

# Communication

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# Ni-catalyzed Carboxylation of Unactivated Alkyl Chlorides with CO<sub>2</sub>

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Supporting Information Placeholder

**ABSTRACT:** A catalytic carboxylation of unactivated primary, secondary & tertiary alkyl chlorides with CO<sub>2</sub> 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,<sup>1</sup> representing straightforward alternatives to classical nucleophilic/electrophilic regimes based on welldefined, and in many instances, air-sensitive organometallic reagents (Scheme 1, path b vs path a).<sup>2</sup> While notorious difficult transformations have been developed, the formidable high activation energy required for effecting  $C(sp^3)$ -Cl cleavage and the inherent proclivity of alkyl metal species towards parasitic β-hydride elimination or homodimerization pathways<sup>3</sup> has contributed to the prevailing perception that unactivated alkyl chlorides cannot be utilized in intermolecular cross-electrophile events.<sup>4,5</sup> If successful, however, such a largely void terrain would not only lead to new knowledge in retrosynthetic analysis, but also would set the stage for iterative techniques with polyhalogenated backbones,<sup>6</sup> a highly rewarding scenario that would dramatically improve our ever-expanding synthetic portfolio.





In recent years, carbon dioxide (CO<sub>2</sub>) has gained considerable momentum as C1 synthon in catalytic endeavors, holding promise to create new paradigms in synthetic sequences.<sup>7</sup> Among these, the ability to prepare carboxylic acids from  $CO_2$  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,<sup>9</sup> we<sup>10</sup> and others<sup>11</sup> 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.<sup>4</sup> 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 CO<sub>2</sub> while obviating the need for stoichiometric organometallic reagents.

### Table 1. Optimization of the Reaction Conditions.<sup>a</sup>



<sup>*a*</sup> **1a** (0.20 mmol), NiBr<sub>2</sub>·glyme (10 mol%), **L4** (24 mol%), Mn (0.60 mmol), TBAB (0.20 mmol) in DMF (0.16 M) at

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60 °C under CO<sub>2</sub> (1 atm). <sup>b</sup> HPLC yields using anisole as internal standard. <sup>c</sup> Isolated yield. <sup>d</sup>NiBr<sub>2</sub>·glyme (5 mol%).

Our study began by evaluating the reaction of UV-active 1a with  $CO_2$  (1 atm). Traces of 2a, if any, were detected under previously reported carboxylation events,<sup>10,11</sup> reinforcing the notion that the carboxylation of 1a would be far from trivial. After some experimentation,<sup>12</sup> a combination of NiBr<sub>2</sub>·glyme, L4, TBAB, Mn in DMF at 60 °C provided the best results, delivering 2a in 85% yield.<sup>13</sup> As expected, the nature of the ligand backbone exerted a profound influence on the reaction outcome. Indeed, rigid phenanthroline backbones possessing orthosubstituents were particularly suited for our purposes, minimizing  $\beta$ -hydride elimination or homodimerization pathways (entries 4-6). As shown in entries 7 and 8, the use of other precatalyts or solvents had a deleterious effect.<sup>12</sup> While one might argue that TBAB might be triggering a Br/Cl exchange en route to alkyl-Ni(II)Br species,<sup>14</sup> the carboxylation with TBAC or LiCl suggests otherwise (entries 9-10).<sup>15</sup> Notably, 5-10% yield of 2a was obtained with 1a-Br or 1a-I, resulting predominantlv in β-hvdride elimination or homodimerization. As expected, control experiments revealed that all variables were critical for success (entries 11-12).<sup>16</sup>

### Table 2. Carboxylation of Unactivated Alkyl Chlorides.<sup>*a,b*</sup>



<sup>*a*</sup> As Table 1, entry 1. <sup>*b*</sup> Isolated yields, average of two independent runs. <sup>*c*</sup> **1q** (1.5 mmol). <sup>*d*</sup> NiBr<sub>2</sub>·diglyme (10 mol%), **L6** (24 mol%), LiCl (1 equiv), 90 °C. <sup>*e*</sup> 50 °C. <sup>*f*</sup> 70 °C. <sup>*g*</sup> Using Zn (3 equiv) and TBAB (2 equiv) in DMA at 80 °C.

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, 2d, 2e and 2j), aryl fluorides (2c), heterocycles (2d, 2e and 2j), amides (2f), aldehydes (2h), ketones (2g), silvl ethers (2p), nitriles (2t), carbamates (20) 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,<sup>17,18</sup> 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  $2z^{19}$ constitutes a rare example of a cross-electrophile coupling of unactivated tertiary alkyl halides,<sup>20</sup> 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 CO<sub>2</sub> insertion at *distal* reaction sites. As shown in Table 3, this was indeed the case, and carbocyclic 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 motion<sup>21</sup> was favored when utilizing secondary alkyl chlorides based on a Ni/L6 couple (4e and 4f).<sup>22</sup>

## Table 3. Cascade Cyclization/Carboxylation Events.



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

<sup>*a*</sup> As Table 1 (entry 1), but using 3 mol% loadings and L5. <sup>*b*</sup> Isolated yields, average of at least two independent runs. <sup>*c*</sup> **3c** (3 mmol). <sup>*d*</sup> Using L6 at 70 °C. <sup>*e*</sup> 90 °C.

The feasibility of promoting an *intermolecular* crosselectrophile coupling reaction with unactivated alkyl chlorides suggested that our methodology could open up possibilities in iterative cross-coupling scenarios of polyhalogenated backbones.<sup>6</sup> As illustrated in Scheme 2, **6** could be selectively prepared from densely halogenated **5** in a catalytic cross-electrophile coupling with *tert*butyl bromide.<sup>20a</sup> Subsequently, Suzuki-Miyaura reaction using a Buchwald protocol under a Pd/XPhos regime<sup>23</sup> resulted in **7**, which ultimately generated **8** upon simple exposure to our optimized 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.

Scheme 2. Iterative Coupling with Polyhalogenated Motifs.



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 was observed regardless of the substrate utilized, suggesting that single-electron transfer processes (SET) and Ni(I) species might come into play.<sup>24,25</sup> 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  $Ni(COD)_2$ .<sup>10a</sup> 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.<sup>26,</sup> Athough we cannot rule out other conceivable pathways,<sup>27</sup> 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<sub>n</sub> en route to putative alkyl-Ni(I) species<sup>28</sup> that might rapidly insert  $CO_2$  into the C(sp<sup>3</sup>)–Ni bond prior SET mediated by Mn,<sup>29</sup> ultimately recovering back the propagating  $Ni(0)L_n$  species.<sup>30</sup>

#### Scheme 3. Mechanistic Experiments.



In summary, we have documented an unconventional *intermolecular* cross-electrophile coupling of *unactivat-ed* primary, secondary or even tertiary alkyl chlorides with  $CO_2$  at atmospheric pressure. The salient features of this novel transformation are the exquisite chemose-lectivity 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**. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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No competing financial interests have been declared.

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