## LETTER

# Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide

Francisco Juliá-Hernández<sup>1</sup>, Toni Moragas<sup>1</sup>, Josep Cornella<sup>1</sup> & Ruben Martin<sup>1,2</sup>

Catalytic carbon–carbon bond formation has enabled the streamlining of synthetic routes when assembling complex molecules<sup>1</sup>. It is particularly important when incorporating saturated hydrocarbons, which are common motifs in petrochemicals and biologically relevant molecules. However, cross-coupling methods that involve alkyl electrophiles result in catalytic bond formation only at specific and previously functionalized sites<sup>2</sup>. Here we describe a catalytic method that is capable of promoting carboxylation reactions at remote and unfunctionalized aliphatic sites with carbon dioxide at atmospheric pressure. The reaction occurs via selective migration of the catalyst along the hydrocarbon side-chain<sup>3</sup> with excellent regioand chemoselectivity, representing a remarkable reactivity relay when compared with classical cross-coupling reactions. Our results demonstrate that site-selectivity can be switched and controlled, enabling the functionalization 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 offers an opportunity to integrate a catalytic platform en route to valuable fatty acids by transforming petroleum-derived feedstocks directly<sup>4</sup>.

Methods that incorporate saturated hydrocarbon chains have traditionally been problematic using palladium catalysts<sup>2</sup>. Pioneering work<sup>5,6</sup>

> Figure 1 | Switchable site-selective catalytic carboxylation at remote sp<sup>3</sup> C-H sites. a, Classical cross-coupling reactions involve the use of alkyl electrophiles with carbon-based counterparts (coloured circles labelled 'C') and occur at the original reaction site (left). Reactivity relay (unconventional coupling) in carbon-carbon bond formation of alkyl electrophiles with switchable site-selectivity gives rise to two divergent products from a common precursor (right, paths a and b). b, Mechanistic rationale for the switchable siteselective carboxylation at remote *sp*<sup>3</sup> C–H sites. Tunable and controllable displacement of the Ni catalyst through a saturated hydrocarbon sidechain (nickel catalytic cycles A and B) is shown. c, Application to the direct catalytic conversion of biomass-derived feedstocks into single fatty acids via a tandem bromination/carboxylation process. Coloured circles represent substituents at the aliphatic side-chain.



<sup>1</sup>Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Avinguda Països Catalans 16, 43007 Tarragona, Spain. <sup>2</sup>ICREA, Passeig Lluïs Companys 23, 08010 Barcelona, Spain.

### LETTER RESEARCH



Figure 2 | Catalytic carboxylation of discrete alkyl halides at remote  $sp^3$  C-H sites. Top, reaction studied, with structure of L1 at right; bottom, products 1–21. All yields are isolated yields, the average of at least two independent runs; the variance is estimated to be within 5%. Ts, *p*-toluensulfonate; TIPS, triisopropylsilyl; Piv, pivaloyl. Reaction

demonstrated that nickel catalysts markedly improved the efficiency of alkyl cross-coupling reactions by minimizing the rate of unproductive  $\beta$ -hydride elimination that leads to alkene by-products. These reports prompted the design of 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 visiblelight 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, carbon–carbon bond formation in hydrocarbons is problematic, owing to the presence of multiple, yet similar, sp<sup>3</sup> C-H positions. Several methodologies have tackled this issue by activating weak sp<sup>3</sup> C-H bonds<sup>11</sup> or by using directing groups at a specific location within the side-chain<sup>12–15</sup>. As part of our interest in nickelcatalysed carboxylations<sup>16,17</sup>, we sought to develop a protocol for incorporating carbon dioxide (CO<sub>2</sub>) at remote sp<sup>3</sup> C-H sites en route to fatty acids (Fig. 1a, right), which are relevant in the manufacture of soaps, detergents, rubber, plastics and dyes<sup>4,18</sup>. Indeed, the global market for carboxylic acids is anticipated to reach approximately \$20 billion by 2023, expanding at an annual growth rate of 5% from 2017 to 2023<sup>4</sup>.

A detailed description of our design principle is outlined in Fig. 1b. Although 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 fine-tuning of the ligand on the nickel catalyst could accelerate the rate of  $\beta$ -hydride elimination from I before CO<sub>2</sub> insertion, providing a



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.  $\pm$ 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.  $\pm$ From the corresponding acetal after hydrolytic workup.

basis for a chain-walking via iterative β-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>11,14,19–21</sup> and/or the use of noble expensive metals<sup>19,22</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 a strategy could be implemented, we speculated that valuable fatty acids could be within reach by directly reacting raw materials derived in bulk from 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 a scenario would constitute a unique platform for converting simple chemical feedstocks into valuable compounds.

We began our investigations by evaluating a proof-of-principle of our Ni-catalysed remote carboxylation with a discrete alkyl halide (2-bromoheptane) and  $CO_2$  (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%; Fig. 2) afforded octanoic acid (1; Fig. 2) in 92% isolated yield as a single regioisomer using Mn as reductant in DMF (dimethylformamide) 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



Figure 3 | Catalytic carboxylation of feedstock materials by regioconvergent events. a, Regioconvergent carboxylation of alkanes (left) with  $CO_2$  via a radical bromination/carboxylation process, to obtain single-regioisomer carboxylic acids (right, boxed). Reaction conditions: Br<sub>2</sub> (1 equiv.), MnO<sub>2</sub> (2 equiv.) and alkane (0.20 M), then as in Fig. 2.

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 used, 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 informative was the chemoselectivity profile, as esters (4, 7, 12), ketones (5, 10, 18), acetals (6, 15), sulfonamides (7, 14), nitriles (8), silvl 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 functionalization via cross-coupling methodologies (4, 14 and 17). 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 by-products were observed in the carboxylations listed in Fig. 2.

As this protocol is conducted in the absence of base, substrates possessing relatively acidic protons in the  $\alpha$  position relative to carbonyl functional groups can be tolerated (5, 7, 8, 18). Although substrates bearing different primary  $C(sp^3)$ –H bonds might lead to siteselectivity 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).

We note that **1** could be selectively obtained in 83% yield from an equimolecular mixture of regioisomeric bromoheptanes, showing the viability of implementing regioconvergent carboxylation processes

**b**, Regioconvergent carboxylation of mixtures of alkenes with carbon dioxide via a hydrobromination/carboxylation process (top) and use of pure  $\alpha$ -olefin **30** (bottom). Reaction conditions: alkene (1 equiv.), HBr in AcOH (1 equiv.), then as in Fig. 2.

(see Supplementary Information). This finding provided 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 from unrefined mixtures of alkenes (Fig. 3b) showcases 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 generally available at an economically viable price, the possibility of using mixtures of olefins from petroleum processing to prepare fatty acids constitutes a powerful alternative to classical Reppe-type carbonylation techniques with toxic and hazardous carbon monoxide<sup>23</sup>. A similar reaction could also be integrated en route to 31 (Fig. 3b) that can simply be converted into 1,12-dodecanedioic acid (DDA), which is an important component of the synthesis of nylon 12 (ref. 24).

The use of 2-bromoheptane-1,1,1- $d_3$  resulted in 1 with substantial deuterium incorporation at C2 and C8, suggesting the viability of targeting differently substituted remote  $sp^3$  C–H sites (see Supplementary information). Specifically, we found an excellent preference for secondary  $sp^3$  C–H sites at 42 °C (32, linear:branched (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 sidechain, delivering either branched (34 and 36) or linear carboxylic

### LETTER RESEARCH



**Figure 4** | **Switchable site-selective carboxylation of unactivated alkyl bromides at remote** *sp*<sup>3</sup> **C**–**H sites.** All yields are isolated yields, the average of at least two independent runs; the variance is estimated to be within 5%. **a**, Top, reactions studied; bottom, scope of reactants. Temperature-dependent switchable site-selective carboxylation at *sp*<sup>3</sup>

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  $pK_a$  of the  $\alpha$ -protons of both amides and esters have similar values ( $pK_a = 30-32$  in DMSO, dimethylsulfoxide). 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  $sp^3$  C–H bond could also participate in the reaction, leading to either **40** (l:b = 85:15) or quaternary carbon centres (**39**, l:b = 1:99). The limits of our regiodivergent strategy were explored with primary alkyl bromides, and showed that even substrates prone to carbon–carbon bond formation before  $\beta$ -hydride elimination<sup>25</sup> can be used for

C–H remote sites is shown. Reaction conditions as in Fig. 2 at the selected temperature. **b**, Retention of configuration of pre-existing stereocentres on the side-chain. Reaction conditions as in Fig. 2 followed by TMSCH<sub>2</sub> treatment. Table at right shows effect of temperature. d.r., diastereomeric ratio; e.r., enantiomeric ratio. \*42 °C.  $\pm 10$  °C.

activating remote  $sp^3$  C–H sites, resulting in either **32** (l:b = 16:84) or **36** (l:b = 1:99).

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

**Online Content** Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

#### Received 27 January; accepted 30 March 2017.

- Colacot, T. New Trends in Cross-coupling: Theory and Applications (RSC Catalysis Series, 2015).
- Kambe, N., Iwasaki, T. & Terao, J. Pd-catalyzed cross-coupling reactions of alkyl halides. *Chem. Soc. Rev.* 40, 4937–4947 (2011).
- Vasseur, A., Bruffaerts, J. & Marek, I. Remote functionalization through alkene isomerization. Nat. Chem. 8, 209–219 (2016).
- Szilagyi, M. in *Patty's Toxicology* Vol. 3 (eds Bingham, E. & Cohrssen, B.) Ch. 48 (Wiley, 2012).
- Netherton, M. R., Dai, C., Neuschutz, K. & Fu, G. C. Room-temperature alkyl-alkyl Suzuki cross-coupling of alkyl bromides that possess β hydrogens. J. Am. Chem. Soc. 123, 10099–10100 (2001).
- Devasagayaraj, A., Studemann, T. & Knochel, P. A new nickel-catalyzed cross-coupling reaction between sp<sup>3</sup> carbon centers. *Angew. Chem. Int. Ed. Engl.* 34, 23–24 (1995).
- Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* 509, 299–309 (2014).
- 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).
- Zuo, Z. et al. Merging photoredox with nickel catalysis: coupling of α-carboxyl sp<sup>3</sup>-carbons with aryl halides. Science **345**, 437–440 (2014).
- White, M. C. Adding aliphatic C–H bond oxidations to synthesis. Science 335, 807–809 (2012).
- 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).
- 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).
- Chu, J. C. K. & Rovis, T. Amide-directed photoredox-catalysed C–C bond formation at unactivated sp<sup>3</sup> C–H bonds. *Nature* 539, 272–275 (2016).
- Mei, T.-S., Patel, H. H. & Sigman, M. S. Enantioselective construction of remote quaternary stereocentres. *Nature* 508, 340–344 (2014).
- Vasseur, Á., Perrin, L., Eisenstein, O. & Marek, I. Remote functionalization of hydrocarbons with reversibility enhanced stereocontrol. *Chem. Sci.* 6, 2770–2776 (2015).
- 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).

- 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).
- Liu, Q., Wu, L., Jackstell, R. & Beller, M. Using carbon dioxide as a building block in organic synthesis. *Nat. Commun.* 6, 5933 (2015).
- 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).
- Johnson, L. K., Killian, C. M. & Brookhart, M. New Pd(II)- and Ni(II)-based catalysts for polymerization of ethylene and α-olefins. J. Am. Chem. Soc. 117, 6414–6415 (1995).
- Bair, J. S. et al. Linear-selective hydroarylation of unactivated terminal and internal olefins with trifluoromethyl-substituted arenes. J. Am. Chem. Soc. 136, 13098–13101 (2014).
- Behr, A. et al. Highly selective tandem-isomerization hydroformylation reaction of trans-4-octene to n-nonanal with rhodium-BIPHEPHOS catalysis. J. Mol. Catal. Chem. 206, 179–184 (2003).
- Wu, X.-F. et al. Transition metal-catalyzed carbonylation reactions of olefins and alkynes: a personal account. Acc. Chem. Res. 47, 1041–1053 (2014).
- Chou, R. T. & Bendler, H. V. Polyamide composition containing ionomer. WO patent WO/2013/101891 (2013).
- 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).
- Singh, S., Bruffaets, J., Vasseur, A. & Marek, I. A unique Pd-catalysed Heck arylation as a remote trigger for cyclopropane selective ring-opening. *Nat. Commun.* 8, 14200 (2017).

Supplementary Information is available in the online version of the paper.

Acknowledgements We are grateful for financial support provided by ICIQ, the European Research Council (ERC-StG-277883 and ERC-2015-PoC-713577), MINECO (CTQ2015-65496-R and Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-0319) and the Cellex Foundation. F.J.-H. and J.C. thank COFUND and Marie Curie Actions for an Intra-European Fellowship (FP7-PEOPLE-2012-IEF-328381).

Author Contributions F.J.-H., T.M. and J.C. performed and analysed the experiments. R.M. wrote the manuscript. All authors commented on the final manuscript and contributed to the analysis and interpretation of the results.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details are available in the online version of the paper. Readers are welcome to comment on the online version of the paper. Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. Correspondence and requests for materials should be addressed to R.M. (rmartinromo@iciq.es).

**Reviewer Information** *Nature* thanks I. Marek and the other anonymous reviewer(s) for their contribution to the peer review of this work.

#### **METHODS**

**General carboxylation procedure.** An oven-dried Schlenk tube containing a stirring bar was charged with NiI<sub>2</sub> (2.5–10.0 mol%), L1 (4.4–17.6 mol%) and Mn powder (3 equiv.). The Schlenk tube was then evacuated and back-filled under a CO<sub>2</sub> flow (this sequence was repeated three times) and finally an atmospheric pressure of CO<sub>2</sub> was established. The corresponding alkyl bromide (0.5 mmol) and DMF (1 M) were added under a CO<sub>2</sub> flow. Once added, the Schlenk tube was closed at atmospheric pressure of CO<sub>2</sub> (1 atm) and stirred at the desired

temperature for 20–48 h. The mixture was then carefully quenched with 2 M HCl to hydrolyse the resulting carboxylate and extracted with EtOAc (three times). The combined organic layer was washed with brine (three times), dried over anhydrous MgSO<sub>4</sub>, filtrated and evaporated. The resulting crude carboxylic acid was purified by conventional flash chromatography in silica gel using hexanes/EtOAc 3:1 with 1% formic acid.

**Data availability.** The data supporting the findings of this study are available within the paper and its Supplementary Information.