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Catalytic Decarboxylation/Carboxylation Platform for Accessing Isotopically Labeled Carboxylic Acids

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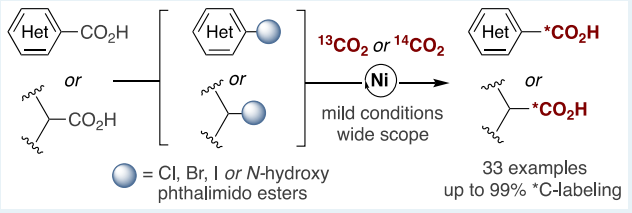
Supporting Information

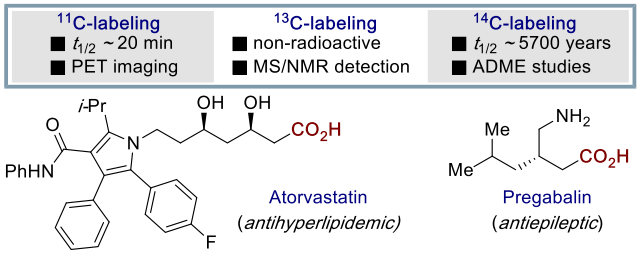
ABSTRACT: An integrated catalytic decarboxylation/carboxylation for accessing isotopically labeled carboxylic acids with $^{13}CO_2$ or $^{14}CO_2$ is described. The method shows a wide scope under mild conditions, even in the context of late-stage functionalization, and does not require stoichiometric organometallics, thus complementing existing carbon-labeling techniques en route to carboxylic acids.



KEYWORDS: *carboxylation, nickel, isotopic labeling, carbon dioxide, carboxylic acid*

The evaluation of the metabolic profile of lead compounds through preclinical testing is of utmost importance in drug discovery.[1] Although these studies require isotopically labeled active pharmaceutical ingredients (APIs), their synthesis is oftentimes more problematic than that of the parent compound, reinforcing the need for strategies that rapidly and reliably incorporate isotopes into molecules.[2] Among different scenarios, carbon labeling is often preferred due to its high sensitivity and lower risk of label metabolic cleavage, rendering the interpretation of preclinical data easy.[3] While ^{11}C is utilized for positron emitting tomography (PET) imaging,[4] its short half-life precludes long-term studies. However, ^{13}C- and ^{14}C-labeling are appropriate for evaluating drug profiles, including absorption, distribution, metabolism, and excretion (ADME), and pharmacokinetic studies (Scheme 1).[5,6] Although radioactive ^{14}C has oftentimes displaced ^{13}C as metabolic tracers, recent advances in mass spectrometry and nuclear magnetic resonance have allowed the latter to be used for similar purposes,[7] thus improving the practicality of these studies by employing stable ^{13}C probes.

Scheme 1. Carbon Isotope Labeling



Prompted by the prevalence of carboxylic acids in biologically active molecules (Scheme 1, bottom),[8] carboxylation reactions with isotopically labeled CO_2 have attracted considerable attention.[9,10] At present, high levels of ^{13}C- and ^{14}C-incorporation can be achieved with stoichiometric and polarized organometallics;[11] however, their high reactivity and low chemoselectivity severely limit the synthetic application of these processes (Scheme 2, top left). Although decarboxylation allows carbon isotopes of carboxylic acids in drug molecules to be rapidly interchanged without modifying the established route to the drug molecule (Scheme 2, top middle/right),[12] such techniques require stoichiometric nickel species[13a] or harsh conditions.[13b] In addition, modest C-labeling exchange is observed due to competitive hydrolysis of the starting precursor or *in situ* carboxylation with initially extruded $^{12}CO_2$.[13] Taken together, these features contribute to the perception that designing a mild, robust, and modular *catalytic* decarboxylation/carboxylation that enables the access to C-labeled aliphatic and aromatic carboxylic acids in high specific activities is deemed necessary. As part of our interest in catalytic carboxylation reactions,[14] we report the successful

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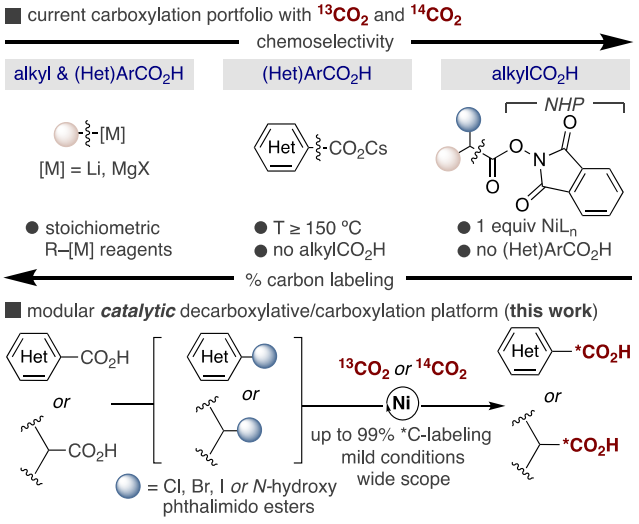
Scheme 2. ^{13}C- and ^{14}C-Labeling Carboxylations with CO_2

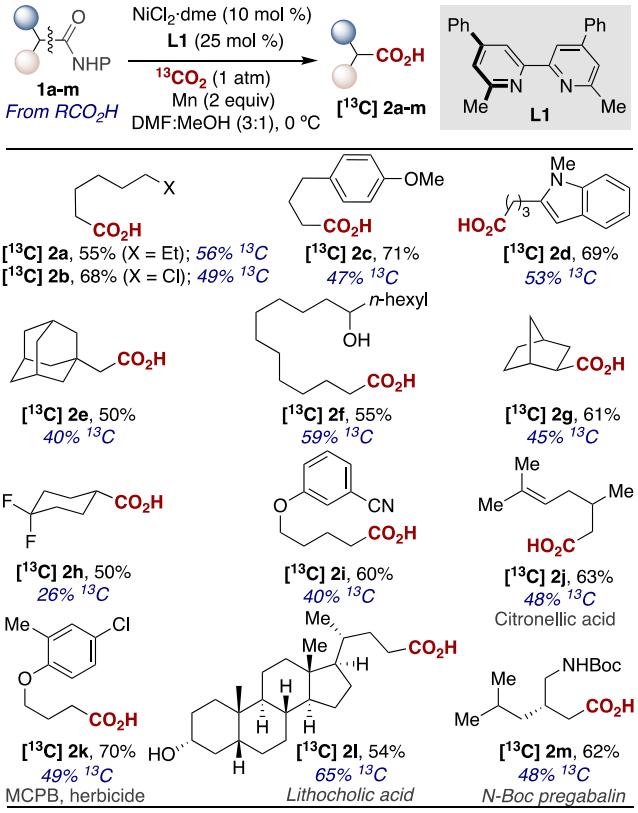


realization of a *catalytic* carbon isotope exchange by merging decarboxylative events with carboxylation protocols with $^{13}CO_2$ or $^{14}CO_2$ via the intermediacy of halogenated species or activated esters (Scheme 2, bottom). Our protocols are distinguished by their mild conditions, versatility, excellent chemoselectivity profile, and high isotopic incorporations (up to >99% C-labeling), thus expediting the design of radiolabeling techniques—even in the context of late-stage functionalization—en route to labeled carboxylic acids while obviating the need for stoichiometric organometallic species.

Our investigations began by evaluating the feasibility of the approach highlighted in Scheme 2 (bottom) with easy-to-handle $^{13}CO_2$ in lieu of radioactive $^{14}CO_2$ and the *N*-hydroxyphthalimido ester **1a**, readily available in a single step from octanoic acid.[15] A judicious optimization of all reaction parameters revealed that a combination of $NiCl_2$·dme (10 mol %) and 6,6′-dimethyl-4,4′-diphenyl-2,2′-bipyridine **L1** (25 mol %) in DMF:MeOH (3:1) at 0 °C with Mn as reducing agent under an atmospheric pressure of $^{13}CO_2$ provided the best results, affording [^{13}**C**]**2a** in 55% yield and 56% ^{12}C/^{13}C-exchange.[15] In line with our expectations, bipyridine and phenanthroline ligands possessing substituents adjacent to the nitrogen atom were critical for success.[16] Indeed, the absence of the latter resulted in negligible conversions, if any, to [^{13}**C**]**2a**, thus showing the structural intricacies on the ligand backbone. Likewise, solvents and reducing agents other than DMF:MeOH or Mn had a deleterious effect on reactivity and specificity, whereas control experiments revealed that all reaction parameters were essential for the catalytic carboxylation to occur.[15]

With a set of conditions in hand, we turned our attention to study the generality of our Ni-catalyzed decarboxylative/carboxylation of *N*-hydroxyphthalimido esters. As shown in Table 1, an array of linear (**2a**−**2f**, **2i**−**2m**) or *α*-branched (**2g**, **2h**) labeled carboxylic acids could easily be within reach from their parent analogues. The chemoselectivity of our ^{12}C/^{13}C-carbon-labeling exchange posed no problems, as nitriles (**2i**), alkenes (**2j**), carbamates (**2m**), or nitrogen-containing heterocycles (**2d**) could all be well-accommodated. Interestingly, not even traces of competitive Ni-catalyzed carboxylation at the C−Cl terminus was observed in **2b** and **2k**,[17] thus leaving ample room for further functionalization via conventional

Table 1. ^{12}C/^{13}C-Isotopic Exchange of Carboxylic Acids[a]



[a]NHP-ester (0.1 mmol), $NiCl_2$·dme (10 mol %), **L1** (25 mol %), Mn (2 equiv), $^{13}CO_2$ (1 atm) in DMF:MeOH (3:1, 0.06 M) at 0 °C.

cross-coupling reactions.[18] Particularly noteworthy was the ability to enable the targeted ^{12}C/^{13}C-exchange at late-stages with advanced carboxylic acid intermediates such as citronellic acid (**2j**), MCPB (**2k**), lithocholic acid (**2l**), or pregabalin (**2m**), thus showing the potential that our catalytic protocol might have in preclinical studies for drug discovery.[19] Putting these results into perspective, the examples shown in Table 1 represent a powerful alternative to existing methodologies based on the utilization of stoichiometric amounts of organometallics[11] or Ni complexes.[13a]

The data shown in Scheme 3 (top) illustrates the prospective impact of our ^{12}C/^{13}C-exchange by converting **3a** and **3b** into their [^{13}**C**]**5a** and [^{13}**C**]**5b** congeners without chromatographic purification.[15] However, a number of daunting challenges remain. Among these, a seemingly trivial extension to ^{13}C-labeled phenyl acetic acids or benzoic acids events still constitutes *terra incognita*; substantial homodimerization is observed in the former whereas a difficult decarboxylation of aryl NHP-esters prevents a ^{12}C/^{13}C-exchange in the latter. More importantly, modest isotope exchange was observed for all substrates shown in Table 1 due to unavoidable hydrolysis of the parent NHP-ester and competitive carboxylation with $^{12}CO_2$. These observations are particularly problematic due to the prevalence of carboxylic acids in APIs as well as the need for maximizing the ^{12}C/^{13}C-exchange for preclinical testing. To this end, we anticipated that the merger of decarboxylative halogenation with the robustness of catalytic carboxylation of organic halides might offer a powerful platform for obtaining otherwise inaccessible carboxylic acids with >99% ^{13}C-content. As shown in Scheme

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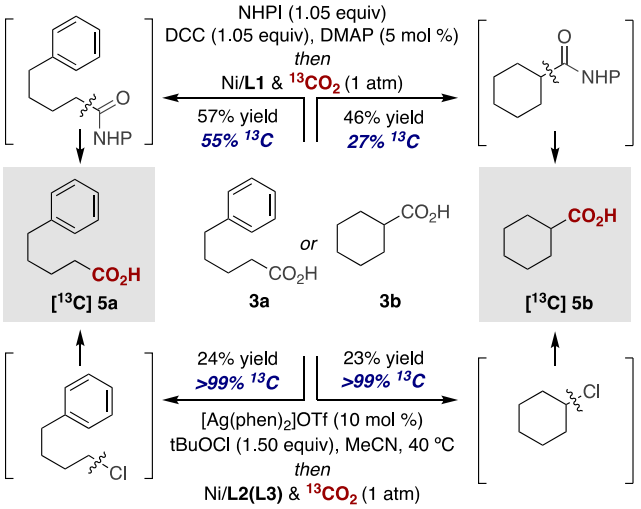
Scheme 3. Direct $^{12}C/^{13}C$-Exchange of Carboxylic Acids[a]



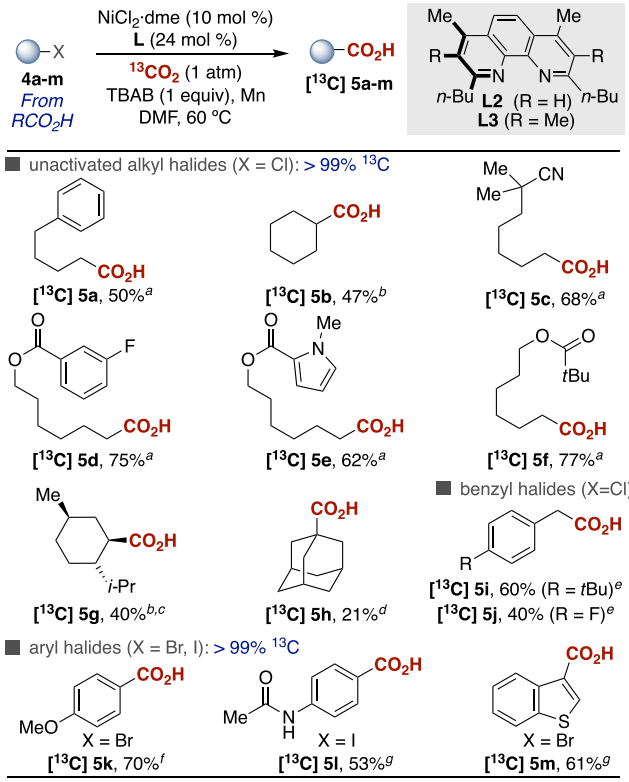
[a]Ni/**L1**, Table 1; Ni/**L2**, $NiBr_2$·dme (10 mol %), **L2** (24 mol %), Mn (2 equiv), TBAB (1 equiv), $^{13}CO_2$ (1 atm) in DMF (0.17 M), at 60 °C; Ni/**L3**, $NiBr_2$·diglyme (10 mol %), **L3** (24 mol %), Mn (3 equiv), LiCl (1 equiv), $^{13}CO_2$ (1 atm) in DMF (0.40 M), at 90 °C.

3 (bottom), this turned out to be the case. Indeed, a Ag-catalyzed decarboxylative halogenation[20] followed by Ni/**L2**- or Ni/**L3**-catalyzed carboxylation afforded [^{13}C]**5a** and [^{13}C]**5b** in slightly lower overall yields to those shown for NHP-esters but with >99% ^{13}C-labeling. Encouraged by these results, we examined the ^{13}C-carboxylation of a host of benzyl, aryl, or unactivated alkyl chlorides obtained via decarboxylative halogenation of the parent carboxylic acids (Table 2). Notably, nitriles (**5c**), esters (**5d**–**5f**), or nitrogen-containing heterocycles (**5e**) do not interfere, obtaining in all cases >99% ^{13}C-labeling. Albeit in lower yields, secondary and tertiary alkyl carboxylic acids such as **5b**, **5g**, or **5h** were within reach, with **5g** being obtained as a single diastereoisomer. Importantly, ^{13}C-labeled aryl acetic acids (**5i**, **5j**) and (hetero)aryl carboxylic acids (**5k**–**5m**)—compounds that were beyond reach from NHP-esters—could also be coupled under Ni/neocuproine or Ni/PPh_3 regimes, thus representing an opportunity to improve upon existing C-labeling techniques.

Aimed at extending the applicability of our carbon isotope exchange, we next focused our attention on converting α-branched carboxylic acids into their labeled linear analogues via chain-walking scenarios,[14a,21] a transformation that has proven elusive in related labeling approaches.[13a] Although in low yields, the preparation of [^{13}C]**2a,5a,6** with >99% ^{13}C-labeling not only demonstrates the successful realization of this goal (Scheme 4) but also sets the basis for designing site-selective radiolabeling techniques at remote sp^3 C–H sites.[22] Given the key role of ^{14}C-radiolabeling in pharmacokinetic and ADME studies,[5] the ability to access ^{14}C-labeled molecules was then explored. Preliminary results successfully highlighted the applicability of this method under otherwise similar conditions.[15] It is particularly noteworthy that [^{14}C]**5i** and [^{14}C]**5k** are obtained in high molar activities (≥2.04 GBq $mmol^{-1}$)[23] with negligible isotope dilution, thus opening a gateway to study the metabolic activity of drugs containing carboxylic acid motifs.

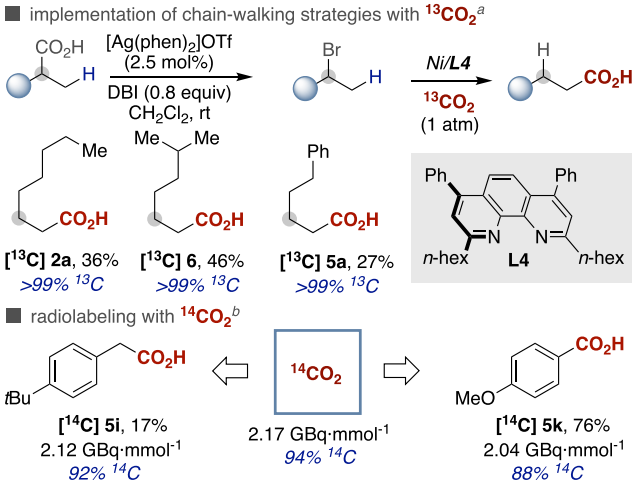
In conclusion, we have developed a simple, efficient, and highly versatile catalytic decarboxylation/carboxylation for carbon isotope exchange of carboxylic acids with $^{13}CO_2$ or

Table 2. Decarboxylative Halogenation/Carboxylation



[a]As Scheme 4, Ni/**L2**. [b]Ni/**L3**. [c]Using **4g** with a 1:1 diastereomeric ratio. [d]As Scheme 4, Ni/**L3**, TBAB (2 equiv), DMA (0.4 M) at 80 °C. [e]$NiCl_2$·dme (10 mol %), PCp_3·HBF_4 (20 mol %), $MgCl_2$ (2 equiv), Zn (5 equiv), DMF (0.5 M) at room temperature. [f]$NiBr_2$·dme (10 mol %), neocuproine (20 mol %), Mn (2 equiv), DMA (0.2 M) at 50 °C. [g]$NiCl_2(PPh_3)_2$ (5 mol %), PPh_3 (10 mol %), TEAI (10 mol %), Mn (3 equiv), DMA (0.25 M) at room temperature.

Scheme 4. Chain-Walking ^{13}C-Exchange and ^{14}C-Labeling



[a]NiI_2 (2.5 mol %), **L4** (4.4 mol %), Mn (2 equiv), DMF (1.0 M), 25 °C, 20 h. [b]Reactions performed with **4i** and **4k** as substrates.

$^{14}CO_2$. This route enables access to labeled aliphatic or aromatic carboxylic acids, even at late-stages, without changing the already established sequence en route to the parent compound, thus offering a robust and economical gateway for rapidly and reliably obtaining preclinical data for lead

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generation in drug discovery. Further work on radiolabeling techniques is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b01921.

Experimental procedures and characterization data including ^{1}H, ^{13}C, and ^{19}F NMR, HRMS, and IR (PDF)

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Notes

The authors declare no competing financial interest.

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