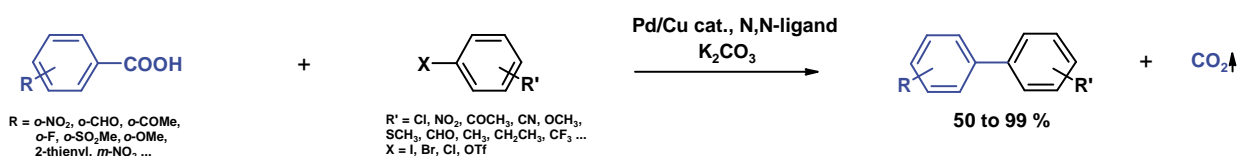


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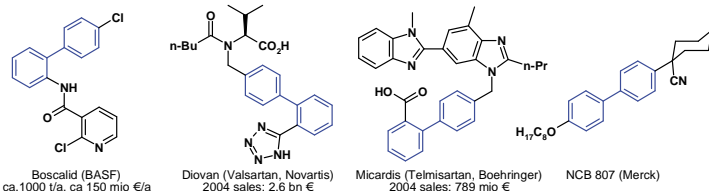
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A decarboxylative coupling of aromatic carboxylic acids with aryl halides has been developed that allows the straightforward synthesis of unsymmetrical biaryls, a substructure often encountered in biological molecules and functional materials. It is mediated by a bimetallic system consisting of a copper/phenanthroline complex that catalyzes the conversion of the carboxylate into an organometallic species and a palladium system that catalyzes the cross-coupling with the aryl halide. The preparative utility of this transformation has been demonstrated by applying it to the preparation of various derivatives in both mg and kg quantities. Moreover, a new protocol has been developed that allows the conversion of non-*ortho*-substituted benzoic acids and thus promises to greatly widen the scope of the transformation.



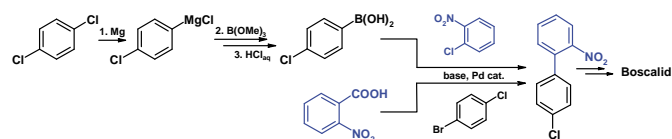
The Biaryl Substructure

The biaryl moiety is an important structural motif in a great number of biologically active compounds and functional molecules as demonstrated by the examples below.



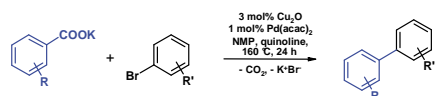
The Synthesis of Biphenyl Derivatives

Over the last decades, the continuously improved, mild and selective Suzuki coupling of arylboronic acids with aryl halides has become the method of choice for laboratory and industrial biaryl synthesis.¹ However, even the Suzuki reaction suffers from a fundamental drawback common to almost all catalytic couplings between aryl nucleophiles and electrophiles: It requires the use of stoichiometric amounts of an expensive organometallic compound, in this case a boronic acid, which must be prepared from sensitive precursors under elaborate anaerobic conditions – on an industrial scale this is often more difficult than the cross-coupling itself. This issue is illustrated below for the synthesis of a Boscalid intermediate, currently one of the largest industrial applications of the Suzuki reaction.

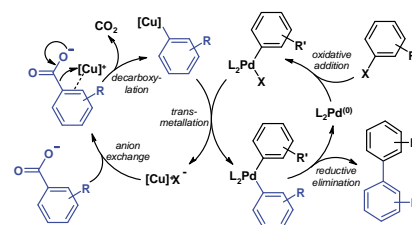


Carboxylic Acid Salts as Sources of Aryl Nucleophiles

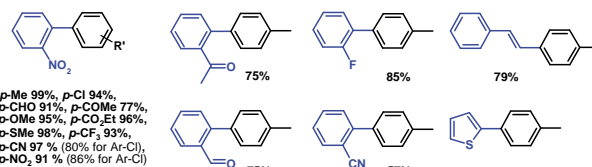
In contrast to organometallic compounds, potassium salts of carboxylic acids are easily available and stable against air and water. In order to utilize them as sources of aryl nucleophiles in a catalytic transformation, we employed copper-phenanthroline complexes to facilitate the extrusion of CO₂ under the formation of an arylcopper species. While these intermediates are converted into the corresponding arenes in the presence of protons,² aprotic conditions allow the transfer of the aryl group from the copper to the palladium(II) species formed by oxidative addition of an aryl halide. Liberation of the biaryl closes the catalytic cycle for the palladium, while the original copper(I)carboxylate is regenerated by ligand exchange between the copper(I) halide and fresh potassium carboxylate.



Decarboxylative Biaryl Synthesis from Carboxylic Acids and Aryl Halides

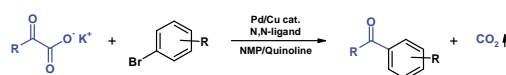


We demonstrated the viability of this concept by coupling various aryl halides with potassium *o*-nitrobenzoate in the presence of 1 mol% palladium(II) acetylacetonate and 3 mol% of a commercially available copper(I)-phenanthroline complex.³ Next, we extended the scope of the reaction to carboxylic acids with coordinating groups in *ortho*-position (e.g. acyl, formyl, fluoro, cyano) then to vinylic and heterocyclic derivatives (cinnamic acid, thiophenecarboxylic acid).⁴ The scope with regard to the carboxylates remained limited as the salt exchange between the potassium carboxylate and the copper halide is not always favorable for the first catalyst system.⁵



Already at this early stage, the industrial applicability of the reaction was demonstrated in cooperation with the Saltigo GmbH in the kg scale synthesis of an *o*-nitrobiaryl intermediate. In the final process less than 0.5 mol% of copper(I) bromide and less than 0.05 mol% palladium(II) acetylacetonate have been employed, and mesitylene (70 % by weight) as the only solvent was required. The product was obtained in pure form by a simple crystallization.⁶

In parallel, we have developed a novel ketone synthesis in which α -ketocarboxylates are decarboxylated at a Cu catalyst, and the resulting acyl anions are coupled with aryl, vinyl or heteroaryl bromides to give the corresponding aryl ketones in excellent yields. The striking feature of this cross-coupling is that the polarity of the bond formation is inverted compared to traditional ketone syntheses as the aryl nucleophiles are coupling with acyl cation equivalents.⁷



We gratefully acknowledge the financial support by Saltigo GmbH.

Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

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