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Communication

Fast Carbon Isotope Exchange of Carboxylic Acids Enabled by Organic Photoredox Catalysis

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ABSTRACT: Carbazole/cyanobenzene photocatalysts promote the direct isotopic carboxylate exchange of C(sp^3) acids with labeled CO_2. Substrates that are not compatible with transition-metal-catalyzed degradation−reconstruction approaches or prone to thermally induced reversible decarboxylation undergo isotopic incorporation at room temperature in short reaction times. The radiolabeling of drug molecules and precursors with [^{11}C]CO_2 is demonstrated.

The synthesis of isotopically labeled molecules is essential to drug development and nuclear medicine. As drug candidates move toward clinical research and human trials, absorption, distribution, metabolism, and excretion (ADME) studies require compounds enriched with long-lived radioisotopes like ^{3}H and ^{14}C.[1] Positron emission tomography (PET) techniques that probe the advance of disease states and can determine the efficacy of drug treatment require molecular targets radiolabeled with short-lived positron-emitting isotopes such as ^{11}C and ^{18}F.[2] The limited availability and high cost of isotopically enriched precursors make the preparation of complex targets challenging. For PET studies, compounds must be synthesized and purified within a few half-lives of the radiolabel ($t_{1/2}$ = 20.3 min for ^{11}C). Approaches that selectively introduce isotopic labels from feedstock sources with compatibility toward common structural motifs found in clinical candidates will have a positive impact on both drug discovery efforts and medical imaging.

Metal-catalyzed ^{1}H/^{3}H exchange is widely used in drug development to introduce long-lived radiolabels into target molecules.[3−9] The loss of ^{3}H labels through (bio)chemical reactions and metabolic shifting due to primary kinetic isotope effects are liabilities of ^{3}H-labeling approaches.[10,11] ADME tracer compounds with greater stability can be obtained by using ^{14}C radiolabels.[12] Similarly, ^{11}C isotopologues of native bioactive molecules enable PET probe generation without changes to their biological or pharmacological properties.[2,13] The incorporation of ^{14}C, ^{13}C, or ^{11}C (*C) units into drug molecules or precursors by the formation of a *C−C bond is challenging and often requires revised synthetic pathways to introduce the label from *CO,[14−18] *CH_3I,[19,20] or other small molecules derived by reduction of *CO_2.[21−25] The direct exchange of carboxylate groups with CO_2 offers the potential for simple and cost-effective syntheses of C-labeled small molecules, particularly as CO_2 (or $BaCO_3$) is the feedstock for all radiolabeled carbon-based precursors.[26] The easy conversion of carboxylic acids into other common functionalities (esters, amides, ketones, alcohols) makes this an attractive tactic for isotope incorporation.

The use of redox-active hydroxyphthalimide ester substrates in combination with Ni-based mediators and stoichiometric metal reductants enables carboxylate groups to undergo net exchange with CO_2 via a series of single electron transfer processes (Figure 1A).[27,28] These reactions are limited to primary alkyl or cyclic secondary alkyl acids lacking β-heteroatoms to achieve >10% label incorporation. The requirements for long reaction times (≥16 h) and use of large excesses of CO_2 (often >20 equiv) make these methods incompatible with ^{11}C PET applications. C(sp^3) acids that form stabilized carbanions upon ionic decarboxylation can undergo exchange with CO_2 spontaneously at high temperatures in the solid state[29] or in solution.[30−32] (Figure 1A). In contrast, compounds that lack strong anion stabilizing groups like nitro- or cyanoarylacetate groups require high reaction temperatures (≥150 °C) and long reaction times (≥24 h) or are simply inert toward exchange. Audisio and co-workers demonstrated the ^{11}C labeling of the arylacetate drugs flurbiprofen and tolmetin by uncatalyzed exchange with [^{11}C]CO_2, although slow kinetics and harsh conditions resulted in low radiochemical yields (RCYs) (7% and 3%, respectively, at 150 °C).[30]

With the goal of developing a mild method for direct carboxylate exchange at rates appropriate for ^{11}C labeling, we considered alternative strategies for C(sp^3)−carboxylate bond cleavage and subsequent CO_2 recapture. Here we show that a family of organic photocatalysts mediate the exchange of CO_2 groups without the need for prior stoichiometric carboxylate activation or high temperatures (Figure 1B). The radical-polar crossover process combines the advantages of low-barrier C−CO_2 bond cleavage initiated by carboxylate single-electron

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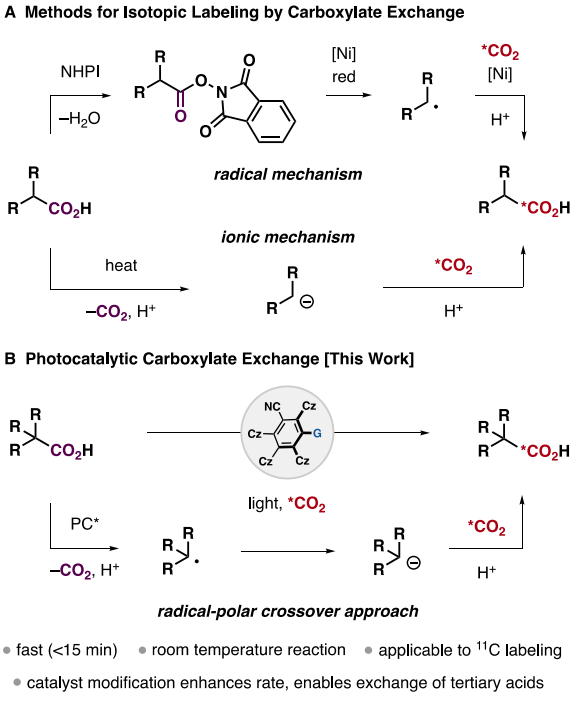

Figure 1. (A) Existing approaches for carboxylate/CO_2 exchange for isotopic labeling (NHPI = *N*-hydroxyphthalimide). (B) Fast, mild isotopic carboxylate exchange by organic photoredox catalysis (Cz = carbazole).

oxidation with the efficient uncatalyzed recombination of carbanion intermediates with CO_2.[33] Tertiary carboxylic acid substrates that are not compatible with either Ni catalysis or thermal reactions can be labeled to useful levels. The kinetics of CO_2 exchange are compatible with ^{11}C labeling of nonsteroidal anti-inflammatory drugs (NSAIDs) and precursors to other bioactive molecules.

Photoredox catalysis can be used to induce decarboxylation by substrate single-electron oxidation, but the recapture of CO_2 under these conditions has not been reported.[34−39] In considering new strategies for reversible decarboxylation of organic acids, we were inspired by König's studies,[40,41] which demonstrated that carbazole/dicyanobenzene-based photocatalysts could mediate decarboxylative electrophile trapping by radical-polar crossover mechanisms.[42] Upon surveying a wide array of organic and metal-based catalysts, we found that 5 mol % 4CzIPN[43,44] enabled the isotopic labeling of ibuprofen (**1**) with $[^{13}C]CO_2$ at room temperature upon irradiation with blue LEDs (52% ^{13}C incorporation, 77% yield). Other donor−acceptor cyanoarenes or isomers of 4CzIPN performed poorly under similar conditions regardless of their redox properties (Figure 2A).[45] Cs_2CO_3 was the optimal base, although other bases could be used (K_2CO_3, DBU). DMA could be replaced with DMSO, but the use of less polar solvents (THF, MeCN) resulted in low ^{13}C incorporation (Figure 2A; see the Supporting Information (SI) for optimization details). Radical traps (TEMPO, BHT) completely inhibit reactivity. The exchange process remains efficient when only 2 equiv of $[^{13}C]CO_2$ is used (43% ^{13}C incorporation, 75% yield).

Under standard reaction conditions, alkylative decyanation of 4CzIPN occurs,[40,41] and this process is important for generating a more active catalyst. The direct use of the benzylated catalyst 4CzBnBN (prepared by reacting 4CzIPN

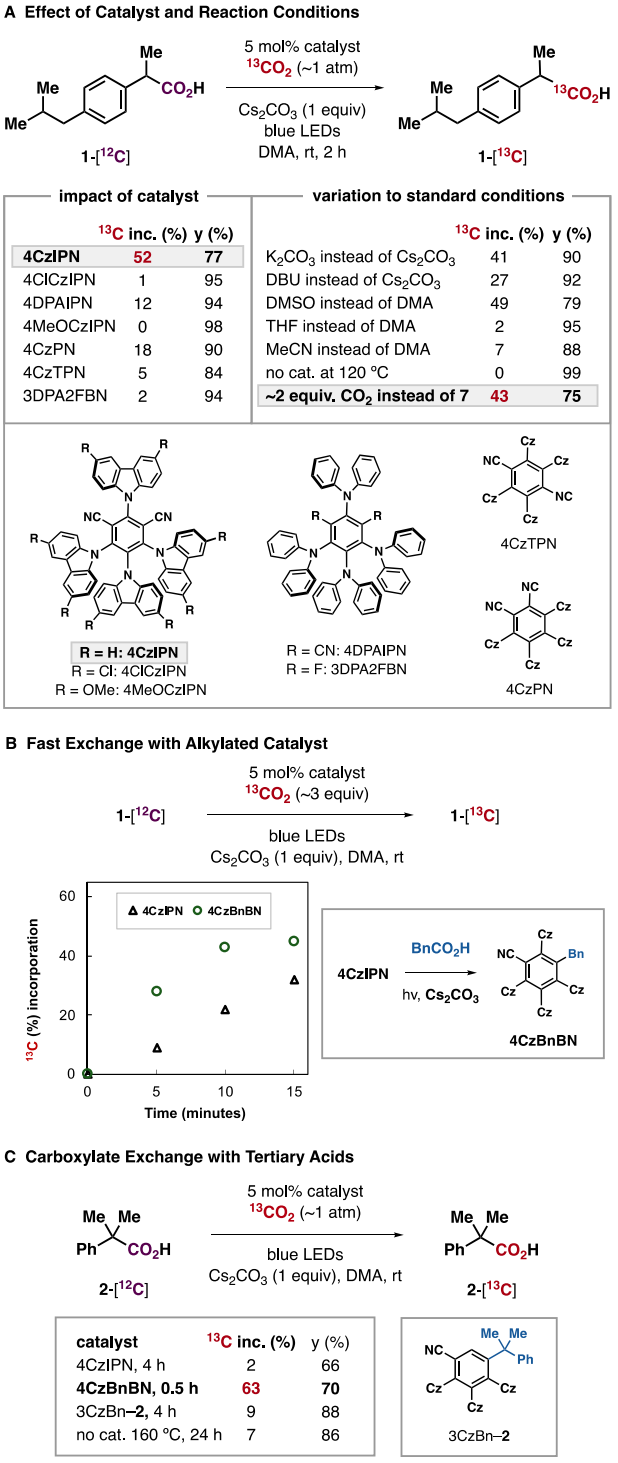

Figure 2. (A) Overview of photocatalyst effects and changes to reaction parameters. (B) 4CzIPN and 4CzBnBN rate comparison for $[^{13}C]CO_2$ exchange with ibuprofen. (C) 4CzBnBN enables carboxylate exchange with tertiary carboxylic acids.

with phenylacetic acid) resulted in a pronounced increase in ^{13}C incorporation rates (Figure 2B). With 3 equiv of $[^{13}C]CO_2$, >40% labeling of ibuprofen was obtained in 10 min using 4CzBnBN, which is double the incorporation observed with 4CzIPN. 4CzBnBN enabled isotopic labeling of more challenging substrate classes. Tertiary acid **2** undergoes efficient labeling using 4CzBnBN (63% ^{13}C incorporation, 70% yield), while low levels of exchange were detected using

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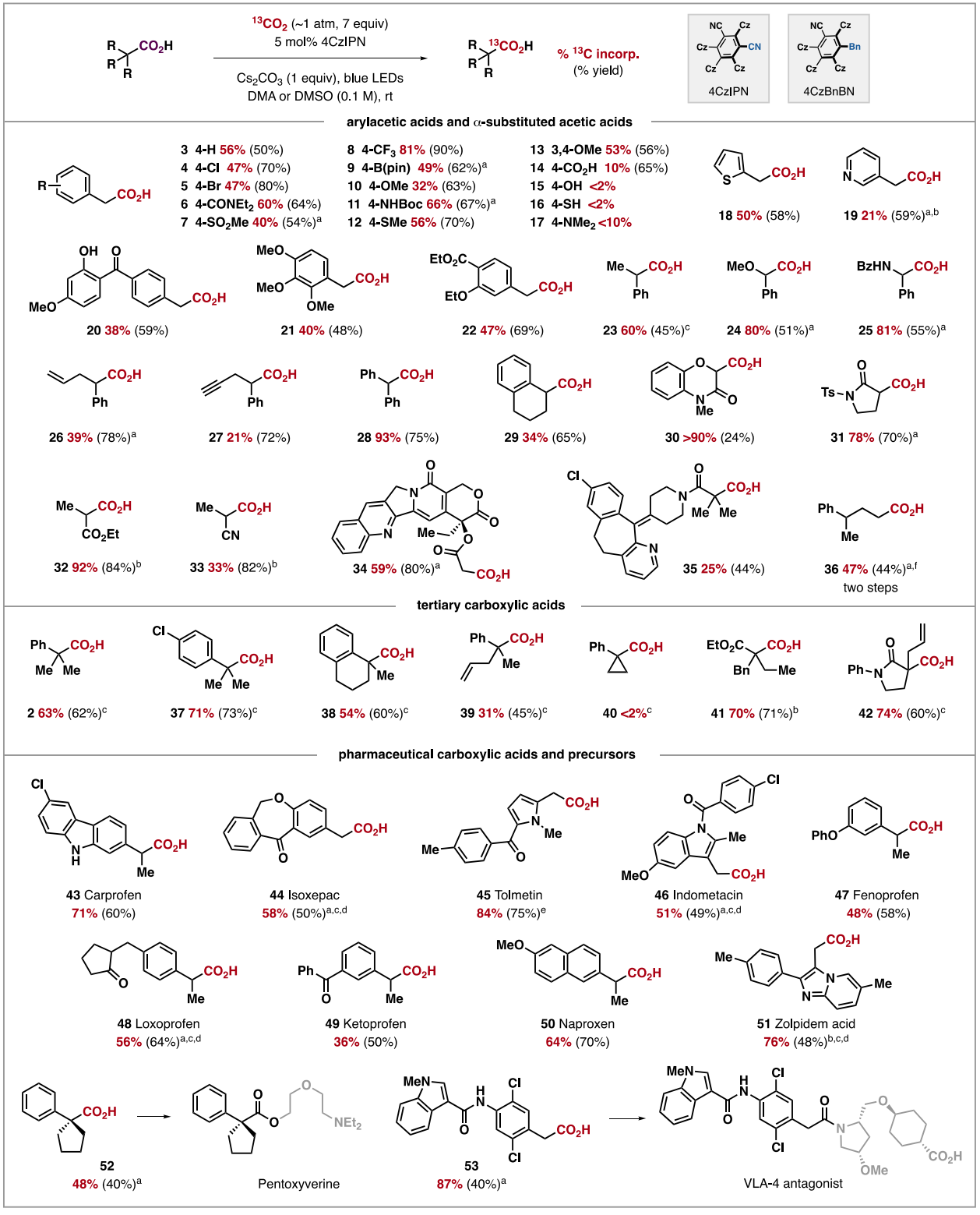

Figure 3. Scope and limitations. Unless otherwise noted, yields are of isolated material. [a]Calibrated ^{1}H NMR spectroscopy yield. [b]Percent ^{13}C incorporation and yield determined after conversion to the benzyl ester. [c]5 mol % 4CzBnBN. [d]~3 equiv of [^{13}C]CO_2. [e]2.5 mol % 4CzIPN. [f]Obtained by Pd/C hydrogenation of allylic carboxylate. See the SI for details.

4CzIPN (2%). The difference in the catalytic activities of these two catalysts with tertiary substrates can be rationalized by the observation that tertiary acid **2** reacts with 4CzIPN to give the carbazole elimination species 3CzBn−**2** (Figure 2C). 3CzBn−**2** is a poor mediator of carboxylate exchange, likely because of attenuated donor−acceptor properties. Catalyst screening studies showed little correlation between the activity in carboxylate exchange and the (pre)catalyst electrochemical potential (see the SI for details). The selective generation of monoalkylated benzonitrile species under the reaction

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conditions appears to be the most important factor in dictating successful carboxylate exchange. For example, 4ClCzIPN undergoes *double* benzylation in the presence of phenylacetic acid to generate an inactive species, while 4MeOCzIPN and 4DPAIPN are *resistant* to benzylation and perform sluggishly (Figure 2A; see the SI for details). These findings should have broader implications for the design and optimization of photocatalytic decarboxylative coupling reactions with donor−acceptor cyanoarenes.

With optimized reaction conditions, the scope and limitations of photoredox-catalyzed carboxylate isotopic exchange were explored (Figure 3). For less challenging substrate classes, the commercially available 4CzIPN catalyst was used. Arylacetates, including those with a halogen (**4**, **5**) or a moderate electron-withdrawing group, including amide (**6**), sulfonyl (**7**), CF_3 (**8**), or Bpin (**9**), underwent smooth carboxylate exchange. Electron-rich arylacetates with methoxy, thioether, or NHBoc group(s) (**10**−**13**, **21**) also underwent ^{13}C labeling using the standard conditions. Heterocycles (**18**, **19**) and more complex structures bearing potentially reactive ketone or phenol groups (**20**) were tolerated. Arylacetates substituted with an α-alkyl, α-alkoxy, or α-NH benzoyl group were productive substrates (**23**−**25**), as were molecules featuring an alkene or terminal alkyne (**26**, **27**). Alkylated or heteroatom-containing β-carboxy amides, β-carboxy lactams, malonate half-esters, and β-carboxy nitriles were compatible substrates (**30**−**33**). The labeling of complex molecules featuring malonate half-esters was possible (**34**, **35**). Labeled alkyl carboxylic acid **36** could be obtained by carboxylate exchange of the corresponding allylic substrate followed by hydrogenation (47% incorporation, 44% yield). A series of tertiary carboxylic acids were isotopically labeled using 4CzBnBN as the catalyst, including α,α-dialkylated arylacetates (**2**, **37**−**39**), a fully substituted malonate half-ester (**41**), and a carboxy lactam (**42**). These tertiary substrates do not undergo significant carboxylate exchange without catalyst under thermal conditions (see the SI for details). Scope limitations include 4-OH- or 4-SH-containing arylacetates (**15**, **16**), simple alkyl acids like cyclohexylcarboxylic acid, and α-cyclopropyl acid **40**.

Photoredox-catalyzed carboxylate exchange enables direct isotopic labeling of drug molecules and synthetic precursors under mild conditions. An array of NSAIDs underwent smooth exchange at room temperature, including those with potentially reactive functionalities and heterocyclic fragments (Figure 3, **43**−**50**). Precursors to other classes of pharmaceuticals and clinical candidates that feature arylacetate units, such as the acid of zolpidem (**51**) or pentoxyverine (**52**) and the core of a VLA-4 antagonist (**53**),[46] could be labeled with good ^{13}C incorporation and yield. In the above cases, replacement of $[^{13}C]CO_2$ with $[^{14}C]CO_2$ would allow for the preparation of compounds with specific activities suitable for most radiolabeling ADME studies (37−300 μCi/mg).

The rapid labeling of arylacetate drug molecules with $[^{11}C]CO_2$ is feasible using a photocatalytic approach.[47] $[^{11}C]$Ibuprofen could be generated in 17% RCY following 10 min of LED irradiation (Figure 4). The use of 4CzBnBN as the catalyst was essential for ^{11}C radiolabeling; no exchange was observed when 4CzIPN was used. N-Protected α-amino acid **25**, fully substituted malonate half-ester **41**, and tertiary arylacetate **52** could be radiolabeled in reasonable yields. These substrates do not undergo ^{11}C-labeling under thermal conditions (see the SI for details). The primary arylacetates of pharmaceutical relevance **53** and felbinac along with the

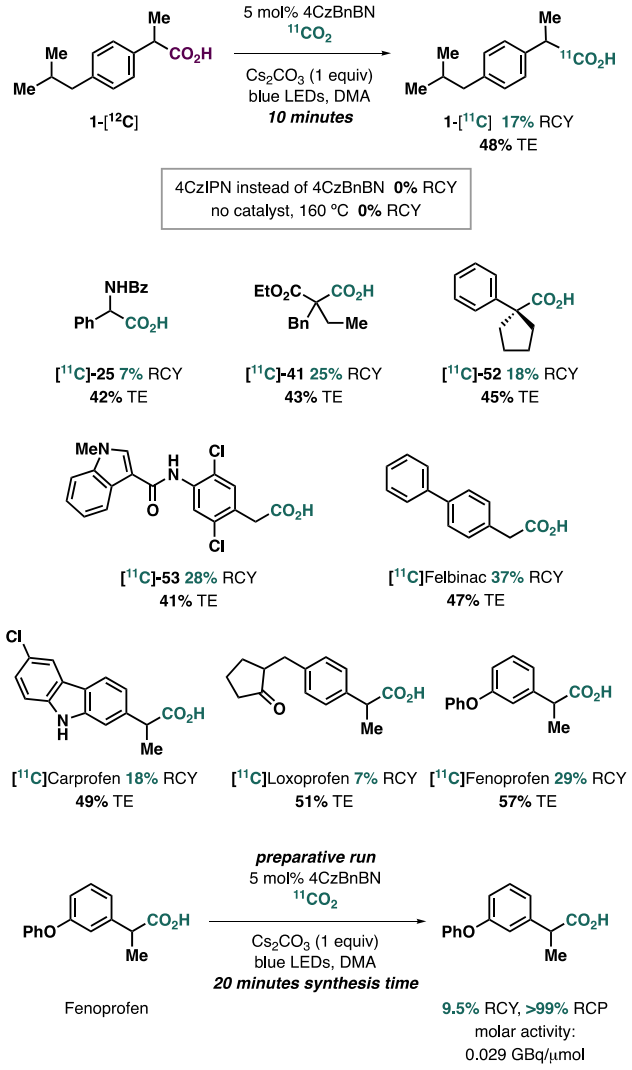

Figure 4. Photoredox-catalyzed carboxylate exchange with $^{11}CO_2$. Data are averages of two runs with 11.6 μmol of precursor and a starting radioactivity of ∼2 GBq. (TE = trapping efficiency of radioactivity in solution; RCP = radiochemical purity; RCY = TE × RCP. RCYs are decay-corrected). See the SI for experimental details.

propionates carprofen, loxoprofen, and fenoprofen could be radiolabeled under the standard conditions in 7−37% RCY. $[^{11}C]$Fenoprofen could be radiolabeled and isolated in 20 min starting from $[^{11}C]CO_2$ (∼2 GBq) to give the product in 9.5% RCY and >99% radiochemical purity with a molar activity of 0.029 GBq/μmol (Figure 4). This level of molar activity is consistent with isotopic exchange reactions and is useful for studying biodistribution processes. The ^{11}C radiolabeling reactions were partially automated using a commercial synthesis module with an external photochemical reactor (see the SI). Efforts toward implementation in a Good Manufacturing Practice (GMP) environment are underway.[48]

In conclusion, organic photoredox catalysis provides a mild and rapid pathway for direct carboxylate exchange, including processes that use $[^{11}C]CO_2$.[49] The reaction conditions and substrate scope complement Ni-catalyzed strategies for isotopic labeling of alkyl carboxylates using CO_2. Compatibility with potentially reactive functional groups, heterocycles, and tertiary acids combined with the opportunity to refine the

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photocatalyst performance should provide an avenue for future use in radiolabeling applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12819.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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