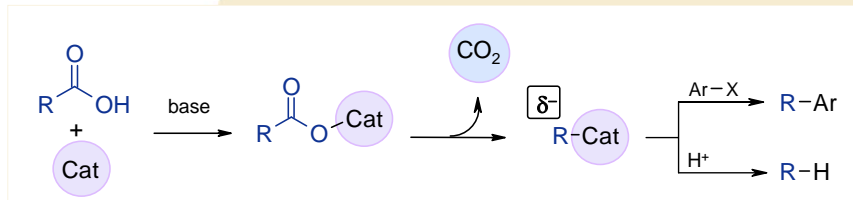


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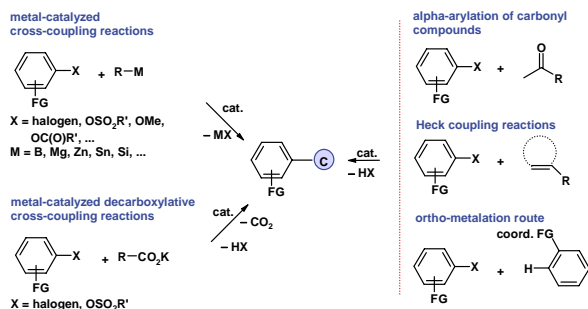
We herein present a new strategy for the regioselective construction of a carbon-carbon bond, in which easily available salts of carboxylic acids are decarboxylated *in situ* to give organometal species that serve as the nucleophilic component in a catalytic cross-coupling reaction. The viability of this concept has been demonstrated with the successful coupling of various aryl and acyl carboxylates with aryl halides and pseudohalides.



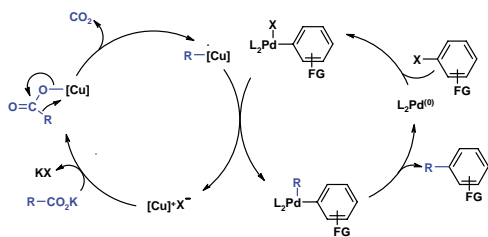
Strategies for aromatic carbon-carbon bond formation

Over the last decades, metal-catalyzed cross-coupling reactions have become established as universal tools for carbon-carbon bond formation.¹ However, their inherent weakness lies in the necessity to generate stoichiometric organometallic reagents in a separate step that are to be used as the carbon nucleophiles.

This drawback can be overcome with modern methods in which the carbon nucleophile is generated under formal C-H activation at a metal catalyst.² Examples include Heck reactions, Sonogashira couplings, α -arylations of carbonyl compounds, and couplings initiated by catalytic *ortho*-metallation steps. Unfortunately, most of these transformations proceed regioselectively only for a limited range of substrate types.



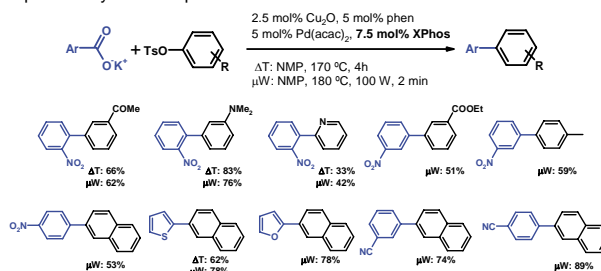
We herein present the redox-neutral decarboxylative cross-coupling as a modern strategy for the regioselective carbon-carbon bond formation without resorting to stoichiometric amounts of organometallic reagents.³ In this type of reaction, a copper(I) or silver(I) catalyst mediates the extrusion of CO₂ from the carboxylates while a palladium complex catalyzes the coupling of the resulting carbon nucleophiles with carbon electrophiles.



The viability of this concept was demonstrated with the regioselective construction of unsymmetrical biaryls⁴ and ketones⁵ from aryl and acyl carboxylates and aryl halides in the presence of bimetallic Cu/Pd catalysts. The performance limit of initial protocols was reached when using non-*ortho*-substituted benzoic acids. The key to understanding this limitation was provided by the observation that copper-catalyzed protodecarboxylations of non-*ortho*-substituted benzoic acids are diminished by the addition of halides unavoidably formed in the process.^{4a}

Scope of the decarboxylative biaryl synthesis

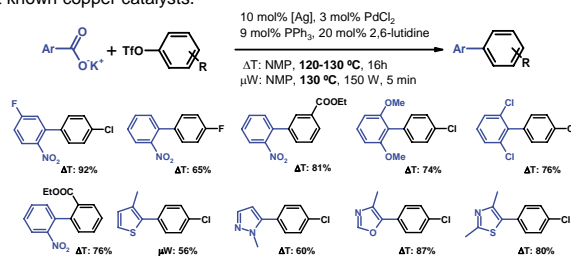
We now overcome this major limitation by demonstrating that an *ortho*-substituent in the aromatic carboxylate is no longer required when aryl triflates⁶ or aryl tosylates⁷ are employed as electrophilic coupling partners. This breakthrough has been achieved by designing new bifunctional Pd/Cu-catalyst systems. The use of microwave irradiation has led to a particularly effective protocol.^{6b}



Having then established that such transformations have a much broader scope than originally perceived, the development of decarboxylation catalysts capable of operating at lower temperatures was in the focus of interest.

Low-Temperature Decarboxylative Cross-Coupling

When reevaluating the potential of silver catalysts for protodecarboxylation reactions, we discovered conditions under which silver salts mediate the extrusion of CO₂ from certain arenecarboxylates with higher efficiency than copper complexes.⁸ Recent results have shown that silver-based catalyst systems can be applied in decarboxylative couplings lowering the reaction temperatures to 120 °C - a temperature more than 50 °C below that of the best known copper catalysts.⁹



This low-temperature protocol, which is particularly suitable for halogenated and heterocyclic arenecarboxylate substrates, represents an important milestone in the evolution of decarboxylative cross-couplings into true synthetic alternatives to traditional couplings of preformed organometallic reagents.

The lower the temperatures at which future catalyst generations can decarboxylate carboxylic acid salts to carbon nucleophiles are, the broader the spectrum of reaction steps which can be resultantly combined *in situ* will be.

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

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