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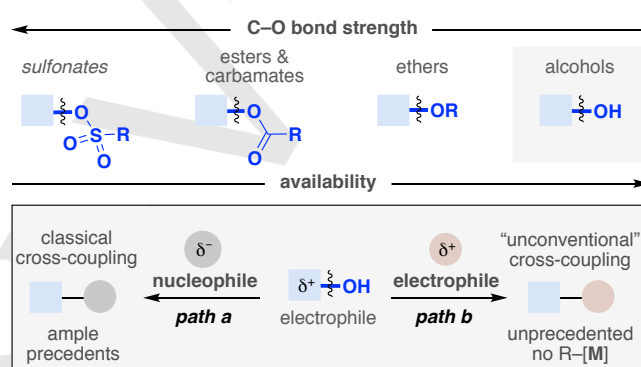
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## Switchable Site-Selective Catalytic Carboxylation of Allylic Alcohols with CO<sub>2</sub>

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**Abstract:** A switchable site-selective catalytic carboxylation of allylic alcohols has been developed in which CO<sub>2</sub> is used with dual roles, both facilitating C–OH cleavage and as C1 source. This protocol is characterized by its mild conditions, absence of stoichiometric organometallic reagents, broad scope and exquisite regiodivergency that can be modulated by the ligand employed.

Metal-catalyzed cross-coupling reactions of C–O electrophiles have recently gained considerable momentum due to the ready availability of alcohols and the design of orthogonal techniques in the presence of organic halides.<sup>[1]</sup> Unlike common C–C bond-formations with activated organic sulfonates, esters, and ethers, the use of simple alcohols as counterparts, arguably the most accessible and simplest C–O derivative, has received much less attention. Despite advances realized in nucleophilic/electrophilic regimes (Scheme 1, bottom left),<sup>[2],[3]</sup> alcohols should ideally be utilized within the realm of cross-electrophile couplings,<sup>[4]</sup> thus avoiding the need for highly reactive nucleophilic entities. However, the remarkable activation barrier required for C–OH scission and the high polarizability of the O–H bond<sup>[5]</sup> left a reasonable doubt that such a counterintuitive scenario could ever be implemented (Scheme 1, bottom right). If successful, however, the realization of such a technique could unravel the inherent potential of simple alcohols in cross-electrophile events, constituting a unique opportunity to provide new tactics for building up complexity from simple precursors.

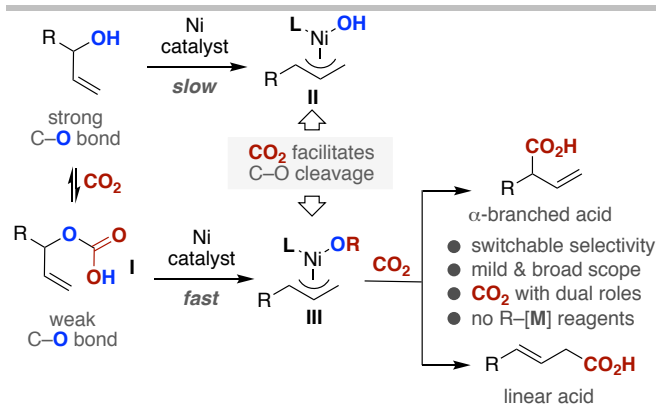


**Scheme 1.** Catalytic C–C Bond-Formation with Alcohols as Coupling Partners

Prompted by the seminal stoichiometric work of Osakada,<sup>[6]</sup> we<sup>[7]</sup> and others<sup>[8]</sup> launched a program aimed at unraveling the potential of nickel-catalyzed reductive carboxylation of organic (pseudo)halides with carbon dioxide (CO<sub>2</sub>). At present, these endeavors unfortunately remain limited to organic halides or particularly activated C–O electrophiles.<sup>[9]</sup> As C–O electrophiles ultimately derive from the corresponding alcohol, we recently questioned whether we could establish a design principle for promoting a more atom- and step-economical technique via direct Ni-catalyzed carboxylation of simple unprotected alcohols in the absence of stoichiometric or air-sensitive organometallic reagents.<sup>[10]</sup> To such end, we hypothesized that CO<sub>2</sub> could be used with dual roles, both as C1 source and as an activating group for C–O bond-cleavage (Scheme 2). Our hypothesis is driven by the known ability of CO<sub>2</sub> to react reversibly with alcohols en route to carbonic acids I,<sup>[11]</sup> thus lowering the activation energy for promoting C–O scission while accelerating the rate of oxidative addition to Ni(0)L<sub>n</sub> (III vs II) prior CO<sub>2</sub> insertion.<sup>[12]</sup> Herein, we describe our results towards this goal by designing a mild, and user-friendly Ni-catalyzed carboxylation of allylic alcohols under atmospheric pressure of CO<sub>2</sub>. We demonstrate that the site-selectivity at the allyl terminus can be discriminated and modulated at will by the ligand employed, leading to either linear or α-branched carboxylic acids.<sup>[13]</sup>

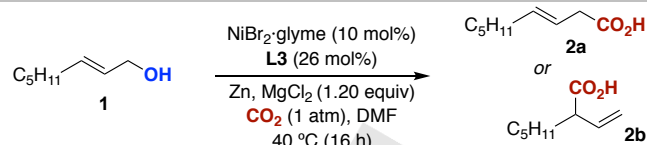
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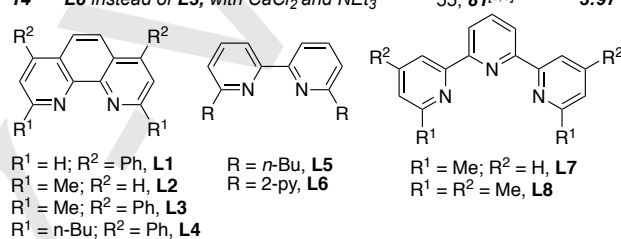


**Scheme 2.** Design Principle for a Carboxylation of Allylic Alcohols with CO<sub>2</sub>

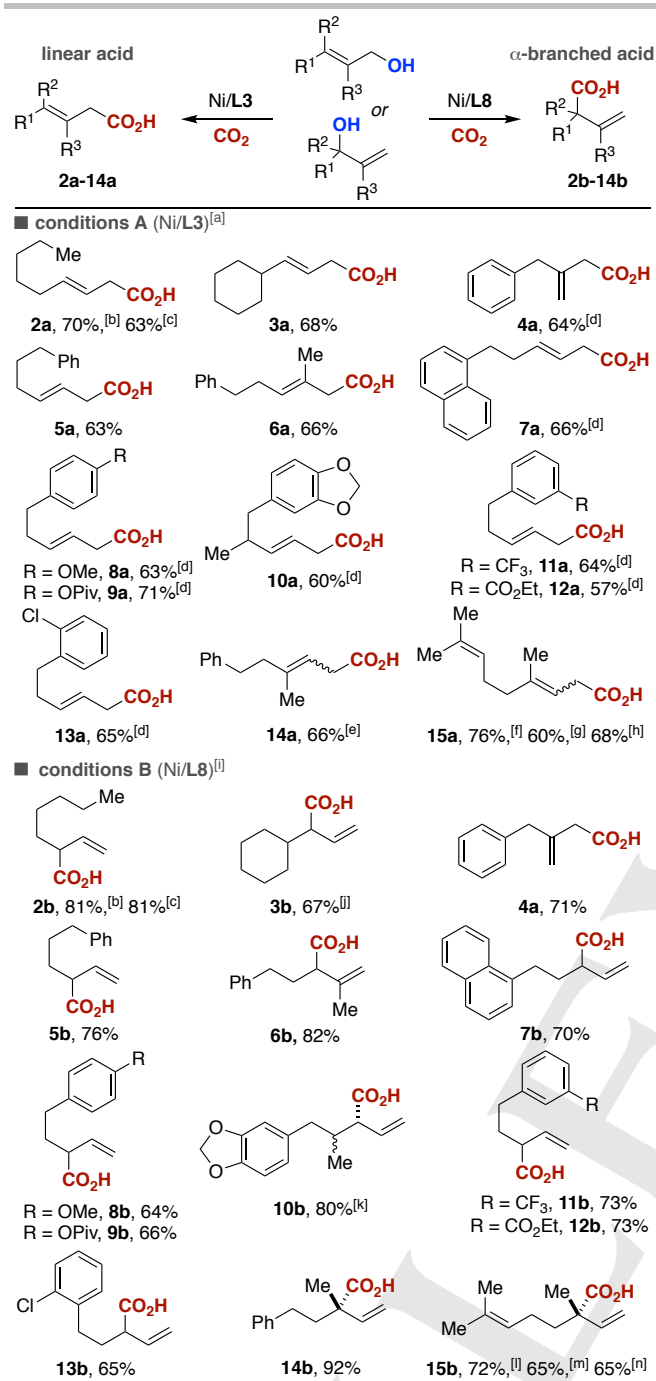
Our study began by evaluating the carboxylation of **1** at atmospheric pressure of CO<sub>2</sub>. Interestingly, neither **2a** nor **2b** were observed under conditions previously developed for other carboxylation events.<sup>[7,8]</sup> After some experimentation, a combination of NiBr<sub>2</sub>·glyme, commercially available **L3**, Zn, MgCl<sub>2</sub> and DMF at 40 °C afforded **2a** in 70% isolated yield with exquisite site-selectivity (**2a:2b** = 99:1).<sup>[14]</sup> Inferior results were consistently observed with Ni sources, additives and solvents other than NiBr<sub>2</sub>·glyme, MgCl<sub>2</sub>, and DMF (entries 2 and 3). Similarly, lower yields were found when MgBr<sub>2</sub> or ammonium salts were used in lieu of MgCl<sub>2</sub> (entries 4 and 5).<sup>[15]</sup> Traces of **2a**, if any, were observed when using Mn or silanes as reducing agents (entry 6). The former finding is particularly noteworthy given the notorious success of Mn as reductant in cross-electrophile couplings,<sup>[4]</sup> including carboxylation protocols.<sup>[7,8]</sup> As expected, the nature of the ligand exerted a profound influence in both reactivity and site-selectivity. While excellent regioselectivities towards **2a** were found with 2,2'-bipyridines and 1,10-phenanthrolines possessing substituents adjacent to the nitrogen atom, better yields were found for the latter (entries 7-11). At present, we hypothesize that these results account for the higher rigidity of 1,10-phenanthrolines, likely increasing the stability of the putative reaction intermediates within the catalytic cycle. Interestingly, bench-stable C6-substituted terpyridines **L7-L8**, resulted in a selectivity switch en route to **2b** under identical reaction conditions to that shown for **L3**, albeit in lower yields (entry 12 and 13).<sup>[16]</sup> It is worth noting that related quaterpyridine analogue such as **L6** failed to provide **2b**.<sup>[17]</sup> These results tacitly suggest that the coordination geometry of the ligand dictates the selectivity pattern, with tridentate ligands being particularly suited for **2b**. Careful fine-tuning of the reaction conditions afforded **2b** in 81% isolated yield with an excellent 3:97 **2a:2b** ratio when using Ni(COD)<sub>2</sub> as catalyst in DMA at rt, and employing both CaCl<sub>2</sub> and NEt<sub>3</sub> as additives (entry 14).<sup>[18]</sup> As anticipated, rigorous control experiments revealed that all of the reaction parameters were critical for success.<sup>[14]</sup>



entry	Deviation from standard conditions <sup>[a]</sup>	yield <b>2a</b> + <b>2b</b> (%) <sup>[b]</sup>	<b>2a:2b</b> <sup>[b]</sup>
<b>1</b>	<b>none</b>	<b>70</b> , <sup>[c]</sup> <b>26</b> <sup>[d]</sup>	<b>99:1</b>
2	Using NiCl <sub>2</sub> ·glyme (Ni(COD) <sub>2</sub> )	58 (69)	99:1
3	DMA (NMP) as solvent	51 (52)	99:1
4	MgBr <sub>2</sub> instead of MgCl <sub>2</sub>	52	99:1
5	<i>n</i> Bu <sub>4</sub> NBr ( <i>n</i> Bu <sub>4</sub> NOAc) instead of MgCl <sub>2</sub>	0 (48)	99:1
6	Mn (Et <sub>3</sub> SiH) instead of Zn	3 (0)	99:1
7	<b>L1</b> instead of <b>L3</b>	3	66:34
8	<b>L2</b> instead of <b>L3</b>	42	99:1
9	<b>L4</b> instead of <b>L3</b>	54	99:1
10	<b>L5</b> instead of <b>L3</b>	23	99:1
11	<b>L6</b> instead of <b>L3</b>	0	-
12	<b>L7</b> instead of <b>L3</b>	18	23:77
13	<b>L8</b> instead of <b>L3</b>	30	4:96
<b>14</b>	<b>L8</b> instead of <b>L3</b> , with CaCl <sub>2</sub> and NEt <sub>3</sub>	55, <b>81</b> <sup>[c,e]</sup>	<b>3:97</b>



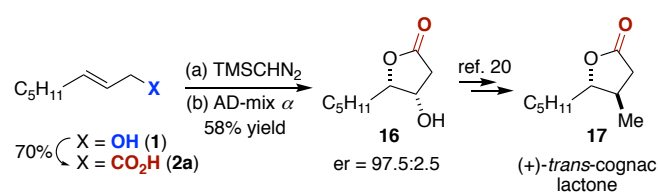
**Scheme 3.** Optimization of the Reaction Conditions. **1** (0.20 mmol), NiBr<sub>2</sub>·glyme (10 mol%), **L3** (26 mol%), Zn (4 equiv), MgCl<sub>2</sub> (1.20 equiv), DMF (0.10 M), CO<sub>2</sub> (1 atm) at 40 °C for 16 h (yields in parentheses refer to yields of the reagents used in parentheses). <sup>[b]</sup> GC yields using anisole as internal standard. <sup>[c]</sup> Isolated yield. <sup>[d]</sup> No MgCl<sub>2</sub>. <sup>[e]</sup> Ni(COD)<sub>2</sub> (10 mol%), **L8** (10 mol%), CaCl<sub>2</sub> (4 equiv), NEt<sub>3</sub> (3 equiv), Zn (1.50 equiv), DMA (0.20 M) at rt.



**Scheme 4.** Scope of the Regiodivergent Carboxylation of Allylic Alcohols with CO<sub>2</sub>. <sup>[a]</sup> Conditions A: as scheme 3, entry 1, at 0.25 mmol scale; Yields of isolated products, average of at least two independent runs. **2a-15a** were all obtained in 99:1 (linear:branched) ratio. **2a-13a** were obtained in  $\geq 92:8$  *E:Z* ratio. <sup>[b]</sup> from linear alcohol. <sup>[c]</sup> from  $\alpha$ -branched alcohol. <sup>[d]</sup> Zn (2.50 equiv) in DMF (0.70 M). <sup>[e]</sup> *E:Z* = 45:55. <sup>[f]</sup> from geraniol, *E:Z* = 94:6. <sup>[g]</sup> from nerol, *E:Z* = 16:84. <sup>[h]</sup> from linalool, *E:Z* = 42:58. <sup>[i]</sup> Conditions B: as scheme 3, entry 14, at 0.25 mmol scale; Yields of isolated products, average of at least two independent runs. With the exception of **3b** and **10b**, all products were obtained in  $\geq 92:8$  (branched: linear) ratio. <sup>[j]</sup> 82:18 (**3b:3a**). <sup>[k]</sup> 85:15 (**10b:10a**) and 1:1 diastereomeric ratio. <sup>[l]</sup> from geraniol. <sup>[m]</sup> from nerol. <sup>[n]</sup> from linalool.

With a reliable access to either **2a** or **2b**, we next turned our attention to evaluate the generality of our Ni-catalyzed switchable site-selective carboxylation of allylic alcohols with

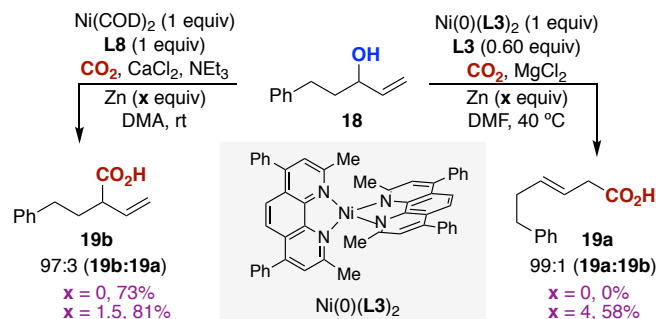
CO<sub>2</sub> by using a Ni/L3 or Ni/L8 couple (Scheme 4). In all cases analyzed, an exquisite site-selectivity was observed regardless of whether linear or  $\alpha$ -branched allylic alcohols were utilized, thus indicating that a substrate-controlled site-selectivity does not come into play. Notably, the substitution pattern on the allyl terminus was largely inconsequential for both reactivity and site-selectivity, obtaining predominantly the corresponding linear or  $\alpha$ -branched carboxylic acids. The presence of esters (**12a**, **12b**), acetals (**10a**, **10b**), alkenes (**15a**, **15b**) or even aryl chlorides (**13a**, **13b**) do not interfere, providing ample room for further functionalization. Likewise, the presence of C–O electrophilic sites susceptible to Ni-catalyzed cross-coupling reactions such as aryl methyl ethers (**8a**, **8b**) or aryl pivalates (**9a**, **9b**) did not compete with the efficacy of the carboxylation event. Particularly noteworthy was the ability to access quaternary centers (**14b** and **15b**), as cross-electrophile endeavors have found little echo with tertiary alkyl electrophiles.<sup>[19]</sup> While a Ni/L3 regime provided predominantly (*E*)-configured isomers, we observed an intriguing dichotomy exerted by the geometry of the starting precursor. Specifically, naturally-occurring geraniol gave rise to **15a** with a higher *E:Z* ratio than structurally isomeric nerol and linalool. While tentative, a subtle  $\eta^1$  to  $\eta^3$  hapticity of the intermediate allyl-Ni complex or the known ability of tethered alkenes on the side-chain to act as intramolecular directing groups might account for these results.<sup>[20]</sup> In contrast, **15b** was exclusively obtained from either geraniol, nerol or linalool with a Ni/L8 couple. It is worth mentioning that substituents in the  $\alpha$ -position of the allyl motif did not erode the site-selectivity, giving rise to **10a** and **10b** in good yields, respectively. The synthetic applicability of our Ni-catalyzed carboxylation in the context of natural product synthesis is further illustrated in Scheme 5. Specifically, a simple three-step sequence consisting of a direct carboxylation of **1a** followed by esterification with TMSCHN<sub>2</sub> and Sharpless asymmetric dihydroxylation afforded **16** in good overall yield, constituting a formal total synthesis of (+)-*trans*-cognac lactone<sup>[21]</sup> **17** and other related natural products.<sup>[22]</sup> Taken together, the results compiled in both Schemes 4 and 5 shows the prospective potential of our methodology.



**Scheme 5.** Formal Total Synthesis of (+)-*trans*-Cognac Lactone.

While an unambiguous understanding on how these reactions work at the molecular level should await further investigations, we turned our attention to gather empirical evidence about the intriguing role of the ligand by studying the reactivity of the putative Ni(0)L<sub>n</sub> species (Scheme 6). Particularly noteworthy was the absence of reactivity when simply exposing **18** to stoichiometric amounts of either Ni(0)(L3)<sub>2</sub><sup>[23]</sup> or Ni(COD)<sub>2</sub>/L8<sup>[24]</sup> in the absence of CO<sub>2</sub>, thus reinforcing the notion that a direct oxidative addition of an allylic alcohol to Ni(0)L<sub>n</sub> does not come into play.<sup>[25]</sup> More importantly, while a Ni(0)(L3)<sub>2</sub> regime required the presence of Zn en route to **19a**,<sup>[23]</sup> the corresponding Ni(COD)<sub>2</sub>/L8 couple cleanly produced **19b** in the absence of reductant, thus evidencing the unique role exerted by the ligand

backbone.<sup>[26]</sup> Although speculative, these results might suggest the intermediacy of  $\eta^1$ -Ni(I) intermediates with bidentate and rigid **L3**, in which CO<sub>2</sub> insertion takes place at the  $\alpha$ -carbon (**19a**),<sup>[27-30]</sup> whereas the presence of tridentate **L8** might result in  $\eta^1$ -Ni(II) intermediates with C–C bond-formation occurring at the  $\gamma$ -carbon (**19b**).<sup>[30-32]</sup>



**Scheme 6.** Preliminary Mechanistic Experiments.

In summary, we have documented a Ni-catalyzed switchable site-selective reductive carboxylation of allylic alcohols, in which regioselectivity is exclusively dictated by the geometry of the ligand backbone. The salient features of this user-friendly method are the broad scope, mild conditions, exquisite site-selectivity profile and the ability of CO<sub>2</sub> to act with dual roles, both as C1 source and as a mediator for facilitating C–O scission. We anticipate that this method will foster systematic investigations for a more prolific use of simple alcohols in cross-electrophile reactions. Further work along these lines is being conducted in our laboratories.

## Acknowledgements

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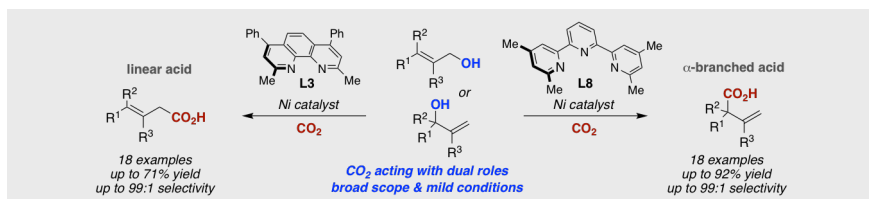
**Keywords:** cross-coupling • nickel • carbon dioxide • C–O cleavage

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- as a proton scavenger to prevent the formation of reduced products. See ref. 13.
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- [23] For the synthesis of Ni(0)(L3)<sub>2</sub> see ref. 7c. When Ni(0)(L3)<sub>2</sub> was used in the absence of additional L3, **19a** was obtained with a 22% isolated yield. An otherwise similar yield was obtained upon treatment of Ni(COD)<sub>2</sub> with L3. At present, we do not have a rationale for the required 1:2.6 ratio of Ni:L3 ratio.
- [24] Despite considerable synthetic efforts, we were unable to prepare Ni(0)(L8) in analytically pure form.
- [25] Although one might argue that allyl chloride intermediates could be generated upon exposure of allyl alcohols to either MgCl<sub>2</sub> or CaCl<sub>2</sub>, control experiments in the absence of CO<sub>2</sub> ruled out this possibility. Additionally, we also demonstrate that allyl chlorides are not competent as reaction intermediates en route to either **19a** or **19b**. See ref. 13.
- [26] Interestingly, 48% of **19b** could be obtained when reacting **18** with Ni(COD)<sub>2</sub>/L8 in the absence of Zn, NEt<sub>3</sub> or CaCl<sub>2</sub>.
- [27] For the in situ generation of Ni(I) from Ni(II): (a) C. A. Laskowski, D. J. Bungum, S. M. Baldwin, S. A. Del Ciello, V. M. Iluc, G. L. Hillhouse, *J. Am. Chem. Soc.* **2013**, *135*, 18272; (b) J. Breitenfeld, J. Ruiz, M. D. Wodrich, X. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 12004; (c) S. Biswas, D. J. Weix, *J. Am. Chem. Soc.* **2013**, *135*, 16192; (d) T. Fujihara, K. Nogi, T. Xu, J. Terao, Y. Tsuji *J. Am. Chem. Soc.* **2012**, *134*, 9106.
- [28] The available experimental data do not allow us to rule out the formation of Ni(I) intermediates by comproportionation, see for example: (e) J. Cornella, E. Gomez-Bengoa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1997; (f) A. Velian, S. Lin, A. J. M. Miller, M. W. Day, T. Agapie, *J. Am. Chem. Soc.* **2010**, *132*, 6296.
- [29] Recently, Ni(I) species have shown to rapidly react with CO<sub>2</sub>: F. S. Menges, S. M. Craig, N. Tötsch, A. Bloomfield, S. Ghosh, H.-J. Krüger, M. A. Johnson *Angew. Chem., Int. Ed.* **2016**, *55*, 1282; *Angew. Chem.* **2016**, *128*, 1304.
- [30] For a mechanistic hypothesis, see ref. 13
- [31] This mechanistic interpretation is somewhat reminiscent of the elegant Pd-catalyzed carboxylation of allenes via η<sup>1</sup>-allyl-Pd(II) intermediates possessing otherwise related tridentate pincer-type ligands in which the CO<sub>2</sub> insertion occurred at the γ-carbon: (a) H.-W. Suh, L. M. Guard, N. Hazari, *Chem. Sci.* **2014**, *5*, 3859; (b) J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2008**, *130*, 15254.
- [32] We cannot rule out that L8 might be redox non-innocent in our carboxylation event. For excellent reviews about redox-active ligands, see: (a) P. Chirik, *Angew. Chem. Int. Ed.* **2017**, DOI: 10.1002/anie.201611959; (b) X. Hu *Chem. Sci.*, **2011**, *2*, 1867.

## COMMUNICATION



A switchable site-selective Ni-catalyzed carboxylation of allylic alcohols has been developed, in which  $\text{CO}_2$  is acting with dual roles, both facilitating the a priori uphill C–OH cleavage and as a C1 source. This method constitutes the first example of a cross-electrophile coupling of unprotected alcohols in the absence of stoichiometric organometallic species. The protocol is distinguished by a broad scope and an exquisite regioselectivity that can be modulated by the ligand employed.

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Page No. – Page No.

Title

Ni-Catalyzed switchable site-selective carboxylation of allyl alcohols with  $\text{CO}_2$