

Site-Selective Catalytic Carboxylation of Unsaturated Hydrocarbons with CO₂ and Water

Morgane Gaydou,^{†,‡} Toni Moragas,^{†,‡} Francisco Juliá-Hernández,^{†,‡} and Ruben Martin^{*,†,§}

[†]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Paisos Catalans 16, 43007 Tarragona, Spain

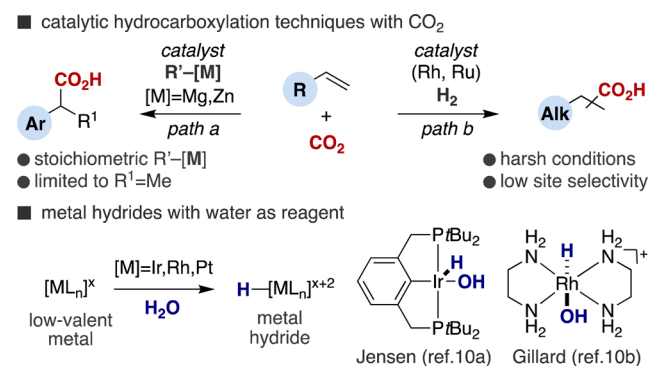
[§]ICREA, Passeig Lluís Companys, 23, 08010 Barcelona, Spain

S Supporting Information

ABSTRACT: A catalytic protocol that reliably predicts and controls the site-selective incorporation of CO₂ to a wide range of unsaturated hydrocarbons utilizing water as formal hydride source is described. This platform unlocks an opportunity to catalytically repurpose three abundant, orthogonal feedstocks under mild conditions.

The utilization of carbon dioxide (CO₂) and alkenes as chemical feedstocks holds promise to streamline synthetic sequences for forging C–C bonds.¹ In particular, the direct catalytic hydrocarboxylation of olefins with CO₂ represents a unique opportunity to convert abundant feedstocks into fatty acids, key building blocks in industrial endeavors.² However, major hurdles have impeded the full adaptation of such a scenario.³ Although Markovnikov selectivity can be obtained with styrenes, these methods make use of air-sensitive, stoichiometric organometallic reagents (Scheme 1, path a),⁴

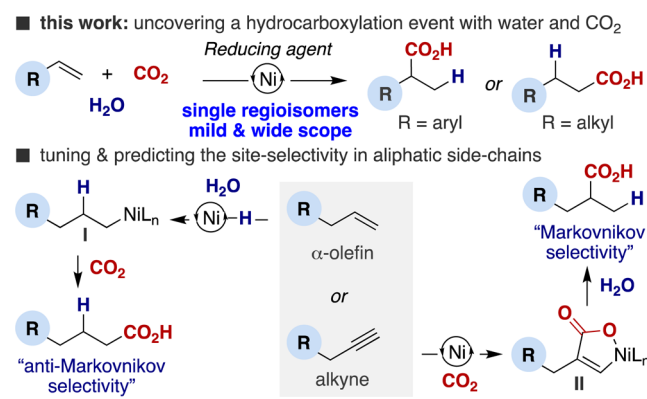
Scheme 1. Catalytic Carboxylation of Olefins and H₂O as Potential Hydride Source



or remain substrate-specific.⁵ Extensions to abundant unactivated internal alkenes or α -olefins are more problematic (Scheme 1, path b),⁶ as noble metals, high CO₂ pressures and elevated temperatures are required. Additionally, the challenge of site-selectivity in these events is preminent, invariably obtaining mixtures of carboxylic acids.⁶ Indeed, the ability to control and fundamentally alter the effective discrimination of a catalytic CO₂ incorporation into unactivated olefins still remains an unanswered challenge.

Recent studies from our group demonstrated that a halogenation/carboxylation sequence allowed for obtaining isomerically pure fatty acids from hydrocarbon feedstocks.⁷ However, the need for halogenated species and activating groups for modulating the site-selectivity still constituted a daunting scenario, reinforcing a change in strategy.⁸ Driven by the ability of some specific low-valent transition metals to generate metal hydrides (Scheme 1, bottom),^{9,10} we questioned whether we could harness water, a renewable feedstock typically employed as proton source, as a mild, inexpensive and safe hydride precursor, thus significantly reducing the chemical footprint of traditional hydride sources used in hydrocarboxylation events (Scheme 2, top).^{3–6} Although we

Scheme 2. Hydrocarboxylation Events with H₂O and CO₂



recognized that such a scenario might unlock an opportunity to repurpose three abundant chemical feedstocks, it was unclear whether such a strategy could be implemented, as the combination of nickel salts and water remains virtually unexplored.¹¹ If successful, we hypothesized that site-selectivity could be rationally predicted and controlled by exploiting the inherent distinct reactivity of easily interconverted alkenes and alkynes¹² with CO₂ via either hydrometalation (I)¹³ or nickelalactone formation (II) (Scheme 2, bottom).¹⁴ Herein, we report our studies toward this goal, resulting in a user-friendly protocol that selectively combines three abundant chemical feedstocks under mild conditions.

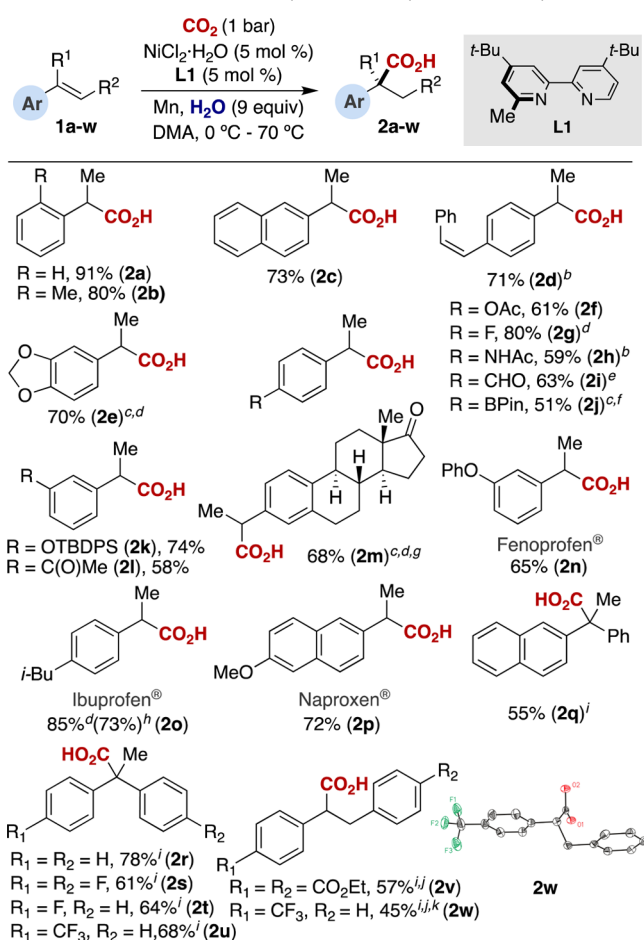
Received: July 21, 2017

Published: August 16, 2017

Our investigations began by evaluating the reaction of styrene with CO₂ at atmospheric pressure. A judicious screening of all the reaction parameters revealed that a combination of NiCl₂·6H₂O (5 mol %), 4,4'-di-*tert*-butyl-6-methyl-2,2'-bipyridine (L1, 5 mol %), water (9 equiv) in DMA at 0 °C using Mn as reducing agent provided **1** in 91% isolated yield as single regioisomer.^{15–17} In line with our expectations,^{7,18} the reaction temperature, the amount of water and the inclusion of substituents adjacent to the nitrogen atom on the ligand backbone had a profound impact on reactivity.¹⁵ Importantly, rigorous control experiments univocally revealed that the presence of both Mn and water are crucial for the generation of the catalytic active species.¹⁵

With a reliable set of conditions in hand, we then turned our attention to study the generality of our protocol (Table 1).

Table 1. H₂O-Mediated Hydrocarboxylation of Styrenes^a



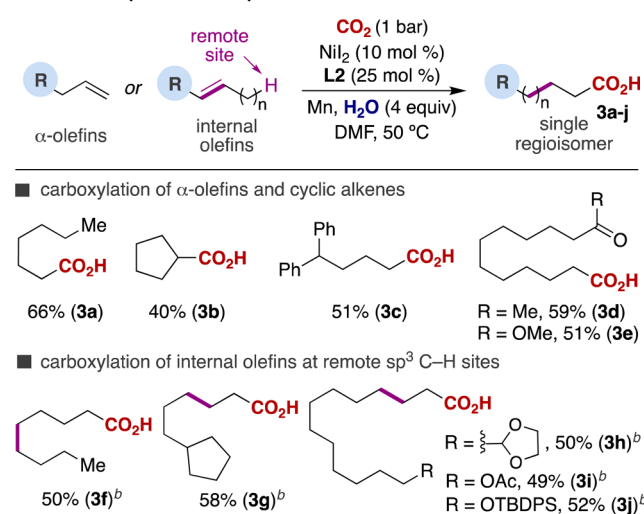
^aIsolated yields, average of two independent runs. Conditions: **1a–w** (0.20 mmol), NiCl₂·6H₂O (5 mol %), L1 (5 mol %), Mn (1.50 equiv), H₂O (9 equiv), CO₂ (1 bar), DMA (0.5 M), 0 °C. ^bIsolated as methyl ester. ^cNiCl₂·6H₂O (10 mol %). ^dAt rt. ^eFrom acetal after workup. ^fH₂O (6 equiv). ^gdr = 1:1. ^h1 g scale. ⁱNiCl₂·glyme (10 mol %), H₂O (1.1 equiv), 70 °C, NMP (0.5 M). ^jH₂O (3.3 equiv). ^k50 °C.

Comparable reactivity was found for electron-rich and electron-poor styrenes, whereas the inclusion of ortho-substituents did not hinder the reaction (**2b**). This method displayed excellent chemoselectivity, as silyl ethers (**2k**), aryl fluorides (**2g**, **2s**, **2t**), esters (**2f**, **2v**), ketones (**2l**, **2m**), acetals (**2e**, **2i**) or amides (**2h**) could be well accommodated. The presence of boronic esters (**2j**) or disubstituted olefins (**2d**) did not interfere,

suggesting the implementation of orthogonal techniques via further functionalization. The prospective potential of this technique was showcased by the preparation of nonsteroidal anti-inflammatory drugs such as Naproxen (**2p**), Fenoprofen (**2n**) or Ibuprofen (**2o**), the latter on a gram scale. In contrast to related styrene hydrocarboxylations,^{3–5} this method could be extended to disubstituted styrenes by simply adjusting the amount of water and temperature, leading to quaternary carbon centers (**2q–2u**), or 1,2-disubstituted analogues (**2v**, **2w**). In the latter, CO₂ incorporation selectively occurred adjacent to the most electron-poor arene,¹³ the structure of which was univocally characterized by X-ray crystallography.¹⁵

Encouraged by these results, we wondered whether our protocol could be extended to industrially relevant unactivated α -olefins, compounds produced on a large scale from ethylene oligomerization.¹⁹ Notably, a cocktail consisting of NiL₂ (10 mol %) and bathocuproine (L2, 25 mol %) allowed to cleanly convert 1-hexene into **3a** in 66% yield as a single regioisomer under atmospheric pressure of CO₂ (Table 2). These results

Table 2. Hydrocarboxylation of Unactivated Olefins^a



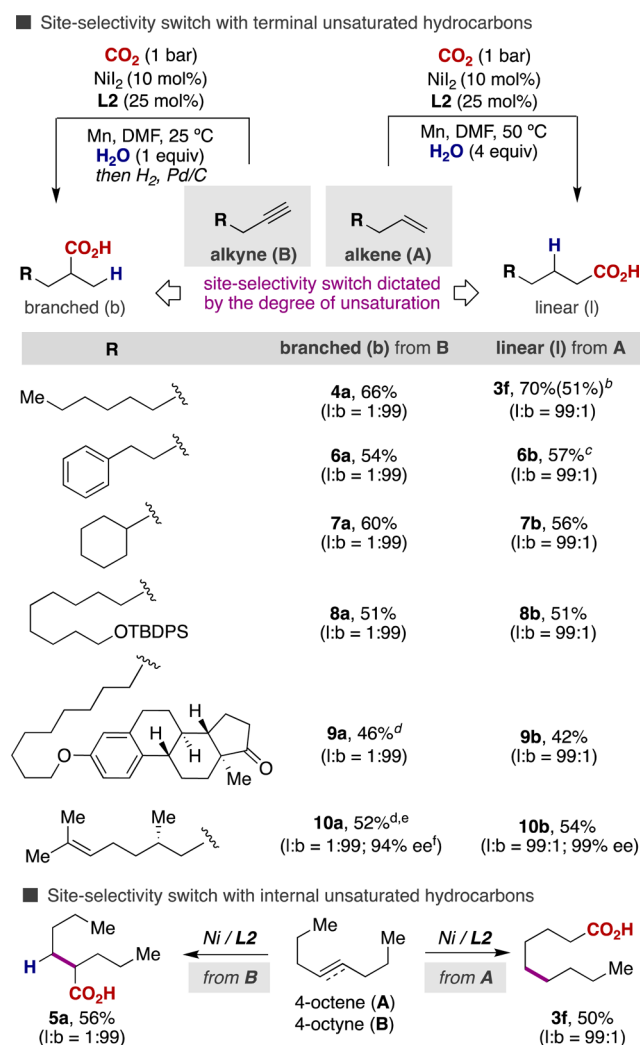
^aIsolated yields, average of two independent runs. Conditions: olefin (0.20 mmol), NiL₂ (10 mol %), bathocuproine (L2, 25 mol %), Mn (3.60 equiv), H₂O (4.0 equiv), CO₂ (1 bar), DMF (0.25 M), 50 °C. ^bH₂O (6.0 equiv) and DMF (0.50 M).

are particularly remarkable taking into consideration the low selectivity profiles found in related carbonylation processes where CO was generated via reverse water–gas shift reactions at elevated temperatures with either Ru or Rh complexes.^{6,20} As shown for **3c–3e** the inclusion of arenes, esters or ketones on the side-chain did not erode the selectivity profile, obtaining exclusively linear acids. Although extending the scope to internal unactivated alkenes was expected to be rather problematic due to their lower binding affinity to metal complexes,²¹ this was not the case. Indeed, cyclic olefins led to **3b**, whereas the use of acyclic olefins, even as *E/Z* mixtures, resulted in the selective CO₂ incorporation at unfunctionalized primary sp³ C–H sites en route to **3f–3j** via iterative β -hydride elimination/migratory insertion sequences (chain-walking).^{21,22} These observations are particularly noteworthy; indeed, the ability to use water as hydride source might significantly reduce the chemical footprint in chain-walking strategies while circumventing the need for stoichiometric organometallic

reagents, halogen precursors reducing agents with high molecular weight such as organosilanes.^{21–23}

Next, we surmised that the distinct reactivity of chemically interchangeable alkynes and alkenes with CO₂ could be turned into a strategic advantage, thus offering a method that might promote a site-selectivity switch in aliphatic side-chains. As shown in Table 3, this turned out to be the case. Although

Table 3. Site-Selectivity Switch in Aliphatic Side-Chains^a



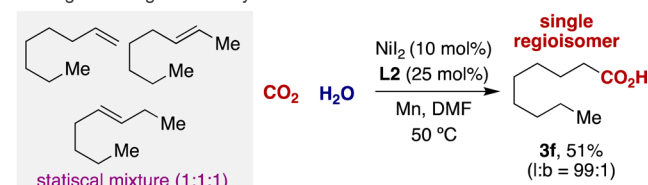
^aIsolated yields, average of two independent runs. Branched: NiL₂ (10 mol %), L2 (25 mol %), B₂nep₂ (10 mol %), Mn (3.6 equiv), H₂O (1.0 equiv), CO₂ (1 bar), DMF (0.17 M) at rt, then H₂ (1 bar), Pd/C (10 mol %). Linear: As Table 2. ^b10 mmol, 5 mol % NiL₂. ^cNaI (1 equiv). ^ddr = 1:1. ^eEt₃SiH (1 equiv) and RhCl(PPh₃)₃ (6 mol %) in lieu of H₂, Pd/C. ^fee determined from the acrylate intermediate.

linear acids **3f**, **6b–10b** were exclusively formed from alkene coupling partners under a NiL₂/L2 regime, a carboxylation/hydrogenolysis event of alkyne counterparts resulted in branched products (**4a–10a**).^{24,25} Notably, no significant erosion in enantioselectivity was found en route to either **10a** or **10b** whereas exclusive linear selectivity was found for **6b**.²² It is worth noting that **3f** could be obtained on a large scale using 5% NiL₂ loading. As expected, such a regioselectivity switch was not limited to terminal alkynes or α -olefins, as **5a** and **3f** were exclusively obtained from the corresponding internal congeners (Table 3, bottom). Collectively, the results of Tables 2 and 3

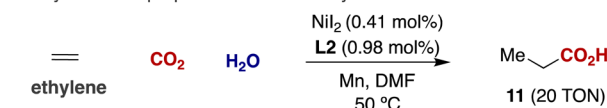
suggested that the valorization of bulk industrially relevant olefins by using inexpensive CO₂ and H₂O as chemical feedstocks would be within reach (Scheme 3). Gratifyingly, **3f**

Scheme 3. Carboxylation of Industrially-Relevant Olefins

■ Regioconvergent carboxylation of unrefined mixtures of alkenes



■ Synthesis of propanoic acid from ethylene



could be obtained as a single regioisomer from unrefined mixtures of olefins (Scheme 3, top). Bolstered by these results, we became intrigued about the prospect of coupling ethylene, the largest-volume organic chemical produced in industry (Scheme 3, bottom).²⁶ Although preliminary, we found that propionic acid (**11**) could be obtained in 20 turnover numbers (TON), representing a proof of concept that could potentially pave the way to design safer alternatives to the BASF process based on hazardous CO and [Ni(CO)₄].²⁷

In summary, we have designed a predictable and tunable site-selective hydrocarboxylation of a wide range of unsaturated hydrocarbons with CO₂ by using water as hydride source.²⁸ This method unlocks an opportunity to selectively repurpose three chemical feedstocks, including bulk industrial olefins. Although future mechanistic work is warranted to unravel the origin of both reactivity and selectivity,²⁹ we believe this study will foster new investigations for building up molecular complexity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07637.

Data for **2w** (CIF)

Experimental procedures, crystallographic data and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*martinromo@icqi.es

ORCID

Ruben Martin: 0000-0002-2543-0221

Author Contributions

[‡]M.G., T.M. and F.J.-H. contributed equally to this work.

Funding

No competing financial interests have been declared.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank ICIQ, European Research Council (ERC-277883 & ERC-2015-PoC-713577), MINECO (CTQ2015-65496-R &

Severo Ochoa Accreditation SEV-2013-0319) and Cellex Foundation for support. We also thank E. Escudero/E. Martin for X-ray crystallographic data.

REFERENCES

- (1) (a) Juliá-Hernández, F.; Gaydou, M.; Serrano, E.; Van Gemmeren, M.; Martin, R. *Top. Curr. Chem.* **2016**, *374*, 45. (b) Börjesson, M.; Moragas, T.; Gallego, D.; Martin, R. *ACS Catal.* **2016**, *6*, 6739. (c) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. *Nat. Commun.* **2015**, *6*, 5933. (d) Zhang, L.; Hou, Z. *Chem. Sci.* **2013**, *4*, 3395. (e) Tsuji, Y.; Fujihara, T. *Chem. Commun.* **2012**, 48, 9956. (f) Huang, K.; Sun, C. L.; Shi, Z. *Chem. Soc. Rev.* **2011**, *40*, 2435.
- (2) Maag, H. *Prodrugs of Carboxylic Acids*; Springer: New York, 2007.
- (3) For indirect, noncatalytic carboxylation techniques based on the intermediacy of stoichiometric organometallic reagents via either hydromagnesation of hydroboration techniques, see: (a) Shao, P.; Wang, S.; Chen, C.; Xi, C. *Org. Lett.* **2016**, *18*, 2050. (b) Ohishi, T.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 8114.
- (4) (a) Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900. (b) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14936.
- (5) For an elegant Rh-catalyzed protocol mediated by visible light requiring particularly activated substrates, see: Murata, K.; Numasawa, N.; Shimomaki, K.; Takaya, J.; Iwasawa, N. *Chem. Commun.* **2017**, 53, 3098.
- (6) (a) Wu, L.; Liu, Q.; Fleischer, I.; Jackstell, R.; Beller, M. *Nat. Commun.* **2014**, *5*, 3091. (b) Ostapowicz, T. G.; Schmitz, M.; Krystof, M.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12119.
- (7) Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. *Nature* **2017**, *545*, 84.
- (8) Gaunt, M.; Williamson, P. *Nature* **2017**, *545*, 35.
- (9) Ozerov, O. V. *Chem. Soc. Rev.* **2009**, *38*, 83.
- (10) For well-defined and structurally characterized noble metal hydrides obtained from water, see: (a) Morales-Morales, D.; Lee, D. W.; Wang, Z.; Jensen, C. M. *Organometallics* **2001**, *20*, 1144. (b) Gillard, R. D.; Heaton, B. T.; Vaughan, D. H. *J. Chem. Soc. A* **1970**, 3126.
- (11) For exceptions in scenarios other than carboxylation events using alkyne counterparts, see: (a) Chen, Y. – G.; Shuai, B.; Ma, C.; Zhang, X. – J.; Fang, P.; Mei, T. – S. *Org. Lett.* **2017**, *19*, 2969. (b) Barrios-Francisco, R.; Benitez-Paez, T.; Flores-Alamo, M.; Arevalo, A.; Garcia, J. *J. Chem. - Asian J.* **2011**, *6*, 842. (c) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653.
- (12) Cossy, J. In *Comprehensive organic functional group transformations II*; Katritzky, A.; Taylor, R. J. K., Eds.; Elsevier: Oxford, 2004.
- (13) Ananikov, V. P.; Beletskaya, I. P. *Top. Organomet. Chem.* **2012**, *43*, 1.
- (14) For a seminal work, see: Burkhardt, G.; Hoberg, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 76.
- (15) See [Supporting Information](#) for details.
- (16) The site-selectivity is tentatively attributed to a hydrometalation scenario that locates the nickel catalyst at the most stable benzylic position (see ref 13). This notion gains credence by the selective deuterium incorporation at the homobenzylic position when using D₂O. See ref 15.
- (17) For a seminal study on the use of Mn in Ni-catalyzed reductive coupling reactions, see: Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920.
- (18) (a) Van Gemmeren, M.; Börjesson, M.; Tortajada, A.; Sun, S. – Z.; Okura, K.; Martin, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 6558. (b) Wang, X.; Nakajima, M.; Serrano, E.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 15531. (c) Borjesson, M.; Moragas, T.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 7504. (d) Serrano, E.; Martin, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 11207. (e) Moragas, T.; Gaydou, M.; Martin, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 5053. (f) Moragas, T.; Cornella, J.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 17702.
- (19) Ittel, S. D.; Johnson, L. K.; Brookhart, M. *Chem. Rev.* **2000**, *100*, 1169.
- (20) For examples of isomerizing alkoxy-carbonylation of fatty acids, see: (a) Roesle, P.; Durr, C. J.; Moller, H. M.; Cavallo, L.; Caporaso, L.; Mecking, S. *J. Am. Chem. Soc.* **2012**, *134*, 17696. (b) Gaide, T.; Bianga, J.; Schlipkoter, K.; Behr, A.; Vorholt, A. *J. ACS Catal.* **2017**, *7*, 4163. (c) Nobbs, J. D.; Low, C. H.; Stubbs, L. P.; Wang, C.; Drent, E.; van Meurs, M. *Organometallics* **2017**, *36*, 391.
- (21) For excellent reviews, see: (a) Vasseur, A.; Bruffaerts, J.; Marek, I. *Nat. Chem.* **2016**, *8*, 209. (b) Larionov, E.; Li, H.; Mazet, C. *Chem. Commun.* **2014**, 50, 9816.
- (22) The means to access **3c** or **5b** as single regioisomers is in sharp contrast with the selective activation at benzylic positions of otherwise analogous substrates with Ni catalysts: He, Y.; Cai, Y.; Zhu, S. *J. Am. Chem. Soc.* **2017**, *139*, 1061.
- (23) For recent metal-catalyzed chain-walking reactions, see: (a) Lin, L.; Romano, C.; Mazet, C. *J. Am. Chem. Soc.* **2016**, *138*, 10344. (b) Dupuy, S.; Zhang, K. – F.; Goutierre, A. – S.; Baudoïn, O. *Angew. Chem., Int. Ed.* **2016**, *55*, 14793. (c) Hamasaki, T.; Aoyama, Y.; Kawasaki, J.; Kakiuchi, F.; Kochi, T. *J. Am. Chem. Soc.* **2015**, *137*, 16163. (d) Mei, T. – S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340. (e) Obligacion, J. V.; Chirik, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 19107. (f) ref 7.
- (24) Although its inclusion had no influence in selectivity, the addition of small amounts of B₂nep₂ resulted in a slight increase in the yield of the reaction. See ref 15, and Cummings, S. P.; Le, T.-N.; Fernandez, G. E.; Quiambao, L. G.; Stokes, B. J. *J. Am. Chem. Soc.* **2016**, *138*, 6107.
- (25) For a selection of catalytic hydrocarboxylations of alkynes, see: (a) Wang, X.; Nakajima, M.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 8924. (b) Takimoto, M.; Hou, Z. *Chem. - Eur. J.* **2013**, *19*, 11439. (c) Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 523. (d) Li, S.; Yuan, W.; Ma, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2578.
- (26) Stechel, E. B.; Miller, J. E. *J. CO₂ Utilization* **2013**, *1*, 28.
- (27) Koelsch, W.; Reppe, W. Patent US 2768968, 1956.
- (28) A European patent application to ICIQ and ICREA has been filled out, with application number EP163823362.
- (29) For deuterated studies with D₂O and a tentative rationale behind the role of water on site-selectivity, see ref 15.