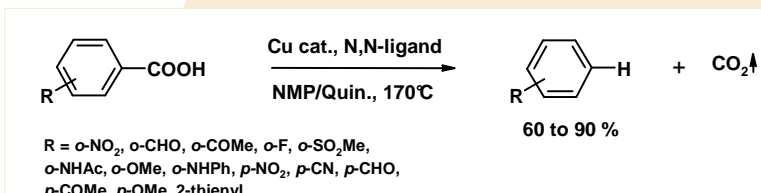


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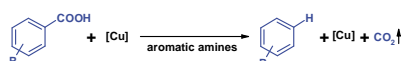
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Abstract: A catalyst generated from copper(I) oxide and 4,7-diphenyl-1,10-phenanthroline for the first time allows the catalytic protodecarboxylation even of deactivated aromatic carboxylic acids, giving rise to the corresponding arenes. The protodecarboxylation of aromatic carboxylic acids is a synthetically valuable transformation as it allows the removal of carboxylate groups left over as a result of the chosen synthetic route. Moreover, an analogous decarboxylation is the rate determining step in our copper/palladium-mediated decarboxylative cross-coupling of carboxylic acids with aryl halides to form biphenyl derivatives.

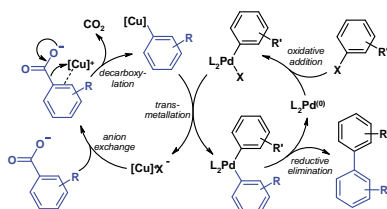


Introduction

The thermal decarboxylation of carboxylic acids is a transformation long known in organic synthesis. However, while the decarboxylation of β-ketonecarboxylic acids proceeds reasonably easy even in the absence of a catalyst, the release of CO₂ from simple aromatic carboxylic acids is much harder to accomplish. Until now, the methods available remain stoichiometric in the heavy metal copper and require harsh conditions. Likewise, the arenecarboxylic acids have to either be *ortho*-substituted with electron-withdrawing groups as nitro or halo, or to contain a heteroatom in order to undergo decarboxylation with reasonable yields.¹



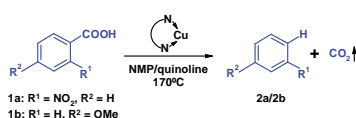
We became interested in catalytic decarboxylations in the context of our work on copper/palladium-mediated decarboxylative cross-coupling of arenecarboxylic salts with aryl halides.² This strategy represents a breakthrough in the synthesis of the biaryl moiety as the use of stoichiometric amounts of organometallic reagents is no longer required. The copper-mediated extrusion of CO₂ from aromatic carboxylates leads to the formation of aryl-copper species as sources of aryl nucleophiles (see scheme below).



Unfortunately, the extension of this transformation proved to be troublesome since the speed of decarboxylation strongly depends on the nature of the carboxylic acid and the balance between the decarboxylation and the cross-coupling step is rather delicate. Consequently, further experiments were carried out focussing on a better understanding of the decarboxylation step separately from the cross-coupling step.

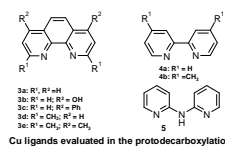
Investigation of the decarboxylation step

We started our investigations with 10 mol% of a copper catalyst in a mixture of NMP and quinoline (3:1), in the absence of the Pd catalyst and aryl halide, but otherwise under conditions similar to those of the decarboxylative cross-coupling.



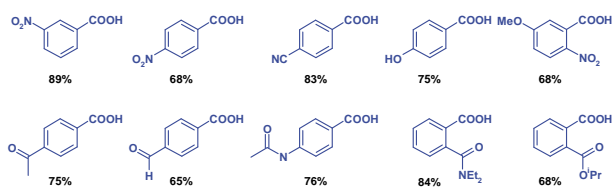
Entry	Substrate	Ligand	Temp (°C)	GC Yield (%)
1	1a	3a	170	92
2	1b	3a	*	35
3	*	3b	*	0
4	*	3c	*	42
5	*	3d	*	9
6	*	3e	*	7
7	*	4a	*	20
8	*	4b	*	31
9	*	5	*	10
10	*	3c	160	11
11	*	3c	180	80
12 ^a	*	3c	170	82
13 ^b	*	3c	170	7
14 ^c	*	3c	170	37

Reaction conditions: 1.00 mmol benzoic acid, 0.10 mmol ligand, 0.05 mmol Cu₂O, 2 mL degassed solvent, 12h. Conversions were determined by GC analysis using *n*-tetradecane as the internal standard. ^a After 24h. ^b Addition of 15 mol% KBr. ^c Addition of 15 mol% LiSO₃CF₃.



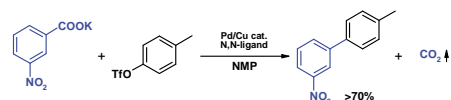
Cu ligands evaluated in the protodecarboxylation

Initial results revealed that a catalyst generated from copper(I) oxide and 4,7-diphenyl-1,10-phenanthroline allows the smooth protodecarboxylation of deactivated aromatic carboxylic acids, while a catalytic amount of a copper(I)-phenanthroline complex was active enough to protodecarboxylate a wide range of *ortho*-substituted carboxylic acids.³ This protocol allows for the first time the catalytic protodecarboxylation even of deactivated aromatic carboxylic acids.



However, the addition of halide ions - which would be inevitably released in the transmetalation step, see scheme above - has an adverse effect on the activity of the copper catalyst. Thus, the key to tackle the present limitation lies in tuning the ligand environment of the copper, and or alternatively using aryl sulfonates as halide-free coupling partners.

Recently, we were able to extend the scope of the reaction even to non-*ortho*-substituted benzoic acids by the use of triflates as halide-free coupling partners. In the presence of 2 mol% of palladium(II) iodide and 7.5 mol% of copper(I) oxide, catalytic turnover was accomplished in the coupling of the potassium *m*-nitro benzoate.



Current work is directed towards the synthesis of different *N,N*-chelating ligands to design a more active decarboxylation catalyst. If a suitable catalyst system for this particularly difficult transformation can indeed be found, it is likely that the scope of the decarboxylative cross-coupling will be extended to a wide range of carboxylic acids.

We gratefully acknowledge the financial support by Saltigo GmbH and the Alexander-von-Humboldt-Stiftung.

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

- [1] a) T. Cohen, R. A. Schambach, *J. Am. Chem. Soc.* **1970**, *92*, 3189; b) T. Cohen, R. W. Berninger, J. T. Wood, *J. Org. Chem.* **1978**, *43*, 837; c) M. Nilsson, *Acta Chem. Scand.* **1966**, *20*, 423.
- [2] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science*, **2006**, *313*, 662; b) L. J. Gooßen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824.
- [3] L. J. Gooßen, W. R. Thiel, N. Rodríguez, C. Linder, B. Melzer, *Adv. Synth. Catal.*, in print (**2007**).