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Carbon Dioxide Radical Anion by Photoinduced Equilibration between Formate Salts and [^{11}C , ^{13}C , ^{14}C]CO $_2$: Application to Carbon Isotope Radiolabeling

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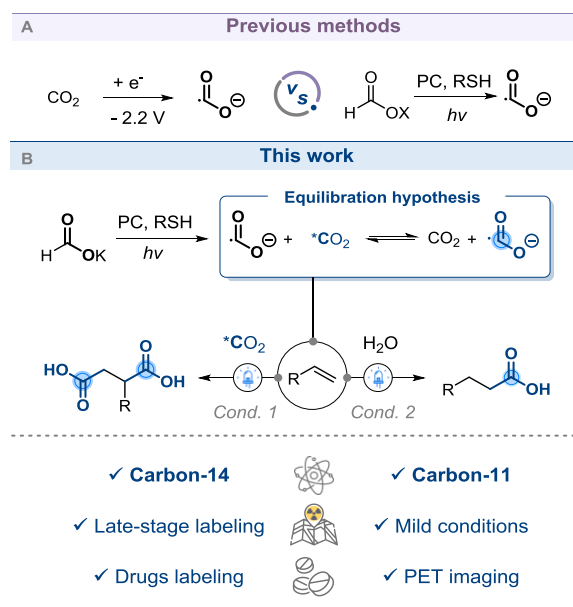
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KEYWORDS Carbon-14 • Carbon-11 • Carbon Dioxide Radical Anion • PET imaging • Isotope Labeling

ABSTRACT: The need for carbon-labeled radiotracers is increasingly higher in drug discovery and development (carbon-14, β^- , $t_{1/2} = 5730$ years) as well as in PET, for *in vivo* molecular imaging applications (carbon-11, β^+ , $t_{1/2} = 20.4$ min). However, the structural diversity of radiotracers is still systematically driven by the narrow available labeled sources and methodologies. In this context, the emergence of carbon dioxide radical anion chemistry might set forth potential unexplored opportunities. Based on a dynamic isotopic equilibration between formate salts and [^{13}C , ^{14}C , ^{11}C]CO $_2$, C-labeled radical anion CO $_2^{\bullet-}$ could be accessed under extremely mild conditions within seconds. This methodology was successfully applied to hydro-carboxylation and di-carboxylation reactions in late-stage carbon isotope labeling of pharmaceutically relevant compounds. The relevance of the method in applied radiochemistry was showcased by the whole-body PET biodistribution profile of [^{11}C]oxaprozin in mice.

Introduction

The fixation of carbon dioxide (CO $_2$) and its valorization as a one-carbon (C1) building block has attracted considerable attention.¹ Carboxylation reactions have specifically benefited of extensive innovation and the use of CO $_2$ as an electrophilic partner, in transformations involving two-electron mechanisms, have been broadly explored.² Conversely, its single-electron reduction and the valorization of the corresponding radical anion (CO $_2^{\bullet-}$) in organic synthesis received less interest (Scheme 1A).³ In 2017, seminal works by Jamison⁴ reported a photoredox catalyzed access to CO $_2^{\bullet-}$ under ultraviolet irradiation (390 nm) and provided concrete evidence that single-electron reduction of CO $_2$ represents a productive strategy for C–C bond formation. A series of reports have shown improvement of the conditions, but the high reduction potential of CO $_2$ ($E^0 = -2.21$ V vs saturated calomel electrode (SCE) in DMF) renders this transformation challenging.^{5,6} A significant step forward towards the mild formation of CO $_2^{\bullet-}$ was achieved from formate salts through a Hydrogen Atom Transfer (HAT).⁷ This strategy was popularized in 2021 by the groups of Wickens, Jui and Li, who recognized that access to CO $_2^{\bullet-}$ was possible starting from formate salts, under photocatalytic conditions.^{8,9,10} The radical anion was further engaged as nucleophilic carbon-radical in Giese-type reactions.¹¹



Scheme 1. A) Current state-of-the-art to access to carbon dioxide radical anion. B) Working hypothesis on the equilibration between [^{12}C]carbon dioxide radical anion and C-labeled

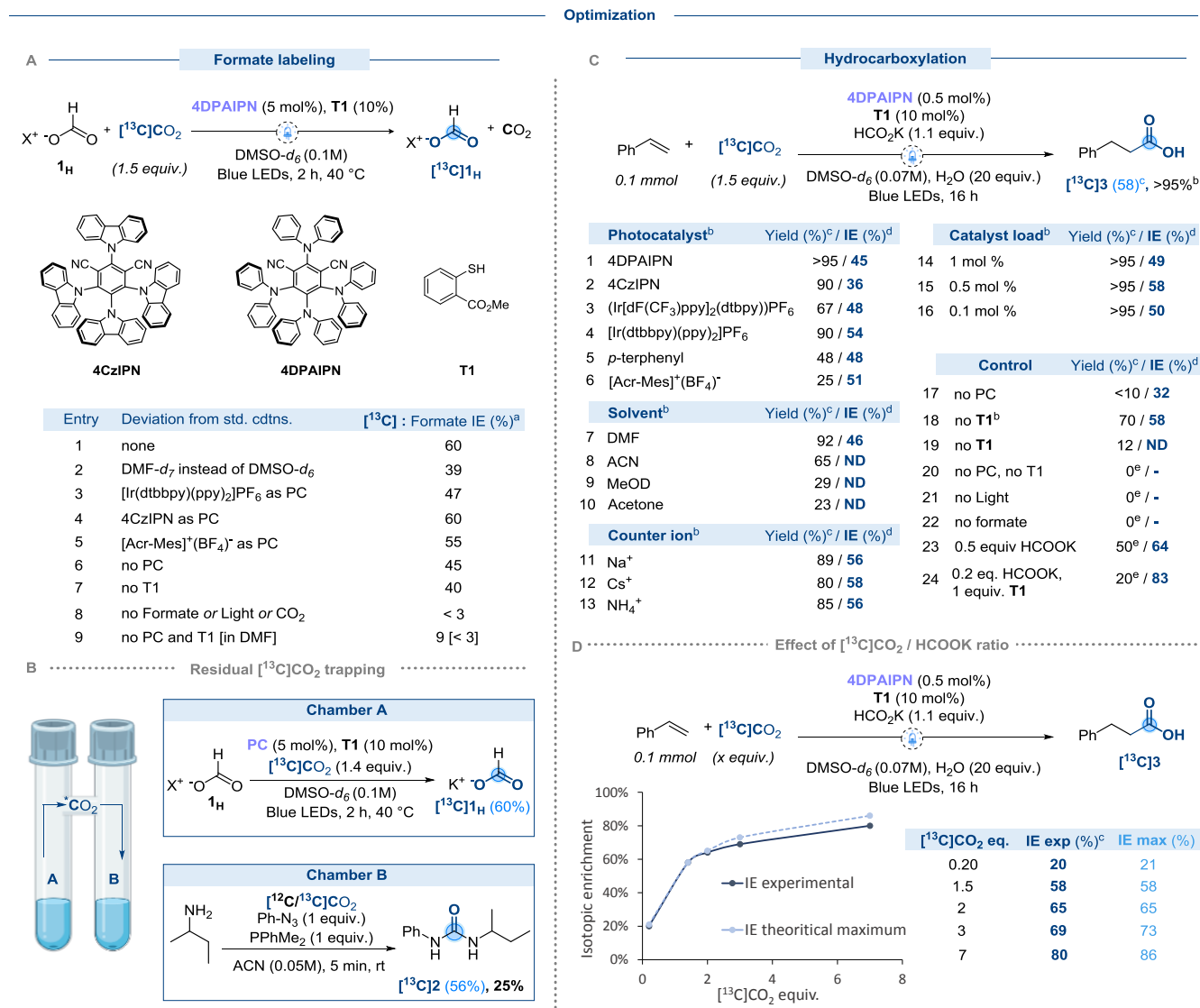
CO₂; opportunities for late-stage ¹⁴C and ¹¹C labeling. PC : photocatalyst.

While advances in single-electron CO₂ chemistry provided a notable synthetic opportunity, this technology remains elusive for applications in the field of carbon-isotope radiolabeling. Carbon-11 (¹¹C, t_{1/2} = 20.4 min, β⁺ emitter) is a reference in positron emission tomography (PET) imaging; but it has a remarkably short half-life and can only be produced extemporaneously, on the nanomolar scale.¹² On the other hand, carbon-14 (¹⁴C, t_{1/2} = 5730 years, β⁻ emitter) is a pivotal tool for tracking the fate of organic compounds and a gold standard for human-ADME studies and crop science development, but the costs related to the source, its handling and the generation of long-lasting waste prevent the use of excess reagent.¹³ Consequently, despite the fact that [¹⁴C]CO₂ (1600 \$.mmol⁻¹) and [¹¹C]CO₂ are primary sources of both isotopes, such inherent challenges prevented using labeled CO₂⁻ technologies.

At first sight, the HAT strategy from formate salts might appear promising, but unfortunately, limitations related to these radiolabeled C1 isotopologues precludes practical utilization. For instance, ¹⁴C-formate, obtained from the reduction of CO₂ often in low chemical purity,¹⁴ is commercially availa-

ble in aqueous solutions at tenfold higher price than carbon dioxide ([¹⁴C]HCOONa 16500 \$.mmol⁻¹). Notwithstanding the growing interest for the carbon dioxide radical anion, to the best of our knowledge, [¹¹C]CO₂⁻ and [¹⁴C]CO₂⁻ remain elusive species, which have never been utilized in radiosynthesis, neither in PET nor in beta-imaging applications.

Herein, we report a strategy enabling access to labeled CO₂⁻, based on the fast equilibration between [¹²C]CO₂⁻ and ¹¹C, ¹³C and ¹⁴C-labeled CO₂ (Scheme 1B). Under mild photocatalytic conditions, formal reduction of [*C]CO₂ to H[*C]COO⁻ takes place within seconds and the generated [*C]CO₂⁻ was reacted in Giese-type radical transformations to access pharmaceutically relevant labeled derivatives. In the process, we discovered an unexpected amide bond rearrangement and accessed to labeled succinimide isotopomers. The relevance of this technology was highlighted by the synthesis of radiotracers with both long- and short-lived carbon isotopes and with the productive ¹⁴C-¹²C and ¹¹C-¹²C bond formation to access [¹⁴C]mesuximide and [¹¹C]oxaprozine. As a proof-of-concept of *in vivo* feasibility, the biodistribution of [¹¹C]oxaprozin was realized by *in vivo* PET imaging in mice.

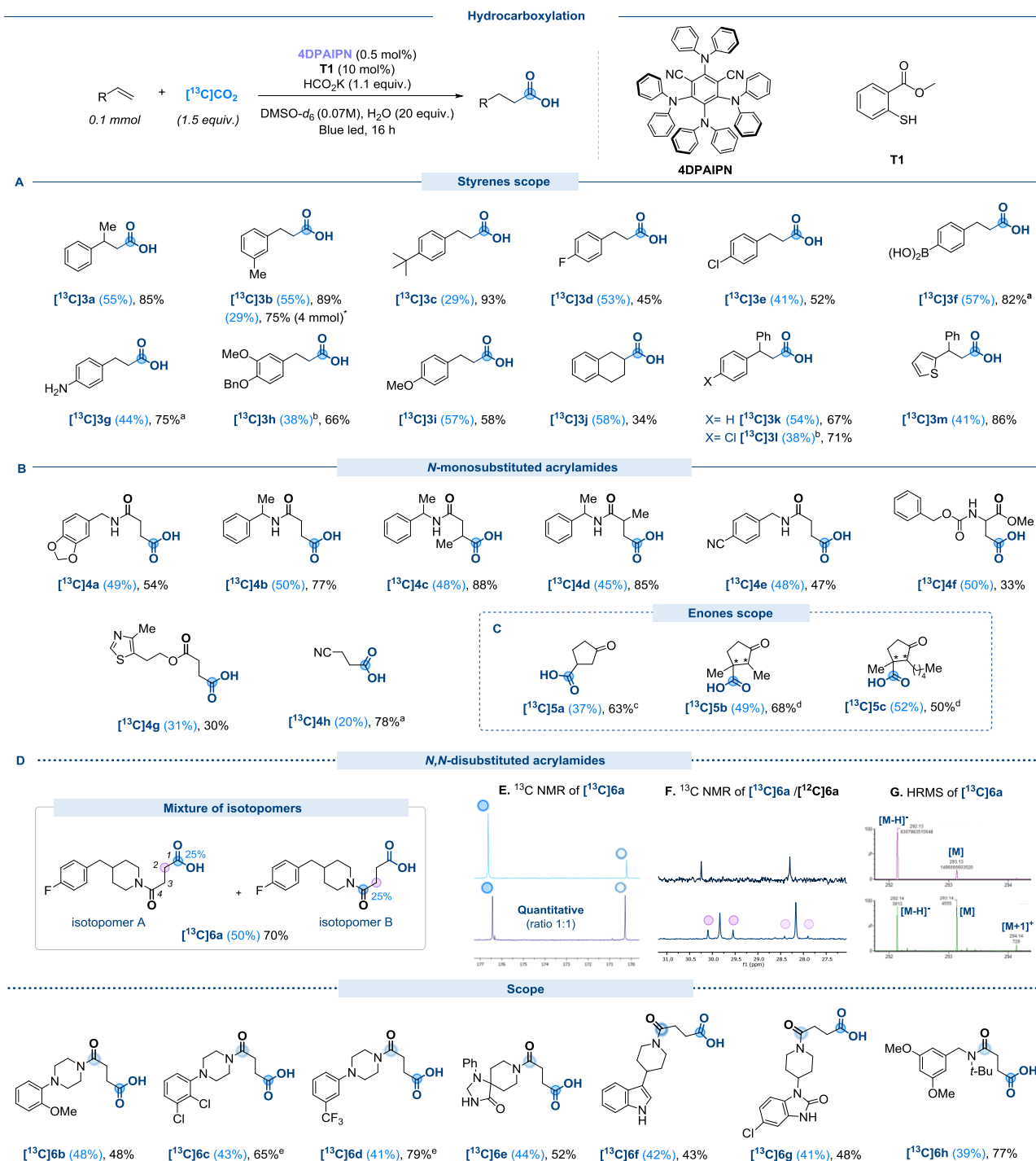


Scheme 2. Optimization of formate labeling with [^{13}C]CO $_2$ and its application to hydro-carboxylation.^a Isotopic enrichment determined by ^1H NMR. ^b reactions performed using 5 mol% of photocatalyst. ^c Yields determined by ^1H NMR using dibromomethane as internal standard. ^d Isotopic enrichment determined by MS. ^e Styrene recovered. ND: Not Determined.

Results and discussion

To enable simple access to C-labeled CO $_2^{\cdot-}$ directly from ^{12}C -labeled CO $_2$, it was hypothesized that *in situ* generation of [^{12}C]CO $_2^{\cdot-}$ from ^{12}C -formate might trigger a reversible redox process in presence of C-labeled CO $_2$, to form the desired [$^{11/14}\text{C}$]CO $_2^{\cdot-}$. While appealing, a number of challenges and pitfalls were anticipated. For instance, the rate of equilibration that has to match with the short half-life of ^{11}C and the inherent stability of the radical anion species, which might undergo accelerated radiolysis (*i.e.* decomposition due to ionizing radiation) related to the decay energy of the radioisotopes. With such questions in mind, we commenced our investigations looking for proof-of-concept to validate the hypothesis using stable labeled [^{13}C]CO $_2$. When a dimethyl sulfoxide

(DMSO) solution of potassium formate [^{12}C]HCOOK in presence of organic photocatalyst 4CzIPN (5 mol%) and 1.5 equiv. of [^{13}C]CO $_2$ was irradiated under blue light (460 nm), the formation of [^{13}C]HCOOK was observed (Scheme 2A). The isotopic enrichment (IE) was shown by the appearance of two satellites at $\delta = 8.58$ and 8.13 ppm in the ^1H -NMR and the signal of ^{13}C -labeled formate in the ^{13}C -NMR at $\delta = 167$ ppm (see supporting information, Figure S3). Though the observed IE of 42% was moderate, the overall process is equivalent to the formal reduction of [^{13}C]CO $_2$ to [^{13}C]HCOOK, a transformation which usually requires the provision of an important source of energy¹⁵ or highly reductant photocatalysts.¹⁶



Scheme 3: Investigation of the scope of the hydrocarboxylation reaction: A) styrenes; B, D) acrylamides; C) enones. E-G) NMR and MS data for [¹³C]6a. Isolated yields unless otherwise stated. IE are shown in blue under brackets. ^a Yields determined by ¹H-NMR using dibromomethane as internal standard. ^b Reaction performed on 0.5 mmol scale using 0.5 equiv. of [¹³C]CO₂. ^c Isolated as hydrazone. ^d Isolated as a mixture of diastereoisomers. ^e Reaction time: 1 hour. * Reaction performed on 4 mmol scale using 0.5 equiv of [¹³C]CO₂.

After optimization (Scheme 2A), the use of 4DPAIPN (5 mol%) and thiol T1 (10 mol%) in DMSO-*d*₆ allowed to form [¹³C]HCOOK in 60% IE after 2 hours, nearly the maximal theoretical value under such stoichiometry (entry 1).¹⁷ 4DPAIPN could be replaced by 4CzIPN without any significant drop in the final IE (Scheme 2A, entry 4). It is worth noting that in the absence of PC or T1 lower IE are observed

(Scheme 2A, entries 6, 7). On the other hand, without both PC and T1 under light irradiation (~40 °C), a not negligible 9% IE was observed in DMSO (entry 9).¹⁸ This background equilibration seems solvent dependent, as in DMF no IE was detected.¹⁹

The photoinduced equilibration was next performed in a two-chamber reactor (Ch.A), and in the adjacent chamber (Ch.B) a Staudinger/aza-Wittig sequence²⁰ was set to react with the residual [¹³C]CO₂ (Scheme 2B). Pleasingly, urea

[¹³C]2 was isolated in 56% IE, thus confirming that a nearly identical isotopic dilution occurred in the headspace.

To confirm the formation of the transient [¹³C]CO₂⁻, we explored the reaction in presence of styrene. In the optimized conditions, the presence of H₂O (20 equiv.) was essential for cleaner crude reaction (see SI, Fig S19) and [¹³C]3 was obtained in >95% NMR yield and 58% IE (Scheme 2C, entry 1). In the absence of H₂O, the formation of a variable amount of di-carboxylation product was observed systematically (*vide infra*).

While 4DPAIPN, 4CzIPN and [Ir(dtbbpy)(ppy)₂]PF₆ were competent PC (Scheme 2C, entries 1, 2, 4). The nature of the formate cation did not affect the transformation both in term of yield and IE (entries 11-13), while DMSO and DMF were best suited solvents (entries 7-10). The PC loading could be drastically diminished, and 0.5 mol% was selected for practicality (entry 15). While the presence of only PC or T1 were able to promote the reactions (though at a less proficient degree, entries 17-19), control experiments have shown that the presence of both PC and T1, potassium formate and light was mandatory in order for the hydro-carboxylation to proceed. Interestingly, when only 0.5 equiv. of HCOOK were utilized, the yield dropped to 50%, while the IE increased to 64% (entry 23). A coherently analogous result was obtained using 0.2 equiv. of HCOOK (entry 24). This result supports the hypothesis that [¹³C]CO₂⁻ is formed in presence of formate salts, thus excluding a direct reduction of CO₂, by the photocatalytic system.

The effect of the stoichiometry of [¹³C]CO₂ was next studied and the addition of precise equivalents of [¹³C]CO₂ was performed using a RC Tritec carboxylation manifold. Pleasingly, the experimental IE nearly overlapped with the expected theoretical values (Scheme 2D). This is a crucial factor for applications to ¹⁴C-radiolabeling, where the control of molar activity (A_m) is a strict requirement for *in vitro* and *in vivo* studies.

With this optimized procedure, we set out to investigate the scope of the transformation on a series of olefin derivatives (Scheme 3). Styrenes could be hydro-carboxylated with yields spanning from 34% to 93% and IE close to the theoretical maxima. When, the reaction was performed at a 4 mmol scale on 3-methylstyrene with 0.5 equiv. of labeled CO₂, pleasingly, [¹³C]3b was isolated in a 75% yield and 29% IE. A good tolerance was observed with diverse *para*- and *meta*-substituents (Scheme 3A). Cyclic dihydronaphthalene [¹³C]3j was converted with moderate yield and 58% IE. The conditions were applicable to substrates bearing functional groups such as primary amines [¹³C]3g, boronic acid [¹³C]3f and aryl chloride [¹³C]3e. The presence of bromine substituents, whether on the aromatic part or the alkene, lead to significant loss of yield.²¹ The presence of methyl was well tolerated on α position [¹³C]3a. Contrariwise, β -substituted styrenes did not react (see SI, Figure S9). On the other hand, 1,1-diphenylethylene derivatives [¹³C]3k-3m were carboxylated in 67 to 86% yields and optimal IE.

N-monosubstituted acrylamides reacted smoothly to provide the corresponding 4-amino-4-oxobutanoic acids [¹³C]4a-4f in moderate to good yields and IE (Scheme 3B). Acrylate and acrylonitrile provided [¹³C]4g and [¹³C]4h in 30 and 78% yield with 31 and 20% IE, respectively. Interestingly, substitutions on the acrylate were tolerated with no impact on either yields or IEs [¹³C]4b-4d. Dehydroalanine (Dha) is an amino acid, found primarily in peptides.²² This non-proteinogenic residue provides strong chemical utility in proteins and was

pioneered by the Davis group and others.²³ Under standard conditions, protected Dha was converted into aspartic acid [¹³C]4f in 33% yield and 50% IE, offering a complementary strategy to access to this labeled amino acid.²⁴

Intriguingly, when *N,N*-disubstituted acrylamides were subjected to identical reaction conditions, we observed systematically two labeled signals in the ¹³C-NMR spectra [¹³C]6a-6h. To disentangle such unexpected results, we focused on product [¹³C]6a. As shown in Scheme 3D, mass spectrometry indicated incorporation of only one ¹³C in the product with 50% IE, excluding doubly labeled product. Comparing with the unlabeled [¹²C]6a, prepared by reacting succinic anhydride with corresponding piperidine, we confirmed that the ¹³C-signal at 170.2 ppm belonged to the carbonyl of the amide (C₄). Additional evidence was provided by the appearance of resonance doublets corresponding to the methylene groups C₂ and C₃ in *alpha* to the carboxylic acid (C₁) and amide (C₄), of the 4-amino-4-oxobutanoic acid, with C₁-C₂ (d, δ = 29.8 ppm, $J_{C_1-C_2}$ = 56 Hz) and C₄-C₃ (d, δ = 28.2 ppm, $J_{C_4-C_3}$ = 51 Hz) coupling constants. While initial ¹³C-NMR spectra (D1 = 4 sec) seemed to point to a higher ¹³C enrichment of C₁, quantitative analysis (D1 = 20 sec) showed equal enrichment. MS/MS fragmentations confirmed this ratio and determined that C₁ and C₄ are both enriched at 25% IE (see SI, pages 58-59). These results confirmed that [¹³C]6a was obtained as mixture of two inseparable isotopomers. Additional investigation highlighted that the rearrangement is complete within 10 minutes and no further isotope incorporation took place when [¹²C]6a was reengaged under standard reaction conditions (see SI, pages S92-93). Since formation of isotopomers was observed exclusively in presence of *N,N*-disubstituted acrylamides, this unexpected behavior might be related to the steric hindrance at the nitrogen (NR₂), which decreases the barrier for N-CO rotation and twist more freely than secondary amides, as previously reported by Lloyd-Jones and Booker-Milburn.²⁵

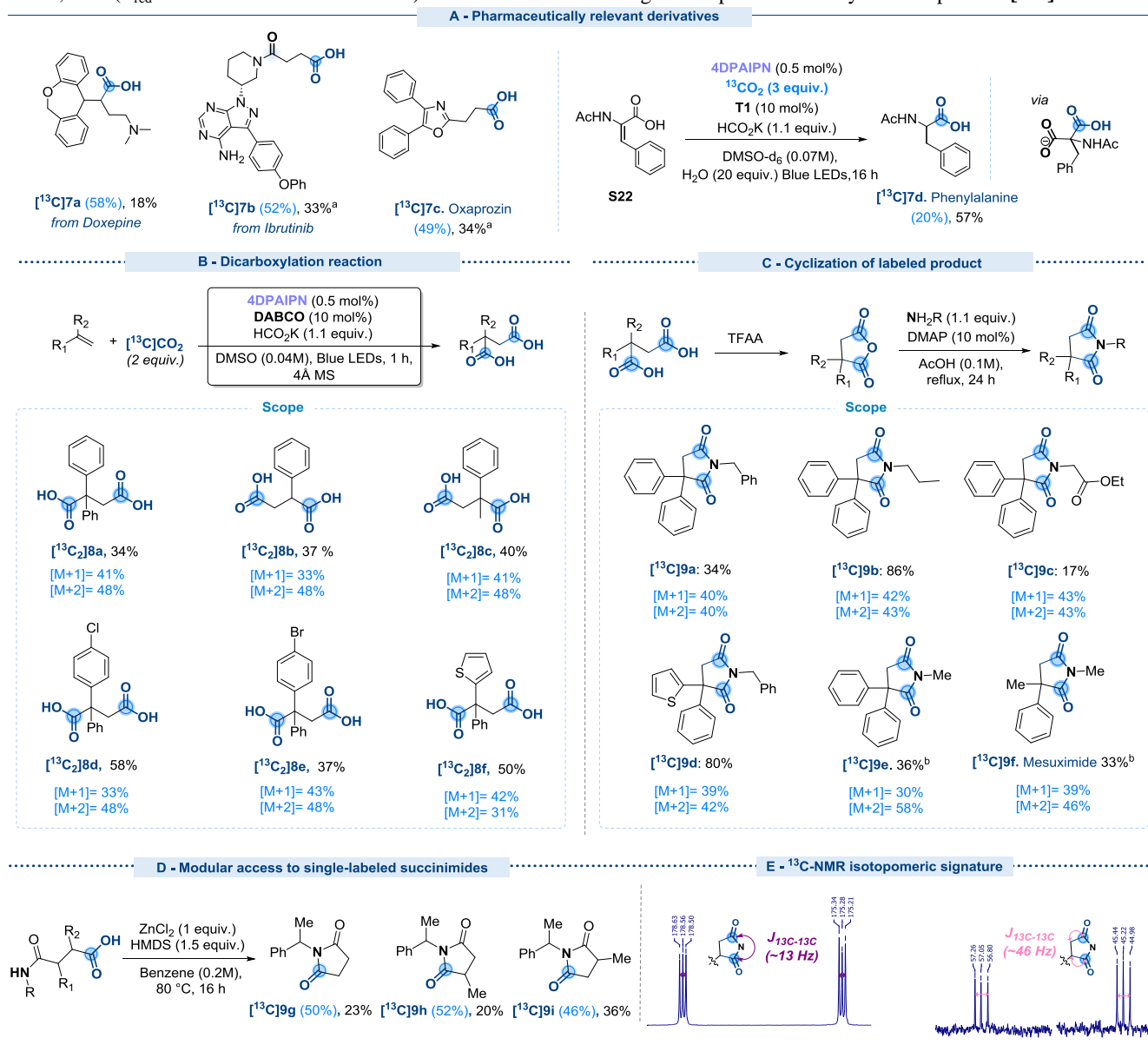
We speculate that after radical carboxylation with [¹³C]CO₂⁻, the carbon-radical in *alpha* to the amide (trapped in presence of TEMPO, see SI, Fig. S18) is next converted into an anionic adduct *via* a reductive radical/polar crossover process thought single electron transfer (SET).²⁶ This carboxylate intermediate might undergo cyclisation to generate the transient mono-labeled succinic anhydride and the piperidine anion. Further nucleophilic addition onto the anhydride provides a mixture of isotopomers (see SI Figure S16, for a plausible mechanistic hypothesis). While so far attempts to trap the labeled succinic anhydride with additional nucleophiles have been unsuccessful, the overall outcome of this transformation allows inserting a carbon isotope into a substituted alkyl amide in one single step from CO₂. Scaffolds of interest were well tolerated including 1,3,8-triazaspiro[4.5]decan-4-one [¹³C]6e,²⁷ and in the same vein, sensitive acrylamides were easily converted into potent drug precursors with good yields and IE [¹³C]6c.²⁸

Pleasingly, pharmaceutical derivatives such as FDA approved doxepine and ibuprofen were functionalized to the corresponding acids [¹³C]7a-7b in 18% and 33% yield and suitable IE (Scheme 4A). In addition, 4,5-diphenyl-2-vinylloxazole reacted in presence of [¹³C]CO₂ to provide oxaprozine [¹³C]7c, a commercial nonsteroidal anti-inflammatory drug, in one single step.²⁹ Previously, [¹⁴C]oxaprozin was labeled from [1,4-¹⁴C]succinic anhydride in presence of benzoin.³⁰ Labeled succinic anhydride is an elaborated precursor obtained in four steps from [¹⁴C]CO₂, by sequential cyanation of

dibromoethane, nitrile hydrolysis and succinic acid dehydration.³¹ The direct labeling of [¹³C]7c exemplifies how radiochemistry can benefit from this late-stage approach.

Furthermore, in presence of 3 equiv. of [¹³C]CO₂, **S22** provided labeled *N*-acetyl phenylalanine [¹³C]7d in 57% yield and 20% IE.³² While this result opens a new avenue to labeled phenylalanine derivatives, according to the reported reduction potential, **S22** (*E*_{red} = -1.60 to -1.70 V vs. SCE)³³ should un-

dergo SET olefin reduction in presence of CO₂⁻, rather than hydro-carboxylation, as previously shown by Jui.³⁴ Indeed, under identical conditions, the corresponding methyl ester underwent selective olefin reduction. However, our results indicate that a different reaction pathway takes place under our reaction conditions, favoring hydro-carboxylation of **S22**, leading to the formation of a malonate intermediate, which undergoes Krapcho decarboxylation to provide [¹³C]7d.³⁵



Scheme 4: A) Labeling of pharmaceutically relevant derivatives. B) Scope of the di-carboxylation. C, D and E) Application to the preparation of labeled succinimides. ^a Reaction time 1 hour. ^b MeNH₂·HCl (5 equiv.). DABCO: 1,4-diazabicyclo[2.2.2]octane. DMAP: 4-dimethylaminopyridine. HMDS: hexamethyldisilazane.

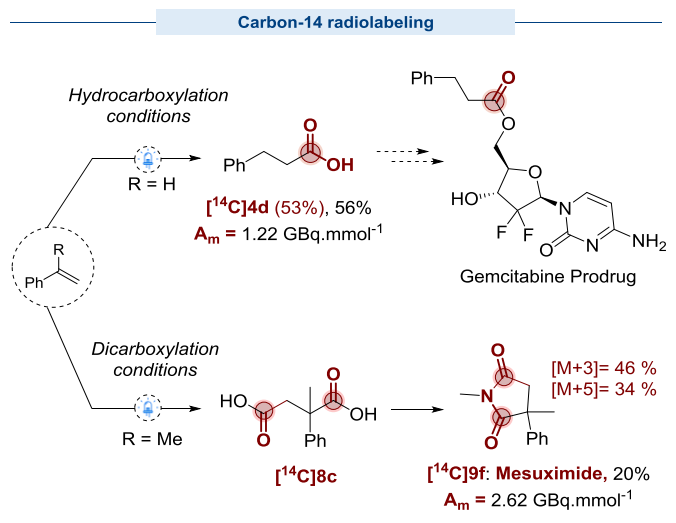
Alkene di-carboxylation was next investigated, as alternative to label succinimides (Scheme 4B).³⁶ To promote the di-carboxylation, an optimization of the reaction condition was performed with only 2 equiv. of labeled CO₂ (see SI, Table S10). In presence of DABCO (10 mol%) and molecular sieves (4 Å), the corresponding succinic acids [¹³C]8a-8f were isolated with both carbonyl positions labeled in 33% to 43% single

and 31% to 48% double ¹³C incorporation (Scheme 4B). Subsequent cyclisation in presence of trifluoroacetic anhydride (TFAA)³⁷ and reaction with primary amines in refluxing acetic acid³⁸ delivered the desired double-labeled succinimides without loss of isotope incorporation. In the event, mesuximide [¹³C]9f, an anticonvulsant sold as a racemate, was isolated 33% yield and 39% single and 46% double enrichment. The peculiar isotopic pattern was confirmed by ¹³C-NMR spectra,

showing resonance doublets corresponding (d, $\delta = 181.2$ ppm, $J_{C1-C2} = 13.5$ Hz, Scheme 4E).

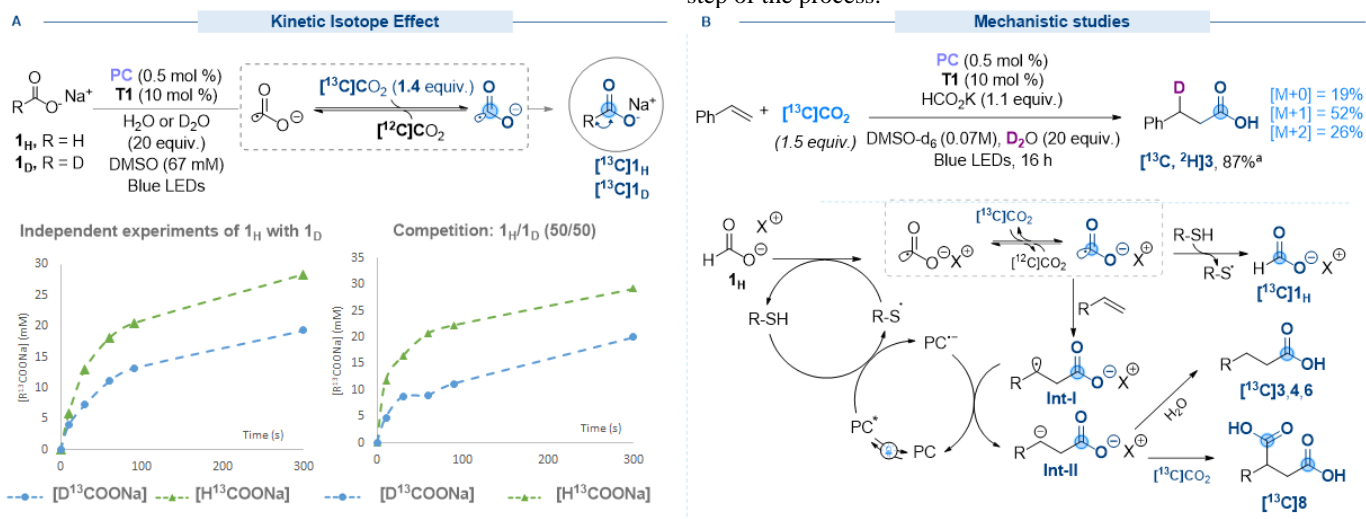
To showcase the modularity of the approach, cyclization of 4-amino-4-oxobutanoic acids [^{13}C]4b, [^{13}C]4c and [^{13}C]4d in presence of ZnCl_2 and hexamethyldisilazane (HMDS) enabled the formation of single-labeled succinimides [^{13}C]9g-9i (Scheme 4D).

While the photoinduced equilibration has shown potential for isotope labeling, questions remained about its applications to radiocarbons, as no data is available on the stability of $\text{CO}_2^{\cdot-}$ in presence of β^+ or β^- emission. When the hydrocarboxylation of styrene was performed with radioactive [^{14}C]CO₂ (1.5 equiv.), pleasingly, a clean reaction was observed and after radio-HPLC purification [^{14}C]4d (Scheme 5) was isolated in 56% yield and 53% IE, corresponding to a molar activity (A_m) of 1.22 GBq.mmol⁻¹. To the best of our knowledge, this is the first time [^{14}C]CO₂⁻ was generated and utilized for productive ¹²C-¹⁴C bond formation. Furthermore, [^{14}C]4d could potentially be valorized in the synthesis of prodrugs such as Gemcitabine.³⁹ Next, the di-carboxylation allowed to obtain [^{14}C]8c, which was engaged in the cyclization/substitution procedure to access to ¹⁴C-double-labeled mesuximide [^{14}C]9f in high A_m . These strategies provide an advantageous and complementary alternative to the state-of-the-art and offer a late-stage access to radiopharmaceuticals for ADME studies.



Scheme 5: Labeling of pharmaceutically relevant substrates with ¹⁴C. See SI for experimental details (page S112-118).

To evaluate the compatibility with the short half-life of ¹¹C, kinetic experiments on the isotopic equilibration were performed (Scheme 6A). Pleasingly, formation of [^{13}C]1h was observed within seconds from [^{12}C]1h, after irradiation. When the reaction was separately repeated starting from [^{12}C]1d and 20 equiv. of D₂O, a lower rate of ¹³C incorporation was observed with a KIE of 1.8. In addition, competitive experiments starting from a 1/1 mixture of [^{12}C]1h and [^{12}C]1d in presence of H₂O (10 equiv.) / D₂O (10 equiv.) showed that % IE of [^{13}C]1h over [^{13}C]1d was systematically higher in favor of the proton-containing isotopologue. These results seem to indicate the cleavage of the C-H bond of formate as the rate-limiting step of the process.⁴⁰



Scheme 6: A) Kinetic investigations from [^{12}C]1h and [^{12}C]1d. PC : 4DPAIPN. See SI for experimental details (S101-103). B) Plausible mechanism for the labeling process. ^a Yield determined by ¹H NMR using dibromomethane as internal standard.

To gain some insight into the reaction mechanism, a series of control experiments were conducted (Scheme 6B and SI). The hydro-carboxylation of styrene under standard conditions in presence of D₂O (20 equiv) delivered product [^{13}C , ²H]3 in 87% yield with ¹³C-labeled carboxylic acid and incorporation of deuterium in benzylic position, which was confirmed ²H-NMR. This result is in agreement with the formation of benzylic carbanion intermediate (**Int II**, Scheme 6B).

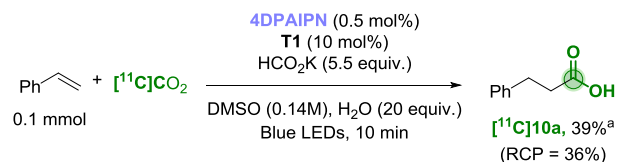
While radical clock experiment did not delivered the labeled product (SI page S97), when the reactions from styrene and acrylamide were conducted in presence of TEMPO (1 equiv., see SI pages S94-96) the corresponding ¹³C-labeled adduct was detected by HRMS, supporting the formation of a transient radical intermediate (**Int-I**, Scheme 6B). To evaluate whether the reaction follows a Giese-type radical addition with [^{13}C]CO₂⁻ or a direct reduction of the alkene to a possible

carbon radical anion intermediate, experiments in the absence of $[^{12}\text{C}]\text{HCOOK}$ in presence of $[^{13}\text{C}]\text{CO}_2$ were conducted. Both with catalytic and stoichiometric amounts of HAT, no formation of the labeled carboxylic acid product nor the reduced alkane were detected. These observations point to-

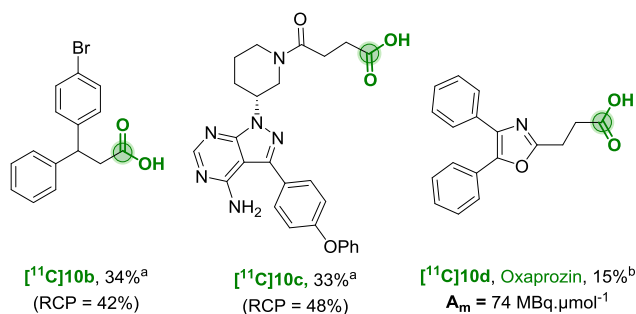
wards a Giese-type mechanism, in agreement with previous work by Li,¹⁰ Guo and Zhu.^{11d} Nonetheless, we cannot completely rule out the possibility of a first reduction of the alkene, but this should represent a minor pathway.

Application to PET imaging

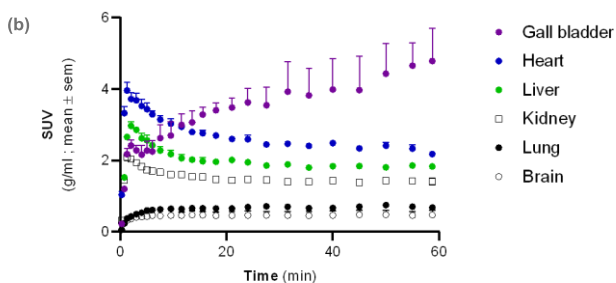
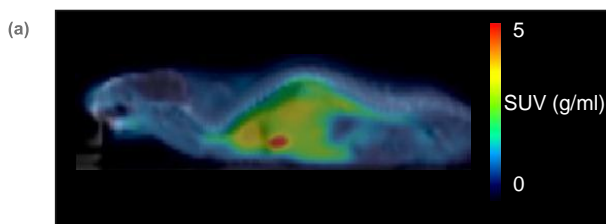
A Hydrocarboxylation with Carbon-11



Scope



B PET imaging of $[^{11}\text{C}]\text{oxaprozin}$



Scheme 7: A) ^{11}C -labeling. ^a Radiochemical conversion = $(A_{\text{EOS}} / A_{\text{CO}_2}) \times \text{RCP}$ with A_{EOS} = decay-corrected activity at the end of the synthesis and A_{CO_2} = starting activity of $[^{11}\text{C}]\text{CO}_2$. ^b Radiochemical yield. B) Biodistribution of $[^{11}\text{C}]\text{10d}$ in the mouse whole body. (a) Average microPET images of $[^{11}\text{C}]\text{10d}$ in mice using standard uptake values (SUV) over 60-min acquisition. Parametric microPET images are overlaid onto a CT mouse for anatomical localization. (b) Time-activity curves of regional $[^{11}\text{C}]\text{10d}$, expressed as SUV values vs. time.

The fast isotope equilibration opened a window of opportunity for ^{11}C -radiolabeling. When the standard reaction conditions were applied with $[^{11}\text{C}]\text{CO}_2$, a 8% radiochemical conversion (RCC) was observed. After optimization, excess of formate (5.5 equiv. in respect to styrene) under 10 min blue LED irradiation allowed to obtain $[^{11}\text{C}]\text{10a}$ in 39% RCC. With these conditions in hand, $[^{11}\text{C}]\text{10b}$ and $[^{11}\text{C}]\text{10c}$ were labeled in 34 and 33% RCC, respectively. To go further, automated radiosynthesis of $[^{11}\text{C}]\text{oxaprozin}$ $[^{11}\text{C}]\text{10d}$ afforded the ready-to-inject radiotracer in 15% RCY and $74 \text{ MBq}\cdot\mu\text{mol}^{-1} A_m$. It is important to highlight that $[^{11}\text{C}]\text{10d}$ has previously been labeled by Szikra *et al.* in a two-step sequence from a Grignard precursor.⁴¹

To show concrete evidence of the utility of the approach for *in vivo* imaging, the whole-body PET biodistribution profile of $[^{11}\text{C}]\text{oxaprozin}$ was investigated in mice (Scheme 7A). The time-activity curves (TACs) depict a rapid uptake of $[^{11}\text{C}]\text{10d}$ in heart, liver and kidney followed by a slow distribution phase (Scheme 7B). High level of radioactivity in the gallbladder is consistent with the previously reported biliary elimination of oxaprozin and/or its metabolites.²³ No radioactivity could be found in the urinary bladder, which suggests limited importance of the urinary pathway for the elimination of $[^{11}\text{C}]\text{oxaprozin}$ or its radiometabolite(s) in mice. The distribution of $[^{11}\text{C}]\text{10d}$ in the brain and peripheral tissues is consistent with the low volume of distribution of oxaprozin estimated in humans, which indicates limited extravascular distribution.²³

Conclusion

In conclusion, we have developed a photocatalytic synthetic access to $\text{CO}_2^{\cdot-}$ from isotopically labeled CO_2 and $[^{12}\text{C}]\text{formate}$ salts. This strategy allows the formal reduction of ^{11}C , ^{13}C , ^{14}C -labeled CO_2 to HCOOK under mild conditions and was applied to the Giese-type hydro-carboxylation to label effectively carboxylic acids, including pharmaceutical derivatives. When applied to *N,N*-disubstituted acrylamides a rearrangement of the succinic acid moiety was observed. This unexpected result allowed to obtain the corresponding label tertiary amides in one-step from CO_2 . When the equilibration process was implemented towards the di-carboxylation of styrenes, doubly-labeled derivatives could be reached efficiently. The modularity of the approach was especially useful towards the labeling of succinimides. The current study demonstrated the possibility to generate and use $[^{11}\text{C}]$ and $[^{14}\text{C}]\text{CO}_2^{\cdot-}$ in radical addition reactions. The convenience of this novel late-stage radio-carboxylation tool was demonstrated by accessing $[^{11}\text{C}]\text{oxaprozin}$ ready-to-inject radiotracer for PET imaging applications.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at <http://pubs.acs.org>.

Detailed experimental procedures and characterization techniques, NMR spectra for obtained compounds.

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Notes

The authors declare no competing interests.

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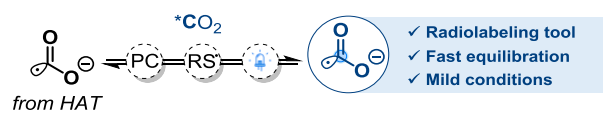
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Applications

● ¹⁴C-labeling

● ¹³C-labeling

● ¹¹C-labeling

