Synthesis of Arylacetic Esters from Benzyl Alcohols and Oxalates

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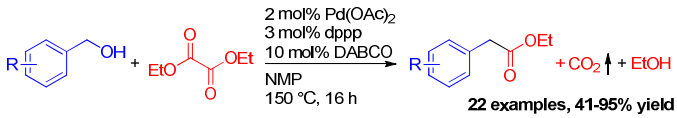
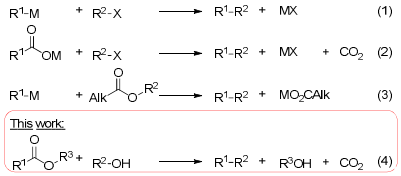
By combining a reversible transesterification between benzylic alcohols and dialkyl oxalates with the catalytic decarboxylation of the resulting esters, a regiospecific C–C-bond forming reaction to α-arylacetates was achieved. In the overall process, CO_2 and a volatile alcohol are the only byproducts. Various α-arylacetates were thus synthesized in high yields from easily accessible starting materials in the presence of catalytic amounts of $Pd(OAc)_2$, dppp, and DABCO.



New Concepts for the C-C Bond Formation

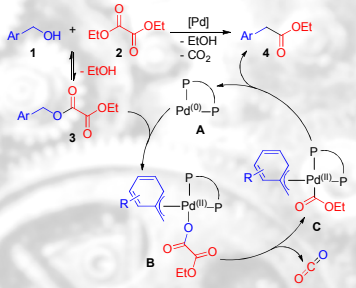
The development of sustainable methodologies for C-C bond formation is among the key objectives in modern organic synthesis. Catalytic cross-couplings have proven to be efficient and versatile tools for assembling even complex molecular structures. In classical, redox-neutral cross-couplings, carbon electrophiles are regiospecifically coupled with carbon nucleophiles. Along with the coupling products, byproducts are formed resulting from the leaving groups, usually metal salts. Within the last decade, several strategies have been developed to overcome the major limitations of this concept, i.e., the necessity to generate sensitive organometallic reagents in an extra reaction step, the use of environmentally questionable organohalides, and the formation of salt waste.[2]



There is still no example of a regiospecific, intermolecular decarboxylative cross-coupling between an alcohol and a carboxylic acid or ester. We envisioned that this kind of C–C-coupling should be achievable by combining a reversible transesterification between an alcohol and an appropriate alkyl carboxylate with a catalytic decarboxylation of the resulting ester. In the overall process, CO_2 and an alcohol would be the only byproducts. As a first example of such a process, we herein disclose a synthesis of α-arylacetic acid esters from benzylic alcohols and diethyl oxalate.[3]

Mechanism

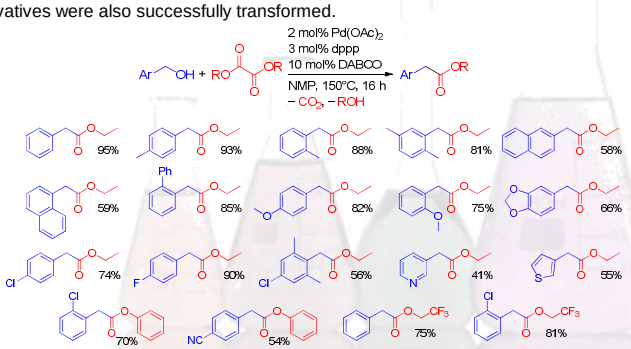
A catalyst system consisting of $Pd(OAc)_2$/dppp and DABCO was found to efficiently promote the decarboxylation of benzyl oxalates to arylacetates under conditions allowing the continuous generation of these compounds from the starting materials.



Control experiments showed that the addition of DABCO as an organocatalyst accelerates the irreversible decarboxylation step. The whole coupling process does not generate inorganic byproducts but only volatile alcohols and gaseous carbon dioxide.

Scope of the Decarboxylative Coupling

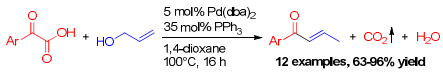
Various benzylic alcohols with common functionalities such as halides or methoxy groups were converted in good yields into the corresponding arylacetic esters. Heterocyclic derivatives were also successfully transformed.



The starting materials are stable, non-hazardous and can be accessed by numerous known synthetic methods.[4] This new protocol is not only applicable for laboratory synthesis, but also for the sustainable production of fine chemicals and pharmaceuticals. The reaction works reliably also on gram scale. Ethyl 2-phenylacetate was synthesized in 95% yield on 50 mmol scale in concentrated solution (7.8 g product / 50 g solvent) with only 1 mol% of the Pd-catalyst.

Extending the Reaction Concept

The concept of an in situ esterification with subsequent decarboxylative coupling was also applied to the decarboxylative allylation of arylglyoxylic acids with allyl alcohol.[5] It is another rare example of a C-C bond forming reaction that is regiospecific and only releases CO_2 and water.



In the presence of catalytic amounts of $Pd(dba)_2$ and PPh_3, the substrates are in an esterification equilibrium with the allyl arylglyoxylates. After oxidative insertion of palladium(0), the organocatalyst PPh_3 mediates the decarboxylation to acyl anion equivalents, which undergo palladium-catalyzed allylation and subsequent isomerization to the corresponding α,β-unsaturated ketones.

Ongoing work

These processes may break the path for the development of a new generation of salt-free cross-couplings. Ongoing work is directed towards the dream reaction between alkyl benzoates and phenols to the corresponding biaryl.

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