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A Photochemical Strategy for Carbon Isotope Exchange with CO₂

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ABSTRACT. A photocatalytic approach for carbon isotope exchange is reported. Utilizing [¹³C]CO₂ and [¹⁴C]CO₂ as primary C1 sources, this protocol allows the insertion of the desired carbon isotope into phenyl acetic acids without the need of structural modifications or pre-functionalization, in one single step. The exceptionally mild conditions required for this traceless transformation are in stark contrast with previous methods requiring the use of harsh thermal conditions.

Keywords : Isotope labeling, Carbon-14, Photoredox catalysis, Carbon dioxide, Decarboxylation

INTRODUCTION

Developments in visible light photoredox catalysis have led to the invention of an ample array of chemical transformations, which would be either challenging or even impossible to perform under thermal conditions. Carbon-carbon bond formation represents an ongoing challenge in photocatalysis and, particularly, in the context carbon dioxide (CO₂) valorization. Indeed, the functionalization of this one-carbon (C1) building block has implications that go far behind the scientific community, and affect the environment and our society as a whole.^{1,2} Recently, successful examples of photocatalytic CO₂ functionalization appeared (Figure 1A).^{3,4,5} In particular, UV or visible-light photoinduced Csp² and Csp³ carboxylations have been investigated in combination with transition-metal catalysts such as nickel,^{4a-d} copper^{4e} and palladium^{4f-j} from aromatic and aliphatic bromides and triflates and by activation of Csp²-H and Csp³-H bonds. In 2019, the group of König has reported on visible-light-mediated carboxylation of benzylic C-H bonds under metal-free conditions in presence of an organic photocatalysts (4-CzIPN).^{5c} More recently, the same group reported on a redox-neutral photocatalytic C-H carboxylation of arenes and styrenes.^{5d} In addition, the transition-metal free photocatalytic di-functionalization of styrenes to the corresponding Csp³-COOH caught much attention.⁶ Finally, examples of Csp³ photo-induced carboxylation generating CO₂ radical anion species using flow chemistry technology has been reported by the group of Jamison.^{5g,6d} Besides valorizing this abundant greenhouse gas and the virtues of mild conditions and facile operations, these transformations are relevant in the field of carbon isotope labeling and particularly for carbon-14 (¹⁴C), where [¹⁴C]CO₂ represents the primary source of radioisotope.⁷ ¹⁴C (β^- emitter, half-life 5730 years) is the gold standard for the preparation of radiotracers utilized in human and veterinary absorption, distribution, metabolism, and excretion (ADME) determination, agrochemical and environmental fate studies.⁸ While ¹⁴C

has traditionally been introduced into biologically relevant target compounds in multi-step fashion, drawbacks related to the limited available raw materials, their prohibitive costs ($[^{14}\text{C}]\text{CO}_2$: 1860 \$ per mmol) and the generation of long-lasting waste are upstanding challenges.⁹

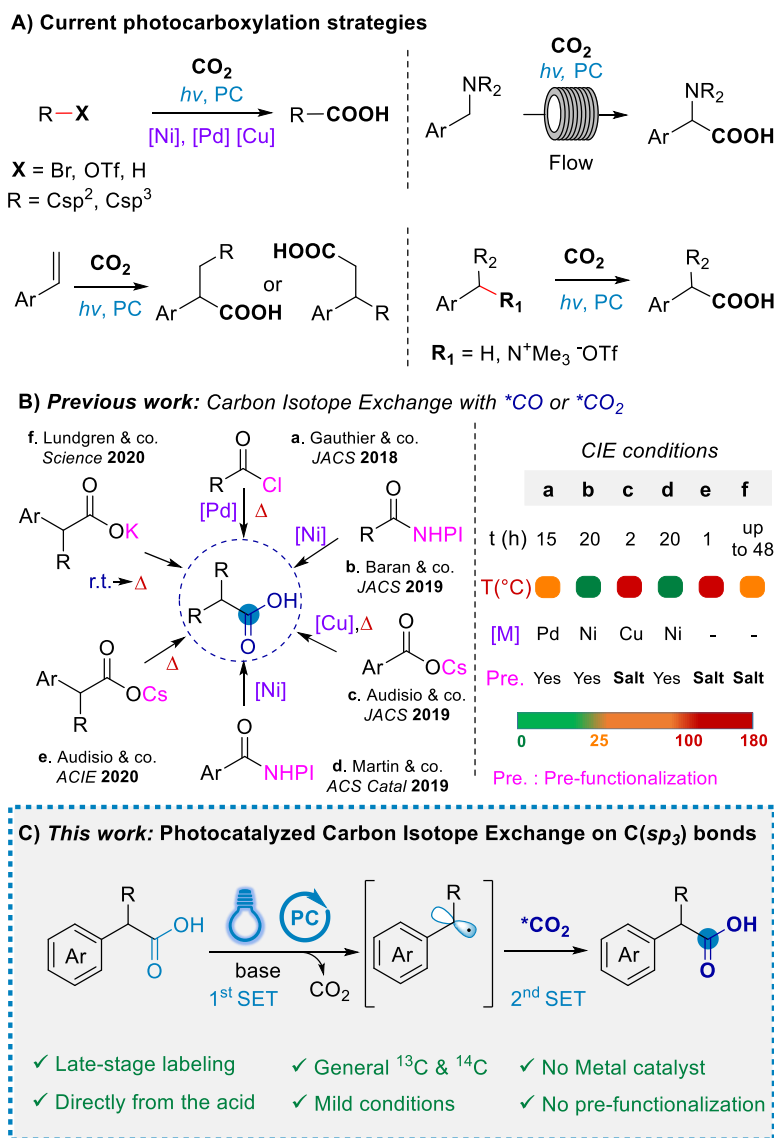


Figure 1: State of the art. (A) Current strategies for photocarboxylation. (B) Reported implementations of CIE. (C) This work: Photocatalysed CIE on PAA. Blue circles represent the positions of isotopically labeled carbon. PC= photocatalyst; SET= single electron transfer.

In the last couple of years, late-stage ^{14}C -labeling has undergone sudden growth.¹⁰ In particular, Carbon Isotope Exchange (CIE), which allows for ^{12}C - ^{12}C bond cleavage and ^{12}C - ^{14}C bond formation in one single step, emerged as privileged strategy (Figure 1B).¹¹ Mostly focused on $^{12}\text{C}/^{14}\text{C}$ CO₂ exchange,¹²⁻¹⁵ these methodologies are mainly based on the use of transition metals. In 2019, the groups of Baran and Martin independently reported on a two-step aliphatic carboxylic acid exchange catalyzed by nickel based on *N*-hydroxyphthalimide (NHPI) activated esters.¹² While the first procedure utilized stoichiometric amounts of metal,^{12a} the second group was able to implement a catalytic version of the transformation.^{12b} The same year, our group described the direct CIE of (hetero)aromatic carboxylic acids using catalytic copper catalysis and thermal activation.¹³ Exchange of $^{12}\text{C}/^{14}\text{C}$ CO was published by Gauthier and co-workers, who developed a palladium-catalyzed CIE on aliphatic and benzoic acid chlorides.¹⁴

In 2020, our group and Lundgren's independently reported the transition metal-free thermal CIE of phenyl acetic acids (PAA).¹⁶ By heating the corresponding cesium or potassium carboxylates in presence of labeled CO₂, reversible decarboxylation/carboxylation takes place and the desired acids were obtained with good isotope incorporation. While appealing, the requirement of harsh thermal heating is compulsory for non-activated PAAs. Prolonged heating at 160 °C for 48 hrs was required to label a series of well-known Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as Ibuprofen, Fenoprofen, Ketoprofen, Naproxen and Diclofenac.¹⁷ Drastic conditions for an extended period of time are generally unsuitable, and especially when handling of radioactive materials is involved.

The invention of a reversible carboxylation process under mild conditions still constitutes a fundamental challenge. Inspired by pioneering works on transition-metal free photocatalysed carboxylation⁴ and the wealth of knowledge on photocatalysed radical decarboxylation of Csp³

carboxylic acids,¹⁸ we report the first photocatalytic approach for CIE (Figure 1B). This protocol allows the insertion of the desired isotope into phenyl acetic acids, including non-natural phenyl glycine amino acids (Figure 1C), at 42 °C only and without the need of structural modifications or pre-functionalization. These exceptionally mild conditions stand in stark contrast with previous methods requiring the use of brutal thermal force.^{19,20}

RESULTS AND DISCUSSION

Optimization of the photocatalytic isotope exchange and study of the scope

The optimized reaction conditions for the photocatalytic CIE of carboxylic acids are shown in Table 1. Model substrate 2-phenylacetic acid **1** was labeled in 72% isolated yield and 51% isotopic enrichment (IE), in presence of the photocatalyst (PC) 4CzIPN (6 mol%), K₃PO₄ and [¹³C]CO₂ as a convenient surrogate for [¹⁴C]CO₂ in dry DMF within 6 hours. The reactions were performed employing 0.1 mmol of substrate and 0.3 mmol of [¹³C]CO₂ were precisely delivered using the RC Tritec manifold.²¹ A higher IE of 62% was obtained by increasing the catalyst load to 12 mol% (entry 2), but the isolated yield diminished to 43%, while proto-decarboxylation side-product **1b** was formed in 47%.

Under the reaction conditions, we noticed that PC **2** was entirely converted into **3** (4CzBnBN), which is likely to be the active PC in the reaction, in agreement with previous reports by König and Tunge.²² Notably, the use of other photocatalysts resulted in low isotope incorporation (Table S4), while only **3** provided comparable results (entry 3). To exclude PC degradation over the reaction condition, **3** was isolated from the crude mixture and successfully reengaged in photocatalytic CIE (see page S12 for details). Other bases such as K₂CO₃ and CsOAc were also compatible but gave lower IE (Table 1, entries 4, 5 and Table S3), while the absence of the base resulted in no reaction (Table 1, entry 6). Importantly, the use of carbonate bases could lead to

potential isotope dilution, providing a source of unlabeled [^{12}C]CO $_2$, as previously reported.²³ When the reaction was performed starting from the corresponding potassium carboxylate [^{13}C]1 was obtained in 50% IE and 94% yield (see SI).

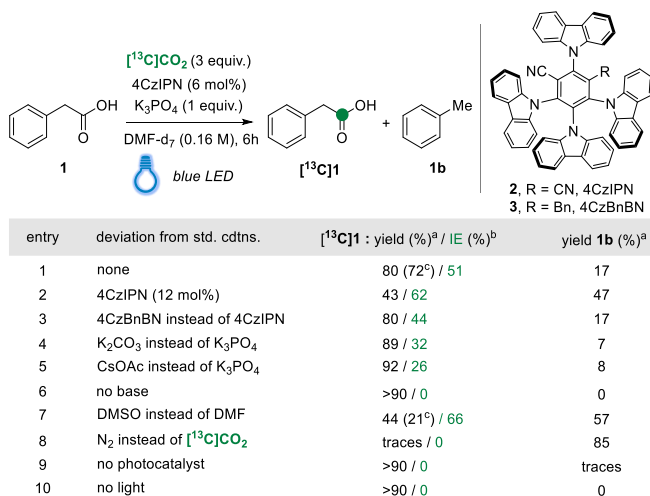


Table 1: Optimization of the reaction. ^a Yields were determined from the crude ^1H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. ^b Isotopic enrichments (IE) were determined by ^1H -NMR and mass spectrometry (see SI for details). ^c Isolated yield. The temperature of the reaction: 42 ± 2 °C.

The use of other polar aprotic solvent such as DMSO provided [^{13}C]1 in 66 % IE, but drastically eroded the yield (entry 7 and Table S2). When [^{13}C]CO $_2$ was replaced by nitrogen complete protodecarboxylation was observed (Table 1, entry 8). Finally, removing 4CzIPN from the reaction or the absence of light resulted in no isotope incorporation, showcasing that no background reaction occurs (Table 1, entries 9 and 10).

With these optimized conditions in hand, we directed our studies toward the scope (Figure 2). Regardless of the position, in presence of electron donating groups on the aromatic ring, isotopic enrichment was observed in substituted phenyl acetic acids bearing alkyl [^{13}C]4-5 or methoxy [^{13}C]6-9 moieties. It is worth to note that higher incorporation was achieved with *ortho* substitution

but a lower isolated yield was obtained ($[^{13}\text{C}]\mathbf{8}$, IE = 71%, 29% yield). Halogen were also tolerated and $[^{13}\text{C}]\mathbf{10-16}$ were labeled in 29 to 70% IE and good yields. Only substrate $\mathbf{13}$ could not be labeled and de-iodination occurred without insertion of ^{13}C . Investigation with stronger electro-withdrawing groups led to successful labeling of various substrates such as trifluoromethyl $[^{13}\text{C}]\mathbf{17-19}$ (IE = 33-70%), *m*-nitrile $[^{13}\text{C}]\mathbf{20}$ (IE = 64%) and ester derivatives $[^{13}\text{C}]\mathbf{21}$ (IE = 63%). Importantly, on this electron poor substrates no background reactions were observed in the absence of PC.^{15b} Labeling of dicarboxylic acids $[^{13}\text{C}]\mathbf{22-23}$ required using DMSO in place of DMF, for solubility reasons, and 2 equiv. of base. It is worth noting that isotope incorporation was also possible in the presence of labile protons such as amide or alcohol $[^{13}\text{C}]\mathbf{27-29}$ (IE = 30-70% and 21-72% yield). Pleasingly, functionalization in benzylic position was not detrimental for the reaction and applying the procedure to such substrates could afford the expected labeled phenyl acetic acids. The presence of alkyl substituents α to the carboxylic acid was tolerated $[^{13}\text{C}]\mathbf{30-33}$. While the *gem*-dimethyl $\mathbf{31}$ was effectively labeled, the presence of a cyclopropyl ring allowed only low exchange ($[^{13}\text{C}]\mathbf{32}$ IE < 5%), even in presence of 4CzBnBN PC. CIE was also performed on particularly challenging non-natural protected amino acids $[^{13}\text{C}]\mathbf{35-36}$ and successfully enable the exchange in 39 to 52% IE. It is worth noting that under our previous thermal CIE conditions, these amino acids were unsuccessful, thus highlighting the superiority of this photocatalytic approach.^{16a}

Next, we turned our attention to the labeling of pharmaceutically relevant derivatives, Felbinac $[^{13}\text{C}]\mathbf{37}$ was labeled with an isotopic enrichment of 63% and 51% yield. Diclofenac $[^{13}\text{C}]\mathbf{38}$ and Fenclofenac $[^{13}\text{C}]\mathbf{39}$ were obtained respectively in 49% and 57% of recovered products with 10% and 35% of isotope incorporation.

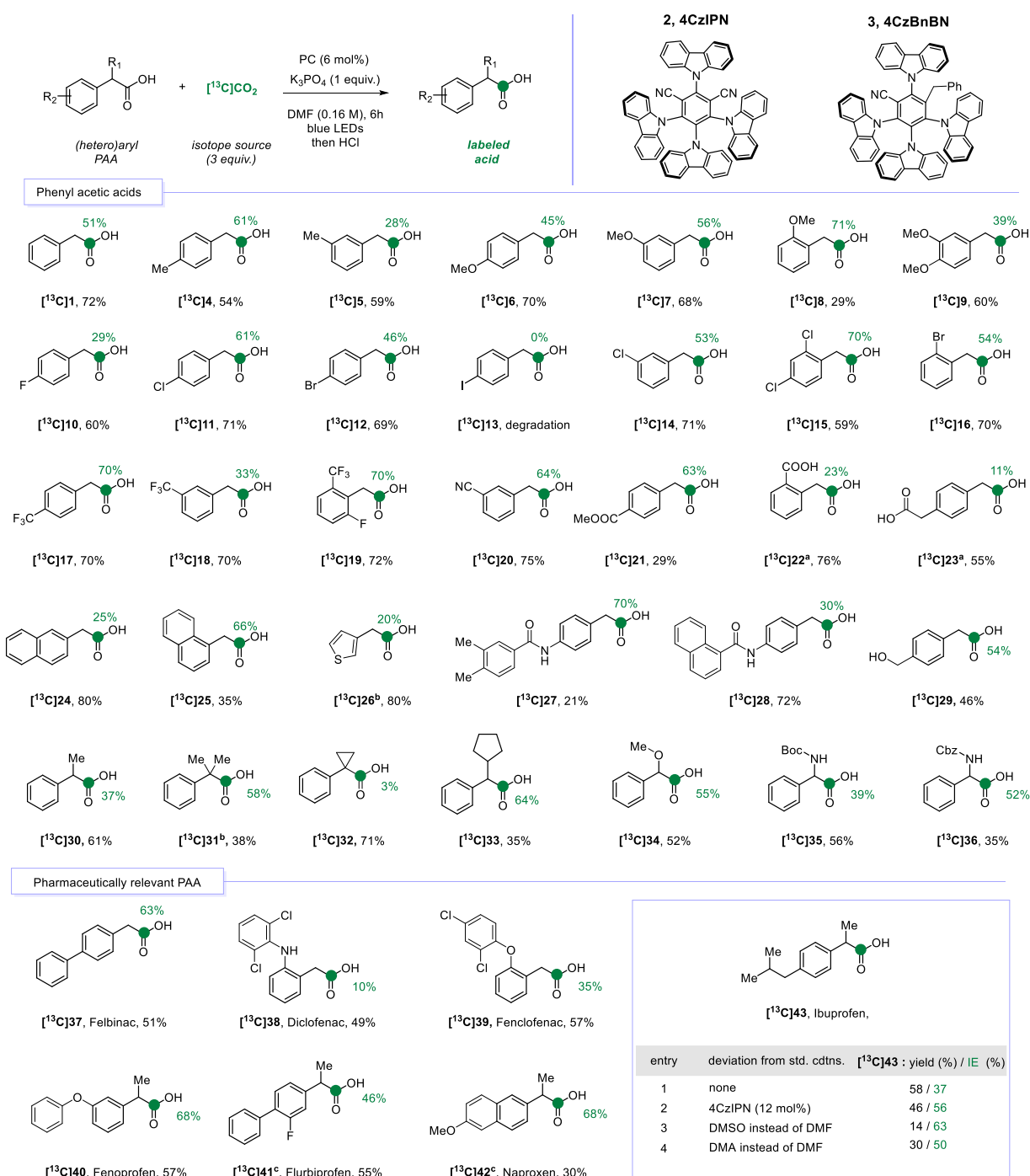


Figure 2: Photocatalyzed CIE labeling of phenyl acetic acids and pharmaceutical compounds. Green colored circles and numbers denote the positions of the carbon atoms labeled and the percent incorporation of the carbon isotope. DMF, *N,N*-dimethylformamide. Reaction conditions: substrate (0.1 mmol, 1 equiv.), PC (6 mol%), K₃PO₄ (1 equiv.), [¹³C]CO₂ (3 equiv.), DMF (0.6 mL), 6 h. ^[a] Using 2 equiv. of K₃PO₄ and DMSO instead of DMF. ^[b] ¹H NMR

yield determined using DMF-d₇ instead of DMF and 1,3,5-trimethoxybenzene as internal standard. [c] Reaction time: 3 h instead of 6 h. The temperature of the reaction: 42 ± 2 °C.

The structural similarity of these drugs shows that the presence of an amine in *ortho* position to the acid have a deleterious effect on both IE and yield. Fenoprofen [¹³C]40 was labeled with 68% of IE and a correct isolated yield of 57%. To obtain labeled [¹³C]41 and [¹³C]42 in useful recovered amounts and avoid extensive proto-decarboxylation, a slight modification of the conditions was required. Reducing the time of the reaction from 6 to 3 hours allowed to isolate Flurbiprofen [¹³C]41 and Naproxen [¹³C]42 with 46% and 68% of isotopic incorporations and 55% to 30% yields, respectively.

An optimization of the reaction was performed to effectively label the most notorious NSAID on the market, Ibuprofen [¹³C]43. It was found that the use 12 mol% of PC allowed an enhancement of the isotopic incorporation with a minor modification of the final isolated yield (IE = 56%, 46%). The utilization of other polar non protic solvents (DMSO and DMA) drastically reduced the isolated yield. As a comparison with our previously developed metal-free thermal CIE, in addition to the milder photocatalyzed conditions of this methodology we observed an improvement in the IE of Naproxen by a factor of 2.3, Diclofenac IE by 1.7 and Ibuprofen by 1.75. Yields have also been improved in the case of Flurbiprofen by a factor of 1.6 and Fenclofenac by 1.4.

Understanding the mechanism of the transformation

We next looked at the potential reaction mechanism of this CIE. During the optimization (Table 1) and substrate scope (Figure 2), we observed that the transformation was systematically affected

by the competing formation of the proto-decarboxylation byproduct and the quality of the solvent (DMF) dramatically influenced the outcome of the reaction.²⁴

When the reaction with substrate **7** was monitored overtime in presence of 3 equiv. of labeled [¹³C]CO₂, optimal isotope incorporation was observed after 6 hours (Figure 3A). Longer reaction times did not provide significant improvement on the % IE.

Then, the effect of the number of equiv. of [¹³C]CO₂ on the reaction was monitored. The precise amount of CO₂ required for carboxylation reactions is most often a neglected parameter and poorly investigated. As shown in Figure 3B, in the absence of sufficient amounts of [¹³C]CO₂ the proto-decarboxylation product **2a** was predominant (up to 0.5 equiv.). When 1 equiv. of electrophile was added, the isotope incorporation observed started to converge towards the expected theoretical value (38% in place of 50% theoretical). Nonetheless, tolyl **2a** was still the major product observed with 65% yield. Only when more than 1.5 equiv. of [¹³C]CO₂ were added, the yield of **7** was satisfying. When more than 3 equiv. of CO₂ were utilized, the costs of labeled reagent were not compensated by the limited benefit over IE and yield.²⁵ Such observations seem to point toward the need of a minimal amount of DMF saturation to achieve optimal yield and isotope incorporation.²⁶ Taking advantage of these results, an iterative approach was explored aiming to maximize the %IE and minimize the amount of [¹³C]CO₂, the costly limiting reagent of the overall process (see SI for details).

When the transformation was performed on a 1:1 mixture of PAAs **6** and **17** bearing opposite electronic substitution patterns, only electron rich [¹³C]**6** was labeled in 43% IE. In contrast, negligible labeling was observed for **17**, which was recovered almost quantitatively (Figure 3C). This result indicates that photocatalytic oxidation happens exclusively on the carboxylate of **6** ($E_{1/2}^{ox} = +0.99$ V), while **17** ($E_{1/2}^{ox} = +1.39$ V) does not participate in the process.²⁷ This result

paves the way for the development of selective CIE transformations. In agreement with previous work by König and co-workers,^{22a} when tropic acid **44** was subjected to the reaction conditions, [¹³C]**44** was isolated in 49% yield and a moderate IE of 18%, together with 19% of styrene product **45** formed through E1cB-elimination reaction, thus supporting the formation of a carbanion intermediate in the reaction (Figure 3D).

A radical clock experiment was performed in presence of allylic acid **46**²⁸ bearing a terminal olefin at the 5-exo position and provided [¹³C]**46** in 39% yield and 64% IE, along with tolyl derivative **2d** in 37% yield (Figure 3E). No traces of the cyclized products **47a** or **b** could be observed, thus suggesting that the radical species would be rapidly reduced to the corresponding anion intermediate. When the radical trap TEMPO (1 equiv.) was added, its incorporation onto the tolyl motif was observed in the reaction crude (see SI for details). This result supports the formation of radicals along the reaction pathway.

Finally, when **6** was subjected to the reaction conditions in presence of excess of styrene (3 equiv.), the labeled [¹³C]**6** was obtained in a moderate enrichment (24% IE) together with acid [¹³C]**48**, in a 2.5:1 ratio. Interestingly, the product of the radical addition to styrene, [¹³C]**48**, was formed with high enrichment (80% IE) close to the theoretical ^{12/13}CO₂ ratio. No other products were observed during the reaction suggesting that **48** was not able to undergo photo-decarboxylation under the tested conditions and can be considered as an end-product. As **48** is a product of different structure than the substrate, the IE is not diluted by the starting phenyl-acetic substrate explaining the higher IE observed when compared to other experiments.²⁹

When deuterium labeled **1d₂** was subjected to standard reaction conditions (Figure 3G), the formation of the desired product [¹³C]-**1d₂** was observed in the crude mixture with identical efficiency in respect to the unlabeled isotopomer **1** (Table 1).

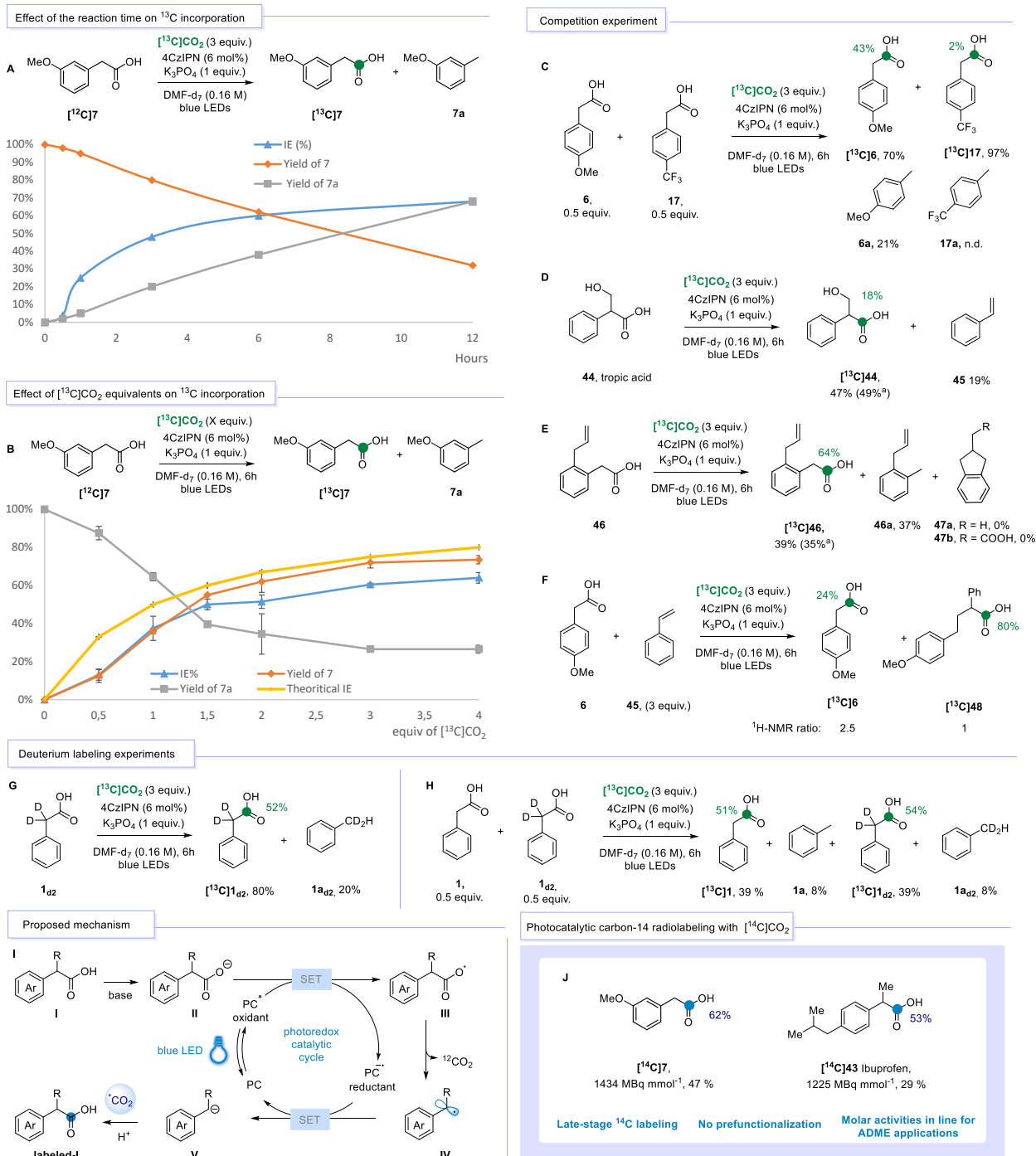


Figure 3: Mechanistic investigations. Green colored circles and numbers denote the positions of the ^{13}C atoms labeled and the percent incorporation of the isotope. Yields were determined from the crude ^1H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. Yields of 7 refers to the inseparable mixture of ^{12}C 7 and ^{13}C 7 isotopomers. ^[a] Isolated yield. J) Photocatalytic CIE radiolabeling with ^{14}C CO₂. Molar activities for ^{14}C in MBq

mmol⁻¹, see SI for details. Blue colored circles and numbers denote the positions of the ¹⁴C atoms labeled and the percent incorporation of the isotope.

To confirm this, a competition experiment was performed (Figure 3H). These results in addition to those of the competition experiment in Figure 3C point towards a reaction mechanism that involves a direct nucleophilic attack, of the *in situ* generated anion, to [¹³C]CO₂ and exclude the concomitant deprotonation of the potassium carboxylate.

On the basis of this series of mechanistic studies and the literature reports,^{5c,22a} a plausible catalytic cycle is presented in Figure 3I. After deprotonation, the potassium carboxylate (**II**) undergoes photocatalytic oxidation to **III** and rapid decarboxylation to provide benzyl radical (**IV**), which is further reduced to carbanion **V**. When sufficient [¹³C]CO₂ is present in the solution (> 1 equiv.), carboxylation will provide the desired labeled material labeled-**I**. A parallel scenario is plausible, as carbanion **V** is sufficiently basic to deprotonate the carboxylate **II**.³⁰ In the process, a dienolate species would be formed that could undergo carboxylation to a malonate intermediate and subsequently labeled-**I**.¹⁶ However, the results of the competition experiment between **6** and **17** (Figure 3C), as well as the deuterium labeling reactions (Figure 3G and H) seem to point against such a parallel mechanism. Nonetheless, substrate dependency cannot be excluded at present.

Photocatalytic Carbon-14 Radiolabeling with [¹⁴C]CO₂

Isotope exchange procedures have revolutionized the way tritium radiolabeling is performed nowadays in the pharmaceutical industry.³¹ On the other hand, carbon-14 has not benefited of such exceptional advances and the concept of CIE has only very recently appeared. To take advantage of this technology, we aimed to validate it on ¹⁴C radiolabeling. As a first proof-of-concept, **7** was

selected as a model substrate. In presence of exactly 0.3 mmol of [^{14}C]CO₂ (3 equiv. cost 580 \$), [^{14}C]7 was effectively labeled in 47% yield and 62% IE, which corresponds to a molar activity (A_m) of 1434 MBq mmol⁻¹, which is fully in line with possible application of ADME and bio-distribution studies routinely performed by pharmaceutical companies in drug development programs. Finally, Ibuprofen [^{14}C]43 was obtained in a satisfying 29% yield and 53% IE (A_m 1225 MBq mmol⁻¹), using 12% of PC 2.

Besides its exceptionally mild and safe conditions, a major advantage of this photoredox radiolabeling over competing transition metal catalyzed procedures is the absence of transition-metal catalyst. This is a very attractive point for safety in animal and human ADME studies, as no residual metal traces are released in the transformation.

CONCLUSION

In conclusion, we developed the first photocatalytic carbon isotope procedure for the carbon labeling of phenyl acetic acids. This reaction proceeds under exceptionally mild reaction conditions compared to previous CIE technologies and provides a complementary approach to the challenging carbon labeling of pharmaceuticals. In the process, mechanistic insights on the transformation were unveiled and the precise addition of [^{13}C]CO₂ showed a strong dependency of reaction outcome both in terms of isotope incorporation and product formation. Finally, it was shown that the implementation of this transformation towards radioactive ^{14}C radiolabeling is possible under safe and cost sustainable conditions. In presence of 3 equiv. of [^{14}C]CO₂, [^{14}C]7 and Ibuprofen [^{14}C]43 were labeled in high molar activities in line with possible application for ADME studies.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

(Word Style “TE_Supporting_Information”). **Supporting Information.**

Experimental procedures and computational details

NMR spectra for obtained compounds

This information is available free of charge on the ACS Publications website.

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