

C–H Functionalization

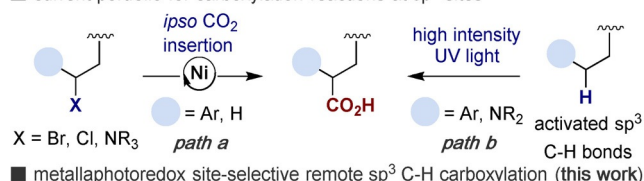
Site-Selective, Remote sp^3 C–H Carboxylation Enabled by the Merger of Photoredox and Nickel CatalysisBasudev Sahoo,^[a] Peter Bellotti,^[b] Francisco Juliá-Hernández,^[a] Qing-Yuan Meng,^[b] Stefano Crespi,^{*,[b]} Burkhard König,^{*,[b]} and Ruben Martin^{*,[a, c]}

Abstract: A photoinduced carboxylation of alkyl halides with CO₂ at remote sp^3 C–H sites enabled by the merger of photoredox and Ni catalysis is described. This protocol features a predictable reactivity and site selectivity that can be modulated by the ligand backbone. Preliminary studies reinforce a rationale based on a dynamic displacement of the catalyst throughout the alkyl side chain.

Metal-catalyzed reductive carboxylation reactions of organic (pseudo)halides with abundant and inexpensive carbon dioxide (CO₂)^[1] have provided new vistas for preparing industrially-relevant carboxylic acids in the absence of stoichiometric organometallic reagents.^[2] Although this area of expertise has reached remarkable levels of sophistication, the vast majority of sp^3 carboxylation reactions primarily rely on *ipso*-CO₂ insertions at prefunctionalized sites (Scheme 1, path a).^[3,4]

From both a conceptual and practical standpoint, the ability to expand the boundaries of CO₂ fixation into unactivated sp^3 C–H sites would be a particularly attractive scenario.^[5] Unfortunately, the available sp^3 C–H carboxylation portfolio indicates that a vast number of daunting challenges remain.^[6] At present, photochemical techniques^[7] remain confined to the activation of sp^3 C–H bonds adjacent to heteroatoms or aromatic rings, invariably requiring high-intensity UV-light irradiation

■ current portfolio for carboxylation reactions at sp^3 sites



Scheme 1. Merging Ni and photoredox catalysts for sp^3 C–H carboxylation.

(Scheme 1, path b).^[8] The latter is particularly problematic given the wide number of functional groups that absorb in the UV region, leading to deleterious side-reactions arising from photoexcitation of the substrate itself, thus reinforcing the need for a sp^3 C–H carboxylation technique with improved flexibility, generality and practicality. A significant step-forward in sp^3 C–H carboxylation has been recently reported by our group within the context of chain-walking reactions; however, stoichiometric amounts of metal salts are inevitably required,^[4d,9] thus hampering the implementation of these processes in industrial endeavors.^[10] Prompted by our interest in nickel catalysis and visible-light-induced processes,^[3b–g,4b–d,9] we wondered whether the merger of these two techniques might enable a CO₂ insertion at remote sp^3 C–H sites in the absence of stoichiometric metal salts, thus offering an unrecognized opportunity in metallaphotoredox^[11,12] and carboxylation reactions.^[1] Herein, we report the successful realization of this goal by using alkyl halides as precursors (Scheme 1, bottom). The protocol is characterized by a site-selectivity pattern that can be modulated by a subtle modification of the ligand backbone, thus resulting in the functionalization at benzylic or even at primary sp^3 C–H sites, arguably the strongest C–H bonds in the alkyl series. Preliminary mechanistic studies suggest that a dynamic displacement of the nickel catalyst throughout the hydrocarbon side chain through Ni^{II} intermediates comes into play.^[13]

Our investigations began by studying the Ni-catalyzed carboxylation of homobenzylic bromide (**1a**) with CO₂ (1 bar; Scheme 2). After systematic evaluation of all reaction parameters,^[14] we found that a protocol based on (L1)NiBr₂, organic photocatalyst 4-CzIPN, K₂CO₃ and Hantzsch ester (HEH) as the

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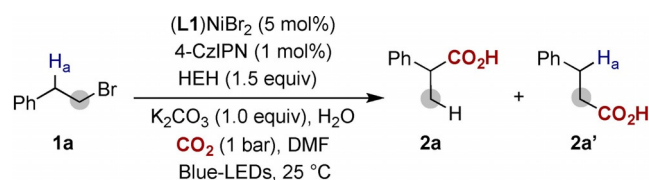
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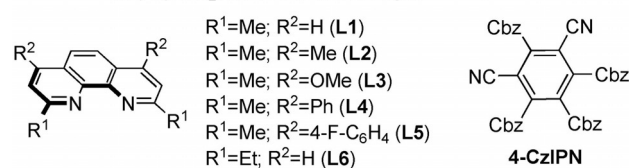
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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/chem.201902095>.

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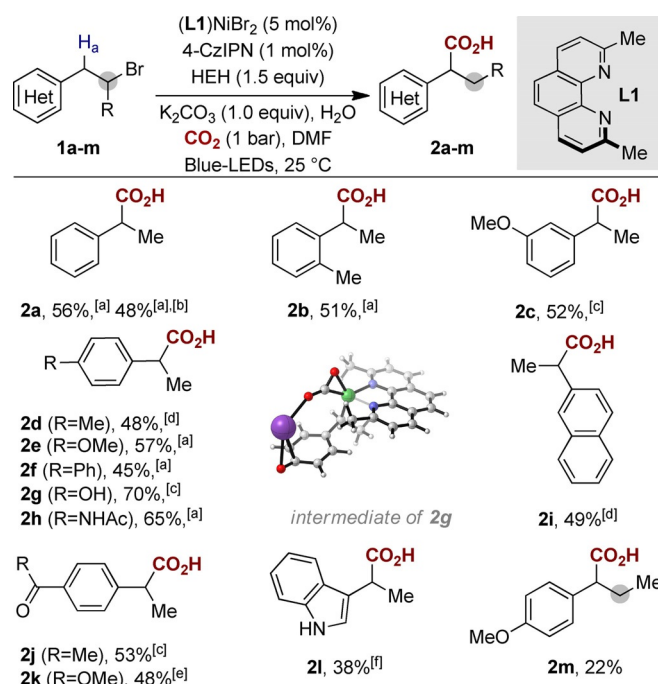
entry	deviation from standard conditions	yield (%) ^{[a],[b]}	2a/2a'
1	none	66 (56)	90:10
2	(L2)NiBr ₂ instead of (L1)NiBr ₂	36	70:30
3	(L3)NiBr ₂ instead of (L1)NiBr ₂	28	71:29
4	(L4)NiBr ₂ instead of (L1)NiBr ₂	30	62:38
5	(L5)NiBr ₂ instead of (L1)NiBr ₂	42	72:28
6	(L6)NiBr ₂ instead of (L1)NiBr ₂	55	85:15
7	NiBr ₂ glyme/L1 instead of (L1)NiBr ₂	58	90:10
8	using HEH (1.0 equiv)	59	90:10
9	using 4 Å MS instead of H ₂ O	50	85:15
10	using LiBr (1.0 equiv)	61	84:16
11	Cs ₂ CO ₃ instead of K ₂ CO ₃	35	42:58
12	no (L1)NiBr ₂ , no 4-CzIPN or no light	0	—



Scheme 2. Optimization of the reaction conditions. 1a (0.20 mmol), (L1)NiBr₂ (5 mol%), 4-CzIPN (1 mol%), HEH (1.5 equiv), K₂CO₃ (1.0 equiv), H₂O (5.0 equiv), CO₂ (1 bar), Blue-LEDs in DMF (0.1 M) at 25 °C for 5 h. [a] Yields determined by NMR using 1,3,5-trimethoxybenzene as standard. [b] Isolated yield, average of two independent runs. 4-CzIPN: 2,4,5,6-tetra(carbazol-9-yl)-isophthalonitrile; DMF = *N,N*-dimethylformamide; Cbz = carbazole; HEH = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

terminal reductant provided the best results, giving rise to the targeted carboxylic acid in 56% isolated yield with a 90:10 branched/linear selectivity (b/l; entry 1). As initially anticipated, subtle modifications on the ligand backbone resulted in a markedly decrease in reactivity; although the inclusion of substituents adjacent to the nitrogen atom was shown to be critical for success,^[15] it became apparent that aryl or alkyl groups at C4 and/or C7 had a deleterious effect in both selectivity and reactivity (entries 2–6). Intriguingly, the utilization of desiccants led to lower yields of 2a (entry 9), thus revealing a non-innocent role exerted by water.^[4d] Unlike related Ni-catalyzed carboxylations of organic (pseudo)halides,^[3] the presence of additives, such as LiBr, was not necessary for the reaction to occur (entry 10); notably, K₂CO₃ provided better results than Cs₂CO₃ (entry 11), showing the influence that the escorting cation might have on reactivity. As anticipated, control experiments in the absence of either (L1)NiBr₂, 4-CzIPN or light resulted in no conversion to 2a (entry 12).

With optimized conditions in hand, we next set out to explore the generality of our light-induced Ni-catalyzed carboxylation at benzylic sp³ C–H sites. As shown in Scheme 3, similar reactivity and site selectivity were obtained for a plethora of homobenzyl bromides independent of whether they possessed electron-rich or electron-poor substituents on the aryl ring. However, it is worth noting that electron-donating groups provided the best yields of the series (2e, 2g, 2h).^[16] As shown

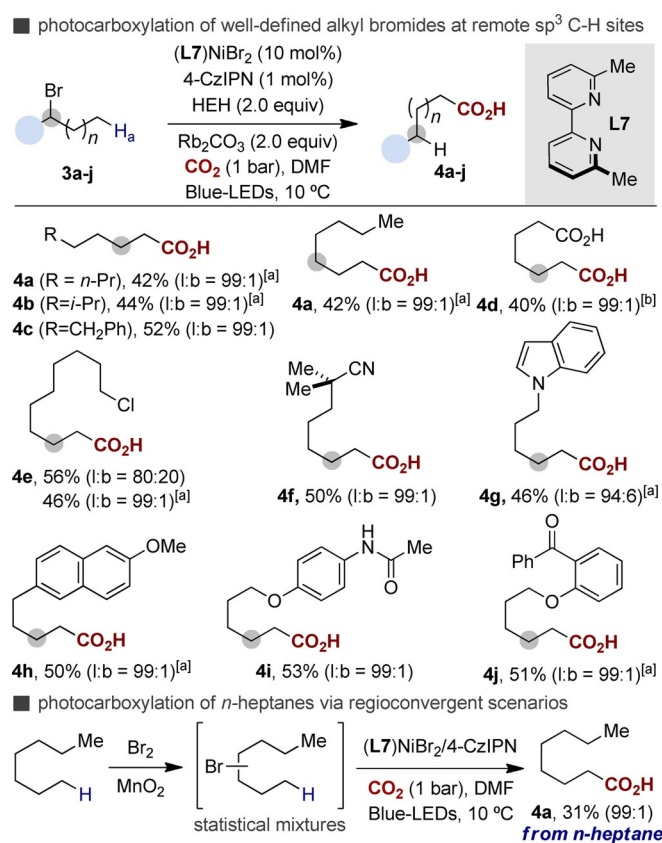


Scheme 3. Benzylic sp³ C–H carboxylation by merging Ni and photoredox catalysis. Conditions: see Scheme 2 (entry 1); yields of isolated products, average of two independent runs. [a] b/l = 90:10. [b] 1.0 mmol scale. [c] b/l = 85:15. [d] b/l = 93:7. [e] Isolated as methyl ester. [f] b/l = 80:20. For additional substrates, see Supporting Information.^[14]

for 2a, the reaction can be scaled-up without significant erosion in yield or site selectivity. Importantly, phenols (2g), amides (2h), ketones (2j) or esters (2k) do not interfere with productive carboxylation at the benzylic sp³ C–H site. Phenol (2g) gave higher yields, most likely through Lewis-acidic assistance of K⁺ during the CO₂ insertion (Scheme 3, middle).^[17] We found that our protocol can be extended to electron-rich unprotected indoles (2i) or secondary homobenzylic bromides (2m), albeit in lower yields. The latter result is particularly interesting, particularly if one takes into consideration the inherent structural limitations observed in otherwise related carboxylation of benzyl halides possessing α-substituents other than methyl groups.^[3f–h]

Although the results summarized in Scheme 3 clearly illustrated the feasibility of a benzylic sp³ C–H carboxylation in the absence of metal reductants, there was a reasonable doubt on whether our protocol could be extended to carboxylation events at distal, primary sp³ C–H sites. Undoubtedly, the successful realization of such a void terrain would unlock new fundamental reactivity within the metallaphotoredox arena^[11,12] while expanding our repertoire when activating strong primary sp³ C–H bonds in the presence of a priori more reactive sites.^[18] As expected, the ligand had a non-negligible impact on both efficiency and site selectivity.^[15] Indeed, the reaction of 2-bromoheptane (3a) under the optimized conditions of Scheme 3 based on a Ni/L1 regime resulted in traces, if any, of 1-octanoic acid (4a). However, a protocol based on Ni/L7 furnished 4a in 42% yield and with exquisite site selectivity (99:1).^[19] Importantly, although an excellent site selectivity was

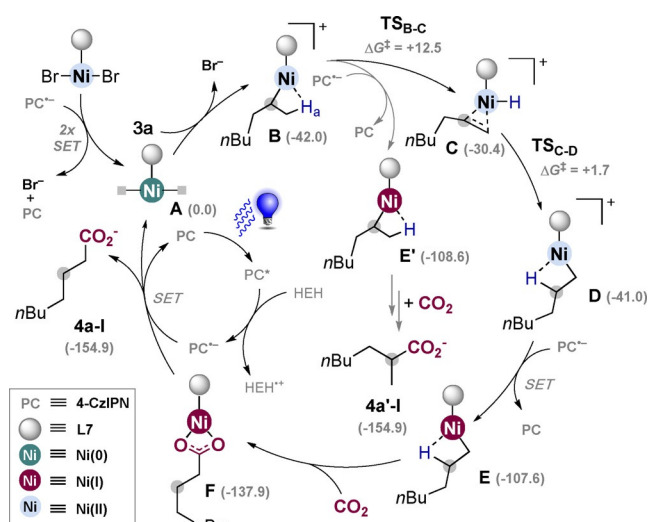
found for a Ni-catalyzed protocol based on 2,9-dihexyl-4,7-diphenyl-1,10-phenanthroline as ligand and Mn as terminal reductant,^[9] a photochemical event based on such ligand backbone resulted in a significant erosion in yield and site-selectivity, thus showing the subtleties of our photocatalytic chain-walking carboxylation.^[14] As shown in Scheme 4, a variety of linear carboxylic acids could be prepared from a range of alkyl bromides in excellent site selectivities through formal $[1,n]$ -migration of the Ni atom throughout the side chain. Although modest yields, the outcome of our remote Ni/photoredox carboxylation at primary sp^3 C–H sites should be assessed against the challenge that it addresses. Particularly noteworthy was the site-selectivity pattern observed for **4g–4j**, with CO_2 insertion occurring at the strongest, primary sp^3 C–H sites. Given that primary alkyl radicals are beyond reach through hydrogen-atom transfer (HAT),^[20] these results constitute an orthogonal gateway with existing UV-mediated carboxylations occurring at weaker benzylic sites or adjacent to heteroatoms through open-shell species (Scheme 1, path b).^[8] Equally interesting was the functional group compatibility in the presence of esters (**4d**), nitriles (**4f**), ketones (**4j**), alkyl chlorides (**4e**) or amides (**4i**). Notably, the alkyl bromide derived from a nonster-



Scheme 4. Catalytic carboxylation at remote sp^3 C–H sites by merging Ni & photoredox catalysis. Conditions: **3** (0.25 mmol), (L7)NiBr₂ (10 mol %), 4-CzIPN (1 mol %), HEH (2.0 equiv), Rb₂CO₃ (2.0 equiv), CO₂ (1 bar), DMF (0.08 M), blue LEDs in DMF at 10 °C for 20 h; yields of isolated products, average of two independent runs. [a] TBAI (1.0 equiv) as additive. [b] Obtained upon hydrolytic workup using methyl 5-bromohexanoate. Regioconvergent photocarboxylation of *n*-heptane: Br₂ (0.25 mmol), MnO₂ (0.50 mmol) in *n*-heptane (1.25 mL) followed by the conditions highlighted above for **4a**.

oidal anti-inflammatory drug such as Nabumetone delivered **4h** in a 99:1 ratio.^[21] Similarly, **4b** was obtained as a single regioisomer, indicating that the reaction took place at the most accessible sp^3 C–H site. Although competitive C3-carboxylation events might occur with electron-rich indoles,^[22] this was not the case (**4g**). Particularly rewarding was the ability to convert *n*-heptane into **4a** (l:b = 99:1) through bromination/chain-walking photocarboxylation (Scheme 4, bottom), standing as a testament to the prospective impact of our protocol to repurpose chemical feedstocks (alkanes and CO₂) in a controllable fashion.

Although unraveling the underpinnings of our Ni/photoredox chain-walking carboxylation at sp^3 C–H sites should await further investigations, we decided to shed light into the mechanism through combined experimental and theoretical studies (Scheme 5).^[14] Synergistic spectroelectrochemical measurements and in situ UV/Vis spectroscopy on (L1)NiBr₂ and (L7)NiBr₂ revealed that low-valent Ni^I and Ni⁰ species are formed during light irradiation in the presence of 4-CzIPN and Hantzsch ester.^[14,23] The assumption that the benzylic carboxylation featured a rather facile β -H elimination from cationic Ni^{II} species was experimentally corroborated by detecting styrenes in small amounts, the concentration of which decays to zero after consumption of the alkyl bromide.^[14] In addition, olefins were not detected in the absence of Ni/L1 or Ni/L7, arguing against base-promoted E2-elimination/olefin carboxylation event. DFT calculations confirmed that species B–D had similar energy and that these species coexist in rapid equilibrium via rather facile β -H elimination from cationic Ni^{II} intermediates.^[24,25] Importantly, DFT calculations revealed a rather unfavorable CO₂ insertion for Ni^{II} species D, either through outer- or inner-sphere mechanisms, reinforcing the notion that CO₂ takes place at a Ni^I center (E) generated upon single-electron transfer (SET), thus giving rise to a Ni^I-carboxylate F.^[26] A final SET can provide **4a–l** while recovering back the propagating



The relative Gibbs free Energy (kcal mol⁻¹) at the SMD(DMF)-BS-UoB97X-D/def2-TZVP/BS-UoB97X-D/6-31G(d) of the intermediates are reported in brackets. All the energies are relative to A, see Ref. [14]

Scheme 5. Mechanistic rationale for the photocarboxylation of **3a**.

Ni⁰/L7 (A) species. Although the activation energy for the SET reduction could not be obtained by DFT calculations, the absence of a kinetic isotope effect and the preferential regioselectivity observed at remote primary sp³ C–H sites (4a-I vs. 4a-I') suggests that the formation of Ni^I species might be the rate-determining step of the reaction. A similar rationale can be drawn for homobenzylic bromides, with an energetic profile that favors CO₂ incorporation at benzylic sp³ C–H sites.^[14] In this case, the selectivity at benzylic sites can be explained by both kinetic and thermodynamic grounds.^[14]

In summary, we have described the merger of photoredox and Ni catalysis as a platform for enabling carboxylation at remote sp³ C–H sites under atmospheric pressure of CO₂, thereby obviating the need for stoichiometric metal reductants. The salient features of this method are the mild conditions and a site-selectivity pattern that can be modulated by the nature of the ligand employed, offering an unrecognized opportunity in the metallaphotoredox arena for the activation of sp³ C–H bonds. Further work along these lines is currently in progress.

Acknowledgements

We thank ICIQ and MINECO (CTQ2015-65496-R) for support. B.S. and P.B. thank European Union Horizon 2020 under the Marie Skłodowska-Curie grant agreement (795961) and Elitenetzwerk Bayern (SynCat) for financial support. We thank C. Riesinger for the initial optimization of the reaction conditions, F. Fricke for the help with substrate scope, R. Hoheisel for spectroelectrochemical measurements, and B. F. Gu for helpful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: carbon dioxide • carboxylation • chain-walking • nickel • photocatalysis

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Manuscript received: May 7, 2019

Accepted manuscript online: May 9, 2019

Version of record online: June 6, 2019