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## C–H Functionalization

# Site-Selective, Remote sp$^3$ C–H Carboxylation Enabled by the Merger of Photoredox and Nickel Catalysis

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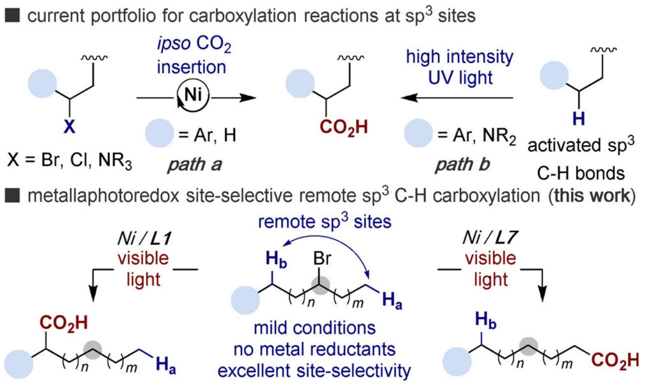
**Abstract:** A photoinduced carboxylation of alkyl halides with $CO_2$ at remote sp$^3$ C–H sites enabled by the merger of photoredox and Ni catalysis is described. This protocol features a predictable reactivity and site selectivity that can be modulated by the ligand backbone. Preliminary studies 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 ($CO_2$)[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*-$CO_2$ insertions at prefunctionalized sites (Scheme 1, path a).[3,4]

From both a conceptual and practical standpoint, the ability to expand the boundaries of $CO_2$ 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 (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 $CO_2$ 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]



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

Our investigations began by studying the Ni-catalyzed carboxylation of homobenzylic bromide (**1 a**) with $CO_2$ (1 bar; Scheme 2). After systematic evaluation of all reaction parameters,[14] we found that a protocol based on (**L1**)$NiBr_2$, organic photocatalyst 4-CzIPN, $K_2CO_3$ and Hantzsch ester (HEH) as the

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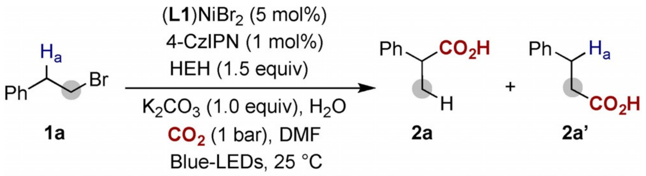
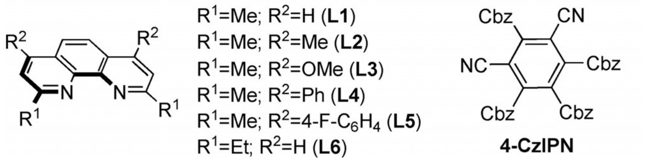
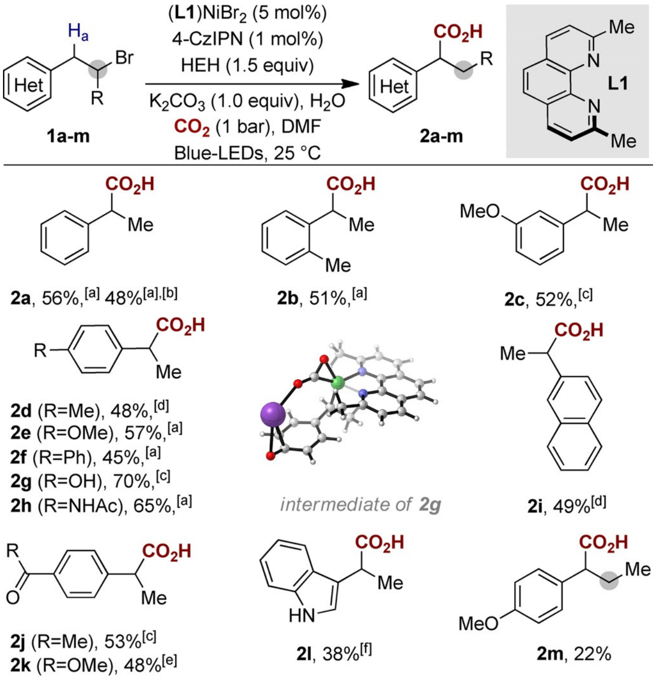


| entry | deviation from standard conditions | yield (%)[a],[b] | 2a/2a' |
|---|---|---|---|
| ***1*** | ***none*** | ***66 (56)*** | ***90:10*** |
| 2 | (**L2**)$NiBr_2$ instead of (**L1**)$NiBr_2$ | 36 | 70:30 |
| 3 | (**L3**)$NiBr_2$ instead of (**L1**)$NiBr_2$ | 28 | 71:29 |
| 4 | (**L4**)$NiBr_2$ 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 4Å MS instead of $H_2O$ | 50 | 85:15 |
| 10 | using LiBr (1.0 equiv) | 61 | 84:16 |
| 11 | $Cs_2CO_3$ instead of $K_2CO_3$ | 35 | 42:58 |
| 12 | no (**L1**)$NiBr_2$, no 4-CzIPN or no light | 0 | — |



**Scheme 2.** Optimization of the reaction conditions. **1 a** (0.20 mmol), (**L1**)$NiBr_2$ (5 mol%), 4-CzIPN (1 mol%), HEH (1.5 equiv), $K_2CO_3$ (1.0 equiv), $H_2O$ (5.0 equiv), $CO_2$ (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.

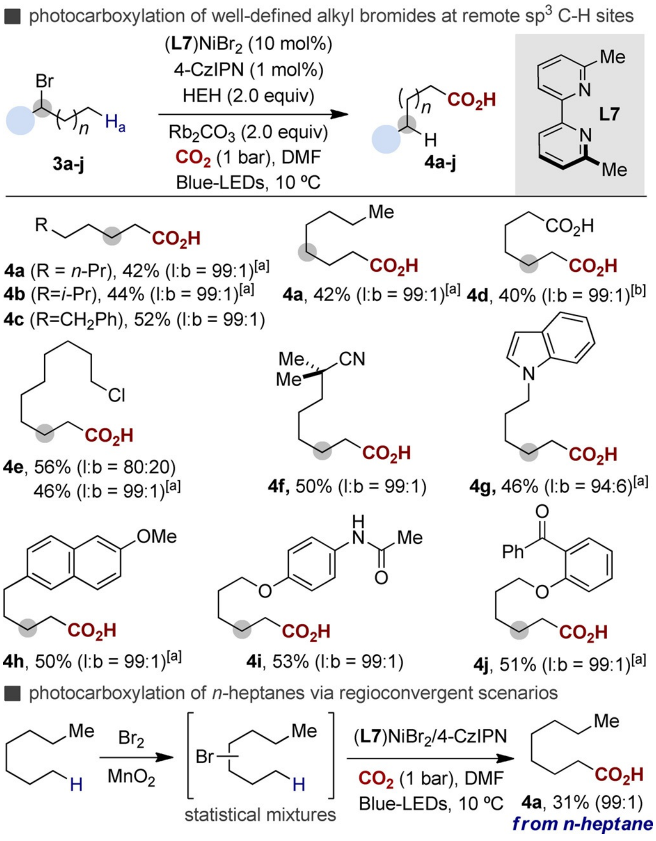


**Scheme 3.** Benzylic $sp^3$ C–H carboxylation by merging Ni and photoredox catalysis. Conditions: see Scheme 2 (entry 1); yields of isolated products, average of two independent runs. [a] b/l = 90:10. [b] 1.0 mmol scale. [c] b/l = 85:15. [d] b/l = 93:7. [e] Isolated as methyl ester. [f] b/l = 80:20.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

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 **2 a** (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, $K_2CO_3$ provided better results than $Cs_2CO_3$ (entry 11), showing the influence that the escorting cation might have on reactivity. As anticipated, control experiments in the absence of either (**L1**)$NiBr_2$, 4-CzIPN or light resulted in no conversion to **2 a** (entry 12).

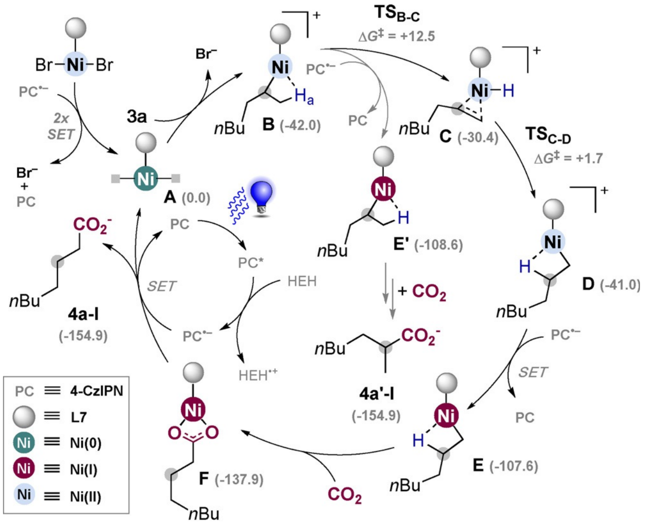
With optimized conditions in hand, we next set out to explore the generality of our light-induced Ni-catalyzed carboxylation at benzylic $sp^3$ C–H sites. As shown in Scheme 3, similar reactivity and site selectivity were obtained for a plethora of homobenzyl bromides independent of whether they possessed 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 (**2 e**, **2 g**, **2 h**).[16] As shown for **2 a**, the reaction can be scaled-up without significant erosion in yield or site selectivity. Importantly, phenols (**2 g**), amides (**2 h**), ketones (**2 j**) or esters (**2 k**) do not interfere with productive carboxylation at the benzylic $sp^3$ C–H site. Phenol (**2 g**) gave higher yields, most likely through Lewis-acidic assistance of $K^+$ during the $CO_2$ insertion (Scheme 3, middle).[17] We found that our protocol can be extended to electron-rich unprotected indoles (**2 l**) or secondary homobenzylic bromides (**2 m**), 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 $sp^3$ 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 $sp^3$ 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 $sp^3$ 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 (**3 a**) under the optimized conditions of Scheme 3 based on a Ni/**L1** regime resulted in traces, if any, of 1-octanoic acid (**4 a**). However, a protocol based on Ni/**L7** furnished **4 a** 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 nonsteroidal 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 CO$_2$) in a controllable fashion.



**Scheme 4.** Catalytic carboxylation at remote sp$^3$ C–H sites by merging Ni & photoredox catalysis. Conditions: **3** (0.25 mmol), (**L7**)NiBr$_2$ (10 mol %), 4-CzIPN (1 mol %), HEH (2.0 equiv), Rb$_2$CO$_3$ (2.0 equiv), CO$_2$ (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: Br$_2$ (0.25 mmol), MnO$_2$ (0.50 mmol) in *n*-heptane (1.25 mL) followed by the conditions highlighted above for **4a.**

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**)NiBr$_2$ and (**L7**)NiBr$_2$ revealed that low-valent Ni$^I$ and Ni$^0$ 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 CO$_2$ insertion for Ni$^{II}$ species **D**, either through outer- or inner-sphere mechanisms, reinforcing the notion that CO$_2$ 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-I** while recovering back the propagating



The relative Gibbs Free Energy (kcal mol$^{-1}$) at the SMD(DMF)-BS-UωB97X-D/def2-TZVP//BS-UωB97X-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**.

Ni$^0$/**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 sp$^3$ C–H sites (**4 a-I** vs. **4 a-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 CO$_2$ incorporation at benzylic sp$^3$ 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 sp$^3$ C–H sites under atmospheric pressure of CO$_2$, 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 sp$^3$ C–H bonds. Further work along these lines is currently in progress.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** carbon dioxide · carboxylation · chain-walking · nickel · photocatalysis

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