Ni-catalyzed Carboxylation of Unactivated Primary Alkyl Bromides and Sulfonates with CO_2

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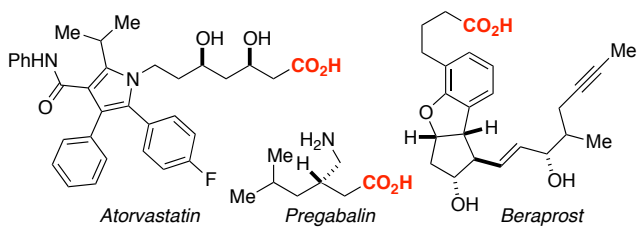
Supporting Information Placeholder

ABSTRACT: A Ni-catalyzed carboxylation of *unactivated* primary alkyl bromides and sulfonates with CO_2 at atmospheric pressure is described. The method is characterized by its mild conditions and a remarkable wide scope without the need for air- or moisture-sensitive reagents, thus becoming a user-friendly and operationally simple protocol en route to carboxylic acids.

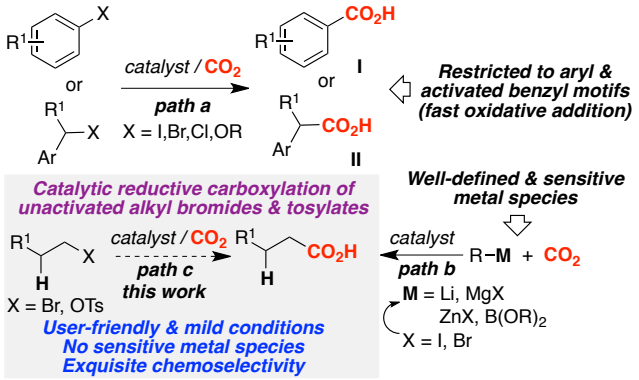
The utilization of CO_2 as an alternative renewable feedstock has recently received a significant attention in the scientific community.[1] Such interest is primarily associated to the fact that CO_2 is nontoxic, abundant and nonflammable, hence constituting an opportunity for carbon sequestration and allowing the implementation of innovative, yet practical, methodologies counterintuitive at first sight.[1] Beyond any doubt, the synthesis of carboxylic acids represents an ideal target in CO_2 fixation since a myriad of molecules such as Atorvastatin, Beraprost, Artesunate, Pemetrezed or Pregabalin, among others, display a significant biological activity (Scheme 1).[2,3]

Scheme 1. Biological Significance of Carboxylic Acids.



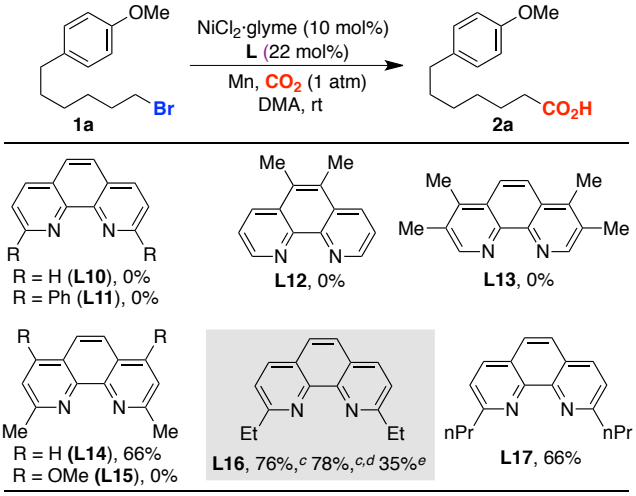
Encouraged by a seminal work of Osakada and Yamamoto,[4] we[5] and others[6] launched a program aimed at unlocking the potential of CO_2 in reductive catalytic reactions (Scheme 2, path a).[7] Unlike carboxylation events based on stoichiometric, well-defined and, in some cases, air-sensitive organometallic species (path b),[8,9] such reductive events offer higher flexibility and ease of execution by using simpler building blocks, thus representing an added value from a simplicity, reliability and step-economical standpoint. Unfortunately, reductive carboxylation protocols are inherently restricted to substrates that rapidly undergo oxidative addition such as aryl[5,6] or benzyl halides (path a).[5a,5b] Ideally, this field should include the use of *unactivated* alkyl electrophiles possessing β-hydrogens. Indeed, these substrates are the most challenging in the cross-coupling arena due to their reluctance towards oxidative addition and the proclivity of *in situ* generated alkyl metal species for β-hydride elimination, homodimerization or hydrogen abstraction pathways, among others. [10] Therefore, at the outset of our investigations it was unclear whether a metal-catalyzed carboxylation event could ever be conducted with *unactivated* alkyl electrophiles.[11] If successful, such a process would offer an unrecognized opportunity in CO_2 fixation while opening up new possibilities via unconventional bond disconnections. Herein we report a mild Ni-catalyzed carboxylation of *unactivated* primary alkyl bromides and sulfonates possessing β-hydrogens with CO_2 (path c). The protocol represents a convenient method to rapidly access carboxylic acids from simple precursors without handling air-, moisture-sensitive reagents or cyanide sources and it is characterized by a wide scope and an excellent chemoselectivity profile.

Scheme 2. Reductive Carboxylation Reactions with CO_2.



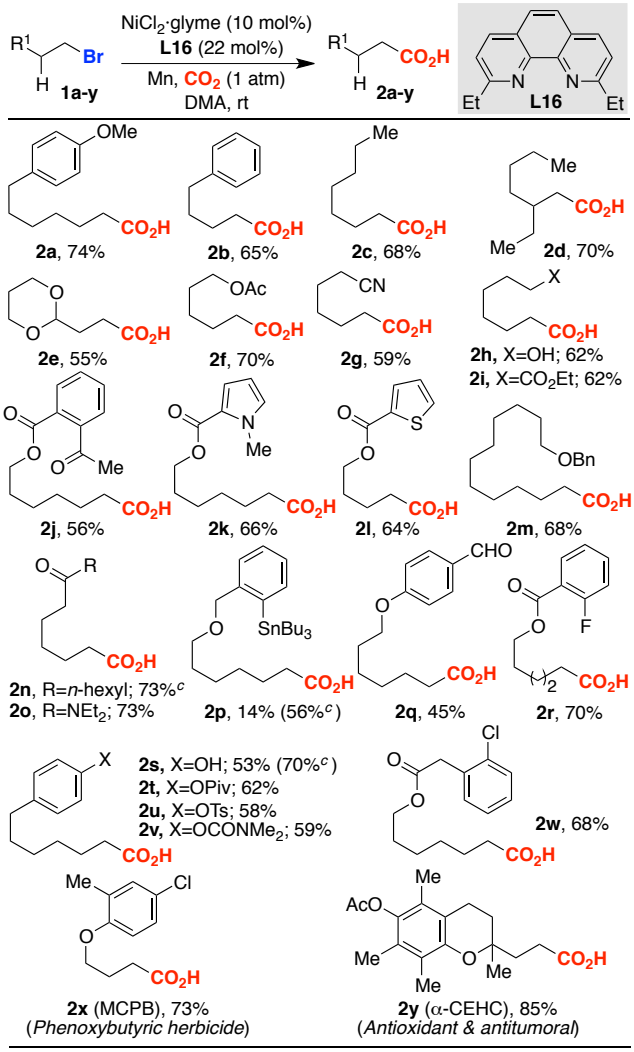
We initiated our investigations with **1a** as the model substrate with CO_2 (1 atm) at room temperature (Table 1). As expected, the conditions previously employed for the carboxylation of aryl halides[5c,6] or primary benzylic halides[5a,5b] failed to convert **1a** into **2a**. Initial screening of metal complexes identified $NiCl_2$·glyme as a competent catalyst with cheap Mn as reducing agent.[12] While nitrogen donors have successfully been employed as ligands in cross-coupling reactions of *unactivated* alkyl halides,[13] no conversion to **2a** was observed with commonly employed bipyridines, tert-pyridines or oxazolines (**L1-L9**).[12] In these cases, dimerization, β-hydride elimination and recovered starting material was observed in the crude reaction mixtures. A similar reactivity pattern was found when employing simple phenanthroline-type ligands (**L10-L13**). We speculated that an increase in the steric bulk around the nitrogen-donor ligand could lead to more robust Ni complexes with enhanced stability and greater activity. In line with this notion, we found that **L14** delivered **2a** in 66% yield. Analogously, **L16**, a bench-stable ligand readily obtained in one-step and in bulk quantities,[14] allowed for obtaining **2a** in a 76% isolated yield. Dimerization and traces of β-hydride elimination byproducts account for the observed mass balance.[15] Importantly, the reaction could be scaled up without any erosion in yield. Intriguingly, subtle changes in the electronic or steric environment of the 1,10-phenanthroline backbones had a deleterious effect (**L15** and **L17**).[16] Control experiments unambiguously revealed that all reaction components were necessary to promote the carboxylation of **1a**.[12,17]

Table 1. Ligand influence on the reaction outcome.[a,b]



[a] Reaction conditions: **1a** (0.15 mmol), $NiCl_2$·glyme (10 mol%), **L** (22 mol%), Mn (0.33 mmol), DMA (0.15 M), at rt under CO_2 (1 atm) for 12 h. [b] Yields were determined by HPLC analysis using naphthalene as internal standard. [c] Isolated yield. [d] **1a** (1.0 mmol). [e] $NiCl_2$·glyme (5 mol%).

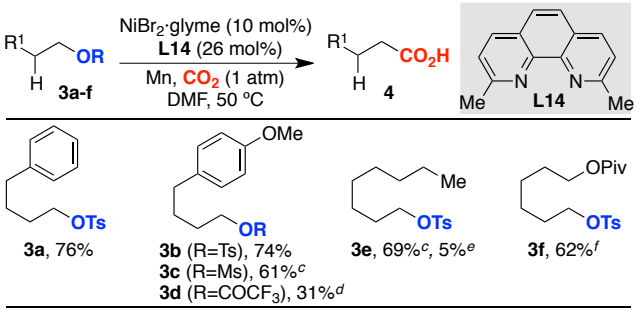
Table 2. Ni-catalyzed Carboxylation of Alkyl Bromides.[a,b]



[a] Reaction conditions: **1a-u** (0.30 mmol), $NiCl_2$·glyme (10 mol%), **L16** (22 mol%), Mn (0.66 mmol), DMA (0.15 M), at rt under CO_2 (1 atm) for 12 h. [b] Isolated yields, average of at least two independent runs. [c] Using **L14** (22 mol%).

Encouraged by these findings, we set out to explore the preparative scope of our reaction. As shown in Table 2, a host of *unactivated* primary alkyl bromides possessing β-hydrogens could be equally accommodated in good yields.[18,19] Particularly illustrative is the chemoselectivity profile of our protocol as esters (**2f, 2i-l, 2r, 2t, 2w** and **2y**), nitriles (**2g**), heterocycles (**2k** and **2l**), acetals (**2e**), amides (**2o**), ketones (**2j** and **2n**) and even aldehydes (**2q**) were tolerated. Notably, unprotected aliphatic alcohols (**2h**), phenols (**2s**) or carbonyl compounds containing relatively acidic α-protons (**2g**, **2i**, **2j**, **2n**, **2o** and **2w)** did not compete with the efficacy of the carboxylation event. At the current level of development, *unactivated* secondary alkyl bromides cannot be employed as coupling partners.[19] Surprisingly, the reaction could also be conducted in the presence of aryltin reagents (**2p**) with **L14**, thus providing ample opportunities for subsequent manipulation. Interestingly, no macrocycle resulting from an intramolecular addition of the aryltin into the C(sp^3)–Br bond or a carboxylation event on the C–Sn bond were detected in the crude material.[19] While conformational restrictions might account for the former, the latter is particularly interesting since organotin reagents have been reported to efficiently undergo carboxylation events.[20] Similarly, **L14** provided better results for **2s**. Site-selectivity could be accomplished in the presence of electrophilic sites amenable for Ni-catalyzed cross-coupling reactions such as aryl pivalates (**2t**),[21] acetates (**2y**),[21] carbamates (**2v**)[21] or aryl fluorides (**2r**).[22] While aryl chlorides,[6a] tosylates[6a] or pivalates[5a] have been used in reductive carboxylation reactions, we found exclusive CO_2 insertion into the C(sp^3)–Br bond (**2t**, **2u-2x**). The synthetic value of this transformation is illustrated by a concise synthesis of compounds that exhibit potent biological activities such as MCPB (**2x**) and α-CEHC (**2y**) from available precursors.[12]

Table 3. Ni-catalyzed Carboxylation of Alkyl Sulfonates.[a,b]



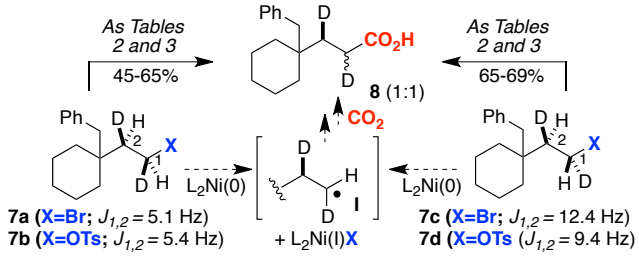
[a] **3a-f** (0.30 mmol), $NiBr_2$·glyme (10 mol%), **L14** (26 mol%), Mn (2.4 equiv), DMF (0.15M) at 50 ºC for 12 h. [b] Isolated yields, average of at least two independent runs. [c] 60 ºC. [d] 100 ºC. [e] 7.5 mol% $NiBr_2$·glyme. [f] 70 ºC.

In light of these results we wondered whether we could extend our Ni-catalyzed reductive carboxylation event to *unactivated* alkyl sulfonates. While the reaction of **3b** under the optimized conditions for alkyl bromides (Table 2) resulted in lower conversions to products, the combination of $NiBr_2$·glyme, **L14** and DMF as the solvent at 50 ºC under 1 atm CO_2 was optimal, furnishing the corresponding carboxylic acid in 76% yield.[12,14] Interestingly, alkyl mesylates (**3c**) or trifluoroacetates (**3d**) could also be employed, albeit in lower yields. Notably, the presence of other C-O electrophiles such as alkyl pivalates did not interfere, resulting in the selective carboxylation of the alkyl sulfonate backbone (**3f**). Overall, we believe the results in Tables 2 and 3 shows the robustness and the prospective impact of our Ni-catalyzed carboxylative protocol when employing *unactivated* alkyl bromides or alkyl sulfonates.[23]

Although an in depth mechanistic study should await further investigations, we wondered whether the reaction was initiated by β-hydride elimination followed by a hydrocarboxylation event.[24] To such end, we subjected 5-phenyl pentene (**5**) under our optimized conditions.

Under the limits of detection, we did not detect any carboxylation reaction.[12] A similar result was obtained when exposing *n*-butylMnBr (**6**) to our Ni/**L16** system in the presence or absence of Mn, thus leaving some doubt about the intermediacy of organomanganese species.[12] In order to shed light into the mechanism, we decided to study the carboxylation reaction of **7a** and **7b** (Scheme 3).[12] A diastereomerically pure **8** was anticipated for a mechanism consisting of a "classical" oxidative addition;[25] on the contrary, a statistical mixture of diastereoisomers in **8** would account for a free-radical mechanism via single electron transfer (SET). As shown in Scheme 3, ^{1}H-NMR spectroscopical analysis of the crude mixture revealed the loss of stereochemical integrity at C1.[26] A similar behavior was found for **7c** and **7d**, an observation that might indicate a scenario consisting of SET processes via Ni(I) species. [27-31] In line with this notion, we observed that radical clocks such as (bromomethyl)cyclopropane and 1-bromo-5-hexene resulted in ring-opened dimerization products.

Scheme 3. Mechanistic experiments.



In summary, we have reported a new catalytic carboxylation of *unactivated* primary alkyl bromides and sulfonates possessing β–hydrogens with CO_2 that gives access to valuable carboxylic acids. This method is characterized by its exquisite functional group compatibility, mild conditions, readily availability of the starting materials and ease of execution without the need for air- or moisture-sensitive materials. Further investigations into the mechanism and the extension to more challenging substrate combinations are currently underway.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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No competing financial interests have been declared.

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we believe that a L:Ni ≥ 2 is needed to stabilize the resting state of the active Ni(0) catalyst while avoiding undesired pathways. A similar Ni:L effect has been observed in other reductive events: (a) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044; (b) see also ref. 5 and 6.

(16) At present, we believe that electron-rich ligands such as **L15** might prevent the binding of CO_2 to the Ni center

(17) While the use of *unactivated* alkyl chlorides resulted in no conversion, the coupling of alkyl iodides delivered 14-19% yield with significant amounts of dimerization events. All attempts to improve these results were not successful.

(18) The coupling of phenethyl electrophiles primarily resulted in dimerization with traces of styrene derivatives

(19) Dimerization and β-hydride elimination account for the mass balance. Although a screening was conducted for substrates with low yields, the results were not satisfactory.

(20) For selected examples: (a) Wu, J.; Hazari, N. *Chem. Commun*. **2011**, *47*, 1069. (b) Shi, M.; Nicholas, K. M. *J. Am. Chem. Soc.* **1997**, *119*, 5057, and citations therein

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(22) The coupling of 1-bromo-4-(6-bromohexyl)benzene resulted in recovered starting material.

(23) The carboxylative event could be conducted in the dark with no erosion in yields, thus suggesting that light is not necessary for the reaction to occur.

(24) For recent metal-catalyzed hydrocarboxylation reactions: (a) Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900. (b) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14936.

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(26) Care must bet taken when selecting the appropriate model substrate for isotope labelling. Whereas the $J_{1,2}$ in **7a** and **7c** are significantly different (Scheme 3), other related γ,γ-unsubstituted alkyl bromide such as (5-bromopentyl)-benzene had similar $J_{1,2}$ in both *erythro* and *threo*-isomers.

(27) In line with such hypothesis, we found that radical scavengers such as TEMPO or BHT inhibited the reaction. Furthermore, aliphatic alcohols are obtained as byproducts when employing alkyl tosylates, an observation that is consistent with a radical pathway. See for example: Madabhushi, S.; Kumar, B. A.; Narender, R. *Tetrahedron Lett*. **1998**, *39*, 2847; (b) Closson, W. D.; Wriede, P.; Bank, S. *J. Am. Chem. Soc*. **1966**, *88*, 1581, and citations therein.

(28) In the absence of CO_2 **7a-d** resulted predominantly in dimerization events and traces of β-hydride elimination.

(29) We cannot rule out that **L14** and **L16** act as a "redox-non innocent ligands". See for example: G. D.; Martin, J. L.: McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.: Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175.

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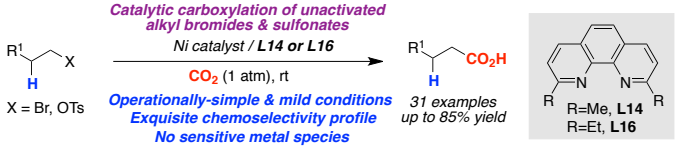
(31) For a mechanistic hypothesis, see Supporting information.


Catalytic carboxylation of unactivated alkyl bromides & sulfonates
Ni catalyst / L14 or L16
CO2 (1 atm), rt
Operationally-simple & mild conditions
Exquisite chemoselectivity profile
No sensitive metal species
X = Br, OTs
31 examples
up to 85% yield
R=Me, L14
R=Et, L16