

Ni-catalyzed Carboxylation of C(sp²)– and C(sp³)–O Bonds with CO₂

Arkaitz Correa,[†] Thierry León,[†] and Ruben Martin^{*†§}

[†] Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007, Tarragona, Spain.

[§] Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys, 23, 08010, Barcelona, Spain

Supporting Information Placeholder

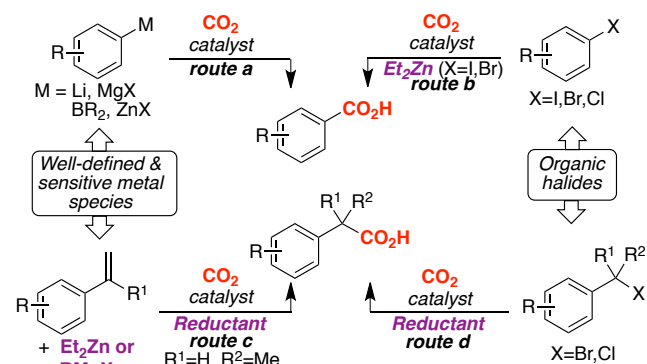
ABSTRACT: In recent years a significant progress has been made for the carboxylation of aryl and benzyl halides with CO₂, becoming convenient alternatives to the use of stoichiometric amounts of well-defined metal species. Still, however, most of these processes require the use of pyrophoric and air-sensitive 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, hence improving the flexibility in catalytic design while increasing our ever-growing synthetic arsenal. Herein, we report a new protocol that deals with the development of a synergistic activation of CO₂ and a rather challenging activation of inert C(sp²)–O and C(sp³)–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 without the use of any sensitive metal species. 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, inert C–O bond-cleavage 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 (CO₂) into valuable compounds has received considerable attention in recent years.² The growing interest of CO₂ 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, Blopess, 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 CO₂,^{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 Et₂Zn 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 (R¹=H), hence limiting the application profile of these rather appealing events.

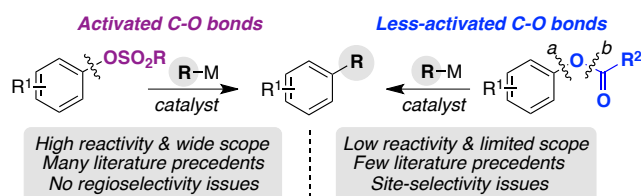
Scheme 1. Metal-catalyzed carboxylation events with CO₂



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 based systems in a catalytic fashion (Scheme 1, *routes b and d*).^{9,10} Although no doubt a step for-

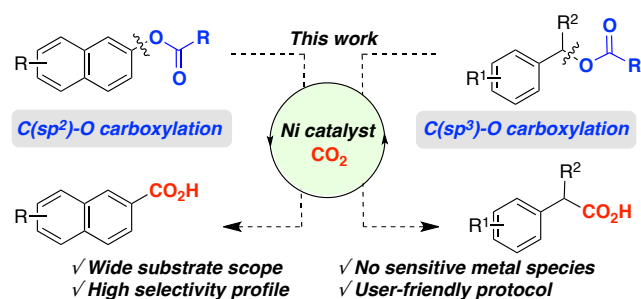
ward, such routes are mostly restricted to organic halide counterparts as well as the use, in many instances, of highly reactive, pyrophoric and air-sensitive Et_2Zn as reducing agent, thereby representing serious drawbacks to be overcome, both from a flexible and synthetic point of view. Therefore, 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.

Scheme 2. Catalytic activation of C–O bonds



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 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 partners¹²⁻¹³ with other nucleophiles like boronic acids or Grignard reagents, among others, 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 $\text{C}(\text{sp}^2)\text{--O}$ bond in aryl ester derivatives ($E = 106 \text{ Kcal/mol}$);^{11f} (b) the natural proclivity of aryl esters for hydrolysis under basic reaction conditions commonly employed in cross-coupling reactions;^{1d} (c) the activation of the C–O bond in aryl esters might occur at two different reaction sites (Scheme 2, *a vs b*), ending up in site-selectivity issues.¹¹ Despite recent advances in the field, to the best of our knowledge, *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.

Scheme 3. Carboxylation of $\text{C}(\text{sp}^2)\text{--O}$ and $\text{C}(\text{sp}^3)\text{--O}$ bonds.



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 $\text{C}(\text{sp}^2)\text{--O}$ but also more challenging $\text{C}(\text{sp}^3)\text{--O}$ 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 have 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 believe these results might have a significant impact in other related C–O bond-cleavage reactions by opening up new perspectives to be implemented in this area of expertise.

Table 1. Optimization of the reaction conditions for **1a**^a

Entry	[Ni] (x mol%)	L (y mol%)	Reducing agent	2a (%) ^b
1	$\text{NiCl}_2(\text{PCy}_3)_2$ (5)	none	Mn	0
2	$\text{NiCl}_2(\text{PPh}_3)_2$ (5)	none	Mn	0
3	$\text{NiCl}_2(\text{dppe})$ (5)	none	Mn	0
4	$\text{NiCl}_2(\text{dppp})$ (5)	none	Mn	0
5	$\text{NiCl}_2(\text{L1})$ (5)	none	Mn	17
6	$\text{NiCl}_2(\text{L1})$ (5)	L1 (10)	Mn	58
7	$\text{NiCl}_2\cdot\text{DME}$ (5)	L1 (15)	Mn	47
8	$\text{NiCl}_2\cdot\text{DME}$ (5)	L2 (15)	Mn	0
9	$\text{NiCl}_2\cdot\text{DME}$ (5)	L3 (15)	Mn	0
10	$\text{NiCl}_2\cdot\text{DME}$ (5)	L4 (15)	Mn	0
11	$\text{NiCl}_2\cdot\text{DME}$ (5)	L5 (15)	Mn	0
12	NiBr_2 (5)	L1 (15)	Mn	48
13	$\text{Ni}(\text{COD})_2$ (5)	L1 (15)	Mn	0
14	$\text{NiCl}_2(\text{L1})$ (5)	COD (10)	Mn	0
15	$\text{NiCl}_2(\text{L1})$ (7)	L1 (10)	Mn	70^c
16	$\text{NiCl}_2(\text{L1})$ (7)	L1 (10)	Zn	0
17	$\text{NiCl}_2(\text{L1})$ (7)	L1 (10)	Al	30
18	$\text{NiCl}_2(\text{L1})$ (7)	L1 (10)	none	0
19	none	none	Mn	0

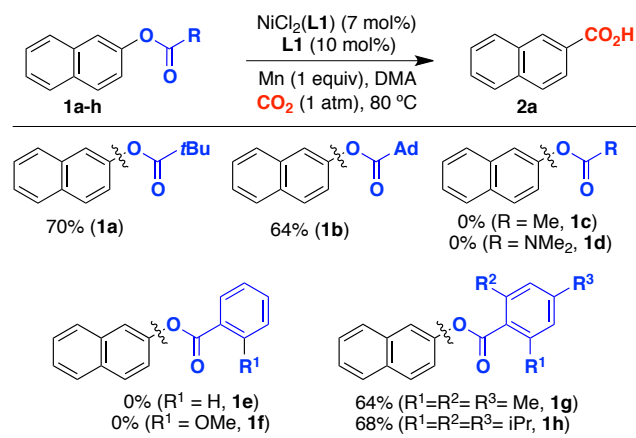
^a **1a** (0.50 mmol), Ni source (x mol%), Ligand (y mol%), Mn (1.0 equiv), CO_2 (1 atm), DMA (0.25 M) at 80 °C for 48 h. ^b HPLC yield using anisole as internal standard. ^c Isolated yield.

RESULTS AND DISCUSSION

Ni-catalyzed reductive carboxylation of $\text{C}(\text{sp}^2)\text{--O}$ 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 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

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 NiCl₂(**L1**) (**L1** = dppf) in combination with cheap Mn powder as reducing agent delivered significant amounts of **2a** (entry 5 vs entries 3-4). 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 NiCl₂·DME or NiBr₂ (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 CO₂ 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.

Table 2. Influence of the aryl ester motif on reactivity^{a,b}

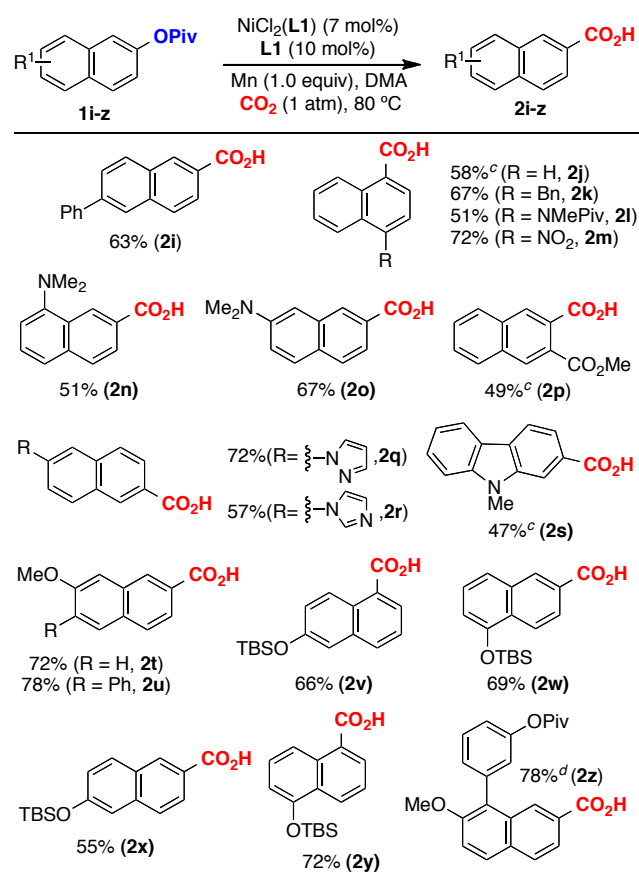


^a As for Table 1, entry 15. ^b Isolated yields, average of at least two independent runs.

Encouraged by these results, we decided to test whether other C(sp²)–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.

Table 3. Ni-catalyzed carboxylation of naphthyl pivalates^{a,b}

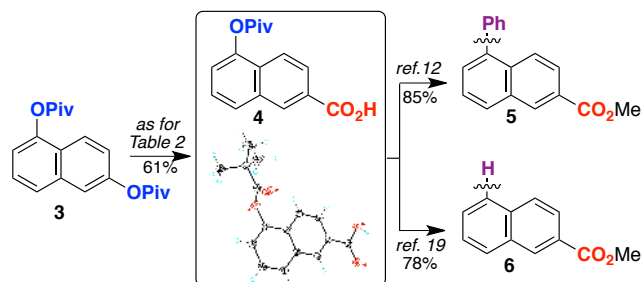


^a As for Table 1, entry 15. ^b Isolated yields, average of at least two independent runs. ^c NiCl₂(dppf) (10 mol%) was utilized. ^d Using 1.0 mmol of **1z**.

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 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 ethers²⁰

undergo C(sp²)-O bond-cleavage using Ni catalysts, we found that our carboxylative protocol could be conducted in 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-OSiR₃ bond-cleavage.¹¹ Of particular interest is **2z** in which we were able to discriminate among different C(sp²)-OPiv residues in high yield and that competitive carboxylation of other C-O bonds was not observed.²¹

Scheme 4. Sequential Ni-catalyzed C-O activation events



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 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.

Table 4. Optimization of reaction conditions for **7a**^a

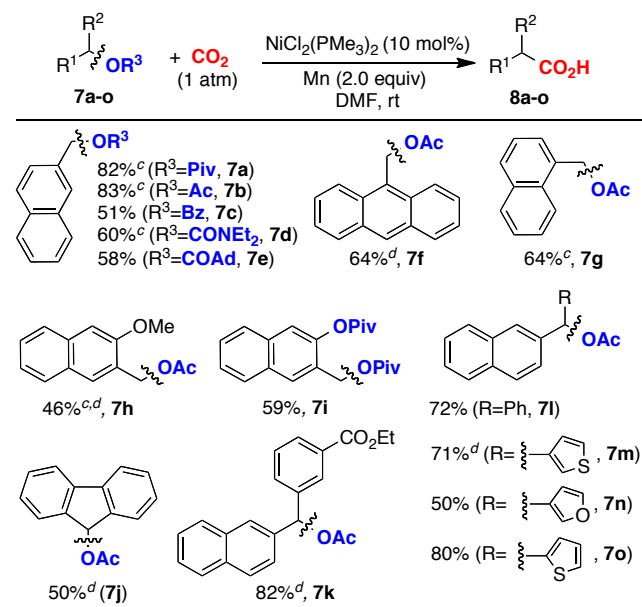
Entry	[Ni]	L (y mol%)	solvent	T (°C)	8a (%) ^b
1	NiCl ₂ (L1)	L1 (10)	DMA	80	0
2	NiCl ₂ (dppp)	dppp (10)	DMA	80	0
3	NiCl ₂ (PPh ₃) ₂	PPh ₃ (10)	DMA	80	0
4	NiCl ₂ (PCy ₃) ₂	PCy ₃ (10)	DMA	80	3
5	NiCl ₂ (PBU ₃) ₂	PBU ₃ (10)	DMA	80	0
6	NiCl ₂ (PMe ₃) ₂	PMe ₃ (10)	DMA	80	31
7	NiCl ₂ (PMe ₃) ₂	PMe ₃ (10)	DMA	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), CO₂ (1 atm), solvent (0.25 M) for 24 h. ^b HPLC yield using anisole as internal standard. ^c 48h. ^d In the absence of Mn. ^e Isolated yield.

Ni-catalyzed reductive carboxylation of benzylic C(sp³)-O bonds. Despite recent advances using benzyl hal-

ides or pseudohalides as coupling partners,^{1d,23} to the best of our knowledge *the direct reductive carboxylation of activated or non-activated C(sp³)-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,9b,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 NiCl₂(PMe₃)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 NiCl₂(PMe₃)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 PMe₃ allowed for obtaining **8a** in 82% isolated yield at room temperature (entry 13); while speculative, we propose that ligand dissociation might occur with PMe₃, 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.

Table 5. Ni-catalyzed carboxylation of benzylic C(sp³)-O bonds

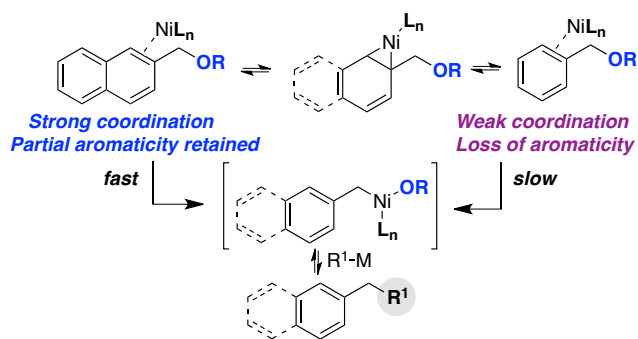


^a As for Table 4, entry 13 after 24 h reaction time. ^b Isolated yields, average of at least two independent runs. ^c 48h. ^d 50 °C.

Unlike the carboxylation of C(sp²)-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(sp³)-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(sp³)-O bonds (**7h**, **7i**) was nicely achieved in the presence of *ortho* C(sp²)-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}

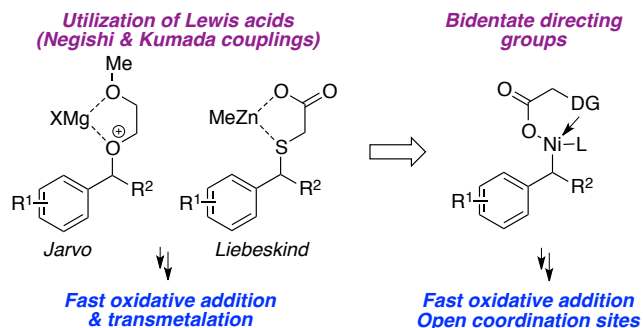
Scheme 5. Extended π -systems vs regular arenes



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 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 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 magni-

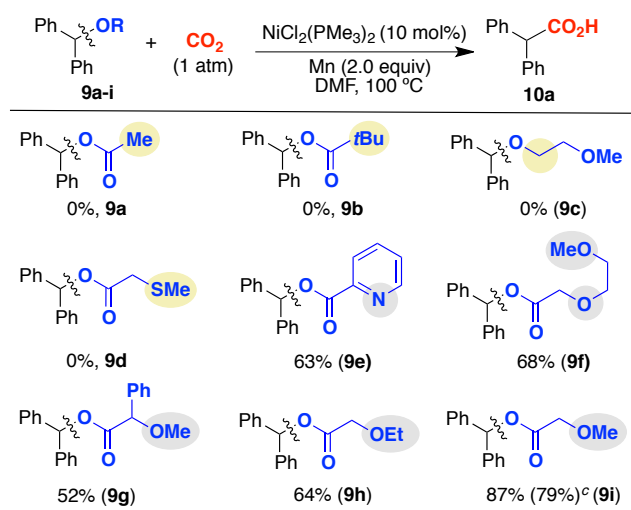
tude less reactive than π -extended systems, and their use constitutes a challenging goal in the C-O bond-cleavage arena. A closer look into Tables 3 and 5 indicates that a similar behavior was observed for our Ni-catalyzed carboxylation of C(sp²)-O and benzylic C(sp³)-O bonds. Consequently, a different strategy was envisioned to couple more challenging substrate combinations lacking a polyaromatic backbone.

Scheme 6. Traceless directing groups for C-O cleavage



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 coworkers 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 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 CO₂ and its subsequent insertion event.

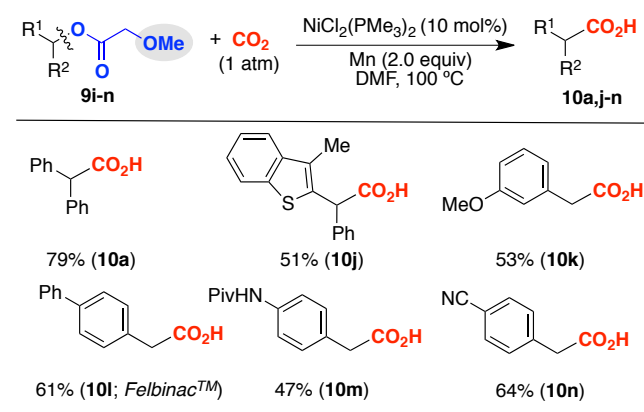
Table 6. Traceless directing groups on the carboxylation of C(sp³)-O bonds^{a,b}



^a **9a-i** (0.50 mmol), NiCl₂(PMe₃)₂ (10 mol%), Mn (2.0 equiv), CO₂ (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.

In order to verify our hypothesis, a variety of C(sp³)-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(sp³)-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-methoxyacetic 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-Corriu^{25b,31} coupling events, reinforcing the notion that carboxylative protocols likely follow a different mechanistic scenario.

Table 7. Ni-catalyzed carboxylation of benzyl esters with traceless directing groups^{a,b}



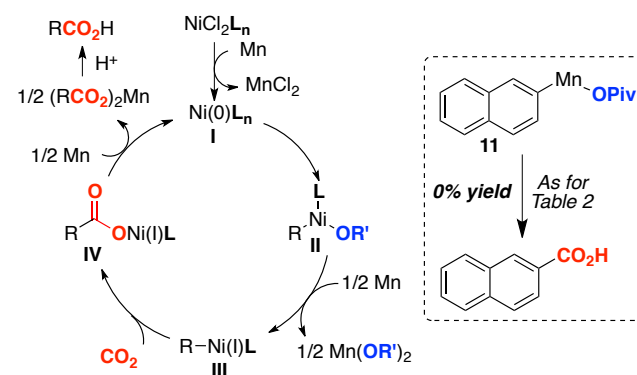
^a As for Table 6. ^b Isolated yields, average of at least two independent runs.

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, 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 prima-

ry 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 the medicinally active FelbinacTM (**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(sp²)-O or C(sp³)-O bond. The 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 CO₂ 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

Scheme 6. Mechanistic proposal



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 CO₂ in a 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 CO₂ via the activation of traditionally considered inert C(sp²)- and C(sp³)-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, 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 catalytic design 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(sp³)-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. We speculate that our study will lead to new knowledge in catalyst design, stimulate new concepts and ideas in one of the most vibrant, intellectually rewarding and promising avenues of research within organic and organometallic chemistry. 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>.

AUTHOR INFORMATION

Corresponding Author

rmartinromo@iciq.es

Funding Sources

The authors declare no competing financial interests

ACKNOWLEDGMENT

We thank ICIQ Foundation, the European Research Council (ERC-277883) and MICINN (CTQ2012-34054) for financial support. Johnson Matthey, Umicore and Nippon Chemical Industrial are acknowledged for a gift of metal and ligand sources. R.M and A.C thank MICINN for a RyC and JdC fellowship. We thank Eddy Martin and Eduardo Escudero for X-Ray crystallographic data.

REFERENCES

- (1) For selected reviews, see: (a) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177. (c) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (d) Diederich, F.; Meijere, A., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004.
- (2) For selected reviews, see: (a) Tsuji, Y.; Fujihara, T. *Chem. Commun.* **2012**, *48*, 9956. (b) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W.A.; Kühn, F. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8510. (c) Martin, R.; Kleij, A. W. *ChemSusChem* **2011**, *4*, 1259. (d) Huang, K.; Sun, C.-L.; Shi, Z.-J. *Chem. Soc. Rev.* **2011**, *40*, 2435. (e) Zhang, L.; Hou, Z. *Chem. Sci.* **2013**, *4*, 3395. (f) Aresta, M., Eds. *Carbon Dioxide as Chemical Feedstock*; Wiley-VCH: Weinheim, 2010. (g) Kielland, N.; Whiteoak, C. J.; Kleij, A. W. *Adv. Synth. Catal.* **2013**, *355*, 2115. (g) Cai, X.; Xie, B. *Synthesis* **2013**, 3305.
- (3) For selected recent carbon dioxide fixation processes, see: (a) Sasano, K.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2013**, *135*, 10954. (b) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314. (c) Li, S.; Yuan, W.; Ma, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2578. (d) Fujihara, T.; Xu, T.; Sema, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 523. (e) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251. (f) Ostapowicz, T. G.; Schmitz, M.; Krystof, M.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12119. (g) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 8858 and references therein.
- (4) Goossen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.
- (5) For a review, see: Correa, A.; Martin, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201.
- (6) For selected references: (a) Ukai, K.; Aoki, M.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 8706. (b) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697. (c) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792. (d) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 2681. (e) Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 7826. (f) Kobayashi, K.; Kondo, Y. *Org. Lett.* **2009**, *11*, 2035.
- (7) (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.
- (8) Selected examples: (a) Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900. (b) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14936. For a related Pd-catalyzed hydrocarboxylation of alkenes, see: (c) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254.
- (9) (a) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974. (b) León, T.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1221. For related electrochemical carboxylative processes of organic halides, see for example: (c) Amatore, C.; Jutand, A.; Khalil, F.; Nielsen, M. F. *J. Am.*

- Chem. Soc.* **1992**, *114*, 7076. (d) Ohkoshi, M.; Michinishi, J.-Y.; Hara, S.; Senboku, H. *Tetrahedron* **2010**, *66*, 7732.
- (10) (a) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9106. (b) Tran-Vu, H.; Daugulis, O. *ACS Catal.* **2013**, *3*, 2417.
- (11) For recent reviews: (a) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29. (b) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (c) Correa, A.; Cornella, J.; Martin, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 1878. (d) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (e) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 1728. (f) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486.
- (12) For selected references using aryl esters, see: (a) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (b) Quasford, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (c) Leowanawat, P.; Zhang, N.; Percec, V. *J. Org. Chem.* **2012**, *77*, 1018. (d) Ehle, A. R.; Zhou, Q.; Watson, M. P. *Org. Lett.* **2012**, *14*, 1202. (e) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124. (f) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929. (g) Tobisu, M.; Yamakawa, K.; Shimasaki, T.; Chatani, N. *Chem. Commun.* **2011**, 47, 2946. (h) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (i) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048.
- (13) For selected references using benzyl esters, see: (a) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (b) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303. (c) Huang, K.; Li, G.; Huang, W.-P.; Yu, D.-G.; Shi, Z.-J. *Chem. Commun.* **2011**, 47, 7224.
- (14) The carboxylation of certain activated aryl sulfonates (ArOTf and ArOTs) was recently disclosed by Tsuji (ref. 10a). For selected palladium-catalyzed carbonylation of sulfonates: (a) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (b) Cai, C.; Rivera, N. R.; Balsells, J.; Sidler, R. R.; McWilliams, J. C.; Shultz, C. S.; Sun, Y. *Org. Lett.* **2006**, *8*, 5161.
- (15) See Supporting Information for further details. In some cases, full conversion was not observed and small amounts of reduced arenes were detected in the crude mixtures.
- (16) For example, see: (a) Cornella, J.; Gómez-Bengoia, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997. (b) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattinig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992.
- (17) The use of ammonium salts as additives has found to be beneficial in Ni-catalyzed reductive couplings: (a) Piber, M.; Jensen, A. E.; Rotländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323. (b) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80. (c) Refs 9b, 10a.
- (18) For selected references: (a) Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4182. (b) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766. (c) Huang, K.; Yu, D.-G.; Zheng, S.-F.; Wu, Z.-H.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 786. (d) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (e) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750.
- (19) For recent selected Ni-catalyzed C-OME bond-cleavage reactions: (a) Wang, C.; Ozaki, T.; Takita, R.; Uchiyama, M. *Chem. Eur. J.* **2012**, *18*, 3482. (b) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439. (c) Álvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352. (d) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1438. (e) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.
- (20) Zhao, F.; Yu, D.-G.; Zhu, R.-Y.; Xi, Z.; Shi, Z.-J. *Chem. Lett.* **2011**, *40*, 1001.
- (21) Despite significant experimentation, traces of benzoic acids were only obtained when using 4-butyl or 4-(trifluoromethyl) phenyl pivalate. Chatani observed a similar behavior in which the lower reactivity of benzene motifs was attributed to the intermediacy of Meisenheimer-type complexes, see ref. 19e. For the performance of other ester motifs with different electronic and steric environments under a variety of different reaction conditions, see ref. 15.
- (22) The formation of the corresponding biscarboxylated product was not detected.
- (23) For recent reviews: (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (b) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.
- (24) The use of aryl pivalates possessing halogenated motifs resulted in no conversion to products together with significant amounts of dehalogenation. See ref. 15.
- (25) The use of extended π -systems has been a requisite for seminal discoveries in the area of inert C–O bond-cleavage reactions, with the vast majority of compounds in the substrate scope being extended π -systems. See for example: (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (b) Taylor, B. L.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790. (c) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083. (d) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097. (e) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566. (f) ref. 13a. (g) ref. 12e. (h) ref. 19e.
- (26) (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939. (c) Chatt, J.; Duncanson, L. A.; Venanzi, L. M. *J. Chem. Soc.* **1955**, 4456.
- (27) Brauer, D. J.; Krueger, C. *Inorg. Chem.* **1977**, *16*, 884.
- (28) The use of phenyl pivalates bearing *ortho* chelating groups such as pyrazole, ester, aldehyde, acetamide or ketone under our optimized conditions for the carboxylation of C(sp²)–O bonds did not lead to the targeted carboxylic acids; unreactive starting material was detected instead in all cases, regardless of the modifications performed in the experimental conditions.
- (29) For a recent review that highlights the particularly beneficial effects of bidentate directing groups, see: Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.
- (30) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449.
- (31) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293.
- (32) The use of the 4-pyridyl analogue of **9e** provided 72% of **10a**; therefore, we cannot rule a synergy between a chelating and inductive effect of the heteroatom in the ester moiety.
- (33) While this manuscript was under revision, Itami and Lei isolated the first arylnickel(II) pivalate complex bearing 1,2-bis(dicyclohexylphosphino)ethane (dcype) as ligand. See: Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384.
- (34) Mn-assisted reduction of Ni(II) to Ni(I) has been well-documented, see: (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442. (b)

Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920. (c) Prinsell, M. R.; Everson, D. A.; Weix, D. J. *Chem. Commun.* **2010**, *46*, 5743. (d) Shrestha, R.; Dorn, S. C. M.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 751. (e) ref. 10. For a recent theoretical study on the crucial role of Ni(I) species in the carboxylation of aryl chlorides, see: Sayyed, F. B.; Tsuji, Y.; Sakaki, S. *Chem. Commun.* **2013**, *49*, 10715.

- (35) We cannot rule out the intermediacy of Ni(0)L(CO₂) species. Indeed, Ni(0)L species have been reported to efficiently bind CO₂ to yield NiL(CO₂) complexes, see: (a) Aresta, M.; Nobile, C. F.; Albano, V. G.; Forni, E.; Manassero, M. *J. Chem. Soc., Chem. Commun.* **1975**, 636. (b) Aresta, M.; Nobile, C. F. *J. Chem. Soc., Dalton Trans.* **1977**, 708. (c) Amatore, C.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 2819.
- (36) For a review on the chemistry of organomanganese compounds, see: Cahiez, G.; Duplais, C.; Buendia, J. *Chem. Rev.* **2009**, *109*, 1434.
- (37) Reetz, M. T.; Haning, H.; Stanchev, S. *Tetrahedron Lett.* **1992**, *33*, 6963.
- (38) At present, we cannot rule out an alternative pathway consisting of the formation of **III** via a comproportionation event of **II** with **I**. A similar comproportionation event has been suggested in other C–O bond-cleavage reactions, see ref. 16a.

Carboxylation via C(sp²)-O or C(sp³)-O bond cleavage

