Decarboxylative Allylation of Glyoxylic Acids

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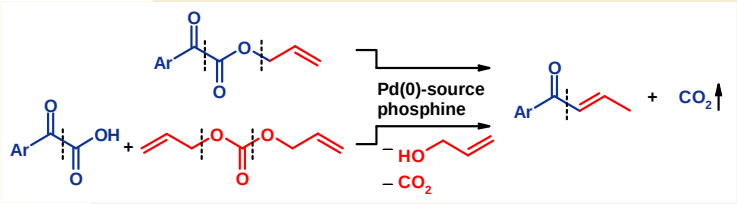
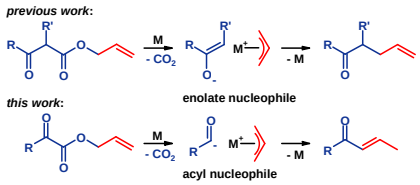
A palladium / phosphine system has been developed that catalyzes the extrusion of carbon dioxide from α-oxocarboxylic acid allyl esters, leading to α,β-unsaturated ketones. The palladium complex activates the substrate and mediates the carbon-carbon bond formation to intermediate allyl ketones, as well as their double bond isomerization. The actual decarboxylation step with formation of the acyl nucleophile is promoted by the phosphine.



Decarboxylative Allylation

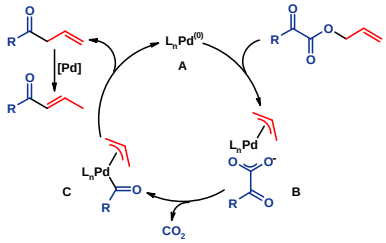
Within recent years, the field of decarboxylative allylation reactions has undergone tremendous development.[1] However, catalytic versions of the Carroll rearrangement extend only to allyl esters of carboxylic acids that – upon extrusion of CO_2 – form highly stable carbanions, for example, enolate, benzyl, α-cyano, or nitronate anions.[1]



We herein report the Pd/phosphine-catalyzed decarboxylative allylation of allyl α-oxocarboxylates as the first example of a decarboxylative allylation involving destabilized carbon nucleophiles.[2] This reaction provides an expedient synthetic entry to α,β-unsaturated ketones, privileged structures in biologically active natural products.[3]

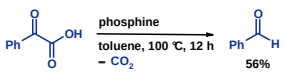
Mechanism

The decarboxylative allylation of α-oxocarboxylates proceeds via a different mechanism than bimetallic decarboxylative cross-coupling reactions.[1] Coordination and oxidative addition of the substrate to a Pd(0) precursor (**A**) lead to the formation of a π-allyl-Pd carboxylate complex (**B**). The phosphine promoted extrusion of CO_2 forms the acyl π-allyl-Pd complex **C** and subsequent reductive elimination gives the allyl ketone, which then rapidly isomerizes to the conjugated vinyl ketone in the presence of palladium.[4]



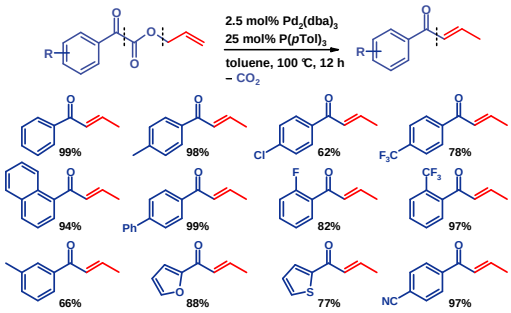
We performed a cross-over experiment in which a mixture of two different allyl α-oxocarboxylates were subjected to the optimized reaction conditions. The fact that all possible products were formed in comparable quantities shows that after the oxidative addition step, the carboxylate ions can dissociate and exchange with other salts, even in the nonpolar solvent toluene.

Further mechanistic investigations revealed that the phosphine acts as an organocatalyst for the decarboxylation step, and also stabilizes the palladium cross-coupling catalyst.

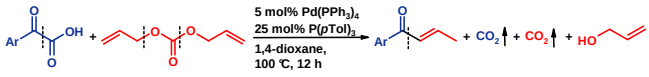


Scope of the Decarboxylative Coupling

α-Oxocarboxylic acid allyl esters can be seen as acyl anion synthons that can be released under the influence of the appropriate catalyst. We have demonstrated the viability of this concept by applying it to a broad range of arylglyoxylic esters. Substrates with electron-rich and -deficient aryl substituents react similarly well, various functional groups are tolerated, and even heterocyclic derivatives could be converted. The reaction also gave a high yield when conducted on gram-scale.



This concept was further extended to an intermolecular transformation by reacting the α-oxocarboxylic acids directly with diallyl carbonate as allyl source.[5] The key advantage of this protocol is that the preformation of allyl esters is not required, which obviates the laborious synthesis and purification of the substrates. Along with CO_2, allyl alcohol is released as the only side product.



Ongoing work

Ongoing work is directed towards combining the phosphine-catalyzed decarboxylation of α-oxocarboxylates with other synthetic transformations that require acyl anion equivalents. Ultimately, this strategy may become a general alternative to established syntheses involving the umpolung of aldehydes.

Literature and Further Reading (see also **www.chemie.uni-kl.de/goossen**)
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[3] (a) G. Ping, H. Taiping, G. Rong, C. Qiu, L. Shigui, *Pest Manag. Sci.* **2001**, *57*, 307. (b) O. Silva, E. T. Gomes, *J. Nat. Prod.* **2003**, *66*, 447. (c) L. A. Arnold, A. Kosinski, E. Estébanez-Perpiñá, R. J. Fletterick, R. Kiplin Guy, *J. Med. Chem.* **2007**, *50*, 5269.
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