A new protocol has been developed that allows the decarboxylative ketonization of aliphatic carboxylic 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., aliphatic 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 regiosomer 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 aliphatic and aryl carboxylic acids, and the aliphatic ketones were obtained in up to 10:1 selectivity over the symmetrical aliphatic and aryl ketones.

### Syntheses of Unsymmetrical Ketones

Aryl alkyl ketones are important structural units in organic chemistry and natural products. Various metal mediators such as metal-organic reagents can be used for the decarboxylative ketonization of these compounds. The most inexpensive synthetic entry is the waste-intensive Friedel-Crafts acylation; however, the products are mostly obtained as isomeric mixtures. More advanced, regioslective syntheses of such products are often too expensive for bulk chemicals.

### 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. Various metal mediators such as lead, magnesium oxide, iron or manganese have been employed in this reaction, leading to the homo-ketonization product. The reaction is believed to proceed via α-acylation and decarboxylation of the resulting β-keto esters.

A metal oxide 4 reacts with a mixture of two carboxylic acids 1 and 2. The carboxylate 5 forms which is not enolisable because it possesses no α-protons. Therefore, the catalytic cycle should proceed only with the mixed carboxylate 6 or the dialkyl carboxylate 8 present in equilibrium. The acyclic residue 6 can then shift to the α-position of the aliphatic carboxylate, forming a β-keto acid 7 which decarboxylates via a retro-ene reaction with formation of the ketone 3. The potential homo ketone side product 9 may form analogously from the carboxylate 8.

### Decarboxylative Cross-Ketonization

As α-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 compound, the aliphatic 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 a few scattered literature reports on this transformation using simple test substrates.

### Development of a Selective Catalytic 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-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 an iron catalyst in an inert, high-boiling solvent. Even after reducing the reaction temperature to 250 °C, a high conversion and a selectivity of 10:1 for the benzyl m-tolyl ketone was obtained.

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