Electrogenerated Sm(II)-Catalyzed CO 2 Activation for Carboxylation of Benzyl Halides

Sakna Bazzi, Emmanuelle Schulz, Mohamed Mellah

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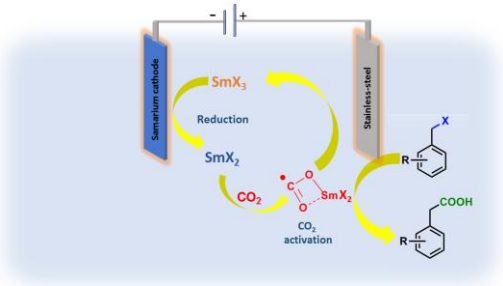
Institut de Chimie Moléculaire et des Matériaux d'Orsay (UMR CNRS 8182), Equipe Catalyse Moléculaire, Université Paris Sud, Université Paris-Saclay, 15, rue Georges Clémenceau, 91405 Orsay, Cedex, France

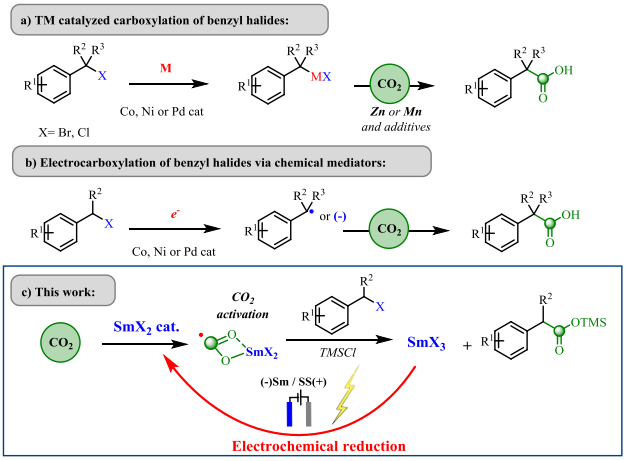


Supporting Information Placeholder

ABSTRACT: Sm(II)-catalyzed carboxylation of benzyl halides is reported through the electrochemical reduction of CO_2. 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(sp^3)-halide activation pathway.

Currently, carbon dioxide (CO_2) 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 CO_2 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 CO_2 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 CO_2.[2,3] Recent advances in catalysis and electrochemistry have independently provided efficient solutions for the chemical transformation of CO_2 (Scheme 1).[3,4]

Scheme 1. Carboxylation strategies for the preparation of phenylacetic acids using CO_2 as a C-1 building block



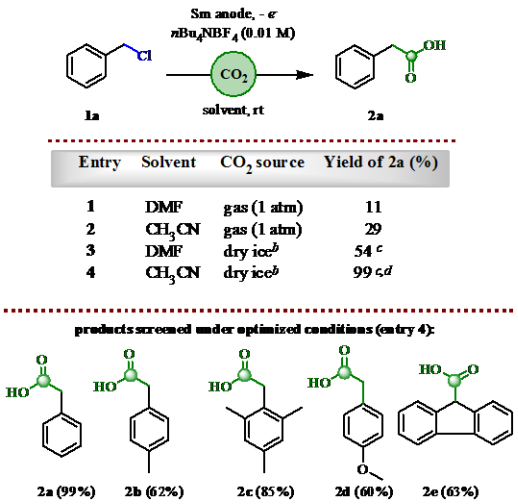
Carboxylic acids, which are high-added-value industrial compounds are in general the most targeted products for this type of transformation. More specifically, phenylacetic acids have received increasing attention as their scaffolds can be found in drugs that are used on a daily basis (e.g., ibuprofen, naproxen).[4] In recent years, elegant metal-catalyzed reactions were developed to produce phenylacetic acids from styrene derivatives[5] 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 $MgCl_2$.[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 CO_2 to yield phenylacetic

acid. The CO_2 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 CO_2 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 CO_2.[12] We depict herein our findings on the catalytic carboxylation of benzyl halides via CO_2 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 CO_2 (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 nBu$_4$NBF$_4$ in DMF with a continuous bubbling of CO_2.



Entry	Solvent	CO_2 source	Yield of 2a (%)
1	DMF	gas (1 atm)	11
2	CH_3CN	gas (1 atm)	29
3	DMF	dry ice[b]	54[c]
4	CH_3CN	dry ice[b]	99[c,d]

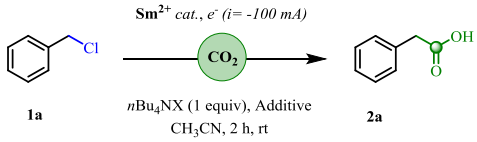
Figure 1. Electrocarboxylation of 1a using Sm "soluble" anode[a]

[a] Standard stochiometric conditions: Undivided cell, fitted with two electrodes a samarium anode (diameter rod = 1 cm) and a stainless-steel cathode grid (20 cm^2), **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] nBu$_4$NBF$_4$ (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 CH_3CN (Figure 1, entry 2). This result is likely due to the higher solubility of CO_2 in CH_3CN (0.59 M *versus* 0.38 M in DMF).[13] In order to increase the availability of CO_2 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 establishement 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 nBu$_4$NBF$_4$ [0.02 M] in CH_3CN 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 cathode[15] 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 SmI_2.[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 nBu$_4$NBF$_4$ by nBu$_4$NOTf, 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]

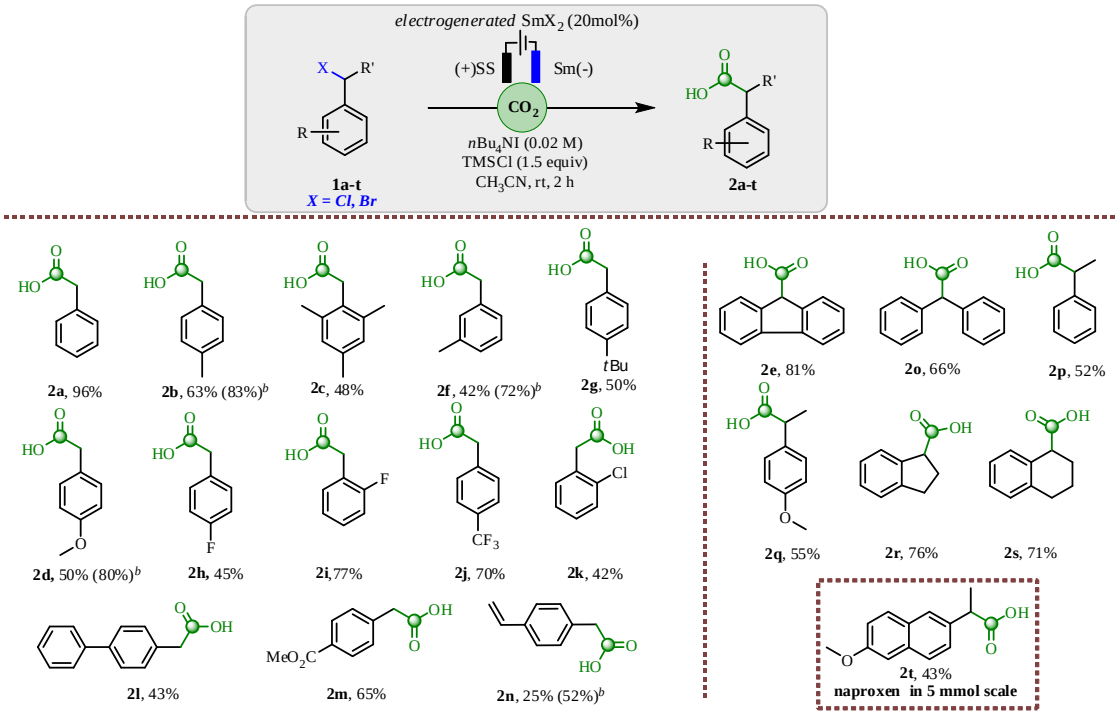


Entry	Sm^{2+} (mol%)	additive	X	Yield[c] (%)
1	20	TMSOTf	BF_4	45
2	20	TMSCl	BF_4	60
3	20	AcOH	BF_4	-
4	20	TsOH	BF_4	-
5	20	MsOH	BF_4	-
6	20	TMSCl	OTf	59
7	20	TMSCl	I	98
8	20	TMSCl[d]	I	96
9	10	TMSCl[d]	I	39
10[e]	20	TMSCl	I	30
11	0	TMSCl	I	-
12	20	none	I	8

[a] Reaction conditions: anode of samarium (rod) and cathode of stainless-steel grid (20 cm2), with a solution of nBu$_4$NX (1 equiv) in CH_3CN (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 nBu$_4$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 cm^2), i = 100 mA, (**1a)** (1 mmol), nBu$_4$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 (±)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. ^{13}C-NMR of the crude reaction mixture revealed the formation of oxalic acid, demonstrating that the samarium can reduce efficiently CO_2. Furthermore, running the electrolysis without CO_2 let **1a** intact. Both experiments clearly confirmed that the carboxylation was initiated by the reaction between the CO_2 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 $SmCl_3$ 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.

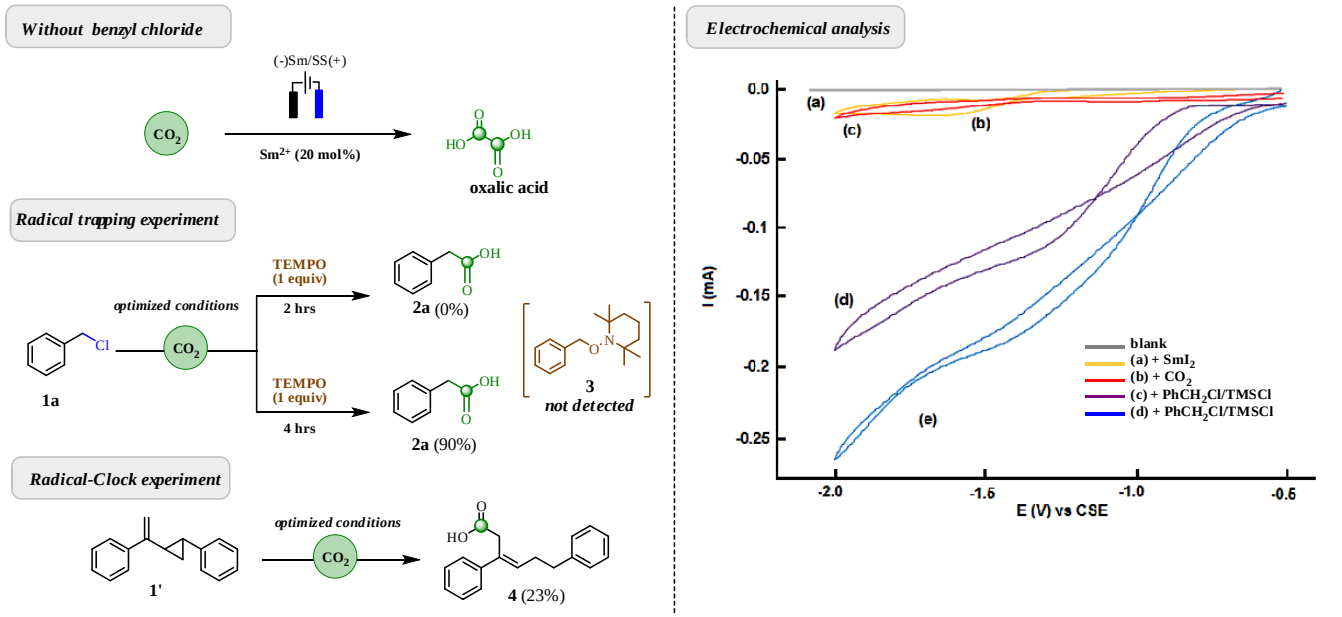
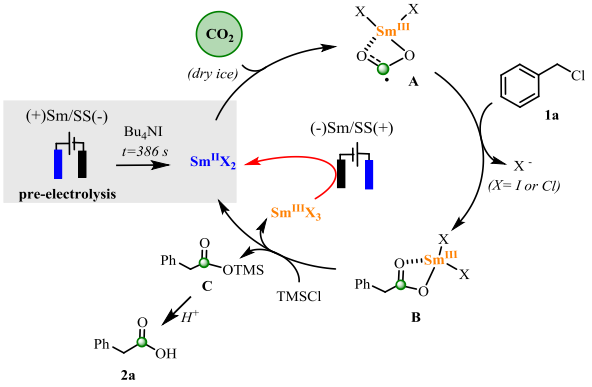


Figure 2. Preliminary mechanistic experiments

Cyclic voltammetry conditions: Glassy carbon working electrode (surface 20 mm^2), Pt wire as counter electrode and SCE reference, scanning potential between - 0.5 and -2 V in CH_3CN with nBu$_4$NPF$_6$ [0.1 M]. Scan rate: 100 mV/s. **(a)** : nBu$_4$NPF$_6$ [0.1 M] in CH_3CN; **(b)** : after introducing 0.2 M of electrogenerated SmI_2; **(c)** : After addition of dry ice to the solution **(b)**; **(d)**: Addition of 0.5 mL of CH_3CN solution containing BnCl [1 M] and TMSCl [1.5 M]; **(e)**: Addition of 0.5 mL of CH_3CN 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 CO_2 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 CO_2. Indeed, the reaction led to product **4** in 23% yield, providing further evidence of the CO_2 radical anion formation. Finally, cyclic voltammetry measurements were conducted to assess the redox behavior of the catalyst. In the absence of CO_2, the quasi-reversible Sm(III)/Sm(II) system was observed at - 1.4 V/ SCE. Once CO_2 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 CO_2. 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 CO_2 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.

In conclusion, we have devised a novel catalytic carboxylation of primary and secondary benzyl halides relying on electrogenerated SmI_2. When compared to previous reports, this electrocarboxylation process proceeds through a different pathway involving a CO_2 activation instead of C(sp^3)-halide one. This approach represents an alternative to other existing CO_2 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

* mohamed.mellah@u-psud.fr

Author Contributions

Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Liu, Q.; Wu, L.; Jackstell R.; Beller, M. Using Carbon Dioxide as a Building Block in Organic Synthesis. *Nat. Commun.* **2015**, 6, 1–15.

(2) (a) Sakakura, T.; Choi, J.-C.; Yasuda, H. Transformation of Carbon Dioxide. *Chem. Rev.* **2007**, 107, 2365–2387. (b) Mikkelsen, M.; Jorgensen, M.; Krebs, F. C. The Teraton Challenge. A Review of Fixation and Transformation of Carbon Dioxide. *Energy Environ. Sci*. **2010**, *3*, 43–81. (c) Maeda, C.; Miyazaki, Y.; Ema, T. Recent Progress in Catalytic Conversions of Carbon Dioxide. *Catal. Sci. Technol.* **2014**, *4*, 1482–1497.

(3) For recent reviews dealing with the use of CO_2, see: (a) Tsuji, Y.; Fujihara, T. Carbon Dioxide as a Carbon Source in Organic Transformation: Carbon–Carbon Bond Forming Reactions by Transition-Metal Catalysts. *Chem. Commun*. **2012**, *48*, 9956-9964. (b) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kühn, F. E. Transformation of Carbon Dioxide with Homogeneous Transition-Metal Catalysts: A Molecular Solution to a Global Challenge? *Angew. Chem., Int. Ed*. **2011**, *50*, 8510-8537. (c) Martin, R.; Kleij, A. W. Myth or Reality? Fixation of Carbon Dioxide into Complex Organic Matter under Mild Conditions. *ChemSusChem* **2011**, *4*, 1259-1263. (d) Huang, K.; Sun, C.-L.; Shi, Z.-J. Transition-Metal-Catalyzed C–C Bond Formation Through the Fixation of Carbon Dioxide. *Chem. Soc. Rev.* **2011**, *40*, 2435-2452. (e) Correa, A.; Martin, R. Metal-Catalyzed Carboxylation of Organometallic Reagents with Carbon Dioxide. *Angew.Chem., Int. Ed.* **2009**, *48*, 6201-6204; (f) Tortajada, A.; Juliá-Hernández, F.; Börjesson, M.; Moragas, T.; Martin,R. Transition-Metal-Catalyzed Carboxylation Reactions with Carbon Dioxide. *Angew. Chem. Int. Ed.* **2018**, *57*, 15948-15982. (g) Yang, Y.; Lee, J.-W. Toward Ideal Carbon Dioxide Functionalization, *Chem. Sci.* **2019**, *10*, 3905-3926.

(4) Maag H. Prodrugs of Carboxylic Acids. In:Prodrugs: New York, NY: Springer, **2007**, 703-729.

(5) (a) Greenhalgh, M. D.; Thomas, S. P. Iron-Catalyzed, Highly Regioselective Synthesis of α-Aryl Carboxylic Acids from Styrene Derivatives and CO_2. *J. Am. Chem. Soc.* **2012**, *134*, 11900-11903. (b) Williams, C. M.; Johnson, J. B.; Rovis, T. Nickel-Catalyzed Reductive Carboxylation of Styrenes Using CO_2. *J. Am. Chem. Soc.* **2008**, *130*, 14936-14937. (c) Hoberg, H.; Peres, Y.; Kruger, C.; Tsay, Y.-H. A 1-Oxa-2-nickela-5-cyclopentanone from Ethene and Carbon Dioxide: Preparation, Structure, and Reactivity. *Angew. Chem. Int. Ed.* **1987**, *26*, 771-773.

(6) (a) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. $MgCl_2$-Accelerated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones, and Carbon Dioxide. *Angew. Chem. Int. Ed.* **2010**, *49*, 4665-4668. (b) Bernhardt, S.; Metzger, A.; Knochel, P. Direct Addition of Functionalized Organozinc Reagents to Carbon Dioxide, Ketones, and Aldehydes in the Presence of $MgCl_2$. *Synthesis* **2010**, 3802-3810.

(7) León, T.; Correa, A.; Martin R. Ni-Catalyzed Direct Carboxylation of Benzyl Halides with CO_2. *J. Am. Chem. Soc.* **2013**, *135*, 1221-1224.

(8) Sayyed, F. B.; Sakaki, S. The Crucial Roles of $MgCl_2$ as a Non-Innocent Additive in the Ni-catalyzed Carboxylation of Benzyl Halide with CO_2. *Chem. Commun*. **2014**, *50*, 13026-13029.

(9) Senboku H. Electrochemical Fixation of Carbon Dioxide. Bhanage, B.M.; Arai M. (Eds.), Transformation and Utilization of Carbon Dioxide, Springer-Verlag, Berlin Heidelberg **2014**, 245-262

(10) (a) Matthessen, R.; Fransaer, J.; Binnemans, K.; De Vos. D.E.; Electrocarboxylation: Towards Sustainable and Efficient Synthesis of Valuable Carboxylic Acids. *Beilstein J. Org. Chem.* **2014**, *10*, 2484-2500. (b) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230–13319.

(11) (a) Silvestri, G.; Gambino, S.; Filardo G.; Gulotta, A. Sacrificial Anodes in the Electrocarboxylation of Organic Chlorides. *Angew. Chem. Int. Ed.*, **1984**, *23*, 979-980; (b) Senboku H.; Katayama, A. Electrochemical Carboxylation with Carbon Dioxide. *Curr. Opin. Green Sustain. Chem.*, **2017**, *3*, 50-54; (c) Sock, O.; Troupel, M.; Périchon, J. Electrosynthesis of Carboxylic Acids from Organic Halides and Carbon Dioxide. *Tetrahedron Lett.*, **1985**, *26*, 1509-1512.

(12) Bazzi, S.; Le Duc, G.; Schulz, E.; Gosmini, C.; Mellah, M. CO_2 Activation by Electrogenerated Divalent Samarium for Aryl Halides Carboxylation. *Org. Biomol. Chem.* **2019**, *17*, 8546-8550.

(13) Gennaro, A.; Isse, A.; Vianello, E., Solubility and Electrochemical Determination of CO_2 in Some Dipolar Aprotic Solvents. *J. Electroanal. Chem.* **1990**, *289*, 203-215.

(14) (a) Sun, L.; Sahloul K.; Mellah, M. Use of Electrochemistry to Provide Efficient SmI_2 Catalytic System for Coupling Reactions. *ACS Catal.* **2013**, *3, 2568−2573.*; (b) Zhang Y.-F.; Mellah, M. Convenient Electrocatalytic Synthesis of Azobenzenes from Nitroaromatic Derivatives Using SmI_2. *ACS Catal.* **2017**, *7*, 8480-8486.

(15) When the samarium electrode is used as the cathode, this later is not consumed allowing its use for a very long time. Of note, before each electrolysis, the Sm electrode is polished and simply washed with acetone.

(16) (a) Nomura, R.; Matsuno, T.; Endo, T. Samarium Iodide-Catalyzed Pinacol Coupling of Carbonyl Compounds. *J. Am. Chem. Soc.* **1996**, *118*, 11666-11667. (b) Aspinall, H. C.; Greeves, N.; Vallas, C. Samarium Diiodide-Catalyzed Diastereoselective Pinacol Couplings. *Org. Lett.* **2005**, *7*, 1919-1922. (c) Orsini, F.; Lucci, E. M. Reformatsky Reactions with SmI2 in Catalytic Amount. *Tetrahedron. Lett.* **2005**, *46*, 1909-1911. (d) Corey, E. J.; Zang, G. Z. Catalytic Reactions of Samarium (II) Iodide. *Tetrahedron. Lett.* **1997**, *38*, 2045-2048.

(17) Of note, Procter and his group reported very recently the first catalytic use of SmI_2, avoiding the need of stoichiometric co-reductant and additives, in a cyclization cascade by radical relay. See : Huang, H.-M.; Mc Dovall, J. J. W.; Procter, D. J. *Nat. Catal*. **2019**, *2*, 211-218.

(18) (a) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688. (b) Rudolph, A.; Lautens, M. Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670. (c) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417-1492.