

Kinetically-Controlled Ni-Catalyzed Direct Carboxylation of Unactivated Secondary Alkyl Bromides without Chain Walking

Jacob Davies,[#] Julien R. Lyonnet,[#] Bjørn Carvalho, Basudev Sahoo, Craig S. Day, Francisco Juliá-Hernández, Yaya Duan, Álvaro Velasco-Rubio, Marc Obst, Per-Ola Norrby,^{*} Kathrin H. Hopmann,^{*} and Ruben Martin^{*,#}



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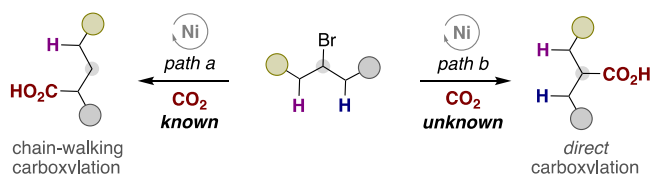


Supporting Information

ABSTRACT: Herein, we report the direct carboxylation of unactivated secondary alkyl bromides enabled by the merger of photoredox and nickel catalysis, a previously inaccessible endeavor in the carboxylation arena. Site-selectivity is dictated by a kinetically controlled insertion of CO₂ at the initial C(sp³)-Br site by the rapid formation of Ni(I)-alkyl species, thus avoiding undesired β-hydride elimination and chain-walking processes. Preliminary mechanistic experiments reveal the subtleties of stereoelectronic effects for guiding the reactivity and site-selectivity.

Ni-catalyzed reductive carboxylation reactions with CO₂ have recently offered innovative replacements to existing protocols for preparing carboxylic acids,¹ which are privileged motifs in a myriad of biologically relevant molecules.² While these techniques have received considerable echo,¹ the utilization of secondary alkyl halides invariably results in carboxylation at distal C(sp³)-H sites via chain walking irrespective of the position of the halide atom (Scheme 1, path

Scheme 1. Carboxylation of Secondary Alkyl Halides



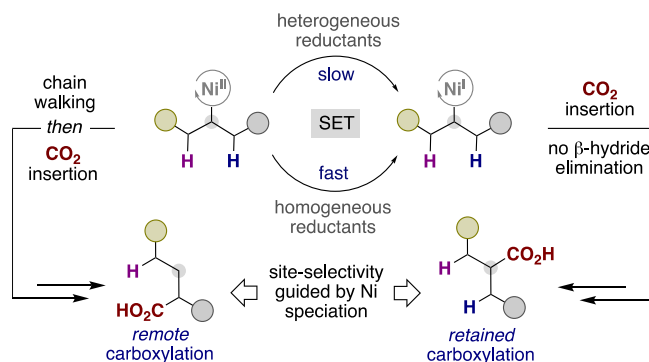
a).³ This is likely due to a particularly problematic CO₂ insertion at the initially generated C(sp³)-Ni bond with site-selectivity of chain walking being dictated by a subtle interplay between electronic and steric effects. This observation has contributed to the perception that a catalytic direct carboxylation of unactivated secondary alkyl halides might represent a chimera, yet a worthwhile endeavor for chemical invention (path b).

In our continuing interest in Ni-catalyzed carboxylations,^{4,5} we wondered whether it would be possible to design a de novo catalytic carboxylation of unactivated secondary alkyl halides. Recent mechanistic studies have shown that CO₂ insertion predominantly occurs at well-defined Ni(I) centers.⁶ We anticipated that accessing alkyl-Ni(I) species from unactivated secondary alkyl halides and low-valent NiL_n would be problematic with commonly employed heterogeneous metal reductants given (a) the low rates at which these entities promote single-electron transfer en route to alkyl-Ni(I)⁷ and (b) the propensity of alkyl-Ni(II) species toward β-hydride

elimination.⁸ If successful, however, a study aimed at designing a retained Ni-catalyzed carboxylation of secondary alkyl halides would not only offer new opportunities in the carboxylation arena¹ but also a starting point for understanding the intricacies of Ni speciation in cross-couplings of sp³ electrophiles.^{9,10} Herein, we report the successful realization of this goal, which culminates in the development of a light-induced Ni-catalyzed retained carboxylation that operates under mild conditions and with excellent chemo- and site-selectivity profiles (Scheme 2, right).

We began our study by conducting the Ni-catalyzed carboxylation of **1a** with CO₂ (1 bar). Traces of **2a**, if any, were detected under previously reported Ni-catalyzed carboxylations of alkyl halides,^{3,4} thus reinforcing the notion that a

Scheme 2. Site-Selectivity Guided by Ni Speciation



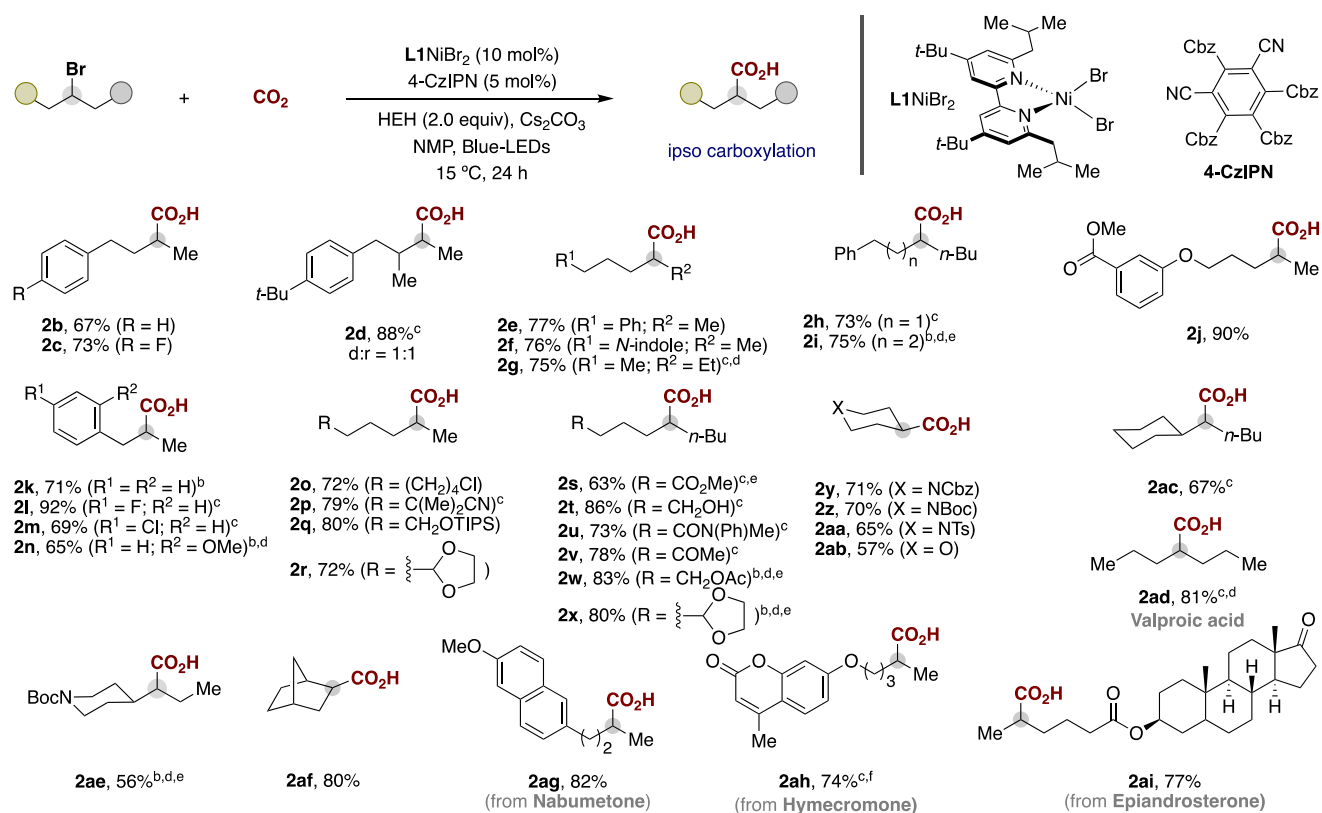
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Table 1. Scope of the Ni-Catalyzed Carboxylation of Secondary Alkyl Bromides^a

^aConditions: same as for Table 2. Isolated yields, average of at least two independent runs; branched/linear selectivities for **2a**–**2ai** rank from 8:1 to 99:1; see the Supporting Information for details. ^b4-CzIPN (10 mol %). ^c4-CzIPN (8 mol %). ^dReaction ran at 10 °C. ^eReaction conducted for 48 h. ^fHEH (3 equiv).

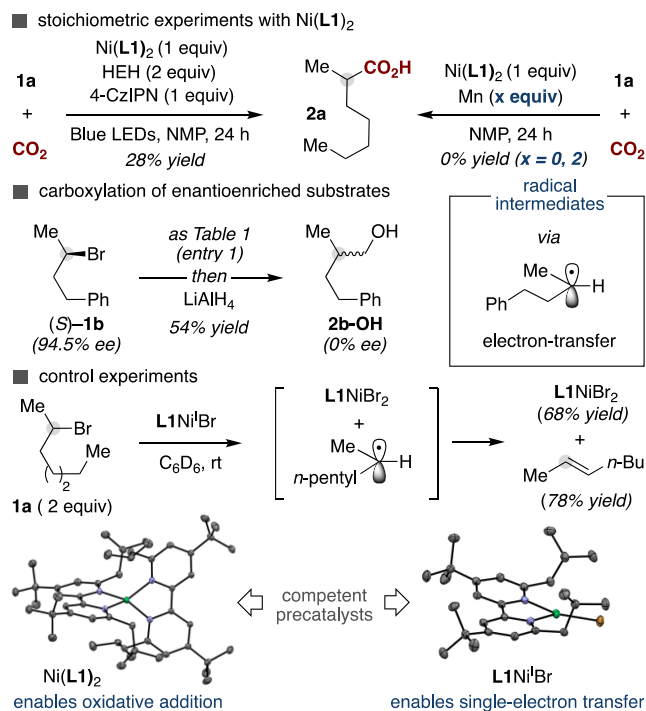
retained C(sp³) carboxylation would be particularly problematic. After some experimentation,¹¹ a protocol utilizing **L1**, 4-CzIPN as photocatalyst, Cs₂CO₃, and Hantzsch ester (HEH) in *N*-methyl-2-pyrrolidone (NMP) under blue LED irradiation at 15 °C provided the best results and afforded **2a** in 81% yield with excellent selectivity (99:1). Under these conditions, negligible CO₂ insertion at distal sp³ C–H sites via chain walking was found in the crude reaction mixtures. As shown in entries 2–6, substituents at the 2,2'-bipyridine core exerted a profound influence in both reactivity and selectivity. Interestingly, low reactivities and selectivities were found at lower concentrations of 4-CzIPN, thus suggesting the importance for accessing alkyl–Ni(I) species prior to CO₂ insertion (entry 7).¹² In addition, bases and solvents other than Cs₂CO₃ and NMP resulted in low yields and selectivities (entries 8 and 9). Notably, the utilization of Mn or DMAP-OED¹³ as reductants in lieu of 4-CzIPN/HEH resulted in little conversion, if any, to **2a** or lower branched selectivities,¹¹ thus confirming the significant influence exerted by photoredox-promoted electron transfer processes (entries 10 and 11). Control experiments revealed that all the reaction parameters were critical for success (entries 12 and 13), whereas no reaction took place with secondary alkyl iodides (**1a-I**), chlorides (**1a-Cl**), or tosylates (**1a-OTs**; see Scheme S7).

With the optimized conditions in hand, we set out to explore the generality of our retained carboxylation of unactivated secondary alkyl bromides. As shown in Table 1, our protocol turned out to be widely applicable. While low selectivities were found for secondary alkyl bromides possessing substituents

other than methyl groups, this observation could be alleviated at higher concentrations of 4-CzIPN to obtain the targeted products with excellent branched selectivity (**2h**, **2s–x**). Notably, the inclusion of branched substituents or aromatic rings in the vicinity did not interfere with productive C(sp³) carboxylation reaction (**2d**, **2k–n**).^{4,10} The chemoselectivity of our method was further illustrated by the presence of esters (**2j**, **2s**, **2w**), amides (**2u**), unprotected alcohols (**2t**), heterocycles (**2f**, **2ah**) or nitriles (**2p**). Although one might argue that the presence of primary alkyl chlorides could lead to competitive carboxylation at the C(sp³)–Cl site,¹⁴ this was not the case, and **2o** was isolated in good yields. Note, however, that alkyl side chains possessing both a primary and secondary alkyl bromide led to complex mixtures of products.¹¹ In addition, no chain-walking carboxylation was observed with secondary alkyl halides decorated with esters or amides on the alkyl side chain.^{4a,15} Along the same lines, no carboxylation adjacent to the nitrogen atom was observed when utilizing nitrogen- or oxygen-containing heterocycles (**2y–aa**, **2ab**, **2ae**).¹⁶ As shown for **2ag–ai**, our method could also be utilized for accessing aliphatic carboxylic acids deriving from nabumetone (**2ag**), hymecromone (**2ah**), or epiandrosterone (**2ai**) in good yields and site-selectivities. In addition, valproic acid **2ad** was within reach in a high yield and site-selectivity.

Next, we turned our attention to studying the underpinnings of our carboxylation reaction (Scheme 3). To this end, we evaluated the reactivities of (L1)₂Ni(0) and L1Ni(I)Br. While the former was easily synthesized by simple exposure of L1NiBr₂ to Mg, comproportionation of Ni(COD)₂ and

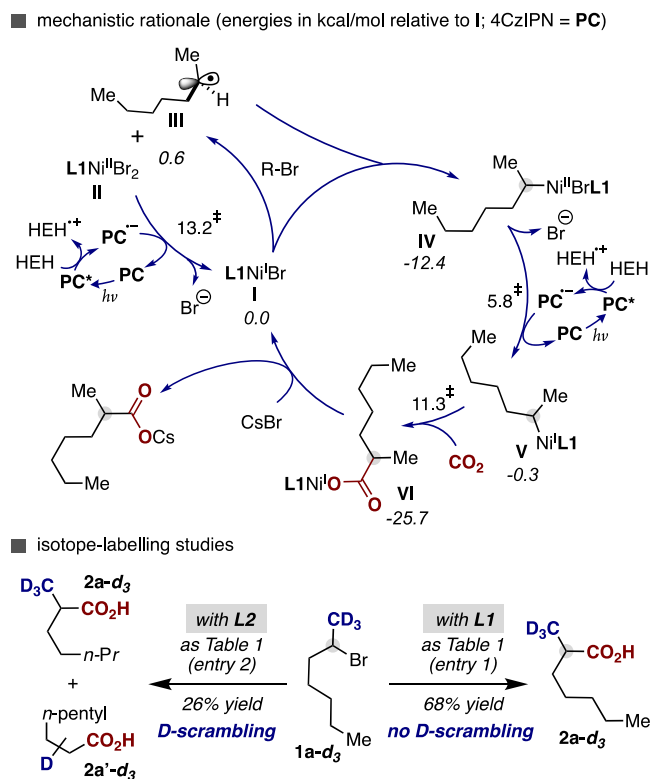
Scheme 3. Preliminary Mechanistic Experiments



L1NiBr₂ was utilized to access the latter.¹¹ The structures of these compounds were unambiguously determined by X-ray diffraction (Scheme 3, bottom). Interestingly, the reaction of (L1)₂Ni(0) with 1a under CO₂ (1 bar) did not give rise to 2a (Scheme 3, top right). An otherwise identical reaction using L1Ni(I)Br led to *trans*-2-heptene as the major product. In contrast with an elegant report by Diao et al., this reaction also resulted in L1NiBr₂ instead of radical homocoupling.¹⁷ Likely, this divergent reactivity originates from L1Ni(I)Br or L1Ni(II)Br₂ being able to readily intercept alkyl radicals prior to β-hydride elimination.¹⁸ The means to generate discrete alkyl-Ni species was assessed by conducting an otherwise identical experiment with Mn or under a 4-CzIPN/HEH regime; while not even traces of 2a were detected in the former, significant amounts of retained carboxylation were found in the latter, thus illustrating the non-negligible influence exerted by homogeneous reductants in both reactivity and selectivity (Scheme 3, top left). As anticipated for a mechanism consisting of radical intermediates, we observed a loss of stereochemical integrity when subjecting (S)-1b (94.5% ee) under a Ni/L1 regime.

Aiming at understanding the intricacies of these processes at the molecular level, we turned our attention to DFT [PBE0-D3BJ,IEFPCM] calculations (Scheme 4). The reducing environment of our reaction conditions together with the tetrahedral center displayed for L1Ni(II)Br₂ and the preferred tetrahedral geometry of the four-coordinate Ni(I) species—imposed by the high-lying antibonding orbital dx²-y²—strongly suggests that the formation of Ni(I) may easily occur during the course of the catalytic carboxylation event.^{19,20} Our theoretical calculations confirmed that single-electron transfer from the reduced photocatalyst to L1Ni(II)Br₂ has a low barrier of 12.6 kcal/mol according to the Marcus equation.^{21,22} Within the limitations from the solvent model employed, bromide dissociation from an in situ generated anionic Ni(I) complex was found to be downhill,²³ thus

Scheme 4. Mechanistic Rationale and Isotope Labeling



making the overall conversion from precatalyst L1Ni(II)Br₂ (II) to L1Ni(I)Br (I) exergonic by 0.4 kcal/mol.²⁴ Subsequently, the latter might react with alkyl bromide 1a via bromide transfer, hence giving rise to L1Ni(II)Br₂ (II) and free radical III with a computed cost of only 0.6 kcal/mol (Scheme 4). Unfortunately, we did not locate a transition state for this process; at the DFT level, it seems this step might constitute a monotonous process without a potential energy barrier and, consequently, it might be diffusion-controlled. The loss of stereochemical information found for (S)-1b (Scheme 3, middle) is consistent with a pathway where radical III escapes the solvent cage. Interception of such species by a newly formed I was found to be strongly exergonic by 12.4 kcal/mol relative to I (Scheme 4).²⁵ The resulting L1Ni(II)-(alkyl)Br (IV) is particularly stable when compared with other Ni complexes within the catalytic cycle, thus suggesting that IV might represent the resting state. A barrier of 18.2 kcal/mol relative to IV was computed for single-electron transfer en route to V (Scheme 4). In analogy with recent literature data on alkyl-Ni(I) complexes,^{6d} CO₂ insertion into V occurs with a low activation barrier (11.6 kcal/mol relative to V, Scheme 4 and Figure 1), thus giving a back-reaction barrier of 37.0 kcal/

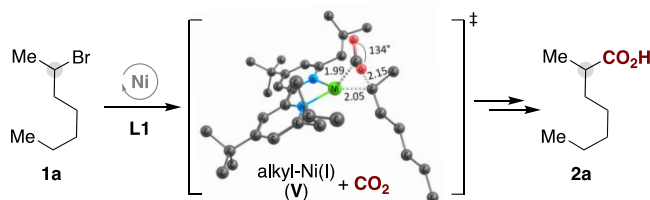


Figure 1. CO₂ insertion at alkyl-Ni(I)L1.

mol which makes the carboxylation step irreversible. Regeneration of the catalytically active **I** might involve transmetalation of **VI** to CsBr while forming a cesium carboxylate.²⁶

Given the subtleties exerted by the ligand on the reaction outcome, we next focused our attention on understanding the erosion in selectivity observed with **L2** (Table 2, entry 2).

Table 2. Optimization of the Reaction Conditions^a

entry	deviation standard conditions	yield (%)	2a:2a' ^b
1	none	81(80) ^c	99:1
2	using NiBr ₂ L2	23	44:56
3	using NiBr ₂ L3	37	99:1
4	using NiBr ₂ L4	46	79:21
5	using NiBr ₂ L5	41	86:14
6	NiBr ₂ L1 (5 mol%)	16	84:16
7	4-CzIPN (1 mol%)	29	88:12
8	K ₂ CO ₃ instead of Cs ₂ CO ₃	75	97:3
9	using DMA instead of NMP	52	84:16
10	using Mn instead of HEH	0	0
11	using DMAP-OED as reductant	9	44:56
12	no Cs ₂ CO ₃	0	0
13	no NiBr ₂ L1 , 4-CzIPN or light	0	0

Reaction scheme: **1a** (Me-Br, Me-CH₂-CH₂-CH₂-CH₂-Br) reacts with NiBr₂**L1** (10 mol%), 4-CzIPN (5 mol%), HEH (2.0 equiv), Cs₂CO₃, CO₂ (1 bar), NMP, Blue-LEDs, 15 °C to yield **2a** (n-pentyl CO₂H) and/or **2a'** (n-pentyl CO₂H).

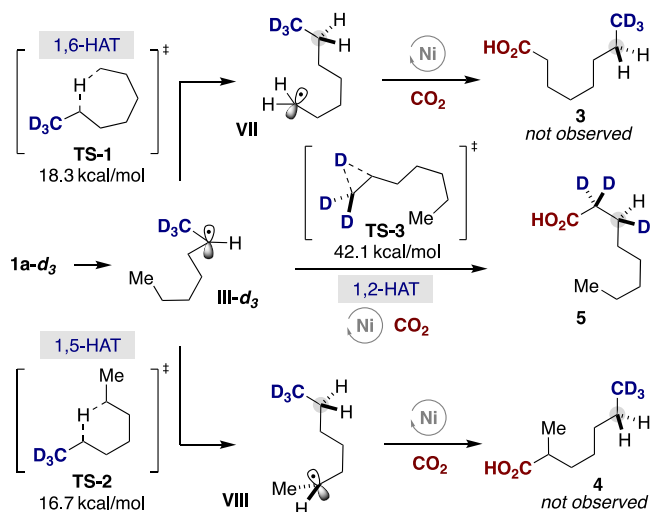
Chemical structures of ligands **L1**, **L2**, **L3**, **L4**, and **L5** are shown. **L1** and **L2** are 2,2'-bipyridyl ligands with R¹ and R² substituents. **L3** has R¹=i-Bu, R²=t-Bu. **L4** has R¹=n-hex, R²=t-Bu. **L5** is a phenanthroline derivative with Ph and n-hex substituents.

^aConditions: **1a** (0.25 mmol), NiBr₂**L1** (10 mol %), 4-CzIPN (5 mol %), HEH (0.5 mmol), Cs₂CO₃ (0.5 mmol), CO₂ (1 bar), and NMP (0.08 M) at 15 °C for 24 h under blue LED irradiation. ^bOther isomers were detected in negligible amounts; GC yields were obtained using anisole as an internal standard. ^cIsolated yield.

Initially, we conducted deuterium-labeling experiments with **1a-d₃** (Scheme 4, bottom). An erosion in deuterium content at C1 was expected for a mechanism consisting of a series of β -hydride elimination/migratory insertion, whereas preservation of the CD₃ fragment was anticipated for a rapid insertion of CO₂ at an in situ generated alkyl-Ni(I) species. As shown, **2a-d₃** was obtained as the only observable product with **L1** (Scheme 4, bottom right), whereas an otherwise identical experiment with **L2** resulted in deuterium scrambling over the alkyl chain (**2a'-d₃**, bottom left), which confirms the striking influence of the 2,2'-bipyridyl core on site-selectivity.¹¹

Taking into consideration the proclivity of alkyl radical intermediates to undergo intramolecular hydrogen atom transfer (HAT) at proximal C(sp³)-H bonds,²⁷ one might argue whether such a pathway could be responsible for the observable deuterium scrambling when promoting the carboxylation of **1a-d₃** under a Ni/L2 regime (Scheme 4). Given that **III** diffuses away and re-enters the catalytic cycle at later stages to form **IV** and that the recombination of **III** with **I** might be diffusion-controlled (Scheme 4),²⁸ we turned our attention to DFT calculations for evaluating the viability of enabling HAT processes from the alkyl radical arising from **1a** (Scheme 5). While our results indicated that a 1,5- or 1,6-HAT from **III** could be within reach, the computed barriers are significantly larger than the expected barrier for recombination of **III** with Ni(I).²⁸ Indeed, neither **3** nor **4** were detected in the crude mixtures, thus arguing against the intermediacy of 1,5 or 1,6-HAT processes. While deuterium scrambling in the carboxylation of **1a-d₃** could also be rationalized by a formal

Scheme 5. Evaluation of Competitive HAT Processes^a



^aThe barriers were computed with **1a**.

1,2-HAT, the high barriers found for such a pathway (42.1 kcal/mol, Scheme 5) indicate otherwise. Although a base-mediated deprotonation from alkyl-Ni(III) species was also considered,²⁹ it is highly unlikely that such intermediates might be formed under strongly reducing conditions. Putting all these observations into consideration, the formation of **2a'-d₃** can be interpreted on the basis of a ligand-dependent β -hydride elimination event (for details, see the Supporting Information, Figure S8 and Table S5). With **IV** as the branching point, the reaction can evolve either via single-electron transfer en route to **V** or via β -hydride elimination arising from an initial loss of a bromide ion. Our data indirectly suggests that the steric bulk exerted by the substituents at the 6,6'-position in **L1** might disfavor the latter pathway, whereas a balanced situation between these pathways might occur with less-sterically encumbered **L2**.

In summary, we describe the successful implementation of a dual-photoredox, Ni-catalyzed direct carboxylation of unactivated secondary alkyl bromides, which is a previously inaccessible endeavor in the catalytic carboxylation arena. Experimental studies and theoretical calculations reveal an intriguing role exerted by the ligand backbone, which minimizes undesired β -hydride elimination events that might otherwise result in chain-walking scenarios while facilitating CO₂ insertion at alkyl-Ni(I) species. The method is characterized by its mild conditions, exquisite selectivity, and wide scope, including challenging substrate classes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c11205>.

Computationally optimized structures (XYZ)

Experimental procedures and spectral and crystallographic data (PDF)

Accession Codes

CCDC 2250012–2250013 and 2250024 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by

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AUTHOR INFORMATION

Corresponding Authors

Per-Ola Norrby – Data Science & Modelling, Pharmaceutical Sciences, R&D, AstraZeneca Gothenburg, SE-431 83 Mölndal, Sweden; orcid.org/0000-0002-2419-0705; Email: Per-Ola.Norrby@astrazeneca.com

Kathrin H. Hopmann – Department of Chemistry, UiT The Arctic University of Norway, N-9307 Tromsø, Norway; orcid.org/0000-0003-2798-716X; Email: kathrin.hopmann@uit.no

Rubén Martín – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; ICREA, 08010 Barcelona, Spain; orcid.org/0000-0002-2543-0221; Email: rmartinromo@iciq.es

Authors

Jacob Davies – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain

Julien R. Lyonnet – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Universitat Rovira i Virgili, Departament de Química Orgànica, 43007 Tarragona, Spain; orcid.org/0000-0001-7466-5011

Bjørn Carvalho – Department of Chemistry, UiT The Arctic University of Norway, N-9307 Tromsø, Norway

Basudev Sahoo – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; orcid.org/0000-0002-9746-9555

Craig S. Day – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; Universitat Rovira i Virgili, Departament de Química Orgànica, 43007 Tarragona, Spain; orcid.org/0000-0002-6931-0280

Francisco Juliá-Hernández – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain; orcid.org/0000-0001-5311-0957

Yaya Duan – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain

Álvaro Velasco-Rubio – Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain

Marc Obst – Department of Chemistry, UiT The Arctic University of Norway, N-9307 Tromsø, Norway

Complete contact information is available at:

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Author Contributions

[#]J. D. and J. R. L. contributed equally to the work.

Notes

The authors declare no competing financial interest.

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(21) See the [Supporting Information](#), Table S3.

(22) For details on the single-electron transfer process, see the [Supporting Information](#), Figure S5.

(23) See the [Supporting Information](#), Table S4.

(24) See the [Supporting Information](#), Figure S12.

(25) In sharp contrast, interception of radical III by II en route to possible Ni(III) species was found to be endergonic by 10 kcal/mol relative to I. See the [Supporting Information](#), Figure S13.

(26) CsBr aggregates might be expected to form under the reaction conditions because of the presence of Cs cations and Br anions.

(27) For selected reviews, see: (a) Capaldo, L.; Ravelli, D.; Fagnoni, M. Direct photocatalyzed hydrogen atom transfer (HAT) for aliphatic C–H bonds elaboration. *Chem. Rev.* **2022**, 122, 1875–1924. (b) Cao,

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