C–C Coupling

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Biaryl Formation Involving Carbon-Based Leaving Groups: Why Not?**

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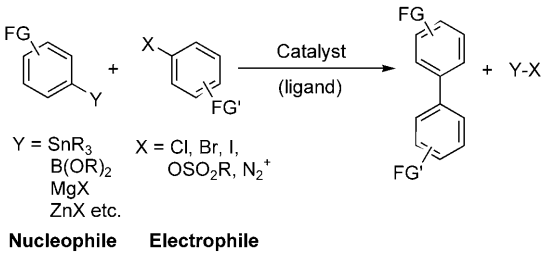
arylation · biphenyls · C–C activation · C–C coupling · leaving groups

Biaryl and polyaryl structures are often found among natural products including medicinally active compounds and they also serve as versatile chiral ligands in synthetic chemistry. The introduction of an aromatic or heteroaromatic ring, most often a (substituted) phenyl ring, is a frequent strategy in the development of a pharmaceutical lead. Aryl–aryl bonds are formed as indicated in Scheme 1 through the



Scheme 1. Transition-metal-mediated synthesis of biaryls.

coupling of a nucleophilic unit Ar–Y (Y = SnR_3, MgX, BR_2, ZnX, corresponding to the Stille, Kumada, Suzuki, and Negishi reactions, respectively) with an electrophilic reagent Ar–X (X = halogen, sulfonate, or a diazonium salt).[1a] Such versatile cross-coupling reactions have been highly successful in synthetic chemistry, but some limitations remain. Thus, rather harsh conditions and/or stoichiometric amounts of an expensive or moisture-sensitive organometallic compounds are in some cases required. As is evident in Scheme 1 in these reactions the aryl–C bond is formed at the expense of an aryl–metal, aryl–halogen, aryl–O, or an aryl–N bond. The direct arylation by functionalization of an aryl C–H bond, where hydrogen is replaced by the aryl group, has recently emerged.[1b]

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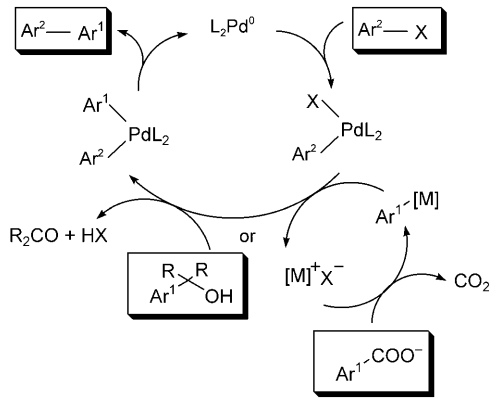
It is generally not appreciated, however, that an aryl–carbon bond can be formed through the cleavage of *another* aryl–C bond, that is, that of a C-based leaving group. This is not the expected process if one compares the energies involved in the cleavage of a halogen atom in aryl halides (bond dissociation energies (BDEs): Ph–I = 67.2 kcal mol^{-1},[2a] Ph–Cl = 97.6 kcal mol^{-1} [2a]) with that of the Ph–CO bond (BDE = 113.8 kcal mol^{-1}, in pyrethroid model esters[2b]) or of a cyano group in benzonitriles (BDE Ph–CN = 134 kcal mol^{-1} [2c]). As a matter of fact, photoinduced substitution of a cyano group in aromatic nitriles was reported 30 years ago[3] but in this case an alkyl group was introduced, not an aryl.[4]

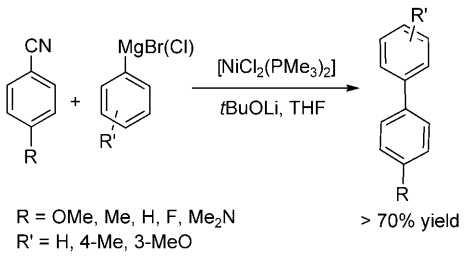
In this context it is interesting that a new class of metal-mediated reactions has been recently reported, in which aryl carbinols, nitriles, and carboxylic acids are used for the synthesis of biaryls in good to excellent yields. Aryl nitriles serve as the electrophilic component in the cross-coupling reaction with aryl Grignard reagents under Ni catalysis (see below). Alternatively, aryl carbinols and aryl carboxylic acids act as the nucleophile in the Pd- (or Pd/Cu-) mediated reactions with organometallic compounds as summarized in Scheme 2.

Conceptually, aryl cyanides may act as pseudo-halides in the catalytic aryl–C bond formation, but only a couple of cases have been reported.[5,6] In contrast to the smooth palladium-catalyzed reactions of aryl halides, the activation of aryl cyanides is restricted to the specific activity of low-valent



Scheme 2. Biaryl synthesis from aryl carbinols and aryl carboxylic acids by Pd- (Pd/Cu-) mediated reactions.

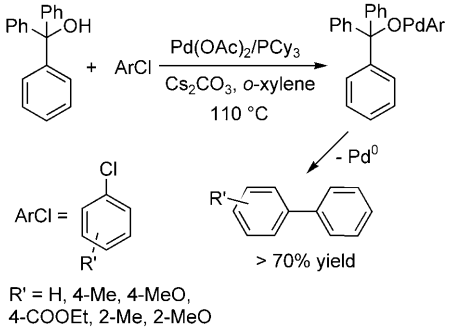
nickel species.[5,6] Miller et al. have recently disclosed the cross-coupling reaction of various benzonitriles with aryl Grignard reagents (2 equiv) in the presence of dichlorobis-(trimethylphosphine)nickel (5 mol%) in refluxing THF.[6a,b] Addition of *t*BuOLi (or PhSLi) was required to suppress the otherwise competing attack at the nitrile carbon (Scheme 3).



Scheme 3. Biaryl formation by activation of aryl–C(N) bonds.

The procedure was successfully applied to benzonitriles bearing either electron-donating or electron-withdrawing substituents as well as to heteroaromatic nitriles (e.g. 2-thiophenecarbonitrile, 2-pyridinecarbonitrile) in > 70% yield. At present, the method cannot compete with the Kumada coupling[7] using aryl halides, although aryl cyanides have found an elegant application in related reactions, in particular in the nickel-catalyzed cross-coupling with alkynylzinc[6c] and alkenyl Grignard[6d] reagents to form the corresponding aryl alkynes and aryl alkenes.

Increasing the stability of the nucleophilic partner in the biaryl synthesis by replacing the aryl metal derivative is, however, more appealing. Miura et al. introduced α,α-disubstituted arylmethanols[8] in this role and suggested the initial formation of an arylpalladium(II) alcoholate, followed by β cleavage and reductive elimination of benzophenone (or acetone, Schemes 2 and 4). In the reaction with aryl chlorides or bromides, however, *ortho* C–H arylation efficiently competes with the desired *ipso* substitution and C–C bond formation. Two approaches were explored for directing the reaction towards the latter path: 1) blocking the *ortho* positions in the starting carbinol or 2) using a bulky phosphine ligand such as PCy_3 (Cy = cyclohexyl) for inducing the β-carbon elimination. The best conditions involved $Pd(OAc)_2$ (5 mol%) as the catalyst, PCy_3 (10 mol%) as the ligand, and

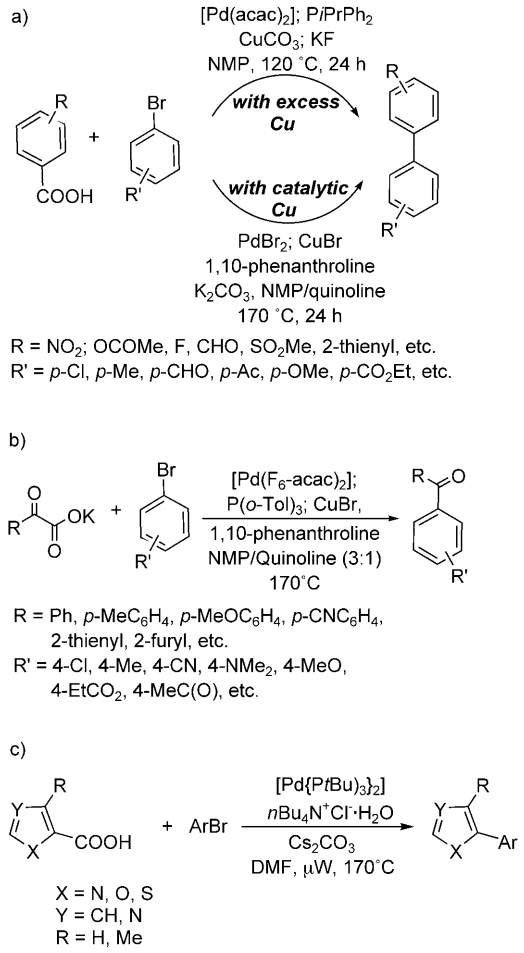


Scheme 4. Pd-catalyzed cross-coupling of aryl carbinols and aryl halides.

cesium carbonate (3 equiv) as the base in refluxing *o*-xylene for 15–48 h. Yields were in the range of 50–95%, and 1–2 equivalents of the aryl bromide were typically used for 1 equivalent of the carbinol (Scheme 4).

The use of bulky and electron-rich phosphines further made it possible to employ aryl chlorides (e.g. 4- or 2-substituted chlorobenzenes) in place of the corresponding bromides to give biphenyls in good yield (74–98%).[9] Noteworthy, crowded biphenyls are accessible by this method despite the bulkiness of the diaryl(dialkyl)carbinol moiety.[9] Heteroaromatic diphenylmethanols likewise reacted under the above conditions and, as an example, were used for the synthesis of oligoaryl compounds containing a thiophene unit. Moreover, cross-coupling of 2-thienyl- and 2-furyl-(diphenyl)methanols with chlorobenzene led to complete reaction within 2 h and yielded 2-phenylthiophenes and 2-phenylfurans, respectively.[9] Other bulky ligands such as P(biphenyl-2-yl)(*t*Bu)$_2$ were found useful for the synthesis of 5,5′-biaryl-2,2′-bithiophenes.[10] Kotschy et al. applied Miura's procedure for the synthesis of α,α-diphenylbenzo[*b*]thienylmethanol derivatives.[11] Thus, α,α-diphenylbenzo[*b*]thien-2-ylmethanol was successfully *ipso*-arylated at position 2, resulting in the selective formation of 2-arylbenzo[*b*]thiophene derivatives (70–97% yields). Similarly, α,α-diphenylbenzo[*b*]thien-3-ylmethanol was coupled with aryl bromides to yield 3-arylbenzo[*b*]thiophenes.[11] α,α-Disubstituted 3-thiophenemethanols formed 2,3-diarylthiophenes by selective 2,3-diarylation in the reaction with aryl bromides under palladium catalysis accompanied by cleavage of the C–H and C–C bonds at the 2- and 3-positions, respectively.[12] α,α-Disubstituted arylmethanols thus may become an alternative to other more aggressive aryl–metal nucleophilic partners although the harsh conditions required (reaction temperature of 130–160 °C) is a strong limitation.

The major breakthrough in the development of C-based leaving groups for biaryl synthesis, however, was reported by Gooßen et al. with the introduction of the decarboxylative cross-coupling of arenecarboxylates with aryl halides.[13,14] The method is based on a bimetallic catalyst system consisting of a copper salt favoring the extrusion of CO_2 from the carboxylate group and a two-electron exchange catalyst (typically based on Pd) which promotes the cross-coupling with the aryl halide (Scheme 5a). The original protocol was applied to aryl bromides and required the use of a stoichiometric amount of the copper salt. Conditions were as follow: 1 equiv aryl bromide, 1.5 equiv carboxylic acid, 1.5 equiv $CuCO_3$, 1.5 equiv KF, 2 mol% $[Pd(acac)_2]$, and 6 mol% P(*i*Pr)Ph$_2$ in the presence of molecular sieves (MS, 500 mg) in *N*-methylpyrrolidine (NMP) at 120 °C. Both the presence of a fluoride and the continuous removal of water (by molecular sieves) were crucial for an efficient reaction.[13,14] Later applications were aimed to limit the large amount of metal copper required; for example, a catalytic amount of the Cu^I derivative could be used provided that the temperature was increased. Typical conditions were: 1–3 mol% $PdBr_2$, 5–10 mol% Cu catalyst, 5–10 mol% 1,10-phenanthroline, and 1 equiv potassium carbonate at 170 °C in NMP/quinoline (3:1).[14] Both electron-rich and electron-poor substituents present on the aryl bromides are well tolerated in the



Scheme 5. Decarboxylative cross-coupling reaction between a) aryl carboxylic acids and aryl halides and b) α-oxocarboxylates and bromoarenes. c) Microwave-assisted Pd-catalyzed cross-coupling arylation reaction of heteroaryl carboxylic acids with aryl bromides.

reaction. A notable variety of carboxylic acids could be converted in the presence of stoichiometric amounts of copper. This protocol was initially limited to benzoic acids bearing electron-withdrawing substituents in the *ortho* position. Replacement of aryl halides by aryl triflates allowed to extend the scope of the cross-coupling reaction to *meta*- and *para*-substituted benzoic acids.[15] In fact, the weakly coordinating triflate anion does not hinder the decarboxylation step as halides do. A further modification of the Cu/Pd catalytic system (PdI_2, bis(*tert*-butyl)biphenylphosphine/CuI, phenanthroline) allowed the coupling even with notoriously nonreactive electron-rich chloroarenes such as ArCl (Ar = 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$).[16] The use of silver salts in place of copper salts seems not advantageous, unless a large amount of Ag_2CO_3 (3 equiv) and high loadings of Pd and As are used, as recently demonstrated by Becht et al.[17]

It is worth mentioning that in a related decarboxylative reaction, α-oxocarboxylic acid salts were used in the cross-coupling reaction with haloarenes to afford ketones.[16,18] The conditions are summarized in Scheme 5b.

Microwave irradiation was used to promote the copper-free Pd-catalyzed synthesis of biaryls starting from heteroaromatic (mainly electron-rich) carboxylates and aryl bromides.[19] Noteworthy, the reaction was completed in only 8 min with Pd[$(P(tBu)_3)_2$] (5 mol%) as the catalyst (typical conditions: 1 equiv $nBu_4NCl{\cdot}H_2O$ and 1.5 equiv Cs_2CO_3 in DMF at 170 °C; Scheme 5c).

In conclusion, the use of carbon-based leaving groups for biaryl synthesis is still in his infancy but it shows great potential. As for the electrophile component, the use of an aryl nitrile, though intriguing, is hardly competitive with the use of aryl halides or esters. As for aryl nucleophiles, the use of α,α-diphenyl(dimethyl)carbinols has the advantage of generating in situ the aryl–metal intermediate through elimination of benzophenone (or better of acetone), but the carbinols are not easily available and at any rate require a further step for their preparation from the corresponding esters. Carboxylic acids (or their metal salts), however, can be considered to be established as valid candidates for the replacement of arene boronic acids or organometallic compounds, which are usually too expensive, difficult to prepare, and with a limited functional-group tolerance. Arene carboxylic acids are largely available, cheap, and easy to handle and store; they have been used for the synthesis of valuable compounds such as the angiotensin II inhibitor valsartan[20] and the agricultural fungicide boscalid.[13] Further elaborations of the protocol should aim to lower the temperature and to minimize environmental impact. This will lead to the widespread use of C-based leaving groups in arylation reactions.

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