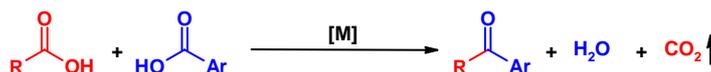


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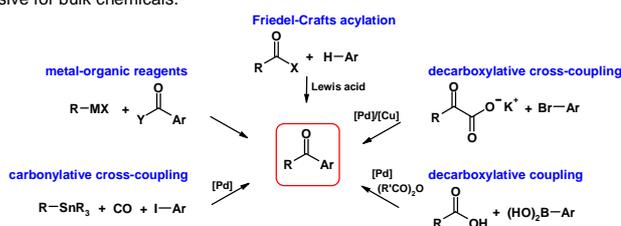
A new protocol has been developed that allows the decarboxylative ketonization of alkyl- with arylcarboxylic acids under relatively mild conditions and in good yields. In the presence of iron-based catalysts, high selectivities for the hetero-coupled products, i.e. alkyl aryl ketones, were achieved when the aliphatic acid was heated together with excess sodium arylcarboxylate. Only CO₂ and water are released as by-products, making this reaction a sustainable alternative to waste-intensive Friedel-Crafts-type processes. In contrast to the latter, only one regioisomer is formed, as the position of the carboxylate group predefines the position of the acylation of the aromatic ring. The reaction was successfully applied to several combinations of alkyl- and aryl- carboxylic acids, and the alkyl aryl ketones were obtained in up to 20:1:0 selectivity over the symmetrical alkyl and aryl ketones.



decarboxylative cross-ketonization

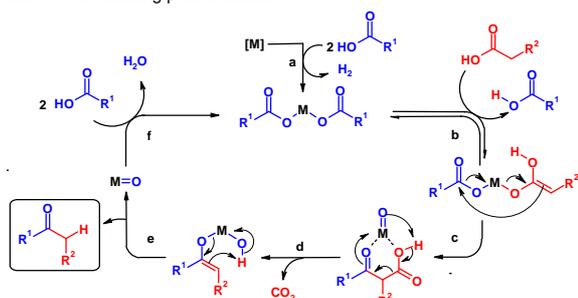
Syntheses of Unsymmetrical Ketones

Aryl ketones are important structural units in organic chemistry. The most inexpensive synthetic entry is the waste-intensive Friedel-Crafts acylation; however, the products are mostly obtained as isomeric mixtures.¹ More advanced, regioselective syntheses of such products are often too expensive for bulk chemicals.²⁻⁴



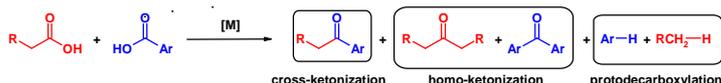
Decarboxylative Ketonization

One of the first examples for the decarboxylative ketonization was reported by Friedel in 1858, who obtained ketones by pyrolysis of calcium carboxylates.⁵ Various metal mediators such as lead, magnesium oxide, iron or manganese have been employed in this reaction, leading to the homo-ketonization product.⁶ The reaction is believed to proceed via α -acylation and decarboxylation of the resulting β -keto esters.



Decarboxylative Cross-Ketonizations

As β -hydrogens are required for the α -acylation step (homoketonizations of benzoic acids are unknown), we reasoned that upon mixing an aliphatic with a more acidic aromatic carboxylic acid in the presence of a metal salt, the alkyl aryl ketones may form preferentially.

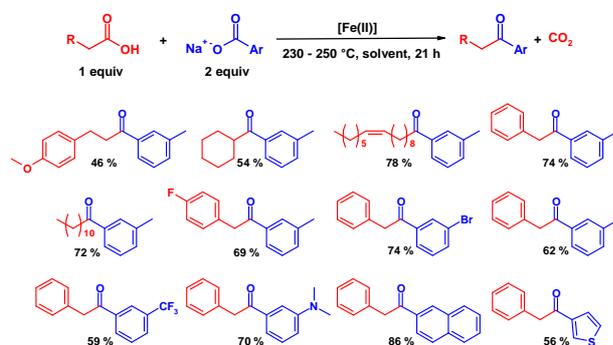


Such decarboxylative cross-ketonizations are challenging because a selectivity over homo-ketonizations and protodecarboxylations is hard to achieve. There are only few, scattered literature reports on this transformation using simple test substrates.^{6d}

Development of a Selective Cross-Ketonization Process

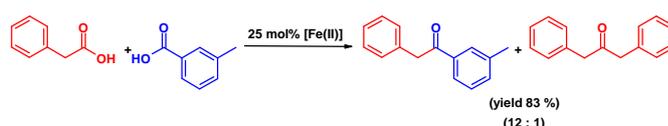
In our search for a selective cross-ketonization protocol, we screened various basic metal salts for the model reaction of phenylacetic acid with *m*-toluic acid at 300 °C. In almost all cases, dibenzyl ketone was formed preferentially. Solely when using iron(II)-based mediators, encouraging selectivities for benzyl *m*-tolyl ketone were observed. After careful catalyst optimization, a straightforward protocol was developed in which aliphatic carboxylic acids are mixed with sodium arenecarboxylates in slight excess and an iron(II) salt in an inert, high-boiling solvent. Even after reducing the reaction temperature to 230 °C, a high conversion and a selectivity of 20:1 for the benzyl *m*-tolyl ketone was obtained.

Following this protocol, various aryl alkyl ketones were synthesized in high yields, many of them inaccessible via Friedel-Crafts-type chemistry. In all cases, the reaction proceeded regioselectively, and the only by-products were homo-ketonization products of the aliphatic carboxylic acids.



The First Catalytic Protocol - Ongoing Work

The next step towards achieving a sustainable alternative to Friedel-Crafts-type chemistry was to reduce the amount of the mediator to catalytic quantities. This proved to be troublesome as the iron(II) oxide formed after completion of the first catalytic cycle decomposes, presumably under disproportionation, with formation of insoluble products. By scavenging the reaction water formed in the process, we achieved multiple turnovers of the iron catalyst and obtained reasonable yields in the presence of only 25 mol% of iron(II). Thus, we demonstrated for the first time that catalytic cross-ketonizations are indeed possible. Future work will be directed towards the discovery of more effective catalyst systems and more selective reaction protocols.



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

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