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Copper-Catalyzed Protodecarboxylation of Aromatic Carboxylic Acids

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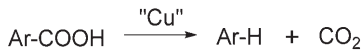
Abstract: A catalyst generated from copper(I) oxide and 4,7-diphenyl-1,10-phenanthroline for the first time allows the catalytic protodecarboxylation even of deactivated aromatic carboxylic acids, giving rise to the corresponding arenes. Based on DFT calculations, a reaction pathway is proposed that accurately reflects the experimental results, such as the observed reactivity order of the substrates.

Keywords: arenes; carboxylic acids; catalysis; copper; decarboxylation

The thermal decarboxylation of carboxylic acids is a transformation long known in organic synthesis.[1] It is of particular synthetic interest for the removal of carboxylate groups left behind as a result of the chosen synthetic route. However, while the decarboxylation of highly activated carboxylic acids, for example, β-oxo acids, diphenylacetic acids, or polyfluorinated benzoic acids proceeds reasonably well even in the absence of a catalyst, the release of CO_2 from simple aromatic carboxylic acids is much harder to accomplish. In 1930, Shepard et al. discovered that halogenated furancarboxylic acids can be decarboxylated at very high temperatures in the presence of stoichiometric amounts of copper or copper salts (Scheme 1).[2] This method was extended to activated benzoic acids by Nilsson,[3] Shepard,[4] and Cohen,[5] who all provided pieces of evidence that σ-bonded arylcopper species must be involved in this process. While the exact mechanism remained the subject of discussion, experimental data revealed that the protodecarboxylation is almost unaffected by the copper source employed, but strongly facilitated by the presence of bipyridine ligands at the copper and the use of aromatic amines as solvents.[6]



Scheme 1. Cu-mediated decarboxylation of benzoic acids.

Stoichiometric copper-mediated decarboxylation reactions were subsequently described for a considerable range of benzoic acids, demonstrating the preparative use of the reaction in organic synthesis.[7] However, significant drawbacks remained: most importantly, the arenecarboxylic acids had to either be *ortho*-substituted with electron-withdrawing groups such as nitro or halo, or to contain a heteroatom in order to undergo decarboxylation with reasonable yields. Moreover, although repeatedly proposed and claimed in patents, we could not find a single example for the decarboxylation of a non-activated benzoic acid derivative that was catalytic in copper.[8,9]

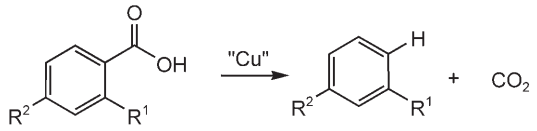
We became interested in catalytic decarboxylations in the context of our work on copper/palladium-mediated decarboxylative cross-couplings of carboxylic acid salts with aryl halides.[10] This transformation represents an attractive new strategy for the synthesis of biaryls using aromatic carboxylates as sources of aryl nucleophiles instead of organometallic compounds. Unfortunately, it is still limited by the insufficent activity of the decarboxylation catalyst. Although the best copper complex achieved more than 300 turnovers in the decarboxylation step for *ortho*-nitro-substituted carboxylic acids, its activity was modest for *meta*- and *para*-substituted derivatives. A key step to tackle the present substrate limitations of this reaction thus lies in the development of new decarboxylation catalysts with significantly improved activity and substrate scope. We herein describe our experimental and theoretical studies that led to the discovery of a new system that for the first time allows the decarboxylation even of deactivated aromatic carboxylic acids using only catalytic amounts of copper.

We started our investigations with 10 mol% of a catalyst generated from Cu_2O and 1,10-phenanthroline in a mixture of NMP and quinoline. As expected from our previous findings, 2-nitrobenzoic acid, an example for an activated substrate, was protodecarboxylated to give nitrobenzene in good yield, while the results were inferior for other carboxylic acids, and only a single turnover was achieved for particular electron-rich substrates such as 4-methoxybenzoic acid (Table 1, entries 1 and 2). The challenge presented by the latter substrate led us to select it as our model compound for the screening of various combinations of Cu sources, ligands, and solvents.

Initially, the results obtained were variable and unsatisfactory, until we began to carefully deoxygenate the reaction solvents. This led to modest, but reproducible catalytic turnovers that allowed further optimization (entry 3).

Among the copper sources tested, halide-free species gave the best results, suggesting that the counterion must not be too strongly coordinating (entries 3–6). Likewise, added halide salts hampered the reaction. Inorganic bases, were mostly tolerated but not beneficial, Lewis acids and coordinating ligands hindered the reaction (entries 7–9). The solvent system, on the other hand, was found to be very important for the reaction outcome: a combination of NMP and quinoline was much more effective than either solvent alone, and superior also to other pure solvents or solvent mixtures (entries 10–16).

Table 1. Optimization of the reaction conditions.[a]



1a: $R^1 = NO_2$, $R^2 = H$
1b: $R^1 = H$, $R^2 = OMe$

2a/2b

Entry	Substrate	Cu source	Ligand	Additive	Solvent	*T* [°C]	**2** [%]
1	**1a**	Cu_2O	**3a**	-	NMP/quinoline[b,c]	170	67
2	**1b**	”	”	-	”	”	12
3	”	”	”	-	NMP/quinoline[b]	”	35
4	”	CuOAc	”	-	”	”	29
5	”	Cu_2CO_3	”	-	”	”	29
6	”	CuBr	”	-	”	”	0
7	”	Cu_2O	”	K_2CO_3	”	”	30
8	”	”	”	$Sc(OTf)_3$	”	”	0
9	”	”	”	PPh_3	”	”	11
10	”	”	”	-	quinoline	”	28
11	”	”	”	-	NMP	”	33
12	”	”	”	-	mesitylene/quinoline[b]	”	20
13	”	”	”	-	DMF/quinoline[b]	”	26
14	”	”	”	-	DMPU/quinoline[b]	”	35
15	”	”	”	-	diglyme/quinoline[b]	”	25
16	”	”	”	-	DMSO/quinoline[b]	”	4
17	”	”	**3b**	-	NMP/quinoline[b]	”	0
18	”	”	**3c**	-	”	”	42
19	”	”	**3d**	-	”	”	9
20	”	”	**3e**	-	”	”	7
21	”	”	**4a**	-	”	”	20
22	”	”	**4b**	-	”	”	31
23	”	”	**5**	-	”	”	10
24	”	”	**3c**	-	”	160	11
25	”	”	”	-	”	180	80
26[d]	”	”	”	-	”	170	82
27	**1a**	”	**3a**	-	”	”	92

[a] *Reaction conditions:* 1.00 mmol benzoic acid, 0.10 mmol Cu, 0.10 mmol ligand, 2 mL degassed solvent, 12 h. Conversions were determined by GC analysis using *n*-tetradecane as the internal standard.
[b] 3:1 mixture of solvents.
[c] Using non-degassed solvents.
[d] After 24 h.

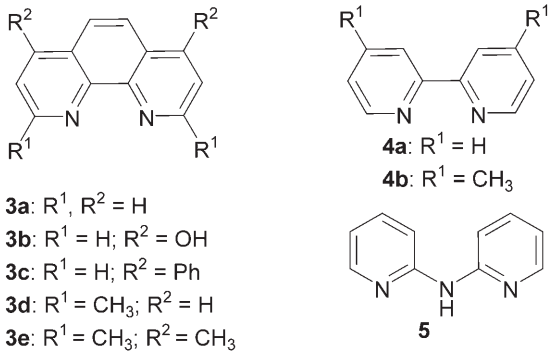
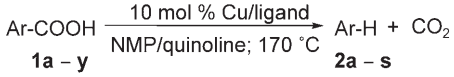


Figure 1. Cu ligands evaluated in the protodecarboxylation reaction.

Chelating nitrogen ligands on the copper strongly facilitate the transformation (Figure 1). Among the unsubstituted ligands, 1,10-phenanthroline was most effective, so that we decided to vary the steric and electronic parameters of this ligand (entries 3, 17–23). We observed that disubstitution in 2,9-positions reduced its activity, presumably due to steric hindrance. Substituents in 4,7-positions were beneficial with the understandable exception of hydroxy groups, for which the dipyridone is the major tautomer. The best results were finally achieved with 4,7-diphenyl-1,10-phenanthroline, a particularly large π-system. An improved conversion was already perceptible after 12 h, and the catalyst still remained active until the starting material was completely consumed. Thus, an excellent yield of the desired product was obtained after 24 h at 170 °C, or alternatively after 12 h at 180 °C (entries 24–26). These optimized conditions were effective also for 2-nitrobenzoic acid, but for this and other activated derivatives, the use of 4,7-diphenyl-1,10-phenanthroline offers little advantage, considering that full conversion can be achieved also with the parent 1,10-phenanthroline ligand (entry 27).

We next set out to explore the generality of the catalytic protocol using various aromatic and heteroaromatic carboxylic acids and were pleased to find that all of them were decarboxylated in reasonable to good yields. Selected results are summarized in Table 2. For *ortho*-substituted derivatives, 1,10-phenanthroline sufficed as the ligand, while for non-acti-

Table 2. Scope of the transformation.[a]



	Ar-COOH	Ar-H	Ligand	Time [h]	Yield [%]/(GC)[b]
1a	*o*-NO_2-C_6H_4-COOH	**2a**	**3a**	12	87 (92)
1b	*p*-MeO-C_6H_4-COOH	**2b**	**3c**	24	80 (81)
1c	*o*-MeO-C_6H_4-COOH	**2b**	**3a**	12	24 (24)
1d	*o*-F-C_6H_4-COOH	**2c**	**3a**	12	n.d. (79)
1e	*o*-PhNH-C_6H_4-COOH	**2d**	**3a**	12	82 (100)
1f	*o*-CHO-C_6H_4-COOH	**2e**	**3a**	12	76 (91)
1g	*o*-MeC(O)-C_6H_4-COOH	**2f**	**3a**	12	87 (100)
1h	*o*-$MeS(O)_2$-C_6H_4-COOH	**2g**	**3a**	12	60 (68)
1i	*o*-*i*-PrOC(O)-C_6H_4-COOH	**2h**	**3a**	12	82 (97)
1j	*o*-$Et_2NC(O)$-C_6H_4-COOH	**2i**	**3a**	12	85 (88)
1k	*m*-NO_2-C_6H_4-COOH	**2a**	**3c**	24	89 (93)
1l	*m*-Me-C_6H_4-COOH	**2j**	**3c**	24	n.d. (60)
1m	*p*-NO_2-C_6H_4-COOH	**2a**	**3c**	16	68 (73)
1n	*p*-CN-C_6H_4-COOH	**2h**	**3c**	16	83 (93)
1o	*p*-CHO-C_6H_4-COOH	**2e**	**3c**	16	65 (80)
1p	*p*-MeC(O)-C_6H_4-COOH	**2f**	**3c**	16	75 (78)
1q	*p*-MeC(O)N-C6H4-COOH	**2k**	**3c**	16	76 (80)
1r	*p*-Et-C_6H_4-COOH	**2l**	**3c**	24	n.d. (92)
1s	*p*-CF_3-C6H4-COOH	**2m**	**3c**	16	n.d. (22)
1t	*p*-Cl-C_6H_4-COOH	**2n**	**3c**	16	n.d. (72)
1u	*p*-HO-C_6H_4-COOH	**2o**	**3c**	12	75 (93)
1v	2-thienyl-COOH	**2p**	**3a**	12	n.d. (58)
1w	2-furyl-COOH	**2q**	**3a**	12	n.d. (62)
1x	1-naphthyl-COOH	**2r**	**3a**	12	83 (100)
1y	2-NO_2-5-MeO-C_6H_3-COOH	**2s**	**3c**	16	90 (93)

[a] *Reaction conditions*: 1.00 mmol carboxylic acid (**1a–y**), 0.05 mmol Cu_2O, 0.10 mmol 1,10-phenanthroline (**3a**) or 4,7-diphenyl-1,10-phenanthroline (**3c**), respectively, 1.5 mL NMP, 0.5 mL quinoline, 170 °C, isolated yields.

[b] GC yields were determined using *n*-tetradecane as the internal standard and were calibrated for each product.

vated derivatives, 4,7-diphenyl-1,10-phenanthroline is required. Although the reaction temperature is high, the conditions are sufficiently mild to be tolerated by a number of functional groups including ethers, esters, nitro, cyano, hydroxy, and aldehyde functions to allow a wide applicability in organic chemistry. While the decarboxylation could not be pushed to completion for all substrates even when extending the reaction time, we never detected more than traces of side products arising from homocoupling or substitution reactions. The work-up procedure is simple: the reaction mixtures are diluted with ether, washed with aqueous hydrochloric acid, and the products are obtained in pure form after removal of the solvent by distillation. Unfortunately, some of the test substrates led to products with such low boiling points that they could not be separated from the diethyl ether even when distilling over a Vigreux column, so that the yield could only be determined by quantitative gas chromatography.

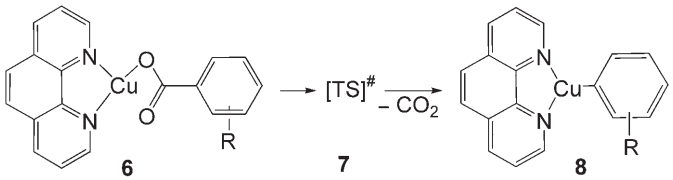
Aliphatic derivatives such as 5-phenylvaleric acid did not decarboxylate under these conditions. This is not surprising as their decarboxylation is known to proceed *via* a different mechanism involving redox processes.[11]

The mechanism of the uncatalyzed thermal decarboxylation of benzoic and substituted benzoic acids was the matter of a series of theoretical investigations starting in the late 1980s.[12] Very recently, BelBruno et al. reinvestigated and resummarized these results.[13] Although the levels of theory applied in those publications were quite different, the transition states of the aryl–CO_2 bond cleavage were localized for the pure acids as well as for water-assisted reactions. Evidently, the values obtained for the barriers of activation differ strongly, but even for activated *ortho*-substituted carboxylic acids and with the best levels of theory (B3LYP/6-311G**), they are remain higher than 59 kcal mol^{-1} for the decarboxylation of the pure acids and 40 kcal mol^{-1} for the water-assisted systems, explaining why high temperatures are required.

In order to substantiate the catalytic effect of copper(I), gain a better understanding of the reaction, and potentially enable a more rational ligand design, we modeled the copper-catalyzed decarboxylation step with the help of DFT calculations.[14] As the catalytic reaction performs better under anaerobic conditions, we exclusively investigated copper(I) species. The experimental finding that the addition of halides hampers the reaction led us to conclude that coordinating anions and carboxylate ions compete for coordination to copper(I). Thus, a species of the type (phen)Cu(O_2C-Ar) is likely to be the best precursor for a successful decarboxylation (Table 3). To elucidate the electronic influence of the aryl substituents R on $\Delta G^{\neq}$ and ΔG_R, we calculated these values for substituted benzoic acids with R = MeO, Me, H, F, NO_2 in *ortho*- or *para*-positions. The results of the calculations are summarized in Table 3.

As can be seen from the calculated free reaction energies, the decarboxylation of all derivatives is endothermic and endergonic at 298 K. In analogy to non-catalyzed reactions,[12e,13] *ortho*-substitutents able to withdraw electron density through the σ-backbone ($NO_2 > F > MeO > Me$) significantly reduce ΔG_R, while *para*-substituents have less of an influence. This trend is even stronger for the free enthalpies of activation. As in the case of ΔG_R, the influence of *para*-substituents is far less pronounced but follows the same order. Our calculations confirm the experimen-

Table 3. DFT calculations on the decarboxylation step.[a]



R	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta G^{\neq}$ [kcal mol^{-1}]	ΔH_R [kcal mol^{-1}]	ΔG_R [kcal mol^{-1}]
o-NO_2	26.78	27.15	9.85	0.75
o-F	30.80	31.42	17.02	6.73
o-OMe	30.60	30.69	19.28	8.47
o-Me	33.99	34.01	25.65	13.65
p-NO_2	35.70	36.05	23.90	12.09
p-F	35.94	35.82	27.48	15.85
p-OMe	35.87	35.94	28.76	17.49
p-Me	36.58	34.01	28.81	13.65
H	36.08	36.12	27.99	16.42

[a] *Conditions*: Gaussian03;[15] B3LYP;[16] 6-31G*;[17] for H, C, N, O, F; Stuttgart RSC 1997 ECP (ECP10MDF)[18] for Cu; T = 298 K.

tal findings in that the reactivity of the benzoic acids is dominated by short-range inductive effects transmitted *via* the σ-backbone, while long-range mesomeric effects through the π-system play only a minor role for their reactivity. They thus help to understand why both methoxy and nitro groups facilitate the reaction, especially when in *ortho*-position.

The geometries of all calculated structures are detailed in the Supporting Information. In the calculated transition states, both CO_2 and $[(phen)Cu]^+$ are bound through the lone pair of the phenyl anion. Notably, carboxylates with electronegative *ortho*-substituents ($NO_2 > F > MeO$) decarboxylate *via* an early transition state, as manifested in a short CO_2–phenyl bond (*ca.* 1.89 Å) and a long Cu–phenyl bond (*ca.* 2.03 Å) (Figure 2). In contrast, all other derivatives show a long CO_2–phenyl bond (*ca.* 2.04 Å) and a short Cu–phenyl bond (*ca.* 1.98 Å), indicating a late transition state, as expected for strongly endothermic reactions.

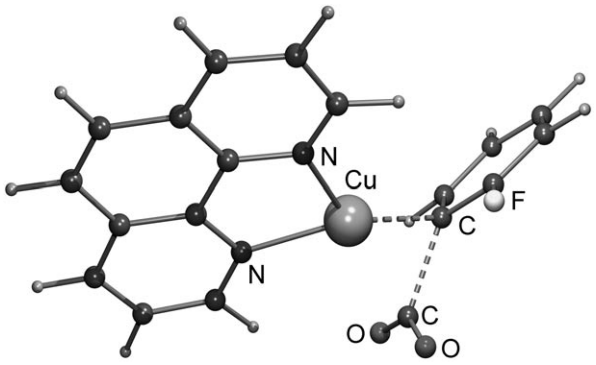


Figure 2. Molecular structure of the transition state of the Cu-catalyzed decarboxylation of 2-fluorobenzoic acid.

In summary, a general protocol for the Cu-catalyzed decarboxylation of non-activated aromatic carboxylic acids has been developed. The reaction pathway has been investigated with the help of DFT calculations, leading to the conclusion that the reaction proceeds *via* a substitution of CO_2 against Cu and a subsequent hydrolytic cleavage of the Cu–C bond. The proposed mechanism correctly predicts the observed reactivity order for the substrates. In current work, we are exploiting the computational pathway outlined herein to guide our search for more active second generation decarboxylation catalysts bearing other N,N-chelating ligands.

Experimental Section

General Methods

Reactions were performed under a nitrogen atmosphere in oven-dried glassware containing a teflon-coated stirrer bar and dry septum. All solvents were purified by standard procedures and deoxygenated by three freeze-pump-thaw cycles prior to use. All reactions were monitored by GC using *n*-tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (phenyl methyl siloxane 30 m × 320 × 0.25, 100/2.3–30–300/3) and a time program beginning with 2 min at 60 °C followed by 30 °C min^{-1} ramp to 300 °C, then 3 min at this temperature. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Redi*Sep* packed columns (12 g). NMR spectra were obtained on Bruker AMX 400 systems using $CDCl_3$ as solvent, with proton and carbon resonances at 400 MHz and 100 MHz, respectively. Mass spectral data were acquired on a GC-MS Saturn 2100 T (Varian).

Catalytic Decarboxylation Exemplified in the Synthesis of Anisole (2b)

An oven-dried vessel was charged with 4-methoxybenzoic acid (**1b**) (152 mg, 1.00 mmol), Cu_2O (7.2 mg, 0.05 mmol), and 4,7-diphenyl-1,10-phenanthroline (**3c**) (33 mg, 0.10 mmol). After purging the vessel with alternating vacuum and nitrogen cycles, a degassed solution of NMP (1.5 mL) and quinoline (0.5 mL) was added *via* syringe. The resulting mixture was stirred for 24 h at 170 °C, poured into aqueous HCl (5 N, 2 mL), and extracted repeatedly with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed by distillation over a Vigreux column affording **2b** as a clear, colorless liquid; yield: 86 mg (80 %). Its spectroscopic data matched those reported in literature for anisole, CAS: [100–66–3]

Acknowledgements

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