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## Remote Carboxylation of Halogenated Aliphatic Hydrocarbons with CO<sub>2</sub>

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**Summary paragraph:** Catalytic carbon-carbon bond-formation has allowed for the streamline of synthetic routes when assembling complex molecules<sup>1</sup>. This is particularly important when incorporating saturated hydrocarbons, common motifs in petrochemicals and biologically-relevant molecules. However, cross-coupling methods involving alkyl electrophiles occur at specific and previously functionalised sites<sup>2</sup>. Herein, we describe the discovery of a catalytic method capable of promoting carboxylation reactions at remote and unfunctionalised aliphatic sites under atmospheric pressure of CO<sub>2</sub>. The reaction occurs via selective migration of the catalyst along the hydrocarbon side-chain<sup>3</sup> and operates with excellent regio- and chemoselectivity profile. Our results demonstrate that site-selectivity can be switched and controlled, allowing for the functionalisation of less-reactive positions in the presence of a priori more reactive ones. Furthermore, we show that raw materials obtained in bulk from petroleum processing, such as alkanes and unrefined mixtures of olefins, can be used as substrates. This constitutes a unique opportunity to integrate a catalytic platform en route to valuable fatty acids

by direct transformation of petroleum-derived feedstocks<sup>4</sup>. We anticipate that our methodology will have a broad impact in the preparation of carboxylic acids from simple chemical feedstocks, and will lead to new knowledge in synthetic design when targeting the controlled functionalisation of saturated hydrocarbon chains.

### **Main Text:**

While the introduction of aromatic residues via palladium-catalysed coupling reactions has become routine, methods that incorporate saturated hydrocarbon chains have been traditionally problematic using palladium catalysts<sup>2</sup>. Pioneering work by Fu<sup>5</sup> and Knochel<sup>6</sup> demonstrated that nickel catalysts dramatically improved the efficiency of alkyl cross-coupling reactions by minimising the rate of unproductive  $\beta$ -hydride elimination that leads to alkene byproducts. Their reports set the stage for designing new nickel-catalysed reactions of unactivated alkyl electrophiles occurring at the initial reaction site, ranging from classical nucleophilic/electrophilic regimes to the coupling of two distinct electrophiles<sup>7</sup>, and culminating in stereoconvergent reactions<sup>8</sup> or visible-light photochemical techniques<sup>9</sup> (Fig. 1A, *left*).

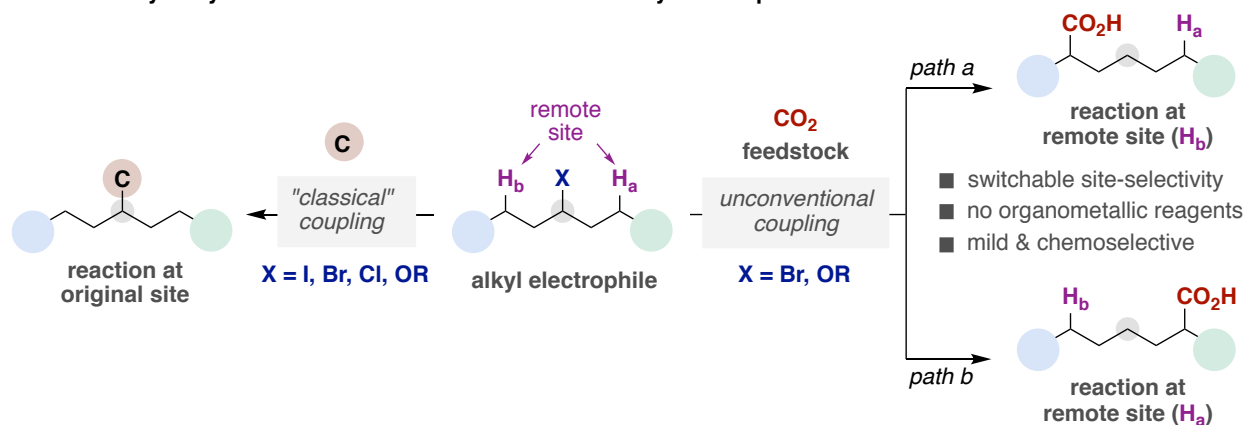
An emerging strategy has been the design of catalytic bond-formation at remote reaction sites<sup>3,10</sup>. However, the implementation of carbon-carbon bond-forming protocols in hydrocarbon frameworks is problematic due to the presence of multiple, yet similar,  $sp^3$  C–H reaction sites within the same skeleton. Elegant methodologies have navigated this question by activating weak  $sp^3$  C–H bonds<sup>11</sup> or by using directing groups at a specific location within the side-chain<sup>12-15</sup>. We speculated that a directing group-free platform aimed at providing a reactivity relay of alkyl electrophiles for activating remote  $sp^3$  C–H sites while combining the factors of predictability and efficiency would enable a unique pathway for carbon-carbon bond-formation

in saturated hydrocarbons, particularly in the absence of organometallic reagents<sup>16</sup>. As part of our interest in nickel-catalysed carboxylations<sup>17,18</sup>, we sought to develop a protocol for incorporating abundant carbon dioxide (CO<sub>2</sub>) at remote sp<sup>3</sup> C–H sites en route to fatty acids (Fig. 1A, *right pathways*), molecules of utmost relevance in the manufacture of soaps, detergents, rubber, plastics or dyes<sup>4,19</sup>. Indeed, several billion pounds of carboxylic acids are produced annually worldwide, and its global market is anticipated to reach approximately \$20 billions by 2023, expanding at an annual growth rate of 5% between 2017 and 2023<sup>4</sup>.

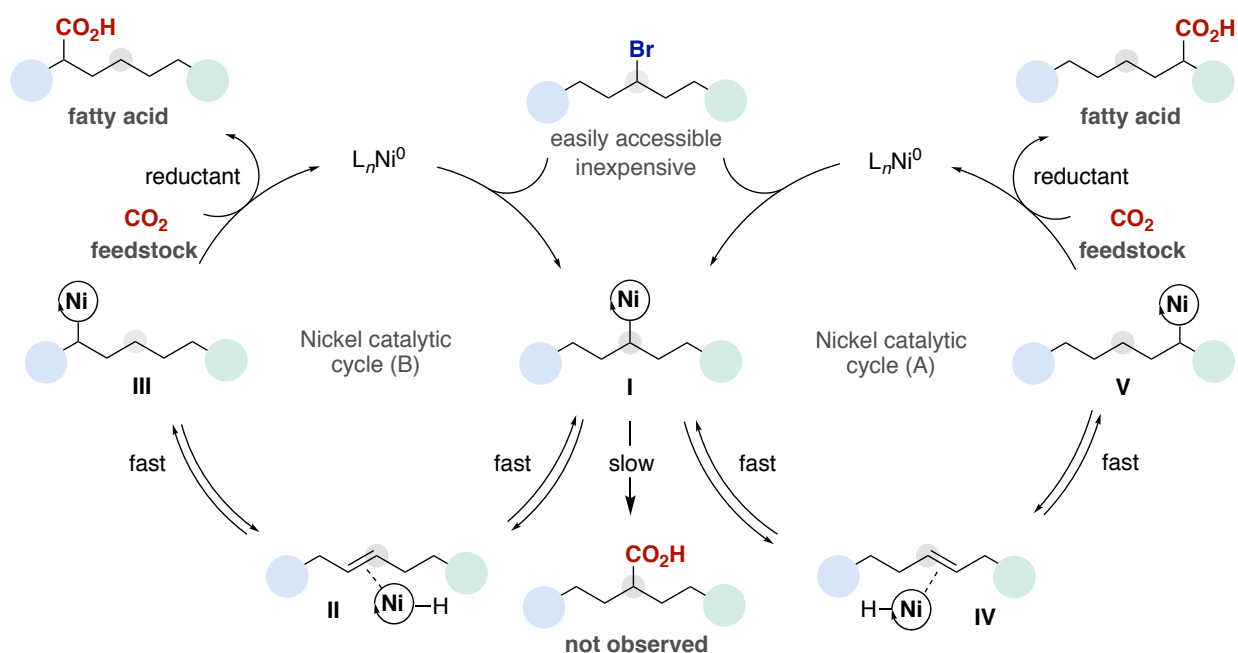
A detailed description of our design principle is outlined in Fig. 1B. While retarding  $\beta$ -hydride elimination has long been the goal of organometallic chemists when using alkyl (pseudo)halides as coupling partners (Fig. 1A, *left*), we questioned whether we could turn a to-be-avoided event into a desirable process. Specifically, we envisioned that the fine-tuning of the ligand on the nickel catalyst could accelerate the rate of  $\beta$ -hydride elimination from **I** prior CO<sub>2</sub> insertion, setting the basis for a chain-walking via iterative  $\beta$ -hydride elimination/migratory insertion sequences<sup>3</sup>. The resulting nickel intermediates **III** and **V** formed via **II** or **IV** would then enable a final CO<sub>2</sub> insertion while ultimately releasing the targeted carboxylic acid. As chain-walking scenarios for forging carbon-carbon bonds remain currently confined to “unidirectional” events that result in the activation of a single reaction site<sup>11,14,16,20,21</sup> and/or the use of noble expensive metals<sup>16,22</sup>, our proposed switchable selectivity platform based on abundant nickel catalysts could unlock a multifaceted challenge for selectively activating less-reactive positions in the presence of a priori more reactive ones. If such strategy could be implemented, we speculated that valuable fatty acids could be within reach by directly reacting raw materials derived in bulk from the petroleum processing such as alkanes or unrefined mixtures of alkenes with CO<sub>2</sub> without requiring the isolation of the corresponding reaction

intermediates (Fig. 1C). Such scenario would constitute a unique platform for converting simple chemical feedstocks into valuable compounds.

**A Reactivity relay in carbon-carbon bond-formation of alkyl electrophiles**

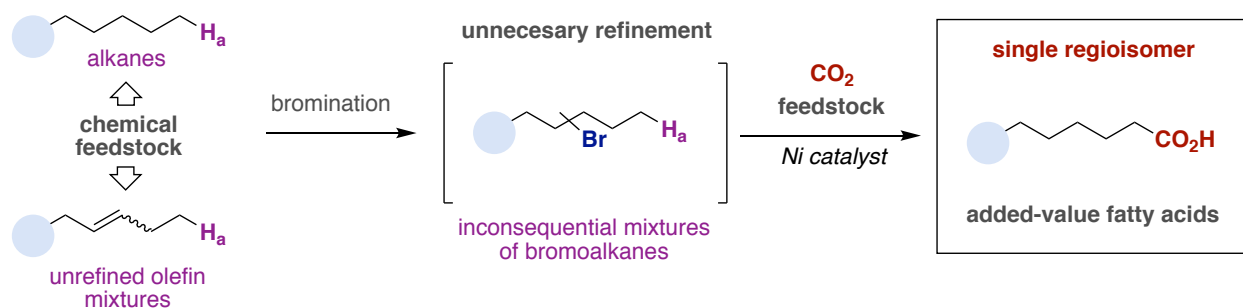


**B Mechanistic rationale for the switchable site-selective carboxylation at remote sp<sup>3</sup> C-H sites**



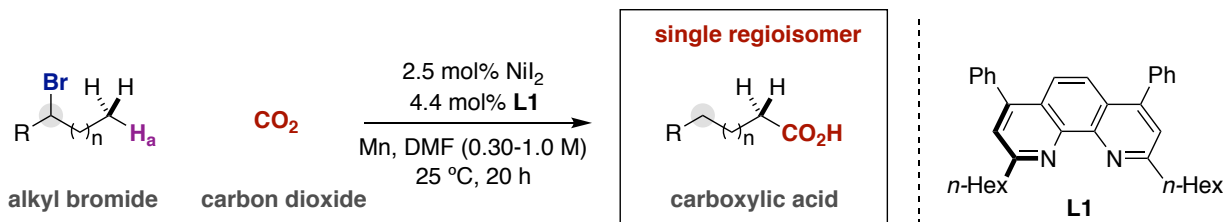
Tunable & controllable displacement of the Ni catalyst through a saturated hydrocarbon side-chain

**C Direct catalytic conversion of biomass-derived feedstocks into single fatty acids**

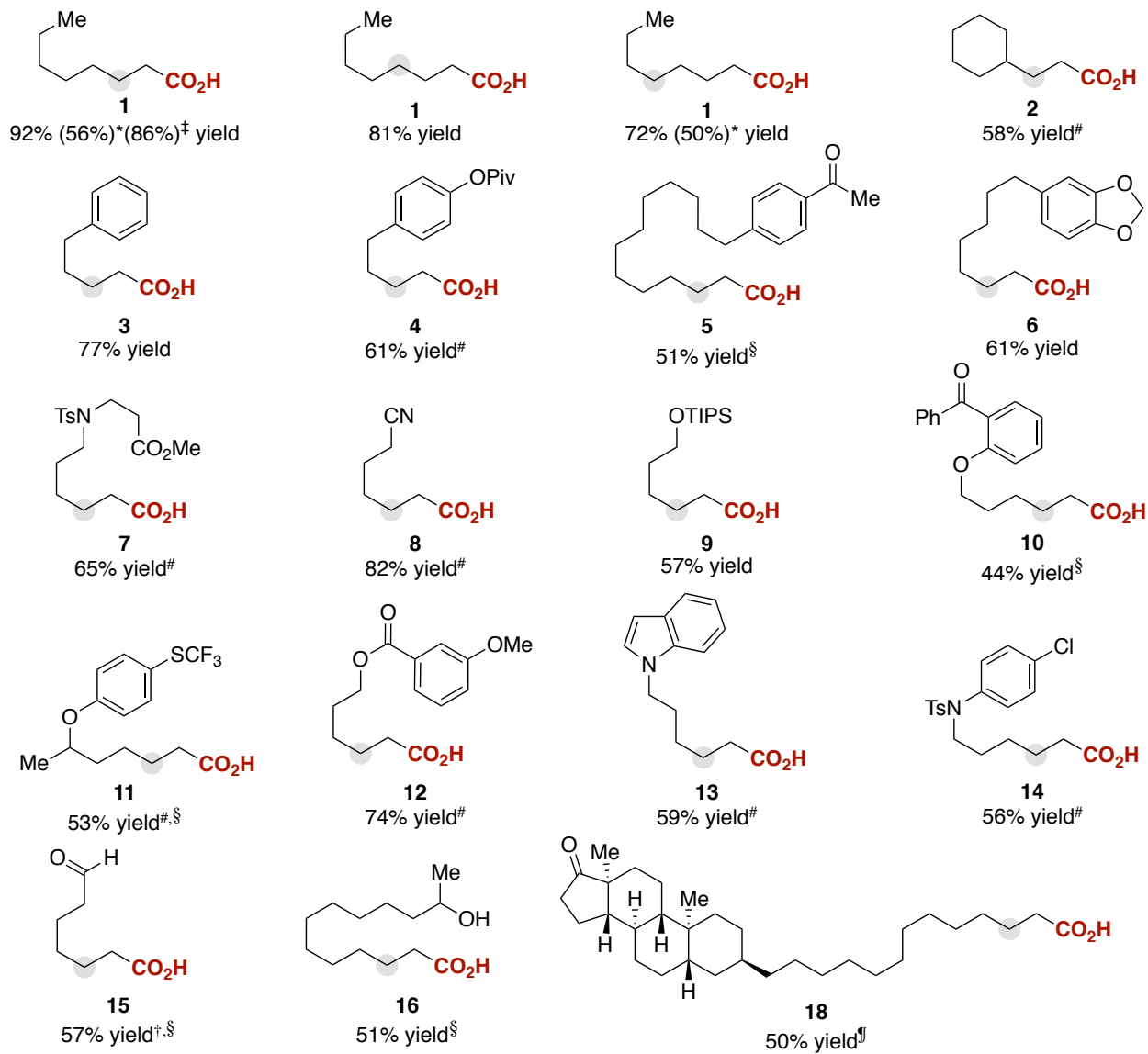


**Fig. 1. Switchable site-selective catalytic carboxylation at remote sp<sup>3</sup> C-H sites**

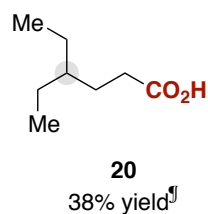
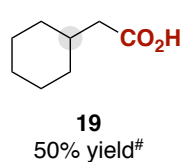
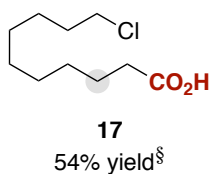
We began our investigations by evaluating the proof-of-principle of our Ni-catalysed remote carboxylation with a discrete alkyl halide (2-bromoheptane) with CO<sub>2</sub> (1 bar) at ambient temperature. After systematically evaluating the reaction parameters, we found that a combination of NiI<sub>2</sub> (2.5 mol%) and bench-stable **L1** (4.4 mol%) afforded octanoic acid (**1**) in 92% isolated yield as single regioisomer using Mn as reductant in DMF at 25 °C. 1,10-Phenanthroline ligands other than **L1** possessing less-sterically encumbered substituents at C2 or C9, or the absence of aromatic groups at C4 or C7 resulted in diminished reactivity (see supplementary information). Control experiments revealed that all of the reaction parameters were critical for success. With optimal conditions in hand, we examined the generality of our transformation by exploring a wide range of discrete secondary alkyl electrophiles (Fig. 2). The reaction turned out to be widely applicable regardless of the constitutional isomer of bromoheptane utilised, yielding exclusively **1** in comparable yields. Notably, the preparation of **1** could be scaled up in 86% yield on a gram scale at 1 mol% Ni. Remarkably, alkyl tosylates could also serve as electrophilic partners. Particularly illustrative was the chemoselectivity profile, as esters (**4**, **7**, **12**), ketones (**5**, **10**, **18**), acetals (**6**, **15**), sulfonamides (**7**, **14**), nitriles (**8**), silyl ethers (**9**), trifluoromethylthiols (**11**), free hydroxyl groups (**16**) or heterocycles (**13**) could all be tolerated, obtaining in all cases linear carboxylic acids. Similarly, aryl/alkyl chlorides or pivalates do not interfere, leaving ample room for further functionalisation via cross-coupling methodologies (**4**, **14** and **17**). Interestingly, no ketone arising from a chain-walking en route to enol-type intermediates in **16** was detected<sup>14</sup>, and perfect linear selectivity was observed in the presence of weak and a priori more reactive benzylic sp<sup>3</sup> C–H bonds within the side-chain (**3-6**)<sup>11</sup>. Variable amounts of internal olefins and reduced byproducts were observed in the carboxylations listed in Fig. 2.



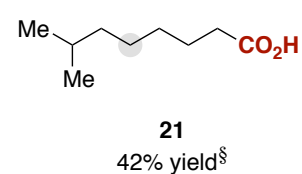
■ secondary alkyl bromides



■ tertiary alkyl bromides



■ site-selectivity



**Fig. 2. Catalytic carboxylation of discrete alkyl halides at remote  $sp^3$  C–H sites.** All yields are isolated yields, average of at least two independent runs. Ts, *p*-toluenesulfonate; TIPS, triisopropylsilyl; Piv, pivaloyl. Conditions: NiI<sub>2</sub> (2.5 mol %), **L1** (4.4 mol %), Mn (3.0 equiv), CO<sub>2</sub> (1 bar), DMF, 25 °C. \* alkyl tosylate as substrate. ‡ 10 mmol scale, NiI<sub>2</sub> (1 mol%), **L1** (1.80 mol%). § NiI<sub>2</sub> (7.5 mol %), **L1** (13.2 mol%). ¶ NiI<sub>2</sub> (10 mol %), **L1** (17.6 mol %). # 10 °C. † from the corresponding acetal after hydrolytic workup.

As this protocol is conducted in the absence of base, substrates possessing relatively  $\alpha$ -acidic protons to carbonyl functions can be tolerated (**5**, **7**, **8**, **18**). Although substrates bearing different primary C( $sp^3$ )–H bonds might lead to site-selectivity issues, exclusive carboxylation took place at the less-hindered primary  $sp^3$  C–H site (**11**). Even single regioisomers could be obtained by using sterically hindered tertiary alkyl bromides **19** and **20**. Excellent site-selectivity could also be accomplished with multiple primary  $sp^3$  C–H sites (**21**).

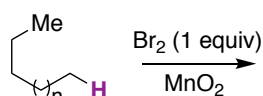
Notably, **1** could be selectively obtained in 83% yield from an equimolecular mixture of regioisomeric bromoheptanes, hence showing the viability for implementing regioconvergent carboxylation processes (see supplementary material). This finding set the basis for unravelling the preparative potential of this method by designing a unified catalytic strategy by which bulk raw materials derived from petroleum processing such as alkanes or alkenes could be used as substrates. The collective one-step synthesis of **1**, **25** and **26** from their alkane congeners (Fig. 3A) or unrefined mixtures of alkenes (Fig. 3B) demonstrates the potential of a catalytic platform that combines chemical feedstocks, demonstrating the synthetic streamlining and the rapid production of added-value compounds from inexpensive raw materials. Neither purification nor isolation of the intermediate halogenated compounds was necessary, showing the robustness of our protocol. As pure  $\alpha$ -olefins are not particularly available at an economically viable price, the



possibility to valorise mixtures of olefins from petroleum processing constitutes a powerful alternative to classical fatty acid synthesis via Reppe-type carbonylation techniques with toxic and hazardous carbon monoxide<sup>23</sup>. A similar scenario could also be integrated en route to **31**, a precursor that can simply be converted into 1,12-dodecanedioic acid (DDA), an important component for the synthesis of Nylon 12<sup>24</sup>.

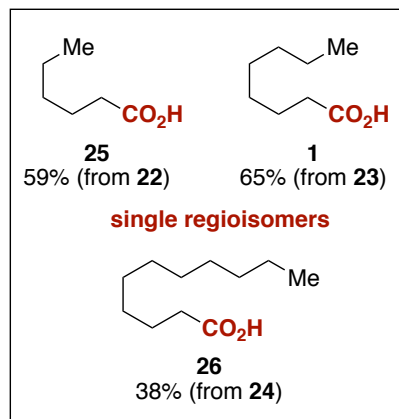
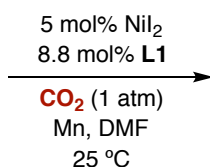
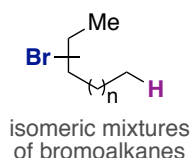
#### A Regioconvergent carboxylation of alkanes with carbon dioxide

multiple  $sp^3$   
C–H bonds

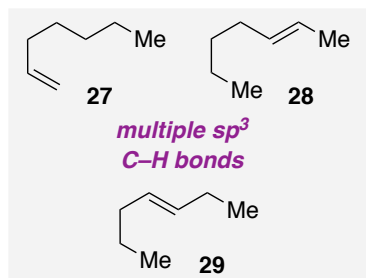


n = 1, **22**  
n = 3, **23**  
n = 6, **24**

no isolation required

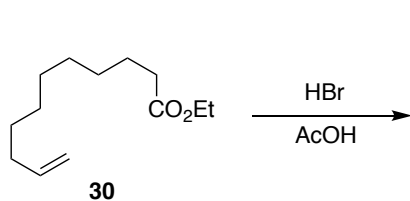
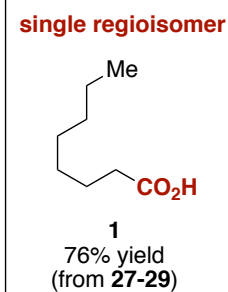
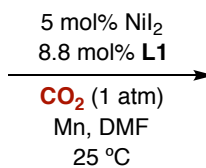
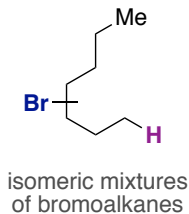


#### B Regioconvergent carboxylation of alkenes with carbon dioxide

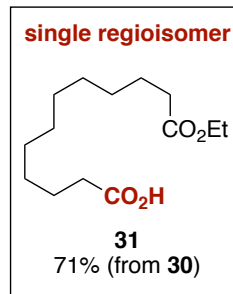
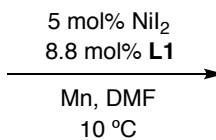
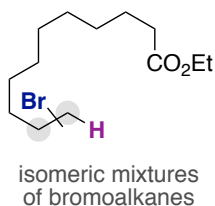


**27:28:29 = 1:1:1**  
isomeric mixtures of olefins

no isolation required



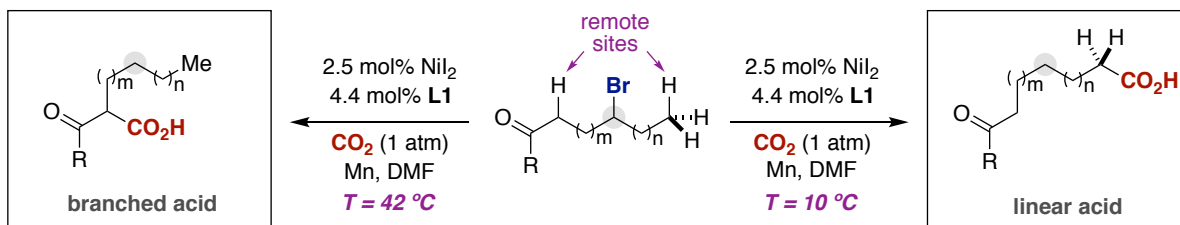
no isolation required



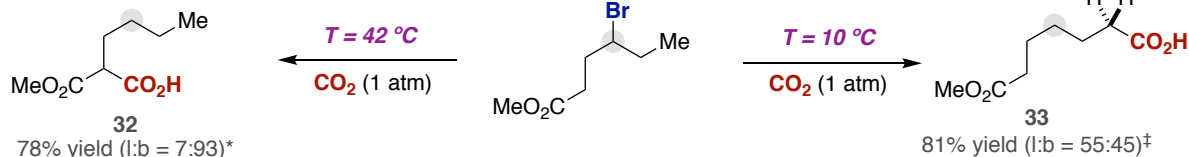
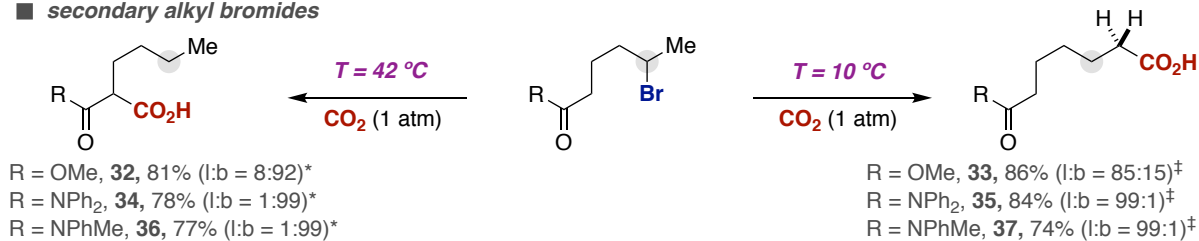
**Fig. 3. Catalytic carboxylation of feedstock materials by regioconvergent events.** Reaction conditions for (A): Br<sub>2</sub> (1 equiv), MnO<sub>2</sub> (2 equiv) and alkane (0.20 M), then as in Fig. 2. Reaction conditions for (B): alkene (1 equiv), HBr in AcOH (1 equiv), then as in Fig. 2.

The use of 2-bromoheptane-1,1,1-*d*<sub>3</sub> resulted in **1** with substantial deuterium incorporation at C2 and C8, suggesting the viability for targeting differently substituted remote sp<sup>3</sup> C–H sites. Specifically, we found an excellent preference for secondary sp<sup>3</sup> C–H sites at 42 °C (**32**, l:b = 8:92), whereas a selectivity switch occurred at 10 °C (**33**, l:b = 85:15) (Fig. 4). As shown for **32** and **33**, lower linear selectivities were found for substrates possessing C–Br bonds proximal to the ester motif. These results suggest that regiodivergency arises from a subtle kinetic and thermodynamic control, forming preferentially an intermediate  $\alpha$ -olefin or an  $\alpha,\beta$ -unsaturated compound that can be thermally-modulated. The generality of this finding could be extended to amides on the side-chain, delivering either branched (**34** and **36**) or linear carboxylic acids (**35** and **37**). The observed 99:1 site-selectivity for amides at either 10 °C or 42 °C cannot be simply attributed to electronic effects, as the pK<sub>a</sub> of the  $\alpha$ -protons of both amides and esters have similar values (pK<sub>a</sub> = 30~32 in DMSO). Regiodivergency could be even accomplished at long-range, a testament to the efficiency of our carboxylation event (**38**, l:b = 6:94). A substrate bearing a tertiary sp<sup>3</sup> C–H bond could also participate in the reaction, leading to either **40** (l:b = 85:15) or quaternary carbon centers (**39**, l:b = 1:99). The limits of our regiodivergent strategy were explored with primary alkyl bromides, showcasing that even substrates prone to carbon-carbon bond-formation prior  $\beta$ -hydride elimination<sup>25</sup> can be used for activating remote sp<sup>3</sup> C–H sites, resulting in either **32** (l:b = 16:84) or **36** (l:b = 1:99).

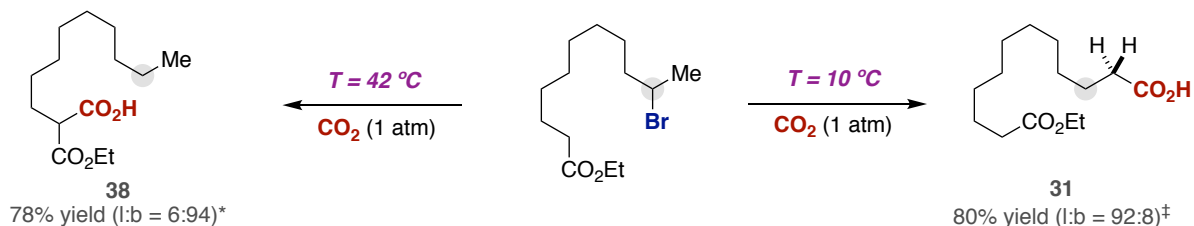
### A Switchable site-selective carboxylation at $sp^3$ C–H remote sites



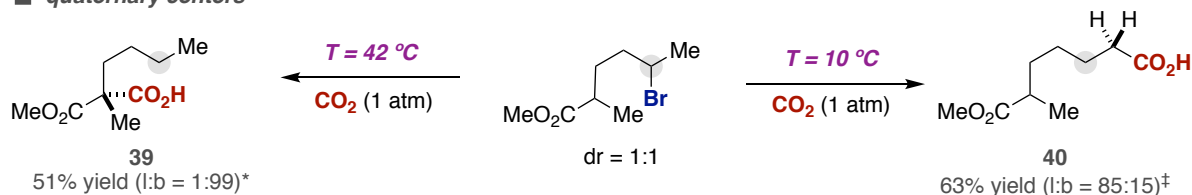
#### ■ secondary alkyl bromides



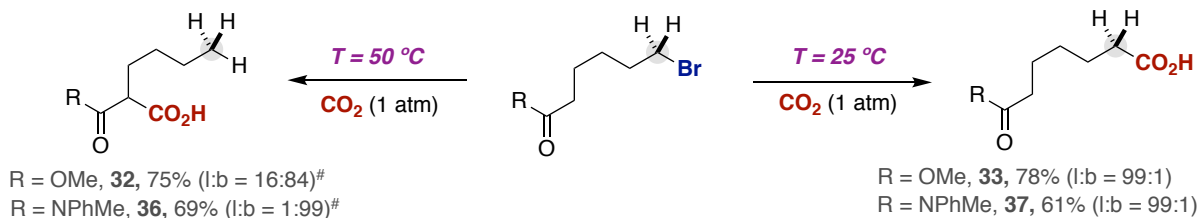
#### ■ long-range remote carboxylation



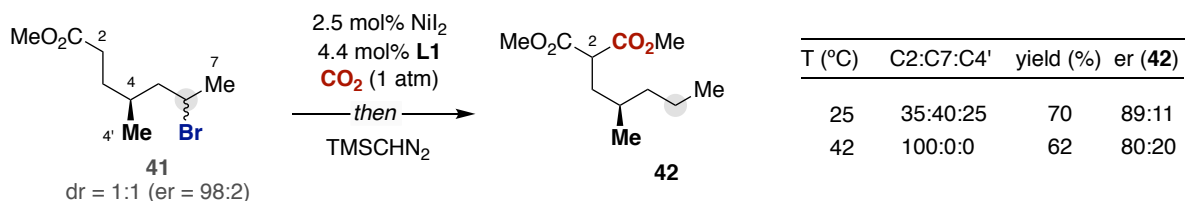
#### ■ quaternary centers



#### ■ primary alkyl bromides



### B Inclusion of pre-existing stereocenters on the side-chain



**Fig. 4. Switchable site-selective carboxylation of unactivated alkyl bromides at remote  $sp^3$  C–H sites.** All yields are isolated yields, average of at least two independent runs (A). Reaction conditions as in Fig. 2 followed by TMSCH<sub>2</sub> treatment (B). \* 42 °C. ‡ 10 °C. # 50 °C.

With an efficient protocol for effecting nickel-catalysed chain-walking carboxylation reactions, we wondered whether the inclusion of pre-existing stereogenic centers on the side-chain would be tolerated. To such end, we conducted the reaction of **41** containing a pre-existing stereogenic center at C4 (er = 98:2). Although we found significant erosion in enantioselectivity at 42 °C (er = 80:20), significant preservation of the chiral integrity at C4 was observed at 25 °C, leading to **42** after subsequent treatment with TMSCHN<sub>2</sub> (er = 89:11). These results tacitly indicate that our nickel catalyst remains ligated to the substrate throughout the chain-walking, constituting a rare example in which pre-existing stereogenic centers are not substantially altered when displacing a catalyst through an alkyl chain<sup>14,26</sup>.

We have established a design principle for the nickel-catalysed carboxylation of alkyl electrophiles with CO<sub>2</sub> at remote  $sp^3$  C–H sites, representing a striking reactivity relay when compared with classical cross-coupling reactions. This new carbon-carbon bond-forming strategy is based on a tunable and controllable chain-walking throughout the alkyl side-chain, enabling regioconvergent events from simple chemical feedstock and exquisite regiodivergency at differently substituted remote sites. The method is characterised by its mildness and chemoselectivity profile, including the preservation of pre-existing stereogenic centers<sup>27</sup>.

## References

1. Colacot, T. *New trends in cross-coupling: Theory and applications* (RSC Catalysis Series, 2015).
2. Kambe, N., Iwasaki, T. & Terao, J. Pd-catalyzed cross-coupling reactions of alkyl halides. *Chem. Soc. Rev.* **40**, 4937-4947 (2011).

3. Vasseur, A., Bruffaerts, J. & Marek, I. Remote functionalization through alkene isomerization. *Nature Chem.* **8**, 209-219 (2016).
4. Szilagy, M. "Aliphatic Carboxylic Acids: Saturated" in *Patty's Toxicology*, E. Bingham, B. Cohrssen, Eds. (Wiley, 2012), vol 3.
5. Netherton, M. R., Dai, C., Neuschütz, K. & Fu, G. C. Room-temperature alkyl-alkyl Suzuki cross-coupling of alkyl bromides that possess  $\beta$  hydrogens. *J. Am. Chem. Soc.* **123**, 10099-10100 (2001).
6. Devasagayaram, A., Studemann, T. & Knochel, P. A new nickel-catalyzed cross-coupling reaction between  $sp^3$  carbon centers. *Angew. Chem. Int. Ed.* **34**, 23-24 (1995).
7. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature*, **509**, 299-309 (2014).
8. Owston, N. A. & Fu, G. C. Asymmetric alkyl-alkyl cross-couplings of unactivated secondary alkyl electrophiles: Stereoconvergent Suzuki reactions of racemic acylated halohydrins. *J. Am. Chem. Soc.* **132**, 11908-11909 (2010).
9. Doyle, A. G. & MacMillan, D. W. C., *et al.* Merging photoredox with nickel catalysis: Coupling of  $\alpha$ -carboxyl  $sp^3$ -carbons with aryl halides. *Science*, **345**, 437-440 (2014).
10. White, M. C. Adding aliphatic C–H bond oxidations to synthesis. *Science* **335**, 807-809 (2012).
11. He, Y., Cai, Y. & Zhu, S. Mild and regioselective benzylic C–H functionalization: Ni-catalyzed reductive arylation of remote and proximal olefins. *J. Am. Chem. Soc.* **139**, 1061-1064 (2017).
12. Choi, G. J., Zhu, Q., Miller, D. C., Gu, C. J. & Knowles, R. R. Catalytic alkylation of remote C–H bonds enabled by proton-coupled electron transfer. *Nature* **539**, 268-271 (2016).
13. Chu, J. C. K. & Rovis, T. Amide-directed photoredox-catalysed C–C bond formation at unactivated  $sp^3$  C–H bonds. *Nature* **539**, 272-275 (2016).
14. Mei, T.-S., Patel, H. H. & Sigman, M. S. Enantioselective construction of remote quaternary stereocentres. *Nature* **508**, 340-344 (2014).
15. For a recent use of alkylzirconium species: Vasseur, A., Perrin, L., Eisenstein, O. & Marek, I. Remote functionalization of hydrocarbons with reversibility enhanced stereocontrol. *Chem. Sci.* **6**, 2770-2776 (2015).

16. For the use of Grignard reagents generated in situ: Dupuy, S., Zhang, K.-F., Goutierre, A.-S. & Baudoin, O. Terminal-selective functionalization of alkyl chains by regioconvergent cross-coupling. *Angew. Chem. Int. Ed.* **55**, 14793-14797 (2016).
17. Correa, A., León, T. & Martin, R. Ni-catalyzed carboxylation of C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-O bonds with CO<sub>2</sub>. *J. Am. Chem. Soc.* **136**, 1062-1069 (2014).
18. Moragas, T., Cornella, J. & Martin, R. Ligand-controlled regiodivergent Ni-catalyzed reductive carboxylation of allyl esters with CO<sub>2</sub>. *J. Am. Chem. Soc.* **136**, 17702-17705 (2014).
19. Liu, Q., Wu, L., Jackstell, R. & Beller, M. Using carbon dioxide as a building block in organic synthesis. *Nature Comm.* **6**, 5933-5947 (2015).
20. For polymerization techniques: Johnson, L. K., Killian, C. M. & Brookhart, M. New Pd(II)- and Ni(II)-based catalysts for polymerization of ethylene and  $\alpha$ -olefins. *J. Am. Chem. Soc.* **117**, 6414-6415 (1995).
21. Hartwig, J. F., *et al.* Linear-selective hydroarylation of unactivated terminal and internal olefins with trifluoromethyl-substituted arenes. *J. Am. Chem. Soc.* **136**, 13098-13101 (2014).
22. Behr, A., *et al.* Highly selective tandem-isomerization hydroformylation reaction of trans-4-octene to nonanal with rhodium-BIPHEPHOS catalysis. *J. Mol. Catal. A Chem.* **206**, 179-184 (2003).
23. Beller, M., *et al.* Transition metal-catalyzed carbonylation reactions of olefins and alkynes: a personal account. *Acc. Chem. Res.*, **47**, 1041-1053 (2014).
24. Chou, R. T. & Bendler, H. V. Polyamide composition containing ionomer, WO2013/101891.
25. Liu, Y., Cornella, J. & Martin, R. Ni-catalyzed carboxylation of unactivated primary alkyl bromides and sulfonates with CO<sub>2</sub>. *J. Am. Chem. Soc.* **136**, 11212-11215 (2014).
26. Singh, S., Bruffaerts, J., Vasseur, A., Marek, I. A unique Pd-catalysed Heck arylation as a remote trigger for cyclopropane selective ring-opening. *Nature Communications* (2017). DOI: 10.1038/ncomms14200.
27. Juliá-Hernández, F., Cornella, J. & Martin, R. Catalytic carboxylation of activated alkanes and/or olefins. EP163823362 (2016).

**Supplementary information** is available in the online version of the paper.

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