

Silver-catalysed protodecarboxylation of *ortho*-substituted benzoic acids†

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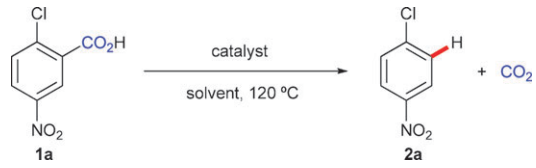
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Catalytic amounts of Ag(I) salts in DMSO have been found to promote the protodecarboxylation of a wide variety of *ortho*-substituted benzoic acids under mild conditions and in excellent yields, highlighting a possible role for silver in decarboxylative cross-couplings.

The ability of carboxylic acid groups to direct the regioselectivity in reactions of aromatic compounds is widely used in organic synthesis.<sup>1</sup> However, their utility is limited when the target compounds do not bear a carboxylic acid group. Consequently, the development of methodologies for their removal after synthesis has received a great deal of attention in the last few years.<sup>2</sup> The first studies on the metal-mediated protodecarboxylation of benzoic acids had limited scope, involved harsh conditions (>200 °C) and the use of stoichiometric amounts of Cu(I) or Hg(II) salts.<sup>3,4</sup> Recently, a catalytic version of this reaction using a Cu<sub>2</sub>O/phenanthroline/quinoline system with a broad scope was reported, albeit the requirements for high temperatures remain (160–190 °C).<sup>5</sup> A palladium-catalysed decarboxylation of *ortho*-dimethoxy-substituted benzoic acids has also been reported, although it requires high catalyst loadings (20%) of expensive Pd(TFA)<sub>2</sub> and the use of trifluoroacetic acid (10 equiv.) as a co-solvent.<sup>6,7</sup> A mild and general methodology for the protodecarboxylation of benzoic acids is therefore still greatly needed.

During our work on the use of bimetallic Pd/Ag systems for the C–H arylation of indoles in the presence of benzoic acids, we observed the protodecarboxylation of the latter.<sup>8</sup> When investigating this side reaction, we determined that Ag(I) salts were actually responsible for the decarboxylation. To the best of our knowledge, despite the fact that silver is traditionally associated with the radical-based Hunsdiecker reaction,<sup>9</sup> and the advent of a plethora of Pd/Ag-based decarboxylative cross-couplings and Heck type reactions,<sup>10</sup> the only report on silver-promoted protodecarboxylation dates back to 1970. This procedure involved high temperatures (240 °C) and the use of stoichiometric amounts of silver.<sup>3c</sup> Herein, we report a simple and convenient procedure for the decarboxylation of *ortho*-substituted benzoic acids catalysed by Ag(I) salts.

Initially, we investigated the protodecarboxylation of 2-chloro-5-nitrobenzoic acid (**1a**) to **2a** (Table 1). Our initial conditions afforded complete conversion to **2a**, but involved an excess of Ag<sub>2</sub>CO<sub>3</sub> at 120 °C in 5% DMSO/DMF

Table 1 Optimization of the Ag-catalysed protodecarboxylation<sup>a</sup>


Entry	Catalyst (mol%)	Catalyst	T/°C	Solvent	Yield (%) <sup>b</sup>
1	150	Ag <sub>2</sub> CO <sub>3</sub>	120	5% DMSO/DMF	96
2	1	Ag <sub>2</sub> CO <sub>3</sub>	120	5% DMSO/DMF	9
3	5	Ag <sub>2</sub> CO <sub>3</sub>	120	5% DMSO/DMF	31
4	10	Ag <sub>2</sub> CO <sub>3</sub>	120	5% DMSO/DMF	98
5	5	Ag <sub>2</sub> CO <sub>3</sub>	120	DMF	27
6	5	Ag <sub>2</sub> CO <sub>3</sub>	120	Dioxane	0
7	5	Ag <sub>2</sub> CO <sub>3</sub>	120	DMSO	57
8	5	Ag <sub>2</sub> CO <sub>3</sub>	120	Toluene	<5
9	5	Ag <sub>2</sub> CO <sub>3</sub>	120	H <sub>2</sub> O	0
10	5	Ag <sub>2</sub> CO <sub>3</sub>	120	AcOH	0
11	10	Ag <sub>2</sub> CO <sub>3</sub>	120	DMSO	100
12	5	Ag <sub>2</sub> CO <sub>3</sub>	140	DMSO	100
13	20	AgOAc	120	DMSO	85
14	10	Ag <sub>2</sub> O	120	DMSO	80
15	20	AgOCOCF <sub>3</sub>	120	DMSO	22
16	6	Ag <sub>3</sub> PO <sub>4</sub>	120	DMSO	79
17	10	K <sub>2</sub> CO <sub>3</sub>	120	DMSO	0
18	20	Pd(TFA) <sub>2</sub>	120	DMSO	0
19	10	Cu <sub>2</sub> O	120	DMSO	0

<sup>a</sup> Conditions: the reactions were carried out using 1.0 equiv. of **1a** and the indicated amount of catalyst in a 0.2 M DMSO solution for 16 h.  
<sup>b</sup> The yield of **2a** was determined by <sup>1</sup>H NMR analysis using an internal standard.

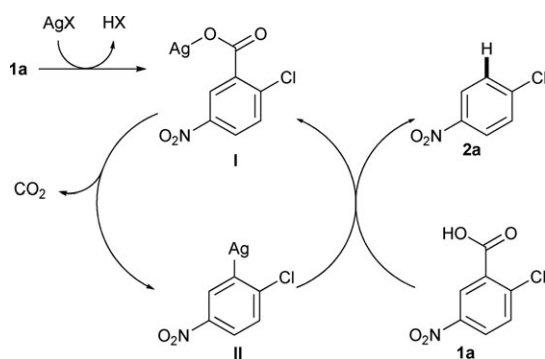
(Table 1, entry 1). Gratifyingly, the reaction proved to be catalytic in Ag(I), producing arene **2a** in quantitative yields with only 10 mol% of Ag<sub>2</sub>CO<sub>3</sub> (Table 1, entries 2–4). Subsequently, a solvent screening using 5 mol% catalyst revealed that DMSO provided higher yields (Table 1, entries 5–10), and complete conversion to **2a** when using 10 mol% Ag<sub>2</sub>CO<sub>3</sub> (Table 1, entry 11). Alternatively, 5 mol% Ag<sub>2</sub>CO<sub>3</sub> also afforded the protodecarboxylation of **1a** in 100% yield, but higher temperatures were required (140 °C; Table 1, entry 12). At this point, a range of Ag(I) salts were tested, showing that a relatively basic counterion is necessary for the reaction to proceed (Table 1, entries 11–16). It is noteworthy that no protodecarboxylation was observed when using catalytic amounts of K<sub>2</sub>CO<sub>3</sub>, Pd(TFA)<sub>2</sub> or Cu<sub>2</sub>O (Table 1, entries 17–19).

A plausible mechanism for the decarboxylation of **1a** mediated by silver salts (AgX) is outlined in Scheme 1. As depicted, an initial acid–base reaction of **1a** and the silver salt generates silver carboxylate **I**. The observed dependence of the reaction on the counterion (X) is consistent with this step.

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**Scheme 1** Proposed mechanism for the silver-catalysed decarboxylation.

Subsequently, **I** undergoes decarboxylation to silver arene **II**, followed by a **1a**-mediated protodemetalation, thus producing **2a** and completing the catalytic cycle by regenerating silver carboxylate **I**. Silver arenes have been previously reported to readily undergo protodemetalation at high temperatures.<sup>11</sup>

We then decided to examine the substrate scope of this new methodology (Table 2). A benzoic acid with an *ortho*-nitro group (**1b**) also led to an essentially quantitative yield of protodecarboxylation product **2b** (Table 2, entry 2). The reaction also proved to be compatible with the inclusion of other electron-withdrawing and donating groups in other positions of the ring (Table 2, entries 3–5), and even hindered doubly-*ortho*-substituted arene **1f** afforded excellent yields of protodecarboxylation (Table 2, entry 6). It is noteworthy that positioning the nitro group in the *meta* position (**2g**) led mostly to the recovery of unreacted starting material (Table 2, entry 7), indicating that an *ortho* substituent is necessary for the reaction to proceed in high yield. Gratifyingly, benzoic acids bearing other *ortho* electron-withdrawing groups, such as Br, Cl and F, including the hindered 2,6-dichlorobenzoic acid **1j**, were found to easily undergo quantitative protodecarboxylation (Table 2, entries 8–11).

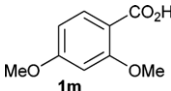
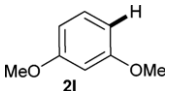
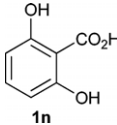
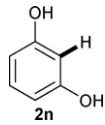
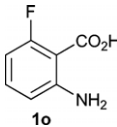
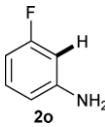
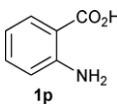
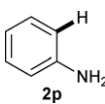
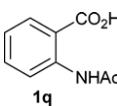
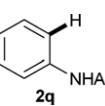
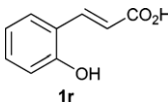
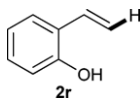
Interestingly, when we attempted the decarboxylation of benzoic acids substituted with the electron-donating MeO group in an *ortho* position, our system also led to complete conversion to the protodecarboxylated products (Table 2, entries 12 and 13). It is remarkable that even when unprotected hydroxyl groups were used, an excellent yield of corresponding arene **2n** was obtained (Table 2, entry 14) without appreciable oxidation. Nitrogen-based electron-donating groups, such as free NH<sub>2</sub>, were also found to be compatible with the reaction conditions, albeit not activating enough on their own (Table 2, entries 15–17). Finally, vinyl carboxylic acids (Table 2, entry 18) were found to be unreactive in our protocol.

A further advantage of our protocol is its practical simplicity. The reactions are not moisture or air sensitive and therefore do not require special precautions. After the reaction is complete, a simple aqueous work-up is used to eliminate any remaining traces of the starting material, affording essentially pure product after removal of the organic solvent, avoiding the necessity for column chromatography or distillation. To further demonstrate the potential of our methodology, we performed the protodecarboxylation of **1b** on a 4.2 g (25 mmol) scale. Pleasingly, 2.8 g of analytically-pure **2b**

**Table 2** Substrate scope for the silver-catalysed protodecarboxylation of benzoic acids<sup>a</sup>

Entry	Benzoic acid	Product	Yield (%) <sup>b</sup>
1			90
2			91
3			94
4			96
5			100
6			86
7			0
8			97
9 <sup>c</sup>			99
10 <sup>c</sup>			96
11 <sup>c</sup>			99
12			91

Table 2 (continued)

Entry	Benzoic acid	Product	Yield (%) <sup>b</sup>
13 <sup>d</sup>			96
14			71
15 <sup>c</sup>			95
16			0
17			0
18			0

<sup>a</sup> Unless otherwise noted, all the reactions were carried out with 10 mol% Ag<sub>2</sub>CO<sub>3</sub> and 1.0 equiv. of benzoic acid in a 0.2 M DMSO solution at 120 °C for 16 h. <sup>b</sup> Yields of isolated pure material. <sup>c</sup> This product was found to be volatile. The reaction was carried out in a sealed vessel and the yield was determined by <sup>1</sup>H NMR analysis using an internal standard. <sup>d</sup> The reaction was carried out at 140 °C.

(91% yield) was obtained without any adjustment to the procedure being required.

In conclusion, we have developed a mild and simple methodology for the silver-catalysed protodecarboxylation of *ortho*-substituted benzoic acids that is compatible with a range of functionalities, such as halogens, NO<sub>2</sub>, alkoxides, and even unprotected phenols and amines. Although the exact reasons for an *ortho*-substituent being required are still under examination, they are most likely to be electronic. Furthermore, these results suggest that decarboxylative cross-coupling reactions using a Pd/Ag system may actually proceed *via* a silver-promoted decarboxylation, instead of the commonly-invoked palladium-catalysed pathway. We are

currently investigating this possibility, as well as the extension of our methodology to other substrates.

During the processing of this manuscript another methodology describing the protodecarboxylation of carboxylic acids with silver salts has been reported.<sup>12</sup>

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