

Ligand-Controlled Regiodivergent Ni-Catalyzed Reductive Carboxylation of Allyl Esters with CO₂

Toni Moragas,^{†,‡} Josep Cornella,^{†,‡} and Ruben Martin^{*,†,§}

[†]Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

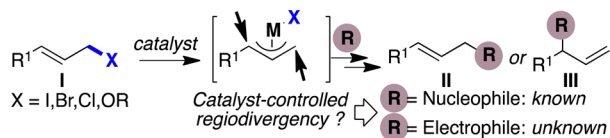
[§]Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys 23, 08010 Barcelona, Spain

S Supporting Information

ABSTRACT: A novel Ni-catalyzed regiodivergent reductive carboxylation of allyl esters with CO₂ 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 in 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

Scheme 1. Regiodivergency in Allyl Electrophiles

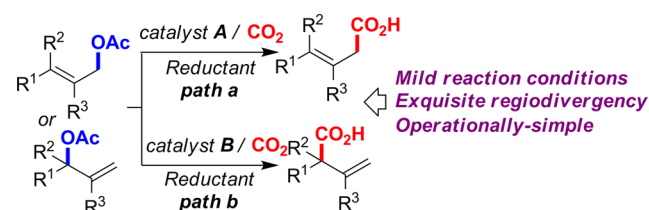


catalyst-controlled regiodivergent reductive event for selectively obtaining II or III from a common allyl electrophile (I) remains an unexplored area of research.

Carbon dioxide (CO₂) has emerged as a powerful synthon and renewable chemical feedstock for organic synthesis.⁶ The interest in designing new catalytic reactions using CO₂ arises from its low cost, high abundance, and lack of toxicity and flammability. Nonetheless, the design of catalytic carboxylation processes is particularly challenging since CO₂ is kinetically inert and not particularly soluble in commonly employed organic solvents at atmospheric pressure, thus resulting in competitive side reactions. In recent years, we⁷ and others⁸ 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

Scheme 2. Regiodivergent Catalytic Carboxylation



for the introduction of the carboxylic motif at any site of the allyl terminus, depending on the ligand employed (paths a and 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, giving it added value when compared with classical techniques based on well-defined allyl organometallic species,^{12,13} halide counterparts, and/or high CO₂ pressures.

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 CO₂ 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 MgCl₂ with **L3**,¹⁶ affording exclusively **2a** in 77% isolated yield at 5 mol% catalyst loading (entry 4).^{17,18} Intriguingly, the use of MgCl₂ 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

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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

L1 (R¹ = H)

L2 (R¹ = Me)

L5 (R = 2-py)

L6 (R = Me)

L7 (R = Ph)

L3 (R² = Me)

L4 (R² = Et)

^a1a (0.25 mmol), NiBr₂·glyme (10 mol%), L (x mol%), reductant (2.40 equiv), DMF (0.17 M), CO₂ (1 atm) at 40 °C for 16 h. ^bDetermined by GC using anisole as internal standard. ^cMgCl₂ (2 equiv) was added. ^dNiBr₂·glyme (5 mol%). ^eIsolated yield. ^fDMA (0.17 M). ^gNa₂CO₃ (20 mol%) was added. ^hZn (1.75 equiv).

conditions, favoring the formation of 3a, albeit in lower yields (entry 6). These results tacitly suggest that the ligand backbone exclusively dictates the selectivity pattern. Fine-tuning of the Ni:L5 ratio, reductant, and solvent and the inclusion of Na₂CO₃ as additive gave 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.

Encouraged by these precedents, we turned our attention to the preparative scope of our Ni-catalyzed regiodivergent carboxylation protocol (Table 2). 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–2k).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 and 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

Table 2. Ligand-Controlled Regiodivergent Carboxylation

Entry	1	2 (using L3) ^{a,b}	3 (using L5) ^c
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			

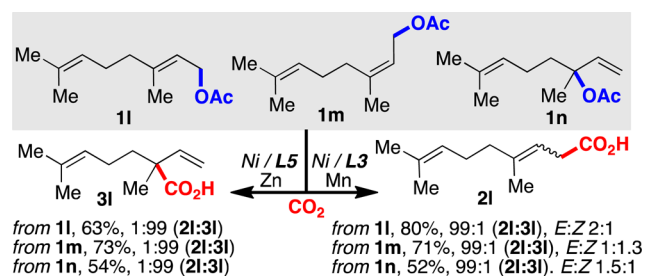
^aUsing L3:1 (0.25 mmol), NiBr₂·glyme (5 mol%), L3 (15 mol%), Mn (0.60 mmol), MgCl₂ (0.50 mmol) in DMF at 40 °C. ^b2a–2j were obtained in \geq 9:1 *E:Z* ratio. ^cUsing L5:1 (0.25 mmol), NiBr₂·glyme (10 mol%), L5 (15 mol%), Zn (0.44 mmol), Na₂CO₃ (20 mol%) in DMA at 40 °C. ^dAt 50 °C. ^eNiBr₂·glyme (10 mol%) at 60 °C. ^f1.5:1 (*E:Z*). ^gNiBr₂·glyme (10 mol%) and L4 (30 mol%). ^h1:1 *syn:anti*. ⁱNiBr₂·glyme (3 mol%). ^j2.3:1 (*E:Z*).

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 toward 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 occurring 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 demonstrate the

robustness and prospective impact of our regiodivergent carboxylation protocol.

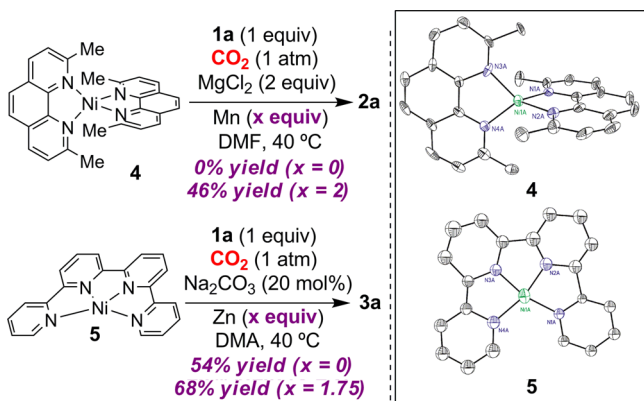
Guided by the assumption that the reaction might not be substrate-controlled, we speculated that a different set of constitutional and configurational isomers could converge to a single carboxylic acid with a protocol based on L3 and L5. In line with our expectations, 1l–1n were exclusively converted into either 2l or 3l in good yields with variable *E:Z* ratios (Scheme 3).¹⁹ We believe these results suggest common

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



reaction intermediates²³ 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}

Scheme 4. Stoichiometric Experiments



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 mechanistic pathway for L5 that differs from other reductive coupling events.⁷ At present, we believe that L5 might behave similarly to pincer-type ligands in related carboxylation events via η^1 -allyl intermediates²⁷ 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.

In summary, we have described a novel, mild, and user-friendly Ni-catalyzed regiodivergent carboxylation of allyl acetates with CO₂. 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 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>.

■ AUTHOR INFORMATION

Corresponding Author

rmartinromo@iciq.es

Author Contributions

[‡]T.M. and J.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(17) Dimerization and reduction account for the mass balance. The inclusion of H₂O (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–2n**, an observation that is in line with the directing effect of tethered alkenes in Ni-catalyzed coupling reactions. See, for example, ref 10d.

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(21) No reaction took place when exposing 4,4-dimethylpent-1-en-3-yl acetate possessing a quaternary carbon in the 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**.

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(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 CO₂ and the γ -carbon of an *in situ*-generated η^1 -allyl metal complex: (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.