

Ni-Catalyzed Carboxylation of Unactivated Alkyl Chlorides with CO₂

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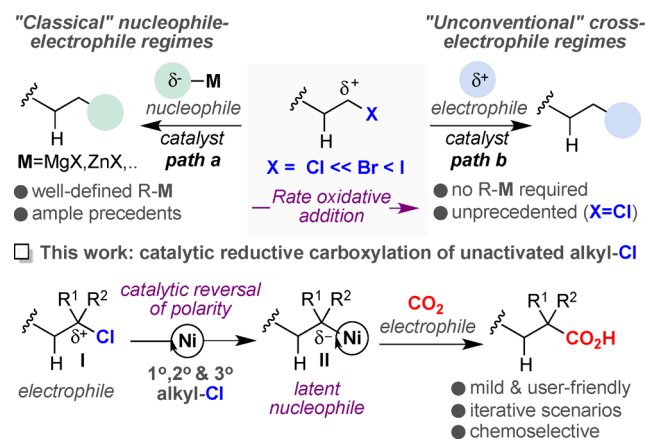
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S Supporting Information

ABSTRACT: A catalytic carboxylation of unactivated primary, secondary, and tertiary alkyl chlorides with CO₂ at atmospheric pressure is described. This protocol represents the first intermolecular cross-electrophile coupling of unactivated alkyl chlorides, thus leading to new knowledge in the cross-coupling arena.

Catalytic cross-electrophile coupling processes of organic (pseudo)halides have gained considerable momentum,¹ representing straightforward alternatives to classical nucleophilic/electrophilic regimes based on well-defined, and in many instances, air-sensitive organometallic reagents (Scheme 1, path

Scheme 1. Unactivated Alkyl Chlorides in Cross-Coupling



b vs path a).² While notorious difficult transformations have been developed, the formidable high activation energy required for effecting C(sp³)-Cl cleavage and the inherent proclivity of alkyl metal species toward parasitic β-hydride elimination or homodimerization pathways³ have contributed to the prevailing perception that unactivated alkyl chlorides cannot be utilized in intermolecular cross-electrophile events.^{4,5} If successful, however, such a largely void terrain not only would lead to new knowledge in retrosynthetic analysis but also would set the stage for iterative techniques with polyhalogenated backbones,⁶ a highly rewarding scenario that would dramatically improve our ever-expanding synthetic portfolio.

In recent years, carbon dioxide (CO₂) has gained considerable momentum as a C1 synthon in catalytic endeavors, holding promise to create new paradigms in

synthetic sequences.⁷ Among these, the ability to prepare carboxylic acids from CO₂ is particularly appealing due to the ubiquity of these recurrent motifs in a myriad of biologically relevant molecules.⁸ Prompted by the work of Osakada,⁹ we¹⁰ and others¹¹ have described catalytic carboxylation techniques of organic (pseudo)halides. Despite the advances realized, (a) the carboxylation of unactivated secondary or tertiary organic (pseudo)halides still constitutes a daunting, yet unsolved, challenge and (b) unactivated alkyl chlorides cannot be employed as coupling partners, neither in carboxylation events nor in intermolecular cross-electrophile coupling reactions.⁴ Herein, we describe the realization of all these challenges by designing a catalytic carboxylation that allows for the coupling of unactivated primary, secondary and even tertiary alkyl chlorides (Scheme 1, bottom). This protocol operates with an exquisite chemoselectivity profile at atmospheric pressure of CO₂ while obviating the need for stoichiometric organometallic reagents.

Our study began by evaluating the reaction of UV-active **1a** with CO₂ (1 atm). Traces of **2a**, if any, were detected under previously reported carboxylation events,^{10,11} reinforcing the notion that the carboxylation of **1a** would be far from trivial. After some experimentation,¹² a combination of NiBr₂·glyme, **L4**, TBAB, and Mn in DMF at 60 °C provided the best results, delivering **2a** in 85% yield.¹³ As expected, the nature of the ligand backbone exerted a profound influence on the reaction outcome. Indeed, rigid phenanthroline backbones possessing *ortho*-substituents were particularly suited for our purposes, minimizing β-hydride elimination or homodimerization pathways (Table 1, entries 4–6). As shown in entries 7 and 8, the use of other precatalysts or solvents had a deleterious effect.¹² While one might argue that TBAB might be triggering a Br/Cl exchange en route to alkyl-Ni(II)Br species,¹⁴ the successful carboxylation with TBAC or LiCl suggests otherwise (Table 1, entries 9–10).¹⁵ Notably, 5–10% yield of **2a** was obtained with **1a**-Br or **1a**-I, resulting predominantly in β-hydride elimination or homodimerization. As expected, control experiments revealed that all variables were critical for success (entries 11–12).¹⁶

Encouraged by these results, we turned our attention to explore the generality of our protocol with a host of unactivated alkyl chlorides (Table 2). In line with our expectations, the reaction was rather general and distinguished by an exquisite chemoselectivity profile, as acetals (**2b**), esters (**2c–2e**, **2j**, and

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Table 1. Optimization of the Reaction Conditions^a

Entry	Deviation from standard conditions	2a (%) ^b
1	none	92 (85 ^c ,67 ^d)
2	L1 instead of L4	0
3	L2 instead of L4	37
4	L3 instead of L4	53
5	L5 instead of L4	60
6	L6 instead of L4	28
7	Ni(COD) ₂ as catalyst	80
8	DMA as solvent	65
9	LiCl as additive at 90 °C	58
10	TBAC as additive	32
11	No TBAB	34
12	No NiBr ₂ ·glyme, no L4, or no Mn	0

^aR = H (L1); R = Me (L2)
^bR¹ = Me; R² = H, L3
^cR¹ = *n*-Bu; R² = Me, L4
^dR¹ = *n*-Bu; R² = Ph, L5
^eR¹ = Me; R² = Me, L6

^a1a (0.20 mmol), NiBr₂·glyme (10 mol %), L4 (24 mol %), Mn (0.60 mmol), TBAB (0.20 mmol) in DMF (0.16 M) at 60 °C under CO₂ (1 atm). ^bHPLC yields using anisole as internal standard. ^cIsolated yield. ^dNiBr₂·glyme (5 mol %).

Table 2. Carboxylation of Unactivated Alkyl Chlorides^{a,b}

^aprimary alkyl chlorides
^bsecondary & tertiary alkyl chlorides

2a, 85%	2b, 79%	2c, 81%	2d (X=O), 57%	2e (X=S), 68%
2f (R=NHCOMe), 70%	2g (R=COMe), 78%	2h (R=CHO), 74%	2i (77%)	2j (83%)
2k, 73%	2l (56%)	2m (X=(CH ₂) ₂ OH), 60%	2n (X=OPiv), 85%	2o (X=NHBoc), 68%
2p (X=OTBDPS), 51%	2q (X=OH), 77%, 70% ^c	2r (X=OPiv), 79%	2s (50%)	2t, 84%
2u, 73%	2v, 53%	2w, 74% ^d	2x, 61% ^{d,e}	2y, 62% ^{d,f}
2z, 41% ^{d,g}				

^aAs Table 1, entry 1. ^bIsolated yields, average of two independent runs. ^c1q (1.5 mmol). ^dNiBr₂·diglyme (10 mol %), L6 (24 mol %), LiCl (1 equiv), 90 °C. ^e50 °C. ^f70 °C. ^gUsing Zn (3 equiv) and TBAB (2 equiv) in DMA at 80 °C.

2n), aryl fluorides (2c), heterocycles (2d, 2e, and 2j), amides (2f), aldehydes (2h), ketones (2g), silyl ethers (2p), nitriles (2t), carbamates (2o), or alkenes (2u) could all be perfectly accommodated. Interestingly, free aliphatic alcohols (2m and 2v) or even their most acidic phenol congeners do not interfere (2q), thus illustrating the potential of our methodology in protecting-group-free strategies. While C–O electrophiles have been utilized in Ni-catalyzed cross-coupling reactions,^{17,18} we found exclusive formation of 2n and 2r, thus providing an additional handle for further functionalization. Although the available literature data suggested that the carboxylation of unactivated secondary or tertiary alkyl halides would be a chimera, we found that 2w–2y were within reach under a Ni/L6 regime using LiCl as additive, even as single diastereoisomers as univocally shown by X-ray crystallography (2x). Albeit in lower yields, the preparation of 2z¹⁹ constitutes a rare example of a cross-electrophile coupling of unactivated tertiary alkyl halides,²⁰ showcasing the full potential of our catalytic protocol. With these conditions in hand, we wondered whether unactivated alkyl chlorides containing alkyne motifs on the side chain could trigger a CO₂ insertion at distal reaction sites. As shown in Table 3, this was indeed the case, and carbocyclic

Table 3. Cascade Cyclization/Carboxylation Events^{a,b}

4a (R=H), 46%	4c (X=H), 77% ^c	4e':4e (3.6:1), 59% ^d	4f':4f (7.1:1), 42% ^d
4b (R=Me), 55%	4d (X=OMe), 76%	4e:4e (2.2:1), 69% ^e	4f:4f (4.6:1), 60% ^e

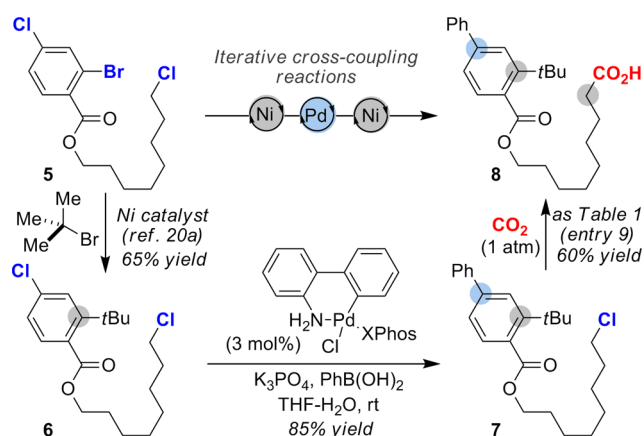
^aAs Table 1 (entry 1), but using 3 mol % loadings and L5. ^bIsolated yields, average of at least two independent runs. ^c3c (3 mmol). ^dUsing L6 at 70 °C. ^e90 °C.

skeletons possessing a carboxylic acid within a rather elusive tetrasubstituted olefin framework were all obtained in good yields (4a–4f) at 3 mol % catalyst loadings, even at 3 mmol scale (4c) using L5. Particularly noteworthy was the observation that a formal *anti*-carbometalation motion²¹ was favored when utilizing secondary alkyl chlorides based on a Ni/L6 couple (4e and 4f).²²

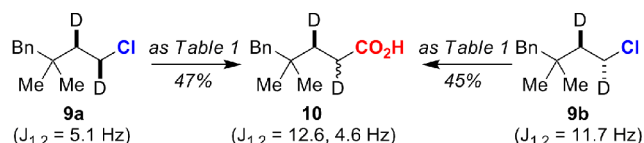
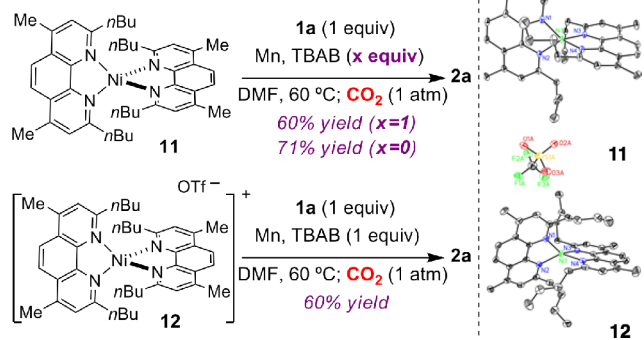
The feasibility of promoting an intermolecular cross-electrophile coupling reaction with unactivated alkyl chlorides suggested that our methodology could open up possibilities in iterative cross-coupling scenarios of polyhalogenated backbones.⁶ As illustrated in Scheme 2, 6 could be selectively prepared from densely halogenated 5 in a catalytic cross-electrophile coupling with *tert*-butyl bromide.^{20a} Subsequently, Suzuki–Miyaura reaction using a Buchwald protocol under a Pd/XPhos regime²³ resulted in 7, which ultimately generated 8 upon simple exposure to our carboxylation conditions based on L4. Taken together, the results of Tables 2–3 and Scheme 2 tacitly illustrates the prospective impact of this methodology in both cross-electrophile couplings and catalytic carboxylation processes.

Next, we decided to gather indirect evidence about the mechanism by studying the stereochemical course of 9a and 9b (Scheme 3). As shown, an erosion of stereochemical integrity

Scheme 2. Iterative Coupling with Polyhalogenated Motifs



Scheme 3. Mechanistic Experiments

Stereochemical course of **9a** and **9b**Stoichiometric studies with **11** and **12**

was observed regardless of the substrate utilized, suggesting that single-electron transfer processes (SET) and Ni(I) species might come into play.^{24,25} Taking this into consideration, we turned our attention to study the reactivity of the putative Ni(0)(L₄)₂ (**11**) and Ni(I)(L₄)₂ (**12**) species, both of which could easily be prepared from Ni(COD)₂.^{10a} As expected, **11** was found to be catalytically competent as reaction intermediates, delivering **2a** in 80% yield. Importantly, **2a** was obtained in comparable yields when using stoichiometric amounts of **11** or **12**, either in the absence or in the presence of TBAB, thus confirming that TBAB was not essential for the reaction to occur and leaving a reasonable doubt about the involvement of in situ generated alkyl-Ni(II)Br species.²⁶ Although we cannot rule out other conceivable pathways,²⁷ at present we propose a catalytic scenario consisting of the initial formation of alkyl-Ni(II)Cl species followed by comproportionation with Ni(0)L_n en route to putative alkyl-Ni(I) species²⁸ that might rapidly insert CO₂ into the C(sp³)-Ni bond prior to SET mediated by Mn,²⁹ ultimately recovering back the propagating Ni(0)L_n species.³⁰

In summary, we have documented an unconventional intermolecular cross-electrophile coupling of unactivated primary, secondary, or even tertiary alkyl chlorides with CO₂ at atmospheric pressure. The salient features of this novel

transformation are the exquisite chemoselectivity profile, mild conditions, and ease of execution, allowing for cascade processes or iterative scenarios. Further extensions to other intermolecular cross-electrophile processes are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04088.

Crystallographic data (CIF)

Crystallographic data (CIF)

Crystallographic data (CIF)

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(12) See [Supporting Information](#) for details.

(13) Traces of β -hydride elimination were observed in the crude mixtures under our optimized reaction conditions.

(14) Under the limits of detection, no alkyl bromide was detected through the course of the reaction of **1a** with TBAB by HPLC monitoring in the absence or presence of CO₂.

(15) Ammonium halides have been proposed to speed up electron-transfer processes from Mn to the metal center: (a) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80 and ref 11f.

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(24) In line with this notion, significant inhibition was observed with radical scavengers such as TEMPO or BHT. The presence of radical species gains credence by observing 5-*exo*-trig cyclization at different Ni/L4 loadings when employing 6-chloro-1-hexene as substrate, suggesting that a radical-escape rebound mechanism might be occurring.

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(26) Importantly, a stoichiometric reaction of **1a** with **11** in the absence of Mn revealed that CO₂ insertion into the C(sp³)-Ni bond occurred. This observation is noteworthy, as all previous carboxylations of unactivated alkyl electrophiles required the presence of Mn, even with stoichiometric amounts of Ni complexes (refs 10c and 10e),

arguably indicating that a different mechanism takes place with alkyl chloride counterparts; see ref 12.

(27) At present, direct CO₂ insertion into the C(sp³)-Ni(II)Cl bond or *in situ* formation of alkyl-Ni(I) species via SET mediated by Mn cannot be excluded.

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