Copper- and Silver-Catalyzed Protodecarboxylation of Carboxylic Acids

Andreas Fromm, Nuria Rodríguez, Christophe Linder, Paul P. Lange
Prof. Dr. Lukas J. Gooßen, Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße 54, 67663 Kaiserslautern
Tel +49 631 205 2046, goossen@chemie.uni-kl.de, afromm@chemie.uni-kl.de

Abstract: The extrusion of CO_2 from aromatic carboxylic acids is the key step in decarboxylative coupling reactions, powerful tools for C–C bond formations and environmentally benign alternatives to Suzuki-Miyaura and similar types of couplings.[1] The decarboxylation can be achieved with catalytic amounts of metal salts in the presence of a suitable ligand. An improvement of the catalyst systems is highly desirable to achieve higher yields in lower reaction times at the same time as milder reaction conditions to extend the substrate scope.

$$Ar\text{-}COOH \xrightarrow{\text{Cu or Ag cat.}} Ar\text{-}H + CO_2$$
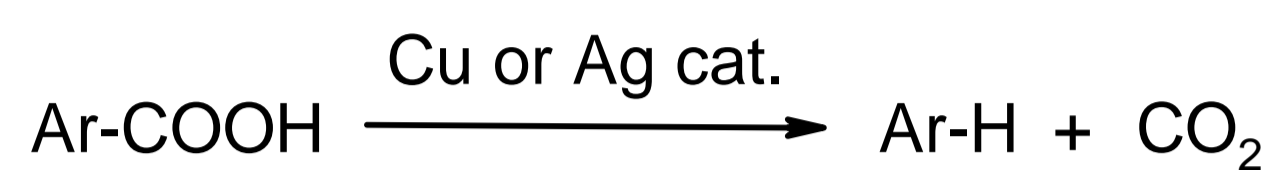
In this work the protodecarboxylation of aromatic carboxylic acids by various copper and silver catalysts is investigated with the help of density functional calculations and experimental studies.[2] The computational results reveal that the catalytic activity of copper(I)–1,10-phenanthroline catalysts increases with the introduction of electron-rich substituents at the phenanthroline ligand. They also predicted that for some substrates, silver complexes should possess a substantially higher decarboxylating activity than copper, which is confirmed by experimental studies, leading to the discovery of a silver(I) catalyst that effectively promotes the protodecarboxylation of various carboxylic acids at temperatures in the range of 80–120 °C – more than 50 °C below those of the best known copper(I) catalyst. The scope of the new system complements that of the copper(I)-based method as it includes benzoates for example, with halogen or ether groups in the *ortho* positions.

Decarboxylative Coupling Reactions

Decarboxylative coupling reactions are of high preparative utility, as they allow using carboxylate salts as substitutes for costly organometallic reagents in C–C bond forming reactions.[1d, e] In these transformations, the carbon nucleophiles are generated via extrusion of CO_2 from carboxylate salts and can subsequently be coupled with a range of carbon electrophiles.[1a, b, 3]
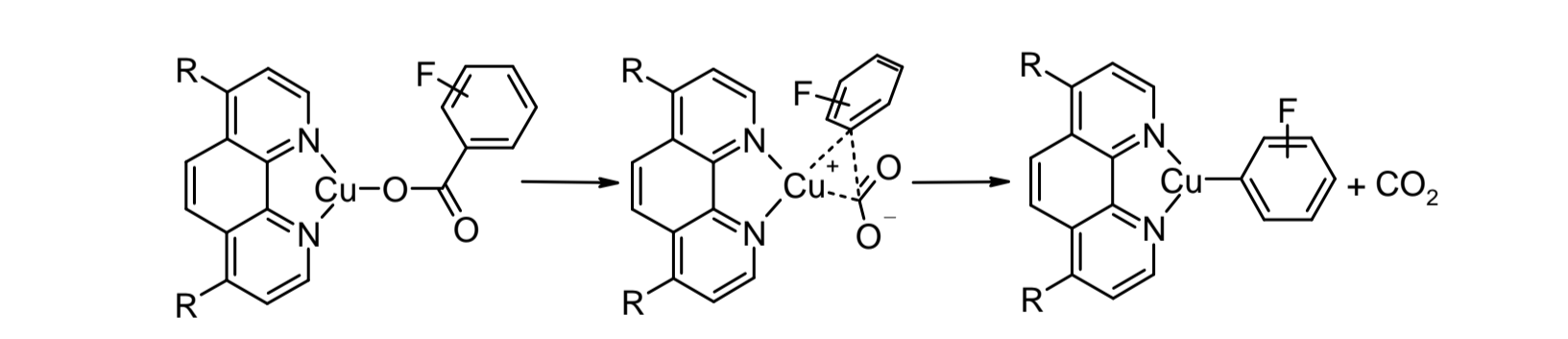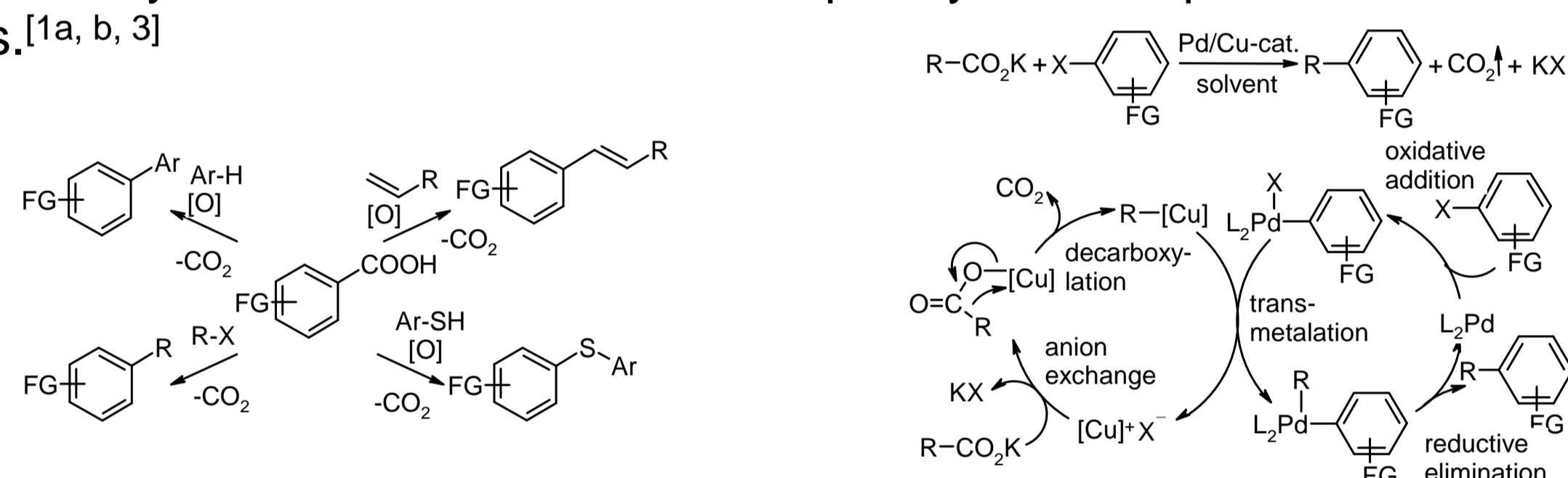
These transformations currently suffer from the rather high reaction temperatures required and/or the narrow range of substrates that are tolerated. All these limitations depend on the performance of the decarboxylation catalyst. An ideal test reaction for the development of more effective catalysts systems is the protodecarboxylation.

Investigation of the Cu-Catalyzed Protodecarboxylation with the Help of DFT Calculations

We recently developed the first protodecarboxylation of arenecarboxylic acids requiring only catalytic amounts of a metal mediator.[1c, 4] By using copper(I)–1,10-phenanthroline-type catalysts, a broad range of diversely functionalized aromatic carboxylic acids was effectively decarboxylated within 16 h at 170 °C.
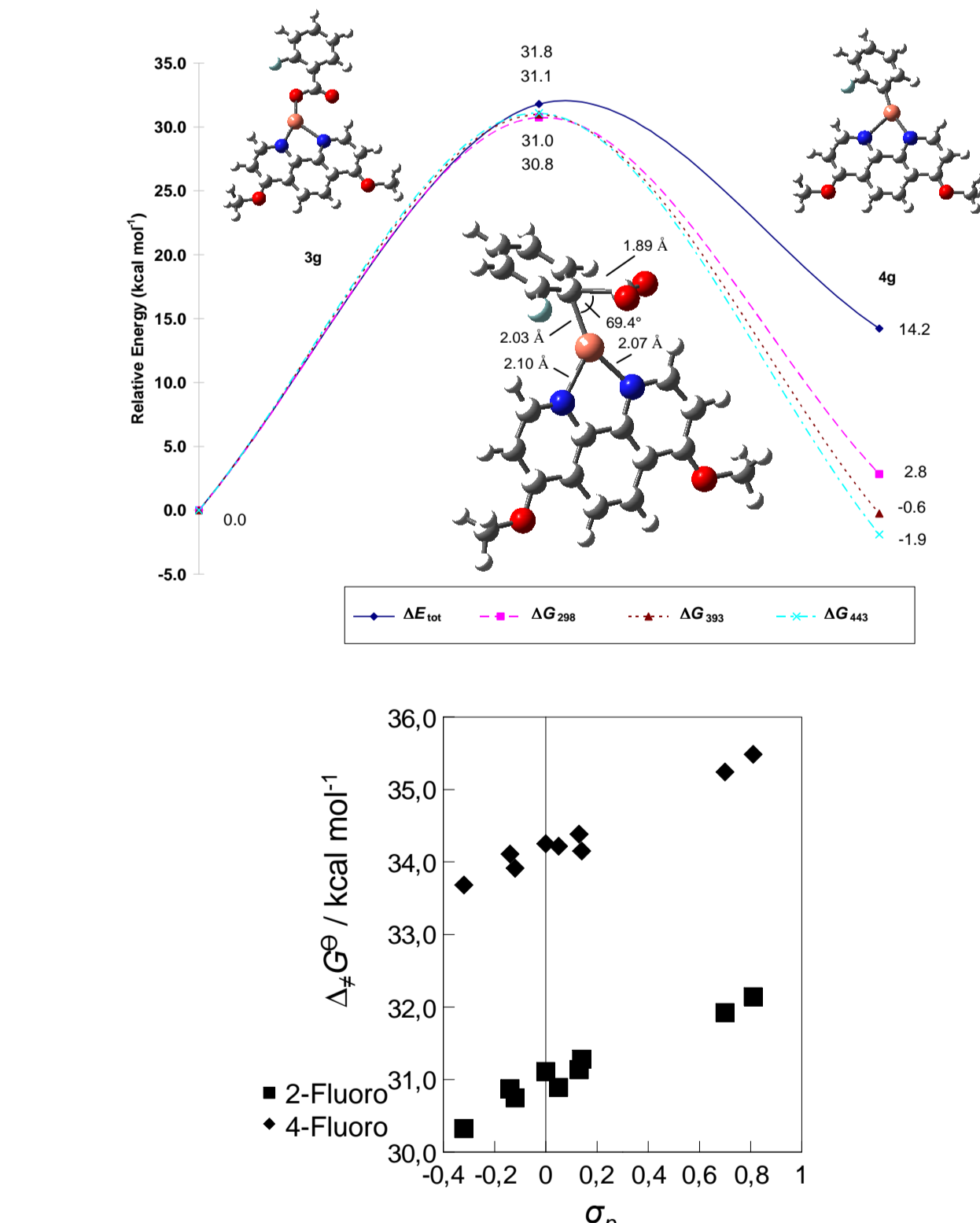
In order to guide our synthetic efforts towards the most promising ligand lead structures and to allow a better understanding of the results of our screening experiments, we performed a series of DFT calculations.[1c, 2] To improve the catalytic activity of the copper-complexes we studied the introduction of suitable substituents on the phenanthroline ring system.

R	σ_p	ortho $\Delta_a G^{\ominus}$	k_{rel}	Y / %[a]	para $\Delta_a G^{\ominus}$	k_{rel}	Y / %[b]
NO₂	0.81	32.1	0.2	-	35.5	0.1	-
CN	0.7	31.9	0.3	64	35.2	0.2	10
OPh	0.14	31.3	0.8	57	34.2	1.2	0
SPh	0.13	31.1	1.0	57	34.4	0.8	34
Ph	0.05	30.9	1.5	55	34.2	1.1	57
H	0	31.1	1.0	65	34.3	1.0	43
OMe	-0.12	30.7	1.9	81	33.9	1.8	6
Me	-0.14	30.9	1.5	75	34.1	1.3	0
NMe₂	-0.32	30.3	3.8	68	33.7	2.6	0

Hammett substituent constants σ_p, standard free Gibbs energies of activation $\Delta_a G^{\ominus}$ / kcal mol⁻¹, relative reaction rates k_{rel} are calculated from the Eyring equation. *Computational conditions*: Gaussian03; B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d); Stuttgart RSC 1997 ECP for Cu. *Reaction conditions*: 1 mmol 2- or 4-nitrobenzoic acid, 5 mol% Cu₂O, 10 mol% ligand, 2 mL of a mixture 3:1 of NMP and quinoline, 170 °C; [a] 2 h; [b] 16 h.
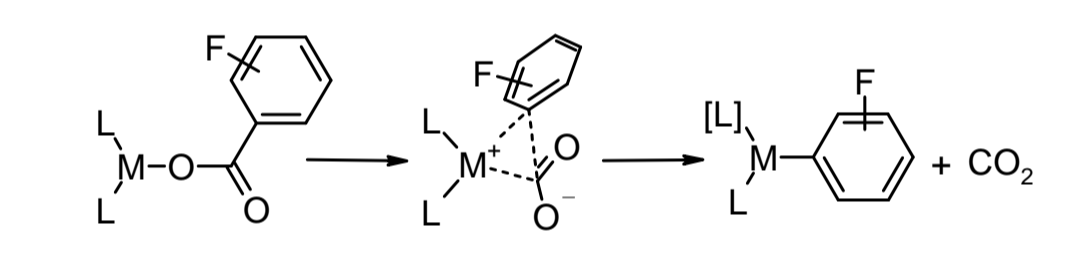
The calculated activation barriers increase with growing electron withdrawing effects of the substituents in 4- and 7-position of the phenanthroline ligand. Plotting the activation barriers against the Hammett substituent constants gives a linear relation. Obtained yields for *ortho*-substituted derivatives correspond to this trend. In the case of *para*-substitution, longer reaction times are required because of the higher activation barriers. At 170 °C this often leads to the decomposition of the ligands.

Investigation of the Ag-Catalyzed Protodecarboxylation with the Help of DFT Calculations

As the effects of different substituents were only limited (calculated increase of relative reaction rates < 4) DFT calculations with Ag instead of Cu were performed.[2] As phenanthroline is not a common ligand for Ag, calculations were carried out in which the silver(I) was stabilized solely by NMP molecules.

L	M	ortho $\Delta_R G^{\ominus}$	$\Delta_a G^{\ominus}$	k_{rel}	para $\Delta_R G^{\ominus}$	$\Delta_a G^{\ominus}$	k_{rel}
phen	Cu	2.1	31.1	1.0	10.8	34.3	1.0
phen	Ag	-0.5	29.6	13.7	7.8	33.2	6.2
NMP	Ag	-9.3	28.8	52.6	-0.7	34.0	1.5

Standard free Gibbs energies of reaction $\Delta_R G^{\ominus}$ and activation $\Delta_a G^{\ominus}$ / kcal mol⁻¹, relative reaction rates k_{rel} are calculated from the Eyring equation. *Computational conditions*: Gaussian03; B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d); Stuttgart RSC 1997 ECP for Cu and Ag.
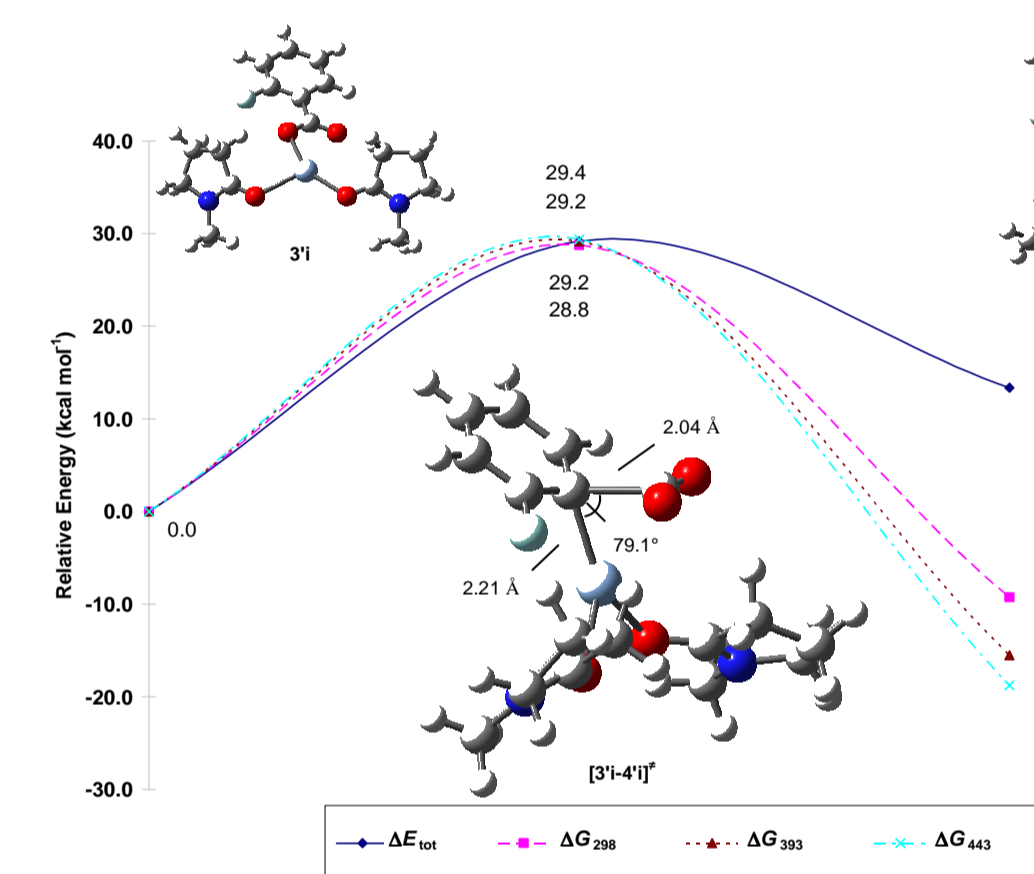
Changing the metal from Cu to Ag did not only change the kinetic but also the thermodynamic parameters of the decarboxylation. While the reaction with Cu/phen is endergonic, the extrusion of CO_2 with Ag/NMP is exergonic. In case of 4-fluorobenzoic acid the activation barrier is almost unchanged while for the *ortho* derivative the barrier is lowered by more than 2 kcal mol⁻¹ which leads to a large relative reaction rate of 53.

Comparison of the Silver- and Copper-Catalyzed Protodecarboxylation

Based on the DFT calculations a protodecarboxylation protocol using AgOAc was developed that effectively decarboxylates arenecarboxylic acids in NMP at 120 °C – 50 °C lower than that of the Cu-based system.[2b]

Formula	Y / %[a]	Y / %[b]	Formula	Y / %[a]	Y / %[b]	Formula	Y / %[a]	Y / %[b]
2-thienyl-CO₂H	80	58	2,6-MeO-C₆H₃-CO₂H	87	0	2-F-C₆H₄-CO₂H	74	79
3-Me-2-thienyl-CO₂H	78	73	2-Br-C₆H₄-CO₂H	76	0	cinnamic acid	76[d,e]	43
3-thienyl-CO₂H	36	78[c]	2-Br-4,5-MeO-C₆H₂-CO₂H	95	0	2-thiophenaglyoxylic acid	41[e]	31
isoquinolinic-1-acid	54	85	2,6-Cl-C₆H₃-CO₂H	76	0	4-HO-C₆H₄-CO₂H	17	75[c]
1-Me-pyrrole-2-CO₂H	77	68	2,4-Cl-C₆H₃-CO₂H	74	0	3-MeO-C₆H₄-CO₂H	38[f]	54[c]
2-NO₂-C₆H₄-CO₂H	92	87	2-Cl-5-NO₂-C₆H₃-CO₂H	85	0	4-MeO-C₆H₄-CO₂H	14[f]	80[c]
2-MeO-C₆H₄-CO₂H	83	24	2-MeS(O)₂-C₆H₄-CO₂H	90	60	3-NO₂-C₆H₄-CO₂H	0	89[c]
2-NO₂-5-MeO-C₆H₃-CO₂H	88	90	2-CF₃-C₆H₄-CO₂H	91	22	4-NO₂-C₆H₄-CO₂H	0	68[c]
2,4,5-MeO-C₆H₂-CO₂H	43	0	2-iPrOC(O)-C₆H₄-CO₂H	71	82	4-CN-C₆H₄-CO₂H	0	83[c]
2,4-MeO-C₆H₃-CO₂H	89	0	4-Ac-C₆H₄-CO₂H	58	87	4-Ac-C₆H₄-CO₂H	0	75[c]

[a] Silver-catalyzed protodecarboxylation: Carboxylic acid (2 mmol), AgOAc (10 mol%), K₂CO₃ (15 mol%), NMP (4 mL), 120 °C, 16 h; [b] Copper-catalyzed protodecarboxylation: Carboxylic acid (1.00 mmol), Cu₂O (5 mol%), 1,10-phenanthroline (10 mol%), NMP (1.5 mL), quinoline (0.5 mL), 170 °C; [c] 4,7-diphenyl-1,10-phenanthroline (0.10 mmol); [d] DMAc (4 mL) instead of NMP; [e] T=140 °C; [f] T=160 °C.

For most heterocyclic carboxylic acids and several *ortho*-substituted benzoic acids, high conversions were achieved with both systems. For benzoic acids bearing halo- or particularly electron-rich substituents in the 2-position, the silver catalyst at 120 °C was superior to the copper systems as predicted by the DFT calculations. The main strength of the copper catalyst lies in the decarboxylation of *meta*- and *para*-substituted benzoic acids.

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

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