Ni-catalyzed Carboxylation of Benzylic C-N bonds with CO$_2$

Toni Moragas,[a] Morgane Gaydou[a] and Ruben Martin*[a],[b]

Abstract: A user-friendly Ni-catalyzed reductive carboxylation of benzylic C–N bonds with CO$_2$ is described. This protocol outperforms state-of-the-art carboxylation techniques of benzyl electrophiles by avoiding commonly observed parasitic pathways such as homodimerization or β-hydride elimination, thus leading to new knowledge in cross-electrophile events.

Cross-electrophile reactions have recently gained considerable attention, becoming direct and practical alternatives to classical nucleophile/electrophile regimes based on stoichiometric organometallic reagents.[1] While the utilization of organic halides and homogeneous reagents has become routine in these endeavors,[1] the 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 protocols based on unconventional, yet practical, electrophilic partners would be highly rewarding, thus improving our flexibility in synthetic design.
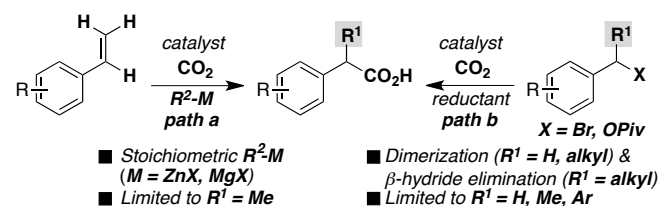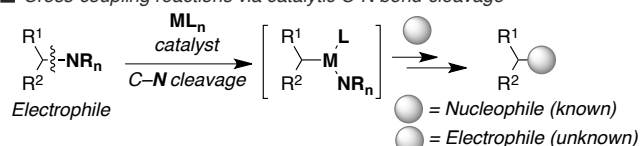

**Scheme 1.** Reductive carboxylation towards phenylacetic acids.

The utilization of carbon dioxide (CO$_2$) as renewable C1 synthon holds great promise to define new paradigms in retrosynthetic analysis.[3] Following the pioneering work of Osakada,[4] we[5] and others[6] have designed reductive carboxylation techniques of organic (pseudo)halides with CO$_2$, becoming alternatives to classical routes requiring organometallic species.[7],[8] Despite the advances realized, a general route towards 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, β-hydride elimination or the limited set of*

substitution patterns that can be introduced (Scheme 1).[5e],[5f],[9],[10] Consequently, filling this gap was deemed crucial, particularly with non-toxic and easy to handle, yet highly reactive, alternative counterparts. Challenged by such 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 a priori inaccessible building blocks via unconventional synergistic C–N cleavage/CO$_2$ insertion. At the outset of our investigations, however, it was unclear whether such protocol could ever be implemented, as ammonium salts were exclusively employed in nucleophile/electrophile regimes using well-defined stoichiometric organometallic entities (Scheme 2, *top*).[12-14] If successful, such a method would represent a previously unrecognized opportunity for promoting C–N activation in cross-electrophile endeavors. Herein, we describe our initial investigations towards this goal (Scheme 2, *bottom*). This user-friendly and operationally-simple new procedure operates at atmospheric pressure of CO$_2$ and *outperforms all other carboxylation protocols of benzyl electrophiles* (Scheme 1), demonstrating that ammonium salts are not merely substitutes of 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 can't be avoided, thus leading to new knowledge in synthetic design.
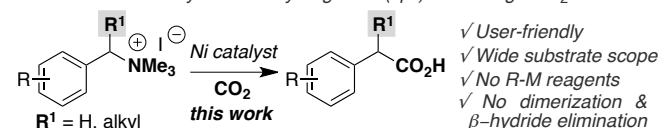
Scheme 2. Cross-electrophile events via C-N cleavage.
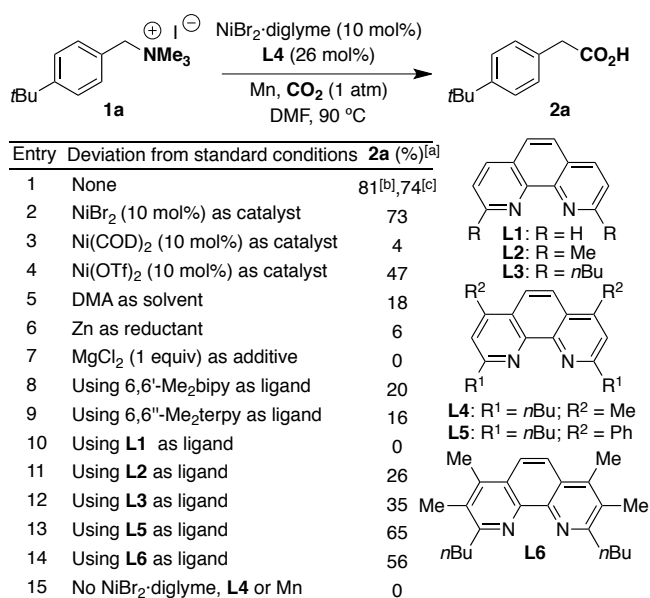
Our study began by evaluating the reaction of **1a** with CO$_2$ at atmospheric pressure (Scheme 3). Notably, not even traces of **2a** were detected under conditions previously employed for other benzyl electrophiles (Scheme 1, *path b*),[5e],[5f] indicating that the activation of C(sp^3)–N bonds would be more problematic than anticipated. After a judicious screening of all reaction parameters,[15] a cocktail consisting of NiBr$_2$·diglyme and **L4**, a bench-stable ligand prepared in multigram scale and in one-step operation,[15] in combination with Mn as reducing agent in DMF afforded **2a** in 81% isolated yield (entry 1).[16] Importantly, *not even traces of homodimerization were observed in the crude mixtures, constituting an important bonus when compared with*

[a]   Dr. T. Moragas, Dr. M. Gaydou, Prof. R. Martin
        Institute of Chemical Research of Catalonia (ICIQ), The Barcelona
        Institute of Science and Technology
        Av. Països Catalans 16, 43007, Tarragona (Spain)
        E-mail: rmartinromo@iciq.es
[b]   Prof. R. Martin
        Catalan Institution for Research and Advanced Studies (ICREA)
        Passeig Lluís Companys, 23, 08010, Barcelona (Spain)

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related carboxylation techniques (Scheme 1, *path b*).[5e],[5f] While other Ni(II) sources provided lower yields (entries 2 and 4), we found that Ni(COD)$_2$ was not competent as precatalyst, suggesting that COD might compete with substrate binding (entry 3).[17] As shown in entries 5 and 6, the use of structurally related DMA, Zn as reducing agent or the inclusion of MgCl$_2$ as additive had a deleterious effect (entries 4-7).[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 non-fused analogues. Although tentative, 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(0)L$_n$ species.[19] As expected, control experiments revealed that all reaction parameters were critical for success (entry 15).[15],[20]

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$_2$bipy as ligand	20
9	Using 6,6''-Me$_2$terpy 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 the 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 ºC for 72 h. [a] HPLC yields using anisole as internal standard. [b] Isolated yield. [c] **L4** (10 mol%).

With these conditions in hand, we focused our attention on the preparative scope of our Ni-catalyzed direct carboxylation 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 bonus from a practical standpoint. As becomes evident from the results compiled in Scheme 4, our synergistic C(sp^3)–N cleavage/CO$_2$ insertion 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 chemoselectivity profile was nicely illustrated by the fact that

ammonium salts containing esters (**1h**), fluorides (**1c**), silyl ethers (**1g**) or acetals (**1m**), among others, were perfectly 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 do not interfere with productive 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 reduced to 5 mol% without significant erosion in yield (**2a**; 70% yield).
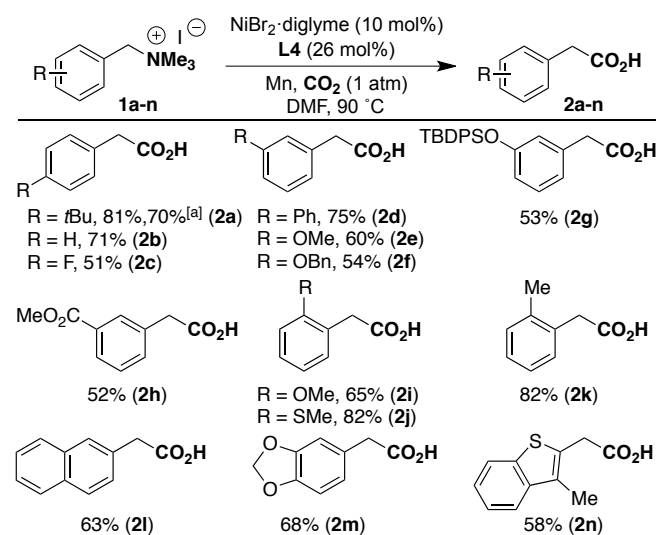
Scheme 4. Carboxylation of primary ammonium salts. Reaction conditions: as for Scheme 3, entry 1; Isolated yields, average of at least two independent runs. [a] **1a** (1.0 mmol), NiBr$_2$·diglyme (5 mol%).

Prompted by the inherent limitations posed by the available catalytic reductive carboxylation techniques en route to α-substituted phenylacetic acids (Scheme 1), we wondered whether our protocol could be extended to secondary benzyl ammonium salts possessing β-hydrogens. Although one might anticipate *parasitic homodimerization or β-hydride elimination pathways*, an issue previously observed in a myriad of cross-electrophile endeavors 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 reduced to 5 mol% without deterioration in yield at large scale. Importantly, a number of substrates possessing β-hydrogens could successfully be carboxylated with equal ease, even with sterically encumbered backbones (**3h**) or groups possessing an innate proclivity for β-hydride elimination (**3e**). Likewise, the reaction was not hampered by the inclusion of nitriles (**4m**), esters (**4f**, **4n**), alkenes (**4g**) as well as *ortho* substituents (**4o**, **4p**). Particularly noteworthy was the ability to couple substrates possessing 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],[5f],[9] To put these results into perspective, while **4c** was obtained in 85% yield from **3c**, the utilization of organic halides (**3c**-Br) or pivalate analogues (**3c**-OPiv) under the

reported optimized conditions[5e],[5f] lead to exclusive β-hydride elimination and dimerization. Although inherently disposed to 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 illustrate that ammonium salts, conceptually and practicality aside, cannot be considered as merely substitutes of organic halides, thus leading to new knowledge in the cross-electrophile coupling arena.[27]
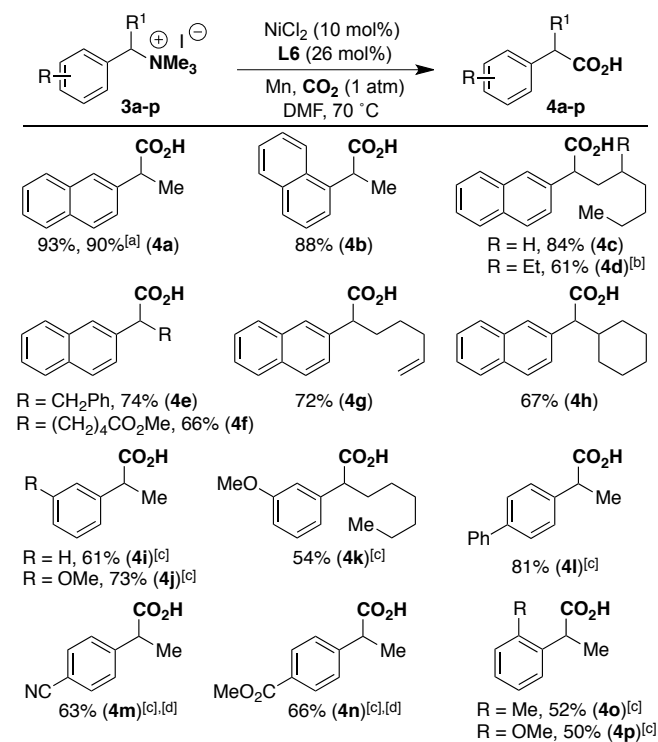

Scheme 5. Carboxylation of secondary ammonium salts. Reaction conditions: **3** (0.20 mmol), NiCl$_2$ (10 mol%), **L6** (26 mol%), Mn (0.80 mmol), CO$_2$ (1 atm) in DMF (0.20 M) at 70 °C for 16 h; Isolated yields, average of at least two independent runs. [a] **3a** (1.0 mmol), NiCl$_2$ (5 mol%). [b]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

Although a comprehensive study detailing the mechanistic underpinnings of this reaction should await further investigations, we decided to study the reactivity of Ni(0)(**L4**)$_2$ (**5**) and Ni(I)(**L4**)$_2$ species (**6**). While 18-electron complex **5** could be prepared in quantitative yield by reacting Ni(COD)$_2$ and **L4** in benzene at 40 °C, **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 substrate, delivering **2a** in 77% and 76% yield, respectively. Intriguingly, while 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 conditions under a **6** regime.[31] Whether these results indicate the involvement of single electron transfer processes[32-34] or comproportionation events[35] via the

intermediacy of benzyl Ni(I) species[36] or other mechanistic implications is subject of ongoing investigations.

In summary, we have described the first cross-electrophile coupling reaction via unconventional C–N 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 endeavors, thus outperforming previously developed carboxylation events. The wide substrate scope and the generality of this new protocol 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.
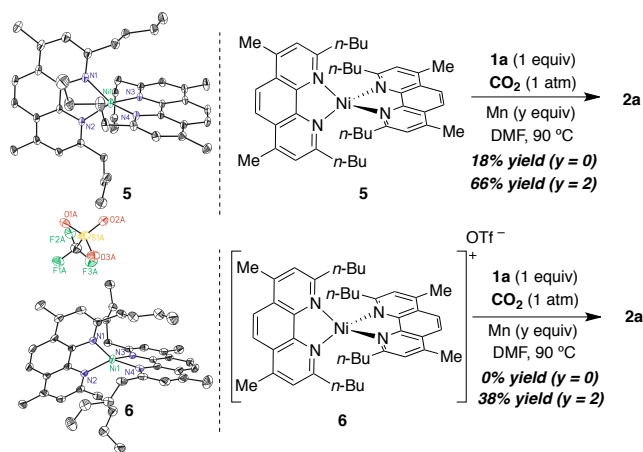
Scheme 6. Stoichiometric experiments with **5** and **6**.

[1]   For selected reviews: a) J. Gu, X.Wang, W. Xue, H. Gong, *Org. Chem. Front.* **2015**, *3*, 1411-1421; b) J. D. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767-1775; c) T. Moragas, A. Correa, R. Martin, *Chem. Eur. J.* **2014**, *20*, 8242-8258; d) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828-6842.

[2]   a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299-309; b) "Organonickel Chemistry" in *Organometallics in Synthesis: Fourth Manual*, (Eds: B.H. Lipshutz), Wiley, Hoboken, N.J., **2013**; c) *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich, A. Meijere), Wiley-VCH, Weinheim, **2004**.

[3]   For selected reviews, see: a) L. Zhang, Z. Hou, *Chem. Sci.* **2013**, *4*, 3395-3403; b) Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*, 9956-

9964; c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kuhn, *Angew. Chem.* **2011**, *123*, 8662-8690; *Angew. Chem., Int. Ed.* **2011**, *50*, 8510-8537; d) K. Huang, C. –L. Sun, Z. –J. Shi, *Chem. Soc. Rev.* **2011**, *40*, 2435-2452; e) R. Martin, A. W. Kleij, *ChemSusChem* **2011**, *4*, 1259-1263; f) T. Sakakura, J. C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365-2387.

[4]   K. Osakada, R. Sato, T. Yamamoto, *Organometallics* **1994**, *13*, 4645-4647.

[5]   a) X. Wang, M. Nakajima, R. Martin, *J. Am. Chem. Soc.* **2015**, *137*, 8924-8927; b) X. Wang, Y. Liu, R. Martin, *J. Am. Chem. Soc.* **2015**, *137*, 6476-6479; c) T. Moragas, J. Cornella, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 17702-17705; d) Y. Liu, J. Cornella, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 11212-11215; e) A. Correa, T. León, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 1062-1069; f) T. León, A. Correa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1221-1224; g) A. Correa, R. Martin, *J. Am. Chem. Soc.* **2009**, *131*, 15974-15975.

[6]   a) K. Nogi, T. Fujihara, J. Terao, Y. Tsuji, *J. Org. Chem.* **2015**, *80*, 11618-11623; b) F. Rebih, M. Andreini, A. Moncomble, A. Harrison-Marchand, J. Maddaluno, M. Durandetti, *Chem. Eur. J.* **2015**, DOI: 10.1002/chem.201503926; c) T. Mita, Y. Higuchi, Y. Sato, *Chem. Eur. J.* **2015**, *21*, 16391-16394; d) K. Nogi, T. Fujihara, J. Terao, Y. Tsuji, *Chem. Commun.* **2014**, *50*, 13052-13055; e) H. Tran-Vu, O. Daugulis, *ACS Catal.* **2013**, *3*, 2417-2420; f) T. Fujihara, K. Nogi, T. Xu, J. Terao, Y. Tsuji, *J. Am. Chem. Soc.* **2012**, *134*, 9106-9109.

[7]   For a review, see: A. Correa, R. Martin, *Angew. Chem.* **2009**, *121*, 6317-6320; *Angew. Chem., Int. Ed.* **2009**, *48*, 6201-6204.

[8]   For selected examples, see: a) A. Ueno, M. Takimoto, W. W. N. O. M. Nishiura, T. Ikariya, Z. Hou, *Chem. Asian J.* **2015**, *10*, 1010-1016; b) M. Takimoto, Z. Hou, *Chem. Eur. J.* **2013**, *19*, 11439-11445; c) S. Li, B. Miao, W. Yuan, S. Ma, *Org. Lett.* **2013**, *15*, 977-979; d) A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem.* **2010**, *122*, 4769-4773; *Angew. Chem., Int. Ed.* **2010**, *49*, 4665-4668; e) T. Ohishi, M. Nishiura, Z. Hou, *Angew. Chem.* **2008**, *120*, 5876-5879; *Angew. Chem., Int. Ed.* **2008**, *47*, 5792-5795; f) J. Takaya, S. Tadami, K. Ukai, N. Iwasawa, *Org. Lett.* **2008**, *10*, 2697-2700; g) C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 7826-7827; h) K. Ukai, M. Aoki, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2006**, *128*, 8706-8707.

[9]   a) M. D. Greenhalgh, S. P. Thomas, *J. Am. Chem. Soc.* **2012**, *134*, 11900-11903; b) C. M. Williams, J. B. Johnson, T. Rovis, *J. Am. Chem. Soc.* **2008**, *130*, 14936-14937. c) H. Hoberg, Y. Peres, C. Kruger, Y. –H. Tsay, *Angew. Chem.* **1987**, *99*, 799-800; *Angew. Chem., Int. Ed.* **1987**, *26*, 771-773.

[10]   Recently, an elegant solution to prevent homodimerization in *primary benzyl alcohol derivatives lacking β-hydrogens* has been accomplished by Weix and co-workers dealing with the use of cobalt phtalocyanine: Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115-1119.

[11]   R. N. Icke, B. B. Wisegarver, G. A. Alles, *Org. Synth.* **1945**, *25*, 89.

[12]   For reviews on catalytic C–N cleavage: a) Q. Wang, Y. Su, H. Huang, *Chem. Soc. Rev.* **2016**, DOI: 10.1039/c5cs00534e. b) K. Ouyang, W. Hao, W. –X. Zhang, Z. Xi, *Chem. Rev.* **2015**, *115*, 12045-12090.

[13]   a) H. Zhang, S. Hagihara, K. Itami, *Chem. Eur. J.* **2015**, *21*, 16796-16800; b) X. –Q. Zhang, Z. –X. Wang, *Org. Biomol. Chem.* **2014**, *12*, 1448-1453; c) P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280-285; d) L. –G. Xie, Z. –X. Wang, *Angew. Chem.* **2011**, *123*, 5003-5006; *Angew. Chem. Int. Ed.* **2011**, *50*, 4901-4904; e) S. B. Blakey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 6046-6047; f) E. Wenkert, A. –L. Han, C. –J. Jenny, *J. Chem. Soc., Chem. Commun.* **1988**, 975-976.

[14]   For selected nucleophile/electrophile regimes via catalytic C–N cleavage not involving ammonium salts: a) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y. –F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* **2015**, *524*, 79-83; b) M. Tobisu, K. Nakamura, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 5587-5590; c) T. Koreeda, T. Kochi, F. Kakiuchi, *J. Am. Chem. Soc.* **2009**, *131*, 7238-7239; d) S. Ueno, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 6098-6099.

[15]   For details see Supporting Information.

[16]   The nature of both the substituents on nitrogen and the counterion of the ammonium salt exerted a profound influence on reactivity. See ref. 15.

[17]   For examples, see: a) A. J. Nett, W. Zhao, P. M. Zimmerman, J. Montgomery, *J. Am. Chem. Soc.* **2015**, *137*, 7636-7639; b) J. Cornella, E. Gomez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997-2009; c) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992-2004.

[18]   For the beneficial role of $MgCl_2$ in cross-electrophile couplings, see for example: a) ref. 5c, 5f and 8d; b) T. Fujihara, Y. Horimoto, T. Mizoe, F. B. Sayyed, Y. Tani, J. Terao, S. Sakaki, Y. Tsuji, *Org. Lett.* **2014**, *16*, 4960-4963; c) C. Zhao, X. Jia, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2014**, *136*, 17645-17651; d) F. Wu, F. Lu, Q. Qian, Q. Ren, H. Gong, *Org. Lett.* **2012**, *14*, 3044-3047; e) H. Yin, C. Zhao, H. You, K. Lin, H. Gong, *Chem. Commun.* **2012**, 7034-7036.

[19]   For an elegant study showing the intriguing impact of different substitution patterns over the 1,10-phenanthroline backbones on catalytic performance, see: C. Cheng, J. F. Hartwig, *J. Am. Chem. Soc.* **2015**, *137*, 592-595.

[20]   While one might argue that **1a** might *in situ* generate benzyl iodide, control experiments revealed no conversion to **2a** with benzyl iodide, neither in the presence nor absence of NMe_3.

[21]   It is worth noting that the carboxylation of benzyl C-O electrophiles was restricted to extended π-systems or to secondary benzyl derivatives lacking aliphatic side-chains. See ref. 5e.

[22]   a) S. R. Dubbaka, P. Vogel, *Angew. Chem.* **2005**, *117*, 7848-7859; *Angew. Chem., Int. Ed.* **2005**, *44*, 7674-7684; b) *Catalyst Poisoning* (Eds.: L. L. Hegedus, R. W. McCabe), Marcel-Dekker, New York, **1984**; c) S. G. Murray, F. R. Hartley, *Chem. Rev.* **1981**, *81*, 365-414.

[23]   For details about the optimization, see ref. 15.

[24]   We found low yields of **4a** with a protocol based on **L4**, suggesting that the success of **L6** might be attributed to electronic effects. For an analogous observation in other catalytic endeavors, see ref. 19.

[25]   For recent reviews dealing with the catalytic α-functionalization of carbonyl compounds with activated electrophiles: a) P. Novák, R. Martin, *Curr. Org. Chem.* **2011**, *15*, 3233-3262; b) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686-718; *Angew. Chem. Int. Ed.* **2010**, *49*, 676-707; c) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082-1146.

[26]   For Ni-catalyzed intramolecular C–C bond-formations of alkyl electrophiles with pending alkenes on the side chain, see for example: a) H. Cong, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 3788-3791; b) M, R. Harris, M. O. Konev, E. R. Jarvo, *J. Am. Chem. Soc.* **2014**, *136*, 7825-7828.

[27]   While preliminary, we have found that 2-naphtyl-trimethylammonium iodide can promote reductive carboxylation event via $C(sp^2)$–N cleavage using dppf as ligand, obtaining 33% yield of the targeted carboxylic acid.

[28]   D. C. Powers, B. L. Anderson, D. G. Nocera *J. Am. Chem. Soc.* **2013**, *135*, 18876-18883.

[29]   CCDC 1448910 (**5**) contain the supplementary crystallographic data for this paper and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac/uk/data_request/cif.

[30]   CCDC 1448911 (**6**) contain the supplementary crystallographic data for this paper and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac/uk/data_request/cif.

[31]   Although speculative, these results might suggest that **6** acts as a precatalyst en route to **5** upon single electron transfer mediated by Mn.

[32]   For the intermediacy of Ni(I) species generated upon single electron transfer processes, see refs. 5b-5f, 6f and the following selected references: a) C. A. Laskowski, D. J. Bungum, S. M. Baldwin, S. A. Del Ciello, V. M. Iluc, G. L. Hillhouse, *J. Am. Chem. Soc.* **2013**, *135*, 18272-18275; b) J. Breitenfeld, J. Ruiz, M. D. Wodrich, X. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 12004-12012; c) S. Biswas, D. J. Weix, *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197.

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

[34] Complete loss of optical purity was observed when promoting the carboxylation of **3i** (99% ee). As control experiments determined that enantioenriched **4i** does not racemize under the reaction conditions, one might argue 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(0)L$_n$ species. See for example: I. M. Yonova, A. G. Johnson, C. A. Osborne, C. E. Moore, N. S. Morrissette, E. R. Jarvo, *Angew. Chem.* **2014**, *126*, 2454-2459; *Angew. Chem. Int. Ed.* **2014**, *53*, 2422-2427.

[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.* **2007**, *119*, 8946-8951; *Angew. Chem., Int. Ed.* **2007**, *46*, 8790-8795; 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 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.* **2016**, *128*, 1304-1307; *Angew. Chem., Int. Ed.* **2016**, *55*, 1282-1285.

COMMUNICATION
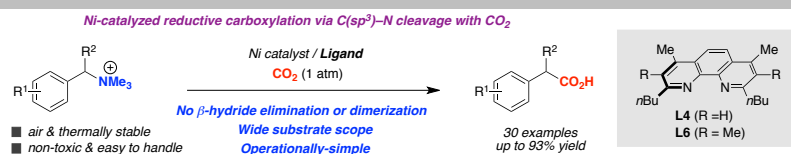
Toni Moragas, Morgane Gaydou and Ruben Martin*
 Author(s), Corresponding Author(s)*

Ni-catalyzed reductive carboxylation via C(sp³)–N cleavage with CO_2

Ni catalyst / **Ligand**
CO_2 (1 atm)

No β-hydride elimination or dimerization
Wide substrate scope
Operationally-simple

- air & thermally stable
- non-toxic & easy to handle

30 examples up to 93% yield

L4 (R =H)
L6 (R = Me)

A novel & user-friendly Ni-catalyzed reductive carboxylation of benzylic C–N bonds with CO_2 is described. This protocol outperforms state-of-the-art carboxylation techniques of benzyl electrophiles by avoiding commonly observed parasitic pathways, thus leading to new knowledge in cross-electrophile events.