct dehydrogenative reaction was also explored for preparing π-conjugated polymers. In 2018, the Aoki group[37] showed a palladium-catalyzed oxidative Csp^2–H/Csp^2–H arylation reaction of 2,2′,3,3′,5,5′,6,6′-octafluorobiphenyl **17** with thiophene analogues to afford the corresponding π-conjugated polymers by a C–H/C–H activation strategy. The authors observed that the polycondensation of **17** with 3,3′-dihexyl-2,2′-bithiophene **18** in the presence of 5 mol% of $Pd(OAc)_2$ using PivOH as additive, Ag_2CO_3 as oxidant and K_2CO_3 as base in a mixture of *N,N*-dimethylformamide (DMF)/dimethyl sulfoxide(DMSO; 20/1) as solvent at 100 °C for 48 h under a nitrogen atmosphere led to formation of the corresponding polymer **19a** with a molecular weight of 53400 g.mol^{-1} in 61% yield after washing with methanol and ethyl acetate (Scheme 7). When lower loading of the oxidant as well as the base have been used under aerobic conditions at 100 °C for 72 h, the corresponding polymer **19b** with a molecular weight of 23200 g.mol^{-1} was obtained in 66% yield. With these optimized conditions, 4% of homocoupling of 3,3′-dihexyl-2,2′-bithiophene was also formed under anaerobic conditions calculated by NMR pectroscopy.

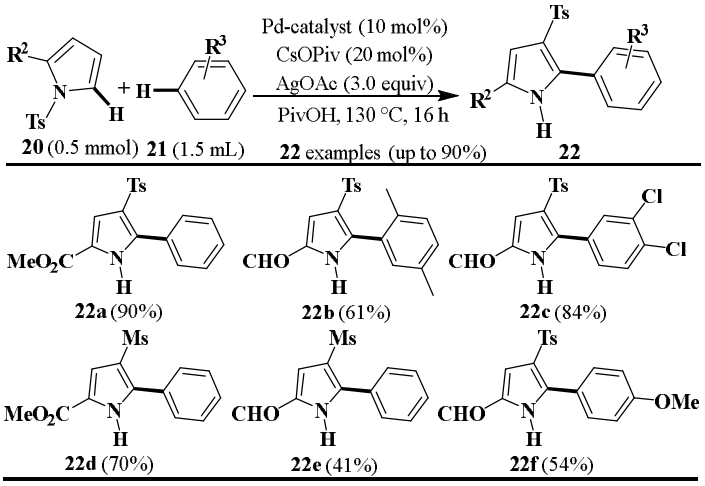


Scheme 7. Palladium-catalyzed cross-dehydrogenative coupling reaction of 2,2′,3,3′,5,5′,6,6′-octafluorobiphenyl with thiophene.

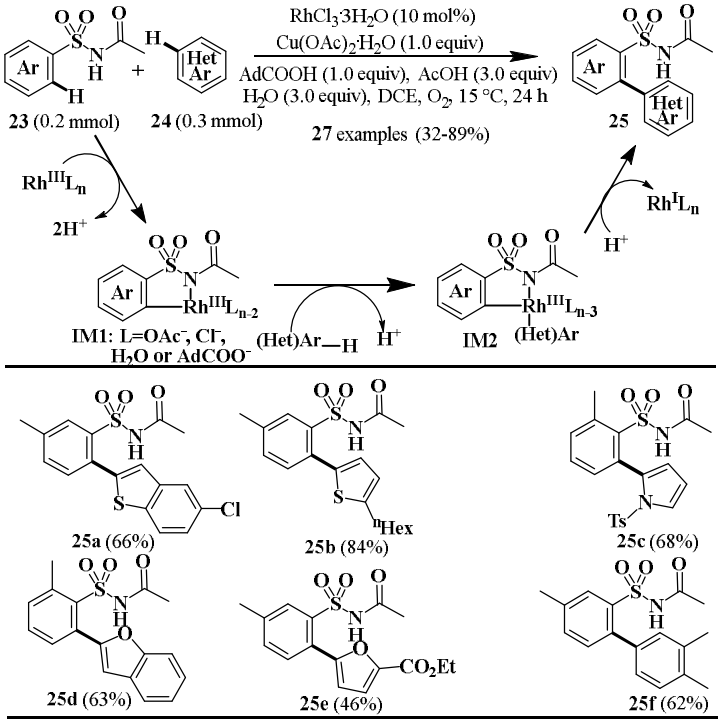
The oxidative arylation reaction was also used by Bharatam and co-workers[38] for the synthesis of 2-arylpyrroles containing a C3-sulfonyl moiety **22**. The reaction was achieved *via* one-pot palladium-catalyzed regioselective C2 arylation of *N*-sulfonylpyrroles **20** followed by intramolecular N1- to C3-sulfonyl migration (Scheme 8). Thus, using 10 mol% of $Pd(OAc)_2$ as catalyst, 20 mol% of CsOPiv as base and AgOAc as oxidant in PivOH as solvent at 130 °C for 16 h, 1-(1-tosyl-1*H*-pyrrol-2-yl)ethan-1-one **20** in the presence of benzene gave in one-pot the 2-aryl-3-sulfonylpyrrole **22**. This approach is compatible with mono-substituted arene **21**, such as nitrobenzene as well as disubstituted arenes such as *o*- and *p*-xylene, 1,2-dichlorobenzene and 1-fluoro-2-nitrobenzene. The authors prepared various C3 sulfonyl 2-arylpyrroles **22a-f** that are otherwise difficult to prepare by the literature procedures.

Owing to promising bioactivities of sulfonamide scaffolds in drug discovery, You *et al.*[39] reported the preparation of biaryl sulfonamides, bi(hetero)aryl sultams, and dibenzo[*b*,*d*]thiophene 5,5-dioxides through an efficient rhodium-catalyzed oxidative C–H/C–H cross-coupling. Hence, the reaction between *N*-(arylsulfonyl)acetamide **23** and (hetero)arene **24** was realised using $RhCl_3.3H_2O$ (10 mol%) as catalyst, $Cu(OAc)_2.H_2O$ (1.0 equiv) and O_2 as oxidant and a mixture of AdCOOH (1.0 equiv)/AcOH (0.3 equiv)/H_2O

(3.0 equiv) as additive in DCE as solvent at 150 °C for 24 h to afford *ortho*-sulfonamido bi(hetero)aryls **25a-f** in moderate to good yield (Scheme 9).



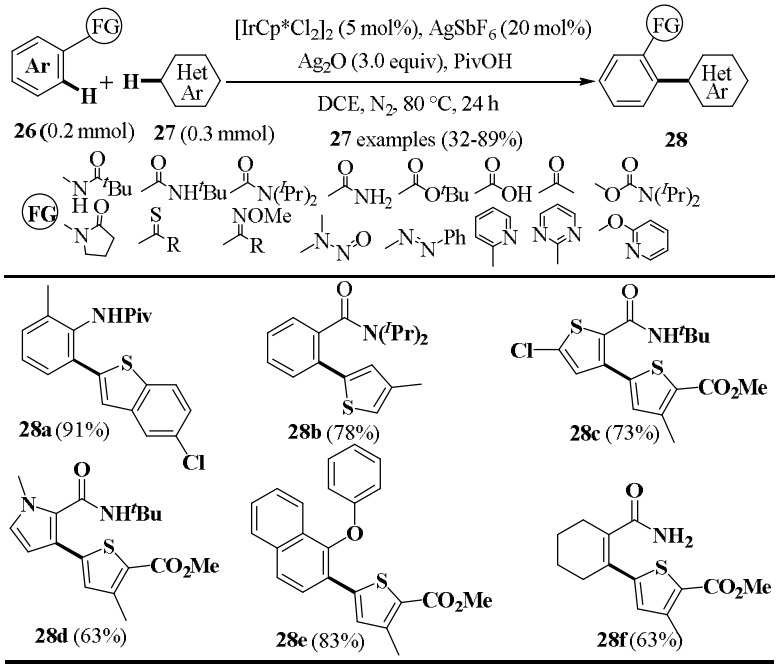
Scheme 8. A one-pot synthesis of synthesis of 2-arylpyrroles containing a C3-sulfonyl moiety from *N*-sulfonylpyrroles.



Scheme 9. Rhodium catalyzed oxidative C−H/C−H cross-coupling of (hetero) aromatic sulfonamides with (hetero)arenes.

The scope of this reaction was further examined using various sulfonamide derivatives such as aryl sulfonamides with either electron-donating or withdrawing groups, heteroaromatic sulfonamides such as thiophene and benzothiophene and 2-naphthylene sulfonamides which provided the desired products in good yields. The authors have investigated also the scope of arenes (such as benzene, phenyl bromide, *o*-xylene and anisole) and heteroarenes (such as thiophenes, benzothiophenes, pyrole, furan, benzofuran and indolizine), which could successfully couple with aryl sulfonamides under the obtimzed conditions to give the desired *ortho*-sulfonamido bi(hetero)aryls in moderate yields. However, the arenes with CO_2Et and F as strong electron-withdrawing groups, *N*-unsubstituted pyroles and indoles were not suitable for this transformation. In this study, the authors also described a plausible mechanistic pathway based on the H/D exchange experiments and previous reports.[40-42] This mechanistic study revealed that the reaction first involves the *ortho*-metalation of sulfonamide **23** to Rh(III) to afford a five membered rhodacyle species **IM1** through C–H bond cleavage. Next, the coordination of the second C–H of the (hetero)arene **24** to Rh(III) produces the (Het)Ar-Rh(III)-(Het)Ar **IM2** intermediate, which undergoes a reductive elimination to generate the desired product **25a-f**. Finally, to complete the catalytic cycle, the released Rh(I) species is reoxidized to Rh(III) by Cu(II)/O_2 (Scheme 9).

To overcome the restriction to specific substrates in the oxidative Ar-H/Ar-H cross-coupling reaction, the same group[43] developed a catalytic platform based on Cp*Ir(III) to afford *ortho*-bi(hetero)aryls **28** using the arenes with 16 types of directing groups and heteroarenes. In this process, the authors prepared first the cationic five-membred Ir(III) complex from *N*-methyl-*N*-phenylnitrous amide **26** and $[IrCp^*Cl_2]_2$, in the presence of NaOAc in DCM at room temperature for 24h, then they added $AgSbF_6$ to the reaction mixture in MeCN at room temperature for 12 h (Scheme 10).

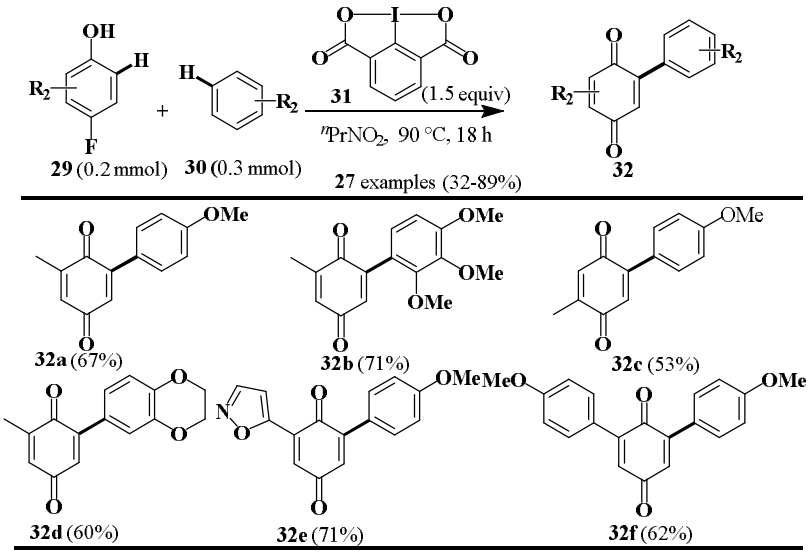


Scheme 10. Iridium-catalyzed oxidative heteroarylation of arenes and alkenes.

Subsequently, the obtained cationic complex reacted with benzothiophene **27** using Ag_2O as oxidant, PivOH as additive in DCE at 80 °C for 24 h to afford the cross-coupled product **28a-f** in moderate yield. The scope of the reaction is wide enough to employ various aromatic substrates such as *N*-methyl-*N*-phenylnitous amides, pivalanilides, tertiary and primary (hetero)aromatic amides, and arenes bearing the oxime ether, azo,

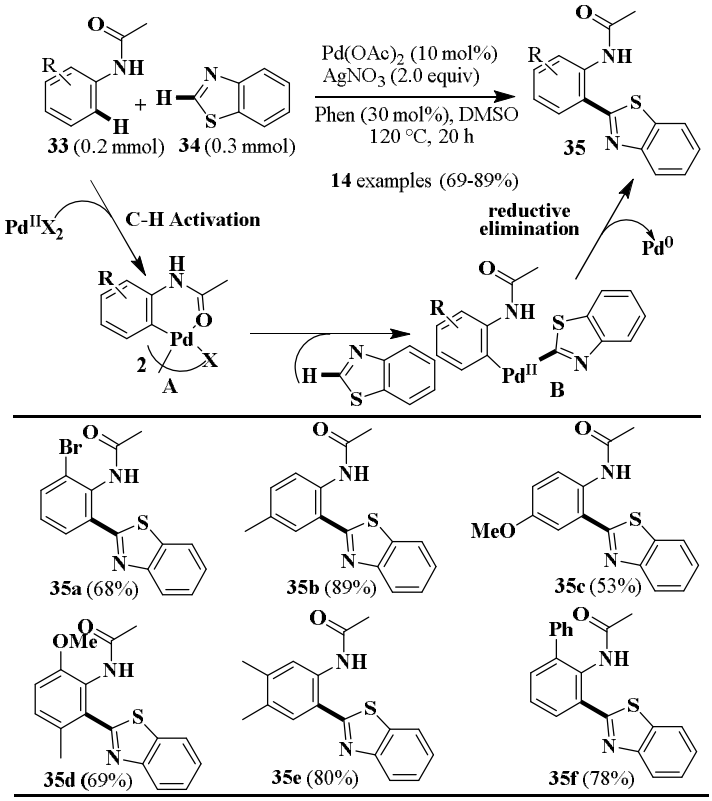
pyridyl, pyrimidyl, or 2-pyrrolidone. The reaction also tolerates aromatic ketones such as acetophenones with various functional groups (methyl, ethyl, isopropyl, methoxyl, phenyl, triphenylamino, fluoro). In this study, the authors subsequently reported a comparative reactivity study between the iridium catalyst and the rhodium catalyst reported above. The obtained results demonstrate clearly that the iridium catalyst is more efficient than rhodium for the oxidative C–H heteroarylation (Scheme 10).

To solve the regioselectivity problem of the cross dehydrogenative coupling reaction of quinone, Patureau and co-workers[44] developed a metal-free cross dehydrogenative arylation method of fluorophenols with arenes using hypervalent iodine oxidants. After the optimization, the reaction was realized using 4-fluoro-2-methylphenol **29** as a starting material, anisole **30** as a partner agent, and iodosodilactone **31** as the oxidant in 1-nitropropane as the solvent at 90 °C for 18 h to afford 1,4-quinone **32a-f** as a single isomer in moderate yield (Scheme 11). This procedure was compatible with various *para*-flurophenyl and arenes with different electron-withdrawing and electron-donating groups on the phenyl ring which smoothly underwent the coupling reaction to afford the corresponding 1,4-quinones in moderate to good yields. Interestingly, the authors also reported the synthesis of 1,2-quinones in moderate yields by using the same optimized conditions from *ortho*-fluorophenols**.** In addition, the diarylated quinones were also developed from *para*-flurophenols and arenes in the presence of hypervalent iodine oxidant **31** in 1-nitropropane at -20 °C for 18 h. With these conditions 2,6-diarylated-1,4- quinone **32f** was obtained in 62% yield.



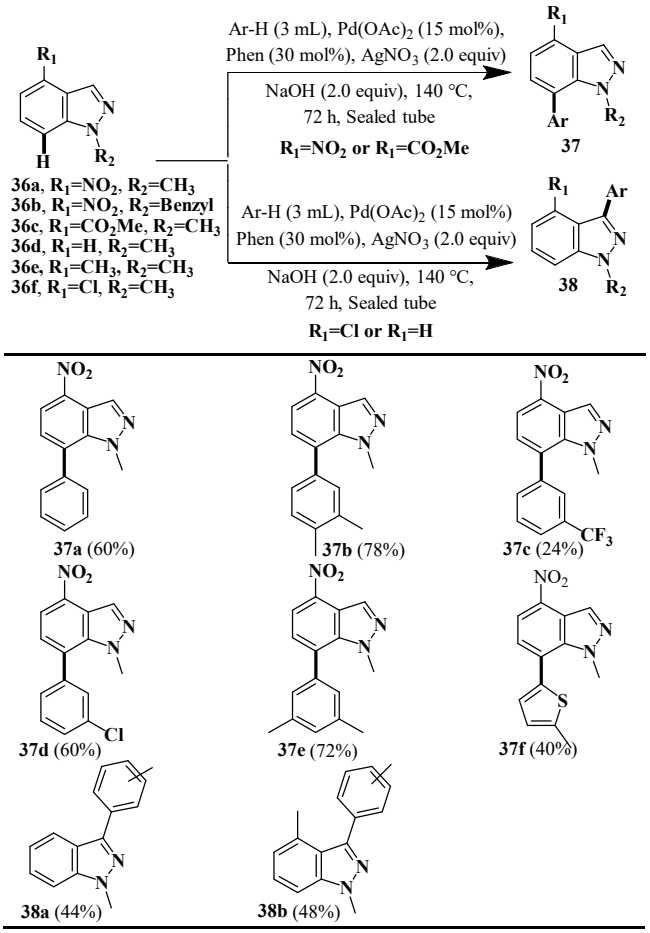
Scheme 11. Regioselective oxidative arylation of fluorophenols.

In the C–H activation of benzothiazole, Kharat *et al.*[45] reported an efficient cross-dehydrogenative coupling process for direct C2 arylation of benzothiazole **34** with arenes containing readily removable acetylamino directing group. In this process, benzothiazole **34** reacted with acetanilide derivatives **33** in the presence of $Pd(OAc)_2$ as a catalyst $AgNO_3$ as an oxidant in DMSO at 120 °C for 20 h to furnish the C2 arylated benzothiazole **35a-f** (Scheme 12). A variety of acetanilide derivatives were tested in this reaction. The authors found that acetanilide containing different electron-withdrawing groups such as methyl, ethyl, methoxy and phenyl and electron-donating groups such as fluro, bromo and chloro, efficiently underwent the oxidative arylation reaction to afford the corresponding arylated products in good yields. Based on previous work, the authors have proposed a plausible mechanism for this reaction. First, the electrophilic Pd(II) catalyst undergoes cyclometalation with acetanilide to afford to afford a five membered palladacycle intermediate **A**. Then, intermediate **A** is coordinated by benzothiazole to give intermediate **B**, which undergoes reductive elimination to afford the desired product and Pd(0) species. Finally, the Pd(0) species is reoxidized to Pd(II) by Ag(I) through oxidative reaction.



Scheme 12. Palladium-catalyzed chemo- and regioselective oxidative cross-dehydrogenative coupling of acetanilides with benzothiazole.

In continuation of the functionalization of the six-membered ring of the 6,5-fused heterocyclic systems,[46,47] our group, in a recent study,[48] reported an efficient palladium-catalyzed oxidative C7-arylation of C4-electron-withdrawing 1*H*-indazole **36** with various arenes and heteroarenes as coupling partners (Scheme 13). The reaction was accomplished in a sealed tube using 10 mol% $Pd(OAc)_2$, 15 mol% phenanthroline, Ag_2CO_3, and NaOH at 140 °C for 72 h. These optimized conditions allowed the preparation of various C7-(Het) arylated 1*H*-indazoles **37a-f**. The scope of this reaction spans an ample variety of arenes with electron-donating (EDG) and electronwithdrawing groups (EWG), or steric hindrance and can be applied to 4-EWG or 4-EDG indazole derivatives. The 1-methyl-4-nitro-1*H*-indazole **36a** treated with EDG monosubstituted arenes such as toluene and *t*-butylbenzene gave a mixture of isomers. While it was treated with the EWG monosubstituted arenes such as (trifluoromethyl)benzene, chlorobenzene and nitrobenzene, the arylation reaction provided only the *meta*-arylated compounds. In the case of 1-benzyl-4-nitro-1*H*-indazole **36b** the arylation reaction with arenes led to the expected products with lower yield which was attributed to the steric hindrance of the benzyl group. The reaction could also be applied to 1-methyl-1*H*-indazole-4-carboxylate **36c** with whatever unsubstituted or substituted arenes, which led to the corresponding C7 arylated derivatives in low yields compared to 1-methyl-4-nitro-1*H*-indazole **36a**. However, in the case of 4-chloro-1-methyl-1*H*-indazole **36f**, no arylation reaction was observed. It is important to mention in this study that when the EWG was replaced with either H or CH_3 group (compound **36d** and **36e**), the oxidative arylation occurred only at the C3 position **38a** and **38b** showing the crucial role of EWG in C4 position. In this study, the authors have also reported a plausible CMD mechanistic pathway based on DFT calculation.

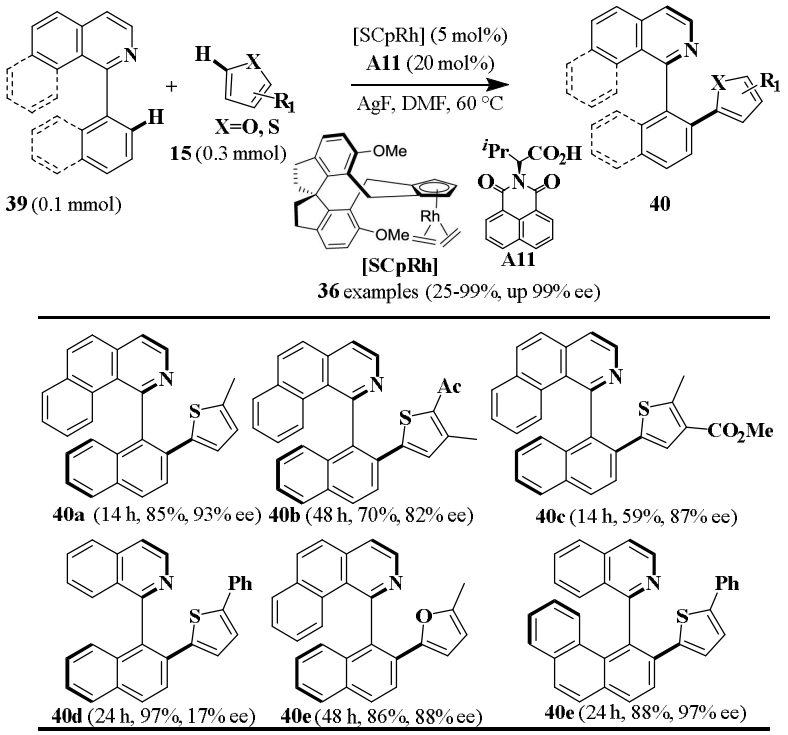


Scheme 13. Palladium-catalyzed site-selective C7 and C3 oxidative arylation of 4-EWG-1*H*-indazoles.

Recently, You and co-workers[49] have developed an elegant enantioselective twofold oxidative C–H arylation between 1-(naphthalene-1-yl)benzo[*h*]isoquinolines and various electron-rich heteroarenes such as thiophenes, furans, benzothiophenes, benzofurans. The reactions were conducted using 5 mol% of [SCpRh], 20 mol% of **A11** in the presence of 3 equiv of AgF in DMF at 60 °C. In a representative example, starting material **39** was treated with 2-methylfuran **15** under the above conditions to afford desired product **40a** in 94% ^{1}H-NMR yield (85% isolated yield) and in good enantioselectivity (93% ee). The absolute configuration of **40a** was assigned by X-ray diffraction analysis. In general, the reaction yields as well as the enanthioselectivities are not affected by the electronic nature of the substituents of the naphthalene ring. It is noticed that the reaction conducted with 1-(naphthalene-1-yl)isoquinoline **39** gave the expected product **40d** in 97% yield but in low enanthioselectivity (17% ee). When 1-(naphthalene-1-yl)isoquinoline **39** with substituents at position 8 of either the isoquinoline ring or the naphthalene ring were used, the enanthioselectivities were highly improved. Some selected examples are shown in Scheme 14.

In a recent interesting study, Wang *et al.*[50] reported the synthesis of 2-(2-arylphenyl)azoles by means of cobalt-catalyzed C–H/C–H cross-coupling reactions. As a model substrate, the authors used the biphenyl **41** containing a picolinamide as a directing group and benzo[*d*]oxazole **42** as an arylating agent. The optimized reaction conditions were found as following [$Co(OAc)_2$ (20 mol%), Ag_2CO_3 (3 equiv), sodium oleate (NaO-Ole) (0.5 equiv) at 135 °C in fluorobenzene for 40 h]. Under these conditions, the CDC between **41** and

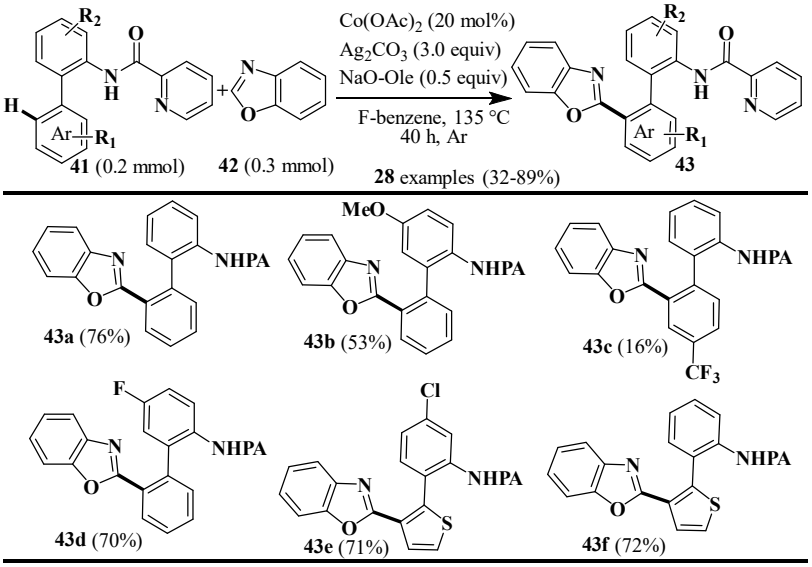
42 led to expected product **43a** in 76% ^{1}H NMR and in 71% isolated yield. The structure of **43a** was also elucidated by X-ray diffraction analysis. In this study, various DG groups were tested leading to no reaction or to low reaction yields compared to picolinamide. Also, only aromatic solvents were suitable and, therefore, no reaction was observed using DCE, TFE or DMF instead of fluorobenzene. However, the use of toluene or chlorobenzene gave the expected arylated product **43a** but in low yield compared to fluorobenzene. The concentration of the reaction mixture led to increased reaction yield. Also, the decrease of the base amount from 1 to 0.6 equivalents have shown improved reaction yields. Representative examples of synthesized 2-(2-arylphenyl)azoles are shown in Scheme 15.



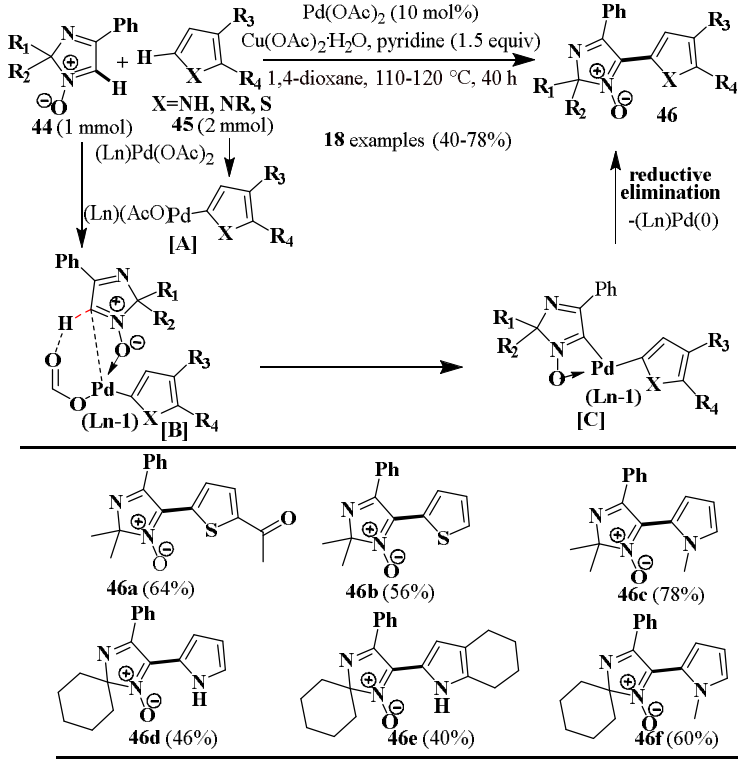
Scheme 14. Rhodium-catalyzed atroposelective oxidative C–H/C–H cross-coupling reaction of 1-aryl-isoquinoline derivatives with heteroarenes.

3. Oxidative Csp^2–H/Csp^2–H cross-coupling reactions between two heteroarenes

Considering the importance of *N*-oxide-based compounds in pharmaceuticals chemistry, Chupakhin *et al.*[51] established the regioselective oxidative arylation of 2*H*-imidazole-1-oxides **44** with pyroles and thiophenes **45** (Scheme 16). Under the following optimized reaction conditions, [pyrroles or thiophenes **45** (2 equiv), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2.H_2O$ (1.5 equiv), pyridine (1.5 equiv), 1,4-dioxane (5 mL) at 110-120 °C for 24 h], a small library of 5-heteroarylated 2*H*-imidazole-1-oxides **46** was obtained in yields ranging between 40% and 78% (see representative examples in Scheme 16). The findings from the H/D exchange experiments suggested that the intermediate **A** took place first which validate the crucial role of pyridine as ligand for the stabilization of the organometallic intermediate in this C–H activation process. Intermediate **A** appears to be coordinated with the oxygen center of 2*H*-imidazole 1-oxides **44** by the ligand-exchange mechanism to form intermediate **B**. Next, the chelate-controlled functionalization of the C1–H bond of nitrone by concerted metallation/ deprotonation transformations seems to give the intermediate **C**. Finally, reductive elimination generates the desired biheterocyclic **46**.

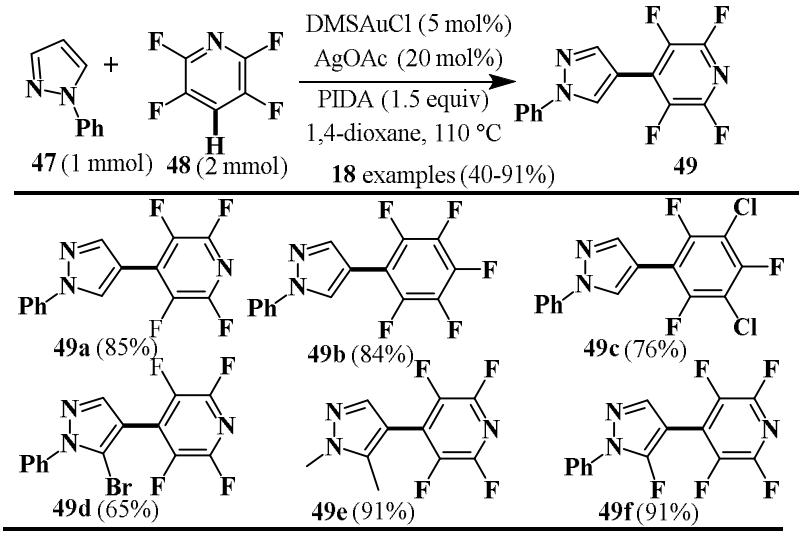


Scheme 15. Synthesis of 2-(2-arylphenyl)azoles by means of cobalt-catalyzed C–H/C–H cross-coupling reactions.



Scheme 16. Palladium-catalyzed cross-dehydrogenative coupling of 2*H*-imidazole-1-oxides.

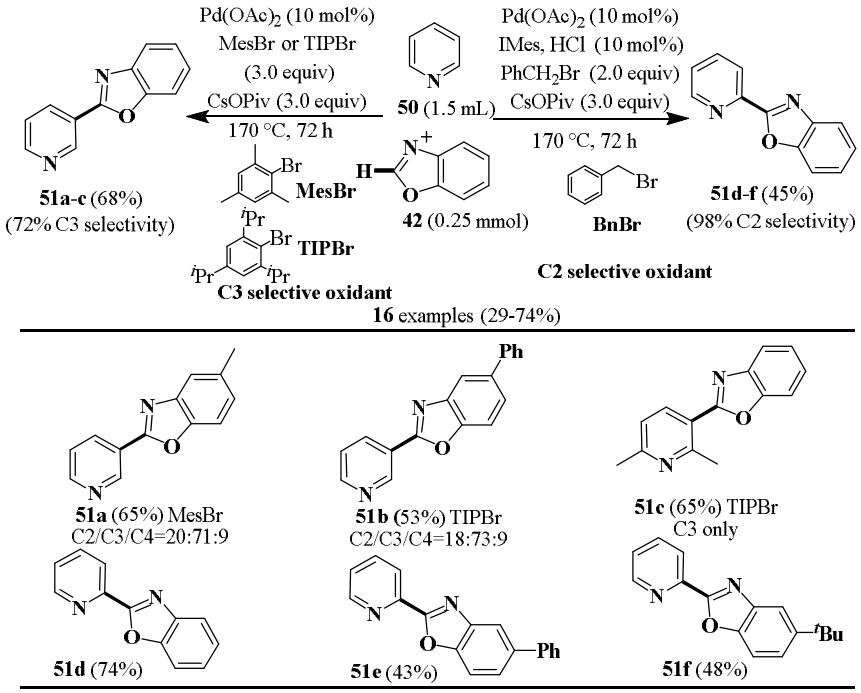
Recently Zhu *et al.*[52] disclosed that the cross-dehydrogenative arylation of pyrazoles **47** is achieved through cooperative Au/Ag dual catalysis in contrary to Au(I)/Au(III) catalytic cycle as routinely proposed for this kind of reactions (Scheme 17). Thus, the combination of experiment and DFT studies in addition to kinetic isotopic effect experiments and ^{19}F-NMR suggested that silver favors C–H activation of fluoroarenes **48** by a concerted metalation deprotonation process (CMD) while Au(III) activates the most electron rich position of pyrazoles **47**. A wide range of multifuoroarenes as arylating agents as well as *N*-arylpyrazoles or *N*-alkylpyrazoles bearing either electron-donating or electron withdrawing groups successfully underwent this oxidative arylation **49** in moderate to high yields.



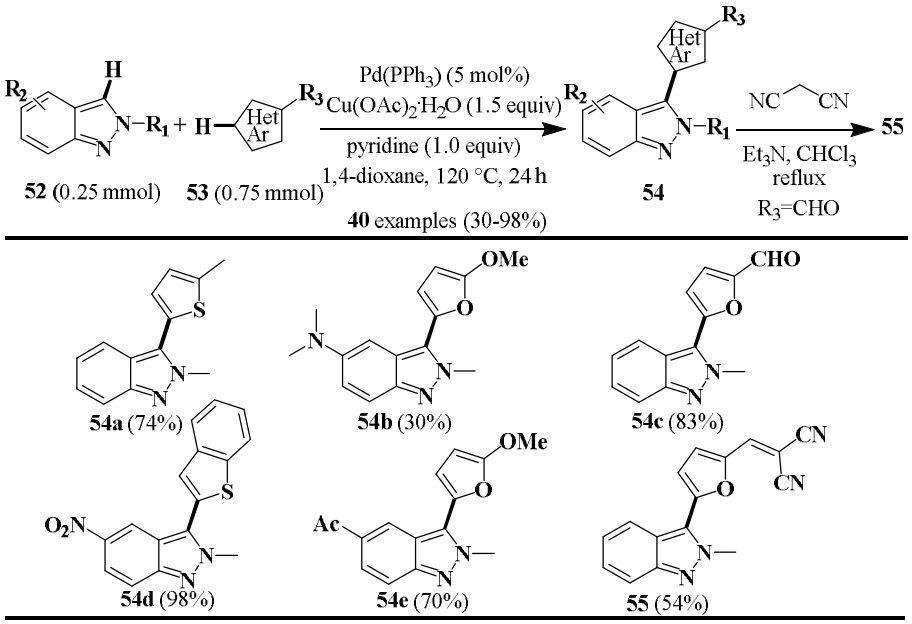
Scheme 17. Palladium-catalyzed cross-dehydrogenative coupling (CDC) of 2*H*-imidazole 1-oxides with pyrroles and thiophenes.

The introduction of organic halides as new oxidants for cross-dehydrogenative coupling of pyridines and benzoxazoles was initiated by Itami *et al.*[53] The ability of aryl bromides to direct CDC to the C3 position and of benzyl bromide to the C2 position has been demonstrated. The CDC reactions at the C3 position of pyridine **50** were carried out using benzoxazoles **42** in the presence of $Pd(OAc)_2$, MesBr or TIPBr as oxidant and CsOPiv at 170 °C for 17 h which led to expected products **51a-c** in yields ranging between 29 and 74% (Scheme 18). The reaction conditions were compatible with a variety of substituents on bezoxazoles (Me, Ph, ^{t}Bu, Cl). C3-selectivity was also observed when substituted pyridine as substrates were used regardless their steric or electronic nature. C2-selective CDC reaction was achieved in very high regioselectivities and in yields up to 74% when benzyl bromide was employed instead of aryl brimiodes as oxidant under previously established conditions **51d-f**.

You *et al.*[54] reported the palladium-mediated oxidative arylation of electron-deficient 2*H*-indazoles **52** with electron-rich heteroarenes **53**, namely, thiophene and furan derivatives. Under the established reaction conditions [$Pd(PPh_3)_4$, $Cu(OAc)_2.H_2O$, pyridine, 1,4-dioxane at 120 °C for 24 h], a large library of C3-heteroaryl-indazoles **54a-e** was prepared with moderate to excellent yields (30 to 98%) (Scheme 19). Remarkably, the designed arylation products as donor-acceptor-type biheteroaryl fluorophores were evaluated for their photophysical properties. Although the C3 substituted 2*H*-indazoles with either thienyl or furanyl moieties have similar emission wavelengths, the furanyl substituents afforded much higher quantum yields. Moreover, the compound **55** obtained from the Knoevenagel condensation of **54c** with malononitrile was shown to penetrate the cell membranes and is accumulated into the mitochondria of living cells. In addition, the cytotoxicity of **55** was evaluated in three HepG2 cell lines showing almost no effect on cell viability.

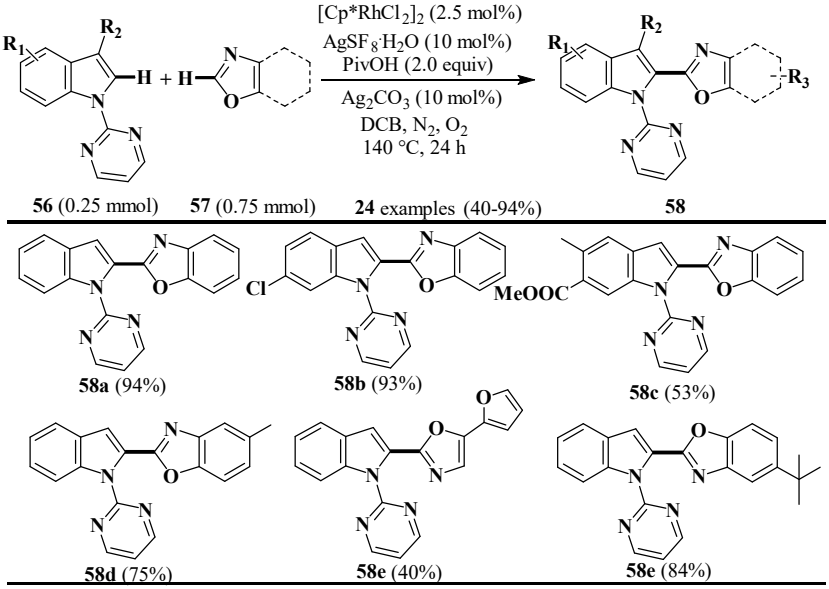


Scheme 18. Palladium-catalyzed cross-dehydrogenative coupling of pyridines and benzoxazoles.



Scheme 19. Palladium-catalyzed oxidative C–H/C–H cross-coupling of electron-deficient 2*H*-indazoles with electron-rich heteroarenes.

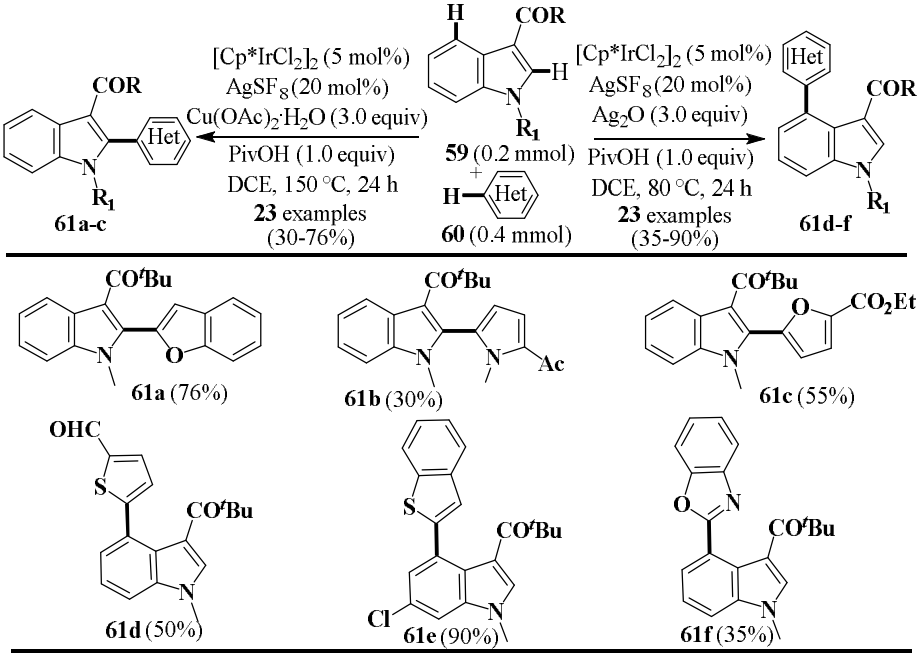
C2 Arylation of indoles **56** with oxazoles **57** under rhodium(III)-catalyzed C–H/C–H cross-couplig was reported by Lan and Wang.[55] The use of pyrimidyl at position C3 as a directing group led to excellent regionselectivity and good to excellent reaction yields (Scheme 20). Thus, the reaction conducted between various substituted indoles and non-substituted benzoxazole using $[RhCp^*Cl_2]_2$, $AgSbF_6$, PivOH, Ag_2CO_3 in DCB at 140 °C for 24 h under an O_2 led to expected C2 arylation products **58a-c** in yields ranging between 53% and 94%. When substituted benzoxazoles were used as arylating agents in the presence of non-substituted indole as substrates, the desired C2 arylated products **58d-e** were obtained in moderate to good yields (40 to 84%).



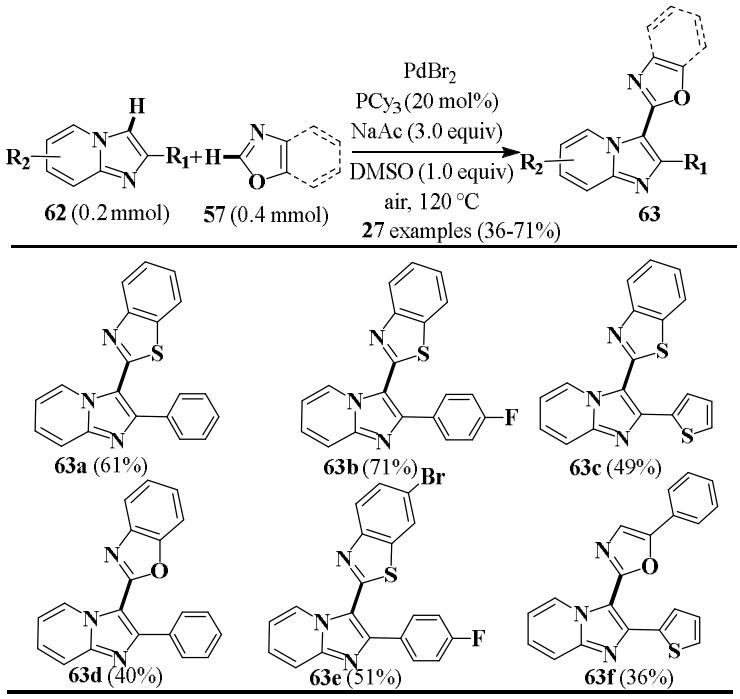
Scheme 20. Rhodium(III)-catalyzed oxidative C–H/C–H cross-coupling between indoles and oxazoles.

Two years later, You[56] reported an iridium-catalyzed C2/C4 regioselective C–H/C–H heteroarylation of indoles **59** and heteroaryl **60** after tuning the C–H activation conditions with the assistance of a pivaloyl group at the C3 position. The oxidative coupling using $[Cp^*IrCl_2]_2$ as a catalyst and $Cu(OAc)_2$ in 1,2-dichloroethane at 150 °C gave C2-heteroarylation of indole **61a-c** (yields were between 35 and 90%), whereas the reaction using the same catalyst and solvent in the presence of $Cu(OAc)_2{\cdot}H_2O$ as an oxidant, produced the C4-heteroarylation products **61d-e** in moderate to good yields (30 to 76%). According to this study and previous literature reports, the authors suggested that the C2-heteroarylation proceeded *via* a concerted metalation-deprotection, while the C4-heteroarylation was governed by a trimolecular electrophilic substitution (SE3) process. Representative examples of C2 and C4-heteroarylated indoles are listed in Scheme 21.

A palladium-catalyzed oxidative C–H/C–H cross-coupling of azoles with imidazo[1,2-*a*]pyridines **62** was reported by Zaho and co-workers.[57] Authors have found the optimized reaction conditions using $PdBr_2$ (10 mol%) as a catalyst, air as a terminal oxidant, PCy_3 (0.2 equiv) as a ligand and NaAc (1 equiv.) as a base in DMSO at 120 °C for 10 h. Various sensitive functional groups were well tolerated under the reaction conditions. The reaction yield was not affected by the electronic nature of the substituents and their position on the aryl unit of 2-arylimidazo[1,2-*a*]pyridines **62**. The replacement of aryl unit at position 2 by either thiophene, naphthalene or aliphatic groups led to expected products in moderate yields. The use of benzoxazole or oxazole instead of benzothiazole **57** as arylating agents provided the expected arylated products **63** in slightly lower yields. Some selected products were tested *in vitro* against various human cancer cells showing interesting anticancer activities. In some cases, those activities were similar to superior as compared with the positive control (5-fluorouracil). Representative examples are shown in Scheme 22.

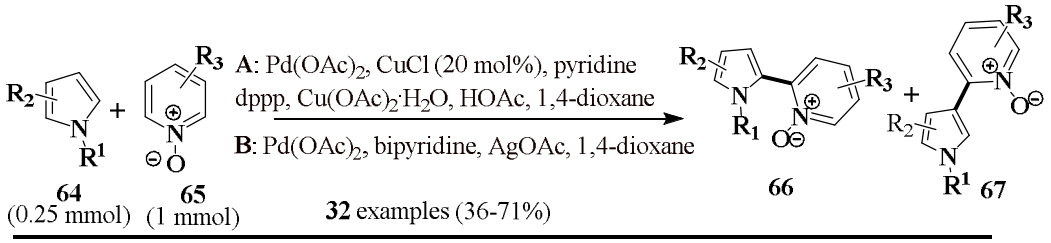


Scheme 21. Regioselective C4−H and C2−H heteroarylation of indoles with heteroarenes.



Scheme 22. Palladium-catalyzed oxidative C–H/C–H cross-coupling of imidazopyridines with azoles.

Tzschucke and Liu reported an oxidative C–H/C–H cross-coupling of pyrroles **64** and pyridine *N*-oxides **65** at either the *α*- or the *β*-position of pyrroles (Scheme 23).[58] $Pd(OAc)_2$ as a catalyst, 2,2′-bipyridine (bpy) as a ligand and AgOAc as a base, and acetic acid as an additive in 1.4-dioxane, promoted the activation of the *α* position with acceptable to good regioselectivities, while the $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$, water as co-catalyst, dppp as a ligand, CuCl and pyridine as additives in 1,4-dioxane, directed the arylation at *β* position with good to excellent selectivities. The *α*-aylated product **66a-f** were isolated in low to moderate yields (5 to 45%) in contrast, *β*-arylated products **67a-f** were obtained in moderate to good yields (26 to 80%) (Scheme 23 and Table1).



Scheme 23. Palladium-catalyzed regioselective dehydrogenative C–H/C–H cross-coupling of pyrroles and pyridine *N*-oxides.

Table 1

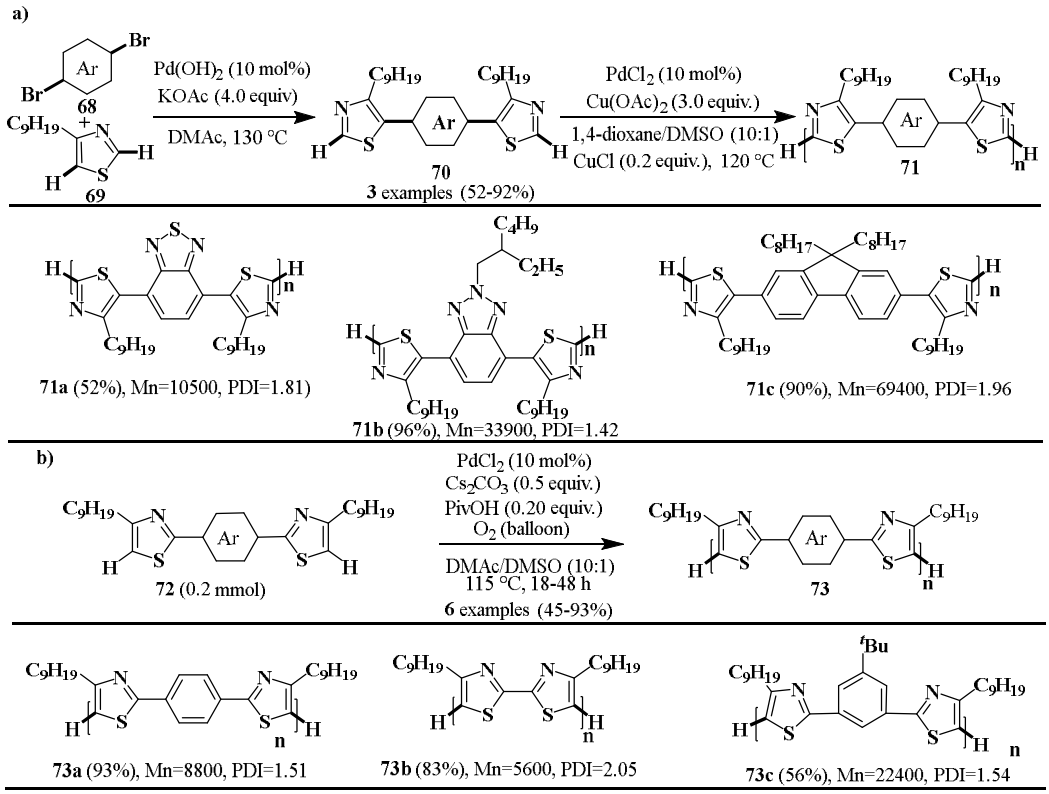
Entry	R^1	R^2	R^3	Yield[a]	67/66
a	Bn	H	4-CO_2Et	64 (33)	90:10 (20:80)
b	Bn	H	4-OMe	42 (36)	89:11 (56:44)
c	Bn	H	2-(2-pyridyl)	0 (16)	– (33:67)
d	Bn	H	Quinoline *N*-oxide	48 (29)	50:50 (10:90)
e	Bn	H	Isoquinoline *N*-oxide	50 (28)	75:25 (7:93)
f	Bn	H	Quinoxaline *N*-oxide	<5 (25)	– (<1:99)

[a]Yield of isolated product obtained under reaction conditions A. Value in parentheses refers to reaction conditions B.

Notably, in the cases of 2(2-pyridyl) as substituent of the pyridine *N*-oxide, the reaction did not work under conditions A, while under conditions B gave the desired product in very low yield and regioselctivity (*α*/*β*, 67/33). Interestingly, when quinolone *N*-oxide, isoquinoline *N*-oxide and pyrazine *N*-oxide were used as substrates instead of pyridine *N*-oxide, the regioselectivities were improved in favor of *α*-arylation products (regioselectivities ranged from 90% to 99%) (Table 1).

Oxidative direct arylation polymerization (Ox-DArP) can be considered as the most atom economical polymerisation technique, involving CH–CH bonds activation, without requiring a dihaloaryl monomer.[59] In 2016, the Wu and You's group reported a rapid access to 2,2′-bithiazole-based copolymers **71** using sequential palladium-catalyzed C–H/C–X and C–H/C–H coupling reactions. In the first step to synthesize monomer **70** by regioselective C5 arylation of thiazole **69** with aryl dihalides **68** using $Pd(OH)_2$, Ox-DArP at C2 of the monomer takes place, yielding polymers **71a-c** with an molecular weight (M_n) up to 69 kg/mol (Scheme 24a).[60]

In addition, the same group described the preparation of bithiazole-based polymers by means of C–H/C–H arylation catalyzed by $PdCl_2$ using O_2 as the sole oxidant.[61] Various *π*-conjugated polymers **73a-c** were thus obtained in yields ranging between 45 and 93% by C–H arylation of monomer **72** under the following reaction conditions: $PdCl_2$ (10 mol%), O_2 (balloon), Cs_2CO_3 (0.5 equiv), PivOH (0.2 equiv) in DMA/DMSO (10:1) at 115 °C, 18 to 48 h (Scheme 24b). The synthesized polymers have high number-average molecular weight ranging from 5600 to 33700. The photophysical properties of those polymers were evaluated showing promising opto-electronic applications (red abd NIR emissions, large Stokes shifts, good crystallinity in the thin film state, air and thermos-stability).

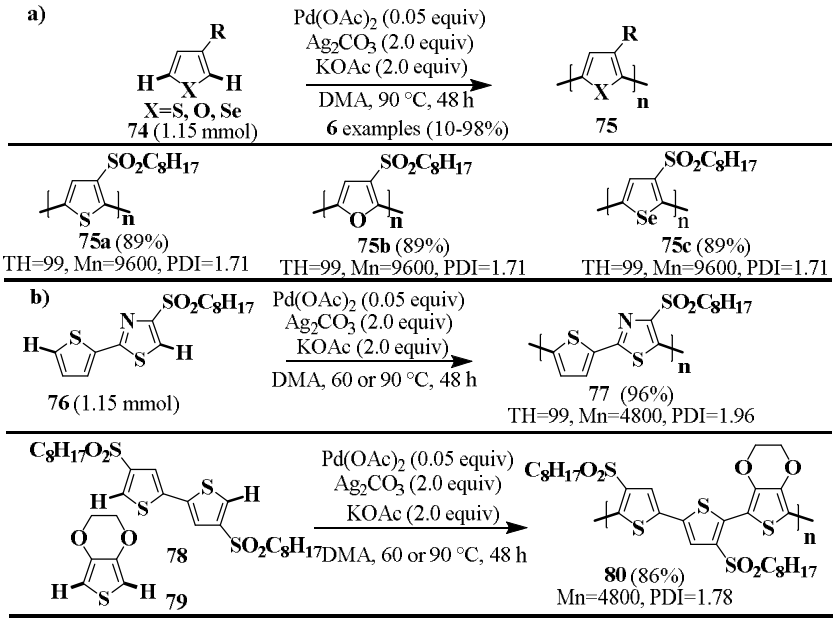


Scheme 24. Palladium-catalyzed C–H/C–H-type DArP of various bis(4-nonylthiazol-2-yl)arenes.

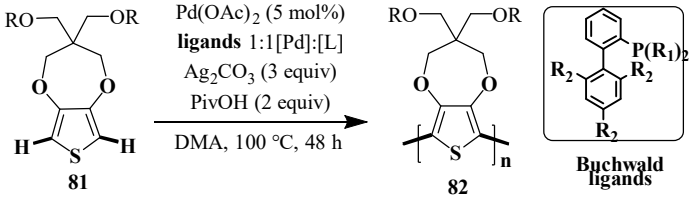
Two years later, the Chen group reported an efficient and mild palladium-catalyzed method for the preparation of π-conjugated polymers by oxidative direct arylation polymerization Ox-DArP.[62] Thus, the homopolymerization of 3-substituent monomers with sulfonyl-based directing group **74** under the optimized reaction conditions [$Pd(OAc)_2/Ag_2CO_3$ was employed as a catalyst/oxidant and KOAc as base in DMA at 90 °C] gave the expected poly(3-octylsulfonylthiophene) **75a** with the highly regioregular (HT) as high as 99%, M_n of 9.6×10^3 and PDI: 1.71 in a nearly quantitative yield 98% (Scheme 25a). Under the optimized conditions, a variety of thiophenes, furans and selenophenes bearing various functional groups, including ester, sulfone, sulfoxide, and oxadiazole, gave medium to good isolated yields and excellent regioselectivities. The optimized reaction conditions were also applied for both homopolymerization of **76** and copolymerization of **78** and **79** producing the expected homopolymerization **77** and copolymerization **80** products, respectively (Scheme 25b). The properties of polymer **77a** were compared with previous data reported for the same polymer. This demonstrates that Ox-DArP is able to produce polymers with properties similar to that obtained through other polymerization methods.

Recently, Reynolds and Collier[63] reported the preparation of a 3,4-propylenedioxythiophene-based polymers (ProDOT) **82** *via* Ox-DArP using C-H arylation at positions 2 and 5 of dihydroProDOT monomer **81**. The polymerizations of polyProDOTs *via* Ox-DArP proceeded using $Pd(OAc)_2$ as the catalyst, Ag_2CO_3 as the oxidant, K_2CO_3 as the base, and PivOH as the proton shuttle in the solvent *N*,*N*-dimethylacetamide (DMAc) at 100 °C for 48 h (Scheme 26). In the absence of an ancillary ligand, polyProDOT **82** was obtained with a number average molecular weight (M_n) of 8.1 kg/mol and a dispersity ($D=M_w/M_n$) of 1.8 was obtained in 57% yield. A series of the biaryl and dialkylphosphine functionalities (such as, CyJohnPhos, JohnPhos, XPhos, ^{t}BuXPhos, ^{t}BuBrettPhos) adding in a 1:1 molar ratio to $Pd(OAc)_2$ were screened giving rise to the desired products **82** in yields ranging between 20% and 94% (Table 2). The authors demonstrated that the

increase of the bulk of the alkylphosphine functionality produces polymers with lower molecular weights compared to ligand-less and less bulky alkylphosphines.



Scheme 25. Ox-DArP Synthesis of poly(3-substituted heteroarenes) and conjugated copolymers.



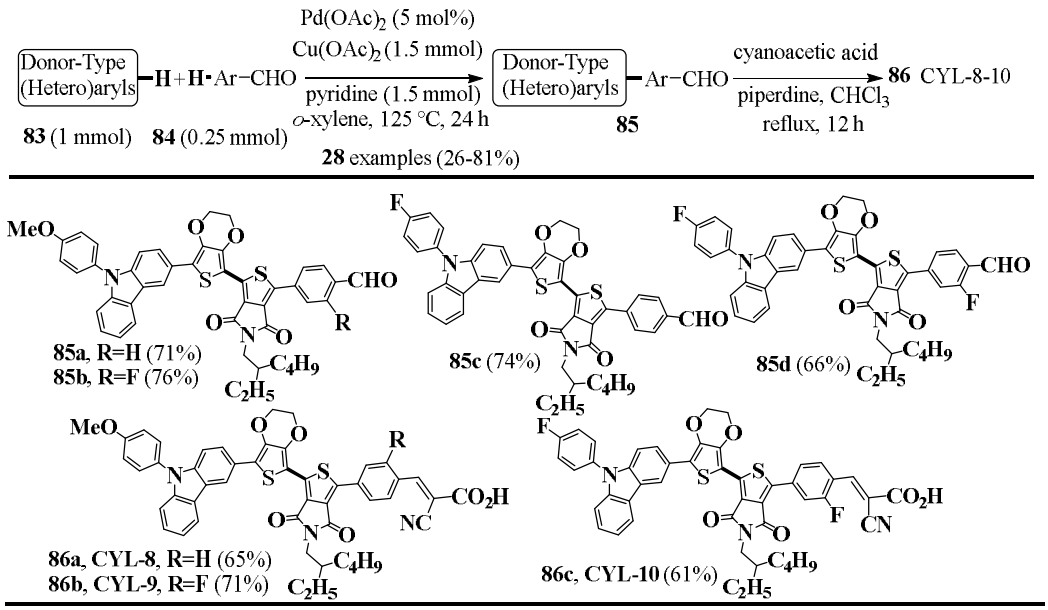
Scheme 26. Synthesis of PolyProDOT *via* oxi-Pd-Ox-DArP and buchwald ligands.

Table 2

Entry	Catalyst/ oxidant	ligand	Mnc (kg/mol)	Đc (Mw/Mn)	Yield (%)
1	$Pd(OAc)_2$/ Ag_2CO_3	none	8.1	1.8	57
2	$Pd(OAc)_2$/ Ag_2CO_3	CyJohnPhos	5.5	1.4	20
3	$Pd(OAc)_2$/ Ag_2CO_3	JohnPhos	6.6	1.6	75
4	$Pd(OAc)_2$/ Ag_2CO_3	XPhos	7.5	1.7	94
5	$Pd(OAc)_2$/ Ag_2CO_3	^{t}BuXPhos	12.5	1.6	92
6	$Pd(OAc)_2$/ Ag_2CO_3	^{t}BuBrettPhos	6.2	1.7	88

For the dye-sensitized solar cells applications, Lui *et al.*[64] optimized and applied the C–H/C–H cross-dehydrogenative coupling of heterocycles **83** with benzaldehyde derivatives **84** for the preparation of various D-p-A organic dyes **85**. Under the reaction conditions [$Pd(OAc)_2$, $Cu(OAc)_2$, pyridine, *o*-xylene, 125 °C, 24 h], a large library of compounds was prepared **85a-d** (Scheme 27). Three organic sensitizers

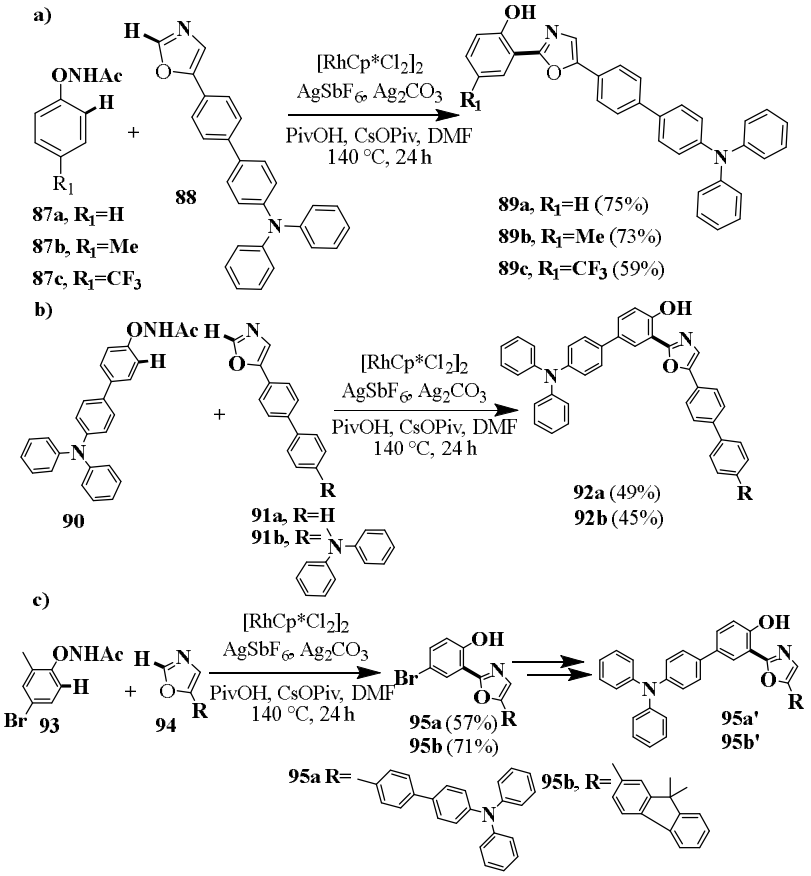
CYL-8-10 86 were evaluated for their UV-Vis absorption and electrochemical characteristics. Among the synthesized molecules, compound **CYL-8 86a** showed a very good power conversion efficiency of 4.85%.



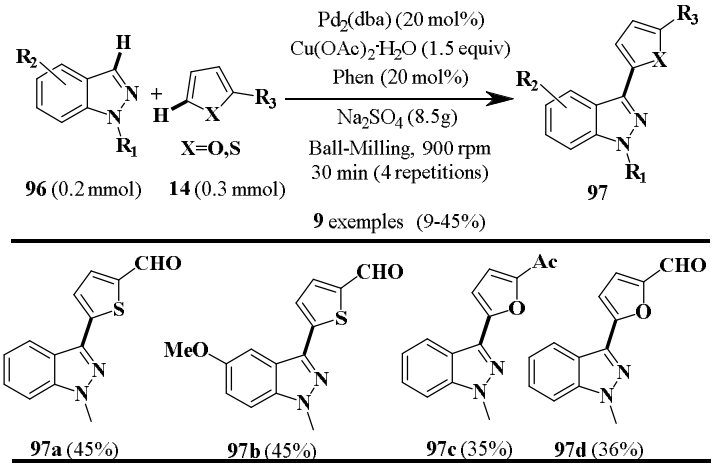
Scheme 27. Palladium-catalyzed C–H/C–H synthetic study directed toward dye-sensitized solar cells applications.

You, Zhou and co-workers[65] used C–H/C–H cross-coupling reaction to prepare either 2-(2'-hydroxyphenyl)oxazoles containing triphenylamine moiety **89a-c** and studied their applications in highly efficient deep-blue OLEDs (Scheme 28a). Later, they reported new analogs **92a** and **92b** containing either one or two triphenylamine and investigated their photoluminescence and electroluminescence properties (Scheme 28b).[66] Both molecules have shown highly efficient excited-state intramolecular proton transfer. Very recently, You *et al.* reported a new study using two new 2-(2'-hydroxyphenyl)oxazole analogs bearing either two triphenylamine moieties (compound **95a'** or one triphenylamine unit and one fluorene moiety **95b'**) (Scheme 28c).[67] The authors demonstrated that compound **95b'** is a mechanically induced single-molecule white-light emission based on excited-state intramolecular proton transfer. Interestingly, all the molecules used in these different studies were prepared using C–H/C–H dehydrogenative coupling under the following reaction conditions [$Cp^*RhCl_2]_2$, $AgSbF_6$, Ag_2CO_3, PivOH, CsOPiv in DMF at 140 °C under N_2 for 24 h]. The C–H/C–H cross-coupling reaction was employed in the last step for the synthesis of **89a-c** from aryles **87** and oxazole containing triphenylamine moiety **88** and **92a-b** from aryle containing triphenylamine moiety **90** with oxazoles **91** while in the case of **95a'** and **95b'** the reaction was employed in the first step using aryle **93** and oxazoles **94**.

Su and co-workers described an efficient mechanochemical method for palladium-catalyzed direct C3-heteroarylation of 1*H*-indazoles using low-cost copper oxidants.[68] Treatment of indazole **96** with thiophenes and furans **14** containing electron withdrawing substituents in the presence of $Pd(OAc)_2$ (10 mol %), 1,10-phen (20 mol %), and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) using silica gel as a grinding auxiliary in a planetary mill gave the C3-heteroarylated 1*H*-indazole derivatives **97a-d** in moderate yields (9-45%) (Scheme 29). The robustness of the developed protocols was further demonstrated by total mechanosynthesis of the intermediate of PLK4 inhibitor CFI-400945 and HIF-1α inhibitor YC-1.

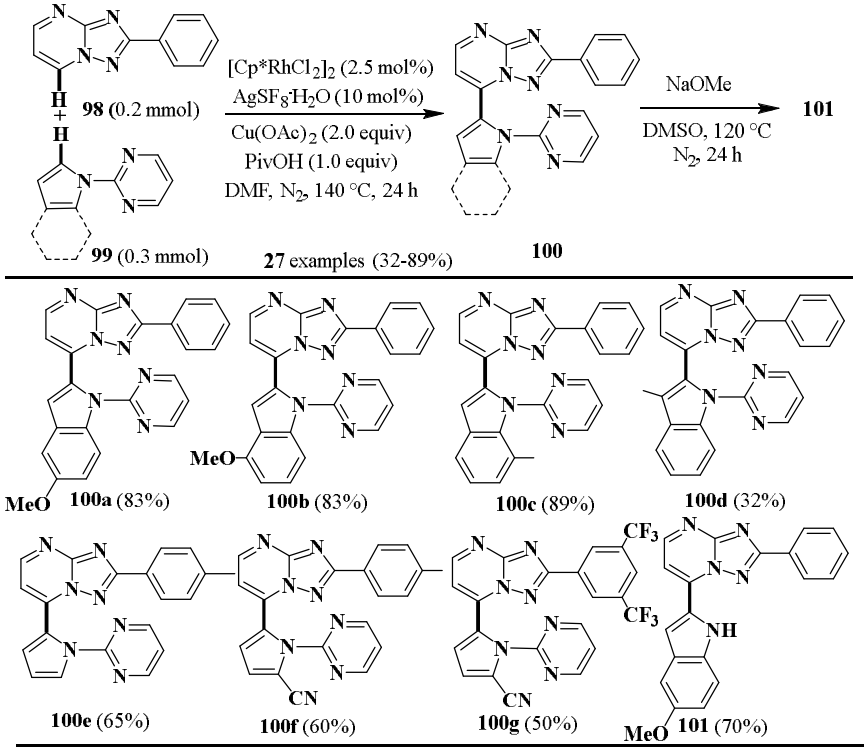


Scheme 28. Rhodium(III)-catalyzed oxidative C–H/C–H cross-coupling synthesi of 2-(20-hydroxyphenyl)oxazoles.



Scheme 29. Palladium-catalyzed C−H/C−H direct heteroarylation of N_1-protected 1*H*-indazoles.

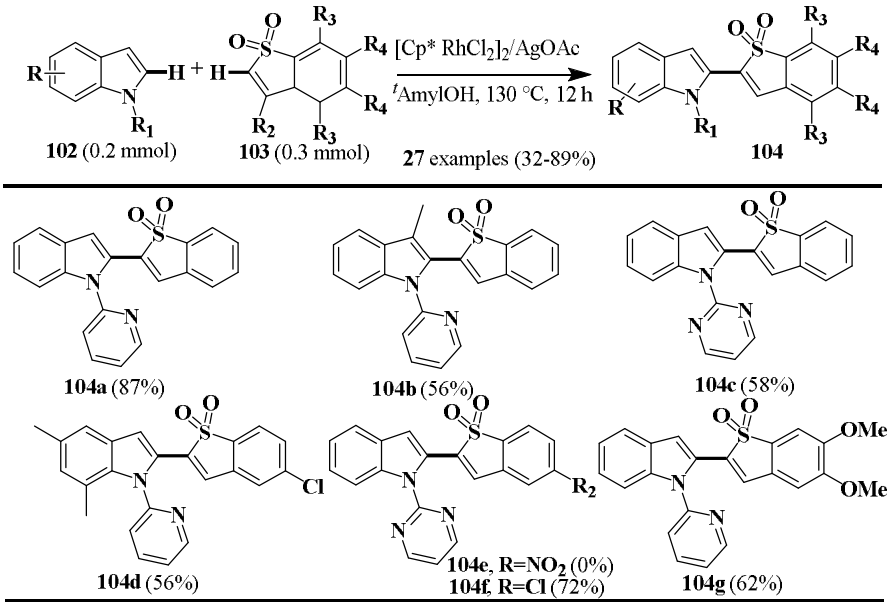
You and co-workers[69] employed rhodium(III)-catalyzed oxidative C−H/C−H cross-coupling of [1,2,4]triazolo[1,5-*a*]pyrimidines (TAP) **98** with indoles and pyrroles **99** as coupling partners to synthesize 7-(indol-2-yl)TAPs or 7-(pyrrol-2-yl)TAPs **100**. Pyrimidine was selected as the directing group to achieve the C2-selective C−H/C−H cross-coupling of indoles with TAPs.[70] The oxidative coupling using $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2$ as oxidant in DMF gave 7-(indol-2-yl)TAPs coupling products in good to excellent yields (Scheme 30). A wide variety of C2-arylated indoles and pyrroles was successfully synthesized by this strategy. However, the 3-substituted indole provided the corresponding product **100d** in low yield, probably due to steric hindrance. The scope of the reaction could also be extended to some pyrrole derivatives, affording 7-(pyrrol-2-yl)TAPs **100e-j** in good yields. The directing group can be easily removed from indole and pyrrole to achieve the corresponding free indoles **101** or pyrroles in moderate to good yields. Extensive research on the structure and photophysical properties of these compounds indicating that 7-(indol-2-yl)TAPs would undergo an excited-state intramolecular proton transfer (ESIPT) fluorophores process and mainly exhibit the keto-form emission, while 7-(pyrrol-2-yl)TAPs only show the enol-form emission.



Scheme 30. Rhodium-catalyzed oxidative C−H/C−H cross-coupling of [1,2,4]triazolo[1,5-*a*]pyrimidines **99** with indoles and pyrroles.

Kumaran and Parthasarathy[71] established other rhodium(III)-catalyzed directing-group-assisted oxidative arylation of *N*-pyridinylindoles **102** with electron-deficient benzo[*b*]thiophene1,1-dioxide **103**. The oxidative coupling using $[RhCp^*Cl_2]_2$ as a catalyst and AgOAc as an oxidant in *t*-amylalcohol gave arylated benzo[*b*]thiophene 1,1-dioxide **104a** in 87% yield. This transformation exhibited a good substrate scope for both coupling partners, with the exception of electron-withdrawing 5-nitrobenzo[*b*]-thiophene 1,1-dioxide **103** failed to give expected product **104f** (Scheme 31). Notably, 5-chlorobenzo[*b*]thiophene-1,1-dioxide reacted well with *N*-pyridinylindole. To further demonstrate the utility of the methodology, the oxidative couplings of

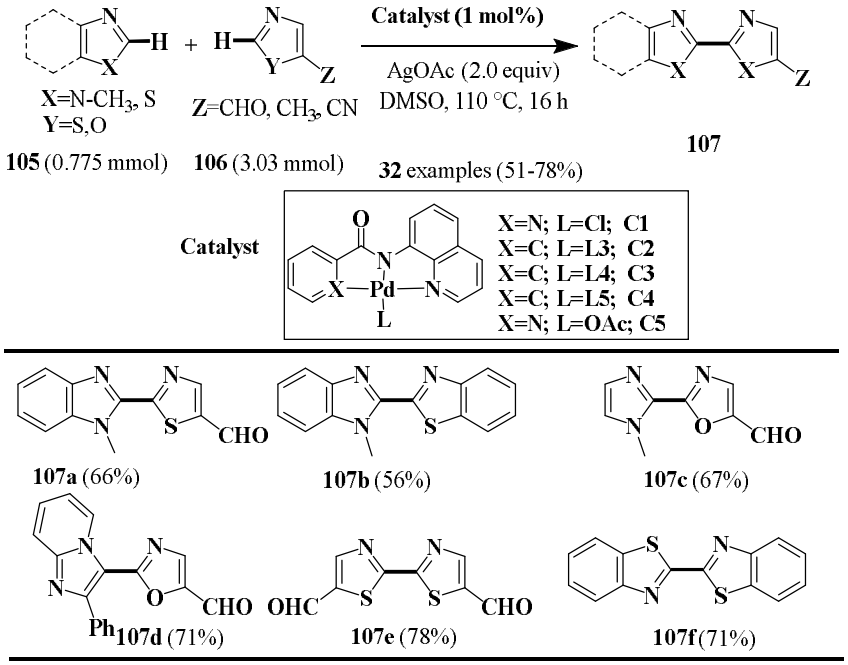
bis-sulfone were carried out under the standard conditions to furnished mono arylated product in 42% yield along with bis-arylated product in 54% yield (Scheme 31).



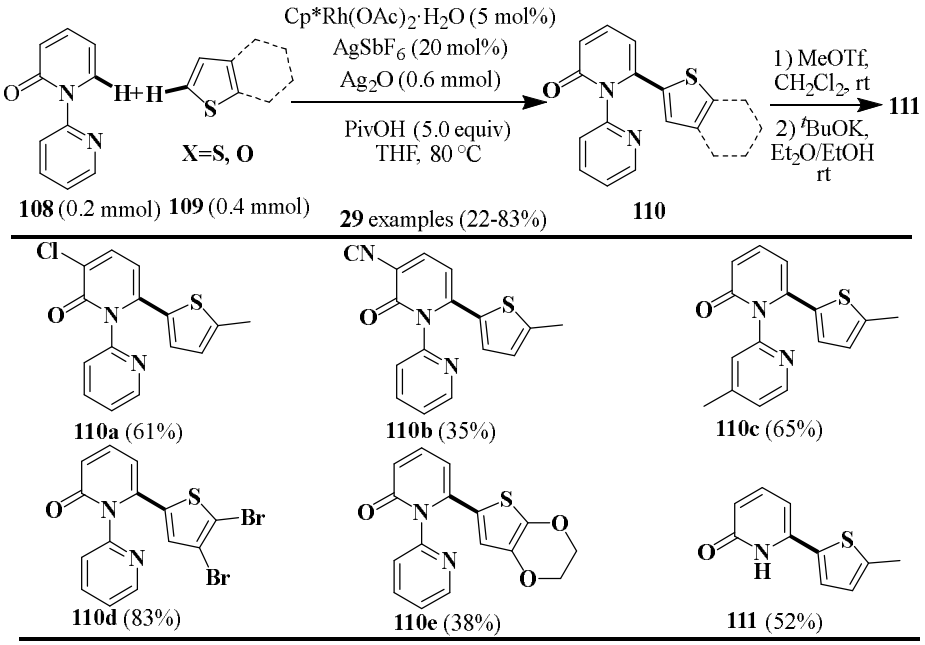
Scheme 31. Rhodium-catalyzed directing-group-assisted oxidative arylation of *N*-pyridinylindoles with benzo[*b*]thiophene1,1-dioxide.

Pincer complexes play an important role in organometallic chemistry. Joshi and co-workers[72] described a series of new class of palladium(II) pincer complexes (**C1−C4)** having NNN and CNN coordination modes and tested their catalytic activities and reusability (Scheme 32). The structure and bonding modes of these complexes were confirmed by single-crystal X-ray diffraction analysis. These complexes were found to be efficient catalysts for the cross dehydrogenative coupling (CDC) reactions of two heteroarenes including benzimidazole, imidazole, benzothiazole, imidazopyridine, thiophene, and furan **105** with benzothiazole, benzoxazole, thiazole, and oxazole **106** using only 1 mol % of catalyst. The catalyst showed excellent tolerance toward different functional groups affording corresponding heterocoupled products **107a-f** in good yields (51-78% yield). The NNN-Pd catalyst **C1** could be recycled up to four consecutive cycles with only a minor loss in its efficiency. A plausible mechanism for the CDC reaction was proposed based on several control experiments, and it was shown that acetate analogue of the palladium catalyst (C5) is an active catalyst and it is generated in situ during the catalytic reaction (Scheme 32).

More recently, Pan and co-workers[73] established rhodium(III)-catalyzed controlled C6-selective oxidative C–H/C–H cross-coupling of 2-pyridones **108** with thiophenes **109** to synthesize the 6-thiophenyl pyridin-2(1*H*)-one derivatives **110a-e**. The *N*-2-pyridyl proved to be the best directing group in this reaction, as no coupling product was observed when *N*-methyl- and *N*-phenyl-2-pyridones were used as substrates. The oxidative coupling using $[Cp^*RhCl_2]_2$ as the catalyst in the combination with $AgSbF_6$, Ag_2O as oxidant and PivOH in CH_2Cl_2 gave the corresponding heteroarylated 2-pyridones in moderate to good yields (Scheme 33). This synthetic methodology was extended to a broad scope of various *N*-pyridyl-2-pyridones and coupling partners. The reaction exhibited high functional group compatibility, including aldehyde, cyano, nitro and halide groups. In addition, thiophenes with strong electron-donating groups and benzofuran could be heteroarylated in relative lower yields under the reaction conditions. Moreover, the directing group can be easily removed from **110c** to achieve 6-(5-methylthiophen-2-yl)pyridin-2(1*H*)-one **111** with free *N–H* group in 52% yield.

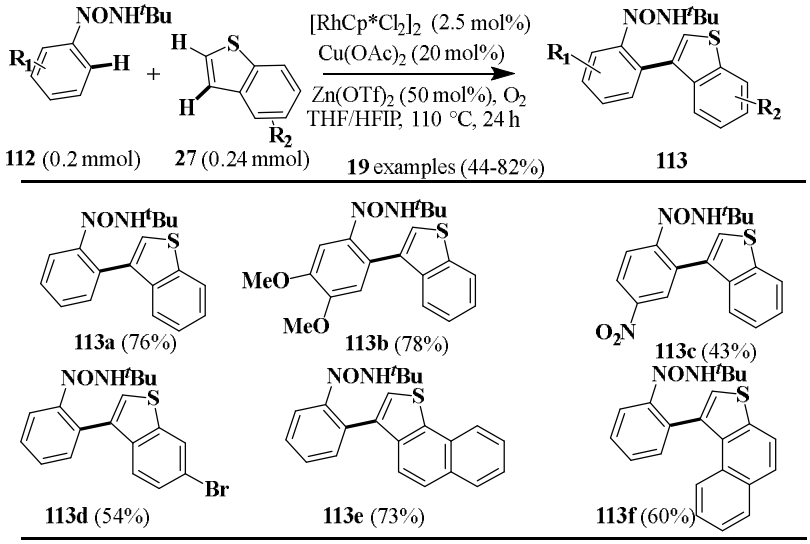


Scheme 32. Palladium complexes of NNN/CNN pincer ligands for oxidative C−H/C−H cross-coupling of heteroarenes.



Scheme 33. Rhodium(III)-catalyzed controlled C6-selective oxidative C−H/C−H cross-coupling of 2-pyridones with thiophenes.

The You group[74] described an interesting study of rhodium regioselective control in aerobic oxidative C−H/C−H coupling for C3-arylation of benzothiophenes **27** with aryle **112**. The optimized catalytic system, composed of $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (20 mol%), and $Zn(OTf)_2$ (50 mol %) in THF/HFIP at 110 °C under an O_2 atmosphere, gave the desired C3-arylated benzothiophene **113a** in 76% yield with a C3/C2 ratio of >20:1 (Scheme 34). It is worth noting that this transformation is accomplished using molecular oxygen as the environmentally benign terminal oxidant in combination with only 20 mol% $Cu(OAc)_2$. The detailed mechanistic experiment studies and DFT calculations provided clear evidence for the crucial roles of OTf^- and OAc^- anions in the rhodium-catalyzed C−H/C−H cross-coupling reactions between benzothiophenes and DG-containing arenes. Under the optimized conditions, the N-(*t*-butyl)benzamides with both electrondonating and electron-withdrawing groups were effective substrates, affording the C3-arylated products **113a-f** in good yields and excellent regioselectivities (no C2-regioisomer was detected by GC-MS analysis).

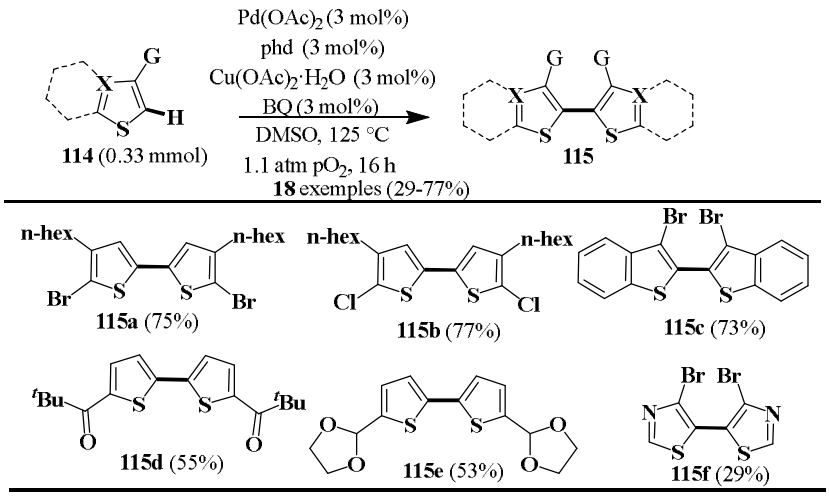


Scheme 34. Rhodium regioselective control in aerobic oxidative C−H/C−H coupling for C3-arylation of benzothiophenes.

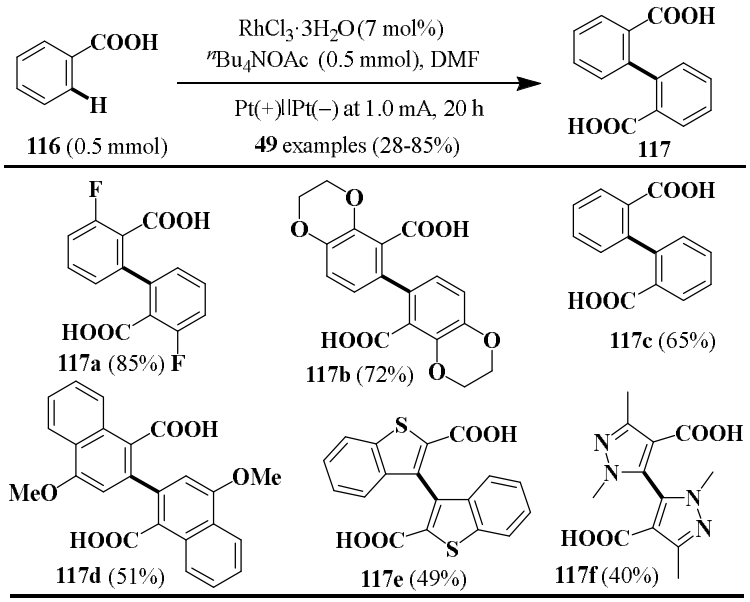
In 2020, Stahl and co-workers[75] reported a novel Pd(II) catalyst system, employing 1,10-phenanthroline-5,6-dione (phd) as the ancillary ligand, that enables aerobic oxidative homocoupling of 2-bromothiophenes and other related heterocycles **114**. This palladium-catalyzed oxidative homocoupling proceeds using $Pd(OAc)_2$, phd, $Cu(OAc)_2{\cdot}H_2O$, 1,4-benzoquinone (BQ) (3 mol % of each) in DMSO at 120 °C under 1.1 atm O_2 for 16 h leading **115a** in 75% yield (Scheme 35). Under the optimized reaction conditions, a series of 2-halo-3-alkylthiophenes and related heterocycles react smoothly to afford desired 2,2-bithiophenes **115a-f** in yields ranging between 29 and 77%. Dihalogenated substrates were also employed giving moderate-to-good yields. Moreover, the authors achieved a gram-scale oxidative coupling of 2-bromo-3-hexylthiophene derivative under the standard conditions generating **115a** in 90% isolated yield.

In 2021, Gooben and co-workers[76] developed rhodium-catalyzed electrocatalytic dehydrogenative C−H/C−H coupling of benzoic cids **116** to access 2,2′-biaryldicarboxylate. The reaction proceeded smoothly in the presence of only 0.3 mol % $RhCl_3{\cdot}3H_2O$ as the catalyst in DMF employed as the solvent. The presence of acetate in the electrolyte was found essential to promote the cross-coupling in high yields. The reaction proceeds better at a temperature of 80 °C and current densities between 0.5 and 3.0 mA (Scheme 36). This protocol exhibited a broad substrate scope and tolerated diverse functionalities. Both electron-rich and electron-deficient benzoic acids, bearing substituents in the *ortho*-, *meta*-, or *para*-position were effective for the transformation into **117** (28-85% yield, 49 examples). This rhodium-catalyzed protocol uses an electric current as an inexpensive and wastefree oxidant, which makes the reaction more sustainable, and can be

conducted without any precautions with regard to the exclusion of air and moisture. In addition, this reaction could be easily performed at multigram scale with 3% catalyst loading.



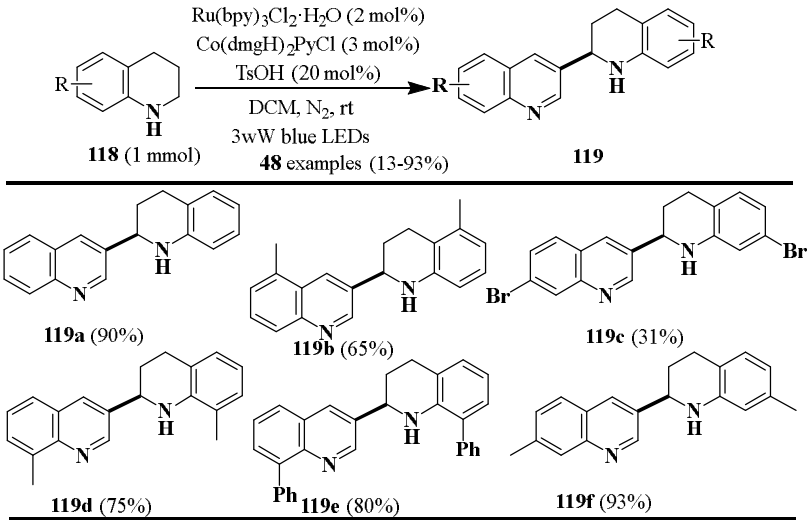
Scheme 35. Palladium-catalyzed aerobic oxidative coupling of thiophenes.



Scheme 36. Synthesis of 2,2′-biaryldicarboxylate *via* rhodium(III)-catalyzed electrocatalytic dehydrogenative C−H/C−H coupling of benzoic acids.

Visible-light photoredox catalysis has been extensively studied. Ru involving visible-light photoredox catalysis has been used in oxidative C−H/C−H cross-coupling reactions. Luo and co-workers[77] established a visible-light photoredox mediated dehydrogenative coupling of 1,2,3,4-tetrahydroquinoline (THQs) **118** to synthesize unsymmetric coupling product **119**. The protocol involved a combining Ru/Co mediated photoredox dehydrogenation and acid promoted enamine/iminium tautomerization. Control experiments

indicated that acid, photocatalyst, cobalt catalyst, and visible light were essential in this reaction, and no desired reaction was observed in their absence (Scheme 37). THQs with a variety of substitutes on the phenyl moiety were tested in this reaction which afforded the desired β-arylation adducts with good to excellent yields.



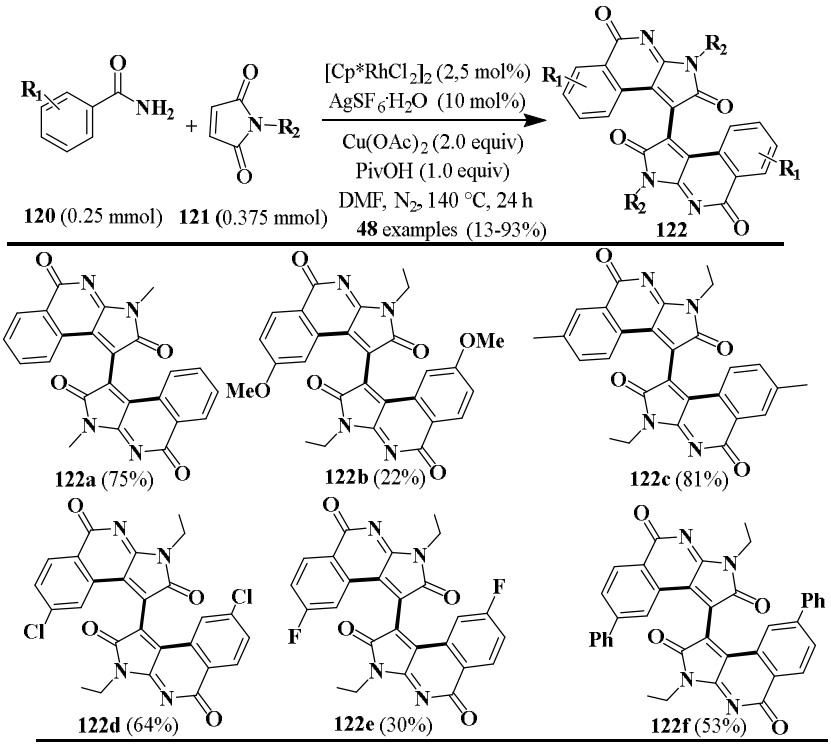
Scheme 37. Visible-light photoredox mediated dehydrogenative coupling of 1,2,3,4-tetrahydroquinoline.

Kumar and co-workers[78] reported a procedure for the synthesis of dimeric 2*H*-pyrrolo[2,3-*c*]isoquinoline-5(3*H*)-diones *via* a ruthenium(II)-catalyzed cascade C−C/C−N/C−C bond formation sequence domino coupling of benzamide and *N*-methylmaleimide. The reaction of benzamide **120** and *N*-methylmaleimide **121** with $[RuCl_2(p\text{-cymene})]_2$, $Cu(OAc)_2 \cdot H_2O$, and $AgBF_4$ in 1,2-dichloroethane at 100 °C for 5 h afforded dimeric pyrrolo[2,3-*c*]isoquinoline-2,5(3*H*)-dione derivatives **122a-e** in 25-81% yields (Scheme 38). Overall, this transformation was compatible with a wide range of substituted benzamides and maleimides. Unfortunately, the *p*-nitrobenzamide and hetreoaromatic benzamide were not compatible under standard conditions. The resulting products showed a substituent-dependent tunable photoluminescence in the orange-red region with reasonably large stokes shifts and interesting redox properties.

4. Conclusions

The recent advances made in direct dehydrogenative C−H functionalization of aryles and heteroaryles have been reviewed. The focus has been made on the oxidative coupling reactions employing 4d and 5d transition metal as catalysts (Pd, Ru, Rh, Ir). Thus, the cross-hydrogenative coupling between an heteroarene and an arene as well as the Csp^2−H/Csp^2−H coupling between two different heteroarenes (including homocoupling of heteroarenes) have been discussed and summarized. The most important aspects related to reaction conditions, progress and results have been discussed, such as scope and limitations of reactions, mechanism and regioselectivity.

In some cases, the site selectivity functionalization and relevant applications of the synthesized (hetero)arylated heteroarenes have also been highlighted. Despite the advantages offered by this environmentally friendly C−H/C–H functionalization reactions, several challenges remain to be solved like the lack of regioselectivity and the use of metal catalysts, sometimes in high loading, which can be expensive and, ocasionally, even toxic. To overcome the limitations of this dehydrogenative C–H functionalization method, many efforts have been made by researchers. Thus, by means of directing groups to control the regioselectivity, very good results could be obtained. In addition, the reduction more and more of catalyst loading will undoubtedly have a very positive impact on both the environment and the reaction's cost.



Scheme 38. Ruthenium(II)-catalyzed synthesis of dimeric 2*H*-pyrrolo[2,3-*c*]isoquinoline-2,5(3*H*)-diones.

Acknowledgements

The authors acknowledge Euromed University of Fes, Cadi Ayyad University and Ibn Zohr University for funding.

References

1. Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192-2452.
2. Jagtap, R. A.; Punji, B. *Asian J. Org. Chem.* **2020**, *9*, 326-342.
3. Wang, D.; Désaubry, L.; Li, G.; Huang, M.; Zheng, S. *Adv. Synth. Catal.* **2021**, *363*, 2-39.
4. Liu, W.; Li, Y.; Xu, B.; Kuang, C. *Org. Lett.* **2013**, *15*, 2342-2345.
5. Vasseur, A.; Muzart, J.; Le Bras, J. *Chem. Eur. J.* **2011**, *17*, 12556-12560.
6. Vasseur, A.; Harakat, D.; Muzart, J.; Le Bras, J. *Adv. Synth. Catal.* **2013**, *355*, 59-67.
7. Li, B. J.; Shi, Z. J. *Chem. Soc. Rev.* **2012**, *41*, 5588-5598.
8. Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138-12204.
9. Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787-8863.
10. Yang, Z.; Yu, J. T.; Pan, C. *Org. Biomol. Chem.* **2021**, *19*, 8442-8465.
11. Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74-100.
12. Miao, J.; Ge, H. *European J. Org. Chem.* **2015**, *2015*, 7859-7868.
13. Zhao, Y.; Xia, W. *Org. Biomol. Chem.* **2019**, *17*, 4951-4963.
14. Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 5142-5148.
15. El Kazzouli, S.; Koubachi, J.; El Brahmi, N.; Guillaumet, G. *RSC Adv*., **2015**, *5*, 15292-15327
16. Faarasse, S.; El Kazzouli, S.; Naas, M.; Jouha, J.; Suzenet, F.; Guillaumet, G. *J. Org. Chem*. **2017**, *82*, 12300-12306

17. Faarasse, S.; El Kazzouli, S.; Suzenet, F.; Guillaumet, G. *J. Org. Chem*. **2018**, *83*, 12847-12854
18. Gambouz, K.; El Abbouchi, A.; Nassiri, S.; Suzenet, F.; Bousmina, M.; Akssira, M.; Guillaumet, G.; El Kazzouli, S. *Molecules* **2020**, 25, 2820-2831
19. Gambouz, K.; El Abbouchi, A.; Nassiri, S.; Suzenet, F.; Bousmina, M.; Akssira, M.; Guillaumet, G.; El Kazzouli, S. *Eur. J. Org. Chem.* **2020**, *2020*, 7435-7439.
20. Faarasse, S.; El Kazzouli, S.; Bourzikat, O.; Bourg, S.; Aci-Sèche, S.; Bonnet, P.; Suzenet, F.; Guillaumet, G. *Adv. Synth. Catal*. **2021**, *363*, 3937-3945.
21. Boujdi, K.; El Brahmi, N.; Dubreuil, S.; Mathé-Allainmat, M.; Akssira, M.; Guillaumet, G.; Lebreton, J.; El Kazzouli, S. *Synthesis* **2022**, *54*, 4834-4842.
22. Naas, M.; El Kazzouli, S.; Essassi, E. M.; Bousmina, M.; Guillaumet, G. *Org. Lett*. **2015**, *17*, 4320-4323.
23. Koubachi, J.; El Brahmi, N.; Guillaumet, G.; El Kazzouli, S. *Eur. J. Org. Chem.* **2019**, *2019*, 2568-2586.
24. El Brahmi, N.; Koubachi, J.; Guillaumet, G.; El Kazzouli, S. in *Targets in Heterocyclic Systems,* Attanasi, O. A.; Gabriele, B; Merino, P.; Spinelli, D.; Eds.; Italian Chemical Society, Rome **2020**, *24*, 130-157.
25. Santoro, S.; Kozhushkov, S. I.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2016**, *18*, 3471-3493.
26. Dhawa, U.; Kaplaneris, N.; Ackermann, L. *Org. Chem. Front.* **2021**, *8*, 4886-4913.
27. Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851-863.
28. Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170-1214.
29. Varun, B. V.; Dhineshkumar, J.; Bettadapur, K. R.; Siddaraju, Y.; Alagiri, K.; Prabhu, K. R. *Tetrahedron Lett.* **2017**, *58*, 803-824.
30. Mao, S.; Li, H.; Shi, X.; Soulé, J. F.; Doucet, H. *ChemCatChem* **2019**, *11*, 269-286.
31. Yang, Y.; You, J. *Prog. Chem.* **2020**, *32*, 1824-1834.
32. Yang, S.; Cheng, R.; Zhao, T.; Luo, A.; Lan, J.; You, J. *Org. Lett.* **2019**, *21*, 5086-5090.
33. Tezuka, N.; Hirano, K.; Uchiyama, M. *Org. Lett.* **2019**, *21*, 9536-9540.
34. Wang, Z.; Wang, F.; Liu, Z.; He, S.; Pu, X.; Yang, Y.; Gao, G. *Chem. Commun.* **2019**, *55*, 10599-10602.
35. Du, C.; Li, P. X.; Zhu, X.; Suo, J. F.; Niu, J. L.; Song, M. P. *Angew. Chem. Int. Ed.* **2016**, *55*, 13571-13575.
36. Hu, J.; Li, G.; Yuan, C.; Huang, Z. Bin; Shi, D. Q.; Zhao, Y. *Org. Lett*. **2016**, *18*, 5998-6001.
37. Aoki, H.; Saito, H.; Shimoyama, Y.; Kuwabara, J.; Yasuda, T.; Kanbara, T. *ACS Macro Lett.* **2018**, *7*, 90-94.
38. Laha, J. K.; Sharma, S.; Bhimpuria, R. A.; Dayal, N.; Dubey, G.; Bharatam, P. V. *New J. Chem.* **2017**, *41*, 8791-8803.
39. Ran, Y.; Yang, Y.; You, H.; You, J. *ACS Catal*. **2018**, *8*, 1796-1801.
40. Vanjari, R.; Guntreddi, T.; Singh, K. N. *Chem. Asian J.* **2016**, *11*, 696-699.
41. Li, S. S.; Qin, L.; Dong, L. *Org. Biomol. Chem.* **2016**, *14*, 4554-4570.
42. Li, X.; Dong, Y.; Qu, F.; Liu, G. *J. Org. Chem.* **2015**, *80*, 790–798.
43. Tan, G.; You, Q.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 6309–6313.
44. Yu, C.; Patureau, F. W. *Angew. Chem. Int. Ed.* **2019**, *58*, 18530-18534.
45. Kianmehr, E.; Fardpour, M.; Kharat, A. N. *Eur. J. Org. Chem.* **2017**, *2017*, 3017-3021.
46. Faarasse, S.; El Brahmi, N.; Guillaumet, G.; El Kazzouli, S. *Molecules* **2021**, *26*, 5763-5801.
47. Nassiri, S.; Bousmina, M.; Suzenet, F.; Guillaumet, G.; El Kazzouli, S. *Eur. J. Org. Chem.* **2023**, *26*, e202300730.
48. Ouazzani Chahdi, C.; Boujdi, K.; El Brahmi, N.; Mathé-Allainmat, M.; Mouhi Eddine, H.; Akssira, M.; Guillaumet, G.; Lebreton, J.; Koubachi, J.; El Kazzouli, S. *Asian J. Org. Chem.* **2023**, *12*, e202300285.
49. Wang, Q.; Zhang, W. W.; Song, H.; Wang, J.; Zheng, C.; Gu, Q.; You, S. L. *J. Am. Chem. Soc.* **2020**, *142*, 15678-15685.
50. Wang, X.; Chen, Y.; Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2020**, *22*, 9331-9336.
51. Akulov, A. A.; Varaksin, M. V.; Charushin, V. N.; Chupakhin, O. N. *ACS omega* **2019**, *4*, 825-834.
52. Li, W.; Yuan, D.; Wang, G.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. *J. Am. Chem. Soc.* **2019**, *141*, 3187-3197.
53. Yamada, S.; Murakami, K.; Itami, K. *Org. Lett.* **2016**, *18*, 2415-2418.
54. Cheng, Y.; Li, G.; Liu, Y.; Shi, Y.; Gao, G.; Wu, D.; Lan, J.; You, J. *J. Am. Chem. Soc*. **2016**, *138*, 4730-4738.
55. Wang, Y.; Lan, J. *Sci. China Chem.* **2018**, *61*, 200-205.
56. Chen, S.; Zhang, M.; Su, R.; Chen, X.; Feng, B.; Yang, Y.; You, J. *ACS Catal.* **2019**, *9*, 6372-6379.

57. Guo, T.; Liang, J. J.; Yang, S.; Chen, H.; Fu, Y. N.; Han, S. L.; Zhao, Y. H. *Org. Biomol. Chem.* **2018**, *16*, 6039-6046.
58. Liu, S.; Tzschucke, C. C. *European J. Org. Chem.* **2016**, *2016*, 3509-3513.
59. Chua, M. H.; Png, Z. M.; Zhu, Q.; Xu, J. *Chem. Asian J.* **2021**, *16*, 2896-2919.
60. Guo, Q.; Jiang, R.; Wu, D.; You, J. *Macromol. Rapid Commun.* **2016**, *37*, 794-798.
61. Guo, Q.; Wu, D.; You, J. *ChemSusChem* **2016**, *9*, 2765-2768.
62. Zhang, Q.; Chang, M.; Lu, Y.; Sun, Y.; Li, C.; Yang, X.; Zhang, M.; Chen, Y. *Macromolecules* **2018**, *51*, 379-388.
63. Collier, G. S.; Reynolds, J. R. *ACS Macro Lett.* **2019**, *8*, 931-936.
64. Ciou, Y. S.; Lin, P. H.; Li, W. M.; Lee, K. M.; Liu, C. Y. *J. Org. Chem.* **2017**, *82*, 3538-3551.
65. Li, B.; Tang, G.; Zhou, L.; Wu, D.; Lan, J.; Zhou, L.; Lu, Z.; You, J. *Adv. Funct. Mater.* **2017**, *27*, 1605245.
66. Li, B.; Zhou, L.; Cheng, H.; Huang, Q.; Lan, J.; Zhou, L.; You, J. *Chem. Sci.* **2018**, *9*, 1213-1220.
67. Huang, Q.; Guo, Q.; Lan, J.; Su, R.; Ran, Y.; Yang, Y.; Bin, Z.; You, J. *Mater. Horizons* **2021**, *8*, 1499-1508.
68. Yu, J.; Yang, X.; Wu, C.; Su, W. *J. Org. Chem.* **2020**, *85*, 1009-1021.
69. Zhang, M.; Cheng, R.; Lan, J.; Zhang, H.; Yan, L.; Pu, X.; Huang, Z.; Wu, D.; You, J. *Org. Lett.* **2019**, *21*, 4058-4062.
70. Zhang, M.; Cheng, R.; Lan, J.; Zhang, H.; Yan, L.; Pu, X.; Huang, Z.; Wu, D.; You, J. *Org. Lett.* **2019**, *21*, 4058-4062.
71. Kumaran, S.; Parthasarathy, K. *J. Org. Chem.* **2021**, *86*, 7987-7999.
72. Shinde, V. N.; Bhuvanesh, N.; Kumar, A.; Joshi, H. *Organometallics* **2020**, *39*, 324-333.
73. Huang, G.; Shan, Y.; Yu, J. T.; Pan, C. *Chem. Eur. J.* **2021**, *27*, 12294-12299.
74. Shi, Y.; Yang, G.; Shen, B.; Yang, Y.; Yan, L.; Yang, F.; Liu, J.; Liao, X.; Yu, P.; Bin, Z.; You, J. *J. Am. Chem. Soc.* **2021**, *143*, 21066-21076.
75. Tereniak, S. J.; Bruns, D. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2020**, *142*, 20318-20323.
76. Zeng, Z.; Goebel, J. F.; Liu, X.; Gooßen, L. J. *ACS Catal.* **2021**, *11*, 6626-6632.
77. Jia, Z.; Yang, Q.; Zhang, L.; Luo, S. *ACS Catal.* **2019**, *9*, 3589-3594.
78. Jaiswal, Y.; Mandal, S.; Das, P.; Kumar, A. *Org. Lett.* **2020**, *22*, 1605-1610.