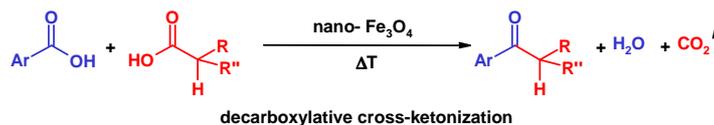


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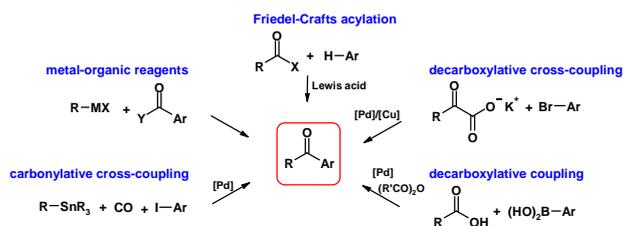
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A new protocol has been developed that allows the decarboxylative ketonization of alkyl- with arylcarboxylic acids under relatively mild conditions and in good yields. In the presence of iron-based catalysts, high selectivities for the hetero-coupled products, i.e. alkyl aryl ketones, were achieved when the aliphatic acid was heated together with an aromatic carboxylic acid. 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 9:1:0 selectivity over the symmetrical alkyl and aryl ketones.¹



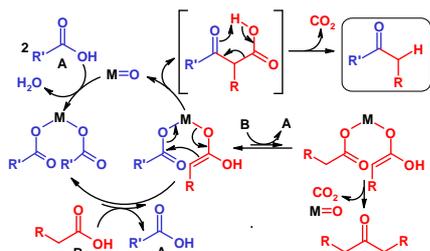
Syntheses of Unsymmetrical Ketones

Aryl alkyl ketones are important structural units in natural products and for chemical industry.² The most inexpensive synthetic entry is the waste-intensive Friedel-Crafts acylation; however, the products are mostly obtained as isomeric mixtures.³ More advanced, regioselective syntheses of such products are often too expensive for bulk chemicals.⁴

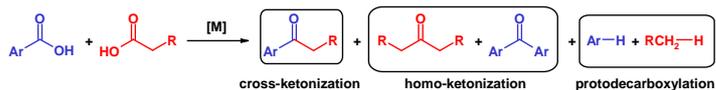


Decarboxylative Ketonization

One of the first examples for the decarboxylative ketonization was reported by Libavius in 16th century, who obtained acetone by pyrolysis of lead acetate. Various metal mediators such as calcium, magnesium oxide, iron, or manganese have been employed in this reaction, leading to the homo-ketonization product.⁵ The reaction is postulated to proceed via α -acylation and decarboxylation of the resulting β -keto acid.



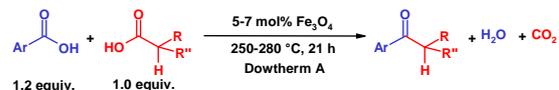
One requirement for the α -acylation step is the presence of α -hydrogens (homo-ketonization of benzoic acid was not observed). Therefore we reasoned that upon mixing an aliphatic with a more acidic aromatic carboxylic acid in the presence of a metal compound, the alkyl aryl ketones may form preferentially.



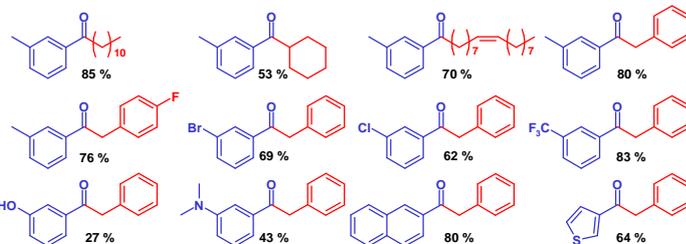
Decarboxylative cross-ketonizations represent a great challenge since high selectivity over homo-ketonization is hard to achieve. There are only few, scattered literature reports on such transformations using simple test substrates.^{6a}

Development of a Selective Catalytic Cross-Ketonization Process

In our search for a selective cross-ketonization protocol, we investigated 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 as the major product. Only in the presence of iron-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 aromatic carboxylic acids and a catalytic amount of magnetite nanoparticle (< 50 nm) in an inert, high-boiling solvent (Dowtherm A). Even after reducing the reaction temperature to 250 °C, a high conversion and a selectivity of 9:1 for the benzyl *m*-tolyl ketone was obtained.¹



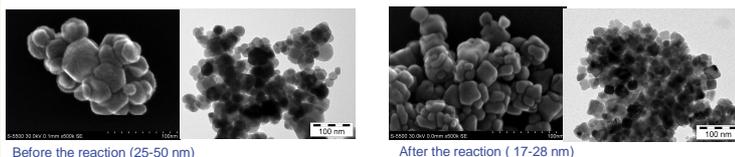
Following this optimized protocol, various aryl alkyl ketones were synthesized in high yields, many of them inaccessible via Friedel-Crafts-type chemistry. In all cases, the reaction proceeded regioselectively, and the only by-products were homo-ketonization products of the aliphatic carboxylic acids.



Characterization of the Catalyst

Due to the magnetic properties of the magnetite, the catalyst can be easily separated from the reaction solution.

The TEM (transmission electron microscopy) and SEM (scanning electron microscopy) analysis of the recycled Fe₃O₄-catalyst revealed a more narrow particle size distribution for the magnetite nanoparticles. This method opens up a new pathway to the synthesis of particles smaller than 20 nm.



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

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