C–H Functionalization

DOI: 10.1002/anie.200902996

Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C–H Bond Cleavage

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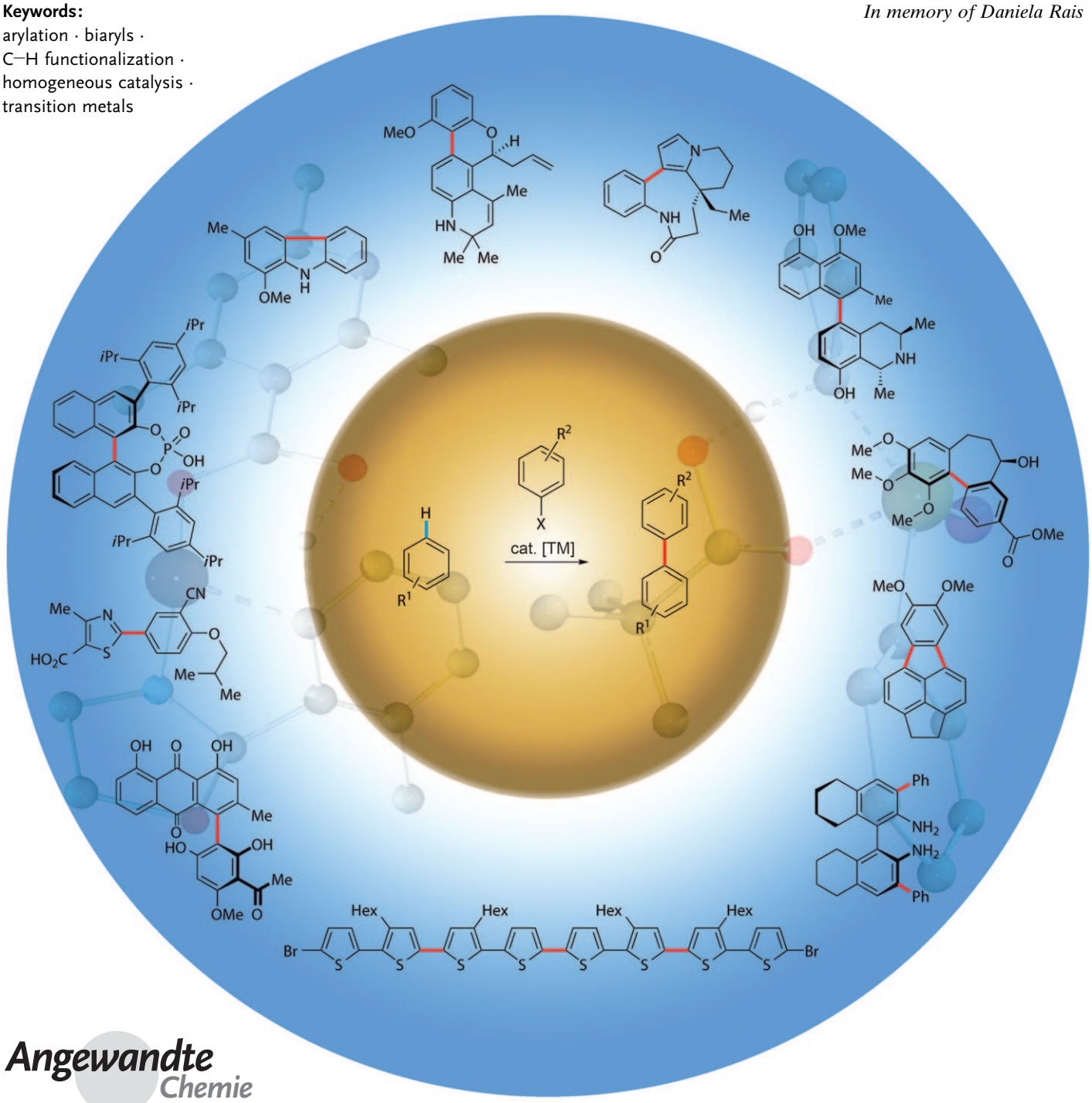
Keywords:
arylation · biaryls · C–H functionalization · homogeneous catalysis · transition metals

In memory of Daniela Rais



The area of transition-metal-catalyzed direct arylation through cleavage of C–H bonds has undergone rapid development in recent years, and is becoming an increasingly viable alternative to traditional cross-coupling reactions with organometallic reagents. In particular, palladium and ruthenium catalysts have been described that enable the direct arylation of (hetero)arenes with challenging coupling partners—including electrophilic aryl chlorides and tosylates as well as simple arenes in cross-dehydrogenative arylations. Furthermore, less expensive copper, iron, and nickel complexes were recently shown to be effective for economically attractive direct arylations.

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1. Introduction

Bi(hetero)aryls are the central structural motifs of various compounds with activities of relevance to different areas, such as biology or material sciences.[1,2] Thus, numerous economically important pharmaceuticals or agrochemicals, such as Glivec (**1**),[3] Valsartan (**2**),[4a,b] Telmisartan (**3**),[4] or Boscalid (**4**)[5] as well as liquid-crystalline NCB 807 (**5**),[6] have bi(hetero)aryl units as indispensable substructures (Figure 1).

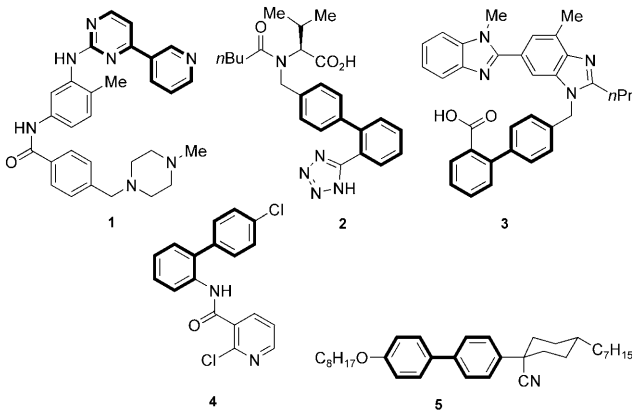
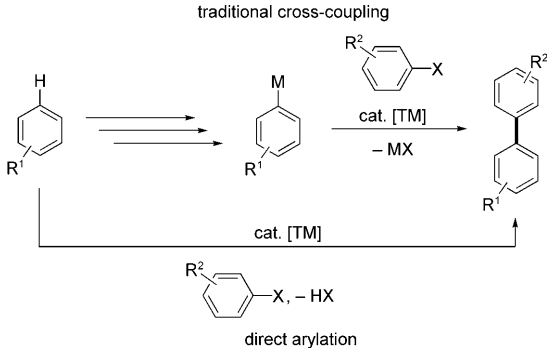


Figure 1. Selected industrially important bi(hetero)aryls.

Based on pioneering studies by Ullmann and co-workers as well as by Goldberg,[7] regioselective syntheses of bi(hetero)aryls predominantly make use of transition-metal-catalyzed cross-coupling reactions between organic (pseudo)halides and stoichiometric amounts of organometallic reagents (Scheme 1).[8,9] Such cross-coupling reactions have matured to being reliable tools for the formation of C(sp^2)–C(sp^2) bonds.

However, the required organometallic nucleophilic reagents, particularly when being functionalized, are often not commercially available or are relatively expensive. Their preparation from the corresponding arenes usually involves a number of synthetic operations, during which undesired by-products are formed, as are during the traditional cross-coupling reactions themselves. Therefore, direct arylation reactions through cleavage of C–H bonds[10] represent an environmentally and economically more attractive strategy (Scheme 1). Importantly, this strategy is not only advantageous with respect to the overall minimization of by-product formation, but also allows for streamlining organic syntheses.[11]



Scheme 1. Comparison between classical cross-coupling and direct arylation.

Catalytic direct arylations by cleavage of C–H bonds can be differentiated on the basis of the nature of the coupling partners into 1) oxidative arylations, and 2) reactions with aryl (pseudo)halides as electrophilic coupling partners (Scheme 2). Oxidative arylations inherently require the presence of sacrificial oxidants, and can be achieved with either stoichiometric amounts of organometallic reagents (Scheme 2a) or (hetero)arenes[12] (Scheme 2b) as arylating reagents. Since the use of organometallic reagents is associated with the formation of stoichiometric amounts of undesired by-products, dehydrogenative arylation is significantly more appealing. This holds true particularly when these transformations can be performed with molecular oxygen as the terminal oxidant. However, achieving regioselectivity in intermolecular cross-dehydrogenative arylation reactions represents a major obstacle. In contrast, direct

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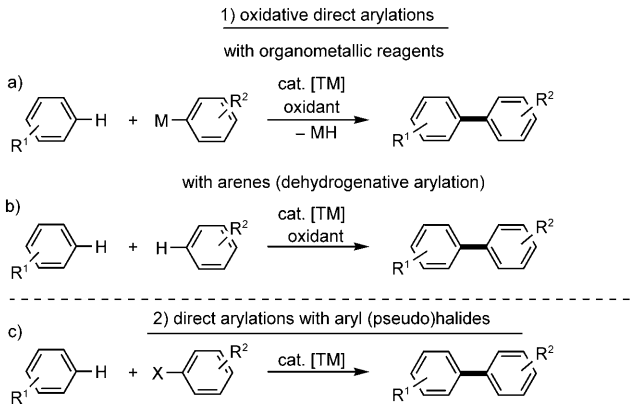
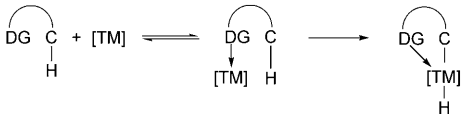


Scheme 2. Strategies for catalytic direct arylation for the synthesis of biaryls. TM = transition-metal catalyst.

arylations with easily accessible, yet inexpensive electrophilic aryl (pseudo)halides do not feature these disadvantages (Scheme 2c), and had, therefore, arguably the greatest impact on bi(hetero)aryl syntheses thus far.

Since organic molecules usually display various C–H bonds with comparable dissociation energies, the development of regioselective methods for direct arylation is a major challenge. Such a reaction is possible when the electronic properties of a given substrate dominate its reactivity. This largely holds true for a variety of heteroarenes as well as electron-deficient arenes, such as oligohalogenated benzene derivatives. In contrast, transformations of electronically neutral arenes often lead to unsatisfactory selectivities. As a result, strategies have been developed which employ (potentially removable) directing groups. Here, a Lewis-basic directing group coordinates to the transition-metal catalyst, which enables an intramolecular cleavage of a C–H bond (Scheme 3).[13] Such a cyclometalation allows intermolecular direct arylations to be accomplished in a highly regioselective fashion.



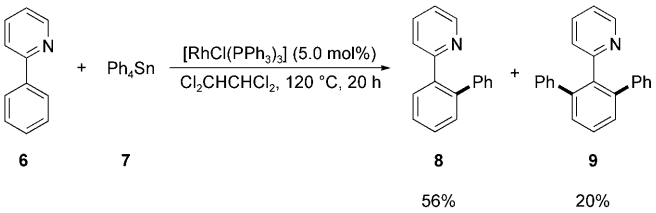
Scheme 3. Regioselective intermolecular cleavage of C–H bonds through the use of directing groups (DG).

A comprehensive review by Lautens and co-workers summarized the state of the art in transition-metal-catalyzed direct arylation until the middle of 2006.[10f] However, exciting progress has been made in this rapidly evolving research area during the last three years. Therefore, we cover herein more recent findings on catalytic direct arylations by C–H bond cleavage for the syntheses of bi(hetero)arenes. Where appropriate, we also include important previously disclosed reports, with a particular emphasis on direct arylation reactions with more challenging (pseudo)halides as the arylating reagents.

2. Direct Arylation with Organometallic Reagents

2.1. Rhodium-Catalyzed Direct Arylation

As a first example of oxidative transition-metal-catalyzed direct arylation with organometallic reagents, Oi, Fukita, and Inoue reported on the direct arylations of 2-aryl-substituted pyridines with the Wilkinson catalyst and stannanes as the arylating reagents (Scheme 4).[14] These reactions proceeded regioselectively as a result of the chelation effect. Although detailed data on the mechanism of the catalytic system were not disclosed, the solvent likely served as the oxidizing agent in these transformations.[15]



Scheme 4. Rhodium-catalyzed direct arylation of 2-phenylpyridine (**6**) with stannane **7**.

A notable advance was achieved by Miura and co-workers with the use of less toxic tetraphenylborates as coupling partners (Scheme 5). Unfortunately, relatively low yields were obtained with the original procedure because of the reduction of starting material **10**,[16] which proved to be necessary for achieving catalytic turnover.

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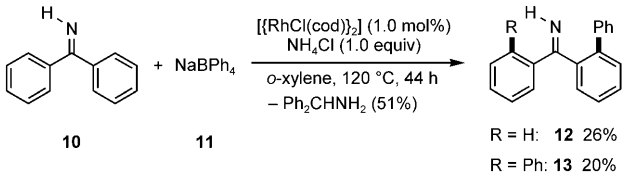
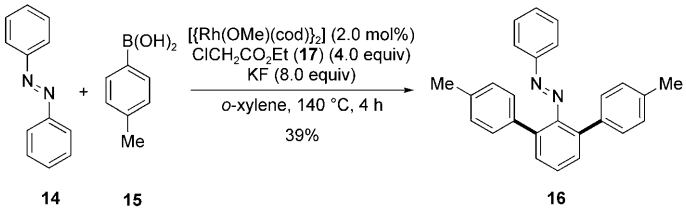


Scheme 5. Rhodium-catalyzed direct arylation with $NaBPh_4$ (**11**).

More recently, this problem was elegantly addressed by the addition of ethyl chloroacetate (**17**) as the sacrificial oxidant.[17] This enabled arenes bearing imidazoles, pyridines, or oxazolines as directing groups to be efficiently arylated. It is particularly notable that azobenzene turned out to be a suitable substrate, and that boronic acids served as more convenient arylating reagents (Scheme 6). According to the



Scheme 6. Rhodium-catalyzed direct arylation of azobenzene (**14**) with $ClCH_2CO_2Et$ (**17**) as the oxidant.

proposed mechanism, chloride **17** oxidatively adds to rhodium hydride **18** in the key step of the catalytic cycle (Scheme 7). Subsequent reductive elimination ensures turnover and regenerates the catalytically active rhodium species **20**.

Rhodium-catalyzed direct arylation could also be accomplished with 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO, **24**) as the terminal oxidant, as reported by Vogler and Studer.[18] Lewis-basic nitrogen-containing functionalities, such as pyridines or imines, were employed here to ensure chelation control, and boronic acids again served as the arylating reagents (Scheme 8). A palladium-catalyzed variant was subsequently devised.[19]

A reaction mechanism for this catalytic system was proposed which relies on the conversion of rhodium(I) aminoalkoxide **25** into the corresponding aryl rhodium(I)

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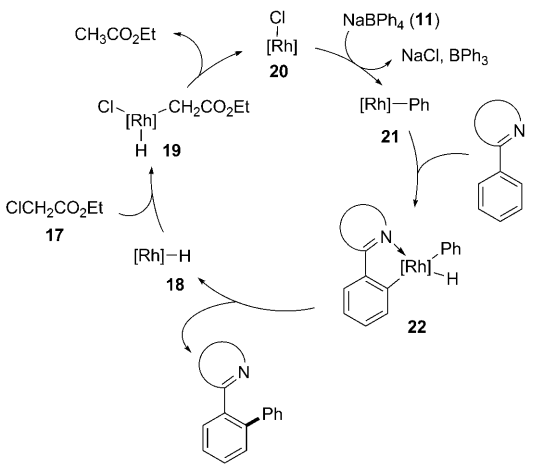
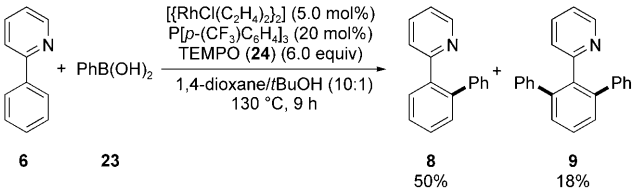
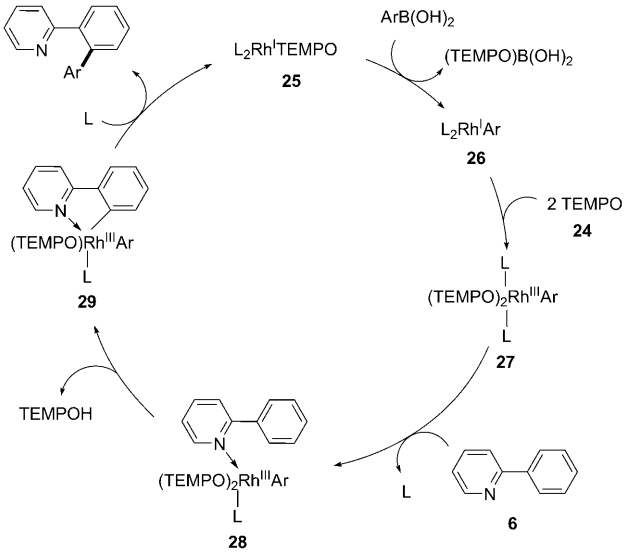


Scheme 7. Proposed mechanism for rhodium-catalyzed direct arylation with $ClCH_2CO_2Et$ (**17**).



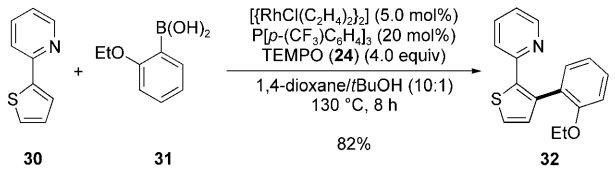
Scheme 8. Rhodium-catalyzed direct arylation with TEMPO (**24**) as an additive.

complex **26** through transmetalation with the boronic acid (Scheme 9).[18] Two equivalents of TEMPO (**24**) then oxidize rhodium(I) species **26**, thereby giving rise to the formation of rhodium(III) complex **27**. This sets the stage for a chelation-controlled cleavage of a C–H bond to selectively yield the cyclometalated complex **29**. Finally, reductive elimination delivers the desired arylation product, and regenerates the catalytically competent rhodium(I) complex **25**.



Scheme 9. Proposed mechanism for rhodium-catalyzed direct arylation in the presence of TEMPO (**24**). $L = P[p\text{-}(CF_3)C_6H_4)]_3$.

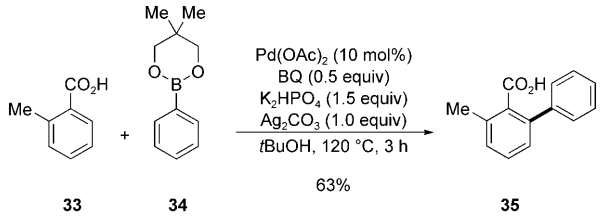
It is noteworthy that this procedure was not restricted to the functionalization of C–H bonds of arenes, but also enabled the direct arylation of heteroarenes (Scheme 10).[18]



Scheme 10. Rhodium-catalyzed direct arylation of heteroarene **30**.

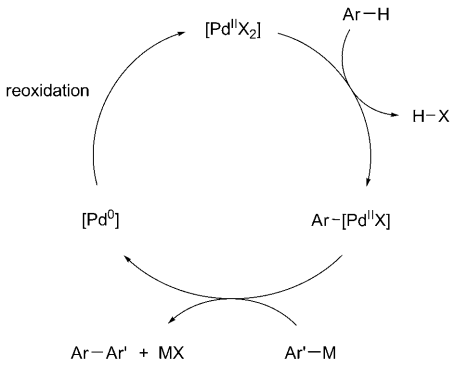
2.2. Palladium-Catalyzed Direct Arylation

Palladium(II)-catalyzed direct alkylation of aromatic C–H bonds with boronic acids was developed by Yu and co-workers.[20] This approach also proved applicable to the functionalization of challenging $C(sp^3)$–H bonds.[21] Based on these $C(sp^2)$–$C(sp^3)$ and $C(sp^3)$–$C(sp^3)$ bond-forming processes, Yu and co-workers developed reaction conditions for the palladium-catalyzed direct arylation of benzoic acids with aryl boronates in the presence of benzoquinone (BQ) and Ag_2CO_3 as additives (Scheme 11).[21] Interestingly, this procedure also enabled the arylation of aliphatic carboxylic acids.



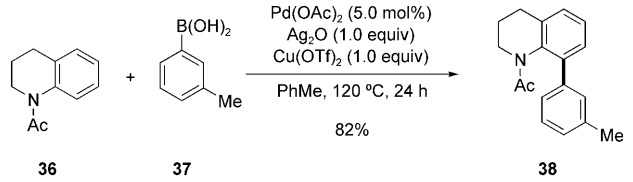
Scheme 11. Palladium(II)-catalyzed direct arylation of benzoic acid **33**.

As to the mechanism, a palladium(II)/palladium(0) catalytic cycle was proposed to be operative in these palladium-catalyzed direct arylations with organometallic arylating reagents, and served as a blueprint for related procedures (Scheme 12).



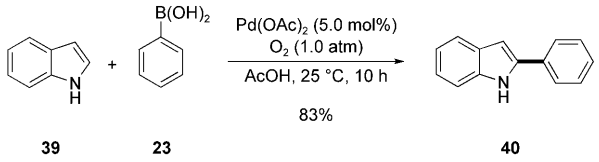
Scheme 12. Generalized mechanism for palladium(II)-catalyzed direct arylation with organometallic reagents.

In independent studies, Shi et al. investigated the palladium-catalyzed direct *ortho* arylation of acetanilides with boronic acids as arylating reagents in the presence of stoichiometric amounts of copper and silver salts (Scheme 13).[22] Remarkably, a variety of important functional groups, as well as air and moisture, were tolerated by the optimized catalytic system.



Scheme 13. Palladium(II)-catalyzed direct arylation of acetanilide **36** with boronic acid **37**.

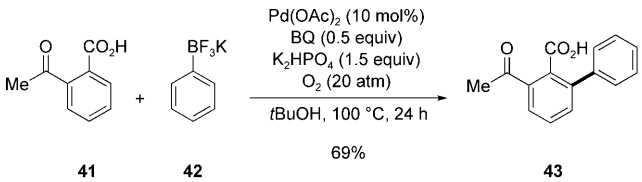
Both of these procedures required the use of metal salts as terminal oxidants, and thus the development of aerobic palladium(II)-catalyzed oxidative arylation constituted a significant improvement (Scheme 14).[23] When acetic acid



Scheme 14. Aerobic palladium(II)-catalyzed direct arylation of indole (**39**).

was used as the solvent, molecular oxygen could be employed as the oxidant for the arylation of electron-rich heteroarenes, a valuable feature with respect to the overall formation of by-products. Furthermore, the same catalytic system was also employed for the efficient aerobic direct arylation of simple arenes not bearing any Lewis-basic directing groups. Since reactions of electron-rich heteroarenes occurred with higher efficiencies than those of electron-deficient heteroarenes, an electrophilic activation of the heteroaromatic C–H bonds was proposed.

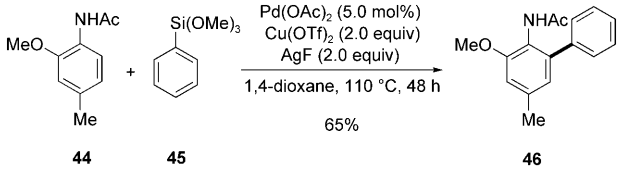
An extension of the palladium(II)-catalyzed direct arylation to include user-friendly trifluoroborates as coupling partners was recently realized under an atmosphere of oxygen or air.[24] Again, sensitive functional groups, such as bromides, nitriles, and enolizable ketones, were well tolerated within this versatile palladium(II)-catalyzed C–H bond functionalization (Scheme 15). However, a limitation was found in the



Scheme 15. Palladium(II)-catalyzed direct arylation with trifluoroborate **42**.

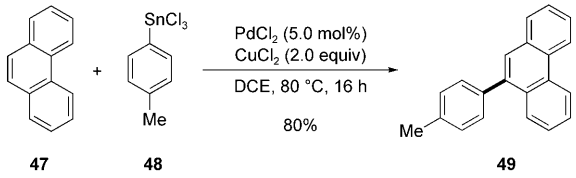
need for applying a relatively high pressure of air or molecular oxygen to obtain satisfactory yields within reasonable reaction times.

Shi and co-workers demonstrated that easily accessible trialkoxyarylsilanes could be employed as an attractive alternative to boron-based arylating reagents.[25] Thus, efficient palladium(II)-catalyzed *ortho* arylations of acetanilides took place in the presence of stoichiometric amounts of $Cu(OTf)_2$ as the oxidant, provided that AgF was used as an stoichiometric additive (Scheme 16). Again, a palladium(II)/palladium(0) manifold was suggested to be operative for these C–H bond functionalizations (see Scheme 12).



Scheme 16. Palladium(II)-catalyzed direct arylation with siloxane **45**.

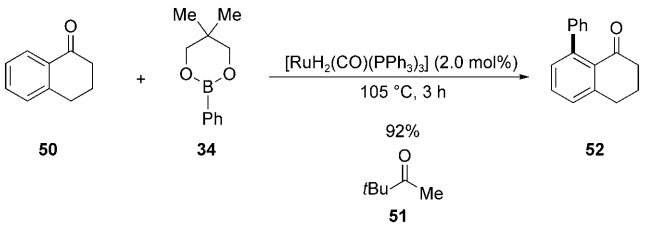
Tin-based arylating reagents were recently further exploited by Oi, Inoue, and co-workers for oxidative palladium(II)-catalyzed direct arylation of simple arenes.[26] Interestingly, inexpensive $PdCl_2$ could be used as the catalyst, as long as stoichiometric amounts of $CuCl_2$ were available as the terminal oxidant (Scheme 17). Preliminary mechanistic studies led the authors to propose a reaction mechanism involving a palladium(IV) species, which is reminiscent of a mechanism proposed earlier by Sanford and co-workers[27] for palladium-catalyzed direct arylation with iodonium salts (see Section 4.1.2). An arylation with a diaryl iodonium salt as the coupling partner was found to give a similar yield as that obtained with an aryl tin reagent under otherwise identical reaction conditions.[26]



Scheme 17. Palladium(II)-catalyzed direct arylation with aryl tin reagent **48**.

2.3. Ruthenium-Catalyzed Direct Arylations

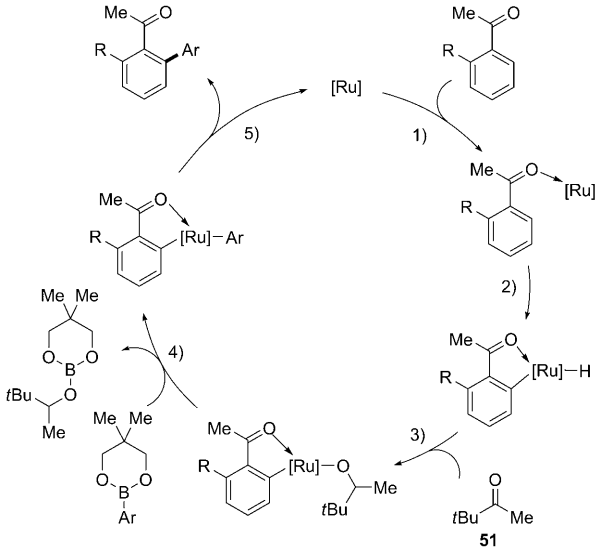
Ruthenium-catalyzed chelation-controlled direct arylation of substrates with oxygen-containing directing groups was accomplished with aryl boronates as the coupling partners. Thus, a variety of aryl ketones were efficiently functionalized in pinacolone (**51**) as the solvent with boronates bearing either electron-donating or electron-withdrawing substituents (Scheme 18).[28,29] Subsequently, this procedure was applied by Sames and co-workers to the catalytic



Scheme 18. Ruthenium-catalyzed direct arylation with boronate **34**.

functionalization of challenging $C(sp^3)$–H bonds in saturated N heterocycles.[30]

Detailed mechanistic studies by Kakiuchi, Chatani et al. revealed that pinacolone (**51**) served here not only as the solvent, but also as the oxidizing agent (Scheme 19).[29]



Scheme 19. Proposed mechanism for ruthenium-catalyzed direct arylation with boronates.

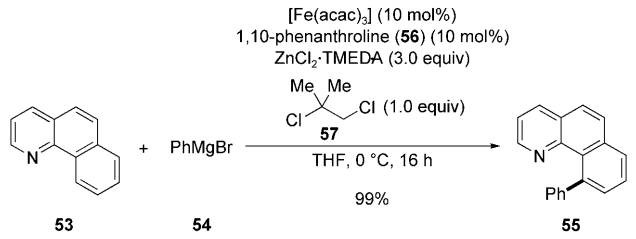
Furthermore, inter- and intramolecular competition experiments with isotopically labeled ketones provided evidence for a coordination of the ruthenium catalyst by the oxygen atom of the aryl ketone. Thus, a mechanism was elaborated consisting of 1) coordination by the substrate, 2) *ortho*-metalation, 3) insertion of pinacolone (**51**) into the [Ru]–H bond, 4) transmetalation, and 5) final reductive elimination.

A recent application of this method to catalytic direct arylation of anthraquinone derivatives set the stage for an efficient synthesis of multiarylated anthracenes.[31]

2.4. Iron-Catalyzed Direct Arylation with Organometallic Reagents

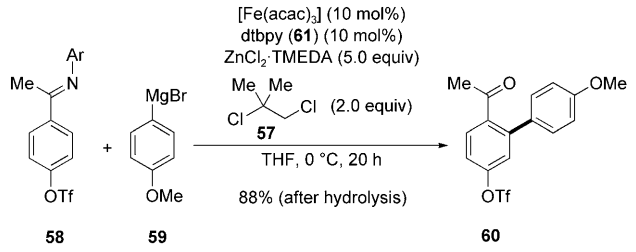
The use of iron catalysts for cross-coupling reactions[32] is highly desirable given the inexpensive nature and low toxicities of these complexes. Recently, Nakamura and coworkers showed that iron-catalyzed direct arylation can be

accomplished by employing zincorganyl compounds as arylating reagents.[33] In this way, arenes displaying Lewis-basic directing groups could be regioselectively functionalized at remarkably low reaction temperatures through chelation control (Scheme 20).



Scheme 20. Iron-catalyzed direct arylation of benzo[*h*]quinoline (**53**).

Interestingly, when ketimines were employed as directing groups, bromides or chlorides were well tolerated as functional groups, and products stemming from traditional cross-coupling reactions were not detected (Scheme 21).[34]



Scheme 21. Iron-catalyzed direct arylation of ketimine **58** (Ar = 4-$MeOC_6H_4$).

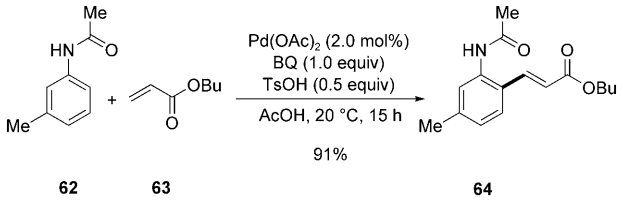
Although mechanistic studies on these remarkable processes were not disclosed, the use of 1,2-dichloroalkane **57** as an additive was found to be mandatory, a feature previously observed for rhodium-catalyzed[14] direct arylation (see Section 2.1). Furthermore, it is interesting to note that these direct arylations were achieved with N,N ligands **56** or **61**, which were more recently shown to allow for efficient copper- (Section 4.2) or nickel-catalyzed (Section 4.3) direct arylation with aryl halides.

Iron-catalyzed direct arylations were thus far only accomplished with aryl zinc reagents derived in situ from the corresponding Grignard reagents through the addition of $ZnCl_2$. Note, however, that iron-mediated direct arylations were recently performed by using boronic acids as the arylating reagents.[35]

3. Dehydrogenative Arylation

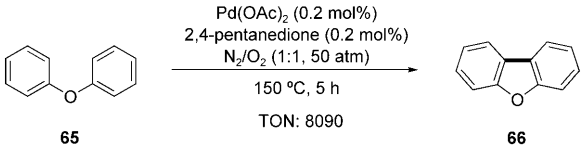
Pioneering examples of the formation of $C(sp^2)$–$C(sp^2)$ bonds by oxidative direct C–H bond functionalizations were described by Moritani, Fujiwara, and co-workers.[36–38] During the last few decades, this process has matured to being a valuable tool for the diastereoselective synthesis of substituted alkenes.[39–41] For example, a highly active catalytic system for oxidative arylation at ambient temperature was recently devised (Scheme 22).[42]

Oxidative palladium-catalyzed functionalization of C–H bonds was, however, not restricted to direct arylation of



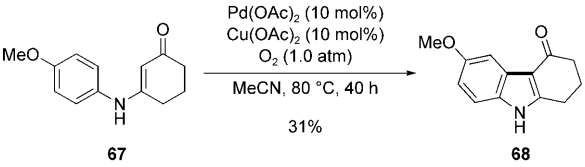
Scheme 22. Direct cross-dehydrogenative arylation with arene **62**.

alkenes, but also turned out to be useful for C_{aryl}–C_{aryl} bond-forming reactions. Hence, oxidative arylation for the synthesis of biaryl compounds could be accomplished with both stoichiometric[43] as well as catalytic[44] amounts of palladium salts. In an early example, entropically favored intramolecular coupling reactions were employed for the preparation of dibenzofuran (**65**, Scheme 23).[45,46]



Scheme 23. Palladium-catalyzed intramolecular dehydrogenative coupling of ether **65**.

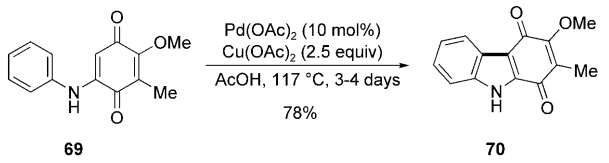
The potential of palladium-catalyzed oxidative arylation reactions is reflected by efficient syntheses of N heterocycles. In an early example, enaminone **67** was cyclized with catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ under aerobic reaction conditions (Scheme 24).[47,48]



Scheme 24. Palladium-catalyzed intramolecular dehydrogenative coupling of enaminone **67**.

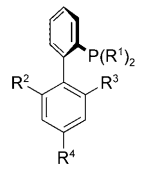
Major contributions by the research groups of Akermark and Knoelker[46,49] set the stage for modular access to various naturally occurring carbazole and indole derivatives with valuable biological activities (Scheme 25).[50–52]

More recently, Ohno and co-workers applied this strategy to a flexible synthesis of diversely substituted carbazoles.[53] Thus, a palladium complex derived from biaryl ligand X-Phos (**71a**, Figure 2)[54] allowed for a reaction sequence consisting of the intermolecular formation of a C–N bond and a subsequent intramolecular oxidative direct arylation (Scheme 26).[53] Reactions with isotopically labeled starting



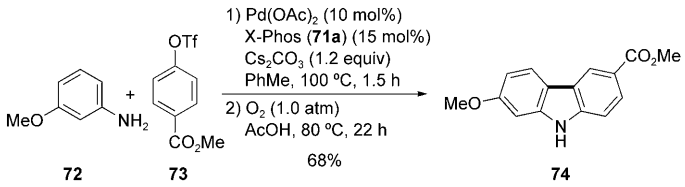
69 70

Scheme 25. Palladium-catalyzed intramolecular dehydrogenative coupling of substrate **69**.



R^1 = Cy, R^2 = R^3 = R^4 = *i*Pr	**71a**
R^1 = *t*Bu, R^2 = R^3 = R^4 = *i*Pr	**71b**
R^1 = Cy, R^2 = NMe_2, R^3 = R^4 = H	**71c**
R^1 = *t*Bu, R^2 = R^3 = R^4 = H	**71d**
R^1 = Cy, R^2 = R^3 = OMe, R^4 = H	**71e**

Figure 2. Electron-rich monophosphine biaryl ligands **71**.

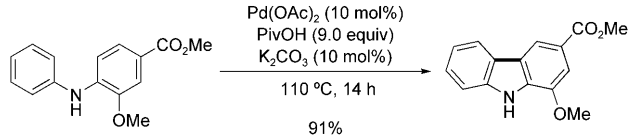


72 73 74

Scheme 26. Synthesis of carbazole **74** by sequential C–N coupling/intramolecular oxidative arylation.

materials as well as intramolecular competition experiments led the authors to propose an electrophilic substitution-type mechanism for the cleavage of the first C–H bond in the oxidative arylation.[53b]

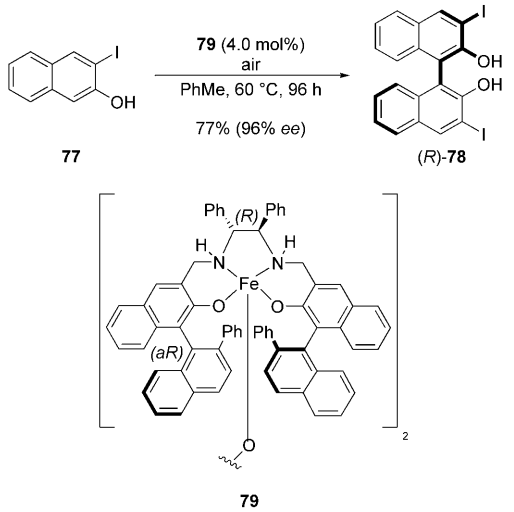
Based on their studies directed towards intermolecular cross-dehydrogenative arylations (see below), Fagnou and co-workers probed a related approach for the synthesis of naturally occurring mukonine (**76**), which proceeded under phosphine-free reaction conditions (Scheme 27).[55]



75 76

Scheme 27. Synthesis of mukonine (**76**) by intramolecular dehydrogenative coupling.

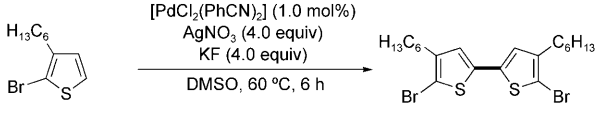
Intermolecular dehydrogenative homocoupling of (hetero)arenes is one of the most useful tools for the preparation of symmetrically substituted 1,1′-binaphthyls, which are, amongst other things, of major importance as ligand precursors in asymmetric catalysis. Comprehensive reviews on such procedures were published elsewhere,[12,56] and a detailed discussion of these transformations is beyond the scope of this Review. However, an illustrative recent example is found in the aerobic oxidative coupling reactions of 2-naphthols, which were accomplished in an asymmetric fashion with an economically attractive iron catalyst by Egami and Katsuki (Scheme 28).[57]



77 79

Scheme 28. Iron-catalyzed enantioselective aerobic homocoupling of naphthol **77**.

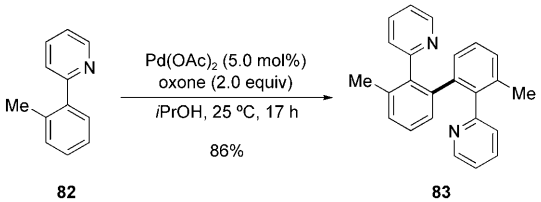
Mori and co-workers devised palladium-catalyzed chemo- and regioselective dehydrogenative homocoupling reactions as the key steps in the syntheses of oligothiophenes (Scheme 29), which are valuable as advanced electronic and photonic materials, such as organic thin-film transistors, liquid crystals, or photovoltaic cells.[58]



80 81

Scheme 29. Palladium-catalyzed intermolecular dehydrogenative homocoupling of thiophene **80**.

2-Aryl pyridines could undergo chelation-assisted palladium-catalyzed dehydrogenative homocoupling reactions by using $Pd(OAc)_2$ as the catalyst and oxone as the stoichiometric oxidant (Scheme 30).[59] Interestingly, these reactions occurred efficiently even at ambient temperature. Detailed

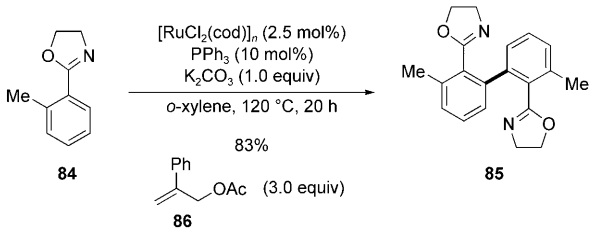


82 83

Scheme 30. Palladium-catalyzed dehydrogenative homocoupling of 2-aryl pyridine **82**.

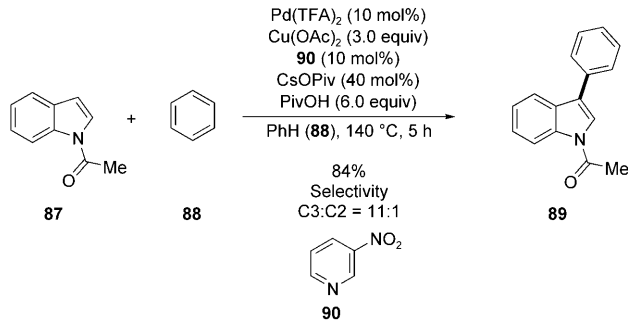
mechanistic studies revealed the formation of palladium(IV) species as key intermediates.[59–61] Note that this oxidative transformation was more recently also accomplished with stoichiometric amounts of copper in the presence of iodine.[62]

Dehydrogenative homocoupling reactions of arenes can not only be performed with palladium catalysts. Indeed, Oi, Inoue et al. found recently that a catalytic system consisting of $[RuCl_2(cod)]_n$ and PPh_3, along with allyl acetate **86** as the sacrificial oxidant, allowed for the regioselective functionalization of C–H bonds on 2-aryl oxazolines (Scheme 31).[63,64] Furthermore, arenes bearing oxazole, imidazole, pyrazole, or thiazole moieties could be homocoupled in a regioselective fashion.

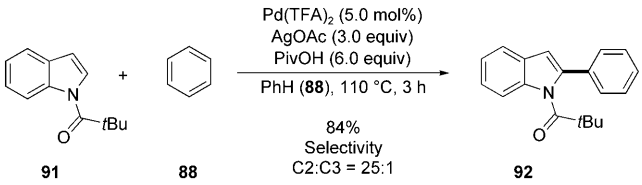


Scheme 31. Ruthenium-catalyzed dehydrogenative homocoupling of 2-aryl oxazoline **84**.

While achieving selectivity in either intramolecular oxidative arylation or intermolecular homocoupling is inherently less difficult, a significant challenge is represented by intermolecular cross-dehydrogenative arylation between two different (hetero)arenes. Advance in this respect was recently accomplished by Stuart and Fagnou,[65,66] who showed that palladium-catalyzed oxidative arylation of indoles could be achieved with unactivated arenes in the presence of $Cu(OAc)_2$ as the stoichiometric oxidant. Notably, these reactions proceeded with high regioselectivity, thereby leading predominantly to functionalization at the C3-position of the indole (Scheme 32). However, high chemoselectivity in favor of cross-dehydrogenative reactions were realized through the use of the arenes in large excess. Interestingly, the selectivity of these oxidative coupling reactions could be altered in favor of arylation at the C2-position of the indole when using AgOAc as an additive (Scheme 33).[67]

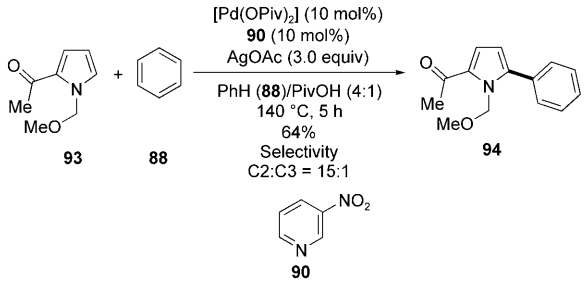


Scheme 32. Palladium-catalyzed cross-dehydrogenative arylation of indole **87** at C3.



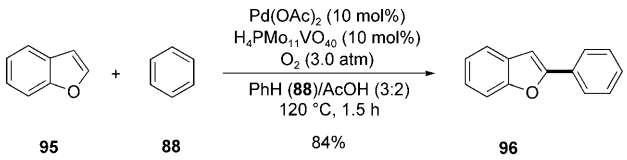
Scheme 33. Palladium-catalyzed cross-dehydrogenative arylation of indole **91** at C2.

It is noteworthy that the presence of valuable functional groups, such as chloro or acetyl substituents, did not affect the course of the reaction, and that pyrroles were also functionalized regioselectively (Scheme 34).[67]



Scheme 34. Palladium-catalyzed cross-dehydrogenative arylation of pyrrole **93**.

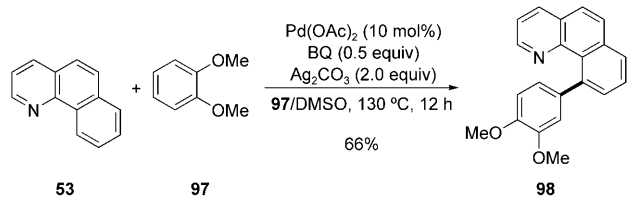
Palladium-catalyzed oxidative arylation of benzofurans was independently reported by DeBoef and co-workers, who devised reaction conditions for the use of molecular oxygen as the terminal oxidant.[68] Here, high regioselectivities were ensured by the use of heteropolymolybdovanadic acid as an additive (Scheme 35).



Scheme 35. Palladium-catalyzed cross-dehydrogenative arylation of benzofuran (**95**).

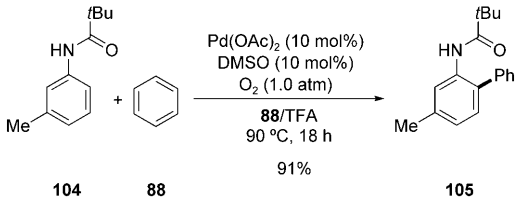
Furthermore, palladium-catalyzed intermolecular oxidative alkenylation of indoles proved to be viable.[69] Interestingly, the regioselectivity here depended strongly on the solvent system employed. These studies led to reaction conditions for the aerobic palladium-catalyzed C–H alkenylations and annulations of pyrroles under exceedingly mild reaction conditions.[70]

Based on their chelation-controlled oxidative homocoupling of 2-aryl pyridines (see above), Hull and Sanford elegantly established reaction conditions for cross-dehydrogenative coupling reactions. For example, benzo[*h*]quinoline (**53**) was efficiently arylated with a variety of arenes acting as the solvent in the presence of stoichiometric amounts of silver salts (Scheme 36).[71] In a related study, ferrocene derivatives



53 97 98

Scheme 36. Palladium-catalyzed cross-dehydrogenative arylation of benzo[*h*]quinoline (**53**).

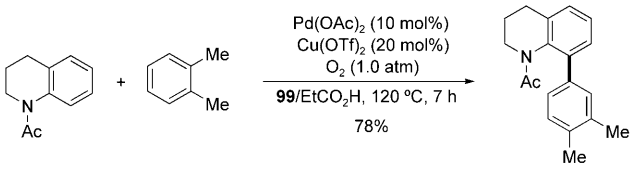


104 88 105

Scheme 39. Aerobic palladium-catalyzed cross-dehydrogenative arylation in the absence of copper salts.

with oxazolines as directing groups were oxidatively arylated in moderate yields with copper salts used as stoichiometric oxidants.[72]

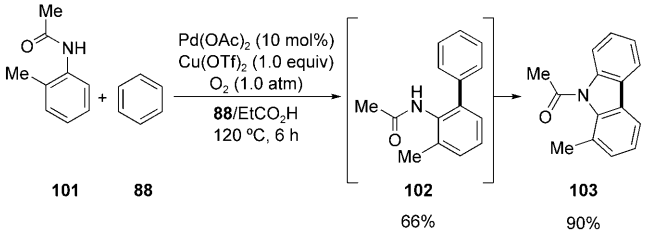
Acetanilides were also shown to be valuable directing groups for oxidative direct arylations, as observed by Shi and co-workers.[73] Remarkably, molecular oxygen could be employed as the terminal oxidant in these transformations, as long as $Cu(OTf)_2$ was present in co-catalytic amounts (Scheme 37).



36 99 100

Scheme 37. Palladium-catalyzed cross-dehydrogenative arylation of anilide **36**.

In addition, a reaction sequence consisting of an intermolecular oxidative arylation and an intramolecular oxidative formation of a C–N bond was exploited for a modular access to substituted carbazoles (Scheme 38).[73]



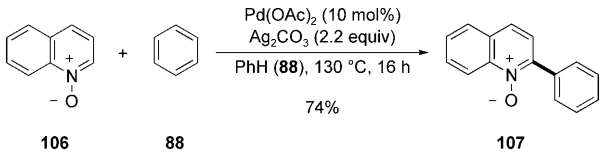
101 88 102 103

66% 90%

Scheme 38. Sequential synthesis of carbazole **103** by cross-dehydrogenative arylation.

Whereas the method developed by Shi and co-workers called for the use of stoichiometric or co-catalytic amounts of copper(II) salts as additives,[73] Buchwald and co-workers conducted palladium-catalyzed cross-dehydrogenative arylations in the absence of additional transition-metal salts.[74] Here, the key to success was the use of TFA as the solvent under an atmosphere of molecular oxygen (Scheme 39). Since transformations of di- or oligofluorinated anilides proceeded only sluggishly, a proton abstraction mechanism (Section 4.1.2) was suggested to be of less importance.

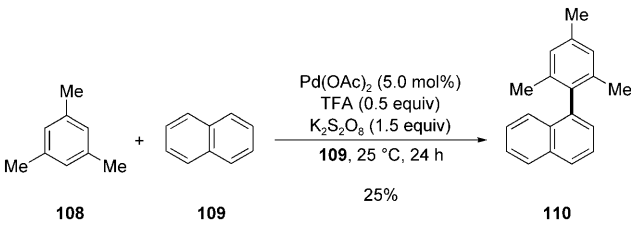
Based on the studies by Fagnou and co-workers on direct arylations of pyridine *N*-oxides with aryl halides (Section 4.1.2),[75] Chang and co-workers explored cross-dehydrogenative arylation of these electron-deficient heteroarenes with simple arenes as arylating reagents (Scheme 40).[76] Although this report constituted an important advance, the optimized reaction conditions involved the use of stoichiometric amounts of Ag_2CO_3 as the terminal oxidant.



106 88 107

Scheme 40. Palladium-catalyzed cross-dehydrogenative arylation of quinoline *N*-oxide (**106**).

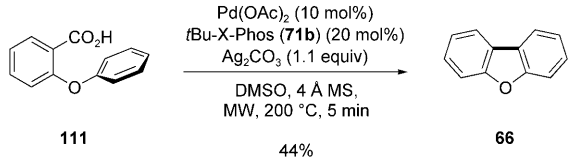
The selective cross-dehydrogenative arylation of simple electronically unbiased arenes were also probed. In more recent studies, Lu and co-workers described palladium-catalyzed oxidative coupling reactions between two unfunctionalized arenes in the presence of $K_2S_2O_8$ (Scheme 41).[77,78] Although the yields were relatively low, the reaction occurred under mild conditions.



108 109 110

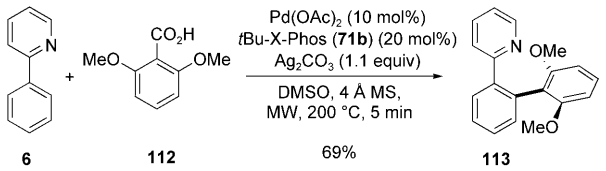
Scheme 41. Palladium-catalyzed cross-dehydrogenative coupling of mesitylene (**108**) with naphthalene (**109**).

With respect to ensuring regioselectivity, a noteworthy alternative to the above-mentioned cross-dehydrogenative coupling reactions is represented by palladium-catalyzed decarboxylative[79–81] direct arylation. Hence, a palladium-catalyzed decarboxylative oxidative coupling through cleavage of the C–H bond was recently reported by Crabtree and co-workers[82] as well as by Glorius and co-workers[83] for the synthesis of biaryls, which enabled efficient syntheses, for example, of dibenzofurans (Scheme 42).



Scheme 42. Palladium-catalyzed intramolecular decarboxylative oxidative coupling.

Furthermore, a variety of arenes bearing Lewis-basic directing groups, such as 2-phenylpyridine (**6**), turned out to be suitable substrates for the corresponding intermolecular transformations. The chelation-controlled decarboxylative oxidative arylation reactions, as developed by Crabtree and co-workers, proceeded with high selectivity (Scheme 43).[82]



Scheme 43. Palladium-catalyzed intermolecular decarboxylative oxidative coupling.

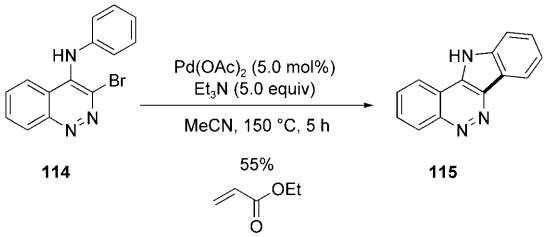
4. Direct Arylation with (Pseudo)Halides or Their Derivatives

4.1. Palladium-Catalyzed Direct Arylation

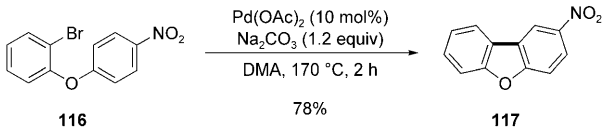
4.1.1. Early Contributions

Early examples of transition-metal-catalyzed intramolecular direct arylations with aryl halides were reported by Ames and Bull. During investigations into palladium-catalyzed intermolecular Mizoroki–Heck reactions, cyclization product **115** was obtained through a catalytic intramolecular direct arylation reaction (Scheme 44).[84] Further studies revealed that alkenes were not mandatory for achieving catalytic turnover. This insight set the stage for an extension of this procedure to the synthesis of further valuable heterocycles (Scheme 45).[85]

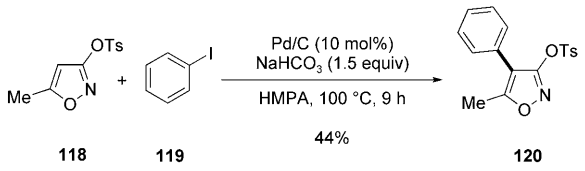
Independently, Tajima and co-workers disclosed the catalytic intermolecular direct arylation of isoxazoles with aryl iodides as electrophiles and a heterogeneous palladium catalyst (Scheme 46).[86]



Scheme 44. Early example of palladium-catalyzed intramolecular direct arylation.



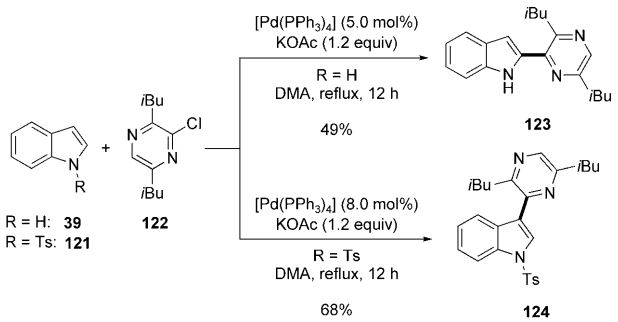
Scheme 45. Palladium-catalyzed intramolecular direct arylation of ether



Scheme 46. Palladium-catalyzed intermolecular direct arylation of isoxazole **118**.

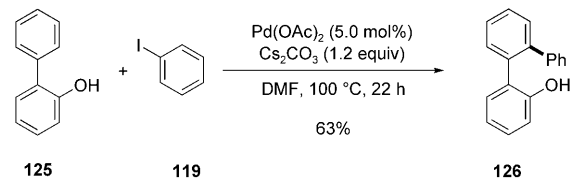
116.

Interesting observations on intermolecular direct arylation reactions of 2,3-unsubstituted indole derivatives were made by Ohta and co-workers. They found that the regioselectivity of these palladium-catalyzed processes strongly depended on the substituents on the nitrogen atom. For example, N-unsubstituted indole **39**,[87] as well as its N-alkylated derivatives,[88] yielded 2-heteroarylated products of type **123**, while the corresponding tosylated indole **121** resulted in functionalization at the C3-position (Scheme 47).[88] It should be pointed out that electron-deficient—thus for an oxidative addition electronically activated—heteroaryl chloride **122** was used as the electrophile in these reactions.



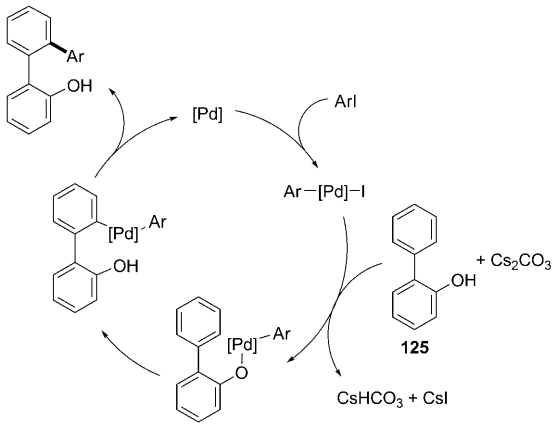
Scheme 47. Palladium-catalyzed intermolecular direct arylation.

Chelation-controlled, regioselective, intermolecular direct arylation of 2-aryl phenols or naphthols with aryl iodides was elegantly established by Miura and co-workers (Scheme 48).[89] The proposed mechanism of this remarkable



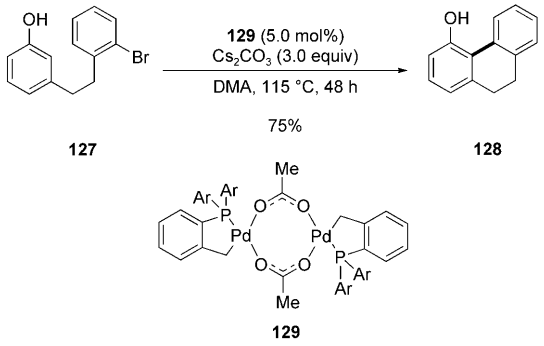
Scheme 48. Palladium-catalyzed chelation-controlled direct arylation of phenol **125**.

transformation involves initial oxidative addition of the aryl iodide to a palladium(0) species, followed by reaction of the resulting palladium(II) complex with the phenolate. Thereafter, chelation-controlled functionalization of the C–H bond at the *ortho* position takes place, and subsequent reductive elimination yields the desired product (Scheme 49).[90]



Scheme 49. Proposed mechanism for the palladium-catalyzed direct arylation of 2-phenylphenol (**125**).

Likewise, Rawal and co-workers employed palladacycle **129** as the catalyst for the intramolecular direct arylation of phenol derivatives by using aryl bromides or iodides as electrophiles (Scheme 50).[91]

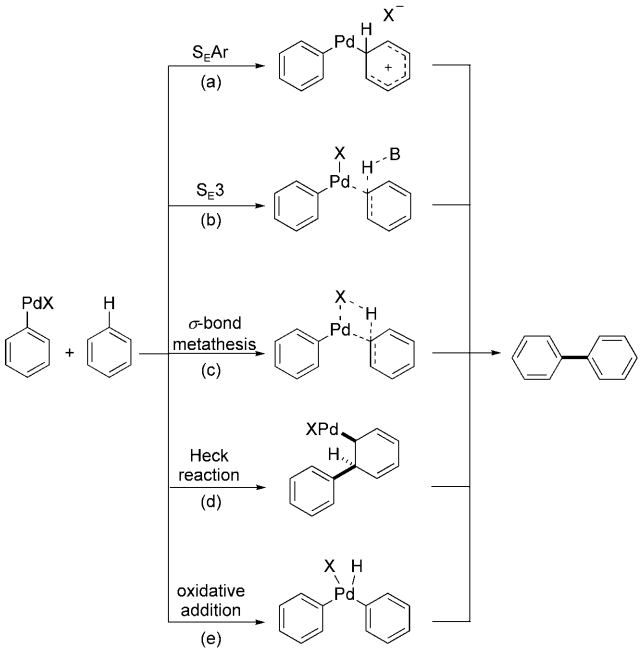


Scheme 50. Palladium-catalyzed intramolecular direct arylation of phenol **127** (Ar = *o*-tolyl).

These early contributions laid the foundation for the development of numerous valuable palladium-catalyzed direct arylation reactions, which largely made use of more reactive (hetero)aryl iodides, triflates, or bromides as the electrophilic coupling partners. Given that these palladium-catalyzed processes were previously comprehensively reviewed,[10b,f] we focus in the subsequent sections on recently disclosed progress in direct arylation with more challenging substrates, as well as novel mechanistic insights.

4.1.2. ***Aryl Triflates, Iodides, Bromides, and Their Derivatives***

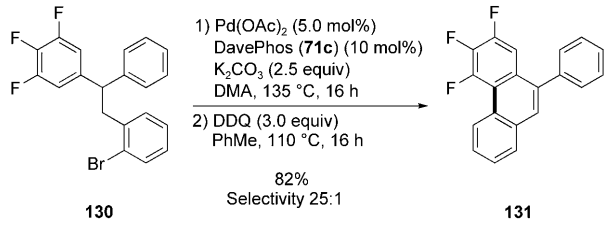
Palladium-catalyzed direct arylations with aryl (pseudo)-halides are believed to proceed through initial oxidative addition of the electrophile to a palladium(0) catalyst. A number of potential mechanisms have been proposed for the subsequent functionalization of the C–H bond.[10f,h] These include an electrophilic aromatic substitution (S_EAr) (Scheme 51a), a concerted S_E3 process (b), a σ-bond metathesis (c), a Heck-type carbometalation (d), and an oxidative addition (e).



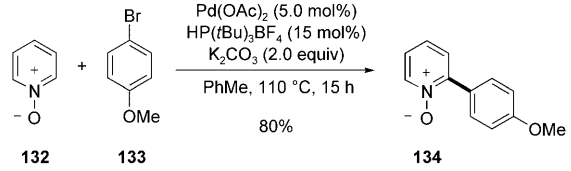
Scheme 51. Proposed mechanisms for the C–H bond functionalization in catalytic direct arylation reactions.

Even though the exact mechanism of a given reaction strongly depends on the nature of the substrates, palladium catalysts, solvents, and/or additives, S_EAr reactions, C–H bond oxidative additions, and Heck processes have historically been favored. However, a number of important recent experimental and computational studies supported concerted S_E3 or σ-bond metathesis mechanisms, which were recently termed concerted metalation/deprotonation (CMD) processes.[92,93] Thus, elegant intramolecular competition experiments by Echavarren and co-workers showed that the less nucleophilic, yet more C–H acidic, fluorinated arene ring of substrate **130** was preferentially functionalized (Scheme 52).[94–97] In combination with computational studies by Maseras and co-workers, a S_EAr mechanism was hence proven to be less likely operative in these transformations.

Fagnou and co-workers observed independently that electron-deficient heteroarenes, such as pyridine *N*-oxide (**132**), could be regioselectively arylated at the C2-position through a palladium(0)/palladium(II) cycle (Scheme 53).[75,98] Notably, this transformation represents a valuable alternative to the use of often unstable organometallic 2-pyridyl deriv-

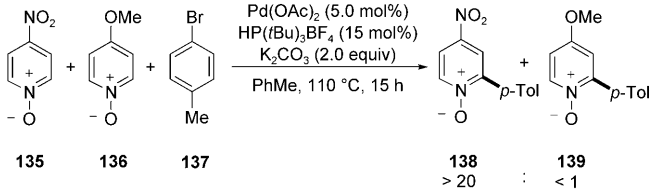


Scheme 52. Intramolecular competition experiment with substrate **130**.



Scheme 53. Palladium-catalyzed direct arylation of pyridine *N*-oxide (**132**).

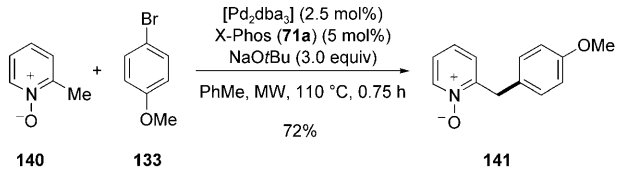
atives[99,100] in traditional cross-coupling reactions.[101] Intermolecular competition experiments revealed that the less nucleophilic, but more C–H acidic pronucleophiles reacted preferentially (Scheme 54). In addition, the observed intermolecular primary kinetic isotope effect (KIE) of 4.7 could not be rationalized with an S_EAr mechanism.[75]



Scheme 54. Intermolecular competition experiment.

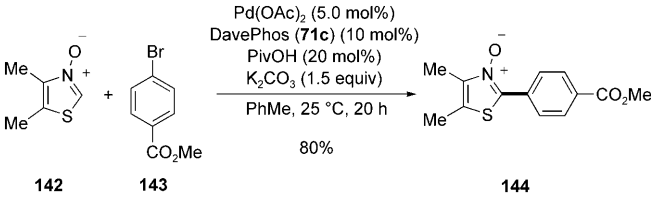
Interestingly, when a methyl group was present at the C2-position of the heteroarene, regioselective arylation could be accomplished at either the C6-position or the heterobenzylic C(sp^3)–H bond through the judicious choice of reaction conditions. Thus, the use of a catalytic system comprising [$Pd_2(dba)_3$] and X-Phos (**71a**), along with NaO*t*Bu as the base, allowed direct arylation to proceed exclusively at the heterobenzylic position (Scheme 55).[102,103]

Moreover, Fagnou and co-workers found that higher reactivity was not only observed for *N*-oxides of electron-deficient six-membered N-heterocycles, but also for *N*-oxides derived from electron-rich five-membered heteroarenes.



Scheme 55. Palladium-catalyzed regioselective direct arylation of pyridine *N*-oxide **140**.

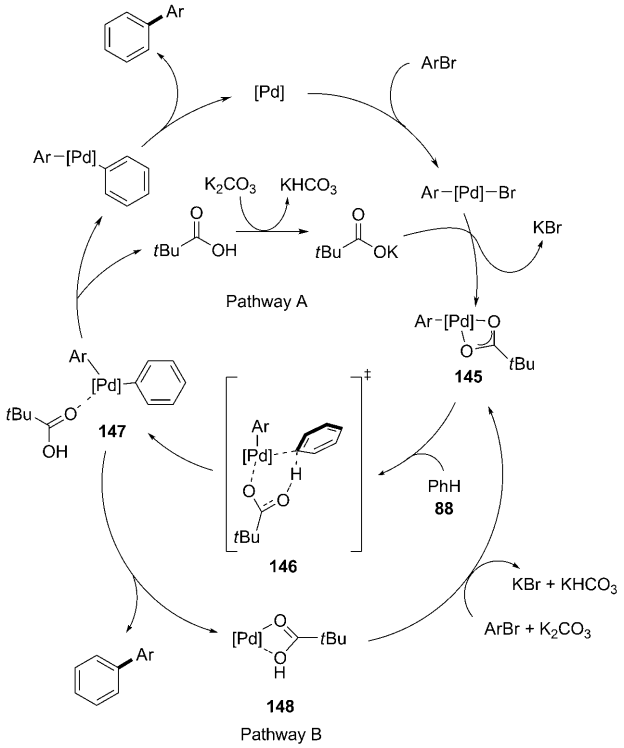
Thus, azole *N*-oxides could be directly arylated at ambient temperature. Here, the catalytic efficiency was significantly improved by the addition of pivalic acid as a co-catalyst, which ultimately enabled the regioselective preparation of fully decorated azoles (Scheme 56).[104,105] The addition of pivalates had previously proven beneficial for palladium-catalyzed direct arylations.[106]



Scheme 56. Palladium-catalyzed direct arylation of azole *N*-oxide **142**.

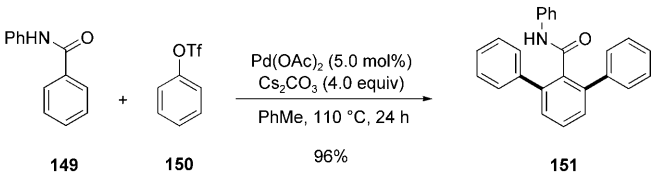
These experimental and computational studies suggested that the pivalate anion acted as a proton shuttle.[97,107] Consequently, a mechanism was proposed in which the pivalate anion displaces a bromide to yield palladium complex **145** (Scheme 57). Subsequently, a CMD occurs[93] to give intermediate **147** through transition state **146**. Thereafter, two different reaction pathways A or B could be operative, both of which regenerate the catalytically active species **145**.

The principle of chelation control has enabled palladium-catalyzed intermolecular direct arylations of arenes to be performed regioselectively. In pioneering studies, Miura and co-workers developed methods for the direct arylation of



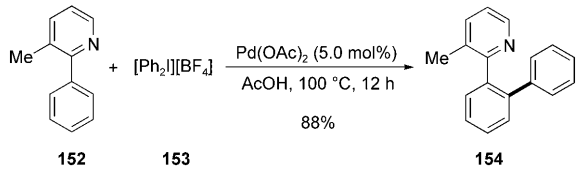
Scheme 57. Proposed mechanism for the direct arylation of arenes in the presence of pivalic acid as a proton shuttle.

aromatic carbonyl compounds, such as ketones, amides, or aldehydes, with aryl bromides or triflates used as the electrophiles (Scheme 58).[108,109]



Scheme 58. Palladium-catalyzed direct arylation of amide **149**.

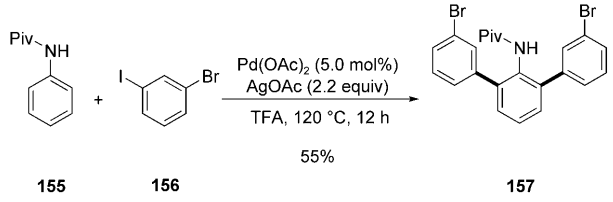
More recently, Sanford and co-workers investigated the use of iodonium salts, such as $[Ph_2I][BF_4]$ (**153**), for the direct arylation of 2-aryl pyridines (Scheme 59).[27] Here, detailed



Scheme 59. Palladium-catalyzed regioselective direct arylation of 2-aryl pyridine **152** with iodonium salt **153**.

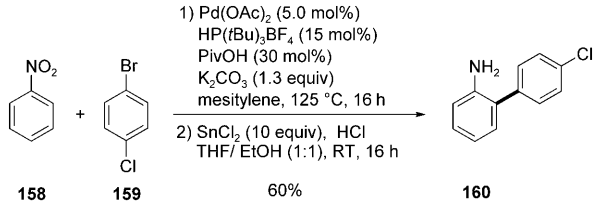
mechanistic studies indicated that a palladium(II)/palladium(IV) catalytic cycle[110–112] was operative rather than a palladium(0)/palladium(II) cycle, which had generally been proposed for direct arylations with aryl (pseudo)halides as electrophiles.[27] Importantly, the same method enabled the regioselective direct arylation of indoles at the C2-position to proceed at ambient temperature.[113] A major limitation of this method is the use of iodonium salts, which are often not commercially available or are relatively expensive to prepare from the corresponding aryl iodides.

More easily accessible aryl iodides were employed by Daugulis et al. for related direct arylations, which required the use of silver salts as additives in stoichiometric amounts. In this way, anilide,[114,115] benzylamine,[116] pyridine, and pyrazole[117] derivatives were regioselectively functionalized with aryl iodides (Scheme 60). Based on competition experiments, as well as, literature precedent for the formation of palladium(IV) species in reactions with alkyl halides,[110–112] a palladium(II)/palladium(IV) mechanism was proposed to be operative in these arylations.[114] With respect to organic synthesis, it is noteworthy that Corey and co-workers and employed this approach for the selective arylation of $C(sp^3)$–H bonds in α-amino acid derivatives.[118]



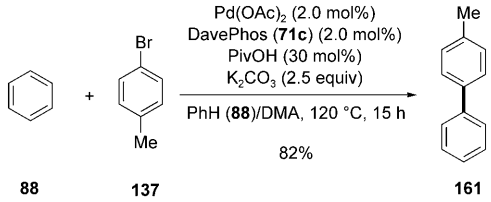
Scheme 60. Palladium-catalyzed chemoselective direct arylation.

A remarkable application of the pivalic acid modified catalytic system to the direct arylation of nitrobenzene derivatives was disclosed by Fagnou and co-workers (Scheme 61).[119] The practical importance of this method was highlighted by an efficient preparation of Boscalid intermediate **160** by a one-pot reaction involving a catalytic direct arylation and a subsequent reduction of the nitro group.



Scheme 61. Synthesis of Boscalid intermediate **160**.

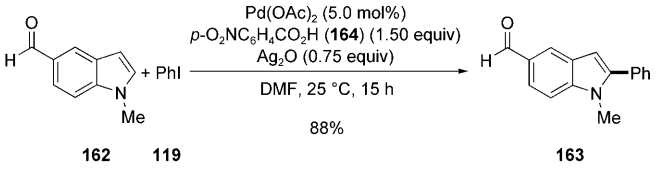
Direct arylations of arenes not bearing directing groups are scarce. In pioneering studies, Dyker et al.[120–124] and Miura et al.[122–124] reported the direct arylation of azulenes and metallocenes. More recently, Lafrance and Fagnou found that co-catalytic amounts of pivalic acid allowed for the effective palladium-catalyzed direct arylation of unactivated arenes, such as benzene (**88**; Scheme 62).[92]



Scheme 62. Palladium-catalyzed direct arylation of benzene (**88**).

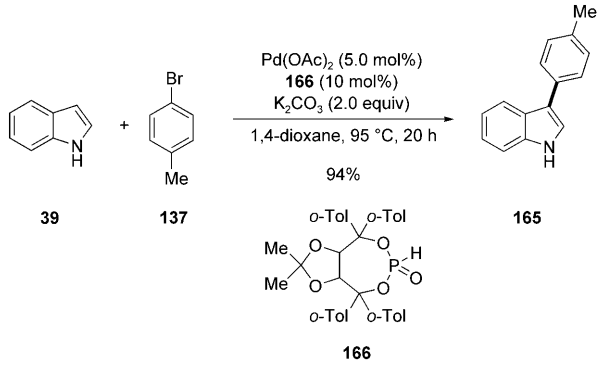
Indoles are arguably the most abundant heteroarene structures in biologically active compounds and natural products.[10j,125] Therefore, significant research effort has been directed towards the development of efficient and regioselective direct arylations of these electron-rich heteroarenes.[126] The intermolecular[127] functionalization of C–H bonds usually proceeded selectively at the C2-position in palladium-catalyzed transformations of 2,3-unsubstituted indoles. For example, Sames and co-workers devised a phosphine-free palladium catalyst for the direct arylation of indoles with C2 selectivity.[128] Highly efficient direct arylations at ambient temperature were, in contrast, accomplished through the use of aryl iodides as arylating reagents, along with *p*-nitrobenzoic acid and Ag_2O as additives (Scheme 63).[129]

More recently, generally applicable methods for the palladium-catalyzed regioselective C3-arylation of 2,3-unsubstituted indoles were elaborated. Zhang, He et al. disclosed a method for the direct arylation of unprotected indole derivatives with C3 selectivity[130] by employing aryl bromides as electrophiles and a well-defined palladium complex derived from a secondary phosphine oxide (SPO).[131,132] Unfortunately, this procedure proved not to be applicable



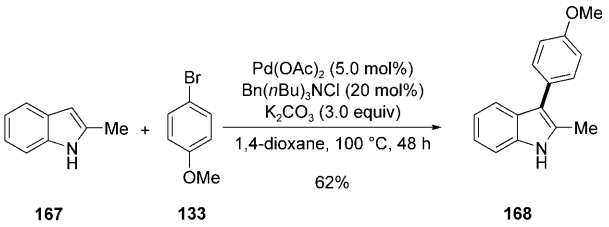
Scheme 63. Palladium-catalyzed regioselective direct arylation of indole **162** at ambient temperature.

to indole derivatives with substituents at the C2-position. In contrast, an in situ generated palladium complex derived from air-stable heteroatom-substituted secondary phosphine oxide (HASPO) preligand **166** set the stage for the regioselective direct arylation of indole derivatives, and notably also of 2-substituted indole derivatives (Scheme 64).[133]



Scheme 64. Palladium-catalyzed direct arylation of indole **39** using HASPO **166** as a preligand.

Furthermore, Bellina et al. showed that the palladium-catalyzed direct arylation of indoles can be achieved at the C3-position by using either PCy_3 or $Bn(nBu)_3NCl$ as additives (Scheme 65).[134] The elegantly developed procedure relying

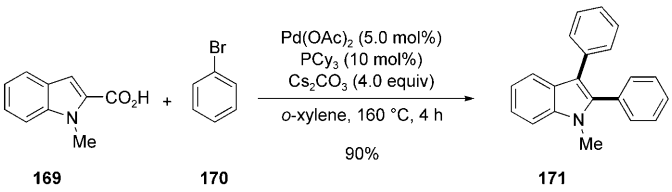


Scheme 65. Palladium-catalyzed direct arylation of indole **167**.

on the use of the latter, as well as a heterogeneous catalytic system ($[Pd(NH_3)_4]^{2+}$/NaY) employed by Djakovitch et al.,[135,136] displayed a remarkably broad scope, which included efficient C–H bond functionalizations of sterically more demanding 2-substituted indoles.

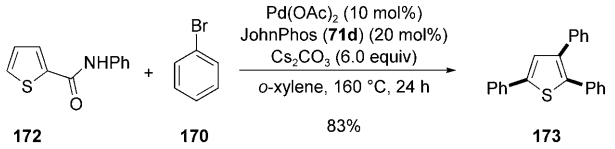
Miura and co-workers developed a sequential arylation involving a direct arylation at the C3-position along with a decarboxylative arylation[81] at the C2-position which provided access to substituted indoles with valuable optical solid-state properties (Scheme 66).[137]

These decarboxylative arylations and related processes were previously exploited by Miura and co-workers for



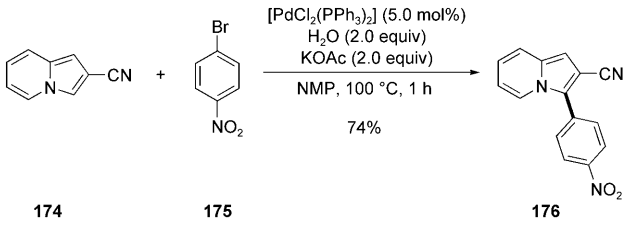
Scheme 66. Palladium-catalyzed sequential direct arylation.

intriguing sequential arylations. In a representative example, a sequence consisting of a direct arylation and a decarbamoylation allowed for the preparation of triarylated product **173** (Scheme 67).[138]



Scheme 67. Palladium-catalyzed multiple arylation of thiophene **172**.

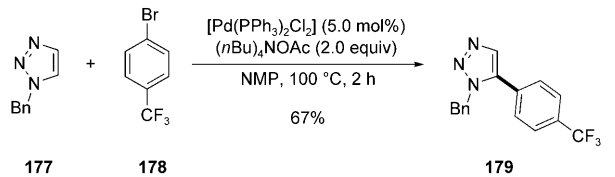
Gevorgyan and co-workers found that the direct arylation of indolizines with aryl bromides proceeded regioselectively at the C3-position (Scheme 68).[139] Detailed mechanistic



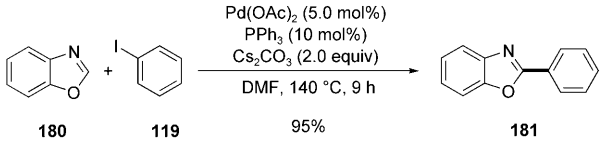
Scheme 68. Palladium-catalyzed direct arylation of indolizine **174**.

studies supported the reaction proceeding by a S_EAr mechanism. The same research group subsequently developed a palladium-catalyzed direct arylation of 1,2,3-triazoles with aryl bromides as the organic electrophiles.[140] On the basis of experimental and computational studies, the authors proposed that the reaction likely proceeds through a S_EAr-type mechanism. In agreement with this proposal, mono-N-substituted triazole **177** underwent exclusive arylation at the C5-position (Scheme 69).

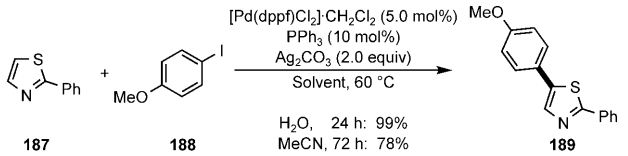
A variety of electron-rich azoles was directly arylated efficiently with aryl iodides, triflates,[141] and bromides as electrophiles.[142] Specifically, benzoxazoles turned out to be excellent substrates for palladium-catalyzed direct arylation, which occurred selectively at the C2-position (Scheme 70).[143]



Scheme 69. Palladium-catalyzed direct arylation of 1,2,3-triazole **177**.

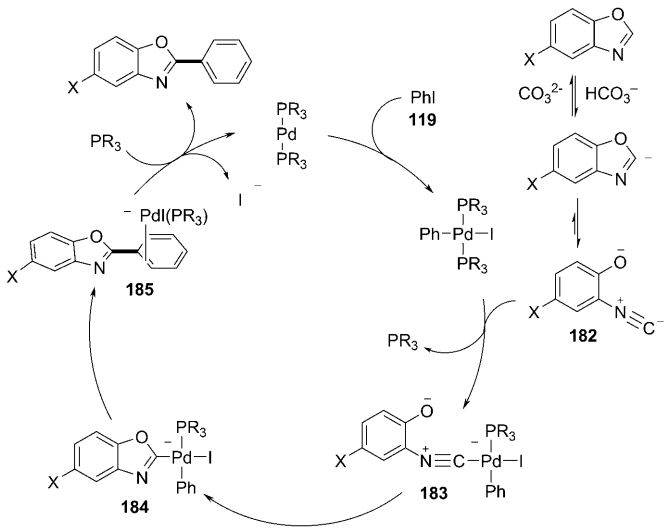


Scheme 70. Palladium-catalyzed direct arylation of benzoxazole (**180**).



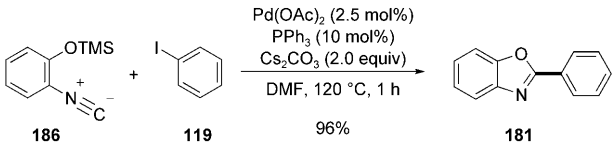
Scheme 73. Solvent effect in the direct arylation of thiazole **187.**

Interestingly, detailed kinetic and computational studies by Sánchez and Zhuravlev provided strong evidence for the formation of phenolates as key intermediates in these transformations.[144] Thus, initial deprotonation of benzoxazole gives rise to a carbanion, which is in equilibrium with 2-isocyanophenolate **182** (Scheme 71). Coordination of a palladium(II) complex to isocyanide **182** subsequently yields precursor **183**, which can undergo a cyclization/reductive elimination sequence. This mechanistic rationale was further supported by the conversion of isocyanide **186** into phenylated benzoxazole **181** under otherwise identical reaction conditions (Scheme 72).



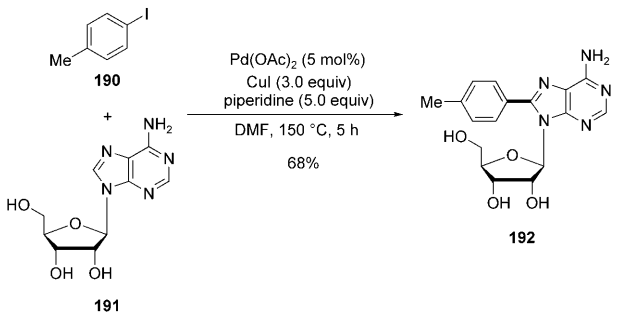
Scheme 71. Proposed mechanism for the palladium-catalyzed direct arylation of benzoxazoles.

A method for the highly efficient palladium-catalyzed direct arylation of thiazoles was recently disclosed by Greaney and co-workers.[145] Interestingly, catalytic reactions proceeded significantly faster when being performed "on water" than those conducted in organic solvents. Aryl iodides served here as electrophiles, and the use of stoichiometric amounts of silver salts was found to be beneficial (Scheme 73). Notably, heteroarenes displaying a set of different functional groups could be employed, a valuable asset for further applications of this method to organic synthesis.



Scheme 72. Palladium-catalyzed arylation of isocyanide **186**.

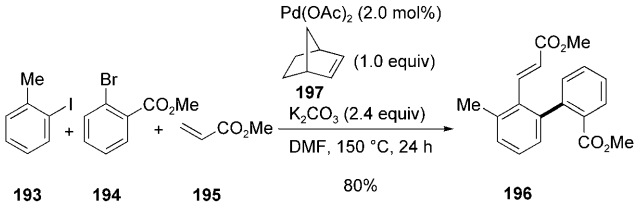
Thus far, only a few applications of catalytic direct arylation through the cleavage of C–H bonds to give more complex organic substrates have been reported.[146] However, biologically relevant purine bases were recently functionalized directly with aryl iodides as coupling partners and stoichiometric amounts of CuI as additives.[147] Hocek and co-workers also found that the secondary amine piperidine allowed for the first direct arylation of unprotected purine nucleosides (Scheme 74).[148] However, minor amounts of diarylated product stemming from N-arylations were formed as undesired by-products here. To address this problem, Fairlamb and co-workers suggested the use of Cs_2CO_3 as a base.[149] This modified procedure proved applicable to a variety of aryl iodides, thereby providing access to a diverse array of arylated adenine nucleosides.



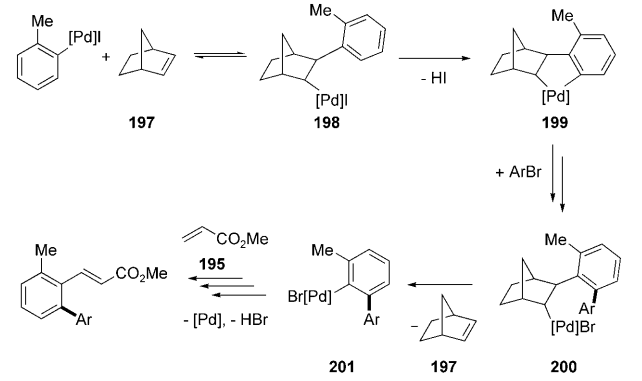
Scheme 74. Palladium-catalyzed direct arylation of purine nucleoside **191**.

The use of strained alkene norbornene (**197**) as a temporary covalent linker for sequential[150] arylation reactions through the functionalization of C–H bonds was elegantly developed by Catellani and Chiusoli.[151] In a remarkable recent report, the chemo- and regioselective direct arylation of *ortho*-C–H bonds in aryl iodides was achieved by using aryl bromides as coupling partners (Scheme 75).[152,153] An intermolecular Mizoroki–Heck reaction served as the final step of the catalytic cycle in this three-component reaction.

The mechanism of these regioselective arylation reactions involves initial oxidative addition of the aryl iodide to a palladium(0) species, and subsequent insertion of norbornene into the formed palladium–carbon bond to give intermediate **198** (Scheme 76). This sets the stage for the regioselective functionalization of an *ortho*-C–H bond in an intramolecular fashion, thereby affording palladacycle **199**. Thereafter, a sequence consisting of formal oxidative addition and reduc-



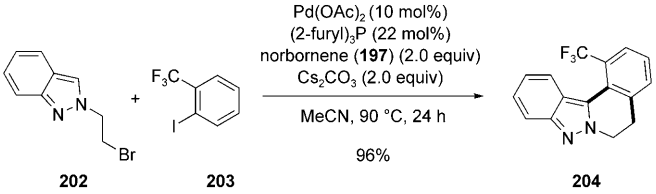
Scheme 75. Palladium-catalyzed norbornene-mediated direct arylation of arene **193**.



Scheme 76. Proposed mechanism for palladium-catalyzed norbornene-mediated direct arylation.

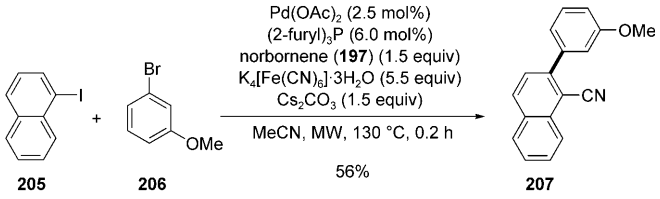
tive elimination affords complex **200**, which evolves into complex **201** through a β elimination. Finally, a Mizoroki–Heck reaction with alkene **195** yields the desired product. Although there is evidence for the formation of palladium(IV) intermediates in comparable functionalizations of *ortho*-C–H bonds when using alkyl halides,[110,112] recent studies suggest that the palladium(IV) species are not the relevant intermediates in the arylation with bromides.[154]

Valuable recent applications of this powerful concept towards the direct arylation of (hetero)arenes were designed by Lautens et al.[155] For example, polycyclic 2*H*-indazoles were obtained by a palladium-catalyzed annulation (Scheme 77),[156] and a direct arylation/cyanation sequence afforded substituted benzonitriles (Scheme 78).[157]



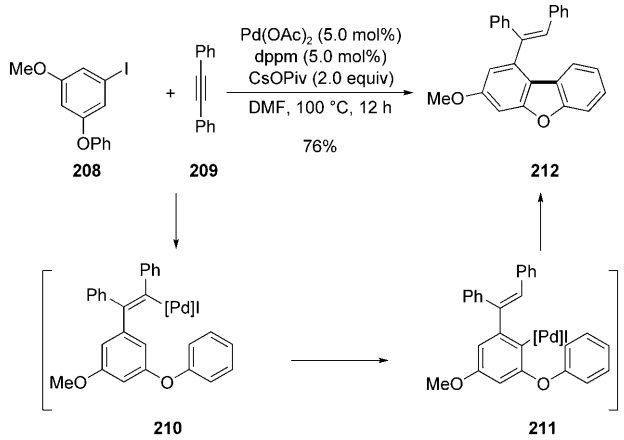
Scheme 77. Synthesis of indazole **204** through functionalization of C–H bonds.

An elegant reaction sequence based on a catalytic direct arylation involving palladium migration was realized by Larock and co-workers. Interestingly, these early reports already highlighted that, among a variety of bases, CsOPiv was optimal.[106] More recently, this strategy was utilized, for example, for the modular synthesis of substituted carbazoles,



Scheme 78. Palladium-catalyzed direct arylation/cyanation sequence.

indoles, and dibenzofurans (Scheme 79).[158] Evidence for the proposed alkenyl to aryl palladium migration mechanism was provided through the use of isotopically labeled starting materials.



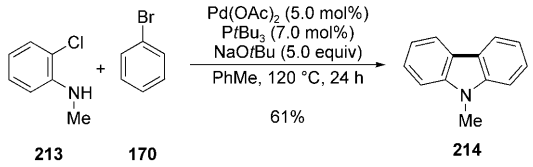
Scheme 79. Catalytic direct arylation involving alkenyl to aryl palladium migration.

4.1.3. Aryl Chlorides

Of the aryl halides, the chlorides are arguably the most useful single class of electrophilic substrates because of their lower cost and the wide range of commercially available compounds. The development of stabilizing ligands enabled applications of these inexpensive substrates to traditional cross-coupling reactions.[159] In contrast, generally applicable methods for the use of aryl chlorides in catalytic direct arylations by cleavage of C–H bonds were only recently developed.

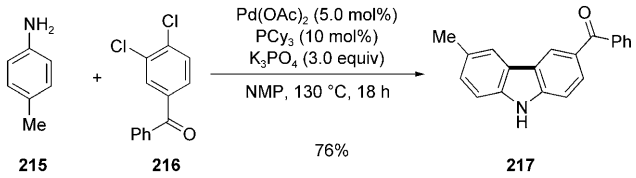
An early example of entropically favored intramolecular direct arylation with aryl chlorides set the stage for the development of a well-designed sequential synthesis of diversely substituted carbazoles.[160–162] Thus, 2-chloroanilines and bromoarenes were efficiently converted into carbazoles through a palladium-catalyzed reaction sequence based on an intermolecular amination with the aryl bromide and a subsequent intramolecular direct arylation with the remaining aryl chloride (Scheme 80). This approach was more recently applied to the synthesis of free NH and fluorinated carbazoles.[163,164]

We developed a direct arylation-based domino reaction, which enabled the efficient synthesis of various N heterocycles, such as indoles and carbazoles, and notably, proved



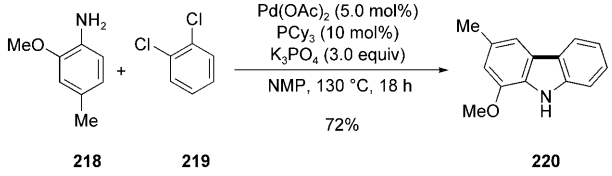
Scheme 80. Palladium-catalyzed sequential synthesis of carbazole **214**.

applicable to substrates bearing solely chlorides as leaving groups.[165] This modular one-pot transformation of 1,2-dichlorides proceeded regioselectively to deliver both N-substituted and free NH carbazoles (Scheme 81).



Scheme 81. Palladium-catalyzed reaction sequence with 1,2-dichloroarene **216**.

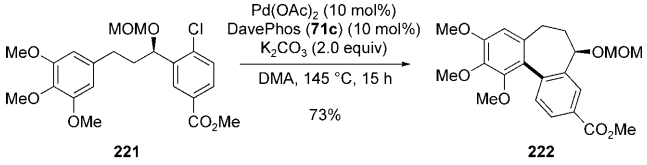
The cost-effective nature of this procedure was illustrated with an efficient synthesis of the cytotoxic, naturally occurring carbazole murrayafoline A (**220**) starting from inexpensive 1,2-dichlorobenzene (**219**; Scheme 82).[165]



Scheme 82. Palladium-catalyzed sequential synthesis of murrayafoline A (**220**).

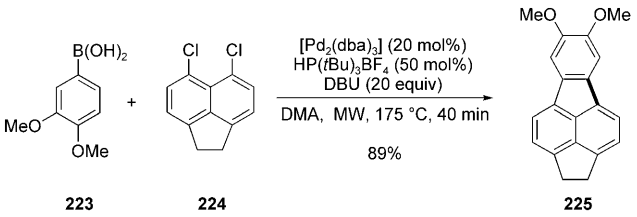
Detailed studies on palladium-catalyzed intramolecular direct arylation with aryl chlorides revealed the beneficial effect of imidazolium salts as N-heterocyclic carbene ligand precursors for the preparation of carbazole, benzofuran, phenanthridine, and chromene derivatives.[166,167] In contrast, the key step of an enantioselective synthesis of allocolchicinoid derivatives occurred most efficiently with a palladium complex derived from the electron-rich phosphine DavePhos (**71c**; Scheme 83).[168]

Palladium-catalyzed intramolecular arylations with aryl chlorides proved not only to be valuable for the synthesis of biologically active compounds, but could also be exploited for



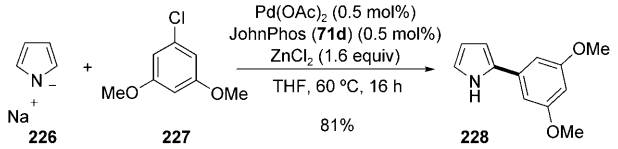
Scheme 83. Palladium-catalyzed intramolecular direct arylation for the synthesis of allocolchicinoid precursor **222**.

the synthesis of functional materials, such as polycyclic aromatic hydrocarbons (PAHs).[169] For example, the preparation of PAHs was accomplished by a palladium-catalyzed cascade reaction involving intermolecular Suzuki–Miyaura reactions and intramolecular direct arylations.[170,171] Accordingly, aryl boronic acids were annulated by dichloroarenes under microwave irradiation reaction conditions (Scheme 84).



Scheme 84. Palladium-catalyzed direct arylation-based cascade reaction for the preparation of aromatic hydrocarbon **225**.

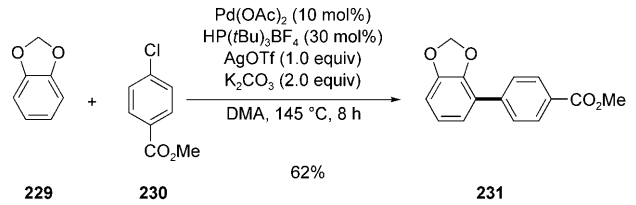
Until recently, only scattered reports have appeared on palladium-catalyzed direct arylations with aryl chlorides that proceeded in an intermolecular fashion, with the C–H bond functionalization by electronically activated heteroaryl chlorides described by Ohta and co-workers being a notable exception.[87,88] Indeed, the development of methods for generally applicable palladium-catalyzed intermolecular direct arylations with aryl chlorides proved to be more challenging. In this context it is noteworthy that a palladium complex derived from the phosphine ligand JohnPhos (**71d**) enabled the conversion of inexpensive aryl chlorides for intermolecular arylations of stoichiometrically metalated pyrroles.[172] With this method, the functionalization of in situ generated N-zincated pyrroles occurred regioselectively at the C2-position (Scheme 85).



Scheme 85. Palladium-catalyzed intermolecular arylation of metalated pyrrole **226**.

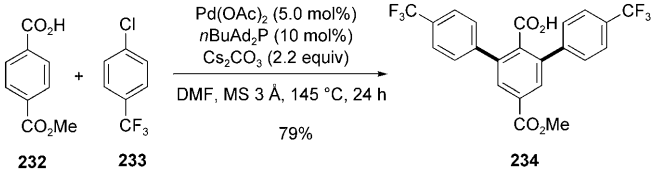
On the basis of their studies on intramolecular direct arylations (see above), Fagnou and co-workers reported two examples of palladium-catalyzed intermolecular direct arylations of arenes with chlorides. Thus, 1,3-benzodioxole (**229**) served as a substrate for the directed direct arylations with aryl bromides, as well as with two aryl chlorides (Scheme 86).[167] Here, the presence of stoichiometric amounts of AgOTf proved to be beneficial to avoid homocoupling of the aryl chloride.

Two methods for the direct arylation of benzoic acids were subsequently disclosed by Daugulis and co-workers, one of which employed aryl chlorides as the electrophiles. Thus, a palladium catalyst derived from the electron-rich phosphine *n*BuAd$_2$P enabled regioselective functionalization of C–H

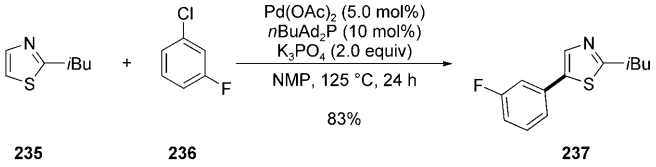


Scheme 86. Palladium-catalyzed direct arylation of 1,3-benzodioxole (**229**).

bonds (Scheme 87).[173] This catalytic system was not limited to the efficient direct arylation of arenes, but also turned out to be applicable to the intermolecular direct arylation of electron-rich heteroarenes with aryl chlorides (Scheme 88).[174]

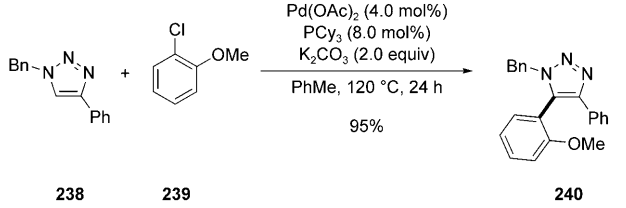


Scheme 87. Palladium-catalyzed direct arylation of benzoic acid **232.**



Scheme 88. Palladium-catalyzed direct arylation of thiazole **235.**

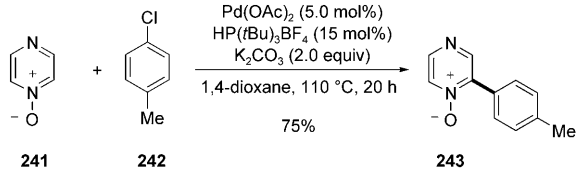
Palladium-catalyzed direct arylation of 1,4-disubstituted heteroaromatic 1,2,3-triazoles with aryl chlorides as the arylating reagents were independently accomplished.[175,176] Although microwave irradiation could be employed for direct arylations at a reaction temperature of 250 °C,[176] a procedure for mild, yet generally applicable palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl chlorides made use of conventional heating.[175] Thus, intermolecular as well as intramolecular arylations were made possible at a reaction temperature of 120 °C, and proved applicable to aryl chlorides, even when being electronically deactivated and/or sterically hindered (Scheme 89).



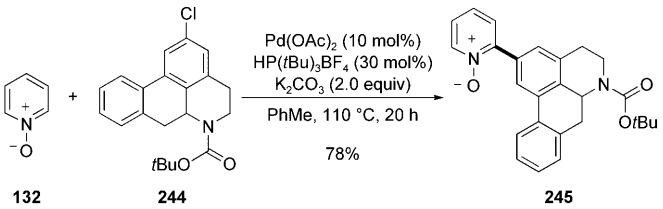
Scheme 89. Palladium-catalyzed direct arylation of 1,2,3-triazole **238** with aryl chloride **239.**

More recently, electronically activated aryl chlorides were employed for the direct arylation of benzoxazoles, thiazoles, furans, and thiophenes by using [PdCl(dppb)(C_3H_5)] as the catalyst.[177]

Electron-deficient heteroarenes, such as diazine *N*-oxides **241**, could be arylated with aryl chlorides through a concerted metalation/deprotonation mechanism with the aid of an in situ generated palladium complex derived from electron-rich phosphine P(*t*Bu)$_3$ (Scheme 90).[178] An elegant application of this method enabled the straightforward synthesis of aporphine analogues in high yields (Scheme 91).[179,180]

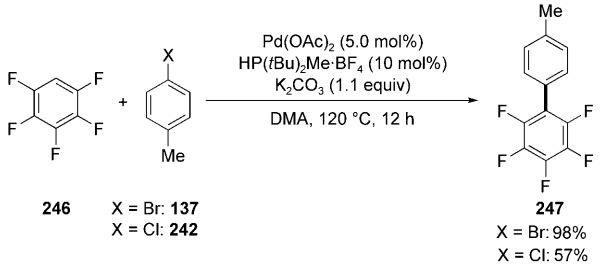


Scheme 90. Palladium-catalyzed direct arylation of diazine *N*-oxide **241**.



Scheme 91. Synthesis of aporphine analogue **245** by direct arylation.

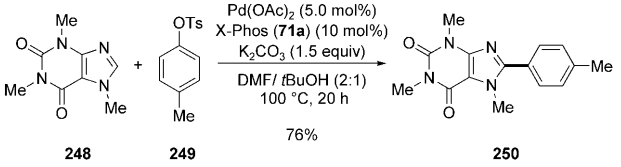
Intermolecular palladium-catalyzed direct arylation of substrates with relatively acidic C–H bonds was not restricted to heteroaromatic *N*-oxides, but could also be accomplished with oligofluoroarenes. Thus, a palladium-catalyst generated in situ from the phosphonium salt HP(*t*Bu)$_2$Me·BF$_4$ allowed the use of aryl iodides, bromides, and chlorides. However, significantly lower yields of the desired product **247** were obtained with the latter electrophiles (Scheme 92).[181] Thereafter, an improved procedure for the direct arylation of oligofluoroarenes was developed, which relied on the use of biaryl monophosphine S-Phos (**71e**).[182] The relative reactivities and selectivities observed when using differently substituted fluoroarenes were explained with a CMD mechanism.[181]



Scheme 92. Palladium-catalyzed direct arylation of electron-deficient arene **246**.

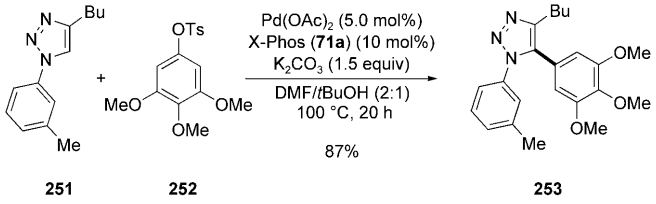
4.1.4. Aryl Tosylates and Mesylates

The use of aryl tosylates or mesylates as electrophiles in cross-coupling reactions is highly desirable, because they can be prepared from readily available starting materials with inexpensive reagents. Furthermore, these sulfonates are easy to handle, given that they are stable towards hydrolysis and are highly crystalline. Unfortunately, their improved stabilities translate into significantly reduced reactivity in catalytic coupling reactions. As a result, methods for palladium-catalyzed direct arylation[183] through cleavage of C–H bonds with these aryl sulfonates were achieved only very recently. Thus, we reported the first palladium-catalyzed direct arylations of electron-rich heteroarenes with aryl tosylates as electrophilic coupling partners.[184] Specifically, a palladium complex derived from phosphine X-Phos (**71a**) set the stage for the efficient direct arylation of various heteroarenes, such as oxazoles or caffeine (**248**; Scheme 93).



Scheme 93. Palladium-catalyzed direct arylation of caffeine (**248**) with tosylate **249**.

Furthermore, this catalytic system allowed for the functionalization of C–H bonds on 1,2,3-triazoles even with electron-rich, thus electronically deactivated, aryl tosylates (Scheme 94).[184]

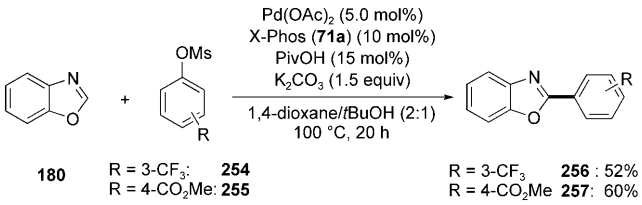


Scheme 94. Palladium-catalyzed direct arylation of 1,2,3-triazole **251** with tosylate **252**.

Processes utilizing aryl mesylates as electrophiles are more atom-economical than those employing tosylates because of their significantly lower molecular weights. Therefore, it is noteworthy that the above mentioned catalyst also facilitated the direct arylation of benzoxazole (**180**) with moisture-stable aryl mesylates (Scheme 95).[184]

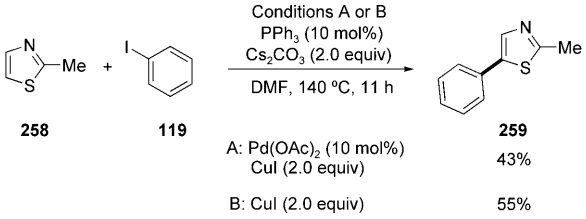
4.2. Copper-Catalyzed Direct Arylation

Until recently, the direct arylation of (hetero)arenes was almost exclusively realized through palladium, rhodium, or ruthenium catalysis. However, an important observation was made by Miura and co-workers, in that the addition of stoichiometric amounts of copper salts proved to be beneficial



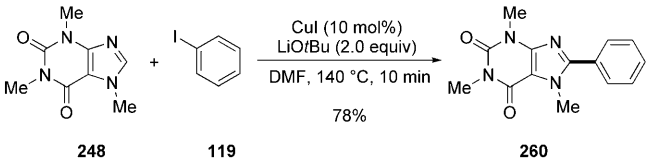
Scheme 95. Palladium-catalyzed direct arylation of benzoxazole (**180**) with mesylates **254** and **255**.

for palladium-catalyzed direct arylation reactions.[143,185,186] Interestingly, in selected examples, higher yields of isolated products were obtained in copper-mediated direct arylations in the absence of a palladium catalyst (Scheme 96).



Scheme 96. Copper-mediated direct arylation of thiazole **258**.

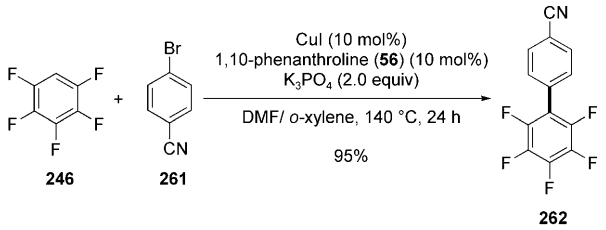
More recently, Do and Daugulis found that catalytic amounts of inexpensive CuI enabled the direct arylation of electron-rich N heteroarenes with aryl iodides as electrophiles (Scheme 97).[187] This ligand-free catalytic system



Scheme 97. Copper-catalyzed direct arylation of caffeine (**248**).

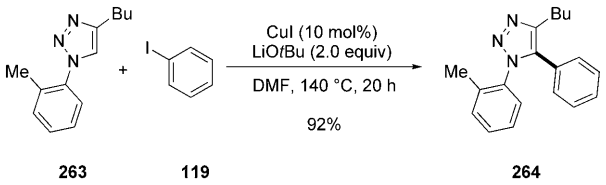
required the use of the relatively strong base LiO*t*Bu, thereby limiting its functional-group tolerance to some extent. As to the reaction mechanism, detailed studies suggested an initial deprotonation of the heteroarene by the base LiO*t*Bu, along with a subsequent lithium–copper transmetalation. Given its deprotonation-based mechanism, the method was found to be restricted to heteroarenes displaying $C(sp^2)$–H bonds with pK_a values (DMSO) below 35.[188]

Substrates bearing more acidic C–H bonds with pK_a values (DMSO) below 27 could, in contrast, be directly functionalized with the weaker base K_3PO_4, provided that 1,10-phenanthroline (**56**) was employed as the ligand. This approach allowed, for example, electron-deficient (hetero)-arenes to be arylated with catalytic amounts of CuI. For example, pyridine *N*-oxides or oligofluoroarenes served as pronucleophiles, and even aryl bromides could be used as electrophilic coupling partners with this N ligand/CuI catalytic system (Scheme 98).[188–190]



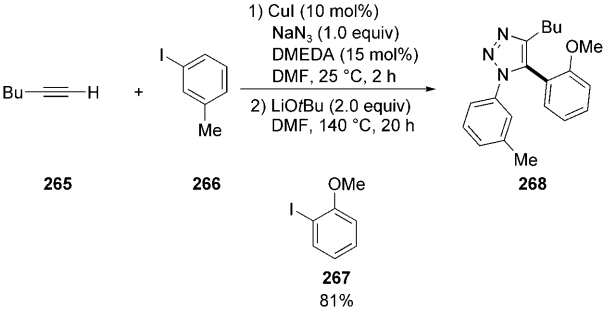
Scheme 98. Copper-catalyzed direct arylation of pentafluorobenzene (**246**).

The remarkable efficiency and selectivity accomplished with copper catalysts in Huisgen cycloadditions of organic azides with alkynes resulted in its application in various research areas, ranging from bioorganic and medicinal chemistry to material sciences.[191] This "click" reaction proceeded regioselectively when using terminal alkynes, thereby providing 1,4-disubstituted 1,2,3-triazoles as the sole products. In contrast, [3+2] cycloadditions of the corresponding internal alkynes for the synthesis of fully substituted 1,2,3-triazoles were found either not to be generally applicable or gave rise to mixtures of regioisomers.[192] An alternative approach was, however, established by the copper-catalyzed direct arylation of 1,4-disubstituted 1,2,3-triazoles, which proceeded chemoselectively at the heteroaromatic groups (Scheme 99).[193]



Scheme 99. Copper-catalyzed direct arylation of 1,2,3-triazole **263**.

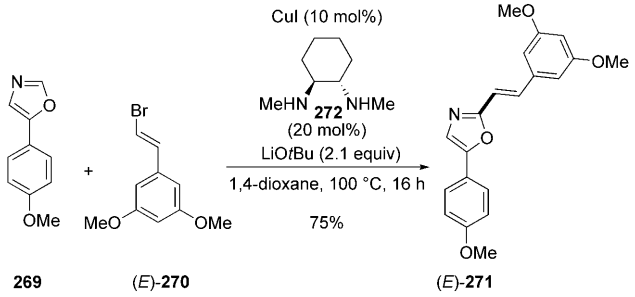
The overall efficiency of this economically attractive strategy was significantly improved by its combination with a mechanistically distinct process within a sustainable one-pot reaction. Since 1,4-disubstituted 1,2,3-triazoles are usually prepared through copper-catalyzed 1,3-dipolar cycloadditions of terminal alkynes with organic azides, the use of a single copper compound for a first direct arylation-based sequential catalysis was probed. This approach allows the modular chemo- and regioselective synthesis of fully substituted 1,2,3-triazoles (Scheme 100). Notably, the overall reaction involved



Scheme 100. Copper-catalyzed modular multicomponent synthesis of 1,2,3-triazole **268**.

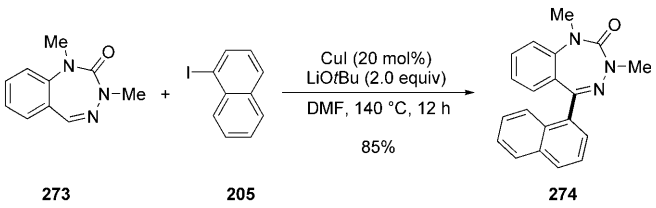
the selective coupling of four components through the formation of one C–C and three C–N bonds.[193]

Highly regio- and diastereoselective copper-catalyzed direct alkenylations of oxazoles were realized with vicinal diamine **272** as the ligand.[194] As was previously observed, the addition of the strong base LiO*t*Bu was mandatory. The scope of this procedure was highlighted by the efficient synthesis of alkaloid annuloline ((*E*)-**271**; Scheme 101).



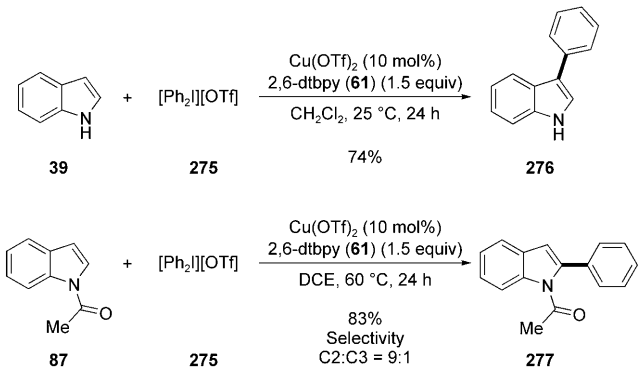
Scheme 101. Synthesis of annuloline ((*E*)-**271**) through copper-catalyzed direct alkenylation.

A very recent application of copper-catalyzed direct arylation to the functionalization of C–H bonds in the privileged pharmacophore benzotriazepine was disclosed by Yotphan, Bergman, and Ellman.[195] Whereas attempted rhodium-catalyzed direct arylations were unsuccessful, a system comprising CuI as the catalyst and LiO*t*Bu as the base resulted in the envisioned transformation. As previously observed, the N-ligand-free catalyst was found to be limited to the use of aryl iodides as electrophilic coupling partners (Scheme 102).



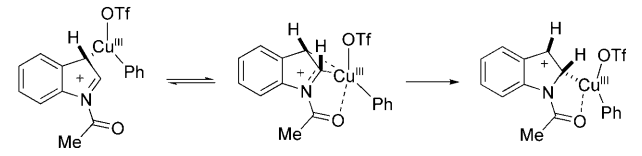
Scheme 102. Copper-catalyzed direct arylation of benzotriazepine **273**.

The regioselective direct arylation of indoles at either the C2- or C3-positions was accomplished by Gaunt and co-workers with a ligand-modified copper catalyst in combination with [Ph_2I][OTf] (**275**) as the arylating reagent.[196] This transformation took place under remarkably mild reaction conditions, and various functional groups were tolerated. As in palladium-catalyzed direct arylations, a major limitation of this procedure is the use of iodonium salts, which are often not commercially available or are relatively expensive. Notably, the regioselectivity of this transformation was strongly dependent on the substituents on the nitrogen atom, a feature somewhat reminiscent of the early observations by Ohta and co-workers in regard to palladium-catalyzed direct arylations.[87,88] While free NH or N-alkylated indoles predominantly gave rise to functionalization at the C3-position, complementary selectivities were observed with *N*-acyl indoles (Scheme 103).[196] The change in selectivity was



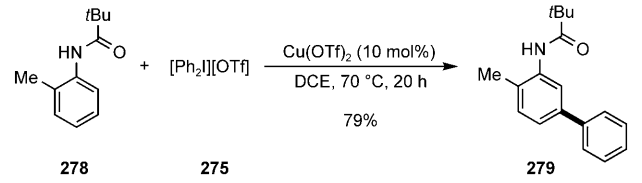
Scheme 103. Copper-catalyzed regioselective direct arylation of indoles **39** and **87**.

attributed by Gaunt and co-workers to an initial functionalization at the C3-position and a subsequent chelation-controlled isomerization when a Lewis-basic acyl substituent was present on the nitrogen atom (Scheme 104).[196]



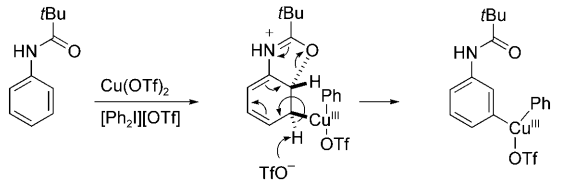
Scheme 104. Mechanistic rationale for the regioselective copper-catalyzed direct arylation of indoles.

meta-Selective functionalization of C–H bonds of monosubstituted arenes has proven to be elusive until recently. Phipps and Gaunt developed a copper-catalyzed *meta*-selective arylation of acetanilides, which made use of $Cu(OTf)_2$ as the catalyst and iodonium salts as the arylating agents (Scheme 105).[197,198] Detailed mechanistic insight into this



Scheme 105. Copper-catalyzed *meta*-selective direct arylation of pivanilide **278**.

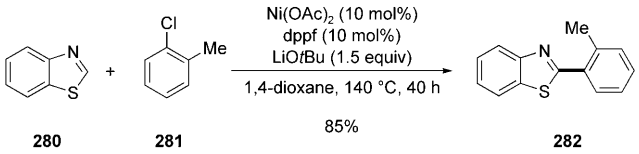
catalytic system is not yet available. However, a highly electrophilic copper(III)-aryl species was proposed to be involved as a key intermediate, which sets the stage for an oxy-cupration of the arene through attack by the carbonyl moiety (Scheme 106). This dearomatization, thus, results in a cupration at the *meta* position. Subsequent rearomatization and reductive elimination finally deliver the desired product.[197]



Scheme 106. Proposed mechanism for copper-catalyzed *meta*-selective direct arylation.

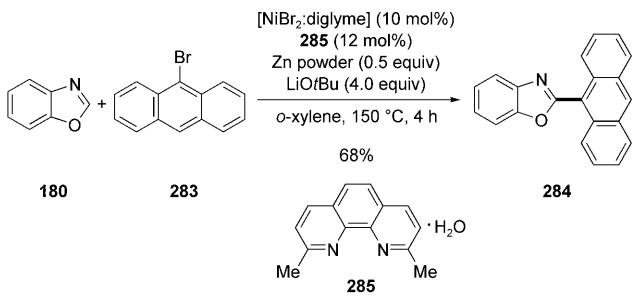
4.3. Nickel-Catalyzed Direct Arylation

An important advance in the functionalization of C–H bonds was recently made with the development of nickel-catalyzed direct arylation of electron-rich heteroarenes, as independently reported by the research groups of Itami[199] and Miura.[200] Optimization studies performed by Itami and co-workers revealed that N,N ligands and inexpensive $Ni(OAc)_2$ allowed the efficient direct arylation of various heteroarenes.[199] As was observed earlier for copper-catalyzed processes, the use of LiO*t*Bu as a base turned out to be necessary to obtain satisfactory yields. Importantly, this procedure enabled catalytic direct arylations with aryl iodides as well as aryl bromides as electrophiles. Furthermore, direct arylations could even be achieved with more convenient aryl chlorides as coupling partners when using dppf as the ligand (Scheme 107).



Scheme 107. Nickel-catalyzed direct arylation of benzothiazole (**280**).

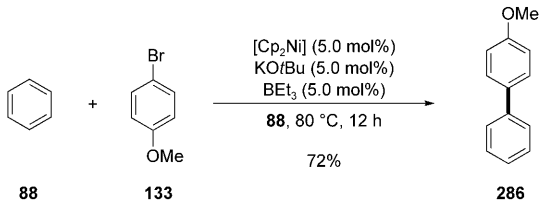
Miura and co-workers made use of $NiBr_2$ as a catalyst precursor, 2,9-dimethyl-1,10-phenanthroline hydrate (**285**) as a ligand, and LiO*t*Bu as a base for the direct arylation of oxazoles or thiazoles at the C2-position.[200] A variety of aryl bromides could be coupled, including electron-rich and sterically hindered derivatives (Scheme 108). The addition of zinc powder was found to be beneficial to ensure the generation of the suggested catalytically competent nickel(0) species. Although detailed information on the mechanism of these transformations is not available, they were proposed to



Scheme 108. Nickel-catalyzed direct arylation of benzoxazole (**180**).

occur through an initial oxidative addition of the aryl halide to a catalytically active nickel(0) species. The generated nickel(II) complex thereafter undergoes a transmetalation with an in situ generated organolithium reagent. Finally, a reductive elimination gives rise to the desired arylated product.

The procedures developed by the research groups of Itami and Miura were only applicable to catalytic direct arylations of electron-rich heteroarenes. However, simple arenes, such as benzene (**88**) and naphthalene (**109**), were recently functionalized by using [Cp_2Ni] as the catalyst in combination with catalytic amounts of BEt_3 (Scheme 109).[201] Furthermore, electron-deficient pyridine could also be employed as a substrate, but yielded, just like naphthalene, mixtures of regioisomers. The observed ratios of regioisomers led to a radical-based mechanism being proposed to be less likely.

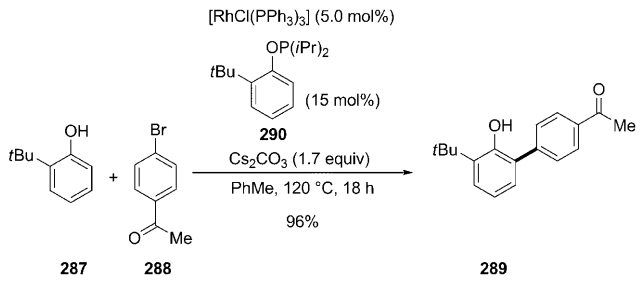


Scheme 109. Nickel-catalyzed direct arylation of benzene (**88**).

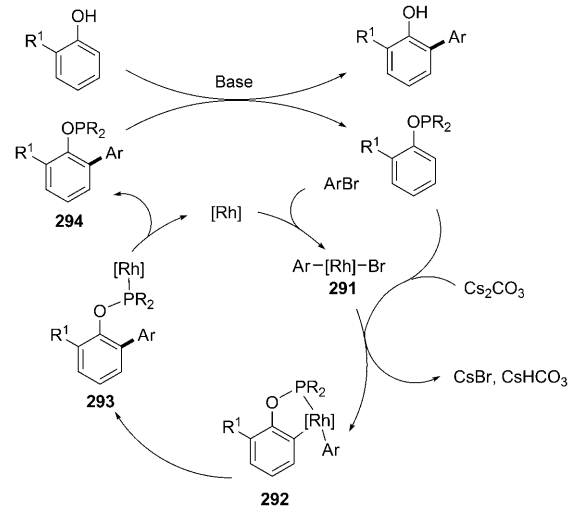
4.4. Rhodium-Catalyzed Direct Arylation

The direct functionalization of C–H bonds of phenols was made possible through rhodium-catalyzed direct arylation with aryl bromides. Thus, Bedford et al. reported that efficient transformations occurred with Wilkinson's catalyst in the presence of the corresponding phosphinites as co-catalysts.[202] Given the remarkably mild reaction conditions, this catalytic system turned out to tolerate a variety of important functional groups, but was found restricted to *ortho*-substituted phenols (Scheme 110).

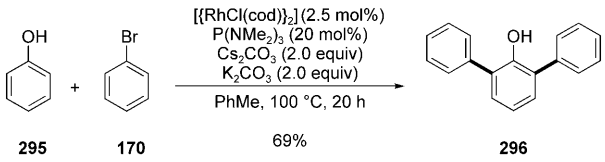
The proposed mechanism commences with an oxidative addition of the aryl bromide to the rhodium(I) catalyst, followed by *ortho*-metalation with the phosphinite. Reductive elimination then occurs to give intermediate **293**. The catalytically active species is regenerated through dissociation of the phosphinite **294** (Scheme 111). Transesterification with the corresponding phenol leads to the desired 2-arylated phenol.[202,203] As a result, the specific phosphinite co-catalyst needs to be prepared for each individual substrate prior to catalysis to avoid formation of undesired and difficult to separate by-products. This limitation was independently addressed by Oi, Inoue et al.[204] as well as by Bedford and Limmert,[205] with the use of inexpensive $P(NMe_2)_3$ as the co-catalyst. Thus, a system comprising [{RhCl(cod)}$_2$] and $P(NMe_2)_3$ proved complementary to the previously reported phosphinite-based catalyst, in that efficient functionalizations of *ortho*-unsubstituted phenols proved viable (Scheme 112).



Scheme 110. Rhodium-catalyzed direct arylation of phenol **287**.



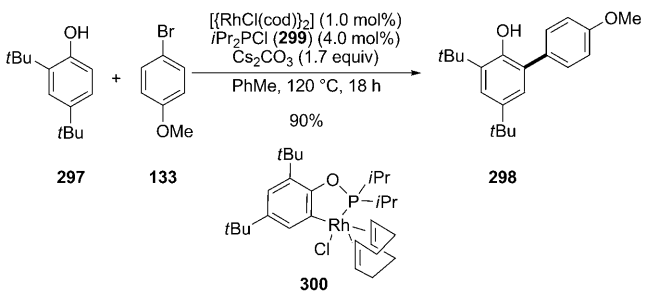
Scheme 111. Proposed mechanism for rhodium-catalyzed direct arylation of phenols.



Scheme 112. Rhodium-catalyzed direct arylation of phenol (**295**).

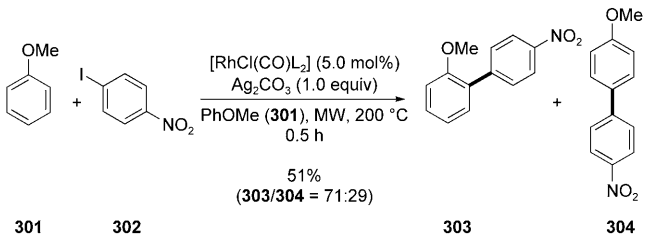
As a less-toxic alternative, chlorophosphines[131,132] were more recently probed as preligands in the rhodium-catalyzed direct arylation of phenols.[206] Among a variety of different chlorophosphine preligands investigated, iPr_2PCl (**299**) gave rise to most efficient catalysis and also enabled a significant reduction in the catalyst loading (Scheme 113). However, a satisfactory efficiency was only obtained with *ortho*-substituted phenols. Independently prepared air-stable rhodium complex **300** was also shown to be catalytically competent. Spectroscopic data indicated an in situ formation of this complex under the reaction conditions, thereby highlighting that these reactions proceed through the formation of a cyclometalated phosphinite complex.

Rhodium-catalyzed direct arylation of simple arenes without directing groups proved viable with $P[(OCH(CF_3)_2)_3]$ as a strong π-accepting ligand under microwave irradiation.[207,208] In the direct arylation of monosubstituted arenes, the absence of chelation control resulted in the formation of



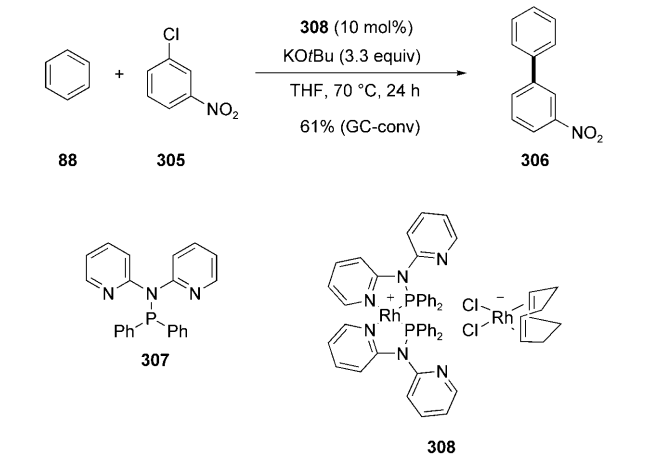
Scheme 113. Direct arylation of phenol **297** using chlorophosphine **299** as a preligand and the well-defined rhodium catalyst **300**.

mixtures of *ortho*- and *para*-substituted regioisomers (Scheme 114). The isomeric ratio indicated that an electrophilic aromatic-substitution-type mechanism was operating.



Scheme 114. Rhodium-catalyzed direct arylation of anisole (**301**). L = P[OCH(CF$_3$)$_2$]$_3$.

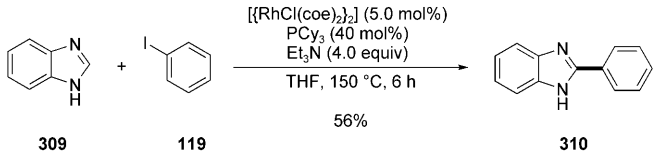
An in situ generated catalytic system consisting of [{RhCl$_2$(cod)}$_2$] and P,N ligand **307**, as well as the isolated homobimetallic complex **308**, were shown to allow the intermolecular direct arylation of electronically unactivated arenes.[209] Interestingly, in addition to aryl iodides and bromides, even less expensive aryl chlorides could be employed as electrophiles (Scheme 115). The functionalization of the C–H bonds of toluene yielded *ortho*-, *meta*-, and *para*-substituted regioisomeric products in a ratio of 71:19:10. On the basis of this observation and a Hammett correlation, a



Scheme 115. Rhodium-catalyzed direct arylation with aryl chloride **305** and homobimetallic rhodium catalyst **308**.

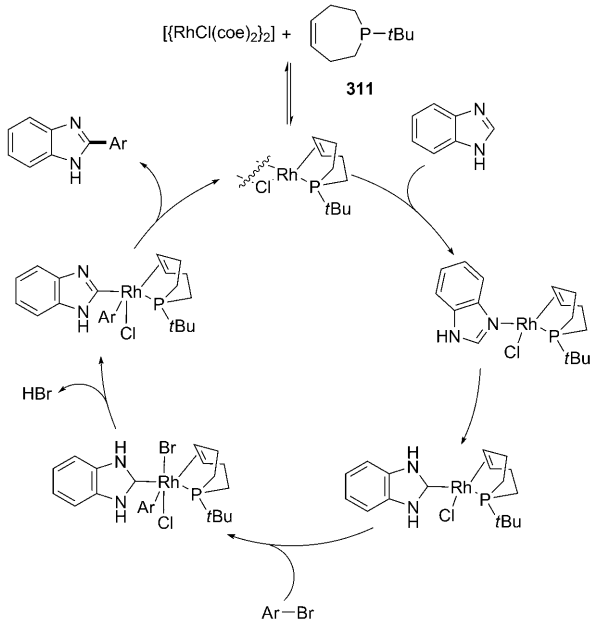
mechanism proceeding through radical intermediates was proposed.

On the basis of detailed mechanistic insight into previously reported catalytic hydroarylation reactions,[10a,e] Bergman, Ellman, and co-workers developed efficient intermolecular rhodium-catalyzed direct arylations of electron-rich N heteroarenes.[210] Here, aryl iodides were employed as the electrophiles with a catalytic system comprising [{RhCl(coe)$_2$}$_2$] and electron-rich phosphine PCy$_3$, which enabled arylations of free NH benzimidazoles at the C2-position (Scheme 116). Further mechanistic studies revealed that



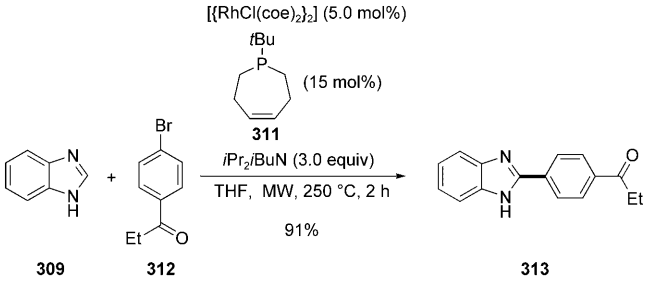
Scheme 116. Rhodium-catalyzed direct arylation of benzimidazole (**309**).

these direct arylation reactions occur through initial tautomerization of the heteroarene, thereby yielding an N-heterocyclic carbene rhodium complex as the key intermediate (Scheme 117). Unfortunately, significant amounts of hydro-



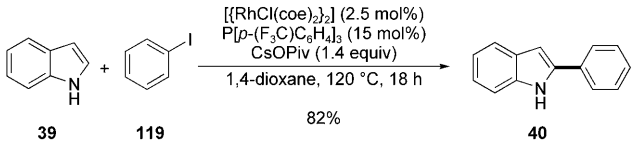
Scheme 117. Proposed mechanism for the rhodium-catalyzed direct arylation of benzimidazole with ligand **311**.

dehalogenated by-products were formed because of the cleavage of the C–H bonds at the organic substituents of the coordinated phosphine ligand. Phosphepine **311** gave rise to a significantly more selective rhodium catalyst,[211] with a significantly broadened application scope, as illustrated by the effective functionalization of C–H bonds with aryl bromides (Scheme 118).[211]



Scheme 118. Rhodium-catalyzed direct arylation with bromide **312**.

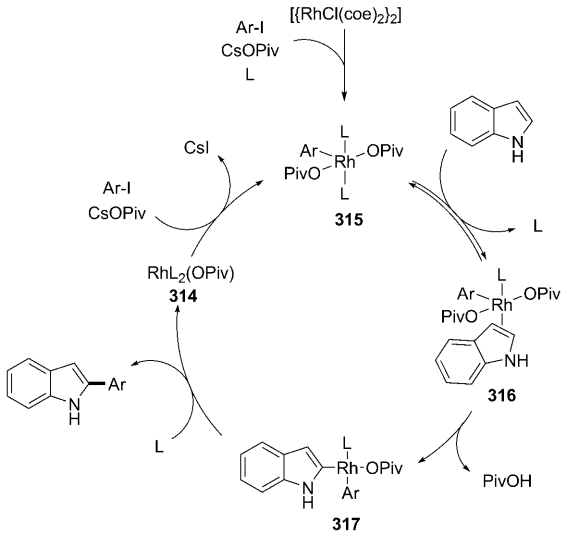
Direct arylation of free NH pyrroles or (aza)indoles at the C2-position were, in contrast, achieved by Sames and co-workers by using a rhodium complex derived from an electron-deficient phosphine by using CsOPiv as the base (Scheme 119).[212] This reaction was proposed to commence



Scheme 119. Rhodium-catalyzed direct arylation of indole (**39**).

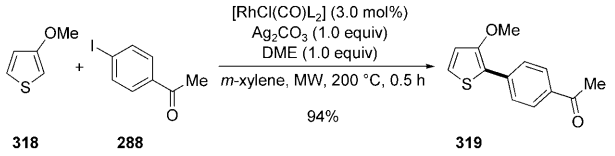
with the oxidative addition of the aryl iodide to rhodium(I) complex **314**, along with a reversible coordination by the indole, thereby yielding rhodium(III) complex **316** (Scheme 120). Subsequent cleavage of the C–H bond is suggested to take place with the assistance of coordinated pivalate. Thereafter, the arylated indole is obtained by reductive elimination, which regenerates the catalytically active rhodium(I) complex **314**.

Furthermore, Itami and co-workers noted that their procedure for rhodium-catalyzed direct arylation was not limited to arenes as pronucleophilic substrates, but also



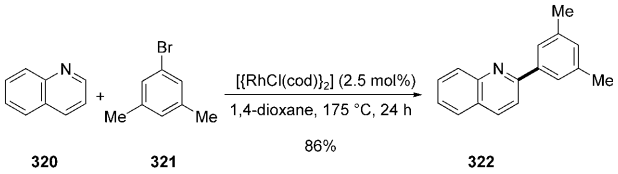
Scheme 120. Proposed mechanism for the rhodium-catalyzed direct arylation of indoles. L = P[*p*-(F$_3$C)C$_6$H$_4$)$_3$].

enabled direct functionalization of heteroarenes.[207,208] Interestingly, the use of DME as an additive allowed highly selective direct arylation with iodides. Furans and thiophenes gave rise to monoarylated products (Scheme 121), whereas indoles delivered mixtures of regioisomers.



Scheme 121. Rhodium-catalyzed direct arylation of thiophene **318**. L = P[OCH(CF$_3$)$_2$)]$_3$.

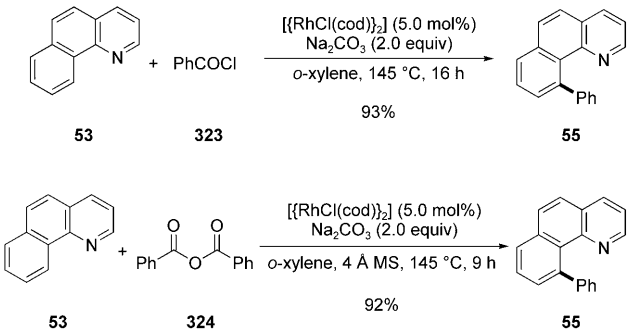
A major advance in the direct functionalization of C–H bonds of pyridine derivatives was recently made by Bergman, Ellman, and co-workers,[213] whereby the direct arylation of simple electron-deficient N heteroarenes proved viable in a highly regioselective fashion. Although these rhodium-catalyzed reactions required relatively high reaction temperatures, no additional ligands were necessary (Scheme 122). In



Scheme 122. Rhodium-catalyzed direct arylation of quinoline (**320**).

comparison with the palladium- or copper-catalyzed direct arylation of pyridine *N*-oxides[75,188] or *N*-iminopyridinium ylides (Sections 4.1 and 4.2),[98] these rhodium-catalyzed methods can be advantageous with respect to both costs and operational simplicity.

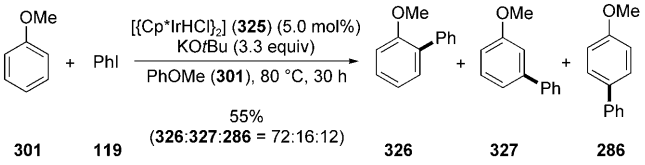
As an alternative to the use of aryl halides, the direct arylation of heteroarenes was more recently accomplished with carboxylic acid chlorides[214] or carboxylic acid anhydrides[215] through decarbonylative processes (Scheme 123). For example, quinoline derivatives were regioselectively arylated with high efficacy when using electrophilic substrates **323** or **324**.



Scheme 123. Rhodium-catalyzed decarbonylative direct arylation with carboxylic acid derivatives **323** and **324**.

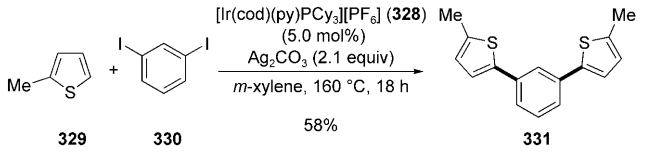
4.5. Iridium-Catalyzed Direct Arylation

Examples of iridium-catalyzed direct arylation reactions are thus far scarce. In a first example, iridium hydride [{Cp*IrHCl}$_2$] (**325**) was found to catalyze the direct arylation of simple arenes.[216] Although this reaction proceeded at a relatively low reaction temperature, it was restricted to aryl iodides as electrophiles and a relatively strong base, that is, KO*t*Bu. When using monosubstituted arene **301** as the substrate, a mixture of *ortho*-, *meta*-, and *para*-disubstituted regioisomeric products was obtained in a ratio of 72:16:12, thereby hinting at a radical-based reaction mechanism (Scheme 124).



Scheme 124. Iridium-catalyzed direct arylation of anisole (**301**).

Direct arylation of electron-rich heteroarenes with aryl iodides were subsequently elaborated with the aid of Crabtree's catalyst (**328**) and stoichiometric amounts of silver salts as additives.[217] With this procedure, twofold functionalization of C–H bonds allowed for the efficient synthesis of highly substituted arenes (Scheme 125). In a low-yielding direct arylation with anisole (**301**), the regioselectivity indicated an electrophilic metalation process being operative.



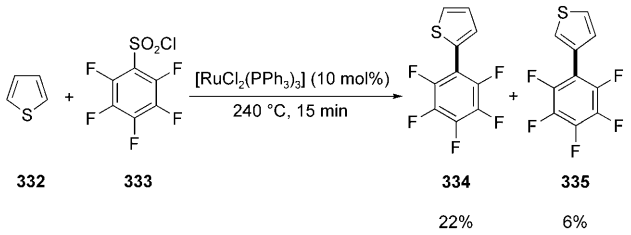
Scheme 125. Iridium-catalyzed direct arylation of thiophene **329**.

4.6. Ruthenium-Catalyzed Direct Arylation

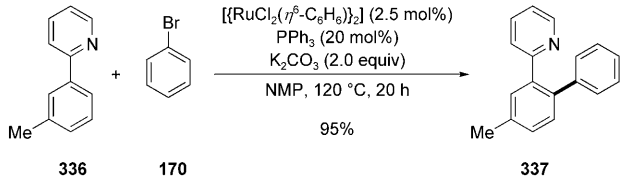
Pioneering studies by the research groups of Lewis[218] and Murai[219] on ruthenium-catalyzed C–C bond formation through the cleavage of C–H bonds provided valuable knowledge for the development of various catalytic hydroarylation reactions,[220,221] and for ruthenium-catalyzed direct arylations. An early example of a ruthenium-catalyzed direct arylation of arenes and thiophene (**332**) with sulfonyl chlorides as the arylating reagent required relatively harsh reaction conditions (Scheme 126).[222]

4.6.1. Aryl Iodides and Bromides

A catalytic system consisting of [{RuCl$_2$(η^6-C$_6$H$_6$)}$_2$] and PPh$_3$ was elegantly exploited by Oi, Inoue et al. for the direct arylation of 2-aryl pyridine derivatives with aryl bromides as the electrophiles (Scheme 127).[223] The same procedure

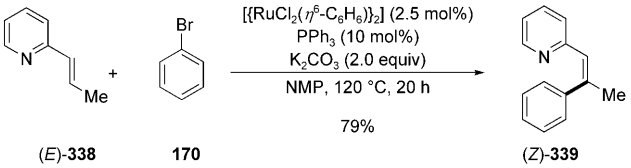


Scheme 126. Ruthenium-catalyzed direct arylation with sulfonyl chloride **333**.



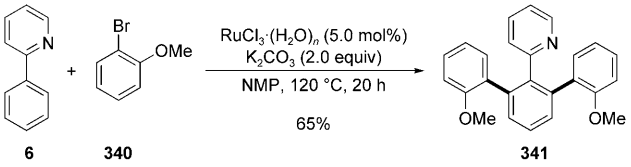
Scheme 127. Ruthenium-catalyzed direct arylation with bromobenzene (**170**).

proved applicable to the directed arylation of substituted ketimines, imidazolines, and oxazolines as pronucleophilic starting materials.[224] Transformations of the latter substrates should prove valuable, since 2-oxazolinyl substituents can be easily converted into a variety of valuable functionalities.[225] Moreover, high-yielding arylation of alkenylic C–H bonds were viable with aryl bromides under otherwise identical reaction conditions (Scheme 128).[226]



Scheme 128. Ruthenium-catalyzed direct arylation of alkene (*E*)-**338** with bromobenzene (**170**).

Phosphine-free ruthenium-catalyzed direct arylation with aryl bromides as electrophiles was viable provided that the polar solvent NMP was employed in combination with soluble RuCl$_3$·(H$_2$O)$_n$ as the catalyst.[227] This system constituted an economically attractive approach to the functionalization of C–H bonds of pyridine, oxazoline, and pyrazole derivatives, even when using more sterically hindered *ortho*-substituted aryl bromides as the electrophilic starting materials (Scheme 129).

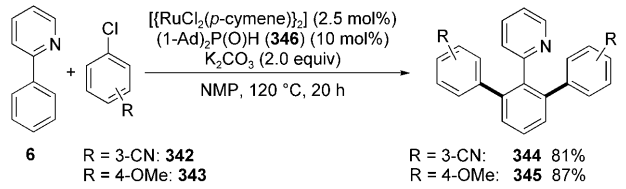


Scheme 129. Ruthenium-catalyzed phosphine-free direct arylation using inexpensive RuCl$_3$·(H$_2$O)$_n$.

Moreover, ruthenium-catalyzed direct arylation with aryl iodides and an aryl iodine(III) dibenzoate as the arylating reagents was more recently performed in the presence of stoichiometric amounts of a peroxide as an additive.[228]

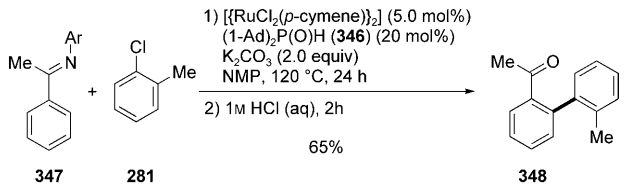
4.6.2. *Aryl Chlorides*

As already illustrated (Section 4.1.3), aryl chlorides are arguably the most useful of the aryl halides as a single class of electrophilic substrates.[159] A first generally applicable method for intermolecular direct arylation with inexpensive aryl chlorides was achieved with an in situ generated ruthenium complex.[229] A complex derived from the secondary phosphine oxide (SPO) $(1\text{-Ad})_2P(O)H$ (**346**) allowed for the efficient and regioselective arylation of arenes bearing Lewis-basic functional groups. As an example, 2-aryl pyridine derivatives were efficiently arylated at the *ortho* position with both electron-deficient and electron-rich—thus, for oxidative addition electronically deactivated—aryl chlorides (Scheme 130).



Scheme 130. Ruthenium-catalyzed direct arylation with aryl chlorides **342** and **343**.

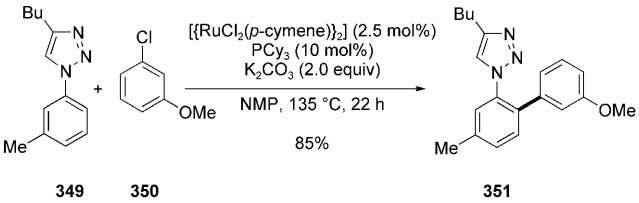
Interestingly, the use of ketimines as directing groups gave rise to the monoarylated products selectively and provided, after hydrolysis, the corresponding ketones, a valuable feature for further functional group transformations (Scheme 131).[229]



Scheme 131. Ruthenium-catalyzed direct arylation of ketimine **347** with aryl chloride **281**. Ar = 4-$MeOC_6H_4$.

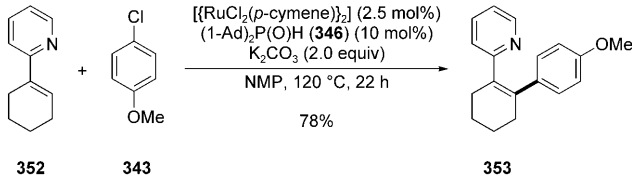
In addition to SPO-derived ruthenium complexes, catalysts generated from different phosphines or N-heterocyclic carbenes were tested in direct arylations with aryl chlorides.[229–233] A catalytic system consisting of $[\{RuCl_2(p\text{-cymene})\}_2]$ and PCy_3, in particular, turned out to be effective for the direct arylation of *N*-aryl-substituted 1,2,3-triazoles (Scheme 132).[230] These arylations proceeded exclusively at the arene because of chelation control, thereby providing a complementary regioselectivity to palladium-[140,175,176] or copper-catalyzed[193] transformations of *N*-aryl-1,2,3-triazoles.

The direct arylation of alkenes as pronucleophiles with inexpensive aryl chlorides occurred with high efficacy and



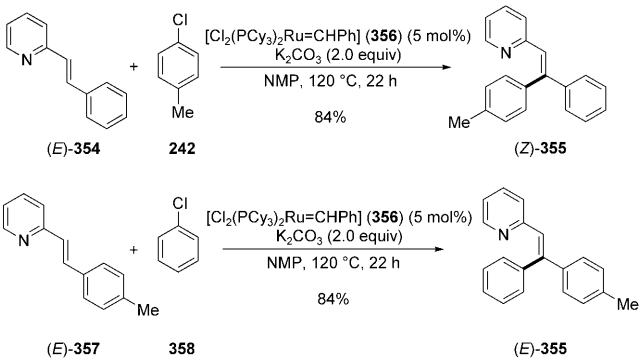
Scheme 132. Ruthenium-catalyzed direct arylation of 1,2,3-triazole **349** with aryl chloride **350**.

excellent diastereoselectivity when using either ruthenium(IV) benzylidene **356** (Grubbs catalyst) or an in situ generated catalyst from SPO **346** (Scheme 133).[231] The



Scheme 133. Ruthenium-catalyzed direct arylation of alkene **352** with aryl chloride **343**.

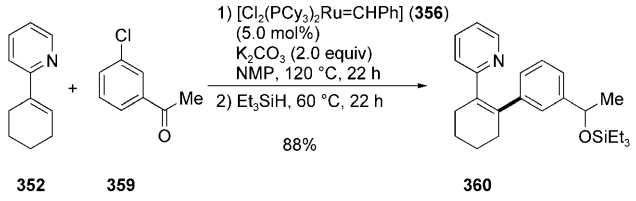
diastereoselectivity of these C–H functionalizations was shown to be complementary to both ruthenium-catalyzed cross-metathesis as well as palladium-catalyzed Mizoroki–Heck reactions (Scheme 134).[234]



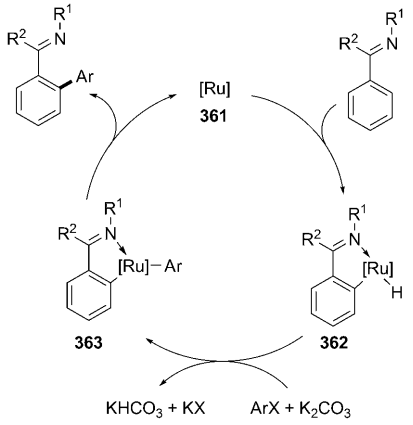
Scheme 134. Ruthenium-catalyzed diastereoselective direct arylation of alkenes.

Furthermore, a ruthenium-catalyzed direct arylation/hydrosilylation reaction sequence was facilitated through the use of a single ruthenium catalyst, which thus enabled two mechanistically distinct transformations (Scheme 135).[231]

Experimental and computational studies on the mechanism of ruthenium-catalyzed direct arylations with (pseudo)-halides were until recently not available. On the basis of mechanistic insight into ruthenium-catalyzed hydroarylation reactions, a catalytic cycle relying on an initial cyclometalation was, however, generally preferred for these transformations (Scheme 136). Hence, a Lewis-basic functionality ensures the regioselective formation of ruthenacycle **362**. A subsequent activation of the aryl halide leads to complex **363**,



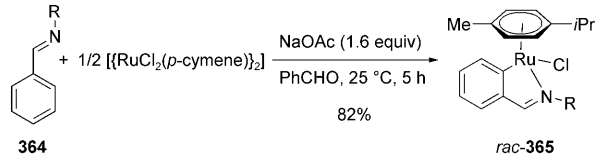
Scheme 135. Ruthenium-catalyzed direct arylation/hydrosilylation sequence.



Scheme 136. Proposed mechanism of ruthenium-catalyzed direct arylation with aryl halides.

which finally undergoes a reductive elimination to afford the desired product and regenerate the catalytically active ruthenium species.

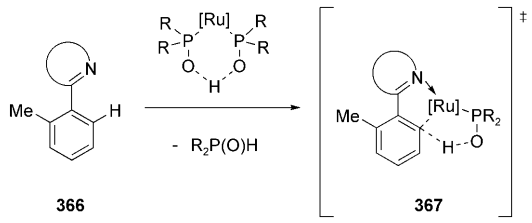
As to the elementary C–H bond-cleavage reaction, it is noteworthy that Davies et al. observed the beneficial effect of NaOAc as an additive for the stoichiometric syntheses of ruthenacycles at ambient temperature (Scheme 137).[235] This



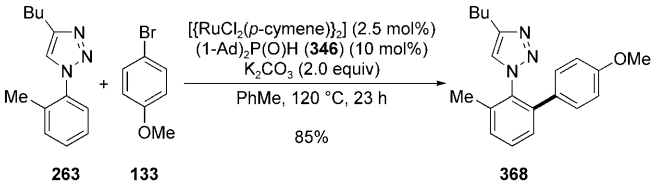
Scheme 137. NaOAc-assisted cyclometalation. R = $(CH_2)_2$OMe.

finding indicated that a CMD[93] mechanism could be operative. DFT calculations by Maseras, Dixneuf, and coworkers further provided strong support for such a scenario in ruthenium-catalyzed direct arylation.[236]

We proposed transition-state model **367** for the mechanism to account for the high efficiencies displayed by (HA)SPO-derived complexes in ruthenium-catalyzed direct arylations (Scheme 138).[237] On the basis of this mechanistic rationale, the first ruthenium-catalyzed direct arylations with aryl halides in less-coordinating apolar solvents, such as toluene, were developed. Thus, a catalytic system derived from SPO **346** enabled regioselective functionalization of C–H bonds on the aromatic ring of *N*-aryl-substituted 1,2,3-triazoles (Scheme 139).[237]

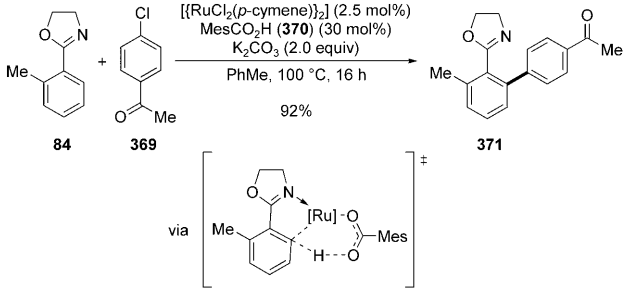


Scheme 138. Proposed concerted metalation/deprotonation mechanism with coordinated (HA)SPO.



Scheme 139. Ruthenium-catalyzed direct arylation in the apolar solvent toluene.

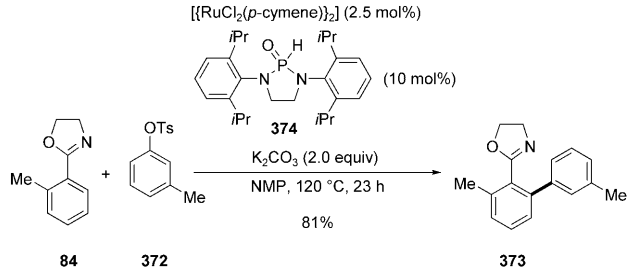
Given that a CMD mechanism was likely operative, carboxylic acids were probed next as co-catalysts in ruthenium-catalyzed direct arylations.[237] Among a variety of additives, mesitylcarboxylic acid (**370**) was found to be optimal, which set the stage for the effective arylation of pyridine, 1,2,3-triazole, oxazoline, and pyrazole derivatives with a broad substrate spectrum. With respect to the electrophilic substrates, the catalytic system was not limited to the use of aryl bromides, but also proved applicable to aryl chlorides (Scheme 140). These transformations were proposed to occur with active participation of the carboxylate group.



Scheme 140. Ruthenium-catalyzed direct arylation with carboxylic acid **370** as a preligand and a proposed transition-state model.

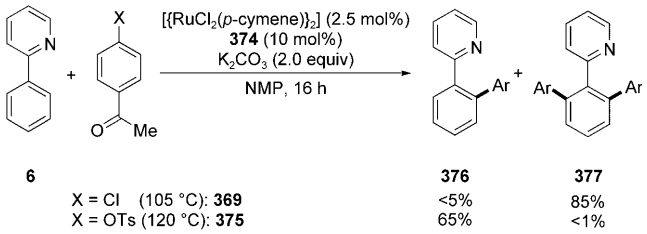
4.6.3. Aryl Tosylates and Phenols

Aryl tosylates are convenient, moisture-stable electrophiles which can be readily synthesized from inexpensive substrates. A ruthenium complex derived from HASPO[131] **374** allowed for the first direct arylation[183] with aryl tosylates.[238] Remarkably, electron-deficient as well as electron-rich tosylates could be employed, with pyridine, oxazoline, and pyrazole derivatives serving as pronucleophiles (Scheme 141). It is interesting to note that selective mono- or diarylation reactions were accomplished through the judi-



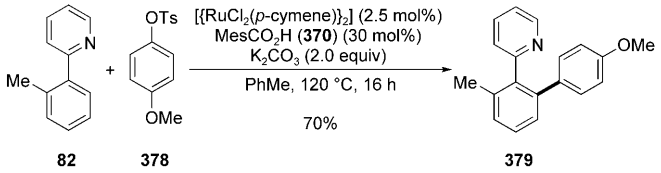
Scheme 141. Ruthenium-catalyzed direct arylation with tosylate **372**.

cious choice of the electrophile. While aryl chlorides gave rise to diarylated products, the use of aryl tosylates selectively afforded the corresponding monoarylated derivatives (Scheme 142).



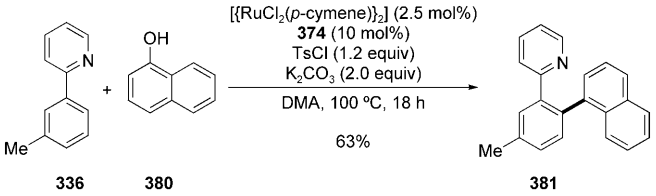
Scheme 142. Selective ruthenium-catalyzed direct arylation through choice of the electrophile. Ar = 4-MeC(O)C_6H_4.

Furthermore, a catalyst system derived from carboxylic acid **370** proved applicable to direct arylations with challenging aryl tosylates as the electrophilic reagents in the apolar solvent toluene (Scheme 143).[237]

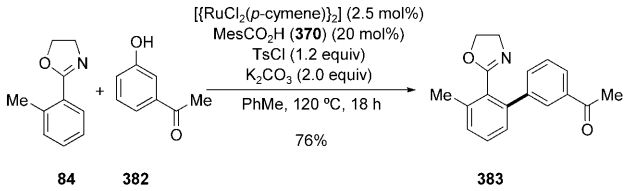


Scheme 143. Ruthenium-catalyzed direct arylation with carboxylic acid **370** as a co-catalyst.

The outstanding stability of ruthenium complexes was further showcased with the development of the first direct arylations with inexpensive and easily available phenols as proelectrophiles.[239] This operationally simple, formal dehydrative direct arylation was achieved in a highly chemo- and regioselective fashion by using a ruthenium catalyst derived from HASPO **374**, along with a sulfonyl chloride as the additive. The transformation proceeded overall with the functionalization of both C–H and C–OH bonds, and the formation of undesired by-products originating from either arylation of the phenol[202] or desulfinylative coupling reactions[240] was not observed (Scheme 144).[239] The procedure proved to be generally applicable, and allowed for the functionalization of arenes with different directing groups by employing either electron-rich or electron-deficient phenols as proelectrophiles. Additionally, the transformation also proceeded with a high efficiency in the apolar solvent toluene, provided that carboxylic acid **370** was present as a co-catalyst (Scheme 145).[239]



Scheme 144. Ruthenium-catalyzed formal dehydrative direct arylation with phenol **380**.



Scheme 145. Ruthenium-catalyzed formal dehydrative direct arylation in the apolar solvent toluene.

5. Summary and Outlook

Direct arylation of (hetero)arenes through the cleavage of C–H bonds has matured into an increasingly viable alternative to traditional cross-coupling reactions. Indeed, effective methods for metal-catalyzed oxidative direct arylation with either organometallic reagents or simple arenes have been developed. From a preparative viewpoint, the transformation of simple arenes is highly attractive. However, the use of atom-economical terminal oxidants and achieving regioselectivity in intermolecular arylations remain significant challenges. Furthermore, generally applicable methods for highly chemoselective intermolecular cross-dehydrogenative arylations with equimolar amounts of starting materials are highly desirable. As an alternative, aryl (pseudo)halides have been widely employed, and recent advances are represented by the use of inexpensive, yet easily available aryl chlorides, tosylates, mesylates, and phenols as (pro)electrophilic coupling partners.

Until very recently, the majority of catalytic direct arylations have been accomplished with palladium, rhodium, or ruthenium catalysts. However, less-expensive copper, iron, and nickel compounds have been shown in the last three years also to be highly active in catalytic direct arylations, and have great potential for future development.

Catalytic direct arylation reactions have undoubtedly witnessed important progress in recent years. However, significant further research efforts are necessary to enable the selective functionalization of C–H bonds in densely functionalized complex starting materials. Additionally, potential applications of transition-metal-catalyzed direct arylations to industrial processes call for an improvement in their regioselectivities and efficiencies. Considering the economically and environmentally benign nature of catalytic

functionalizations of C–H bonds, further exciting developments are, therefore, expected in this rapidly evolving research area.

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
aq	aqueous
BQ	*p*-benzoquinone
*i*Bu	isobutyl
*t*Bu	*tert*-butyl
CMD	concerted metalation/deprotonation
cod	1,4-cyclooctadiene
coe	cyclooctene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DFT	density functional theory
DMA	*N*,*N*′-dimethylacetamide
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*′-dimethylethylenediamine
DMF	*N*,*N*′-dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphanyl)butane
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
dppm	bis(diphenylphosphanyl)methane
dtbpy	di-*tert*-butyl-2,2′-bipyridine
ee	enantiomeric excess
(HA)SPO	(heteroatom-substituted) secondary phosphine oxide
KIE	kinetic isotope effect
L	ligand
Mes	mesityl
MOM	methoxymethyl ether
Ms	methanesulfonyl
MS	molecular sieves
MW	microwave irradiation
NHC	N-heterocyclic carbene
NMP	1-methyl-2-pyrrolidinone
PAH	polycyclic aromatic hydrocarbon
Piv	pivalate
*i*Pr	isopropyl
S_EAr	electrophilic aromatic substitution
TEMPO	2,2′,6,6′-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TON	turnover number
Ts	4-toluenesulfonyl

We sincerely thank all our co-workers engaged in the C–H bond-functionalization projects for their invaluable contributions; their names appear in the references. Cited reports from our laboratories were partly funded by the DFG, the Fonds der Chemischen Industrie, the Alexander von Humboldt foundation (fellowships to R.V. and A.R.K.), and the Spanish Ministerio de Educación y Ciencia (fellowship to R.V). Furthermore, we gratefully acknowledge Stefan Beußhausen for help with preparation of the manuscript.

Received: June 3, 2009
Published online: December 8, 2009

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