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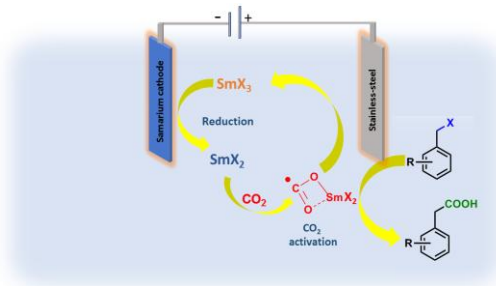
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Electrogenerated Sm(II)-Catalyzed CO₂ Activation for Carboxylation of Benzyl Halides.

Sakna Bazzi, Emmanuelle Schulz and Mohamed Mellah*

Institut de Chimie Moléculaire et des Matériaux d'Orsay (UMR CNRS 8182), Equipe Catalyse Moléculaire, Université Paris Sud, Université Paris-Saclay, 15, rue Georges Clémenceau, 91405 Orsay, Cedex, France

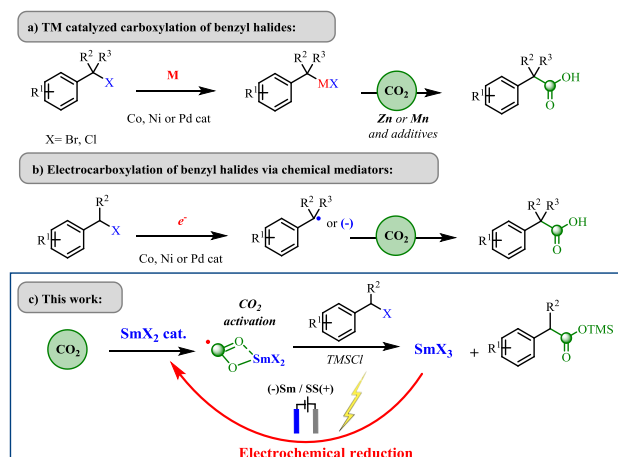


Supporting Information Placeholder

ABSTRACT: Sm(II)-catalyzed carboxylation of benzyl halides is reported through the electrochemical reduction of CO₂. The transformation proceeds under mild reaction conditions to afford the corresponding phenylacetic acids in good to excellent yields. This user-friendly and operationally simple protocol represents an alternative to traditional strategies, which usually proceeds through C(sp³)-halide activation pathway.

Currently, carbon dioxide (CO₂) represents one of the major contributors to the greenhouse effect in the atmosphere. Thus, in the past decade, scientists, notably organic chemists, have dedicated substantial research efforts to find ways to fix CO₂ and to convert it into valuable chemicals.¹⁻³ The difficulty is that, due to the thermodynamic stability of its CO bond, the insertion of CO₂ into an organic moiety remains challenging, especially if we aim at high reactivities and functional group tolerance. Nucleophiles such as Grignard and organolithium reagents are typically required for direct activation of CO₂.^{2,3} Recent advances in catalysis and electrochemistry have independently provided efficient solutions for the chemical transformation of CO₂ (Scheme 1).^{3,4}

Scheme 1. Carboxylation strategies for the preparation of phenylacetic acids using CO₂ as a C-1 building block



Carboxylic acids, which are high-added-value industrial compounds are in general the most targeted products for this type of transformation. More specifically, phenylacetic acids have received increasing attention as their scaffolds can be found in drugs that are used on a daily basis (e.g., ibuprofen, naproxen).⁴ In recent years, elegant metal-catalyzed reactions were developed to produce phenylacetic acids from styrene derivatives⁵ or organozinc reagents.⁶ In 2013, Martin and co-workers described the first catalytic carboxylation of primary benzyl chlorides, featuring a nickel-based catalytic system, to generate phenylacetic acids.⁷ Although remarkable, this reaction still required the use of over-stoichiometric amounts of Zn and MgCl₂.⁸

Electrochemistry represents a viable alternative by eliminating the use of toxic and hazardous reducing agents.^{9,10} Major advances have been made with the use of sacrificial anodes (e.g. Mg, Al), which enabled the *in situ* formation of an organometallic species.¹¹ In general, the electrocarboxylation of benzyl halides involves an initial reduction, forming either the benzyl radical or the anion, which can then react with CO₂ to yield phenylacetic

acid. The CO₂ activation offers probably an alternative to reach more efficient carboxylation by avoiding the side products resulting from dehalogenation or dimerization, which are common drawbacks in all these transformations.⁷ To the best of our knowledge, the direct carboxylation of alkyl halides starting with CO₂ reduction has not yet been described in the literature.

Recently, we reported a procedure for the carboxylation of aryl halides with the use of a “soluble” Sm anode, affording functionalized benzoic acids from aryl chlorides. We demonstrated that the electrolysis enabled the generation *in situ* of a powerful Sm(II) species, which directly reduced CO₂.¹² We depict herein our findings on the catalytic carboxylation of benzyl halides via CO₂ activation promoted by electrochemically generated Sm(II) species to access highly sought-after phenylacetic acids, including Naproxen.

As a first step, we explored the carboxylation of benzyl chloride (**1a**) as a benchmark reaction, using a Sm anode to produce Sm(II) reagent under 1 atm CO₂ (Figure 1). We performed the electrolysis in an undivided cell under standard stoichiometric conditions.¹² The reaction was implemented by introducing **1a** in a solution of *n*Bu₄NBF₄ in DMF with a continuous bubbling of CO₂.

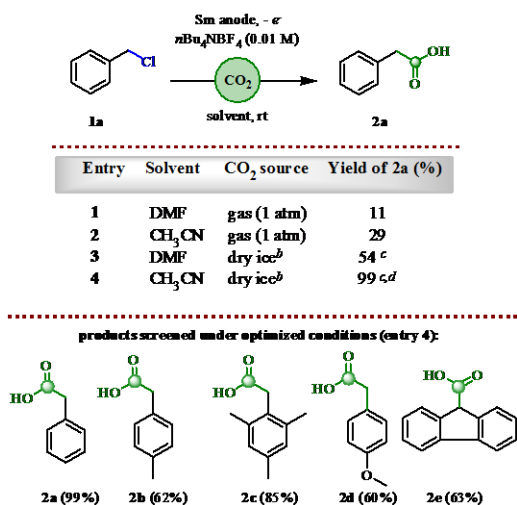


Figure 1. Electrocarboxylation of **1a using Sm “soluble” anode^a**

^a Standard stoichiometric conditions: Undivided cell, fitted with two electrodes a samarium anode (diameter rod = 1 cm) and a stainless-steel cathode grid (20 cm²), **1a** (5 mmol), solvent (50 mL), 4 hours at 0.1 A. Isolated yields; ^b the temperature was monitored during the addition of dry ice, and it remained between 20–23°C; ^c **1a** (1 mmol) after 2 h; ^d *n*Bu₄NBF₄ (0.04 M).

The reaction occurred with low conversion and led to the formation of acid **2a** in a low yield (Figure 1, entry 1), which could be improved to 29% by replacing DMF with CH₃CN (Figure 1, entry 2). This result is likely due to the higher solubility of CO₂ in CH₃CN (0.59 M *versus* 0.38 M in DMF).¹³ In order to increase the availability of CO₂ in solution, dry ice was employed

and, to our delight, **2a** was obtained in quantitative yield (Figure 1, entry 4). Then, we evaluated the scope of the carboxylation with a series of benzyl chlorides. The corresponding phenylacetic acids were obtained in yields ranging from 60 to 99% (Figure 1). It is noteworthy that this carboxylation was not limited to primary benzyl chlorides but could be also extended to secondary benzyl chlorides (see **2e** in Figure 1).

We then turned our attention to the establishment of a catalytic version (Table 1). Building on our precedent reports regarding the implementation of catalytic procedures,¹⁴ we conducted a pre-electrolysis using a solution of *n*Bu₄NBF₄ [0.02 M] in CH₃CN at a constant current intensity of 0.1 A. This first step was carried out to generate 20 mol % of Sm(II) with respect to the substrate (1.0 mmol). The benzyl chloride **1a** and an oxophilic reagent (3.0 equiv.) were then added to the solution. From there, the polarity of the electrode was inverted to act as a cathode¹⁵ throughout the electrolysis, achieved at a constant current intensity of 0.1 A. It is important to stress that the use of an oxophilic reagent is critical in catalytic processes involving Sm^{II}.^{16,17} Indeed, this additive promotes the cleavage of the Sm^{III}-O bonds. In this way, the released trivalent Sm(III) species can be reduced onto the cathode to regenerate the Sm(II) active species. The use of TMSOTf resulted in the formation of the targeted acid **2a** in 45% yield. Interestingly, switching from TMSOTf to TMSCl increased the yield to 60% (Table 1, entry 1 and 2). Various Brønsted acids were also screened as a proton source (Table 1, entry 3–5) in the hope that the resulting Sm salts could be reduced without having to rely on a Si-based additive. However, the reactions were completely shut down, and **1a** remained intact. The effect of Sm ligand was also evaluated by replacing *n*Bu₄NBF₄ by *n*Bu₄NOTf, but it did not have a significant impact (Table 1, entry 6).

Table 1. Electrogenerated Sm(II)-catalyzed carboxylation of benzyl chloride **1a.^{a,b}**

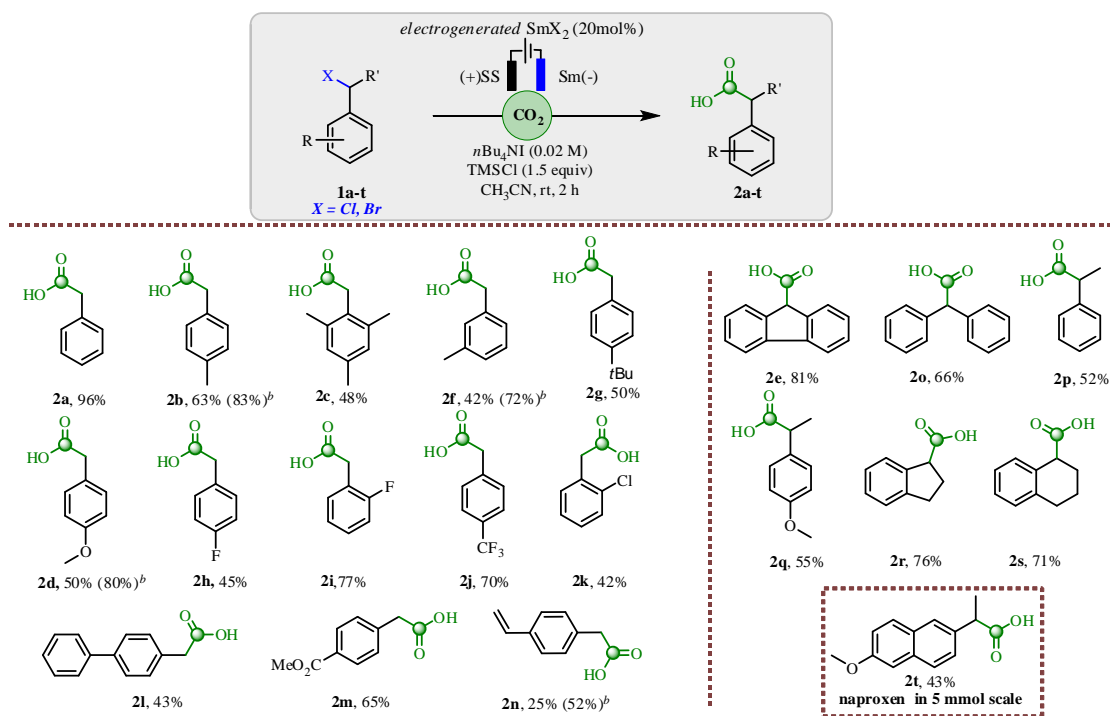
Entry	Sm ²⁺ (mol%)	additive	X	Yield ^c (%)
1	20	TMSOTf	BF ₄	45
2	20	TMSCl	BF ₄	60
3	20	AcOH	BF ₄	-
4	20	TsOH	BF ₄	-
5	20	MsOH	BF ₄	-
6	20	TMSCl	OTf	59
7	20	TMSCl	I	98
8	20	TMSCl ^d	I	96
9	10	TMSCl ^d	I	39
10 ^e	20	TMSCl	I	30
11	0	TMSCl	I	-
12	20	none	I	8

^a Reaction conditions: anode of samarium (rod) and cathode of stainless-steel grid (20 cm²), with a solution of *n*Bu₄NX (1 equiv) in CH₃CN (50 mL). The electrolysis was performed for 386 seconds at *i* = 100mA, before switching the polarity of the electrodes and adding dry ice, **1a** (1 mmol) and the additive (3 mmol). Dry ice was added in small pieces each 15 min; ^b the temperature was monitored during the addition of dry ice, and it remained between 20–23°C; ^c Isolated yields; ^d TMSCl 1.5 mmol. ^e Glassy carbon cathode instead of Sm cathode.

In contrast, the use of $n\text{Bu}_4\text{NI}$ improved drastically the reactivity, providing **2a** in 98% yield and the amount of TMSCl could be lowered to 1.5 equivalent without being detrimental to the outcome of the electrocarboxylation (Table 1, entry 7, 8). Eventually, we found out that using a catalytic loading of 20 mol% was essential for a smooth functioning of the reaction. Control experiments were carried out to ascertain the role of each parameter. Thus, the use of a glassy carbon cathode instead of a samarium one furnished **2a** in only 30% yield, which confirmed the need for a Sm cathode in order to efficiently regenerate the Sm(II) catalytic species.^{14a} The direct reduction onto the Sm cathode without catalyst left **1a** intact (Table 1, entry 11). As anticipated, the catalytic turnover cannot be achieved without TMSCl as only 8% of **2a** was isolated (Table 1, entry 12). With these optimized conditions in hand, we explored the scope of the

reaction by using a series of commercially available benzyl chlorides and bromides (Scheme 2). We were pleased to find that the transformation tolerated a wide range of substituted benzyl halides bearing both electron-donating (**1b-1d** and **1f-g**) and withdrawing groups (**1h-1m**). Besides, our electrocatalytic reaction demonstrated excellent chemoselectivity. Accordingly, additional functionalities (halides (**2h**, **2i**, and **2k**), esters (**2m**), and alkenes (**2n**) remained intact without any dehalogenation or dicarboxylation side reactions. The reaction was not precluded by the presence of ortho substituents (**2c**, **2i**, and **2k**). Of note, benzyl bromides could be also subjected to the carboxylation conditions to access similar compounds in higher yields (see **2b**, **2d**, **2f**, and **2n**). Another interesting trademark is the excellent reactivity of secondary benzyl chlorides, which gave the relevant products with no yield drop (**2e** and **2o-2t**).

Scheme 2. Sm(II)-catalyzed electrocarboxylation of benzyl chlorides^a



^a Standard catalytic conditions: Undivided cell, fitted with two electrodes: cathode of samarium rod (diameter 1 cm) and anode of stainless-steel grid (20 cm²), $i = 100$ mA, (**1a**) (1 mmol), $n\text{Bu}_4\text{NI}$ (1 mmol), TMSCl (1.5 mmol), solvent (50 mL), 2 h. Dry ice was added in small pieces each 15 min. ^b Isolated yields obtained from benzyl bromides.

It is even more appealing when one considers the low propensity of secondary alkyl chlorides to undergo oxidative addition in organometallic-based strategies, making their carboxylation still challenging.^{7,18} Finally, as a proof of the robustness of our electrocatalytic process, we succeeded to prepare (\pm)Naproxen **2t** in 43% yield on a 5 mmol scale. Then, we conducted complementary experiments to gain some insight into the mechanism (Figure 2 and SI for details). Therefore, the electrolysis was performed in the absence of benzyl chloride, which produced a white-grey precipitate. ¹³C-NMR of the crude reaction mixture revealed the formation of oxalic acid, demonstrating that the samarium can reduce efficiently CO₂.

Furthermore, running the electrolysis without CO₂ let **1a** intact. Both experiments clearly confirmed that the carboxylation was initiated by the reaction between the CO₂ radical anion and the benzyl chloride. The influence of the samarium ligand was also evaluated by carrying out the electrocatalytic carboxylation with chloride as the only possible source of ligand for samarium, using benzyl chloride, TMSCl and 20 mol% of SmCl₃ as a catalyst (see SI). The reaction delivered the phenylacetic acid in 75% yield, indicating that the ligand exchange was not the key step of the electrocarboxylation.

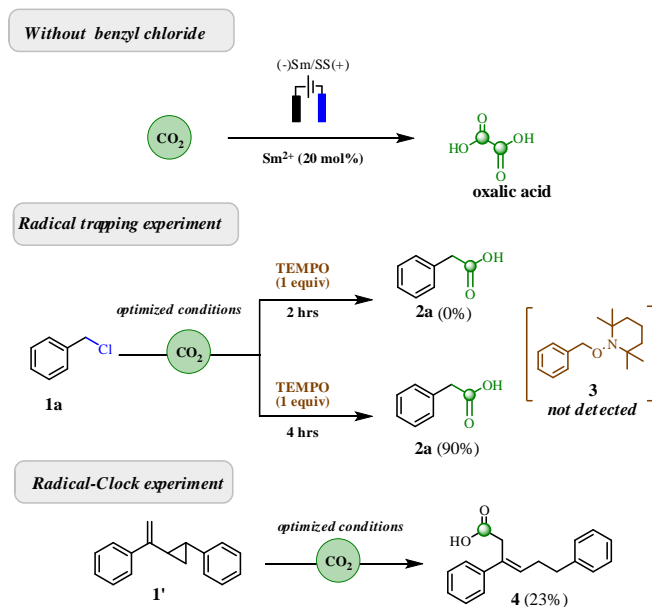


Figure 2. Preliminary mechanistic experiments

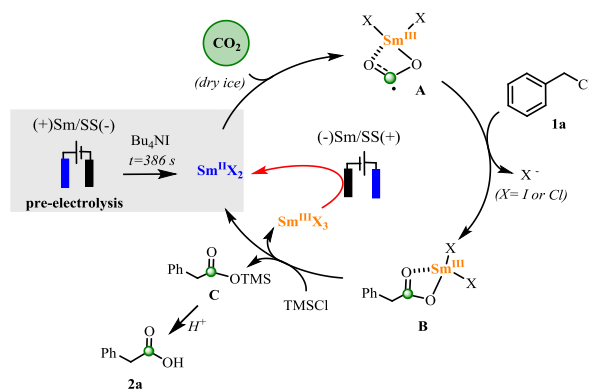
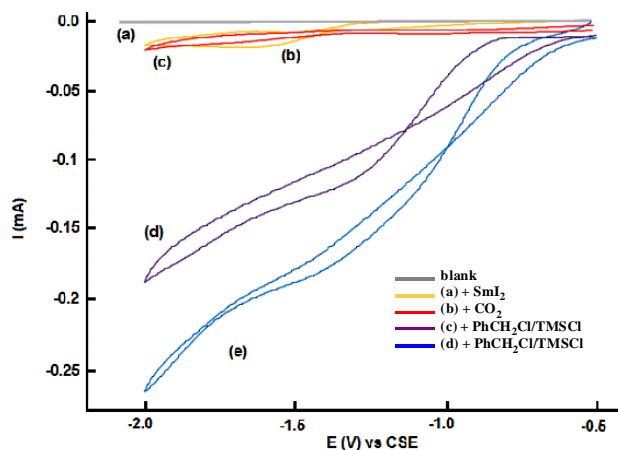
Cyclic voltammetry conditions: Glassy carbon working electrode (surface 20 mm²), Pt wire as counter electrode and SCE reference, scanning potential between -0.5 and -2 V in CH₃CN with *n*Bu₄NPF₆ [0.1 M]. Scan rate: 100 mV/s. (a) : *n*Bu₄NPF₆ [0.1 M] in CH₃CN; (b) : after introducing 0.2 M of electrogenerated SmI₂; (c) : After addition of dry ice to the solution (b); (d) : Addition of 0.5 mL of CH₃CN solution containing BnCl [1 M] and TMSCl [1.5 M]; (e) : Addition of 0.5 mL of CH₃CN solution containing BnCl [1 M] and TMSCl [1.5 M] to solution (d).

In addition, radical trapping experiments were performed by adding TEMPO (1 equiv.) to the reaction mixture (Figure 2). Even though the TEMPO was completely consumed, the formation of product **3** was not observed, which suggests that the generation of the benzyl radical did not occur. It is also noteworthy that **2a** was not obtained either. On the other hand, prolonging the electrolysis time to 4 hours afforded **2a** in a 90% yield. Thus, we assumed that TEMPO had quenched the CO₂ radical anion in the first place but, after the complete consumption of the radical scavenger, the reactivity could be restored to yield **2a**. Moreover, a radical clock experiment was performed with the aim of isolating a compound resulting from the insertion of CO₂. Indeed, the reaction led to product **4** in 23% yield, providing further evidence of the CO₂ radical anion formation. Finally, cyclic voltammetry measurements were conducted to assess the redox behavior of the catalyst. In the absence of CO₂, the quasi-reversible Sm(III)/Sm(II) system was observed at -1.4 V/ SCE. Once CO₂ was introduced, a weak reduction wave was noticed with a potential shift around -1.8 V/SCE and the oxidation wave disappeared. This behavior confirmed the chemical interaction between Sm(II) and CO₂. Then, the addition of a mixture of substrate **1a** and TMSCl (ratio 1:1.5) triggered a significant reduction wave, which started at -0.95 V/SCE and increased significantly upon further addition of this mixture. Overall, this electrochemical behavior of the catalyst proves the appearance of a catalytic current.

Based on these experiments, the following mechanism is proposed for this electrochemical process (Scheme 3). Initially, Sm(II) could reduce the carbon dioxide into the CO₂ radical anion **A**, before being engaged in a radical substitution with benzyl chloride to produce the samarium carboxylate intermediate **B**. Then, TMSCl would furnish the silyl ester **C**, which leads to the carboxylic acid **2a** upon treatment. Finally, the catalyst would be recovered by reduction onto the samarium cathode.

Scheme 3. Proposed mechanism.

Electrochemical analysis



In conclusion, we have devised a novel catalytic carboxylation of primary and secondary benzyl halides relying on electrogenerated SmI₂. When compared to previous reports, this electrocarboxylation process proceeds through a different pathway involving a CO₂ activation instead of C(sp³)-halide one. This approach represents an alternative to other existing CO₂ fixation methodologies that require the preparation of well-defined and sensitive organometallic reagents. This catalytic process provides streamline access to valuable phenylacetic acids, including Naproxen. Further developments of an enantioselective carboxylation reaction and an extension to unactivated alkyl halides are currently under investigation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications. Experimental procedures, compounds data, and spectra.

AUTHOR INFORMATION

Corresponding Author

Author Contributions

Notes

The authors declare no competing financial interests.

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