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 labelled 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 radiolabelling of drug molecules and precursors with [^{11}C]CO_2 is demonstrated.

The synthesis of isotopically labelled molecules is essential to drug development and nuclear medicine. As drug candidates move towards 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 radiolabelled with short-lived positron-emitting isotopes such as ^{11}C or ^{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 (^{11}C $t_{1/2}$ = 20.3 minutes). Approaches that selectively introduce isotopic labels from feedstock sources with compatibility towards 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-labelling approachs.[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.[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-labelled small molecules, particularly as CO_2 (or $BaCO_3$) is the feedstock for all radiolabelled 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 (Fig 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 and use of large excesses of CO_2 (≥16 h, often >20 equiv. CO_2) make these methods incompatible for ^{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] (Fig 1A). In contrast, compounds that lack strong anion stabilizing groups like nitro- or cyanoaryl acetate groups require high reaction temperatures (≥150 ºC), long reaction times (≥24 hours), or are simply inert towards exchange. Audisio and co-workers demonstrated the ^{11}C-labelling 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 (RCY) (7% and 3% respectively at 150 ºC).[30]

With the goal of developing a mild method for direct carboxylate exchange at rates appropriate for ^{11}C-labelling, 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 (Fig 1B). The radical-polar crossover process combines the advantages of low barrier C–CO_2 bond cleavage initiated by carboxylate single electron oxidation with the efficient, uncatalyzed recombination of carbanion intermediates with CO_2.[33] Tertiary carboxylic acid substrates not compatible with either Ni-catalysis or thermal reactions can be labelled to useful levels. The kinetics of CO_2 exchange are compatible with ^{11}C labelling of nonsteroidal anti-inflammatory drugs (NSAIDs) and precursors to other bioactive molecules.

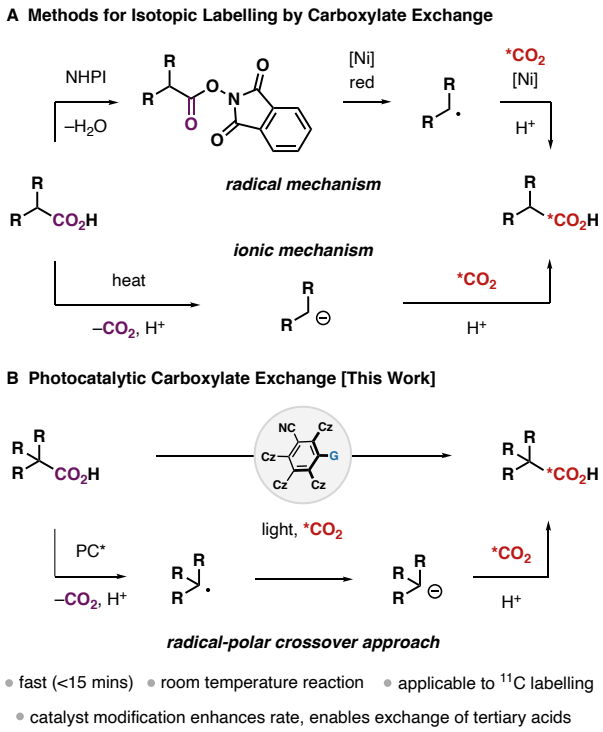

Figure 1. (**A**) Existing approaches for carboxylate/CO_2 exchange for isotopic labelling (NHPI = N-hydroxyphthalimide). (**B**) Fast, mild isotopic carboxylate exchange by organic photoredox catalysis (Cz = carbazole)

Photoredox catalysis can be used to induce decarboxylation by substrate single electron oxidation, however 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 Konig'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 labelling 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 (Fig 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 (Fig 2A, see the SI for optimization details). Radical traps (TEMPO, BHT) completely inhibit reactivity. The exchange process remains efficient when using only 2 equivalents of [^{13}C]CO_2 (43% ^{13}C incorporation, 75% yield).

Under standard reaction conditions alkylative decyanation of 4CzIPN occurs,[40-41] this process is important to generating a more active catalyst. The direct use of benzylated catalyst 4CzBnBN (prepared by reacting 4CzIPN with phenylacetic acid) resulted in a pronounced increase in ^{13}C incorporation rates (Fig 2B). With 3 equivalents of [^{13}C]CO_2 >40% labelling of Ibuprofen was obtained in 10 minutes using

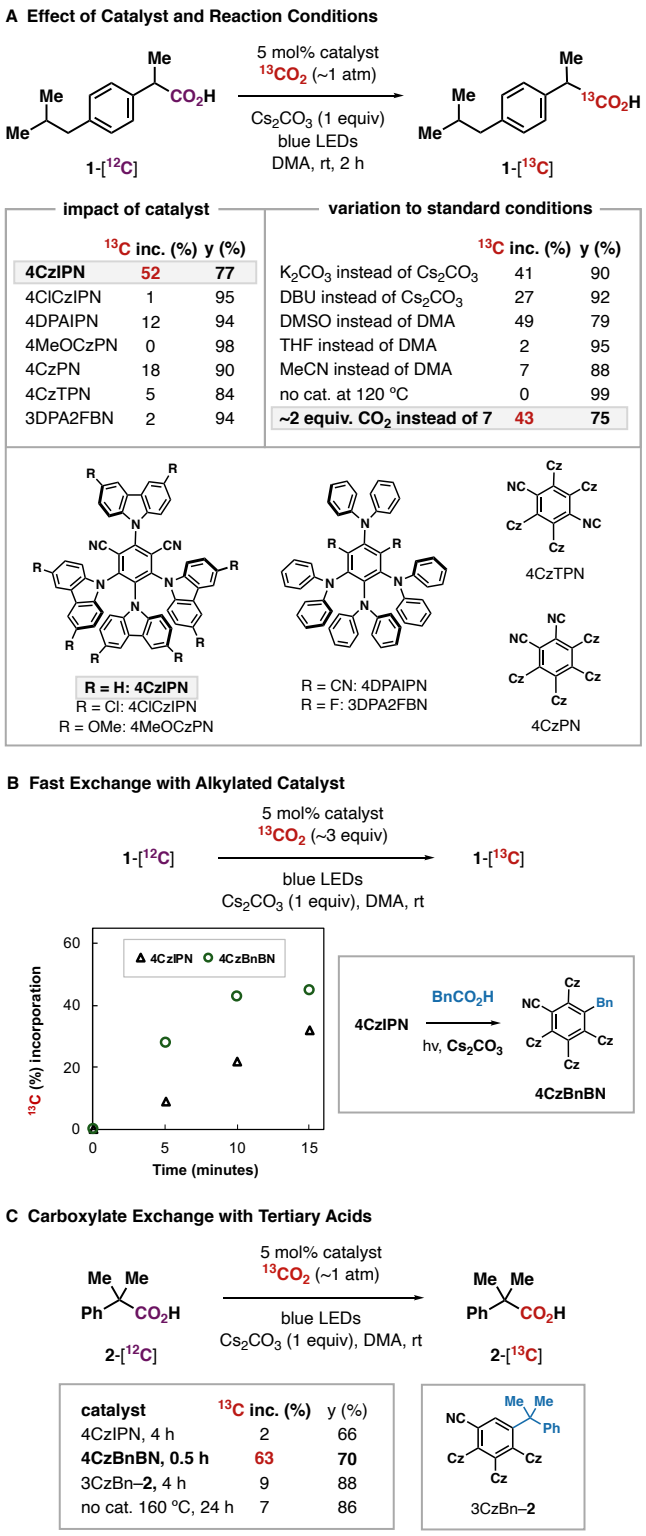

Figure 2. (A) Overview of photocatalyst effects and changes to reaction parameters. **(B)** 4CzIPN and 4CzBnBN rate comparison for [^{13}C]CO_2 exchange with Ibuprofen. **(C)** 4CzBnBN enables carboxylate exchange with tertiary carboxylic acids.

4CzBnBN, which is double the incorporation observed with 4CzIPN. 4CzBnBN enabled isotopic labelling of more challenging substrate classes. Tertiary acid **2** undergoes efficient labelling using 4CzBnBN (60%

^{13}C incorporation, 70% yield), while low levels of exchange were detected using 4CzIPN (2%). The difference in catalytic activity with tertiary substrates between these two catalysts can be rationalized by the observation that tertiary acid **2** reacts with 4CzIPN to give a carbazole elimination species 3CzBn-**2** (Fig 2C). 3CzBn-**2** is a poor mediator of carboxylate exchange, likely owing to attenuated donor-acceptor properties. Catalyst screening studies showed little correlation between activity in carboxylate exchange and (pre)catalyst electrochemical potentials (see the SI for details). The selective generation of monoalkylated benzonitrile species under the reaction 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 (Fig 2A, see the SI for details). These findings should have broader implications when designing and optimizing photocatalytic decarboxylative coupling reactions with donor-acceptor cyanoarenes.

With optimized reaction conditions, the scope and limitations of photoredox catalyzed carboxylate isotopic exchange were explored (Fig 3). For less challenging substrate classes, the commercially available 4CzIPN catalyst was used. Arylacetates, including those with halogens (**4**, **5**), moderate electron-withdrawing groups including amides (**6**), sulfonyls (**7**), CF_3 groups (**8**), and Bpin units (**9**) underwent smooth carboxylate exchange. Electron-rich arylacetates with methoxy, thioether, or NHBoc groups (**10**–**13**, **21**) also underwent ^{13}C-labelling using the standard conditions. Heterocycles (**18**, **19**) and more complex structures bearing potentially reactive ketone or phenol groups (**20**) were tolerated. Arylacetates substituted with α-alkyl, α-alkoxy, and α-NH benzoyl groups 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 labelling of complex molecules featuring malonate half-esters was possible (**34**-**35**). A series of tertiary carboxylic acids were isotopically labelled using 4CzBnBN as the catalyst, including α, α-dialkylated arylacetates (**2**, **37**-**39**), fully substituted malonate half-esters (**41**), and carboxy lactams (**42**). These tertiary substrates do not undergo significant carboxylate exchange without catalyst under thermal conditions (see SI for details). Scope limitations include 4-OH or 4-SH containing arylacetates (**15**-**16**), simple alkyl acid **36**, and the a-cyclopropyl acid **40**.

Photoredox catalyzed carboxylate exchange enables direct isotopic labelling 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 (Fig 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 VLA-4

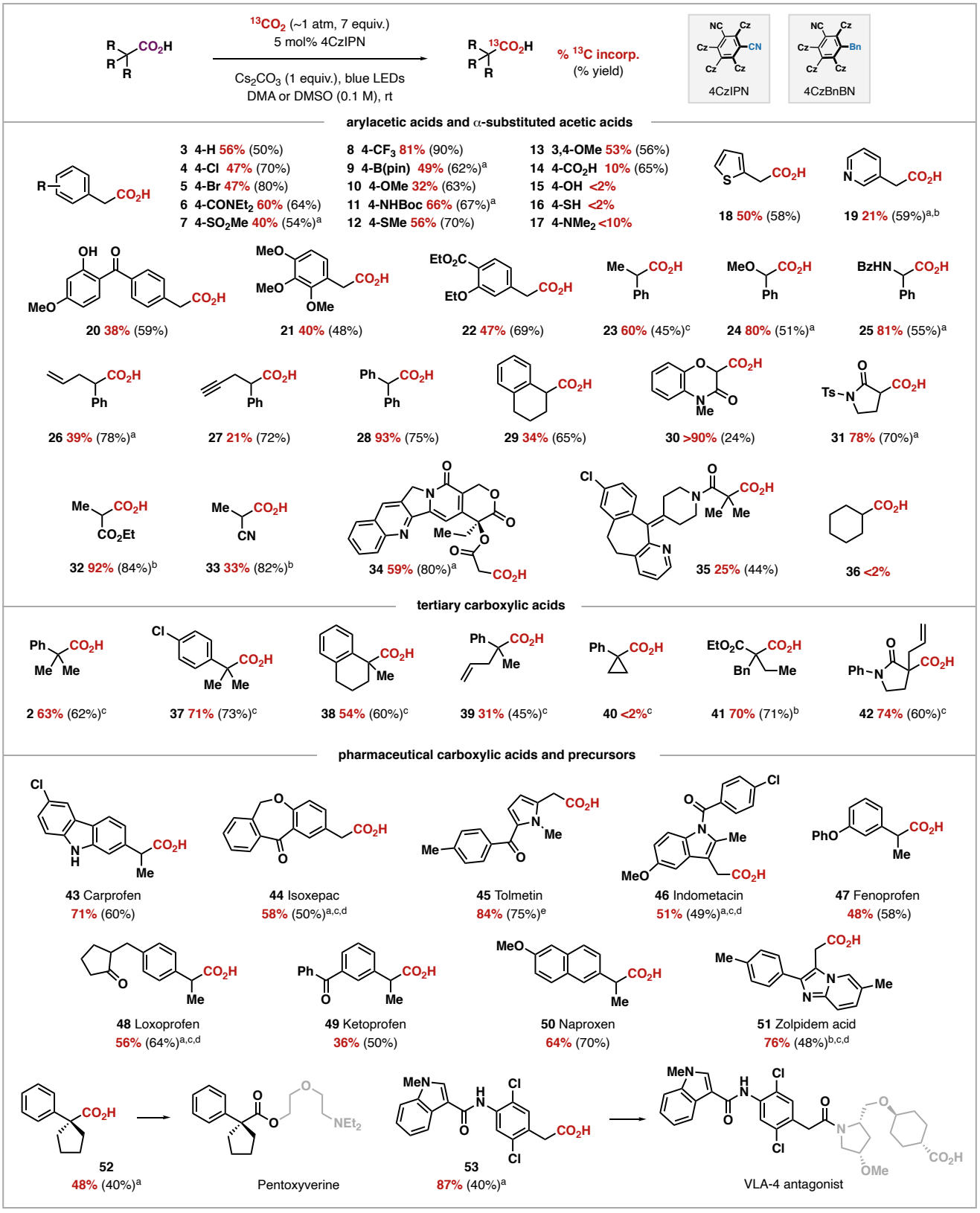

Figure 3. Scope and limitations. Unless noted yields are of isolated material. [a] Calibrated ^{1}H NMR spectroscopy yield; [b] %^{13}C incorporation and yield determined after conversion to benzyl ester; [c] 5 mol% 4CzBnBN; [d] ~3 equiv. [^{13}C]CO_2, [e] 2.5 mol% 4CzIPN. See the SI for details

antagonist (**53**),[46] could be labelled 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 radiolabelling ADME studies (37-300 mCi/mg).

The rapid labelling of arylacetate drug molecules with [^{11}C]CO_2 is feasible using a photocatalytic approach.[47] [^{11}C]Ibuprofen could be generated with 20% radiochemical yield (RCY) following 10 minutes of LED irradiation (Fig 4). Use of 4CzBnBN catalyst was essential for ^{11}C-radiolabelling; no exchange was observed when using 4CzIPN. Thermal conditions (160 ºC) provided no radiolabeled product. Related targets Carprofen, Loxoprofen, and Fenoprofen could be radiolabelled under the standard conditions in 7–29% RCY, as could the tertiary acid substrate **52**. [^{11}C]Fenoprofen could be radiolabelled and isolated in 20 minutes 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/mmol (Fig 4). This level of molar activity is consistent with isotopic exchange reactions and is useful for studying biodistribution processes.

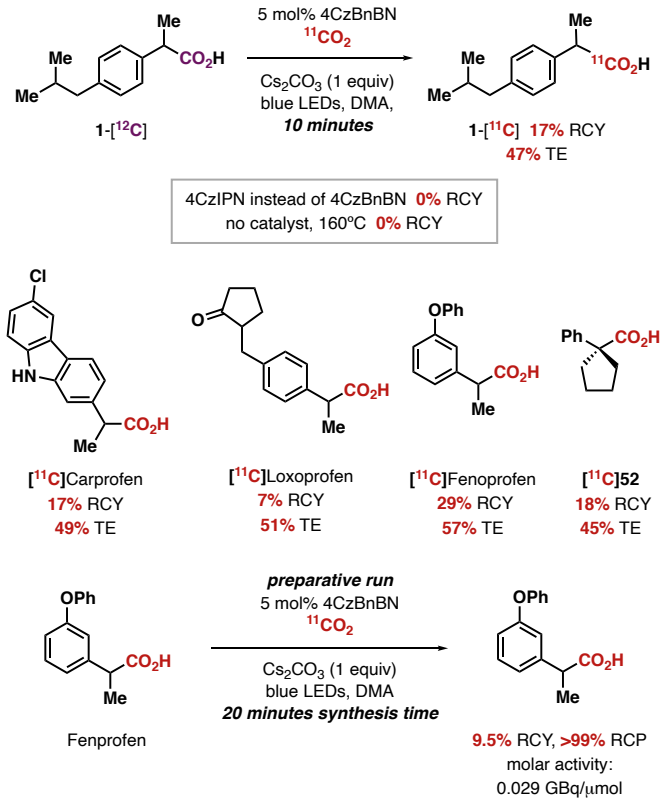

Figure 4. Photoredox catalyzed carboxylate exchange with $^{11}CO_2$ (TE = trapping efficiency of radioactivity in solution; RCP = radiochemical purity; RCY = TE × RCP).

In conclusion, organic photoredox catalysis enables a mild and rapid pathway for direct carboxylate exchange, including processes that use [^{11}C]CO_2. The reaction conditions and substrate scope complement Ni-catalyzed strategies for isotopic labelling of alkyl carboxylates using CO_2. Compatibility with potentially reactive functional groups, heterocycles, and tertiary acids, combined with the opportunity to refine photocatalyst performance should provide an avenue for future use in radiolabelling applications.

Acknowledgments

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