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Ni-Catalyzed Carboxylation of C(sp^2)– and C(sp^3)–O Bonds with CO_2

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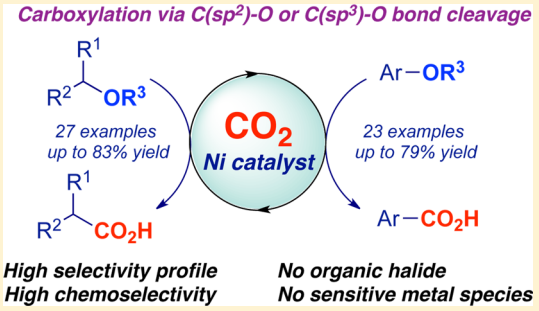
Supporting Information

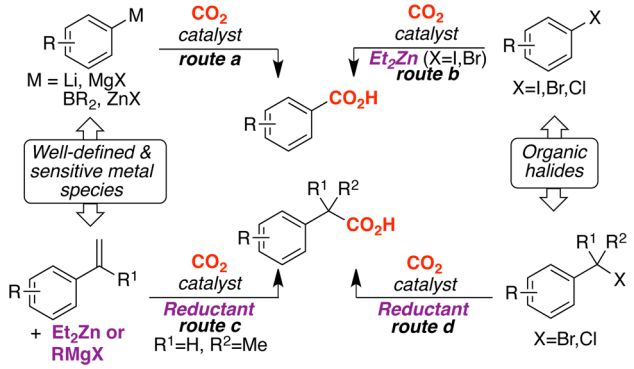
ABSTRACT: In recent years a significant progress has been made for the carboxylation of aryl and benzyl halides with CO_2, becoming convenient alternatives to the use of stoichiometric amounts of well-defined metal species. Still, however, most of these processes require the use of pyrophoric and air-sensitive reagents and the current methods are mostly restricted to organic halides. Therefore, the discovery of a mild, operationally simple alternate carboxylation that occurs with a wide substrate scope employing readily available coupling partners will be highly desirable. Herein, we report a new protocol that deals with the development of a synergistic activation of CO_2 and a rather challenging activation of inert C(sp^2)–O and C(sp^3)–O bonds derived from simple and cheap alcohols, a previously unrecognized opportunity in this field. This unprecedented carboxylation event is characterized by its simplicity, mild reaction conditions, remarkable selectivity pattern and an excellent chemoselectivity profile using air-, moisture-insensitive and easy-to-handle nickel precatalysts. Our results render our method a powerful alternative, practicality and novelty aside, to commonly used organic halides as counterparts in carboxylation protocols. Furthermore, this study shows, for the first time, that traceless directing groups allow for the reductive coupling of substrates without extended π-systems, a typical requisite in many C–O bond-cleavage reactions. Taking into consideration the limited knowledge in catalytic carboxylative reductive events, and the prospective impact of providing a new tool for accessing valuable carboxylic acids, we believe this work opens up new vistas and allows new tactics in reductive coupling events.



INTRODUCTION

The design of novel metal-catalyzed C–C bond forming reactions based on available chemical feedstock constitutes a formidable goal in synthetic organic chemistry, holding great promise for defining new paradigms in sustainable development.[1] In this regard, the means to convert carbon dioxide (CO_2) into valuable compounds has received considerable attention in recent years.[2] The growing interest of CO_2 as C1 building block in both academic and pharmaceutical laboratories relies on its low-cost, lack of toxicity, high abundance and tremendous potential as a renewable carbon source.[3] Given that carboxylic acids are privilege motifs in a wide number of natural products, agrochemicals or pharmaceutically relevant compounds such as Lipitor, Blopress, Prandin or Vancomycin, among many others, chemists have been challenged to devise new direct, effective and attractive catalytic routes to introduce the carboxylic acid unit into organic compounds.[4] Indeed, the recent years have witnessed a renaissance on the development of mild carboxylation protocols of stoichiometric organometallic species with CO_2,[5,6] thus becoming viable alternatives to classical methods for preparing carboxylic acids (Scheme 1, *route a*).[4] Still, however, the air-sensitivity as well as the reliability for ultimately obtaining these organometallic species from the corresponding aryl halides limit the application profile of these methods, particularly from an experimental ease and step-economical point of view.[7] Alternatively, the use of styrenes with stoichiometric, and sensitive Et_2Zn or Grignard reagents as reducing agents allowed for rapidly obtaining phenyl acetic acids (Scheme 1, *route c*);[8] unfortunately, however, the method was restricted to unsubstituted styrenes (R^1=H), hence limiting the application profile of these rather appealing events.

Scheme 1. Metal-Catalyzed Carboxylation Events with CO_2



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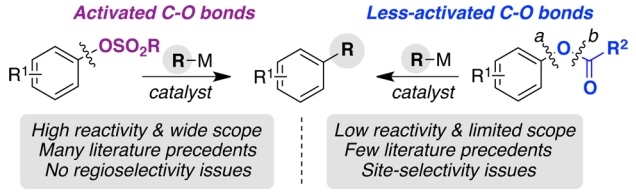
Recently, our group,[9a,b] Tsuji[10a] and Daugulis[10b] reported a direct reductive carboxylation of aryl and benzyl halides in the presence of Pd, Ni and Cu catalysts (Scheme 1, *routes b* and *d*).[9,10] Although no doubt a step forward, such routes are mostly restricted to organic halide counterparts as well as the use, in many instances, of highly reactive, pyrophoric and air-sensitive Et_2Zn as reducing agent, thereby representing serious drawbacks to be overcome, both from a flexible and synthetic point of view. Therefore, the discovery of mild, operationally simple and alternate carboxylative protocols that occur with a wide substrate scope employing readily available coupling partners would not only significantly improve the flexibility in catalytic design, but also allow for the implementation of innovative new tactics in this field.

Owing to their general low-cost, readily availability and high thermal stability, phenol derivatives have emerged as versatile and cost-efficient alternatives to aryl halides in the cross-coupling arena (Scheme 2).[11] Unlike the use of activated aryl

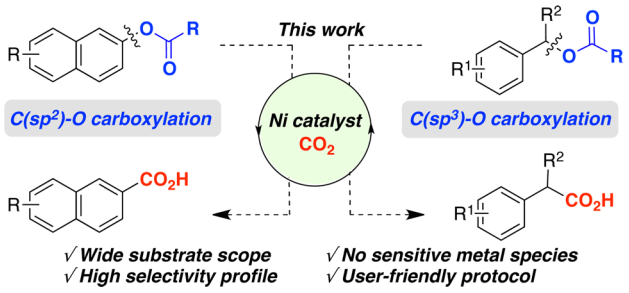
Scheme 2. Catalytic Activation of C−O Bonds



sulfonates such as aryl triflates, mesylates or tosylates (Scheme 2, *left*),[1d] a rather limited number of catalytic cross-coupling methodologies have been described with simpler aryl esters as coupling partners[12,13] via C−O bond-cleavage (Scheme 2, *right*). Indeed, there are several obstacles for developing reactions of this type: (a) the relatively high activation energy associated to the C(sp^2)−O bond in aryl ester derivatives (E = 106 kcal/mol);[11f] (b) the natural proclivity of aryl esters for hydrolysis under basic reaction conditions commonly employed in cross-coupling reactions;[1d] (c) site-selectivity issues since the activation of the C−O bond in aryl esters might occur at two different reaction sites (Scheme 2, *a* vs *b*).[11] Despite recent advances in the field *the metal-catalyzed direct carboxylation of aryl or benzyl esters with CO_2 via C−O bond-cleavage has not yet been described in the literature.*[14] Beyond any doubt, such methodology could provide new vistas for preparing valuable carboxylic acids from renewable chemical feedstock and replacing commonly employed organic halides by C−O electrophiles derived from commercially available and cheap phenols or benzyl alcohols. Practicality and flexibility aside, the interest for such a route is illustrated by the possibility of conducting an unprecedented synergistic activation of CO_2 and inert C−O bonds in aryl or benzyl esters, a highly promising but much less-established area of expertise.

Herein, we describe our investigations on the first Ni-catalyzed reductive carboxylation of esters via C−O bond-cleavage with CO_2. We demonstrate that not only C(sp^2)−O but also more challenging C(sp^3)−O bonds could be activated and coupled with an electrophilic counterpart such as CO_2 in the presence of a suitable reducing agent (Scheme 3). These transformations proceed at atmospheric CO_2 pressure, operate with a wide substrate scope and do not require either air- or moisture sensitive reagents, thus becoming a user-friendly protocol for obtaining carboxylic acids from readily available precursors. Although the requirement for extended π-systems

Scheme 3. Carboxylation of C(sp^2)− and C(sp^3)−O Bonds

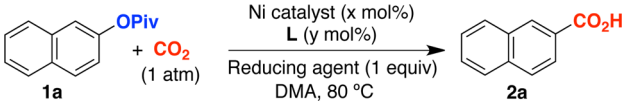


has limited the application profile of many C−O bond-cleavage reactions, we also demonstrate that the use of traceless bidentate directing groups allows for the coupling of much more challenging substrates that do not possess the inherent stabilization associated to extended π-systems. We speculate these results will have a significant impact in other related C−O bond-cleavage reactions.

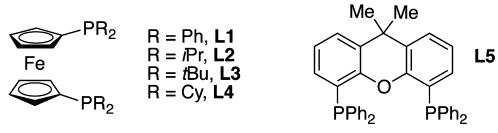
RESULTS AND DISCUSSION

Ni-Catalyzed Reductive Carboxylation of C(sp^2)−O Bonds. We started our investigations with 2-naphthyl pivalate (**1a**) as the model substrate. Guided by our previous studies with CO_2,[9a,b] we anticipated that the nature of the catalyst, solvent, ligands, temperature and additives would have a critical influence on reactivity. Accordingly, the effect of such variables was systematically examined (Table 1).[15] We found that Ni catalysts based upon monodentate phosphine ligands were particularly inefficient (entries 1 and 2). These results are in

Table 1. Optimization of the Reaction Conditions for 1a[a]



Entry	[Ni] (x mol%)	L (y mol%)	Reducing agent	2a (%)[b]
1	$NiCl_2(PCy_3)_2$ (5)	none	Mn	0
2	$NiCl_2(PPh_3)_2$ (5)	none	Mn	0
3	$NiCl_2$(dppe) (5)	none	Mn	0
4	$NiCl_2$(dppp) (5)	none	Mn	0
5	$NiCl_2$(**L1**) (5)	none	Mn	17
6	$NiCl_2$(**L1**) (5)	**L1** (10)	Mn	58
7	$NiCl_2$·DME (5)	**L1** (15)	Mn	47
8	$NiCl_2$·DME (5)	**L2** (15)	Mn	0
9	$NiCl_2$·DME (5)	**L3** (15)	Mn	0
10	$NiCl_2$·DME (5)	**L4** (15)	Mn	0
11	$NiCl_2$·DME (5)	**L5** (15)	Mn	0
12	$NiBr_2$ (5)	**L1** (15)	Mn	48
13	$Ni(COD)_2$ (5)	**L1** (15)	Mn	0
14	$NiCl_2$(**L1**) (5)	COD (10)	Mn	0
15	***$NiCl_2$(L1) (7)***	***L1 (10)***	***Mn***	***70[c]***
16	$NiCl_2$(**L1**) (7)	**L1** (10)	Zn	0
17	$NiCl_2$(**L1**) (7)	**L1** (10)	Al	30
18	$NiCl_2$(**L1**) (7)	**L1** (10)	none	0
19	none	none	Mn	0



[a] **1a** (0.50 mmol), Ni source (x mol %), ligand (y mol %), Mn (1.0 equiv), CO_2 (1 atm), DMA (0.25 M) at 80 °C for 48 h. [b] HPLC yield using anisole as internal standard. [c] Isolated yield.

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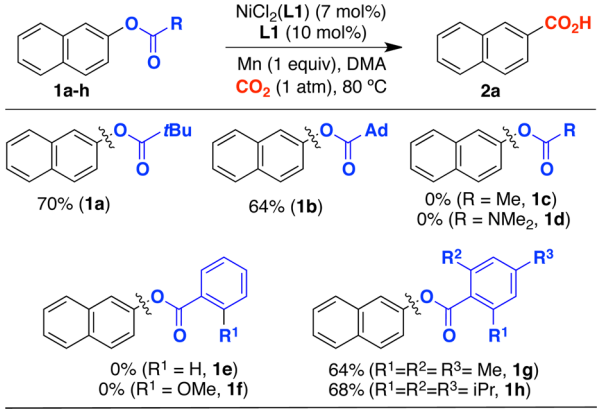
sharp contrast with the ability of such catalysts to promote the carboxylation of aryl chlorides[10a] or benzyl halides,[9b] hence showing the distinctive features of our transformation as well as illustrating the perception that carboxylative protocols are strongly ligand-dependent. After some experimentation, we found that the use of bench-stable $NiCl_2$(**L1**) (**L1** = dppf) in combination with cheap Mn powder as reducing agent delivered significant amounts of **2a** (entry 5). Interestingly, the addition of **L1** resulted in a markedly increase in yield (entry 6), suggesting a stabilization of the resting state of the catalyst. Although structurally related, other ferrocene-type phosphines did not deliver even traces of **2a**, showing the subtleties of our system (entries 8−10). A similar behavior was observed for bidentate ligands with a wider bite angle such as Xantphos (**L5**, entry 11). Overall, these results show that **L1** uniquely assisted the targeted synergistic carboxylative event via C−O bond cleavage. While $NiCl_2$·DME or $NiBr_2$ (entries 7 and 12) could also be utilized, we found that $Ni(COD)_2$ was not a suitable catalyst (entry 13); accordingly, we observed that the inclusion of COD (1,5-cyclooctadiene) as an additive had a negative effect (entry 14), likely suggesting that COD competes with substrate binding.[16] Surprisingly, the addition of ammonium salts as additives had a deleterious impact on reactivity, an observation that is in contrast with recently developed carboxylative protocols.[17] Notably, a slight increase in catalyst loading allowed for obtaining **2a** in 70% isolated yield. Among all reducing agents analyzed, Mn was found crucial for the reaction to occur (entry 15 vs entries 16−17). As anticipated, control experiments in the absence of either Ni precatalyst, reducing agent or CO_2 confirmed that all these components are needed for our reductive carboxylation (entries 18 and 19).[15] It is worth noting that, under our optimized reaction conditions (entry 15), none of the required reagents are either air- or moisture-sensitive, constituting an additional bonus from a practical and operational point of view.

Encouraged by these results, we decided to test whether other C(sp^2)−O electrophiles could also be employed under our reaction conditions. As shown in Table 2, steric effects played a crucial role; whereas **1c** remained intact, the bulkier **1b** furnished **2a** in comparable yields as for **1a**. Likewise, sterically demanding **1g** and **1h** smoothly afforded **2a**, but recovered starting material was observed with less bulky **1e** and **1f**. Interestingly, we found that **1d**, commonly employed in Suzuki-Miyaura or Kumada-Corriu reactions via C−O bond-cleavage,[18] was completely inert under our optimized reaction conditions. At present, we believe that a bulkier substituent on the acyl terminus might stabilize the transient Ni species within the catalytic cycle, thus preventing decomposition pathways. In light of these results, we decided to utilize aryl pivalates in further studies due to their better atom-economical features as well as the remarkable water solubility of the generated pivalic residue, hence facilitating the isolation of products.

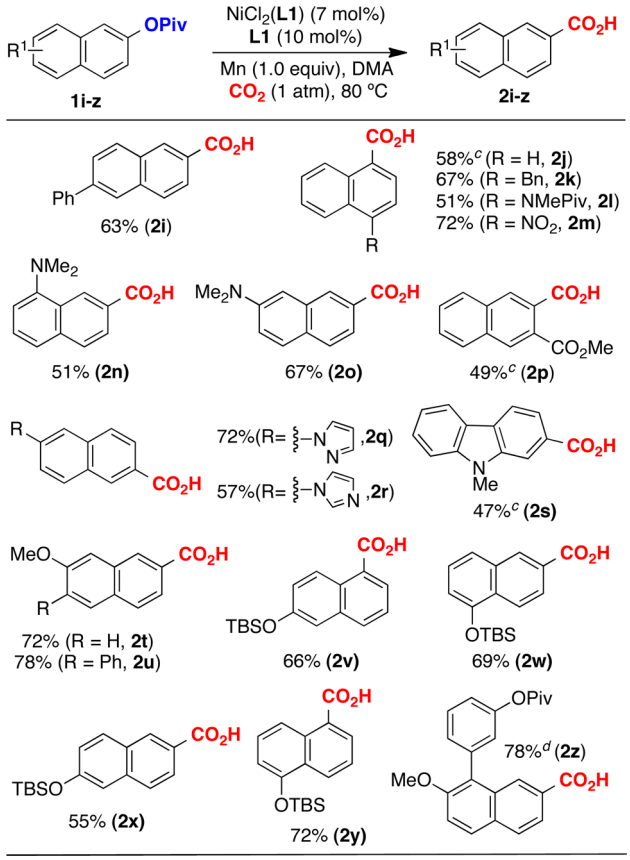
We next turned our attention to study the preparative scope of our reaction utilizing a wide variety of aryl pivalates as substrates (Table 3). Notably, a wide range of substituted

Table 2. Influence of the Aryl Ester Motif on Reactivity[a,b]



[a]As for Table 1, entry 15. [b]Isolated yields, average of at least two independent runs.

Table 3. Ni-Catalyzed Carboxylation of Naphthyl Pivalates[a,b]



[a]As for Table 1, entry 15. [b]Isolated yields, average of at least two independent runs. [c]$NiCl_2$(dppf) (10 mol %) was utilized. [d]Using 1.0 mmol of **1z**.

naphthyl derivatives bearing both electron-withdrawing and electron-donating groups could be carboxylated in moderate to good yields. The chemoselectivity was clearly demonstrated as amines (**2n**, **2o**), amides (**2l**), esters (**2p**), nitro (**2m**) and nitrogen-containing heterocycles such as pyrazole (**2q**), imidazole (**2r**) or carbazole (**2s**) were perfectly accommodated. In line with other related C−O bond-cleavage reactions,[11] the reaction was slightly hampered by *ortho* substituents (**2p**). Strikingly, we found that strongly coordinating nitrogen donors in **2q** and **2r** do not interfere, indicating the low Lewis acidity, if any, of our operating catalyst. Although recent reports in the literature have shown that aryl methyl ethers[12g,16a,19] and silyl ethers[20] undergo C(sp^2)−O bond-cleavage using Ni catalysts, we found that our carboxylative protocol could be conducted in

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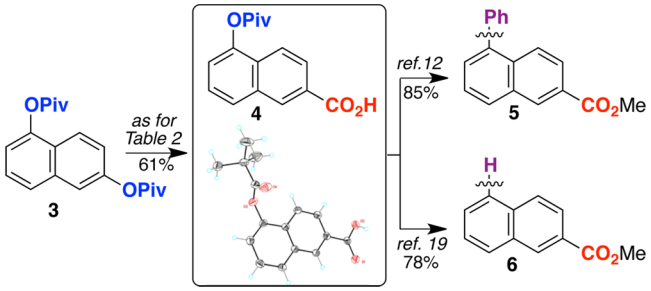
the presence of such motifs. These results are in line with the argument that high temperatures and relatively Lewis-acidic entities are required for C−OMe and C−OSiR$_3$ bond-cleavage.[11] Of particular interest is **2z** in which we were able to discriminate among different C(sp^2)−OPiv residues in high yield and that competitive carboxylation of other C−O bonds was not observed.[21]

On the basis of these results, we anticipated that our carboxylative reaction could be amenable for site-selectivity based on subtle steric and electronic differences among similarly reactive C−O bonds. As shown in Scheme 4, this

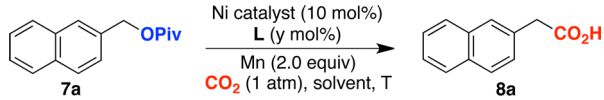
Scheme 4. Sequential Ni-Catalyzed C−O Activation Events



was indeed the case and we obtained a single regioisomer (**4**) that was unambiguously characterized by NMR spectroscopy and X-ray crystallography.[15,22] Subsequently, we successfully performed a Ni-catalyzed Suzuki-Miyaura coupling[12b] and a Ni-catalyzed reductive cleavage event,[12g,16a,19c] obtaining **5** and **6**, respectively, that formally result from a consecutive catalytic functionalization of C−O bonds. We believe the results in Scheme 4 reinforce the notion that site-selectivity among C−O bonds is not only feasible, but it also represents a powerful strategy for accessing functionalized analogues.

Ni-Catalyzed Reductive Carboxylation of Benzylic C(sp^3)−O Bonds. Despite recent advances using benzyl halides or pseudohalides as coupling partners,[1d,23] to the best of our knowledge *the direct reductive carboxylation of activated or nonactivated C(sp^3)−O bonds has no precedents in the literature*. Prompted by our success when employing aryl pivalates as substrates (Table 3), we wondered whether such optimized protocol could be amenable for the coupling of benzylic pivalates such as **7a**. Unfortunately, however, no reaction occurred under such reaction conditions (Table 4, entry 1); such observation is in agreement with the remarkable ligand-dependence of carboxylative processes,[9a,b,10] hence challenging the general perception that benzylic coupling partners are typically more reactive than regular aryl domains. As for the coupling of aryl pivalates, the nature of the ligand backbone played a crucial role; after a judicious screening of the key experimental variables,[15] we found that the use of NiCl$_2$(PMe$_3$)$_2$ (entry 6) provided much better results than other nickel precatalysts bearing bidentate or even related monodentate phosphine ligands. This finding, together with the results disclosed in Table 1, clearly evidence the intimate interplay between ligand and substrate. As shown in entry 9, the yield of **8a** could be drastically improved by using DMF as the solvent and operating at 40 °C with NiCl$_2$(PMe$_3$)$_2$ as catalyst. The use of other Ni precatalysts, however, furnished **8a** in comparatively much lower yields (entries 10−12). Interestingly, the absence of additional PMe$_3$ allowed for obtaining **8a** in 82% isolated yield at room temperature (entry 13); while

Table 4. Optimization of Reaction Conditions for 7a[a]



Entry	[Ni]	L (y mol%)	solvent	T (° C)	**8a** (%)[b]
1	NiCl$_2$(**L1**)	**L1** (10)	DMA	80	0
2	NiCl$_2$(dppp)	dppp (10)	DMA	80	0
3	NiCl$_2$(PPh$_3$)$_2$	PPh$_3$ (10)	DMA	80	0
4	NiCl$_2$(PCy$_3$)$_2$	PCy$_3$ (10)	DMA	80	3
5	NiCl$_2$(PBu$_3$)$_2$	PBu$_3$ (10)	DMA	80	0
6	NiCl$_2$(PMe$_3$)$_2$	PMe$_3$ (10)	DMA	80	31
7	NiCl$_2$(PMe$_3$)$_2$	PMe$_3$ (10)	DMA	40	54
8	NiCl$_2$(PMe$_3$)$_2$	PMe$_3$ (10)	THF	40	0
9	NiCl$_2$(PMe$_3$)$_2$	PMe$_3$ (10)	DMF	40	69
10	NiCl$_2$·DME	PMe$_2$Ph (20)	DMF	40	34
11	NiCl$_2$·DME	PMe$_3$ (20)	DMF	40	43
12	NiBr$_2$·diglyme	PMe$_3$ (20)	DMF	40	28
13[c]	***NiCl$_2$(PMe$_3$)$_2$***	***none***	***DMF***	***rt***	***0,[d] 82[e]***
14	none	none	DMF	rt	0

[a]**7a** (0.50 mmol), Ni source (10 mol %), **L** (*y* mol %), Mn (2.0 equiv), CO_2 (1 atm), solvent (0.25 M) for 24 h. [b]HPLC yield using anisole as internal standard. [c]48 h. [d]In the absence of Mn. [e]Isolated yield.

speculative, we propose that ligand dissociation might occur with PMe$_3$, setting up the stage for a k^2-coordination with the aliphatic pivalate motif. As expected, no reaction occurred in the absence of reducing agent (entry 13) or Ni precatalyst (entry 14). It is important to highlight that the final optimized reaction conditions for the coupling of **7a** did not employ either air- or moisture sensitive reagents.

Unlike the carboxylation of C(sp^2)−O bonds that was found to be specific for sterically demanding ester derivatives (Table 2), the nature of the leaving group on the carboxylation of C(sp^3)−O bonds did not have such a profound effect on reactivity. In this respect, we found that our optimized reaction conditions were not only efficient for pivalate **7a** but also for less hindered substrates such as acetate **7b**, carbamate **7d** and other ester derivatives (**7c**, **7e**). Taking into consideration that benzyl acetates are the most atom-economical C−O electrophiles among the ester series, we turned our attention to the scope of the reaction using such motifs. As shown in Table 5, selective carboxylation of benzylic C(sp^3)−O bonds (**7h**, **7i**) was nicely achieved in the presence of *ortho* C(sp^2)−O moieties, albeit in moderate yields. As for other related C−O bond-cleavage events,[11] the reaction of substrates possessing the reactive site in the C1 position was rather sluggish, thus obtaining the desired products in lower yield (**7g**). Notably, our protocol was also found efficient for the carboxylation of secondary benzyl-type derivatives (**7j**−**7o**). Among these, it is particularly interesting that substrates bearing esters (**7k**) or heterocyclic motifs such as thiophene (**7m**, **7o**) and furan (**7n**) smoothly underwent the targeted carboxylation in good yields. The latter is particularly important as the use of heterocyclic motifs was found to have a negative impact when using benzyl halides as substrates.[9b,24]

Ni-Catalyzed Reductive Carboxylation of C−O Bonds Using Traceless Directing Groups. A close survey of the literature data indicates that a non-negligible number of Ni-catalyzed cross-coupling methodologies based upon inert C−O bond-cleavage are essentially limited to substrates possessing π-extended systems such as naphthalene or anthracene, among others.[11] While a comprehensive analysis of such behavior still awaits further studies, Chatani suggested that Meisenheimer-type complexes might eventually be formed with such

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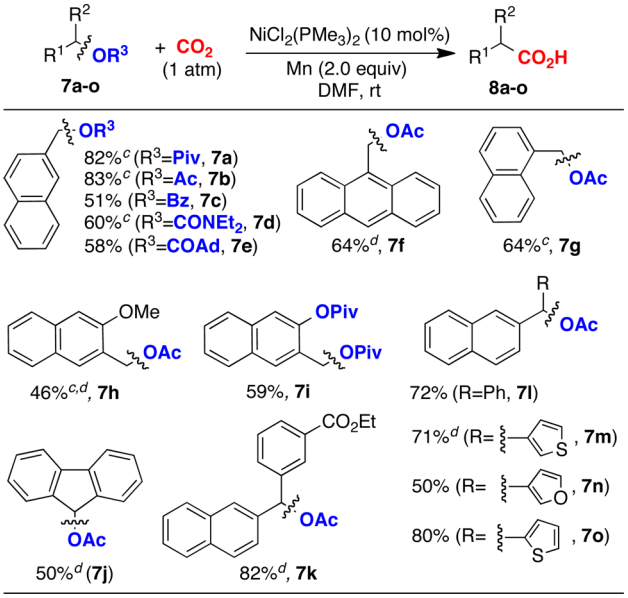
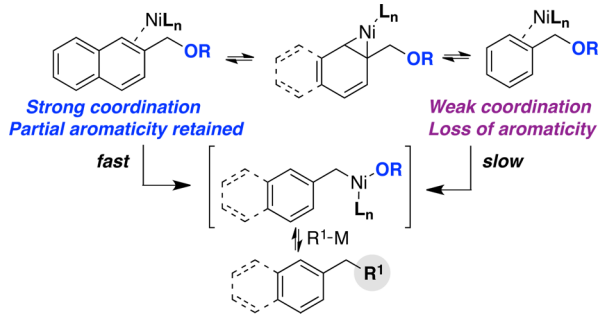
Table 5. Ni-Catalyzed Carboxylation of Benzylic C(sp^3)-O Bonds[a,b]



[a]As for Table 4, entry 13 after 24 h reaction time. [b]Isolated yields, average of at least two independent runs. [c]48h. [d]50 °C.

substrates, thus explaining the lower reactivity associated to simple phenyl-containing compounds.[21,25] We recently postulated that a partial dearomatization of the arene ring might occur under certain reaction conditions.[16a] Accordingly, we hypothesized that an extended π-system might bind to the Ni center in a η^2-fashion via the Dewar-Chatt-Duncanson model, hence retaining, unlike a regular arene, certain aromaticity that provides an extra stabilization (Scheme 5).[26] This latter premise

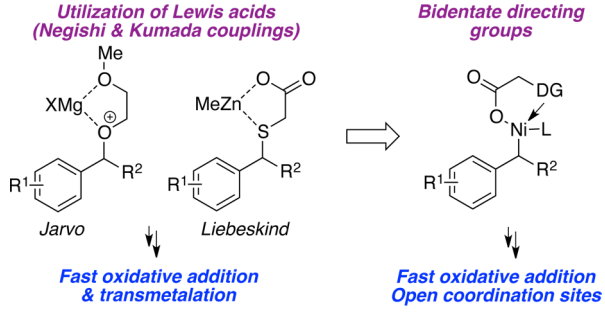
Scheme 5. Extended π-Systems vs Regular Arenes



is in analogy with the known ability of extended π−systems to bind tightly to Ni(0) complexes; indeed, Krüger unambiguously reported the X-ray structure of a complex containing anthracene coordinated to the Ni(0) center in a η^2−fashion with tricyclohexylphosphine as the ligand.[27] Interestingly, a related binding mode was not observed when using a regular arene derivative.[27] Taken together, all these observations are in agreement with regular arenes being several orders of magnitude less reactive than π-extended systems, and their use constitutes a challenging goal in the C−O bond-cleavage arena. A closer look into Tables 3 and 5 indicates that a similar behavior was observed for our Ni-catalyzed carboxylation of C(sp^2)−O and benzylic C(sp^3)−O bonds. Consequently, a different strategy was envisioned to couple more challenging substrate combinations lacking a polyaromatic backbone.

The use of chelation assistance has shown to be an effective strategy that allows functionalization at particularly difficult reaction sites.[28,29] Prompted by a seminal discovery of Liebeskind when using benzyl thioethers,[30] Jarvo and co-workers recently reported a particularly elegant approach using directing groups to efficiently promote Kumada-Corriu[25b,31] or Negishi-type coupling[25c] reactions of benzyl ethers. The rationale behind Jarvo's and Liebeskind's hypothesis was the utilization of Lewis acidic metal species to strongly chelate ether-containing groups, significantly weakening the C−O(S) bond and accelerating the rate of oxidative addition and transmetalation (Scheme 6, *left*). Taking into consideration the

Scheme 6. Traceless Directing Groups for C−O Cleavage



absence of strongly Lewis acidic metals in our carboxylative protocol, we envisioned that the presence of a hemilabile directing group in the ester motif might accelerate the rate of oxidative addition with regular arenes (Scheme 6, *right*). Furthermore, we postulated that such hemilabile directing group would open coordination sites on the Ni center, hence facilitating the binding of CO_2 and its subsequent insertion event.

To verify our hypothesis, a variety of C(sp^3)−O electrophiles derivatives bearing a hemilabile directing group in the side chain were prepared and subjected under the conditions highlighted in Table 5 for the carboxylation of benzylic C(sp^3)−O bonds (Table 6). As expected, we found that acetate **9a** or pivalate **9b** did not deliver the desired carboxylic acid **10a**, even at 100 °C. These results clearly manifest the low reactivity associated to regular arenes in comparison with the success when employing naphthyl derivatives (Table 5). Similarly, we found that **9c** and **9d** were absolutely inert under our reaction conditions, even in the presence of Lewis acids,[15] a strategy previously employed in related endeavors (Scheme 6, *left*). Following up our working hypothesis (Scheme 6, *right*), we next focused our efforts on benzyl ester derivatives possessing hemilabile ligands on the side chain. In line with our expectations, we found significant amounts of **10a** when utilizing the pyridyl framework **9e**.[29,32] A similar reactivity could also be accomplished when using ethers on the side chain with different substitution patterns (**9f**−**9i**). As shown, we found that **9i**, easily prepared from commercially available 2-methoxy acetic acid, provided the best results, giving rise to **10a** in 79% isolated yield. At present, we believe that the difference on reactivity of **9f**−**9i** is mainly attributed to steric effects. A simple comparison of the performance of **9c** or **9d** and **9i** highlights the critical role of the acyl unit and the thioether motif on reactivity. Such results are rather controversial as **9c** and **9d** have successfully been applied in Negishi[25c] or Kumada-

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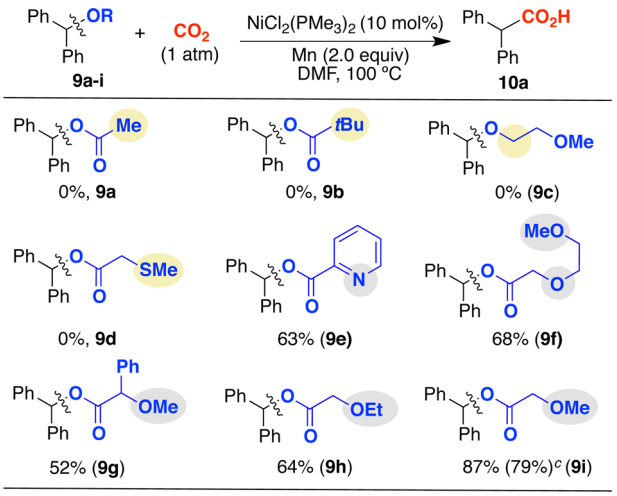
Table 6. Traceless Directing Groups on the Carboxylation of C(sp^3)−O Bonds[a,b]

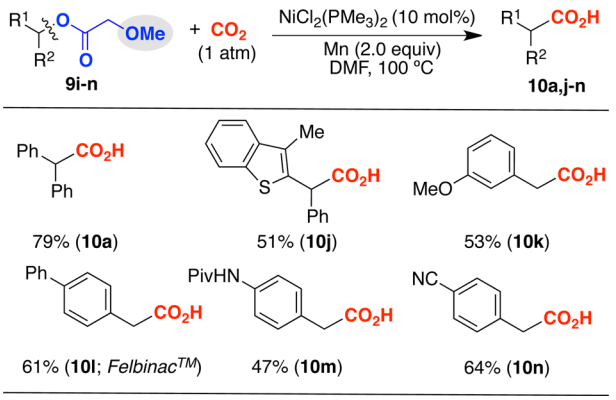


[a]**9a−i** (0.50 mmol), $NiCl_2(PMe_3)_2$ (10 mol %), Mn (2.0 equiv), CO_2 (1 atm), DMF (0.25 M) at 100 °C for 24 h. [b]HPLC yield using anisole as internal standard. [c]Isolated yield, average of at least two independent runs.

Corriu[25b,31] coupling events, reinforcing the notion that carboxylative protocols likely follow a different mechanistic scenario.

Prompted by these results, we next focused our attention on the preparative scope of the carboxylation of benzyl ester derivatives lacking π-extended systems. As depicted in Table 7,

Table 7. Ni-Catalyzed Carboxylation of Benzyl Esters with Traceless Directing Groups[a,b]

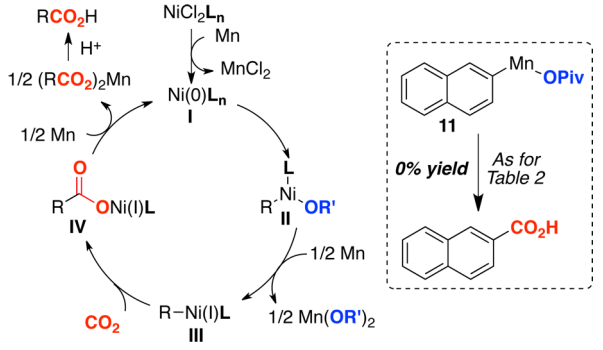


[a]As for Table 6. [b]Isolated yields, average of at least two independent runs.

the use of our traceless directing group strategy allowed for the preparation of differently substituted phenyl acetic acids in moderate to good yields, both employing secondary or primary benzyl ester derivatives. A variety of functional groups such as amides (**10m**), nitriles (**10n**) or heterocycles (**10j**) were perfectly accommodated, an observation that is in analogy with the functional group compatibility of the carboxylation events highlighted in Tables 3 and 5. It is worth mentioning that medicinally active Felbinac (**10l**) can be easily prepared by applying our optimized reductive carboxylation procedure. Unfortunately, however, the inclusion of hemilabile directing groups did not have a beneficial effect when attempting the carboxylation of regular aryl esters.[15] Overall, we believe the results in Tables 2−7 do not only show the excellent activity and functional group compatibility, but also the robustness of our carboxylative protocol for designing strategies en route to functionalized aromatic frameworks.

Mechanistic Proposal. Although a detailed mechanistic picture requires further investigations, we tentatively propose a catalytic cycle in analogy with previously developed Ni-catalyzed reductive carboxylation protocols.[9b,10a] We believe the reaction commences with an initial Mn-assisted reduction of the Ni(II) precatalyst followed by oxidative addition into the corresponding C(sp^2)−O or C(sp^3)−O bond (Scheme 7). The

Scheme 7. Mechanistic Proposal



resulting Ni(II) intermediate II[33] could be further reduced by Mn to yield a more nucleophilic Ni(I) species (III),[34] thus setting up the stage for a CO_2 insertion event.[35] A final transmetalation with Mn would regenerate the active Ni(0)L species (I) and a manganese carboxylate that upon hydrolytic workup delivers the corresponding carboxylic acid. Given the critical role of Mn,[36] we wondered whether our carboxylation protocol proceeded via *in situ* formed organomanganese species that might be generated from a transmetalation event of III with $Mn(OR')_2$. To such end, we prepared **11** following up a methodology described by Reetz.[37] Upon exposure of **11** to our optimized reaction conditions, we found no conversion to products. While such experiment might suggest that organomanganese species are not responsible for the observed reactivity, care must be taken in generalizing this; indeed, the preparation of **11** is invariably accompanied by the generation of salts, and their presence has shown to have a deleterious impact on reactivity.[15] The catalytic activity for the carboxylative reaction of **1a** was suppressed by the addition of radical scavengers such as TEMPO. Furthermore, we found that enantiomerically enriched **7l** provided racemic **8l**.[15] While these results could be explained by either organometallic or radical pathways, a mechanistic hypothesis based upon the involvement of single electron transfer processes (SET) seems the more plausible avenue.[38]

CONCLUSIONS

The rapidly expanding field of catalytic carboxylation processes, as evidenced by elegant developments in this area of expertise, nicely illustrates the enormous potential in synthetic organic chemistry. The method presented herein represents a significant step forward within the field of catalytic reductive carboxylation, thus increasing the ever-expanding repertoire of our synthetic arsenal. Our investigations study, for the first time, a new opportunity to unlock the potential of catalytic reductive events by using aryl or benzyl esters and CO_2 in a

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synergistic fashion, hence uncovering new reactivity profiles counterintuitive at first sight. The attractiveness of this study is based on the ability to couple readily available aryl or benzyl esters with CO_2 via the activation of traditionally considered inert C(sp^2)− and C(sp^3)−O bonds. In this manner, this technique can be visualized as a novel innovative bond disconnection synthetic strategy while providing a previously unrecognized opportunity for assembling valuable carboxylic acids. The operational simplicity, the absence of air- or moisture-sensitive reagents, together with the excellent preparative scope and chemoselectivity profile of this method holds great promise for the utilization of ester derivatives as a powerful alternative to the commonly used organic halides in catalytic carboxylation processes. Indeed, a number of relevant phenyl acetic acids bearing heterocyclic motifs (Tables 5 and 7), which were inaccessible by our previous Ni-catalyzed carboxylation of benzyl halides,[9b] are now within reach via C−O bond-cleavage using benzyl ester derivatives. We believe these results illustrate not only the unique outcome of C−O electrophiles as substrates but also significantly increase the flexibility in carboxylative protocols.

While many C−O bond-cleavage reactions remain limited to π-extended systems, this study demonstrates that a traceless hemilabile directing group overcomes such limitation when using C(sp^3)−O motifs, a yet unexplored avenue in catalytic reductive events using C−O electrophiles as counterparts. Although additional investigations are warranted to expand the scope and improve even further catalytic performance, we anticipate that the excellent selectivity profile of this new carboxylative protocol might serve as a reference source for practitioners in the field. Further studies regarding the extension to other coupling partners 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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