Cross-Coupling Reactions

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New Approaches for Decarboxylative Biaryl Coupling

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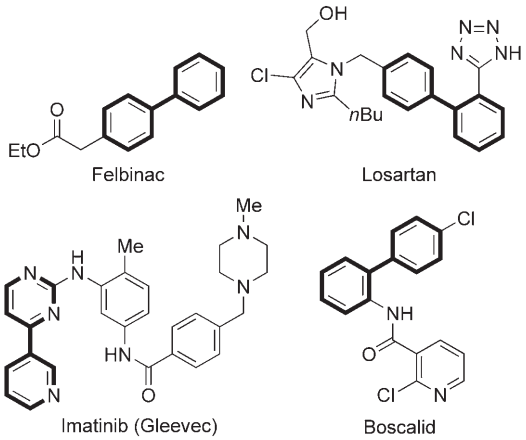
Biaryl motifs are widely represented in organic molecules with important biological or physical properties.[1] Among these are the non-steroidal antiinflammatory drug felbinac, the antihypertensive drug losartan, the anticancer drug imatinib, and the agrochemical agent boscalid (Scheme 1).



Scheme 1. Examples of biaryl-containing drugs and agrochemicals.

Over the past decades, transition-metal-catalyzed cross-coupling methods,[2,3] the most popular of which is the Suzuki–Miyaura coupling,[4] have been successfully employed for the synthesis of biaryl compounds [Eq. (1), M_T = transition metal]. However, these methods suffer from their lack of atom and step economy, as they require the preparation and use of a stoichiometric organometallic coupling partner. Alternative methods have begun to emerge in the past few years. The direct arylation through C–H activation constitutes an appealing alternative [Eq. (2)].[5,6] In this approach the regioselectivity of C–H bond functionalization is the major issue, but it can be solved by directing-group or electronic effects. A third and equally interesting approach that was recently introduced consists of a decarboxylative cross-coupling reaction between a haloarene and an arene carboxylic acid [Eq. (3)].[10,11] The carboxylic acid function ensures the regioselectivity of the reaction (in the same way that the main-group metal does in conventional cross-coupling reactions), and only carbon dioxide is produced as waste. This approach takes inspiration from living organisms that can generate carbanion equivalents by enzymatic decarboxylation of carboxylic acids. The high availability of arene carboxylic acids renders this "biomimetic" route particularly attractive.

Pioneering studies of transition-metal-mediated decarboxylative biaryl coupling were reported in the late 1960s by Nilsson.[7] These studies involved an Ullmann-type reaction between an aryl copper intermediate, generated by thermal decarboxylation of an arenecarboxylic acid with a stoichiometric amount of copper(I), and an aryl iodide. However, the impracticality of this method impaired further developments in this area until recent breakthroughs appeared.

In 2002, Myers et al. reported a versatile decarboxylative Heck-type reaction between arenecarboxylic acids and olefins under palladium catalysis [Eq. (4)].[8a,b] This process was shown to involve a dimethylsulfoxide-coordinated aryl palladium(II) trifluoroacetate intermediate.[8c] This work

Conventional cross-coupling reactions

$$Ar^1\text{—}M + X\text{—}Ar^2 \xrightarrow{M_T\ cat.} Ar^1\text{—}Ar^2 + M\text{—}X \quad (1)$$

M = SnR_3, BR_2, ZnX... X = halide, OTf...

Direct arylation

$$Ar^1\text{—}H + X\text{—}Ar^2 \xrightarrow{M_T\ cat.} Ar^1\text{—}Ar^2 + H\text{—}X \quad (2)$$

Decarboxylative cross-coupling reactions

$$Ar^1\text{—}CO_2H + X\text{—}Ar^2 \xrightarrow{M_T\ cat.} Ar^1\text{—}Ar^2 + H\text{—}X + CO_2 \quad (3)$$

$$Ar\text{—}CO_2H + \text{—}R \xrightarrow[Ag_2CO_3]{Pd(O_2CCF_3)_2\ cat.} Ar\text{—}R \quad (4)$$

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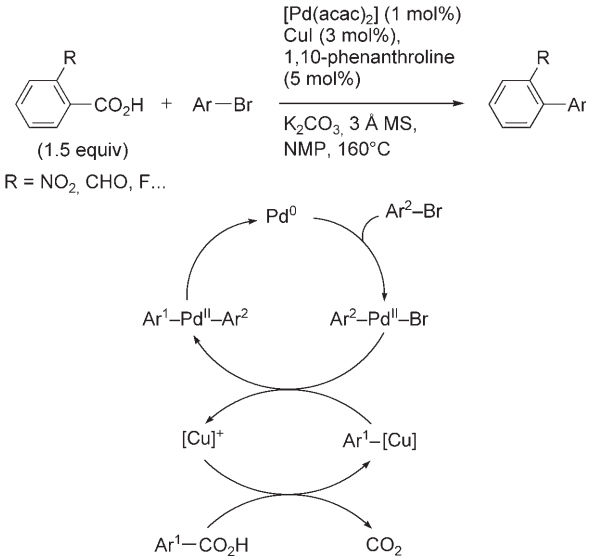
represents a milestone in the development of decarboxylative Pd-catalyzed cross-coupling reactions.[9]

Two Pd-catalyzed variants of decarboxylative biaryl cross-coupling reactions were recently reported by Forgione, Bilodeau, and co-workers on the one hand,[10] and Gooßen et al. on the other hand.[11] In the first report, a variety of heteroaromatic carboxylic acids (pyrroles, furans, oxazoles, thiazoles, thiophenes, and benzofurans) were coupled with aryl bromides by means of palladium(0) catalysis to give the corresponding biaryl compounds (Scheme 2).[12] Optimal conditions featured [Pd{(P(*t*Bu)$_3$}$_2$] (5 mol%) as catalyst, cesium carbonate (stoichiometric amount) as base, and tetra-*n*-butylammonium chloride hydrate as additive in *N*,*N*-dimethylformamide (DMF) under microwave irradiation at 170°C. Yields were in the range 23–88%, and 2 equivalents of the carboxylic acid component were used. A reasonable mechanism was proposed for this process (Scheme 2) that involves an electrophilic palladation at the 3-position of the heterocycle, followed by C3–C2 palladium migration with loss of CO_2 and reductive elimination. This proposal was supported by several experimental observations.

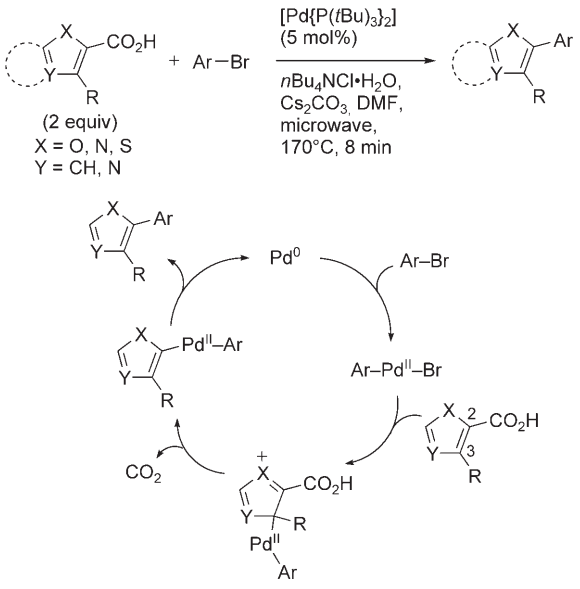
This type of mechanism implies that this process is limited to *heteroaromatic* compounds that bear a carboxylic acid in the 2-position. However, the presence of the carboxylic acid on the heterocycle ensures complete regioselectivity control, which would not be possible by a C–H activation process (an unsubstituted heterocycle gave, under the same conditions, a mixture of 2- and 5-substituted regioisomers).

The second report, by Gooßen et al., features a very different decarboxylative cross-coupling approach (Scheme 3).[11] A copper(I) salt was used to effect the decarboxylation of a 2-substituted arenecarboxylic acid to give the corresponding aryl copper species. The latter transmetalated to an aryl palladium bromide complex formed from a palladium(0) catalyst and an aryl bromide. In initial experiments, a stoichiometric amount of copper(II) ($CuCO_3$) was used in conjunction with a catalytic amount of palladium(0) (generated from [Pd(acac)$_2$] P*i*PrPh$_2$); good yields (up to 97%) of biaryl compounds were obtained under relatively mild reaction conditions (NMP, 120°C, 24 h). By employing somewhat harsher conditions (NMP, 160°C, 24 h), the authors were able to perform this process under double palladium(0)/copper(I) catalytic conditions with as low as 1 mol% Pd and 3 mol% Cu (Scheme 3). This reaction, which currently seems to be limited to arene carboxylic acids bearing a coordinating *ortho* substituent, represents a major advance in the field of biaryl cross-coupling reactions. Its application to the synthesis of a boscalid (Scheme 1) precursor (4-chloro-2′-nitrobiphenyl) demonstrated its potential utility for industrial applications.

In conclusion, the decarboxylative methods reported by Forgione, Bilodeau, and co-workers and by Gooßen et al. for the synthesis of biaryl compounds open new perspectives in cross-coupling chemistry. The generalization of these preliminary studies can be expected. Decarboxylative coupling re-



Scheme 3. Pd/Cu-catalyzed decarboxylative coupling of arene carboxylic acids and aryl bromides and proposed mechanism.[11] MS = molecular sieve, NMP = *N*-methylpyrrolidine.



Scheme 2. Pd-catalyzed decarboxylative coupling of heteroaromatic carboxylic acids and aryl bromides and proposed mechanism.[10]

actions, together with methods based on C–H activation, should provide both academic and industrial researchers with a set of new possibilities for the construction of biaryl bonds that does not require organometallic reactants.

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