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Ni-Catalyzed Direct Carboxylation of Benzyl Halides with CO_2

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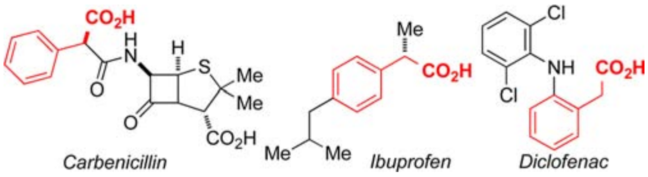
Supporting Information

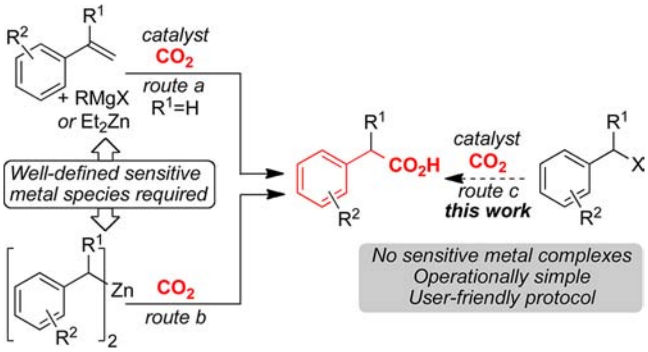
ABSTRACT: A novel Ni-catalyzed carboxylation of benzyl halides with CO_2 has been developed. The described carboxylation reaction proceeds under mild conditions (atmospheric CO_2 pressure) at room temperature. Unlike other routes for similar means, our method does not require well-defined and sensitive organometallic reagents and thus is a user-friendly and operationally simple protocol for assembling phenylacetic acids.

Carbon dioxide (CO_2) is abundant, inexpensive, nonflammable, and attractive as an environmentally friendly chemical reagent.[1] Indeed, the fixation of CO_2 holds great promise for revolutionizing approaches toward the elaboration of chemicals of industrial significance. In this regard, metal-catalyzed carboxylation protocols have become excellent alternatives to the classical methods for preparing carboxylic acids.[1] Illustrative examples are the direct carboxylation of arylmetal species and other carbon nucleophiles such as alkynes and activated C−H bonds.[2] Recently, we[3a] and others[3b] described the carboxylation of aryl bromides and chlorides with CO_2 en route to benzoic acids. Unfortunately, these protocols cannot be utilized to access aliphatic backbones, namely phenylacetic acids. The interest in these compounds arises from the fact that a wide number of complex molecules such as vancomycin, carbenicillin, ibuprofen or diclofenac, among many others, display significant biological activity (Scheme 1).

Scheme 1. Significance of Phenylacetic Acids



Scheme 2. Synthesis of Phenylacetic Acids



In recent years, metal-catalyzed hydrocarboxylation of styrene derivatives (Scheme 2, route a)[4] and carboxylation of dialkylzinc species (Scheme 2, route b)[5] have provided direct access to phenylacetic acids. Unfortunately, however, the limitation to unsubstituted styrenes (R^1 = H, route a), the low α/β selectivity observed in some cases (route a), and the use of sensitive metal complexes in stoichiometric amounts (e.g., Grignard reagents or pyrophoric Et_2Zn) (route a) or the need for well-defined dialkylzinc derivatives (route b) constitute significant drawbacks to be overcome. Thus, the development of a user-friendly and operationally simple catalytic protocol *without* the need for sensitive metal complexes would be highly appreciated. Despite the impressive preparative scope when alkyl halides are utilized as electrophiles in cross-coupling reactions,[6] to the best of our knowledge the direct carboxylation of alkyl halides has not yet been described in the literature.[7,8] Herein we report the first catalytic carboxylation of primary, secondary, and tertiary benzyl halides utilizing CO_2 as the source of carbon, thus exploring an unrecognized opportunity to prepare phenylacetic acids from commercially available and cheap starting materials.

We initially explored the carboxylation of 4-*tert*-butylbenzyl chloride (**1a**) as the model substrate using nickel catalysts under 1 atm CO_2 (Table 1). After considerable experimentation, we found that the combination of $NiCl_2$·glyme (10 mol %), $PCp_3·HBF_4$ (Cp = cyclopentyl) (20 mol %), Zn dust as the reducing agent, and $MgCl_2$ as the additive in *N*,*N*-dimethylformamide (DMF) under 1 atm CO_2 provided the best results, giving rise to 4-*tert*-butylphenylacetic acid (**2a**) in 70% isolated yield (entry 1). Control experiments in the absence of either metal, ligand, or $MgCl_2$ confirmed that these species play a critical role in the carboxylative coupling reaction (entries 2−4). Furthermore, Zn dust was found to be essential for the reaction to occur (entry 5).[9,10] Other nickel sources such as $Ni(acac)_2$ (entry 6) and the structurally related ligand PCy_3 (Cy = cyclohexyl) (entry 7) provided **2a** in lower yields, thus showing the subtleties of our protocol. It is noteworthy that the use of other additives such as tetraethylammonium iodide (TEAI),[11] $MgBr_2$ (entries 8 and 9) or solvents (entry 11) was not beneficial. Interestingly, the carboxylation was completely suppressed when the reaction was conducted at a slightly higher temperature (entry 10); in line with these

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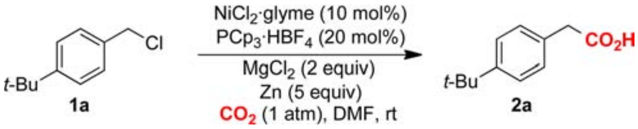
Table 1. Ni-Catalyzed Carboxylation of 1a with CO_2[a]



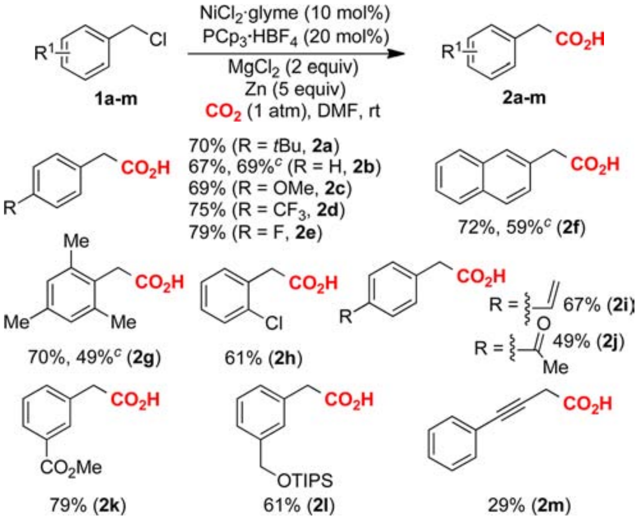
entry	change from standard conditions	yield of **2a** (%)[b]
1	none	74 (70[c])
2	without $NiCl_2$·glyme	0
3	without PCp_3·HBF_4	20
4	without $MgCl_2$	28
5	without Zn	0
6	$Ni(acac)_2$ instead of $NiCl_2$·glyme	43
7	PCy_3 instead of PCp_3	62
8	TEAI[d] instead of $MgCl_2$	0
9	$MgBr_2$ instead of $MgCl_2$	42
10	40 °C instead of rt	0
11	DMI[e] instead of DMF	21
12	10 atm instead of 1 atm CO_2	43

[a] Standard conditions: **1a** (0.5 mmol), $NiCl_2$·glyme (10 mol %), PCp_3·HBF_4 (20 mol %), $MgCl_2$ (2 equiv), Zn (5 equiv), CO_2 (1 atm) and DMF (0.50 M) at r.t. [b] HPLC yield using anisole as an internal standard. [c] Isolated yield. [d] TEAI = tetraethylammonium iodide. [e] DMI = 1,3-dimethyl-2-imidazolidinone.

striking observations, a higher CO_2 pressure had a deleterious effect on the reaction outcome (entry 12).

Encouraged by these results, we next turned our attention to the preparative scope of this reaction (Table 2). Gratifyingly, a wide range of substituted benzyl halides bearing both electron-withdrawing and electron-donating groups could be carboxylated in moderate to good yields. As is evident from the results compiled in Table 2, our carboxylative protocol showed an excellent chemoselectivity profile. Thus, alkenes (**2i**), ketones (**2j**), esters (**2k**), aryl halides (**2e**, **2h**) and silyl ethers (**2l**) were perfectly accommodated and remained intact. Additionally, the process was not hampered by ortho substitution (**2g**, **2h**). Particularly noteworthy was the exquisite selectivity in the presence of aryl halides[3] (**2e**, **2h**) or styrenes (**2i**),[4] thus allowing for orthogonal modifications via conventional cross-coupling reactions.[12] In most instances, the less expensive benzyl chlorides provided higher yields than the corresponding benzyl bromides (**2f**, **2g**). Propargyl halides also underwent the carboxylation, although in lower yields (**2m**).[13,14] Overall, we believe these results show not only the excellent activity and functional group compatibility but also the robustness of our carboxylative reaction.

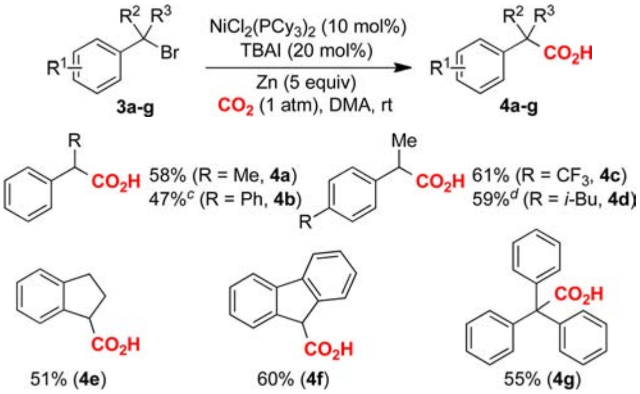
Table 2. Carboxylation of Primary Alkyl Halides[a,b]



[a] As for Table 1, entry 1. [b] Isolated yields (averages of at least two independent runs) are shown. [c] Using the alkyl bromide.

The low propensity of secondary alkyl halides to undergo oxidative addition and the innate proclivity of the initially formed alkylmetal species toward unproductive β-hydride elimination makes the coupling of secondary alkyl halides particularly challenging.[6] Indeed, the reaction of **3a** under the optimized conditions for primary benzyl halides (Table 2) resulted in recovery of the starting material. Pleasingly, we found that the combination of $NiCl_2(PCy_3)_2$ (10 mol %), tetrabutylammonium iodide (TBAI) (20 mol %), Zn dust as the reducing agent, and *N*,*N*-dimethylacetamide (DMA) as the solvent at room temperature under 1 atm CO_2 was optimal for secondary benzyl halides, furnishing **4a** in 58% yield (Table 3).[15] As shown in Table 3, α-alkyl and α-aromatic substitutions on the alkyl halide backbone, regardless of the electronic effects on the aryl ring, were equally tolerated (**4a**−**g**). Cyclic systems were similarly reactive under our catalytic protocol, affording **4e** and **4f** in 51 and 60% yield, respectively. Notably, tertiary alkyl halide **3g** could be utilized as well, affording **4g** in 55% yield. Interestingly, we showed that ibuprofen (**4d**) was within reach from readily available and cheap starting materials.

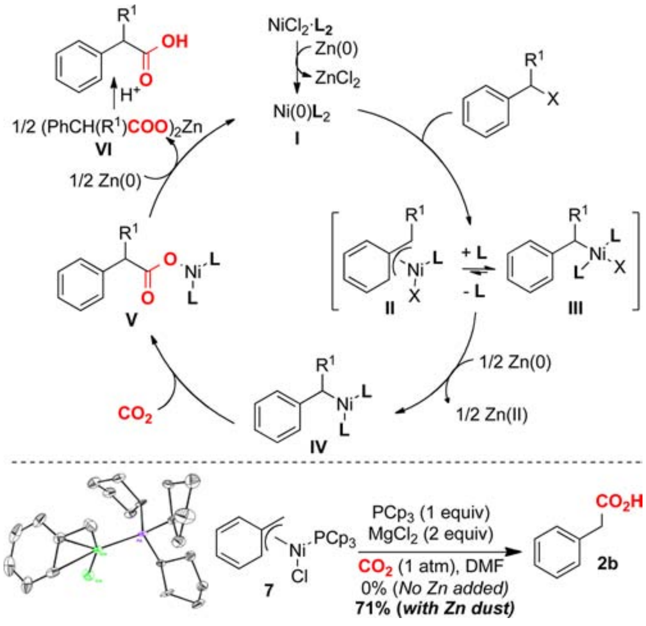
Table 3. Carboxylation of Secondary and Tertiary Alkyl Halides[a,b]



[a] Reaction conditions: **3** (0.5 mmol), $NiCl_2(PCy_3)_2$ (10 mol %), TBAI (20 mol %), Zn (2.5 mmol), CO_2 (1 atm), and DMA (0.50 M) at rt. TBAI = tetrabutylammonium iodide. [b] Isolated yields (average of at least two independent runs) are shown. [c] 50 °C. [d] 40 °C.

Taking into consideration the crucial role of Zn and the tendency of alkylmetal species to undergo β-hydride elimination, we wondered whether our coupling reaction proceeded via in situ formation of alkylzinc species[16] or styrene derivatives.[4] Interestingly, the reaction of benzylzinc bromide (**5**) and styrene (**6**) under the optimized reaction conditions in Tables 2 and 3 resulted in either no conversion or exclusive formation of toluene;[17] not even traces of the corresponding phenylacetic acids **2b** or **4a** were observed in the crude reaction mixtures. *These results tacitly suggest that* **5** *and* **6** *are not competent as reaction intermediates*. We tentatively propose a catalytic cycle consisting of an initial reduction of the Ni(II) precatalyst promoted by Zn followed by oxidative addition to the corresponding alkyl halide, thus delivering an η^3- and η^1-bound nickel complexes **II** and **III** (Scheme 3).[18] It is expected that **II** and **III** would indeed be in rapid equilibrium as suggested by Jamison in a recent disclosure.[19] Zn would then mediate the generation of Ni(I) species **IV**, setting the stage for CO_2 insertion en route to **V**. A final treatment with Zn would regenerate the active $Ni(0)L_2$ species and provide zinc carboxylate **VI**, which upon hydrolytic workup would deliver the expected product. While the role of $MgCl_2$ remains to be elucidated, at present we speculate that this additive might act as either a Lewis acid[5a] to facilitate CO_2 insertion or as an activator of Zn dust.[20]

Scheme 3. Proposed Catalytic Cycle



While unraveling all of the basic features of the catalytic scenario shown in Scheme 3 was rather complicated, we set out to explore the reactivity of the putative oxidative addition species **II** (Scheme 3). Following the methodology described by Carmona,[18] we prepared **7** in high yield by reacting benzyl chloride with $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) and PCp_3 in Et_2O. The structure of **7** in the solid state (depicted in Scheme 3) clearly shows the η^3 hapticity of the Ni complex.[17] Gratifyingly, we found that complex **7** did not undergo carboxylation in the absence of Zn but on the contrary afforded **2a** in 71% yield in the presence of Zn dust (Scheme 3, bottom).[17,21] Moreover, we found that the coupling of alkyl halides was completely inhibited by the addition of radical scavengers such as 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) or butylated hydroxytoluene (BHT).[22] Furthermore, the coupling of optically pure (*R*)-**3a** (94% ee) resulted in racemic **4a**. Although the lability of the initially generated organometallic intermediate might account for this result, the mechanistic hypothesis depicted in Scheme 3 involving single-electron transfer processes seems more plausible.

In summary, we have described a novel, direct, and efficient Ni-catalyzed carboxylation of primary, secondary, and tertiary benzyl halides with CO_2 via C(sp^3)−halide activation. We believe that our protocol constitutes a user-friendly and operationally simple coupling reaction for the preparation of phenylacetic acids under mild reaction conditions with an excellent chemoselectivity profile. The transformation represents a straightforward alternative to other existing methodologies that require the preparation of well-defined and sensitive organometallic reagents. Further mechanistic studies as well as the development of an enantioselective carboxylation reaction and the extension to unactivated alkyl halides are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectral data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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