Ligand-controlled Regiodivergent Ni-Catalyzed Reductive Carboxylation of Allyl Esters with CO_2

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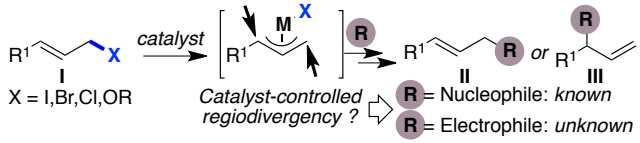
Supporting Information Placeholder

ABSTRACT: A novel Ni-catalyzed regiodivergent reductive carboxylation of allyl esters with CO_2 has been developed. This mild, user-friendly and operationally-simple method is characterized by an exquisite selectivity profile that is dictated by the ligand backbone.

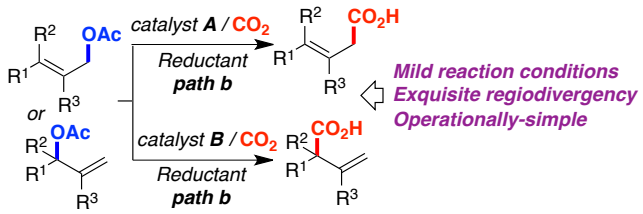
The ability to control the outcome of catalytic reactions by the fine-tuning of the catalyst structure is central in the cross-coupling arena.[1] Despite the advances realized, the development of catalytic regiodivergent protocols from a common precursor in a rational and predictable manner remains a formidable challenge,[2] thus offering a unique opportunity to improve our ever-growing chemical portfolio. Intriguingly, while allyl electrophiles have been successfully employed as coupling partners with nucleophilic counterparts,[3] the utilization of these motifs *in catalytic reductive protocols* is not as commonly practiced as one might anticipate.[4,5] This is probably due to the difficulty for discriminating at will both ends of the initially generated π-allyl metal complex,[3] resulting in regioselectivity issues (Scheme 1, **II** *vs* **III**). Indeed, a *catalyst-controlled regiodivergent reductive event* for selectively obtaining **II** *and* **III** from a common allyl electrophile (**I**) remains an unexplored area of research.

Scheme 1. Regiodivergency in Allyl Electrophiles



Carbon dioxide (CO_2) has emerged as a powerful synthon and renewable chemical feedstock for organic synthesis.[6] The interest for designing new catalytic reactions using CO_2 arises from its low cost, high abundance and lack of toxicity and flammability. Nonetheless, the design of catalytic processes based on carbon dioxide is particularly challenging since CO_2 is kinetically inert and not particularly soluble in commonly employed organic solvents at atmospheric pressure, thus resulting in competitive side-reactions. In recent years, we[7] and others[8] launched a program to unravel the potential of catalytic reductive carboxylation events using aryl or alkyl electrophiles en route to carboxylic acids, privileged motifs in a wide variety of pharmaceuticals and agrochemicals.[9] Although these reactions have reached remarkable levels of sophistication,[7,8] a ligand-controlled selectivity in carboxylation events is unknown, leaving ample opportunities to improve upon existing carboxylation techniques. Herein, we summarize our investigations aiming at the development of an unprecedented regiodivergent catalytic reductive carboxylation strategy (Scheme 2).[10] The protocol is inherently modular, allowing for the introduction of the carboxylic motif at any site of the allyl terminus depending on the ligand employed (paths a & b). To the best of our knowledge, this constitutes the *first time that the nature of the ligand dictates the outcome of carboxylation events.*[11] The transformation is mild and user-friendly, constituting an added value when compared with classical techniques based on well-defined allyl organometallic species,[12,13] halide counterparts and/or high CO_2 pressures.

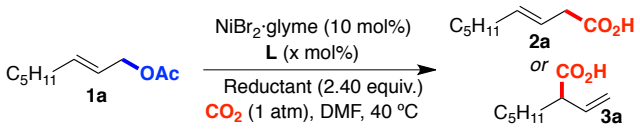
Scheme 2. Regiodivergent Catalytic Carboxylation



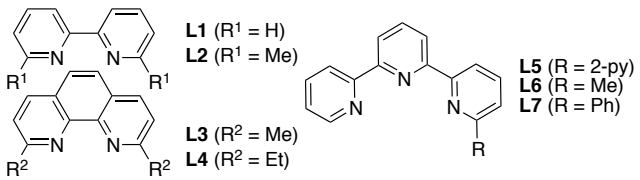
We started our investigations using **1a** as the model substrate and the influence of all reaction components was systematically examined. As for other carboxylation reactions,[7,8] we anticipated that the efficiency of the reaction would be strongly ligand dependent. As shown in Table 1, this was indeed the case. After some experimentation,[14,15] we found that C2-substituted bipyridine **L2** in DMF and Mn as reductant at atmospheric CO_2 pressure was particularly suited for our purposes (entry 2). More importantly, such seemingly trivial modification at C2 was critical for improving the reactivity and selectivity pattern (entry 1 *vs* 2). Although **L3** and **L4** resulted in a decrease of selectivity (entry 3), a survey of additives revealed that both reactivity and **2a:3a** ratio could be accentuated by adding $MgCl_2$ with **L3**,[16] afford-

ing exclusively **2a** in 77% isolated yield at 5 mol% catalyst loading (entry 4).[17,18] Intriguingly, the use of $MgCl_2$ did not have any influence for **L2**, thus showing the subtleties of our system. Strikingly, the use of commercially available quaterpyridine **L5** resulted in a *selectivity switch under identical reaction conditions*, favouring the formation of **3a**, albeit in lower yields (entry 6). These results tacitly suggest that the ligand backbone exclusively dictates the selectivity pattern. The fine-tuning of the Ni:**L5** ratio, reductant, solvent and the inclusion of Na_2CO_3 as additive allowed for obtaining **3a** in 72% isolated yield with an excellent **3a:2a** ratio (entry 9).[17,18] While similar selectivity was observed for **L6** and **L7** (entries 10 and 11), the best results were found with **L5**. As anticipated, control experiments revealed that all reaction components were crucial for success.[14] Taking into consideration the lack of precedents when using **L5** in the cross-coupling arena, we anticipate that **L5** might open up perspectives in ligand design for effecting otherwise inaccessible coupling processes.

Table 1. Optimization of the Reaction Conditions[a]

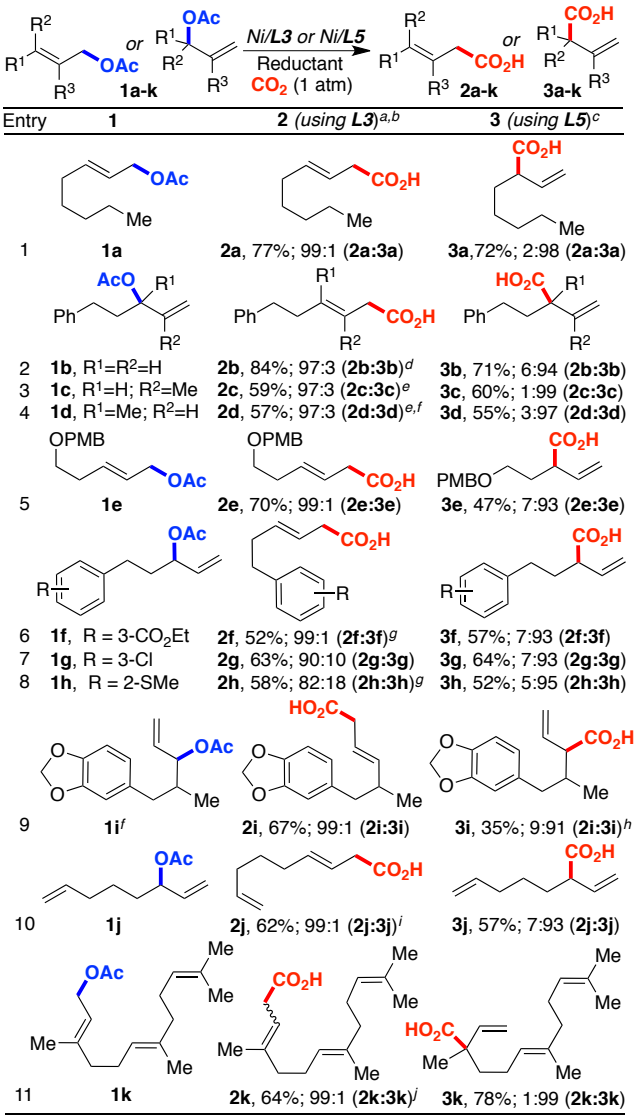


Entry	L (x mol%)	Reductant	Yield 2+3 (%)[b]	2a:3a[b]
1	**L1** (22)	Mn	8	81:19
2	**L2** (22)	Mn	47	93:7
3	**L3** (22)	Mn	58	75:25
4	***L3 (15)***[c,d]	***Mn***	***77***[e]	***99:1***
5	L4 (22)	Mn	70	53:47
6	L5 (22)	Mn	10	8:92
7	**L5** (22)[f]	Zn	28	5:95
8	**L5** (15)[f]	Zn	41	3:97
9	***L5 (15)***[f,g]	***Zn***[h]	***72***[e]	***2:98***
10	**L6** (15)[f,g]	Zn[h]	4	1:99
11	**L7** (15)[f,g]	Zn[h]	11	5:95



[a] **1a** (0.25 mmol), $NiBr_2$·glyme (10 mol%), **L** (x mol%), reductant (2.40 equiv.), DMF (0.17 M), CO_2 (1 atm) at 40 °C for 16 h. [b] Determined by GC using anisole as internal standard. [c] $MgCl_2$ (2 equiv.) was added. [d] $NiBr_2$·glyme (5 mol%). [e] Isolated yield. [f] DMA (0.17 M). [g] Na_2CO_3 (20 mol%) was added. [h] Zn (1.75 equiv.).

Table 2. Ligand-controlled Regiodivergent Carboxylation

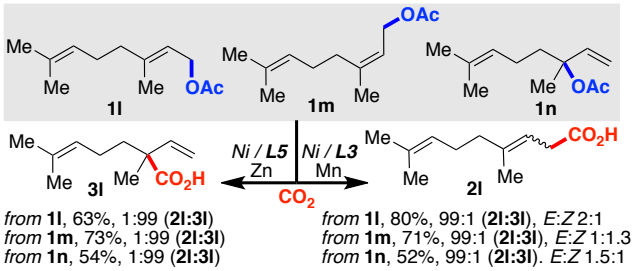


[a] Using **L3**: **1** (0.25 mmol), $NiBr_2$·glyme (5 mol%), **L3** (15 mol%), Mn (0.60 mmol), $MgCl_2$ (0.50 mmol) in DMF at 40 °C. [b] **2a-2j** were obtained in ≥9:1 *E*:*Z* ratio. [c] Using **L5**: **1** (0.25 mmol), $NiBr_2$·glyme (10 mol%), **L5** (15 mol%), Zn (0.44 mmol), Na_2CO_3 (20 mol%) in DMA at 40 °C. [d] At 50 °C. [e] $NiBr_2$·glyme (10 mol%) at 60 °C. [f] 1.5:1 (*E*:*Z*). [g] $NiBr_2$·glyme (10 mol%) and **L4** (30 mol%). [h] 1:1 *syn*:*anti*. [i] $NiBr_2$·glyme (3 mol%). [j] 2.3:1 (*E*:*Z*).

Encouraged by these precedents, we turned our attention to the preparative scope of our Ni-catalyzed regiodivergent carboxylation protocol (Table 1). As shown, a variety of allyl acetates were all carboxylated in good yields and excellent regioselectivities depending on the ligand utilized. As expected, the carboxylation strategy based on **L3** resulted in the predominant formation of *E*-configured isomers (**2a-k**).[19] Remarkably, a high selectivity profile was obtained regardless of whether linear or α-branched allyl acetates were utilized. These results reinforce the notion that our regiodivergent protocol does not operate under substrate-control and that the ligand exclusively dictates the selectivity pattern. As

shown for **1c-1d**, the inclusion of substituents on the allyl motif did not have a deleterious effect on selectivity. The preparation of carboxylic acids bearing a quaternary center (**3d** and **3k**) is particularly noteworthy since Ni-catalyzed reductive coupling reactions of tertiary alkyl electrophiles are virtually inexistent.[20] The chemoselectivity profile of our method is further illustrated by the presence of ethers (**1e**), acetals (**1i**), esters (**1f**), thioethers (**1h**) or alkenes (**1j** and **1k**). Strikingly, while the inclusion of thioether motifs in the side chain had a negative impact for **2h**, no erosion in selectivity was found when operating under a **L5** regime, hence suggesting that thioethers compete with substrate binding with **L3**. Interestingly, the selectivity towards **3i** was not affected by substituents in the α position of the allyl acetate fragment (**1i**), albeit **3i** was obtained in lower yield.[21] The successful preparation of **2k** and **3k** from naturally ocurring farnesyl acetate **1k** highlights the robustness of our protocol in the presence of multiple double bonds. Moreover, the carboxylation could be conducted without affecting the aryl chloride entity, providing an additional functional handle via cross-coupling techniques (**2g** and **3g**). Importantly, we found that the carboxylation of **1j** could be conducted without noticeable 5-exo-*trig* cyclization (**2j** and **3j**).[22] Overall, the data in Table 2 demonstrates the robustness and prospective impact of our regiodivergent carboxylation protocol.

Scheme 3. Convergent Synthesis of 2l and 3l from 1l-1n

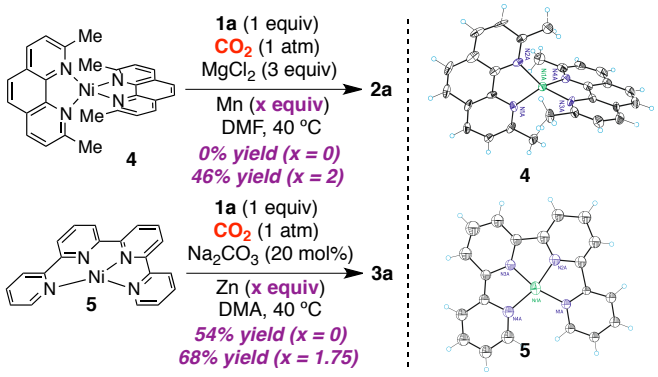


from **1l**, 63%, 1:99 (**2l:3l**)
from **1m**, 73%, 1:99 (**2l:3l**)
from **1n**, 54%, 1:99 (**2l:3l**)

from **1l**, 80%, 99:1 (**2l:3l**), *E:Z* 2:1
from **1m**, 71%, 99:1 (**2l:3l**), *E:Z* 1:1.3
from **1n**, 52%, 99:1 (**2l:3l**). *E:Z* 1.5:1

Guided by the assumption that the reaction might not be substrate-controlled, we speculated that a different set of constitutional and configurational isomers could converge to a single carboxylic acid with a protocol based on **L3** and **L5**. In line with our expectations, **1l-1n** were exclusively converted into either **2l** or **3l** in good yields with variable *E/Z* ratios (Scheme 3).[19] We believe these results suggest common reaction intermediates[23] and increase the flexibility in synthetic design for preparing carboxylic acids from different precursors. Although a mechanistic study should await further investigations, we set out to explore the intermediacy of **L3-** and **L5**-Ni complexes. Following a procedure described by Nocera,[24] we prepared air-sensitive **4** and **5** by reacting **L3** or **L5** with $Ni(COD)_2$ in THF and their structures were univocally characterized by X-ray crystallography (Scheme 4).[14,25] Intriguingly, while **2a** could only be obtained in the presence of a reducing agent by using **4**, **3a** was cleanly produced with **5**, *even in the absence of reductant*.[26] These experiments confirm that the ligand backbone dictates the selectivity pattern and strongly suggest a different mechanistic pathway for **L5** that differs from other reductive coupling events. At present, we believe that **L5** might behave similarly to pincer-type ligands in related carboxylation events via η^1-allyl intermediates[27] and that the additional pyridine motif might be acting as a hemilabile ligand, thus tempering the catalytic activity on the Ni center and preventing decomposition pathways.

Scheme 4. Stoichiometric Experiments



In summary, we have described a novel, mild and user-friendly Ni-catalyzed regiodivergent carboxylation of allyl acetates with CO_2. This protocol constitutes the first regiodivergent catalytic reductive coupling of allyl electrophiles and provides consistent evidence that the ligand dictates the selectivity pattern. We anticipate that this study will lead to new knowledge in catalyst design by using unconventional ligand backbones. Further investigations into the mechanism and the development of an asymmetric version 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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(12) For the carboxylation of allyl boronates, see: (a) Duong, H. A.; Huleatt, P. B.; Tan, Q. –W.; Shuying, E. L. *Org. Lett.* **2013**, *15*, 4034. For the carboxylation of allyl stannanes: (b) Hruszkewycz, D. P.; Wu, J.; Hazari, N.; Incarvito, C. D. *J. Am. Chem. Soc.* **2011**, *133*, 3280. (c) Shi, M.; Nicholas, K. M. *J. Am. Chem. Soc*. **1997**, *119*, 5057.

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(14) See Supporting information for details.

(15) No products were detected under previously reported Ni-catalyzed reductive carboxylation reactions (ref. 7b, 7c, 8c).

(16) For the beneficial role of $MgCl_2$ in carboxylation reactions or reductive events, see: (a) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett*. **2012**, *14*, 3044. (b) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665. (c) Ref. 7c.

(17) Dimerization and reduction account for the mass balance. The inclusion of H_2O (10–100 mol%) shut down the reactivity.

(18) We found identical results when scaling up the reaction of **1a** (1 mmol) under a **L3** or **L5** regime.

(19) Lower *E/Z* ratios were found for **2k-n**, an observation that is in line with the directing effect of tethered alkenes in Ni-catalyzed coupling reactions. See for example: ref. 10d.

(20) For remarkable exceptions: (a) Luo, L.; Zhang, J. –J.; Ling, W. –J.; Shao, Y. –L.; Wang, Y. –W.; Peng, Y. *Synthesis* **2014**, *46*, 1908. (b) Yang, D.; Belardi, J. K.; Micalizio, G. C. *Tetrahedron Lett.* **2011**, *52*, 2144. (c) Refs. 7c and 8a

(21) No reaction took place when exposing 4,4-dimethylpent-1-en-3-yl acetate possessing a quaternary carbon in α-position under the conditions based upon **L5**. Likewise, no reaction was observed with cyclohex-2-en-1-yl acetate.

(22) At higher Ni/**L3** loadings we observed **2j** and 5-exo-*trig* cyclization in a linear relationship, suggesting that a radical-escape-rebound mechanism could be operating. Indeed, the reaction of **1j** with Ni/**L3** was inhibited by addition of radical scavengers such as TEMPO or galvinoxyl. Intriguingly, **3j** was the only observable product with Ni/**L5**, reinforcing the notion that a different interplay operates for **L5**.

(23) In line with this notion, we found that racemic **3b** was obtained from (R)-**1b** (65% *ee*) under a Ni/**L5** regime.

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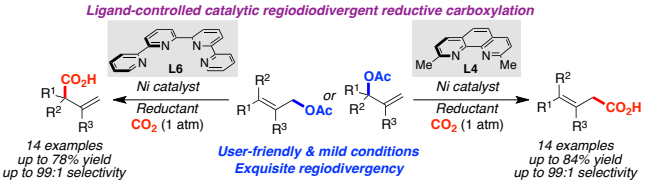
(26) The use of stoichiometric $Ni(COD)_2$/**L3** or $Ni(COD)_2$/**L5** in provided otherwise identical reactivity to **4** and **5**.

(27) Tridentate, pincer-type ligands have shown to promote a related α-branched carboxylation of allenes. The mechanism is believed to proceed via the formation of a new C-C bond between CO_2 and the γ-carbon of an *in situ* generated η^1-allyl metal complexes, see: (a) Suh, H.–W.; Guard, L. M.; Hazari, N. *Chem. Sci*. **2014**, *5*, 3859. (b) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc*. **2008**, *130*, 15254.


Ligand-controlled catalytic regiodiodivergent reductive carboxylation
L6
Ni catalyst
Reductant
CO2 (1 atm)
or
L4
Ni catalyst
Reductant
CO2 (1 atm)
14 examples
up to 78% yield
up to 99:1 selectivity
User-friendly & mild conditions
Exquisite regiodivergency
14 examples
up to 84% yield
up to 99:1 selectivity