

## Remote $sp^2$ C–H Carboxylation via Catalytic 1,4-Ni Migration with $\text{CO}_2$

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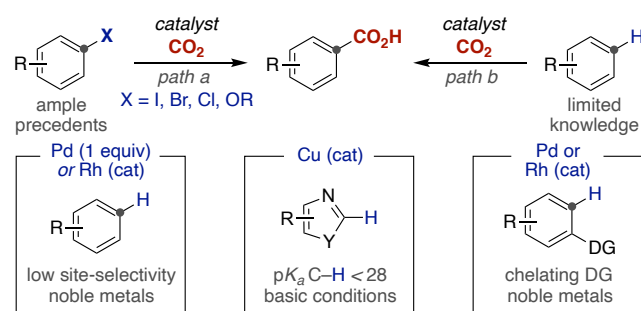
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Supporting Information Placeholder

**ABSTRACT:** A remote catalytic reductive  $sp^2$  C–H carboxylation of arenes with  $\text{CO}_2$  (1 bar) via 1,4-Ni migration is disclosed. This protocol constitutes the first catalytic 1,4-Ni migration reported to date, thus offering new vistas in the Ni-catalyzed reductive coupling arena while providing an unconventional new platform for incorporating electrophilic sites at remote  $sp^2$  C–H linkages.

The recent years have witnessed the design of catalytic reductive carboxylations of aryl (pseudo)halides with  $\text{CO}_2$  en route to benzoic acids,<sup>1</sup> privileged motifs in biologically-active molecules.<sup>2</sup> Although remarkable levels of sophistication have been reached, prefunctionalization at the targeted  $sp^2$  reaction site is required prior to  $\text{CO}_2$  insertion (Scheme 1, *path a*).<sup>1</sup> Beyond any doubt, the pursuit of an alternative catalytic carboxylation at previously unfunctionalized  $sp^2$  C–H sites might constitute, conceptually and practicality aside, a worthwhile endeavor for chemical invention (*path b*).<sup>3</sup>

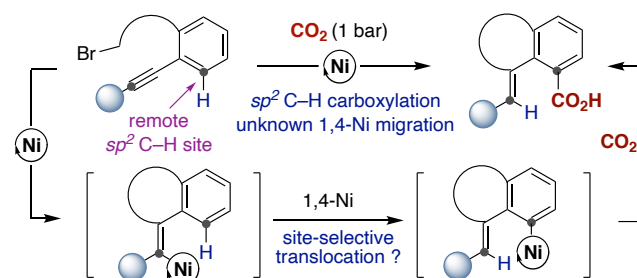
### Scheme 1. $sp^2$ Carboxylation Reactions with $\text{CO}_2$ .



Prompted by a seminal work of Fujiwara with stoichiometric amounts of Pd complexes,<sup>4</sup> significant efforts have been made to unlock the potential of  $sp^2$  C–H carboxylations by employing either acidic  $sp^2$  C–H linkages<sup>5</sup> or strategies requiring chelating groups (Scheme 1, *bottom*).<sup>6</sup> However, extensions to non-acidic  $sp^2$  C–H bonds are beyond reach in the former, whereas the absence of

chelating groups results in site-selectivity issues, invariably requiring noble metals and/or stoichiometric organometallic reagents (*bottom left*).<sup>7</sup> These observations have contributed to the perception that a *de novo* catalytic  $sp^2$  C–H carboxylation strategy without recourse to noble metals or organometallics might provide fundamentally new knowledge in both  $sp^2$  C–H functionalization and carboxylation processes. Under this premise, we wondered whether a new catalytic blueprint could be designed via a cascade-type process based on a site-selective 1,4-Ni migration,<sup>8</sup> thus setting the basis for a formal  $\text{CO}_2$  insertion at remote  $sp^2$  C–H bonds (Scheme 2). At the outset of our investigations, however, it was unclear whether such a strategy could be implemented, as (1) *catalytic* 1,4-Ni translocation<sup>9</sup> remains an unknown cartography in cross-coupling reactions,<sup>10–14</sup> and (2) site-selectivity issues might come into play due to competitive catalytic carboxylation at the  $sp^3$  C–Br site<sup>15</sup> or at the alkyne motif.<sup>16</sup> If successful, we recognized that such a scenario might offer a conceptually new reactivity mode in the reductive cross-coupling arena for tackling the functionalization of otherwise inaccessible  $sp^2$  C–H reaction sites.<sup>17</sup> Herein, we report the successful realization of this goal. Our protocol is characterized by its mild conditions, wide substrate scope – including challenging substrate combinations – without the need for handling air- or moisture sensitive reagents, and an exquisite site-selectivity pattern.

### Scheme 2. $sp^2$ C–H carboxylation via 1,4-Ni Migration.



Our investigations began by evaluating the remote  $sp^2$  C–H carboxylation of **1a** with  $\text{CO}_2$  (Table 1). As expected, conditions previously employed for the reductive carboxylation of aryl halides failed to provide even traces of **2a**,<sup>18</sup> mainly resulting in statistical mixtures of carboxylic acids arising from  $\text{CO}_2$  insertion at the vinyl motif (*E,Z*-**2a'**). After judicious choice of the reaction parameters, a combination of  $\text{NiBr}_2$ ·diglyme, **L5** and  $\text{Mn}_{89}\text{Cr}_{11}$  was found to be critical for success,<sup>19</sup> delivering **2a** in 77% yield with an excellent site-selectivity profile (94:6).<sup>20</sup> As shown in entries 2-5, subtle changes in the electronic or steric environment of the 2,2'-bipyridine core had a non-negligible impact on reactivity.<sup>21</sup> Strikingly, erosion in both yield and site-selectivity was observed when employing metal reductants other than  $\text{Mn}_{89}\text{Cr}_{11}$  (entries 6-8).<sup>22</sup> While one might argue that the presence of Cr atoms might dictate the site-selectivity pattern, the results shown in entries 7 and 8 indicate otherwise.<sup>14</sup> At present we have no explanation for this behavior. While inferior results were found with  $\text{Ni}(\text{cod})_2$  or DMSO (entries 9,10), no erosion in yield or selectivity was found when utilizing air- and moisture-stable  $\text{NiBr}_2(\text{L5})_2$ , constituting an additional bonus from a user-friendly standpoint (entry 11).

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

entry	deviation	standard conditions	2a (%) <sup>b</sup>	2a' (%) <sup>b</sup>
1	none		77	5
2	L1 instead of L5		0	0
3	L2 instead of L5		75	8
4	L3 instead of L5		56	6
5	L4 instead of L5		19	7
6	Mn instead of MnCr		40	9
7	using Mn/CrCl <sub>3</sub> (10 mol%)		43	14
8	using Mn/CrCl <sub>2</sub> (10 mol%)		3	45
9	using Ni(cod) <sub>2</sub> as catalyst		64	4
10	DMSO instead of DMF		0	0
11	using $\text{NiBr}_2(\text{L5})_2$ (10 mol%)		77 (80%) <sup>c</sup>	5

<sup>a</sup> **1a** (0.20 mmol),  $\text{NiBr}_2$ ·diglyme (10 mol%), **L5** (20 mol%), MnCr alloy (0.25 mmol) in DMF (0.2 M) at 15 °C under  $\text{CO}_2$  (1 atm). <sup>b</sup> Determined by <sup>1</sup>H NMR analysis using trimethoxybenzene as internal standard. <sup>c</sup> Isolated yield

Encouraged by these findings, we turned our attention to studying the generality of our cascade process with a host of unactivated alkyl bromides. As evident from the results compiled in Table 2, structures containing thioethers (**2d**), methoxy arenes (**2b**), trifluoromethylated derivatives (**2c**, **2i**) or heterocycles (**2o**) could perfectly be tolerated. Even aryl halides (**2g**, **2h** and **2r**) or organoboranes (**2e**) could be accommodated, thus constituting an orthogonal gateway for subsequent manipulation via cross-coupling reactions. Notably, acetylenes end-capped with either sterically hindered arenes (**2m**) or aliphatic motifs (**2j-2l**) posed no problems. Equally relevant was the observation

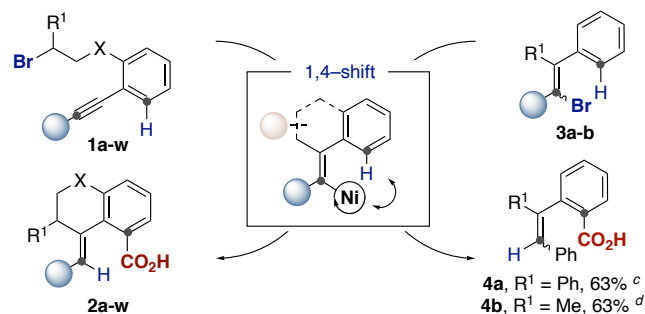
that the targeted carboxylation occurred regardless of the steric properties at the acetylene backbone or the employment of secondary unactivated alkyl bromides (**2p**, **2q**). Interestingly, the inclusion of different substitution patterns on the arene backbone did not interfere with productive 1,4-migration, albeit in lower yields (**2r**, **2s**).<sup>23</sup> The successful carboxylation of silicon-tethered alkyl bromides is particularly important, as the corresponding carboxylic acids **2t-2w** could be homologated via C–Si cleavage at later stages, thus easily accessing non-fused analogues (Scheme 4, *bottom*).

**Table 2.  $sp^2$  C–H Carboxylation of Alkyl Bromides.<sup>a,b</sup>**

<b>2a</b> (R=H), 81%	<b>2d</b> (R=SMe), 57%	<b>2f</b> (R' <sup>1</sup> =Me; R''=H), 88%
<b>2b</b> (R=OMe), 82%	<b>2e</b> (R=BPIn), 61%	<b>2g</b> (R' <sup>1</sup> =F; R''=H), 84%
<b>2c</b> (R=OCF <sub>3</sub> ), 55%		<b>2h</b> (R' <sup>1</sup> =Cl; R''=H), 77%
		<b>2i</b> (R' <sup>1</sup> =Me; R''=CF <sub>3</sub> ), 81% <sup>c</sup>
<b>2j</b> (R=CH <sub>2</sub> Cp), 81%		
<b>2k</b> (R=Bn), 62%		
<b>2l</b> (R=Cy), 79%		
<b>2m</b> (R=Mes), 84%		
<b>2n</b> (R=C <sub>6</sub> H <sub>5</sub> O <sub>2</sub> ), 58%		
<b>2o</b> (R=3-Th), 71% <sup>d</sup>		
		<b>2p</b> (R' <sup>1</sup> =Me), 84%
		<b>2q</b> (R' <sup>1</sup> =Et), 81%
<b>2r</b> (R' <sup>1</sup> =H; R''=F), 40%	<b>2t</b> (R <sup>2</sup> =Ph), 58% <sup>e</sup>	<b>2w</b> , 36% <sup>f</sup>
<b>2s</b> (R' <sup>1</sup> =OMe; R''=H), 56%	<b>2u</b> (R <sup>2</sup> = <i>p</i> -OMeC <sub>6</sub> H <sub>4</sub> ), 63% <sup>e</sup>	
	<b>2v</b> (R <sup>2</sup> =CH <sub>2</sub> Cp), 64% <sup>e</sup>	

<sup>a</sup> As Table 1, entry 11. <sup>b</sup> Isolated yields, average of two runs, **2a-w**:**2a-w'** ≥ 90:10. <sup>c</sup> **2i**:**2i'** = 87:13. <sup>d</sup> **2o**:**2o'** = 76:26. <sup>e</sup> **L2** (20 mol%) & MnCr (2.5 equiv). <sup>f</sup>  $\text{NiBr}_2$ ·diglyme (15 mol%) **L2** (30 mol%) & MnCr (2.5 equiv), **2w**:**2w'** = 80:20.

**Scheme 3.  $sp^2$  C–H Carboxylation of Vinyl Bromides.<sup>a,b</sup>**

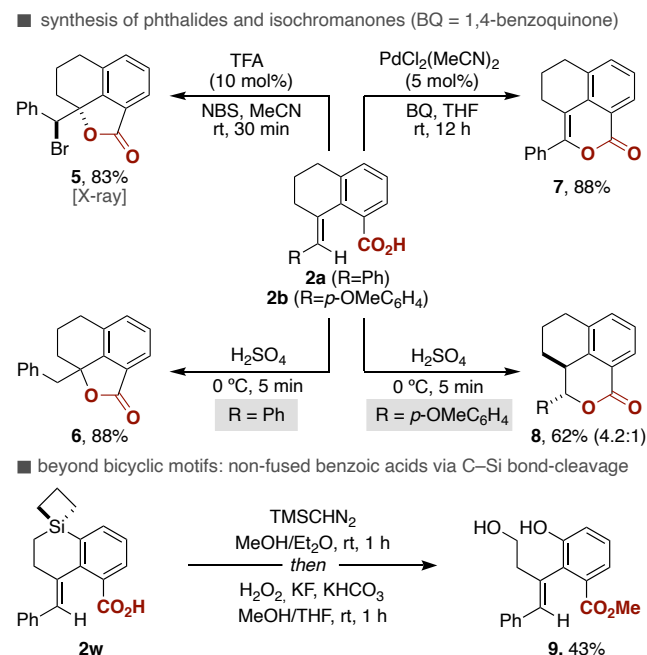


<sup>a</sup> As Table 1, entry 11, using DMA. <sup>b</sup> Isolated yields, average of two independent runs. <sup>c</sup> Z:E = 2.4:1. <sup>d</sup> Z:E = 3.3:1.

The successful preparation of **2a-2w** suggested that an

otherwise similar 1,4-Ni migration scenario could be within reach by using simple vinyl halides as substrates. As shown in Scheme 3, this turned out to be the case, and vinyl bromides containing either alkyl or aromatic substituents could trigger the targeted  $sp^2$  C–H carboxylation en route to **4a** and **4b** regardless of whether *E/Z* mixtures of **3a-b** were utilized.<sup>24</sup> While tentative, this observation suggests an initial *E/Z*-isomerization of the oxidative addition Ni(II) species prior to 1,4-Ni migration, probably via the intermediacy of carbene-type species.<sup>25</sup> The prospective impact of our 1,4-Ni migration technique is further illustrated in Scheme 4. As shown, complex molecular isochromanone or phthalide architectures could be accessed from **2a** or **2b** depending on the reaction conditions utilized. Thus, bromolactonization can be easily accomplished by exposing **2a** to NBS in TFA (**5**)<sup>26</sup> whereas clean formation of phthalide **6** was observed with H<sub>2</sub>SO<sub>4</sub> instead.<sup>27</sup> Similarly, while isochromanone **7** could be obtained via Pd-catalyzed oxidative regimes,<sup>28</sup> the saturated isochromanone analogue **8** was within reach from **2b** instead. More importantly, the successful preparation of **9** in an unoptimized 43% yield tacitly indicates that the presence of silicon fragments can be turned into a strategic advantage for accessing functionalized polyhydroxylated carboxylic acids, thus expanding the application profile of our technology.<sup>29</sup>

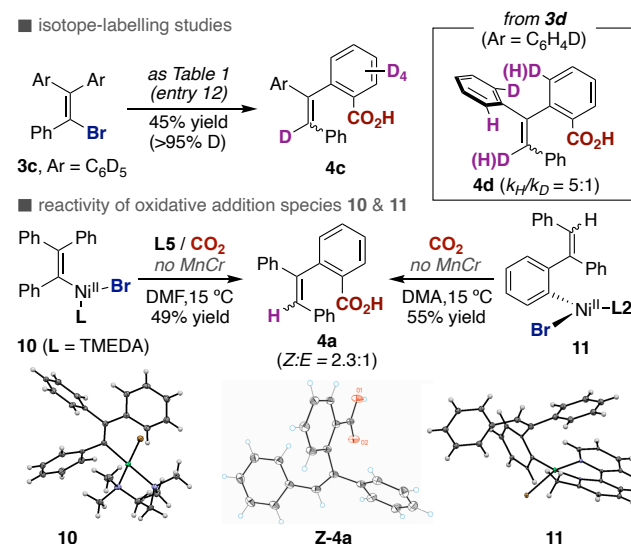
#### Scheme 4. Application Profile.



Intrigued by the favorable reactivity profile shown in Table 2 and Schemes 2-3, we conducted experiments with isotopically labelled substrates (Scheme 5, *top*). As shown, full deuterium incorporation at the vinyl position (>95% D) was observed in **4c** upon exposing **3c** to our optimized NiBr<sub>2</sub>/L5 regime, thus corroborating that a [1,4]–

Ni migration occurs at the *ortho*  $sp^2$  C–H bond prior to CO<sub>2</sub> insertion. Interestingly, while a significant intramolecular kinetic isotope effect was observed in the reductive carboxylation of **3d** ( $k_H/k_D = 5:1$ ; Scheme 5, *top right*), no intermolecular kinetic isotope effect was found by comparing the rates of **3a** and **3c**.<sup>19</sup> Although tentative, this observation suggests a rate-determining step occurring before or after the 1,4-migration event.<sup>30</sup> Still, however, there was a reasonable doubt on whether [1,4]–Ni migration and the subsequent CO<sub>2</sub> insertion occurred at Ni(I) or Ni(II) centers. To such end, we turned our attention to unravel such mechanistic intricacies by isolating the putative oxidative addition species at either the vinyl or aryl terminus. Interestingly, **10** and **11** could be prepared by reacting the aryl (vinyl) halide with Ni(cod)<sub>2</sub> and TMEDA or L2 in THF.<sup>31</sup> The structure of these complexes in the solid state is depicted in Scheme 4 (*bottom*).<sup>32</sup> As anticipated, the carboxylation of **10** only occurred *in the presence* of L5, thus illustrating the importance of 2,2'-bipyridine ligands in the targeted carboxylation reaction. More importantly, **4a** could be obtained from **10** or **11** *in the absence of external metal reductant*, strongly suggesting that both 1,4–Ni migration and CO<sub>2</sub> insertion occurs at Ni(II) centers.<sup>33</sup> This observation can hardly be underestimated, as it challenges the prevailing perception that CO<sub>2</sub> insertion occurs at Ni(I)–carbon bonds<sup>34</sup> and that a 1,4-shift should take place at Ni(I) centers,<sup>9</sup> thus opening up new knowledge in catalyst design, particularly in the reductive cross-coupling arena.<sup>17</sup> Whether CO<sub>2</sub> insertion occurs at four-coordinated or six-coordinated species via octahedral complexes is subject of ongoing studies in this laboratory.<sup>35</sup>

#### Scheme 5. Preliminary Mechanistic Studies.



In summary, we have documented the first catalytic 1,4-nickel migration as a vehicle to enable CO<sub>2</sub> insertion at remote and previously unfunctionalized  $sp^2$  C–H reaction sites, an unrecognized opportunity in both the carboxylation and reductive cross-coupling arena. The salient

features of this protocol are the exquisite chemo- and site-selectivity, mild conditions and application profile. Further extensions to other cross-couplings initiated by 1,4-Ni migration are currently underway in our laboratories.

## ASSOCIATED CONTENT

### Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectral and crystallographic data (PDF)

Data for **2a** (CCDC- 1992997) (CIF)

Data for **2a'** (CCDC- 1992996) (CIF)

Data for **NiBr<sub>2</sub>(L5)<sub>2</sub>** (CCDC- 1993001) (CIF)

Data for **4a** (CCDC- 1992998) (CIF)

Data for **5** (CCDC- 1992999) (CIF)

Data for **10** (CCDC- 1993000) (CIF)

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### Funding Sources

No competing financial interests have been declared.

## ACKNOWLEDGMENT

We thank ICIQ and FEDER/MCI –AEI/PGC2018-096839-B-I00 for financial support. Prof. A. Berkessel is acknowledged for a generous gift of Mn/Cr. M. B., B. S. and D. J.-M. thank MINECO, European Union's Horizon 2020 under Marie Skłodowska-Curie grant agreement (795961) and Alexander von Humboldt foundation for predoctoral and postdoctoral fellowships. We sincerely thank E. Escudero and E. Martin for X-Ray crystallographic data.

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assess the functional group compatibility beyond the compounds employed in Table 2. See ref. 19.

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