

Patrizia Mamone,^a Christoph Oppel,^a Lukas J. Gooßen.^{a*}

^aInstitut für Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße 54, 67663 Kaiserslautern
Tel +49 631 205 2046, goossen@chemie.uni-kl.de

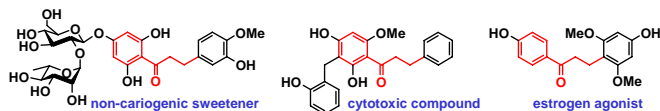
A new protocol has been developed that allows the decarboxylative ketonization of alkyl- with arylcarboxylic acids under relatively mild conditions and in good yields. In the presence of iron-based catalysts, high selectivities for the hetero-coupled products, i.e. alkyl aryl ketones, were achieved when 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 10:1:0 selectivity over the symmetrical alkyl and aryl ketones.¹



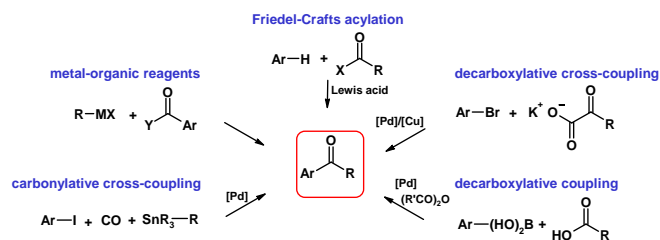
decarboxylative cross-ketonization

Syntheses of Unsymmetrical Ketones

Aryl alkyl ketones are important structural units in organic chemistry and natural products.²

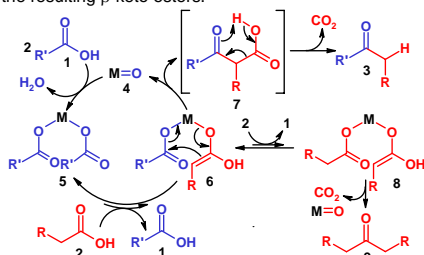


The most inexpensive synthetic entry is the waste-intensive Friedel-Crafts acylation; however, the products are mostly obtained as isomeric mixtures.³ More advanced, regioselective syntheses of such products are often too expensive for bulk chemicals.⁴



Decarboxylative Ketonization

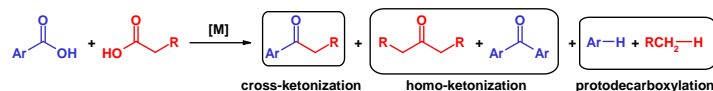
One of the first examples for the decarboxylative ketonization was reported by Friedel in 1858, who obtained ketones by pyrolysis of calcium carboxylates.⁵ Various metal mediators such as lead, magnesium oxide, iron or manganese have been employed in this reaction, leading to the homo-ketonization product.⁶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



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 acylic residue in **6** can then shift to the α -position of the aliphatic carboxylate, forming a β -keto acid **7** which decarboxylates via a retro-oxo-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

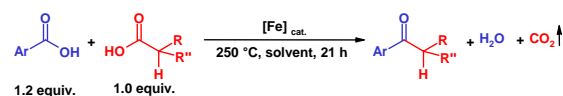
As α -hydrogens are required for the α -acylation step (homoketonizations of benzoic acids are unknown), we reasoned that upon mixing an aliphatic with a more acidic aromatic carboxylic acid in the presence of a metal compound, the alkyl aryl ketones may form preferentially.



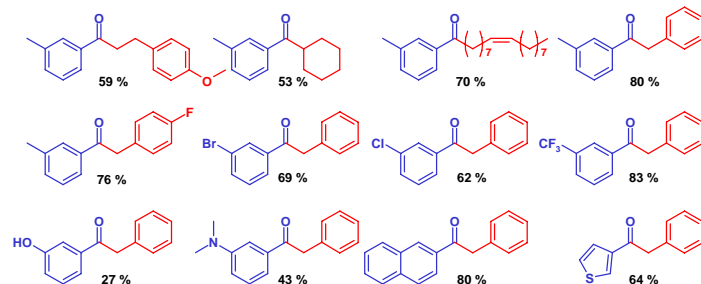
Such decarboxylative cross-ketonizations are challenging because a selectivity over homo-ketonizations and protodecarboxylations is hard to achieve. There are only few, scattered literature reports on this transformation using simple test substrates.^{6d}

Development of a Selective 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 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.



We thank Cognis GmbH for financial support and the Landesgraduiertenförderung Rheinland-Pfalz for a PhD fellowship to Patrizia Mamone.

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

- [1] Lukas J. Gooßen, Patrizia Mamone, Christoph Oppel, *Adv. Synth. Catal.* **2010**, accepted.
- [2] a) F. A. Tomás-Barberán, M. N. Clifford, *J. Sci. Food Agric.* **2000**, *80*, 1073; b) K. Ichikawa, M. Kitaoka, M. Taki, S. Takaishi, Y. Iijima, M. Boriboon, T. Akiyama, *Planta Med.* **1997**, *63*, 540; c) N. Nakatani, M. Ichimaru, M. Moriyasu, A. Kato, *Biol. Pharm. Bull.* **2005**, *28*, 83.
- [3] a) P. H. Gore, *Chem. Rev.* **1955**, *55*, 229; b) C. W. Schellhammer in *Methoden der Organischen Chemie* (Houben-Weyl), Band VII/2a (Hrsg.: E. Müller), Thieme, Stuttgart, **1973**, S.15.
- [4] a) M. Tanaka, *Tetrahedron Lett.* **1979**, *28*, 2601; b) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815; c) M. P. Cooke, *J. Org. Chem.* **1986**, *51*, 951; d) L. J. Gooßen, F. Rudolph, C. Oppel, N. Rodríguez, *Angew. Chem. Int. Ed.* **2008**, *47*, 3043; e) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100.
- [5] C. Friedel, *Justus Liebigs Ann. Chem.* **1858**, *108*, 122.
- [6] a) T. H. Easterfield, C. M. Taylor, *J. Chem. Soc.* **1911**, *99*, 2298; b) D. M. Cowan, G. H. Jeffrey, A. I. Vogel, *J. Chem. Soc.* **1940**, 171; c) R. Davis, H. P. Schultz, *J. Org. Chem.* **1962**, *27*, 854; d) C. Granito, H. P. Schultz, *J. Org. Chem.* **1963**, *28*, 879; e) S. Gerchakov, H. P. Schultz, *J. Org. Chem.* **1967**, *32*, 1656; f) E. Müller-Erlwein, *Chem. Ing. Tech.* **1990**, *62*, 416; g) M. Renz, A. Corma, *Eur. J. Org. Chem.* **2004**, 2036.