Selective Copper- or Silver-Catalyzed Decarboxylative Deuteration of Aromatic Carboxylic Acids

Martin Rudzki, Ana Alcalde-Aragonés, Wojciech I. Dzik, Nuria Rodríguez, Lukas J. Gooßen*

Department of Chemistry, Organic Chemistry, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, 67663 Kaiserslautern, Germany

Fax +49(631)2053921; E-mail: goossen@chemie.uni-kl.de

Received 10 October 2011; revised 14 November 2011

Abstract: The practical utility of decarboxylative transformations in organic synthesis is discussed, and the decarboxylative deuteration of (hetero)aromatic carboxylic acids is disclosed as a further example. Various monodeuterated arenes were synthesized under mild conditions, in a single step from easily accessible aromatic carboxylic acids and deuterium oxide. Copper catalysts were found to have the widest scope, but silver catalysts are superior for some *ortho*-substituted benzoates. A few substrates, e.g. quinoline-2-carboxylic acid, decarboxylate even in the absence of a metal catalyst.

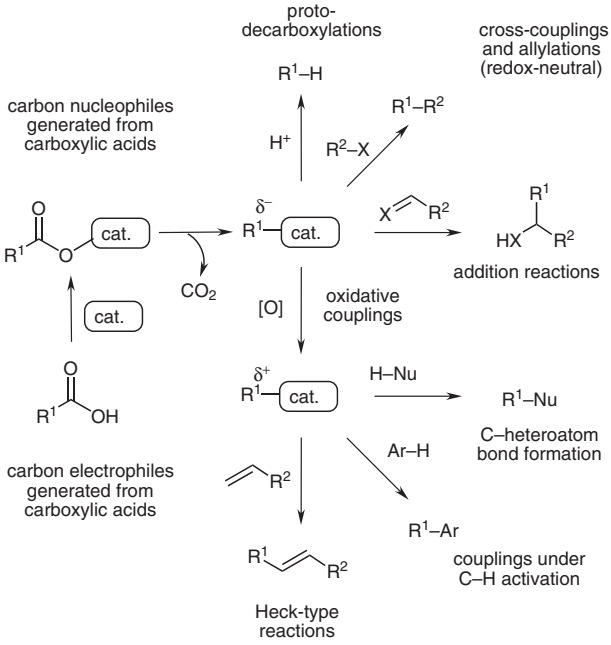
Key words: arenes, carboxylic acids, catalysis, decarboxylation, deuteration

In recent years, carboxylic acids have been rediscovered as an advantageous substrate class for transition-metal-catalyzed transformations.[1] Decarboxylative couplings, in particular, have attracted substantial attention. In 2002, Myers reported a Heck-type reaction as the first example of an oxidative decarboxylative coupling in which carbon electrophiles are generated from aromatic carboxylates.[2] In 2006, inspired by pioneering observations by Nilsson et al.,[3] we disclosed a redox-neutral decarboxylative coupling in which carbon nucleophiles are generated in situ from metal arenecarboxylates via extrusion of carbon dioxide (CO_2).[4] A related concept was utilized by Steglich[5] and also Forgione and Bilodeau et al.[6] for the arylation of heteroarenes.

Since then, catalytic decarboxylative couplings have rapidly developed into a generally applicable synthetic strategy for C–C and C–heteroatom bond formation.[7] In the redox-neutral reaction variants, carbon nucleophiles are generated via the extrusion of CO_2 and are directly coupled with an electrophilic partner. Examples are the regioselective synthesis of biaryls from aromatic or heteroaromatic carboxylates and aryl electrophiles,[4,8] or the analogous synthesis of aryl ketones or azomethines from α-oxocarboxylates.[9] In the oxidative reaction variant, carboxylic acids undergo decarboxylation and are oxidatively coupled with carbon- or heteroatom-based nucleophiles[10] or olefins (Scheme 1).[2,11]

Decarboxylative couplings are regiospecific because the new bond is formed at a position predefined by the carboxylate group. Their key advantages lie in the use of inexpensive and broadly available carboxylate salts instead of costly and air-sensitive pre-formed organometallic reagents.

The protodecarboxylation of aromatic carboxylic acids, in which the carboxylate group is replaced by a hydrogen atom, represents the simplest decarboxylative transformation.[12] This reaction is of substantial interest as a simple model for investigating specific aspects of complex decarboxylative coupling reactions. Besides, it is synthetically useful in removing surplus carboxylate groups that may be remnants from a chosen synthetic route,[13] e.g. the synthesis of indoles via the Reissert reaction[14] or the synthesis of pyridines via the Hantzsch reaction.[15] Miura and Satoh employed this approach to remove carboxylate groups after using them as directing groups in a C–H functionalization step.[16] Recently, a method for the synthesis of *meta*-substituted biaryls by direct *ortho*-arylation of benzoates, followed by in situ removal of the directing carboxylate group, was disclosed by Larrosa et al.[17]



Scheme 1 Overview of decarboxylative coupling reactions

Few carboxylic acids, e.g. β-oxocarboxylic acids, are known to readily decarboxylate in the absence of a metal catalyst or mediator.[18] The extrusion of CO_2 from the ma-

SYNTHESIS 2012, 44, 184–193
Advanced online publication: 05.12.2011
DOI: 10.1055/s-0031-1289638; Art ID: T96611SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: State University of New York at Binghamton. Copyrighted material.

Biographical Sketches

Martin Rudzki was born in Piekary Śląskie (Poland). He studied chemistry at the TU Kaiserslautern (Germany), which included an internship at Merck KGaA in Darmstadt, and was awarded a Wiley-VCH prize. His diploma thesis covered the field of decarboxylations, especially protodecarboxylation of heteroaromatic carboxylic acids and decarboxylative deuteration. His graduate research in the group of L. J. Gooßen was funded by the Deutsche Bundesstiftung Umwelt. Currently he is a project manager at SGS Institut Fresenius GmbH in Taunusstein (Germany).

Ana Alcalde was born in Pamplona (Spain) in 1983. She received her diploma in 2006 from the University of Valencia, where she went on to pursue doctoral research in organic chemistry. In 2010, she was a visiting researcher in the Gooßen group. Since June 2011, she has worked at the Catalonian Ambient Intelligence and Accessibility Center at the Autonomous University of Barcelona. Her research interests include catalyst design and novel catalytic materials, reactions in supercritical fluids, and environmentally benign chemical processes.

Wojciech I. Dzik was born in 1982 in Columbus, OH (USA). He studied Chemistry at the University of Warsaw (Poland), where he was awarded an M.Sc. degree in 2006. Subsequently, he conducted doctoral research under the guidance of B. de Bruin and J. N. H. Reek at the University of Amsterdam (Netherlands), and completed his Ph.D. in 2011. Currently, he is a Humboldt postdoctoral fellow in the group of L. J. Gooßen at the TU Kaiserslautern (Germany), and works on the development of new decarboxylative coupling reactions.

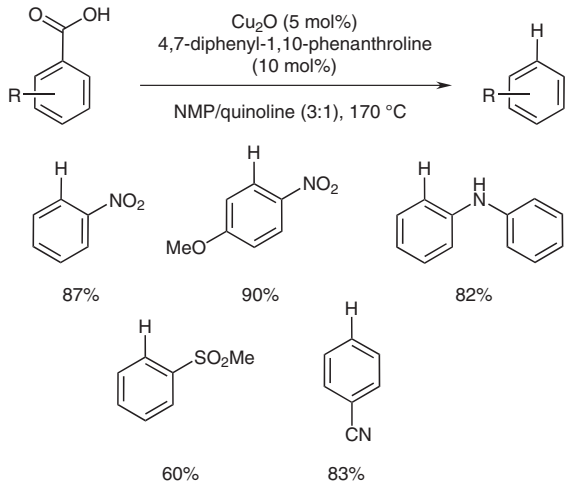
Nuria Rodríguez was born in 1978 in Valencia (Spain). After completion of her chemistry studies at the University of Valencia, she gained her doctorate in the group of G. Asensio and M. Medio-Simón. She worked with L. J. Gooßen as a Humboldt postdoctoral fellow starting 2006. The emphasis of her work was the development of decarboxylative cross-coupling reactions. In 2011, she took up a Ramon y Cajal research position at the University of Madrid (Spain). Her current research focuses on the development of catalytic systems for the activation of inert C–H bonds.

Lukas J. Gooßen graduated in chemistry from the University of Bielefeld, with research stays in Michigan with A. Ashe III, and Berkeley with K. P. C. Vollhardt. He received his doctorate at the TU Munich in 1997, supervised by W. A. Herrmann. After a postdoctoral stay with K. B. Sharpless and a position as laboratory head at Bayer, he gained his habilitation with M. T. Reetz at the MPI für Kohlenforschung. He then took up a position at the RWTH Aachen and in 2005, became Professor of Organic Chemistry at the TU Kaiserslautern. His current research focuses on the development of sustainable catalytic transformations.

Downloaded by: State University of New York at Binghamton. Copyrighted material.

jority of aromatic carboxylic acids needs to be promoted by aqueous acid[19] or by more effective transition-metal mediators, such as copper,[3,20] silver,[21] or mercury salts.[22] In early work, stoichiometric amounts of metal salt and high temperatures were used in the protodecarboxylation of aromatic carboxylic acids. For instance, halogenated furancarboxylic acids were protodecarboxylated by Shepard et al. using copper metal or copper salts at temperatures between 210 °C and 300 °C.[20a] Nilsson,[3,20b] Sheppard,[20c] and Cohen[20d] improved this method by combining copper with bipyridine ligands and/or aromatic amine solvents. With this protocol, activated aromatic and vinylic carboxylic acids can also be converted into the corresponding protonated substrates. Only few highly activated carboxylic acids were successfully protodecarboxylated when using catalytic amounts of copper sources.[23,24]

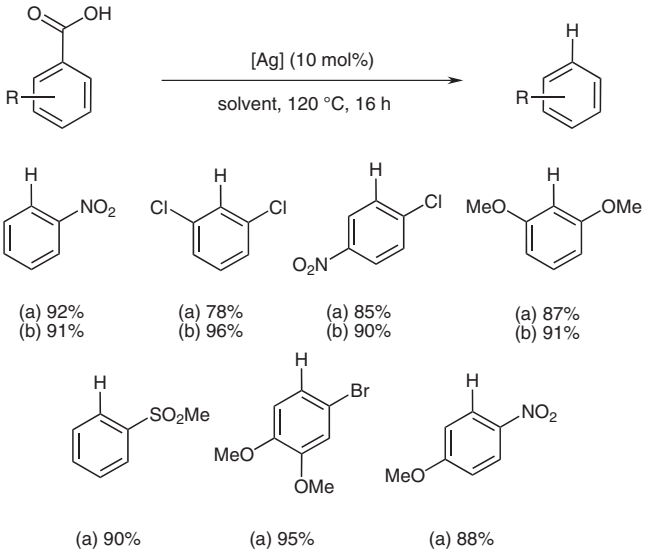
Recent years have brought about significant improvements in this field, and effective copper- and silver-based catalyst systems capable of protodecarboxylating a broad range of carboxylic acids have been disclosed. New catalysts based on copper/4,7-diphenyl-1,10-phenanthroline complexes were shown to promote effectively the decarboxylation of various carboxylic acids (Scheme 2).[25] The reaction conditions [Cu_2O (5 mol%), 4,7-diphenyl-1,10-phenanthroline (10 mol%), NMP–quinoline, 170 °C] tolerate a number of functionalities, e.g. methoxy, nitro, or cyano groups. This protocol was further improved by using modern microwave technology, which allows reduction of the reaction time from several hours to a few minutes, even when using a simple 1,10-phenanthroline ligand.[26]



Scheme 2 Examples of copper-catalyzed protodecarboxylations by Gooßen et al.[27b]

The copper-based catalysts are particularly suited for *meta*- and *para*-substituted benzoic acids. In contrast, silver-based catalyst systems are highly effective for several *ortho*-substituted or heterocyclic derivatives, which give low or no yields with copper.[27,28] Our recently developed catalyst system, consisting of silver acetate and potassium carbonate in *N*-methyl-2-pyrrolidinone, allows for the protodecarboxylation of a broad scope of *ortho*-substituted benzoic acids (Scheme 3, results a).[27b]

Larrosa et al. independently developed a silver carbonate/dimethyl sulfoxide catalyst system with a comparable substrate scope (Scheme 3, results b).[28a] They further demonstrated that in combination with 5 mol% acetic acid, their catalyst system also allows the decarboxylation of various heteroaromatic carboxylic acids.[28b]



Scheme 3 Examples of silver-catalyzed protodecarboxylations by (a) Gooßen et al.[27b] and (b) Larrosa et al.[28a]

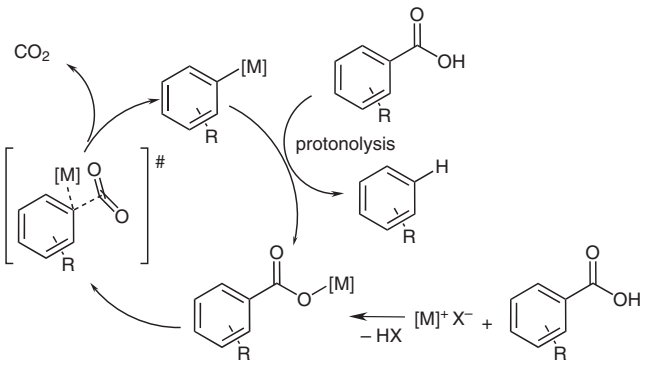
Rhodium-catalyzed protodecarboxylations proceed at relatively low temperatures;[29] the catalyst system is generated from $[(cod)Rh(OH)]_2$ and 1,3-bis(diphenylphosphino)propane. It promotes the protodecarboxylation of a small range of *ortho*,*ortho*-disubstituted benzoic or otherwise activated carboxylic acids already at 110 °C in a solvent mixture of toluene and aqueous sodium hydroxide.

Kozlowski et al. reported that a catalyst system consisting of 20 mol% palladium(II) trifluoroacetate in dimethyl sulfoxide–*N*,*N*-dimethylformamide (1:20) allows the protodecarboxylation of electron-rich, 2,6-disubstituted benzoic acids at the remarkably low temperature of 70 °C.[30] Excess trifluoroacetic acid is added to increase the rate of protodemetalation, which is too slow otherwise. The stability of the intermediate aryl–metal species is even more pronounced when starting from gold carboxylates, which readily extrude CO_2 but do not undergo protonolysis.[31]

While decarboxylations of aliphatic carboxylic acids are believed to follow a radical pathway,[32] the mechanism of the copper-mediated protodecarboxylation of aromatic carboxylic acids was shown to proceed via aryl–metal intermediates.[33] The reaction mechanisms of both copper- and silver-catalyzed protodecarboxylations of aromatic carboxylic acids were elucidated by DFT calculations,

Downloaded by: State University of New York at Binghamton. Copyrighted material.

 © Thieme Stuttgart · New York



Scheme 4 Mechanism of the copper- and silver-catalyzed protodecarboxylation of aromatic carboxylic acids

which correctly predicted the observed reactivity sequence for benzoic acids (Scheme 4).[25,27]

Building on the above studies of catalytic protodecarboxylations, we herein present an efficient route to monodeuterated aromatic compounds via the extrusion of CO_2 from O-deuterated aromatic carboxylates.

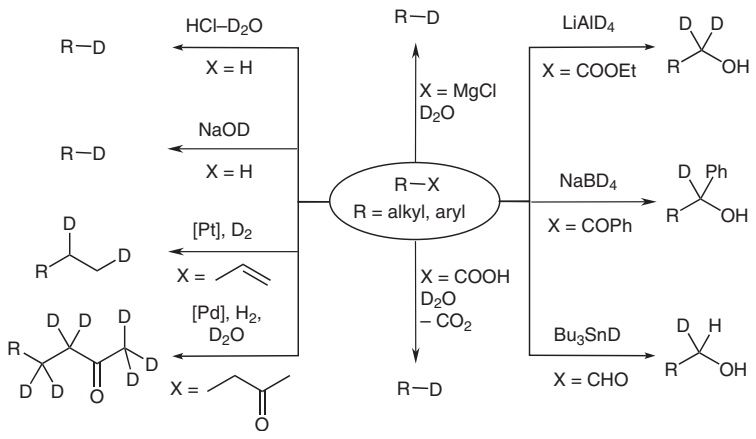
Deuterium-labeled compounds are of interest in several fields of chemistry, including investigations of reaction mechanisms, drug metabolism, kinetic studies or molecular structure analysis. The classic approach to deuterate molecules regioselectively is to reduce functional groups with deuteride sources such as $LiAlD_4$,[34] $NaBD_4$,[35] or Bu_3SnD (Scheme 5, right).[36] The deuterolysis of organometallic compounds with D_2O also leads to the formation of the corresponding deuterated compounds (Scheme 5, top).[37] Other popular deuteration methods include H–D exchange reactions catalyzed by acid,[38] base,[39] and transition-metal catalysts,[40] and the addition of D_2 across double bonds (Scheme 5, left).[41]

The extrusion of CO_2 from O-deuterated aromatic carboxylates represents a promising approach for the regiospecific introduction of a single deuteron (Scheme 5, bottom). To date, there are only a few reports of the synthesis of deuterium-labeled compounds by the decarboxylation of carboxylic acids. Matsubara et al. reported a decarboxylative deuteration of aliphatic carboxylic acids under hydrothermal conditions. However, this method requires rather harsh conditions and leads to the formation of perdeuterated compounds.[42] Several aliphatic acids were decarboxylated photochemically, with selective formation of monodeuterated compounds.[43] A regioselective synthesis of monodeuterated arenes is even harder to accomplish. Morita et al. reported that monodeuterated benzene is formed when heating calcium benzoate and calcium deuteroxide to 300 °C.[44] Erlenmeyer et al. demonstrated that the decarboxylative deuteration of mellitic acid [$C_6(COOH)_6$)] leads to the formation of benzene-d_6.[45] This concept was also employed by Zoltewicz et al. to synthesize deuterated pyridine derivatives.[46]

We believed that the synthesis of monodeuterated arenes might be possible under much milder conditions using the new decarboxylation catalysts that we developed in the course of our work on decarboxylative couplings.[25–27] These copper- or silver-based catalysts effectively mediate the extrusion of CO_2 from aromatic carboxylates with regioselective formation of an aryl–metal bond in the *ipso*-position. If the subsequent protonolysis is performed with deuterons rather than protons, monodeuterated compounds should be obtained.

In order to apply the concept of decarboxylative deuteration to the broadest possible range of substrates, we investigated several complementary protodecarboxylation catalysts in analogous deuterodecarboxylation reactions. Judging from comparative protodecarboxylation studies,[27b] one would expect copper systems to be the catalysts of choice for non-*ortho*-substituted arenes, while silver catalysts should be optimal for some *ortho*-halo-substituted benzoic acids. However, especially for some heteroaromatic substrates, it was not clear which catalyst system would be the most effective. We thus comparatively studied copper- and silver-based catalysts in the protodecarboxylation of several heteroaromatic carboxylic acids **1a–d** (Table 1).

For the protodecarboxylation of 1*H*-indole-2-carboxylic acid (**1a**), the copper catalyst [Cu_2O, 1,10-phenanthroline, NMP–quinoline (3:1), 170 °C] gave better results than silver (AgOAc, NMP, 120 °C). For benzothiophene-2-carboxylic acid (**1b**), the silver catalyst proved to be more effective than copper.

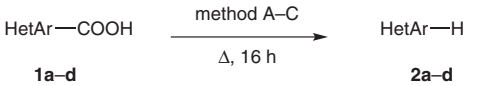


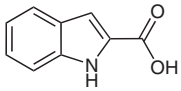
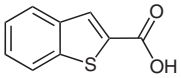
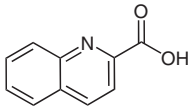
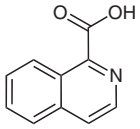
Scheme 5 Synthetic entries to deuterium-labeled compounds

© Thieme Stuttgart · New York

Downloaded by: State University of New York at Binghamton. Copyrighted material.

Table 1 Protodecarboxylation of Heteroaromatic Carboxylic Acids[a]



HetAr-COOH	Catalyst	Method	Yield[b] (%)
	Cu	A	98
	Ag	B	22
	–	C	0
1a			
	Cu	A	64
	Ag	B	79
	–	C	0
1b			
	Cu	A[c]	55
	Ag	B	11
	–	C	57
1c			
	Cu	A[c]	84
	Ag	B	59
	–	C	98
1d			

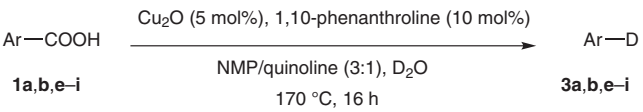
[a] The reactions were performed on 1-mmol scale; Method A: Cu_2O (5 mol%), 1,10-phenanthroline (10 mol%), NMP–quinoline (3:1, 2 mL), 170 °C, 16 h. Method B: AgOAc (10 mol%), NMP (2 mL), 120 °C, 16 h. Method C: NMP (2 mL), 170 °C, 16 h.
[b] The yields were determined by GC using tetradecane as internal standard.
[c] Without quinoline.

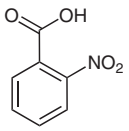
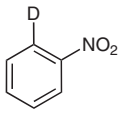
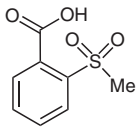
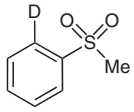
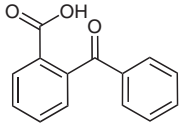
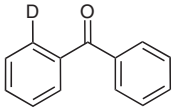
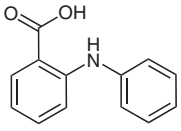
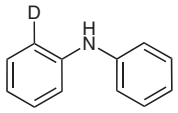
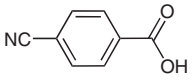
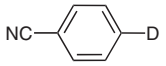
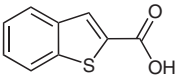
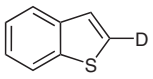
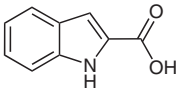
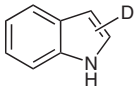
For six-membered nitrogen heterocycles with carboxylate groups directly adjacent to the ring nitrogen atom, the thermal protodecarboxylation was found to be more effective than the analogous reaction in the presence of either metal catalyst. Thus, quinoline-2-carboxylic acid (**1c**) and isoquinoline-1-carboxylic acid (**1d**) smoothly deuterodecarboxylated at 170 °C. These observations indicate that in the case of **1a** and **1b**, the decarboxylation involves an aryl–metal species, whereas quinolinecarboxylic acids **1c** and **1d** decarboxylate via a different mechanism.

This study in combination with preceding work allowed us to decide on the optimal method to use for the protodecarboxylation of each class of aromatic carboxylate **1**.

We next embarked on the development of deuterium analogues of copper-, silver-, and non-catalyzed protodecarboxylation protocols. The principal challenge was to find convenient processes for effectively replacing all protons in the reaction medium with deuterons. For the copper-catalyzed reactions, it proved to be most practical to add an excess of D_2O in three portions into the *N*-methylpyrrolidin-2-one–quinoline solution of the carboxylic acid and copper oxide/1,10-phenanthroline catalyst while stirring the mixture at 110 °C. The remaining gaseous D_2O and the HDO formed in the process were removed in a continuous flow of nitrogen gas. The resulting reaction mixture was stirred at 170 °C for 16 hours. We applied this method to the deuterodecarboxylation of 2-nitrobenzoic acid (**1e**) as a test substrate. Indeed, the desired nitrobenzene-*2-d* (**3e**) was formed in 72% yield and an excellent 99% degree of deuteration (Table 2, entry 1). Encouraged by this result, we applied the same method to other benzoic acids including 2-(methylsulfonyl)benzoic acid (**1f**), 2-benzoylbenzoic acid (**1g**), 2-(phenylamino)benzoic acid (**1h**), 4-cyanobenzoic acid (**1i**), and benzothiophene-2-carboxylic acid (**1b**). The deuterodecarboxylation proceeded with high regioselectivity and

Table 2 Copper-Catalyzed Decarboxylative Deuteration of Aromatic Carboxylic Acids (Method A′)[a]



Entry	Ar-COOH	Ar-D	DG[b] (%)	Yield (%)
1			99	72
	1e	**3e**		
2			77	50
	1f	**3f**		
3			80	77
	1g	**3g**		
4			50	64
	1h	**3h**		
5			40	58[c]
	1i	**3i**		
6			67	68
	1b	**3b**		
7			55:45[d]	54[d]
	1a	**3a/3a′**		

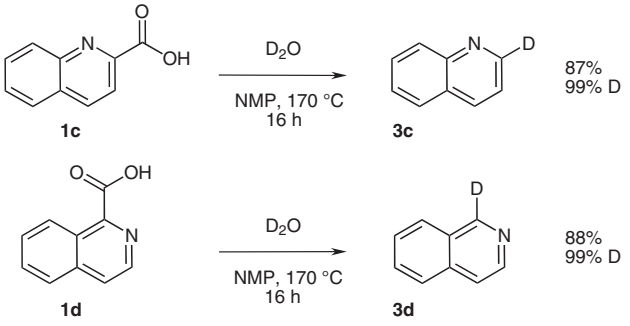
[a] Reaction conditions: **1** (1 mmol), Cu_2O (5 mol%), 1,10-phenanthroline (10 mol%), NMP–quinoline (3:1, 2 mL), D_2O, 16 h, 170 °C.
[b] DG = deuteration grade, calculated by integration of the ^1H NMR signals.
[c] With 4,7-diphenyl-1,10-phenanthroline.
[d] A mixture of **3a** (deuteration at C2) and **3a′** (deuteration at C3) 55:45.

Downloaded by: State University of New York at Binghamton. Copyrighted material.

 © Thieme Stuttgart · New York

the corresponding monodeuterated products were obtained in moderate to good yields and deuteration grades. A remarkable exception is 1*H*-indole-2-carboxylic acid (**1c**), where substantial scrambling of the deuterium was observed, leading to the formation of a 55:45 mixture of *ipso*- and *ortho*-monodeuterated indole **3a** and **3a′**. This result implies that for this specific substrate class, copper can easily move between the C2 and the C3 position, which provides an explanation for the lack of regiospecificity that we had observed when trying to apply our decarboxylative arylation reaction to indoles.[47]

We next tested whether the catalyst-free H/D exchange protocol (NMP, 170 °C) that had been most effective for the protodecarboxylation of quinoline- **1c** and isoquinolinecarboxylic acids **1d** could also be used for the analogous deuteration. Indeed, when a solution of the acid **1c** or **1d** in *N*-methyl-2-pyrrolidinone was subjected to proton–deuteron exchange as described above and subsequently heated to 170 °C for 16 hours, the desired monodeuterated quinoline **3c** and isoquinoline **3d** were formed in excellent yields and deuteration grades (Scheme 6).



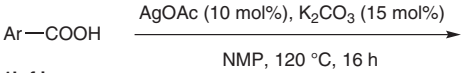
Scheme 6 Catalyst-free decarboxylative deuteration (method C′) of quinoline-2-carboxylic acid (**1c**) and isoquinoline-1-carboxylic acid (**1d**)

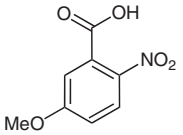
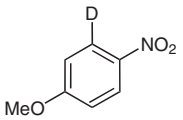
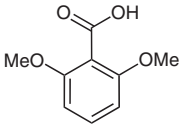
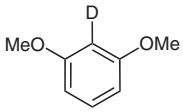
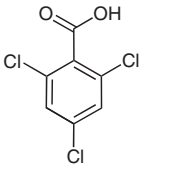
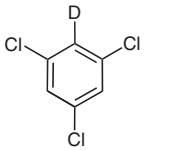
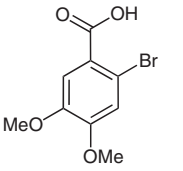
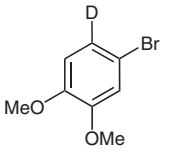
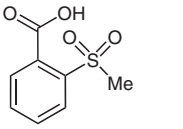
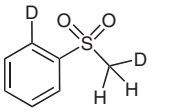
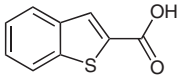
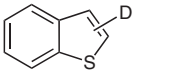
It is remarkable that the deuteration grades drop significantly in several cases although we were confident that we had completely exchanged all acidic protons in the reaction medium with deuterons. It appears that for these substrates, the *N*-methylpyrrolidin-2-one solvent, although its pK_a is as high as 37,[48] serves as a proton source in this side reaction. A similar process may account for protodecarboxylations observed as side reactions in decarboxylative cross-couplings under rigorously anhydrous conditions.[49]

Finally, we investigated the silver-catalyzed deuterodecarboxylation of *ortho*-methoxy- and halo-substituted benzoic acids **1j–m**. The protocol had to be especially adapted to account for the particular volatility of the deuterated products derived from these substrates. Because the silver-catalyzed decarboxylation starts already at 110 °C, it takes place to a significant extent before all protons in the reaction medium are exchanged for deuterons, resulting in low deuteration grades and partial evaporation of the desired products. Therefore, the proton–deuteron exchange needed to be complete prior to catalyst addition. Thus, D_2O was added portionwise to the solid carboxylic acid, the resulting solution was then stirred for a few minutes at 100 °C and the excess HDO and D_2O were removed in vacuo. After three such cycles, the resulting deuterated carboxylic acid was dissolved in NMP, added to a reaction vial containing silver(I) acetate, and the mixture was stirred at 120 °C for 16 hours.

This method allows the conversion of *ortho*-substituted benzoic acids such as 5-methoxy-2-nitrobenzoic acid (**1j**), 2,6-dimethoxybenzoic acid (**1k**), 2,4,6-trichlorobenzoic acid (**1l**), and 2-bromo-4,5-dimethoxybenzoic acid (**1m**)

Table 3 Silver-Catalyzed Decarboxylative Deuteration of Aromatic Carboxylic Acids (Method B′)[a]



Entry	Ar-COOH	Ar-D	DG[b] (%)	Yield (%)
1	 **1j**	 **3j**	99	97
2	 **1k**	 **3k**	99	77
3	 **1l**	 **3l**	72	71
4	 **1m**	 **3m**	99	75
5	 **1f**	 **3f/3f′**	65:33[c]	94
6	 **1b**	 **3b/3b′**	93:15[d]	61

[a] Reaction conditions: **1** (1 mmol), AgOAc (10 mol%), K_2CO_3 (15 mol%), D_2O, NMP (2 mL), 16 h, 120 °C.
[b] DG = deuteration grade, calculated by integration of the ^{1}H NMR signals.
[c] ^{1}H and ^{2}D NMR show 65% deuteration at the phenyl ring and 33% deuteration at the methyl group.
[d] ^{1}H and ^{2}D NMR show 93% deuteration at C2 and 15% deuteration at C3.

Downloaded by: State University of New York at Binghamton. Copyrighted material.

into the corresponding monodeuterated arenes in high yields and good to excellent deuteration grades (Table 3, entries 1–4). This method led to improved yields for compound **3f** compared to the copper system (entry 5). However, an exchange of one of the protons for deuterium in 33% of the methyl groups was observed for silver. Benzothiophene (**1b**), which was deuterated regiospecifically with the copper system, underwent detectable deuterium scrambling when using the silver-based catalyst (entry 6).

In conclusion, monodeuterated arenes can be selectively synthesized via deuterodecarboxylation of (hetero)aromatic carboxylic acids. This methodology has high potential for the selective deuterium-labeling of aromatic compounds for biochemical or mechanistic investigations. Both copper- and silver-based catalyst systems are suitable for this transformation and provide the desired *ipso*-deuterated arenes in good to excellent yields and deuteration grades. Remarkably, quinoline- and isoquinolinecarboxylic acids gave monodeuterated heterocycles in excellent yields in the absence of a metal catalyst. Deuterium scrambling was observed in the course of the copper-catalyzed decarboxylation of indole-2-carboxylic acid and the silver-catalyzed deuterodecarboxylation of benzothiophene-2-carboxylic acid.

All reactions were carried out with deoxygenated solvents in oven-dried glassware under an N_2 atmosphere. NMP was dried by removing H_2O as a toluene azeotrope. Quinoline was freshly distilled and all inorganic bases were dried for 2 h in vacuo at r.t. prior to use. The solvents were degassed using freeze-pump-thaw method. All other compounds are commercially available and were used without further purification. Mass spectral data were acquired on a GC-MS Saturn 2100 T (Varian).

Copper-Catalyzed Decarboxylative Deuteration; General Procedure for Method A′

A 20-mL crimp-cap vial was charged with the carboxylic acid **1** (1.00 mmol), Cu_2O (7.2 mg, 0.05 mmol), and 1,10-phenanthroline (18 mg, 0.10 mmol). NMP (1.5 mL), quinoline (0.5 mL), and D_2O (370 μL, 20.3 mmol) were added via syringe. The resulting mixture was stirred for 10 min at 110 °C under a constant flow of N_2 to remove the water isotopomers. Two further portions of D_2O (370 μL, 20.3 mmol) were added, each time followed by 10 min of purging. For the actual decarboxylative deuteration, the vessel was sealed, and the mixture was heated to 170 °C for 16 h. It was then poured into aq 5 M HCl (2 mL) and extracted repeatedly with Et_2O (2-mL portions). The combined organic layers were washed with aq $NaHCO_3$ (2 mL) and brine (2 mL), dried ($MgSO_4$), and filtered. The corresponding arene **3** was obtained in pure form after distilling off the solvents over a Vigreux column.

Silver-Catalyzed Decarboxylative Deuteration; General Procedure for Method B′

A Schlenk tube was charged with the carboxylic acid **1** (1.00 mmol). D_2O (2 mL, 110 mmol) was added via syringe, and the resulting mixture was stirred at 100 °C for 15 min, and the D_2O/HDO mixture was removed in vacuo. For the actual carboxylative deuteration, NMP (2 mL) was added via syringe, and the resulting soln was added to a reaction vessel charged with AgOAc (17.2 mg, 0.10 mmol) and K_2CO_3 (20.0 mg, 0.15 mmol). The resulting mixture was stirred at 120 °C for 16 h. Then, it was allowed to cool to r.t., diluted with Et_2O (2 mL), poured into aq 5 M HCl (2 mL), and extracted repeatedly with Et_2O (2-mL portions). The combined organic layers were washed with aq $NaHCO_3$ (2 mL) and brine (2 mL), dried ($MgSO_4$), and filtered. The corresponding arene **3** was obtained in pure form after removal of the solvent by distillation over a Vigreux column.

Uncatalyzed Decarboxylative Deuteration; General Procedure for Method C′

A 20-mL crimp-cap vial was charged with the carboxylic acid **1** (1.00 mmol). NMP (2.0 mL) and D_2O (370 μL, 20.3 mmol) were added via syringe. The resulting mixture was stirred for 10 min at 110 °C under a constant flow of N_2 to remove the water isotopomers. Two further portions of D_2O (370 μL, 20.3 mmol) were added, each time followed by 10 min of purging. For the actual decarboxylative deuteration, the vessel was sealed, and the mixture was heated to 170 °C for 16 h. It was then poured into H_2O (2 mL) and extracted repeatedly with Et_2O (2-mL portions). The combined organic layers were washed with aq $NaHCO_3$ (2 mL) and brine (2 mL), dried ($MgSO_4$), and filtered. The corresponding arene **3** was obtained in pure form after distilling off the solvents over a Vigreux column.

1*H*-Indole-*2-d* (3a) and 1*H*-Indole-*3-d* (3a′)

3a: [CAS Reg. No. 3972-52-9]; **3a′**: [CAS Reg. No. 57754-36-6]

Following method A′ from 1*H*-indole-2-carboxylic acid (**1a**, 173 mg, 1.00 mmol) gave **3a/3a′** (64 mg, 54%) as an off-white solid; ratio **3a/3a′** 55:45 mixture; mp 49.3 °C.

Indole-*2-d* (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (br s, 1 H), 7.71 (m, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 7.25 (m, 1 H), 7.18 (m, 1 H), 6.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 127.8, 123.9 (t, ^1J = 28 Hz), 122.0, 120.7, 119.8, 110.0, 102.6.

^{2}H NMR (60 MHz, CH_2Cl_2): δ = 7.22 (s, 55%), 6.57 (s, 45%).

MS: *m*/*z* (%) = 119 (18), 118 (100), 117 (97), 91 (32), 90 (61), 89 (45), 63 (21).

Benzothiophene-*2-d* (3b)

[CAS Reg. No. 63724-94-7]

Following method A′ from benzothiophene-2-carboxylic acid (**1b**, 178 mg, 1.00 mmol) gave **3b** (92 mg, 68%) as a colorless solid; mp 26.2 °C.

Following method B′ yielded a mixture of benzothiophene-*2-d* (**3b**) and benzothiophene-*3-d* (**3b′**) [CAS Reg. No. 15816-45-2].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.5 Hz, 1 H), 7.87 (t, *J* = 7.2 Hz, 1 H), 7.40 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 139.6, 126.1 (t, ^1J = 27 Hz), 124.2, 124.1, 123.7, 123.6, 122.7.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 7.52 (s, 1 D).

MS: *m*/*z* (%) = 136 (15), 135 (100), 134 (46), 91 (15), 90 (24), 69 (15), 63 (15).

Quinoline-*2-d* (3c)

[CAS Reg. No. 15793-81-4]

Following method C′ from quinoline-2-carboxylic acid (**1c**, 173 mg, 1.00 mmol) gave **3c** (113 mg, 87%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (m, 2 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 7.73 (t, *J* = 7.0 Hz, 1 H), 7.56 (t, *J* = 7.0 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8 (t, ^1J = 27 Hz), 148.1, 136.0, 129.3, 129.2, 128.3, 127.7, 126.4, 120.9.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 8.92 (s, 1 D).

MS: *m*/*z* (%) = 130 (100), 103 (25), 76 (15), 63 (10), 50 (15), 40 (3).

 © Thieme Stuttgart · New York

Downloaded by: State University of New York at Binghamton. Copyrighted material.

Isoquinoline-*1-d* (3d)
[CAS Reg. No. 15793-88-1]

Following method C′ from isoquinoline-1-carboxylic acid (**1d**, 173 mg, 1.00 mmol) gave **3d** (115 mg, 88%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.69 (m, 1 H), 7.66 (d, *J* = 4.0 Hz, 1 H), 7.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9 (t, ^1J = 27 Hz), 142.7, 135.7, 130.3, 128.5, 127.5, 127.2, 126.4, 120.5.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 9.23 (s, 1 D).

MS: *m*/*z* (%) = 130 (100), 103 (30), 76 (15), 63 (10), 50 (15), 40 (5).

2-Nitrobenzene-*d* (3e)
[CAS Reg. No. 32488-51-0]

Following method A′ from 2-nitrobenzoic acid (**1e**, 167 mg, 1.00 mmol) gave **3e** (89 mg, 72%) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.54–7.57 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.0, 134.5, 129.2, 129.1, 123.1 (t, ^1J = 26 Hz).

^{2}H NMR (60 MHz, $CHCl_3$): δ = 8.27 (s, 1 D).

MS: *m*/*z* (%) = 123 (45), 93 (30), 77 (100), 65 (25), 51 (70).

Methyl Phenyl-*2-d* Sulfone (3f)
Following method A′ from 2-(methylsulfonyl)benzoic acid (**1f**, 200 mg, 1.00 mmol) gave **3f** (79 mg, 50%) as a white solid; mp 88.1 °C.
Following method B′ gave **3f/3f′** (147 mg, 94%); ratio **3f/3f′** 65:33.

IR: 3021 (s), 3008 (s), 2927 (s), 1583 (w), 1419 (s), 1448 (s), 1328 (s), 1288 (vs), 1228 (s), 1147 (vs), 1085 (s), 966 (s), 775 (s), 750 (m), 688 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.4 Hz, 1 H), 7.67 (m, 1 H), 7.59 (m, 2 H), 3.06 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 140.5, 133.7, 129.4, 129.3, 127.1 (t, ^1J = 25 Hz), 44.5.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 7.62 (s, 1 D).

MS: *m*/*z* (%) = 142 (33), 95 (68), 94 (49), 78 (100), 77 (74), 51 (55), 50 (33).

GC/HRMS (EI): *m*/*z* [M^+] calcd for $C_7H_7DO_2S$: 157.0308; found: 157.0308.

Benzophenone-*2-d* (3g)
[CAS Reg. No. 72302-35-3]

Following method A′ from 2-benzoylbenzoic acid (**1g**, 226 mg, 1.00 mmol) gave **3g** (140 mg, 77%) as a colorless solid; mp 48.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.4 Hz, 3 H), 7.60 (t, *J* = 7.4 Hz, 2 H), 7.50 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 137.6, 137.5, 132.4, 129.8 (t, ^1J = 24 Hz), 128.3, 128.2.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 7.87 (s, 1 D).

MS: *m*/*z* (%) = 184 (48), 183 (67), 182 (24), 106 (63), 105 (100), 77 (15), 51 (14).

***N*-Phenylbenzen-*2-d*-amine (3h)**
Following method A′ from 2-(phenylamino)benzoic acid (**1h**, 215 mg, 1.00 mmol) gave **3h** (109 mg, 64%) as a colorless solid; mp 54.1 °C.

IR: 3405 (s), 3383 (s), 3035 (m), 1594 (vs), 1518 (vs), 1495 (s), 1415 (s), 1321 (vs), 1172 (m), 881 (s), 748 (vs), 700 (m), 690 (vs), 627 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.5 Hz, 4 H), 7.11 (d, *J* = 7.5 Hz, 3 H), 6.96 (t, *J* = 6.5 Hz, 2 H), 5.73 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 143.0, 129.3, 129.2, 121.0, 120.9, 117.8, 117.2 (t, ^1J = 24 Hz).

^{2}H NMR (60 MHz, acetone): δ = 7.19 (s, 1 D).

MS: *m*/*z* (%) = 171 (18), 170 (81), 169 (100), 168 (60), 167 (26), 51 (26), 50 (17).

GC/HRMS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{10}DN$: 170.0954; found: 170.0963.

Benzonitrile-*4-d* (3i)
[CAS Reg. No. 13122-35-5]

Following method A′ from 4-cyanobenzoic acid (**1i**, 147 mg, 1.00 mmol) using 4,7-diphenyl-1,10-phenanthroline as the ligand gave **3i** (57 mg, 58%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.64 (m, 2 H), 7.43–7.47 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.2 (t, ^1J = 26 Hz), 132.0, 128.8, 118.7, 112.3.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 7.29 (s, 1 D).

MS: *m*/*z* (%) = 104 (100), 76 (60), 63 (10), 50 (50).

5-Methoxy-2-nitrobenzene-*d* (3j)
Following method B′ from 5-methoxy-2-nitrobenzoic acid (**1j**, 197 mg, 1.00 mmol) gave **3j** (150 mg, 97%) as an off-white solid; mp 51.2 °C).

IR: 3117 (m), 2976 (m), 2939 (m), 1601 (s), 1587 (vs), 1497 (vs), 1483 (vs), 1457 (s), 1339 (vs), 1330 (vs), 1250 (vs), 1240 cm^{-1} (vs).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 9.9 Hz, 1 H), 6.98 (m, 2 H), 3.93 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.6, 141.5, 125.9, 125.7 (t, ^1J = 25 Hz), 114.0, 113.9, 56.0.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 8.26 (s, 1 D).

GC/HRMS (EI): *m*/*z* [M^+] calcd for $C_7H_6DNO_3$: 154.0473; found: 154.0475.

2,6-Dimethoxybenzene-*d* (3k)
[CAS Reg. No. 49771-99-5]

Following method B′ from 2,6-dimethoxybenzoic acid (**1k**, 187 mg, 1.00 mmol) gave **3k** (106 mg, 77%) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.0 Hz, 1 H), 6.52 (d, *J* = 8.0 Hz, 2 H), 3.80 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.9, 129.9, 106.2, 100.2 (t, ^1J = 24 Hz), 55.3.

^{2}H NMR (60 MHz, $CHCl_3$): δ = 6.53 (s, 1 D).

MS: *m*/*z* (%) = 140 (19), 139 (100), 138 (8), 110 (29), 109 (6), 96 (12), 64 (11).

2,4,6-Trichlorobenzene-*d* (3l)
[CAS Reg. No. 16463-22-2]

Following method B′ from 2,4,6-trichlorobenzoic acid (**1l**, 225 mg, 1.00 mmol) gave **3l** (130 mg, 71%) as a white solid; mp 62.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 135.4, 127.2, 126.9 (t, ^1J = 24 Hz).

Downloaded by: State University of New York at Binghamton. Copyrighted material.

© Thieme Stuttgart · New York

^{2}H NMR (60 MHz, acetone): δ = 7.51 (s, 1 D).

MS: *m*/*z* (%) = 185 (58), 184 (94), 183 (100), 182 (68), 147 (45), 76 (38), 75 (41).

2-Bromo-4,5-dimethoxybenzene-*d* (3m)
Following method B′ from 2-bromo-4,5-dimethoxybenzoic acid (**1m**, 269 mg, 1.00 mmol) gave **3m** (163 mg, 75%) as a colorless liquid.

IR: 3001 (vs), 2957 (vs), 2939 (vs), 2905 (vs), 2837 (vs), 1583 (s), 1493 (vs), 1461 (s), 1435 (s), 1361 (s), 1254 (vs), 1214 (s), 1026 (s), 836 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1 H), 6.74 (s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 148.3, 123.1 (t, ^1J = 26 Hz), 114.8, 112.6, 112.4, 56.1, 56.0.

^{2}H NMR (60 MHz, acetone): δ = 7.06 (s, 1 D).

GC/HRMS (EI): *m*/*z* [M$^+$] calcd for $C_8H_8DBrO_2$: 218.9849; found: 218.9856.

Acknowledgment

We thank C. Oppel for helpful discussions and Nanokat, the DFG (SFB/TRR 88 3MET), the A. v. Humboldt foundation (fellowships to N.R. and W.I.D.), and the Deutsche Bundesstiftung Umwelt (fellowship to M.R.) for financial support.

References

(1) (a) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100. (b) Gooßen, L. J.; Gooßen, K.; Rodríguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem.* **2008**, *80*, 1725. (c) Gooßen, L. J.; Winkel, L.; Döhring, A.; Ghosh, K.; Paetzold, J. *Synlett* **2002**, 1237; and cited literature.
(2) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.
(3) Nilsson, M. *Acta Chem. Scand.* **1966**, *20*, 423.
(4) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.
(5) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J.* **2000**, *6*, 1147.
(6) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.
(7) For a recent review, see: Rodríguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030.
(8) (a) Lange, P. P.; Gooßen, L. J.; Podmore, P.; Underwood, T. *Chem. Commun.* **2011**, *47*, 3628. (b) Gooßen, L. J.; Lange, P. P.; Rodríguez, N.; Linder, C. *Chem. Eur. J.* **2010**, *16*, 3906. (c) Gooßen, L. J.; Rodríguez, N.; Lange, P. P.; Linder, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 1111. (d) Gooßen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P. *Chem. Eur. J.* **2009**, *15*, 9336. (e) Gooßen, L. J.; Zimmermann, B.; Linder, C.; Rodríguez, N.; Lange, P. P.; Hartung, J. *Adv. Synth. Catal.* **2009**, *351*, 2667. (f) Gooßen, L. J.; Rodríguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (g) Gooßen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 7103. (h) Gooßen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473. (i) Gooßen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824.
(9) (a) Collet, F.; Song, B.; Rudolphi, F.; Gooßen, L. J. *Eur. J. Org. Chem.* **2011**, 6486. (b) Rudolphi, F.; Song, B.; Gooßen, L. J. *Adv. Synth. Catal.* **2011**, *353*, 337. (c) Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 3043.
(10) (a) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, *47*, 6312. (b) Wang, C. Y.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (c) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (d) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (e) Zhang, F.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2768. (f) Fang, P.; Li, M.; Ge, H. *J. Am. Chem. Soc.* **2010**, *132*, 11898. (g) Li, M.; Ge, H. *Org. Lett.* **2010**, *12*, 3464. (h) Wie, J.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (i) Duan, Z.; Ranjit, S.; Zhang, P.; Xiaogang, L. *Chem. Eur. J.* **2009**, *15*, 3666.
(11) (a) Hu, P.; Kan, J.; Su, W. P.; Hong, M. C. *Org. Lett.* **2009**, *11*, 2341. (b) Fu, Z. J.; Huang, S. J.; Su, W.; Hong, M. *Org. Lett.* **2010**, *12*, 4992. (c) Sun, Z.-M.; Zhang, J.; Zhao, P. *Org. Lett.* **2010**, *12*, 992. (d) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (e) Zhang, S. L.; Fu, Y.; Shang, R.; Guo, Q. X.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 638.
(12) Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; Wiley: New York, **2001**, 732.
(13) For a review on removable directing groups see: Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.
(14) Noland, W. E.; Baude, F. J. *Org. Synth. Coll. Vol. V*; John Wiley & Sons: London, **1973**, 567.
(15) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637.
(16) (a) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 5776. (c) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024.
(17) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem. Int. Ed.* **2011**, *50*, 9429.
(18) Baeyer, A.; Perkin, W. H. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 59.
(19) Chuchev, K.; BelBruno, J. J. *THEOCHEM* **2007**, *807*, 1.
(20) (a) Shepard, A. F.; Winslow, N. R.; Johnson, J. R. *J. Am. Chem. Soc.* **1930**, *52*, 2083. (b) Nilsson, M.; Ullenius, C. *Acta Chem. Scand.* **1968**, *22*, 1998. (c) Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. F. *J. Am. Chem. Soc.* **1970**, *92*, 3187. (d) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189. (e) Kolarovič, A.; Fáberová, Z. *J. Org. Chem.* **2009**, *74*, 7199.
(21) Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* **1970**, *24*, 3353.
(22) Gilman, H.; Wright, G. F. *J. Am. Chem. Soc.* **1933**, *55*, 3302.
(23) Malonic acids and phenylacetic acids can also be decarboxylated with catalytic amounts of Cu: (a) Toussaint, O.; Capdevielle, P.; Maumy, M. *Synthesis* **1986**, 1029. (b) Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1984**, *40*, 3229. (c) Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1987**, *28*, 539.
(24) Pfirmann, R.; Schubert, H. EP 741122, **1996**.
(25) Gooßen, L. J.; Thiel, W. R.; Rodríguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007**, *349*, 2241.
(26) Gooßen, L. J.; Manjolinho, F.; Khan, B. A.; Rodríguez, N. *J. Org. Chem.* **2009**, *74*, 2620.
(27) (a) Gooßen, L. J.; Linder, C.; Rodríguez, N.; Lange, P. P.; Fromm, A. *Chem. Commun.* **2009**, 7173. (b) Gooßen, L. J.; Rodríguez, N.; Linder, C.; Lange, P. P.; Fromm, A. *ChemCatChem* **2010**, *2*, 430.
(28) (a) Cornella, J.; Sanchez, C.; Banawa, D.; Larrosa, I. *Chem. Commun.* **2009**, 7176. (b) Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5710.
(29) See ref. 11c.

 © Thieme Stuttgart · New York

Downloaded by: State University of New York at Binghamton. Copyrighted material.

(30) Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 2441.
(31) Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. *Chem. Commun.* **2011**, *47*, 5455.
(32) (a) Snow, R. A.; Degenhardt, C. R.; Paquette, L. A. *Tetrahedron Lett.* **1976**, *17*, 4447. (b) Biermann, U.; Friedt, W.; Lang, S.; Lühs, W.; Machmüller, G.; Metzger, J. O.; Rüschgen, K. M.; Schäfer, H. J.; Schneider, M. P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2206.
(33) Cohen, T.; Berninger, R. W.; Wood, J. T. *J. Org. Chem.* **1978**, *43*, 837.
(34) Zohar, E.; Ram, M.; Marek, I. *Synlett* **2004**, 1288.
(35) Guaragna, A.; Pedatella, S.; Pinto, V.; Palumbo, G. *Synthesis* **2006**, 4013.
(36) Keck, G. E.; Krishnamurthy, D. *J. Org. Chem.* **1996**, *61*, 7638.
(37) (a) Bickelhaupt, F.; Newcomb, M.; DeZutter, C. B.; de Boer, H. J. R. *Eur. J. Org. Chem.* **2008**, 6225. (b) Lauer, W. M.; Noland, W. E. *J. Am. Chem. Soc.* **1953**, *75*, 3689. (c) Wiberg, K. B. *J. Am. Chem. Soc.* **1955**, *77*, 5987.
(38) Werstuik, N. H.; Kadai, T. *Can. J. Chem.* **1974**, *52*, 2169.
(39) (a) Backstrom, N.; Watt, C. I. F. *Tetrahedron Lett.* **2009**, *50*, 3234. (b) Castell, J. V.; Martinez, L. A.; Miranda, M. A.; Tarrega, P. *J. Labelled Compd. Radiopharm.* **1994**, *34*, 93.
(40) (a) Erdogan, G.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 10354. (b) Heys, R. *J. Chem. Soc., Chem. Commun.* **1992**, 680. (c) Sajiki, H.; Aoki, F.; Esaki, H.; Maegwa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 1485.
(41) Lee, T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 2568.
(42) Matsubara, S.; Yokota, Y.; Oshima, K. *Org. Lett.* **2004**, *6*, 2071.
(43) Itou, T.; Yoshimi, Y.; Nishikawa, K.; Morita, T.; Okada, Y.; Ichinose, N.; Hatanaka, M. *Chem. Commun.* **2010**, *46*, 6177.
(44) Morita, N.; Titani, T. *Bull. Chem. Soc. Jpn.* **1935**, *10*, 557.
(45) Erlenmeyer, H.; Lobeck, H. *Helv. Chim. Acta* **1935**, *18*, 1464.
(46) Zoltewicz, J. A.; Smith, C. L.; Meyer, J. D. *Tetrahedron* **1968**, *24*, 2269.
(47) Gooßen, L. J. unpublished results.
(48) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305.
(49) Goossen, L. J.; Knauber, T. *J. Org. Chem.* **2008**, *73*, 8631.

Downloaded by: State University of New York at Binghamton. Copyrighted material.

© Thieme Stuttgart · New York