Synthetic Methods

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Nickel-Catalyzed Carboxylation of Benzylic C−N Bonds with CO_2

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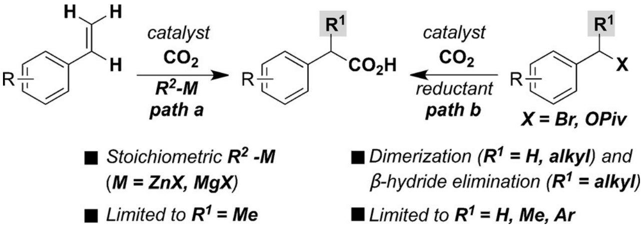
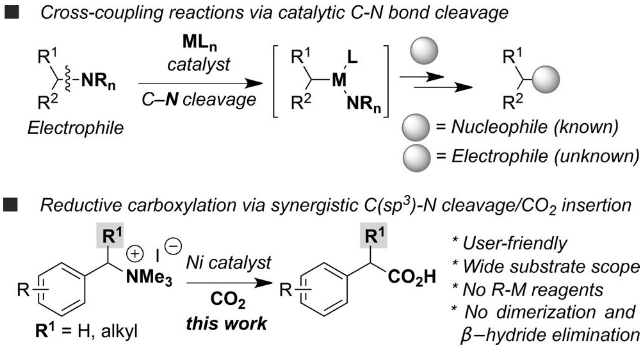
Abstract: *A user-friendly Ni-catalyzed reductive carboxylation of benzylic C−N bonds with CO_2 is described. This procedure outperforms state-of-the-art techniques for the carboxylation of benzyl electrophiles by avoiding commonly observed parasitic pathways, such as homodimerization or β-hydride elimination, thus leading to new knowledge in cross-electrophile reactions.*



Scheme 1. Reductive carboxylation routes towards the formation of phenylacetic acids.

Cross-electrophile reactions have recently gained considerable attention, having become direct and practical alternatives to classical nucleophile/electrophile procedures based on stoichiometric organometallic reagents.[1] Although the utilization of organic halides and homogeneous reagents has become routine in these methods,[1] extension to other coupling partners is still largely underdeveloped, an important drawback when compared with the broad applicability of classical nucleophile/electrophile events.[2] Undoubtedly, new catalytic procedures based on unconventional, yet practical, electrophilic partners would be highly beneficial and would facilitate considerable flexibility in terms of synthetic design.

The use of carbon dioxide (CO_2) as a renewable C1 synthon holds significant promise for defining new paradigms in retrosynthetic analysis.[3] Following the pioneering work of Osakada et al.,[4] we[5] and others[6] have designed reductive carboxylation techniques of organic (pseudo)halides with CO_2, providing alternatives to classical routes requiring organometallic species.[7,8] Despite the advances realized, a general route towards the synthesis of α-substituted phenylacetic acids, privileged motifs in a myriad of bioactive molecules, still remains elusive. It is worth noting that the current cross-electrophile portfolio of benzyl derivatives, including reductive carboxylation techniques, is unfortunately plagued by unavoidable dimerization and β-hydride elimination, and is restricted by the limited set of substitution patterns that can be introduced (Scheme 1).[5e,f,9,10] Consequently, filling this gap was deemed crucial, particularly with nontoxic and easy to handle, yet highly reactive, alternative counterparts. Challenged by this perception, we wondered whether air and thermally stable ammonium salts, highly crystalline solids that are readily prepared in one-step from available amine precursors,[11] could improve upon carboxylation reactions while leading to rather inaccessible building blocks through unconventional synergistic C−N cleavage/CO_2 insertion. At the outset of our investigations, however, it was unclear whether such a procedure could ever be implemented, as ammonium salts were exclusively employed in nucleophile/electrophile regimes using well-defined stoichiometric organometallic compounds (Scheme 2, top).[12–14] If successful, such a method would provide a new opportunity to promote C−N activation in cross-electrophile reactions. Herein, we describe our initial investigations towards this goal (Scheme 2, bottom). This user-friendly and operationally simple new procedure operates at an atmospheric pressure of CO_2 and outperforms all other procedures for the carboxylation of benzyl electrophiles (Scheme 1), demonstrating that ammonium salts are not merely substitute reagents for organic (pseudo)halides. We believe these results will pave the way for utilizing ammonium salts in cross-electrophile coupling events where homodimerization and β-hydride elimination pathways cannot be avoided, thus leading to new knowledge in the synthetic design.



Scheme 2. Cross-electrophile reactions through C−N bond cleavage.

Our study began by evaluating the reaction of **1a** with CO_2 at atmospheric pressure (Scheme 3). Notably, not even traces of **2a** were detected under conditions previously

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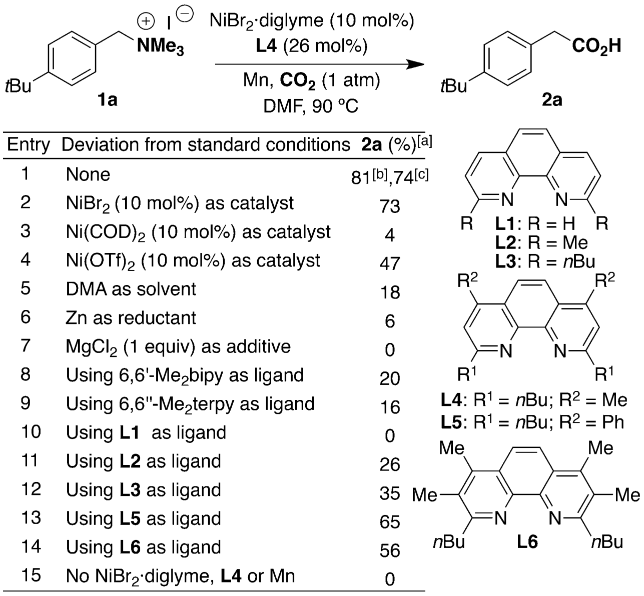
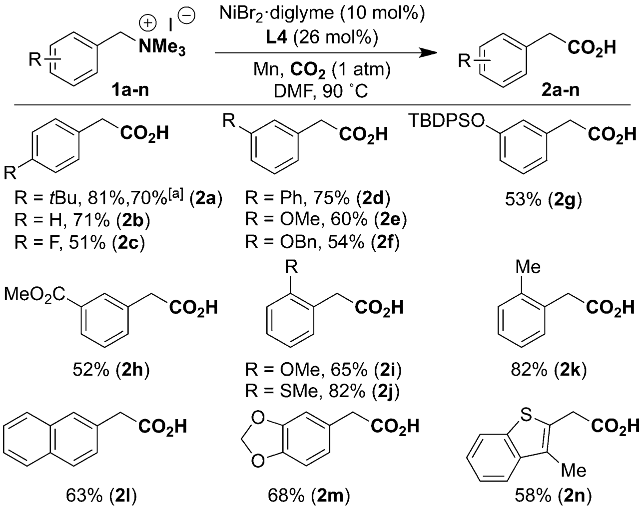


Entry	Deviation from standard conditions	**2a** (%)[a]
1	None	81[b],74[c]
2	$NiBr_2$ (10 mol%) as catalyst	73
3	$Ni(COD)_2$ (10 mol%) as catalyst	4
4	$Ni(OTf)_2$ (10 mol%) as catalyst	47
5	DMA as solvent	18
6	Zn as reductant	6
7	$MgCl_2$ (1 equiv) as additive	0
8	Using 6,6'-Me_2bipy as ligand	20
9	Using 6,6''-Me_2terpy as ligand	16
10	Using **L1** as ligand	0
11	Using **L2** as ligand	26
12	Using **L3** as ligand	35
13	Using **L5** as ligand	65
14	Using **L6** as ligand	56
15	No $NiBr_2$·diglyme, **L4** or Mn	0

Scheme 3. Screening of reaction conditions. Reaction conditions: **1a** (0.20 mmol), $NiBr_2$·diglyme (10 mol%), ligand (26 mol%), Mn (0.40 mmol), CO_2 (1 atm) in DMF (0.40 M) at 90°C for 72 h. [a] Yields determined by HPLC using anisole as internal standard. [b] Yield of isolated product. [c] **L4** (10 mol%).

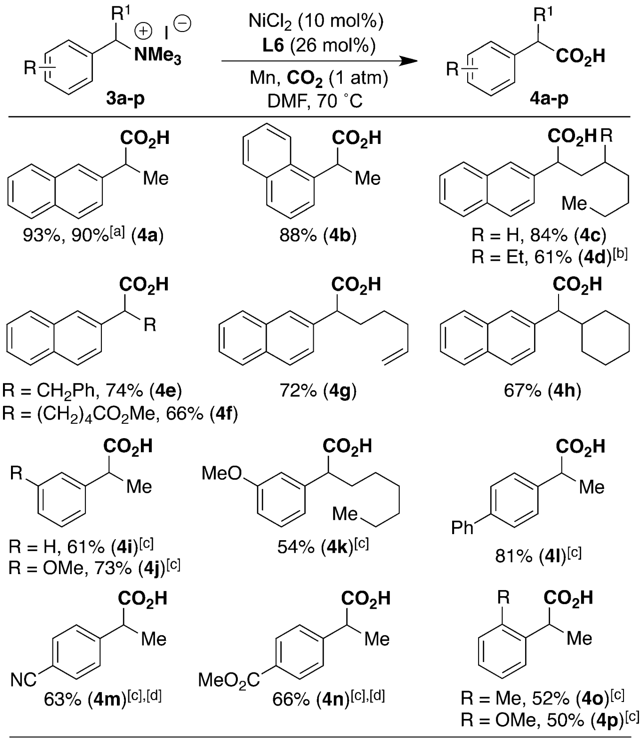
employed for other benzyl electrophiles (Scheme 1, path b),[5e,f] indicating that the activation of $C(sp^3)-N$ bonds would be more problematic than anticipated. After a judicious screening of all reaction parameters,[15] $NiBr_2$·diglyme and **L4** (Scheme 3), a bench-stable ligand preparable in one step and on a multigram scale,[15] were combined with Mn as the reducing agent in DMF to afford **2a** in 81% yield (entry 1).[16] Importantly, no traces of homodimerization products were detected in the crude reaction mixtures, in direct contrast to related carboxylation techniques (Scheme 1, path b).[5e,f] While other Ni^{II} sources provided lower yields (entries 2 and 4), we found that $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) was not a suitable precatalyst, suggesting that COD might compete with substrate binding (entry 3).[17] As shown in entries 5 and 6, the use of the structurally related solvent dimethylacetamide (DMA), Zn as reducing agent, or the inclusion of $MgCl_2$ as an additive had a deleterious effect.[18] As anticipated, subtle differences in the ligand backbone exerted a profound influence on the reaction outcome. Specifically, we found an increased reactivity of 1,10-phenanthrolines over bipyridines or terpyridines, presumably due to their significant backbone rigidity compared to nonfused analogues. Although speculative, we believe that the greater activity of **L4** over the **L1**–**L6** series is attributed to an intimate interplay of electronic and steric effects of the substituents on the 1,10-phenanthroline backbone, thus increasing the robustness, reactivity, and stability of the propagating Ni^0L_n species.[19] As expected, control experiments revealed that all reaction parameters were critical for success (entry 15).[15,20]

With these conditions in hand, we focused our attention on the preparative scope of our Ni-catalyzed direct carboxylation reaction of primary benzyl ammonium salts with CO_2 (Scheme 4). Importantly, **1a**–**1n** were all prepared from the corresponding amines in one step and used without further purification, thus representing a significant advantage from a practical standpoint. As becomes evident from the results compiled in Scheme 4, our synergistic $C(sp^3)-N$ cleavage/CO_2 insertion reaction was largely insensitive to electronic changes on the aromatic ring and could perfectly accommodate non-extended π systems.[21] Similarly, the inclusion of *ortho* substituents posed no problems (**2i**–**2k**). The reaction showed an excellent chemoselectivity profile, with ammonium salts containing various functional groups, such as esters (**1h**), fluorides (**1c**), silyl ethers (**1g**), or acetals (**1m**), being easily accommodated. Although one might argue that the inclusion of thioethers might be problematic due to the strong binding affinity of sulfur atoms to Ni centers,[22] we found that such motifs did not interfere with the formation of **2j**. Likewise, the presence of heteroaryl rings could be tolerated with equal ease (**2n**). This operationally simple procedure was also found to be scalable, and catalyst loadings could be decreased to 5 mol% without significant erosion in yield (**2a**; 70% yield).



Scheme 4. Carboxylation of primary ammonium salts. Reaction conditions: as for Scheme 3, entry 1; yields of isolated products are given as an average of at least two independent runs. [a] **1a** (1.0 mmol), $NiBr_2$·diglyme (5 mol%). Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl.

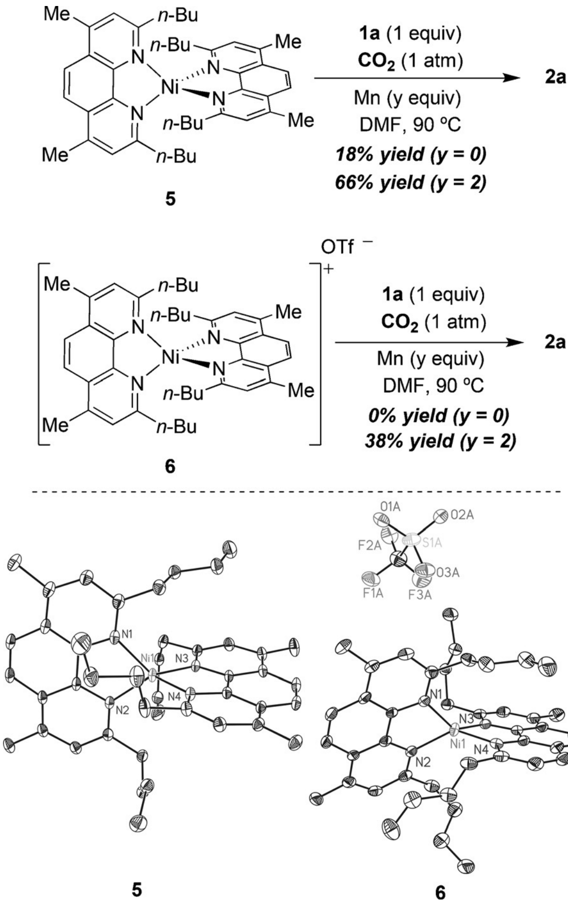
Prompted by the inherent limitations posed by the available catalytic reductive carboxylation techniques for the synthesis of α-substituted phenylacetic acids (Scheme 1), we wondered whether our procedure could be extended to secondary benzyl ammonium salts possessing β-hydrogen atoms (Scheme 5). Although parasitic homodimerization or β-hydride elimination pathways could be anticipated, an issue previously observed in a myriad of cross-electrophile reactions of benzyl derivatives, this was not the case, and we found that a $NiCl_2$/**L6** regime afforded **4a** in 93% yield.[23,24] As for Scheme 4, we found that catalyst loadings could be decreased to 5 mol% without deterioration in yield at a large scale. Importantly, a number of substrates possessing β-hydrogen



Scheme 5. Carboxylation of secondary ammonium salts. Reaction conditions: **3** (0.20 mmol), NiCl$_2$ (10 mol %), **L6** (26 mol %), Mn (0.80 mmol), CO$_2$ (1 atm) in DMF (0.20 M) at 70 °C for 16 h; yields of the isolated products given as an average of at least two independent runs. [a] **3a** (1.0 mmol), NiCl$_2$ (5 mol %). [b] **4d** (1:1 d.r.). [c] 90 °C for 72 h. [d] Isolated as the corresponding methyl ester upon treatment with TMSCHN$_2$.

atoms could be successfully carboxylated with similar ease, even when the ammonium salt contained sterically encumbered backbones (**3h**) or was functionalized with groups possessing an innate proclivity for β-hydride elimination (**3e**). Similarly, the reaction was not hampered by the inclusion of nitriles (**4m**), esters (**4f**, **4n**), alkenes (**4g**), or *ortho* substituents (**4o**, **4p**). Particularly noteworthy was the ability to couple substrates having β-alkyl chains other than methyl groups (**4c**–**h**, **4k**), showcasing the utility of this process when compared to benzyl electrophiles or styrene derivatives (Scheme 1).[5e,f,9] To put these results into perspective, while **4c** was obtained in 84 % yield from **3c**, the utilization of organic halides (**3c**-Br) or pivalate analogues (**3c**-OPiv) under the reported optimized conditions[5e,f] lead exclusively to β-hydride elimination and dimerization. Although inherently predisposed towards intramolecular C−C bond formations, the presence of esters (**3f**) or alkenes (**3g**) on the side chain did not interfere, obtaining exclusively **4f** and **4g**.[25,26] Taken together, the results of Schemes 4–5 show that ammonium salts cannot be considered as merely substitutes of organic halides, thus leading to new knowledge in the cross-electrophile coupling arena.[27]

Although a comprehensive study detailing the mechanistic underpinnings of this reaction will require further investigations, we decided to study the reactivity of Ni^{0}(**L4**)$_2$ (**5**) and Ni^{I}(**L4**)$_2$ compounds (**6**). While 18-electron complex **5** was prepared in quantitative yield by reacting Ni(COD)$_2$ and **L4** in benzene at 40 °C, complex **6** was prepared from **5** upon exposure to AgOTf in THF at RT.[15,28] As shown in Scheme 6, both structures were unambiguously characterized by X-ray crystallography.[29,30] Interestingly, **5** and **6** were found to be catalytically competent when using **1a** as the substrate, delivering compound **2a** in 77 % and 76 % yield, respectively. Intriguingly, although a non-negligible erosion in yield of **2a** was found when reacting **1a** with **5** in a stoichiometric fashion in the absence of Mn, no reaction took place under otherwise identical reaction conditions under a **6** regime.[31] Whether these results indicate the involvement of single-electron-transfer processes,[32–34] comproportionation events[35] via benzyl Ni^{I} intermediates,[36] or other mechanistic implications is the subject of ongoing investigations.



Scheme 6. Stoichiometric experiments with **5** and **6**.

In summary, we have described the first cross-electrophile coupling reaction via unconventional C−N bond cleavage/CO$_2$ insertion. The success is attributed to the use of a new set of ligands with unprecedented reactivity while preventing parasitic reaction pathways commonly observed in cross-electrophile reactions, thus outperforming previously developed carboxylation events. The wide substrate scope and the generality of this new procedure might lead to new knowledge in ligand design and augurs well for implementing C−N counterparts in cross-electrophile events. Further investigations along these lines are currently underway in our laboratories.

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[31] Although speculative, these results might suggest: a) that **6** acts as a precatalyst en route to **5** upon single electron transfer mediated by Mn, and b) the intermediacy of benzyl Ni(I) species from in situ generated benzyl Ni(II) complexes mediated by Mn. For similar erosion in yields when performing stoichiometric experiments, see Refs. [5a–c].

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[33] A significant inhibition was detected in the presence of radical scavengers, such as 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) or galvinoxyl, for either **2a** or **3a** (17–45 % yield).

[34] Complete loss of optical purity was detected when promoting the carboxylation of **3i** (99 % *ee*). As control experiments determined that enantioenriched **4i** does not racemize under the reaction conditions, it could be argued that radical intermediates must come into play. Care, however, must be taken when generalizing this since racemization might occur from bimolecular mechanisms from in situ generated η^3-Ni^{II} intermediates upon reaction with Ni^0L_n species. See, for example: I. M. Yonova, A. G. Johnson, C. A. Osborne, C. E. Moore, N. S. Morrissette, E. R. Jarvo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2422 – 2427; *Angew. Chem.* **2014**, *126*, 2454 – 2459.

[35] For selected comproportionation events en route to Ni^I species, see: a) Ref. [17b]; b) A. Velian, S. Lin, A. J. M. Miller, M. W. Day, T. Agapie, *J. Am. Chem. Soc.* **2010**, *132*, 6296 – 6297; c) V. B. Phapale, E. Bunuel, M. García-Iglesias, D. J. Cardenas, *Angew. Chem. Int. Ed.* **2007**, *46*, 8790 – 8795; *Angew. Chem.* **2007**, *119*, 8946 – 8951; d) G. D. Jones, J. L. Martin, C. McFarland, O. R. Allen, R. E. Hall, A. D. Haley, R. J. Brandon, T. Konovalova, P. J. Desrochers, P. Pulay, D. A. Vicic, *J. Am. Chem. Soc.* **2006**, *128*, 13175 – 13183.

[36] Recently, Ni^I species have been shown to rapidly react with CO_2: F. S. Menges, S. M. Craig, N. Tötsch, A. Bloomfield, S. Ghosh, H.-J. Krüger, M. A. Johnson, *Angew. Chem. Int. Ed.* **2016**, *55*, 1282 – 1285; *Angew. Chem.* **2016**, *128*, 1304 – 1307.

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