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Gold(I)-Catalyzed Protodecarboxylation of (Hetero)Aromatic Carboxylic Acids

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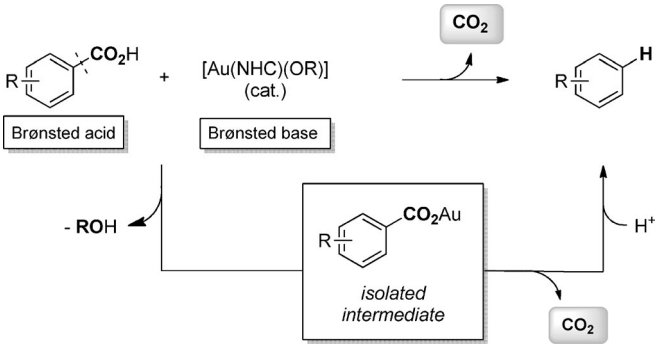
Readily available, inexpensive and easy to handle, carboxylic acids have been shown to be very effective, greener coupling partners compared to costly organometallic reagents for the formation of C–C bonds.[1] In these transformations, carbon nucleophiles are generated after decarboxylation of the carboxylic acid and subsequently coupled with a range of electrophiles.[2] However, these procedures have long suffered from the requirement for high temperatures. Developing more effective catalyst systems for the decarboxylation step, with the protodecarboxylation as a model reaction, has appeared to be key in accessing lower temperature decarboxylative couplings for use with a broader range of substrates. Moreover, protodecarboxylation, on its own, is of particular interest as a method to remove carboxylic acid moieties used as directing groups in the synthesis of complex molecules.[3] Protodecarboxylation was extensively studied in the 1970s with stoichiometric amounts of Hg,[4] Cu[5] and Ag.[6] The first report of a catalytic protodecarboxylation reaction appeared in 2007 and was pioneered by Goossen and co-workers. The reaction was carried out with 10 mol% of Cu_2O/phenanthroline/quinoline.[7] This group showed that the use of chelating nitrogen ligands as well as aromatic amines as solvent greatly enhanced the rate of the decarboxylation. The procedure was applicable to a broad range of benzoic acids and was particularly efficient with a nitro group in the *ortho* position but could also be applied to *meta*- and *para*-substituted benzoic acids. However, the procedure required high temperatures (160–190 °C) and the use of the expensive and bulky bathophenanthroline (4,7-diphenyl-1,10-phenanthroline) ligand for non-activated benzoic acids. The reaction also proceeds when the metal centre is changed to silver[8] or palladium.[9] With the former, although lower temperatures (ca. 120 °C) can be accessed, the system is limited to *ortho*-substituted benzoic acids and heterocyclic derivatives. Similarly, very low temperatures (ca. 70 °C) can be reached with palladium but the substrate range is narrowed to very electron-rich benzoic acids such as 1,3,5-trimethoxybenzoic acid derivatives. Moreover it involves the use of as much as 20 mol% of expensive Pd-$(TFA)_2$ as the catalyst.[9] The use of high catalyst loadings also requires expensive and time-consuming product purification steps, which are unattractive for applications in the pharmaceutical industry, for example.

In 2010, we reported a straightforward procedure to obtain stable aryl gold complexes by decarboxylation of (hetero)aromatic carboxylic acids with the Brønsted base [Au(IPr)(OH)] (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) complex at low temperature.[10] This first insight into the decarboxylation reaction with gold revealed a similar reactivity trend to silver. Indeed, the methodology was particularly effective with electron-rich *ortho*-substituted benzoic acids or heterocyles bearing a carboxylic moiety in the α position. The gold(I)-mediated decarboxylation of (hetero)aromatic carboxylic acids prompted us to explore the *catalytic* potential of [Au(NHC)(OR)] (NHC = *N*-heterocyclic carbene) in the protodecarboxylation reaction. We report herein the protodecarboxylation of (hetero)aromatic carboxylic acids catalyzed by gold (Scheme 1).



Scheme 1. Proposed gold(I)-catalyzed protodecarboxylation of benzoic acids.

The new system permits low-temperature decarboxylation with activated substrates and most importantly combines the advantages of both copper and silver methods (activated and deactivated substrates). To the best of our knowledge, this is the first report of a protodecarboxylation reaction with a catalytic amount of gold(I).

During our exploration of the reactivity of [Au(NHC)(OR)] complexes, we observed that mixing [Au(IPr)(OAc)] (**1**) with 1 equivalent of 2,6-dimethoxybenzoic acid **2** at 110 °C in wet toluene afforded 1,3-dimethoxybenzene (**3**)

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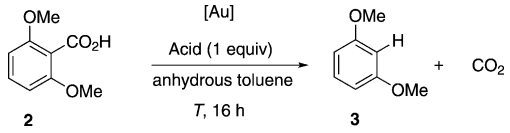
instead of the expected gold aryl complex after 2 h. The in situ formation of one equivalent of AcOH was believed to be responsible for the cleavage of the C_{aryl}–Au bond. We surmised that it would be possible to develop a general one-step protodecarboxlation reaction with only a catalytic amount of [Au(NHC)(OR)] complexes under milder conditions than previously reported. Initially, the catalyst system (Table 1) was assessed.

Table 1. Gold-catalyzed protodecarboxylation of 2,6-dimethoxy-benzoic acid.[a]



2 3

Entry[a]	Catalyst (mol%)	Acid	T [°C]	Yield [%][b]
1[c]	[Au(IPr)(OAc)] (100)	–	110	100
2[c]	[Au(IPr)(OAc)] (5)	–	110	20
3[c]	[Au(IPr)(OH)] (5)	AcOH	110	23
4	[Au(IPr)(OH)] (5)	AcOH	110	50
5	[Au(SIPr)(OH)] (5)	AcOH	110	100
6	[Au(SIPr)(OH)] (3)	AcOH	110	55
7	[Au(SIPr)(OH)] (3)	AcOH	120	85
8	[Au(SIPr)(OH)] (3)	PivOH	120	100
9	[Au(SIPr)(OH)] (3)	TFA	120	70
10	[Au(SIPr)(OH)] (3)	$PhCO_2H$	120	63
11	[Au(SIPr)(OH)] (3)	TfOH	120	35
12	[Au(SIPr)(OH)] (3)	$(Piv)_2O$	120	90
13	[Au(SIPr)(OH)] (2)	$C_3H_7CO_2H$	120	90
14	**[Au(SIPr)(OH)] (2)**	**$AdCO_2H$**	**120**	**100**
15	[Au(SIPr)(O_2C*n*Bu)](2)	–	120	95
16	**[Au(SIPr)(O_2CAd)](2)**	**–**	**120**	**100**
17	[Au(SIPr)(O_2CAd)](1)	–	120	65

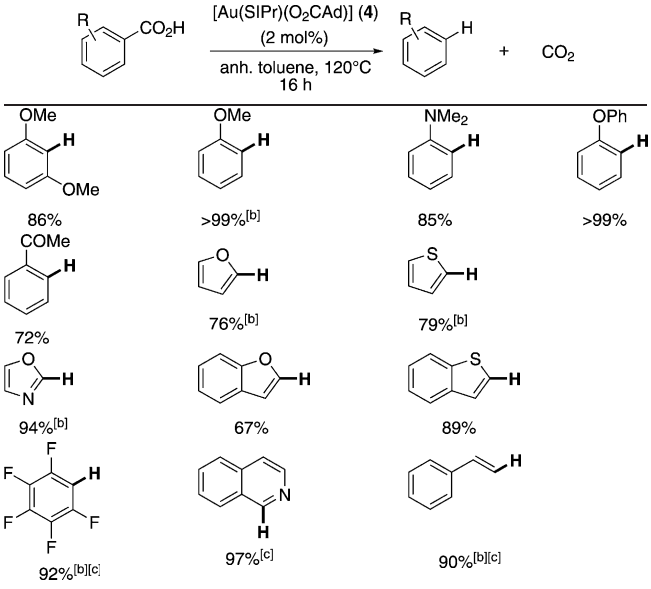
[a] Reaction conditions: [Au], additive (1 equiv), benzoic acid (0.5 mmol), anhydrous toluene (1.5 mL), 16 h. [b] GC yield with *n*-tetradecane as internal standard. [c] Technical grade toluene.

Decreasing the catalyst loading to 5 mol% led to a significant drop in the yield (Table 1, entry 2). Treatment of [Au(IPr)(OH)] in situ with AcOH did not dramatically affect the yield of the reaction (Table 1, entry 3). Noteworthily, although the reaction could be conducted in the absence of additives, the results obtained were variable and reproducibility issues were encountered. The use of anhydrous toluene was found to greatly enhance the rate and yield of the reaction (Table 1, entry 4). Alternatively, changing the ligand from IPr to SIPr (SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) resulted in quantitative yield suggesting that, as previously reported,[7] more electron-rich (basic) complexes favour the decarboxylation step (Table 1, entry 5).[11] An increase of the temperature to 120 °C was necessary to maintain good yields when only 3 mol% of [Au(SIPr)(OH)] was used (Table 1, entry 7). The role of mild to strong acid additives was then probed. Pivalic acid, butyric acid and adamantane-1-carboxylic acid all afforded **3** in quantitative yield (Table 1, entries 8, 13 and 14). A further decrease in catalyst loading still gave high turnovers with butyric acid and adamantane-1-carboxylic acid but led to variable results with pivalic acid (Table 1, entries 13 and 14).

The use of well-defined gold complexes furnished **3** in slightly better yield with butyric acid (Table 1, entry 15) and in quantitative yield with adamantane-1-carboxylic acid (Table 1, entry 16). To circumvent handling of hazardous, corrosive and unpleasantly odorous acid, [Au(SIPr)(O_2CAd)](**4**) was finally selected as the optimum catalyst system. Under these optimized conditions, 80% of the product was formed after reaction times of only 8 h.

We then explored the substrate scope and substituent effects under the optimized conditions. Selected results are summarized in Table 2. A range of electron-rich *ortho*-substituted benzoic acids and heteroaromatic carboxylic acids (heteroatom in the α position) were found to undergo decarboxylation, affording the corresponding arenes in good to excellent yields. All reactions reached completion within 16 h. As with silver systems, this reactivity trend highlights, as previously observed, the benefits of potential coordinating groups in the *ortho* position to the gold binding site, which possibly facilitate the decarboxylation step.[8] Gratifyingly, higher yields, compared to silver and copper, could be obtained with cinnamic acid (76% with Ag and 0% with Cu) and electron-deficient isoquinoline-1-carboxylic acid (92% with Ag and 85% with Cu)[12] with our catalyst system, although 3 mol% was necessary for the latter for full conversion of substrate. As expected, pentafluorobenzoic acid was also successfully employed as it is known that the decarboxylation of polyfluorinated benzoic acids proceeds reasonably well.

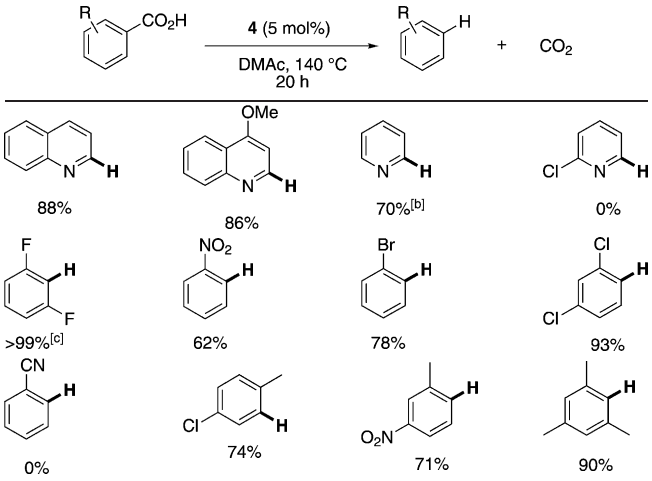
Table 2. Gold-catalyzed protodecarboxylation of (hetero)aromatic carboxylic acids.[a]



[a] Reaction conditions: **4** (2 mol%), substrate (0.5 mmol), anhydrous toluene (1.5 mL), 120 °C, 16 h. Isolated yield given unless otherwise stated. [b] NMR yield with either hexamethylbenzene or 1,3,5-trimethoxybenzene as internal standard. [c] 3 mol% catalyst.

In our first report, we observed that decarboxylation of *ortho*-substituted benzoic acids bearing electron-withdrawing groups were a particular challenging class of substrates with gold in comparison to copper and silver systems.[10] Additional reaction time and increased temperatures were necessary to afford the gold aryl products in satisfactory yields. Yet, some substrates such as 2-nitrobenzoic acids reacted poorly and could only be transformed in 50% yield. A series of experiments was conducted with various electron-deficient *ortho*-substituted benzoic acids under our optimized conditions but led to modest results (ca. <50% yield). Under adjusted reaction conditions, a wider range of substrates could be successfully converted compared to our initial report (Table 3).

Table 3. Gold-catalyzed protodecarboxylation of substituted-benzoic acids.[a]

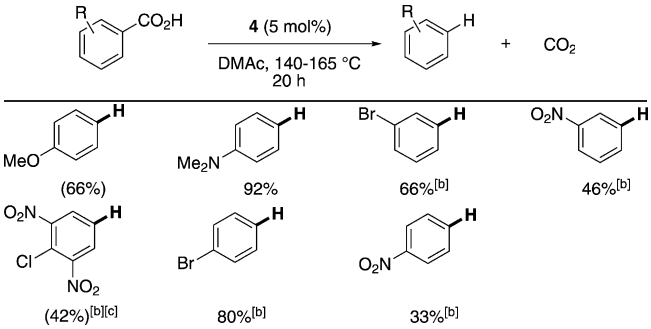


[a] Reaction conditions: **4** (0.025 mmol), substrate (0.5 mmol), anhydrous DMAc (1.5 mL), 140 °C, 20 h. Isolated yield given unless otherwise stated. [b] NMR yield with either hexamethylbenzene or 1,3,5-trimethoxybenzene as internal standard. [c] 3 mol% catalyst.

All reactions were analyzed after 20 h. Lower yields are only due to incomplete conversion. In this regard, the protodecarboxylation proceeded smoothly with pyridyl rings and nitro- and halogen-substituted benzoic acids that provide opportunities for further functionalization of products. Only traces of product were detected for very electron-deficient 2-chloropyridine and the reaction did not proceed at all with 2-cyanobenzoic acid. Interestingly, the latter substrate was also reacted poorly with silver and copper systems (11% with Ag and 0% with Cu).[13] As expected, lower reactivity was observed with 2-nitrobenzoic acid, with the product isolated in only 62% yield with our system which is in striking contrast to copper and silver systems:[1c,1d,7–8] This suggests that the mechanism may be different for Au/Cu/Ag. To our satisfaction, even poorly activated *ortho*-toluic acid derivatives were also amenable to the method, smoothly giving the corresponding arenes in good yields. In comparison, the latter were completely absent from the silver scope and only the protodecarboxylation of *meta*- and *para*-toluic acid have been reported under copper catalysis.[8a]

To expand the scope of the transformation and investigate a possible similar reactivity trend between gold and copper metals, we next embarked on an exploration of completely de-activated aromatic carboxylic acids (Table 4).

Table 4. Gold-catalyzed protodecarboxylation of *meta*- and *para*-substituted benzoic acids.[a]



[a] Reaction conditions: **4** (0.025 mmol), substrate (0.5 mmol), anhydrous DMAc (1.5 mL), 140 °C, 20 h. Isolated yield given unless otherwise stated. GC yields are in parentheses. [b] 165 °C. [c] 10 mol% catalyst for 48 h.

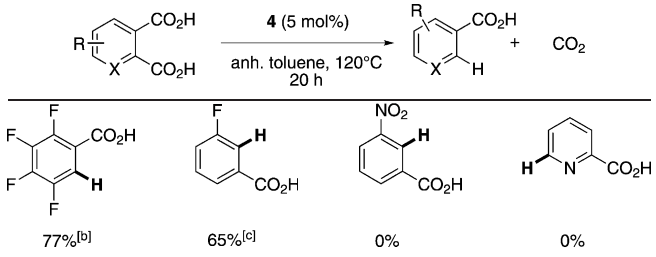
To our delight, under the same reaction conditions electron-rich *para*-substituted benzoic acids underwent smooth decarboxylation to obtain the corresponding arenes in good yields. In direct comparison, only 14% yield could be obtained at 160 °C with the silver system for the 4-methoxybenzoic acid.[12] At a higher temperature of 165 °C, an even wider range of deactivated carboxylic acids could be targeted, including *m*- and *p*-bromobenzoic acid and *m*- and *p*-nitrobenzoic acid (no conversion was observed under silver catalysis).[12] However for the latter, the reactions could not be pushed to the same degree of completion as 2-nitrobenzoic acid. Even very electron-deficient 2-chloro-3,5-dinitrobenzoic acids could be converted in 42% yield in 48 h with 10 mol% of catalyst. These results highlight the remarkable reactivity enhancement induced by the (NHC)–gold(I) system.

In 2009, Larrosa and co-workers reported the selective monoprotodecarboxylation of aromatic dicarboxylic acids exploiting the activating effect of the α heteroatom of pyridines and *ortho*-substituents such as nitro or fluorine groups.[8c]

Hence, to further explore the reactivity of our system, we subjected (hetero)aromatic dicarboxylic acids, which were previously used in the Larrosa study, to our methodology (Table 5). Complete regioselectivity was observed with fluorophthalic acids at 120 °C to afford the resulting benzoic acids in good yields.

The selected examples demonstrate that the scope of the new Au system is broader than Pd systems and complementary to both Ag and Cu systems. This new procedure is not only limited to *ortho*-substituted benzoic acids but also performs well with *meta*- and *para*-substituted acids under simi-

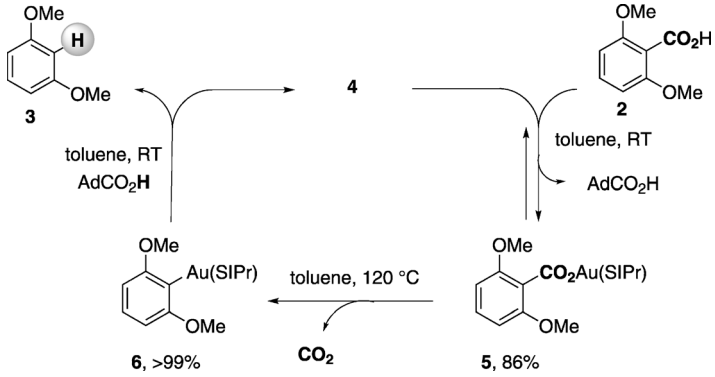
Table 5. Gold-catalyzed monoprotodecarboxylation of aromatic dicarboxylic acids.[a]



[a] Reaction conditions: **4** (0.025 mmol), substrate (0.5 mmol), anhydrous toluene (1.5 mL), 120 °C, 20 h. Isolated yield given unless otherwise stated. [b] 2 mol % of catalyst. [c] NMR conversion.

lar conditions to those used for Cu systems. A further advantage of our protocol is its simplicity. In toluene, the pure product can be obtained after simple filtration to remove the catalyst and acid. In *N,N*-dimethylacetamide (DMAc), aqueous work-up allows for the removal of acids, and after removing the solvent, the crude is triturated with pentane and filtered off to eliminate the catalyst and afford the pure product.

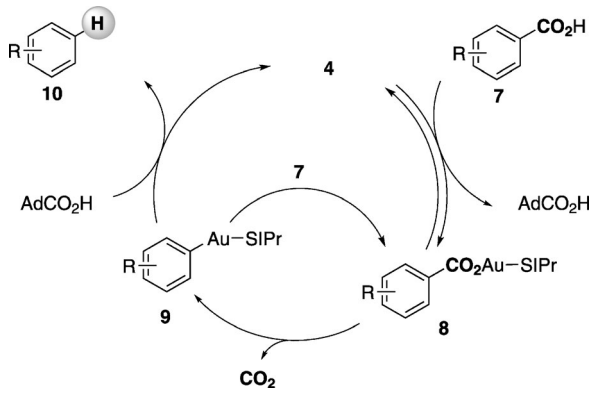
To shed light on the mechanism of the protodecarboxylation reaction, stoichiometric experiments were carried out (Scheme 2). The reaction of **4** with **2** at 25 °C in toluene afforded a mixture of the gold carboxylate species **5** in equilibrium with **4** in a 1/1 ratio (86 % combined isolated yield). Formation of $AdCO_2H$ during the reaction allows for the cleavage of the newly formed Au–O bond and makes the process reversible. Intermediate **5** could nonetheless be obtained cleanly by reaction of [Au(SIPr)(OH)] with **2** as previously reported, due to the stability of the C–Au bond to presence of water.[10] A solution of **5** in anhydrous toluene was heated at 120 °C for 2 h to afford the gold aryl complex **6** in quantitative yield. Complexes **5** and **6** were fully characterized by NMR spectroscopy and elemental analysis.



Scheme 2. Isolation of intermediates in the protodecarboxylation reaction mediated by gold(I).

The crystal structures of the analogous complexes bearing the IPr ligand ([Au(IPr)(O_2C-2,6-$(OMe)_2C_6H_3$)] and [Au(IPr)(2,6-$(OMe)_2C_6H_3$)]) have been previously reported.[10] The reaction of **6** with adamantane-1-carboxylic acid in toluene at room temperature led to the quantitative formation of **3** and **4**.[14] Of note, isolated species **5** and **6** showed also good (albeit lower) activity, in the protodecarboxylation of **2** and afforded **3** in 72 and 76 % yield respectively.

On the basis of experimental observations, the following mechanism for the gold-catalyzed protodecarboxylation of (hetero)aromatic carboxylic acids can be proposed (Scheme 3). The acid/base reaction between the carboxylic acid **7** and **4** furnishes gold carboxylate species **8** that, after liberation of CO_2, leads to the formation of a gold aryl intermediate **9**. We believe that under catalytic conditions, both **7** and adamantane-1-carboxylic acid could be used as proton sources to cleave the Au–C bond of **9**. This would most likely be dependent on the pK_a of the benzoic acid. Whereas the reaction of **9** with adamantane-1-carboxylic would regenerate catalyst **4**, its reaction with starting material **7** would directly form the gold carboxylate species **8**.



Scheme 3. Proposed mechanism for the gold(I)-catalyzed protodecarboxylation of (hetero)aromatic carboxylic acids.

In summary, a general protocol for the Au-catalyzed protodecarboxylation of (hetero)aromatic carboxylic acids has been developed. It was successfully applied to activated and de-activated benzoic acids and is compatible with a wide range of functionalities. Notably, the reaction requires relatively low catalyst loadings, and the isolation and purification of the reaction products is straightforward; this protocol is therefore both practical, and suitable for use in telescoped reaction sequences for which column chromatographic purification is undesirable (e.g. in directed C–H activation/protodecaroboxylation/further functionalisation routes). Moreover, the isolation and full characterization of key reaction intermediates has provided important insights into the mechanistic details. Finally, the carboxylato complex **5** and σ-bonded gold aryl complex **6** have been shown themselves to be active in the protodecarboxylation reaction and possibly involved in the overall catalytic transformation. Further mechanistic investigations on this and related transformations are currently underway in our laboratories.

Experimental Section

General procedure 1 for the protodecarboxylation of (hetero)aromatic carboxylic acids: A mixture of carboxylic acid (0.5 mmol) and [Au(SIPr)-(O_2CAd)] **(4)** (0.025 mmol) in anhydrous DMAc (1.5 mL) was stirred at 140 °C. After 20 h, the crude mixture was quenched with 2 M HCl (2 mL) and the aqueous phase extracted with Et_2O (5 mL). The latter was washed then with 1 M NaOH (10 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). The crude mixture was concentrated and then triturated with pentane, filtered and washed with pentane (3×2 mL). Concentration under reduced pressure gave the desired pure product.

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Keywords: catalysis · decarboxylation · gold · N-heterocyclic carbene · protodeauration

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