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Research Article

Photochemical Strategy for Carbon Isotope Exchange with CO_2

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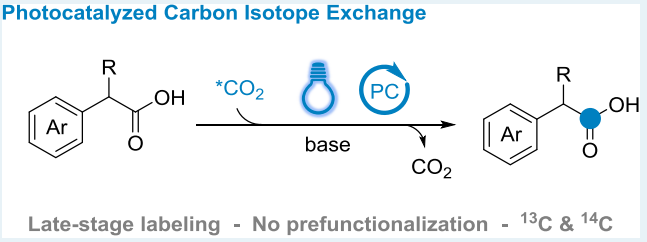
ABSTRACT: A photocatalytic approach for carbon isotope exchange is reported. Utilizing $[^{13}C]CO_2$ and $[^{14}C]CO_2$ as primary C1 sources, this protocol allows the insertion of the desired carbon isotope into phenyl acetic acids without the need for structural modifications or prefunctionalization in one single step. The exceptionally mild conditions required for this traceless transformation are in stark contrast with those for 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 (CO_2) 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 CO_2 functionalization appeared (Figure 1A).[3−5] In particular, UV or visible light photoinduced Csp^2 and Csp^3 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 the activation of Csp^2−H and Csp^3−H bonds. In 2019, the group of König reported visible-light-mediated carboxylation of benzylic C−H bonds under metal-free conditions in the presence of an organic photocatalyst (4CzIPN).[5c] More recently, the same group reported a redox-neutral photocatalytic C−H carboxylation of arenes and styrenes.[5d] In addition, the transition-metal-free photocatalytic difunctionalization of styrenes to the corresponding Csp^3−COOH attracted much attention.[6] Finally, examples of Csp^3 photoinduced carboxylation generating CO_2 radical anion species using the flow chemistry technology have 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 (^{14}C), where $[^{14}C]CO_2$ represents the primary source of radioisotope.[7] ^{14}C (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, and agrochemical and environmental fate studies.[8] While ^{14}C has traditionally been introduced into biologically relevant target compounds in a multistep fashion, drawbacks related to the limited availability of raw materials, their prohibitive costs ($[^{14}C]CO_2$: 1860 $ per mmol), and the generation of long-lasting waste are upstanding challenges.[9]

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 the ^{12}C−^{12}C bond cleavage and ^{12}C−^{14}C bond formation in one single step, emerged as a privileged strategy (Figure 1B).[11] Mostly focused on $[^{12}C]/[^{14}C]CO_2$ exchange,[12−15] these methodologies are mainly based on the use of transition metals. In 2019, the groups of Baran and Martin independently reported 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 $[^{12}C/^{14}C]CO$ was published by Gauthier and co-workers, who developed a palladium-catalyzed CIE on aliphatic and benzoic acid chlorides.[14]

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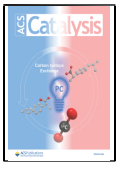

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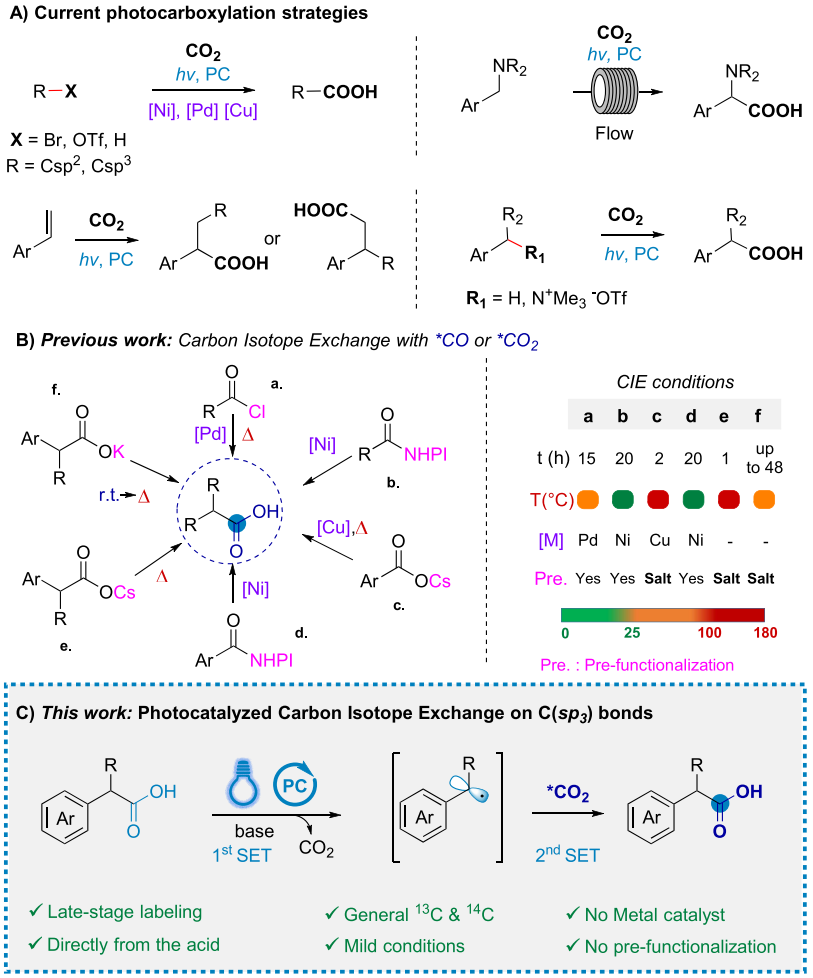
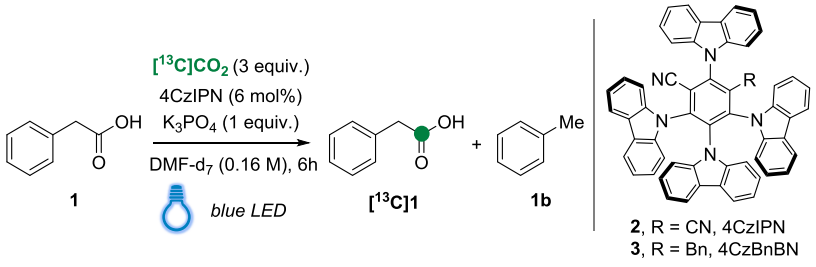


Figure 1. State of the art. (A) Current strategies for photocarboxylation. (B) Reported implementations of CIE. (C) This work: photocatalyzed CIE on PAA. Blue circles represent the positions of isotopically labeled carbon. PC, photocatalyst; SET, single electron transfer. (a) ref 14, (b) ref 12a, (c) ref 13, (d) ref 12b, (e) ref 16a, and (f) ref 16b.

Table 1. Optimization of the Reaction



entry	deviation from std. cdtns.	[^{13}C]1: yield (%)[a]/IE (%)[b]	yield **1b** (%)[a]
1	none	80(72[c])/51	17
2	4CzIPN (12 mol%)	43/62	47
3	4CzBnBN instead of 4CzIPN	80/44	17
4	K_2CO_3 instead of K_3PO_4	89/32	7
5	CsOAc instead of K_3PO_4	92/26	8
6	no base	>90/0	0
7	DMSO instead of DMF	44(21[c])/66	57
8	N_2 instead of [^{13}C]CO_2	traces / 0	85
9	no photocatalyst	>90/0	traces
10	no light	>90/0	0

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

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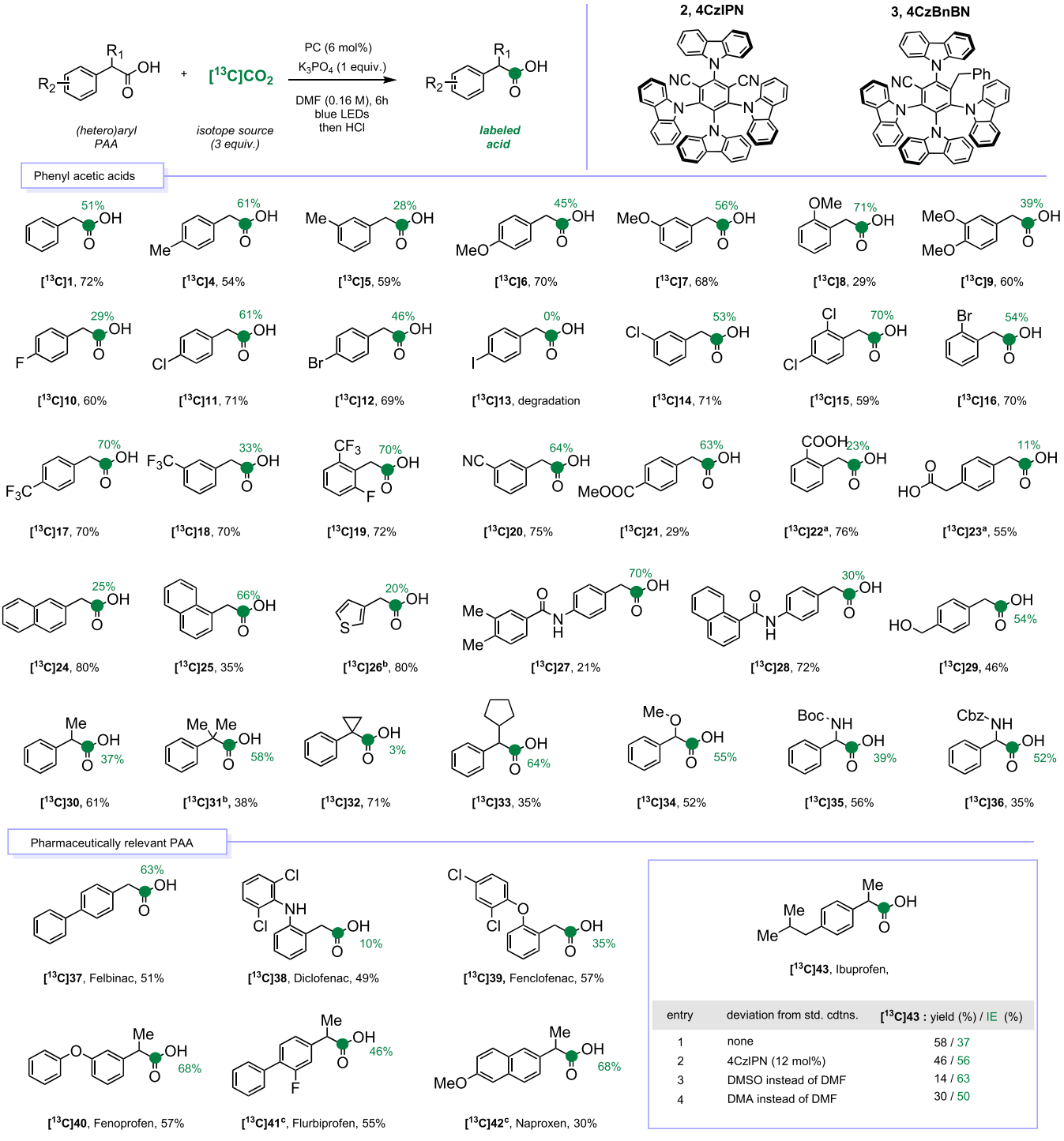

entry	deviation from std. cdtns.	[13C]43 : yield (%) / IE (%)
1	none	58 / 37
2	4CzIPN (12 mol%)	46 / 56
3	DMSO instead of DMF	14 / 63
4	DMA instead of DMF	30 / 50

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%), K_3PO_4 (1 equiv.), [^{13}C]CO_2 (3 equiv.), DMF (0.6 mL), 6 h. [a] Using 2 equiv. of K_3PO_4 and DMSO instead of DMF. [b] ^{1}H NMR yield determined using DMF-d_7 instead of DMF and 1,3,5-trimethoxybenzene as the internal standard. [c] Reaction time: 3 h instead of 6 h. The temperature of the reaction: 42 ± 2 °C.

In 2020, our group and Lundgren's independently reported the transition-metal-free thermal CIE of phenyl acetic acids (PAAs).[16] By heating the corresponding cesium or potassium carboxylates in the presence of labeled CO_2, reversible decarboxylation/carboxylation takes place and the desired acids are obtained with good isotope incorporation. While appealing, the requirement of harsh thermal heating is compulsory for nonactivated PAAs. Prolonged heating at 160 °C for 48 hrs was required to label a series of well-known nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, fenoprofen, ketoprofen, naproxen, and diclofenac.[17] Drastic conditions for an extended period of time are generally unsuitable, especially when handling of radioactive materials is involved.

The invention of a reversible carboxylation process under mild conditions still constitutes a fundamental challenge.

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Inspired by pioneering works on transition-metal-free photocatalyzed carboxylation[4] and the wealth of knowledge on the photocatalyzed radical decarboxylation of Csp^3 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 for structural modifications or prefunctionalization. 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. The model substrate 2-phenyl acetic acid **1** was labeled in a 72% isolated yield and 51% isotopic enrichment (IE) in the presence of the photocatalyst (PC) 4CzIPN (6 mol %), K_3PO_4, and $[^{13}C]CO_2$ as a convenient surrogate for $[^{14}C]CO_2$ in dry DMF within 6 h. The reactions were performed employing 0.1 mmol of substrate and 0.3 mmol of $[^{13}C]CO_2$, which 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 protodecarboxylation side product **1b** was formed in a 47% yield.

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 conditions, **3** was isolated from the crude mixture and successfully re-engaged in photocatalytic CIE (see page S12 for details). Other bases such as K_2CO_3 and CsOAc were also compatible but gave lower IE (Table 1, entries 4 and 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 a 94% yield (see the SI).

The use of other polar aprotic solvents 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 the 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 noting that higher incorporation was achieved with ortho substitution but a lower isolated yield was obtained ($[^{13}C]$**8**, IE = 71%, 29% yield). Halogens were also tolerated, and $[^{13}C]$**10**−**16** were labeled in 29−70% IE and good yields. Only substrate **13** could not be labeled, and deiodination occurred without the insertion of ^{13}C. Investigation with stronger electron-withdrawing groups led to successful labeling of various substrates such as trifluoromethyl $[^{13}C]$**17**−**19** (IE = 33−70%), *m*-nitrile $[^{13}C]$**20** (IE = 64%), and ester derivatives $[^{13}C]$**21** (IE = 63%). Importantly, on these electron-poor substrates, no background reactions were observed in the absence of PC.[16b] Labeling of dicarboxylic acids $[^{13}C]$**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 $[^{13}C]$**27**−**29** (IE = 30−70 and 21−72% yield). Pleasingly, functionalization in the 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 $[^{13}C]$**30**−**33**. While the *gem*-dimethyl **31** was effectively labeled, the presence of a cyclopropyl ring allowed only low exchange ($[^{13}C]$**32** IE <5%) even in the presence of 4CzBnBN PC. CIE was also performed on particularly challenging non-natural protected amino acids $[^{13}C]$**35**−**36** and successfully enabled the exchange in 39−52% 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 $[^{13}C]$**37** was labeled with an isotopic enrichment of 63 and 51% yields. Diclofenac $[^{13}C]$**38** and fenclofenac $[^{13}C]$**39** were obtained, respectively, in 49 and 57% of recovered products with 10 and 35% of isotope incorporation.

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

An optimization of the reaction was performed to effectively label the most notorious NSAID in the market, ibuprofen $[^{13}C]$**43**. It was found that the use of 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 nonprotic 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 protodecarboxylation 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 the presence of 3 equiv. of labeled $[^{13}C]CO_2$, optimal

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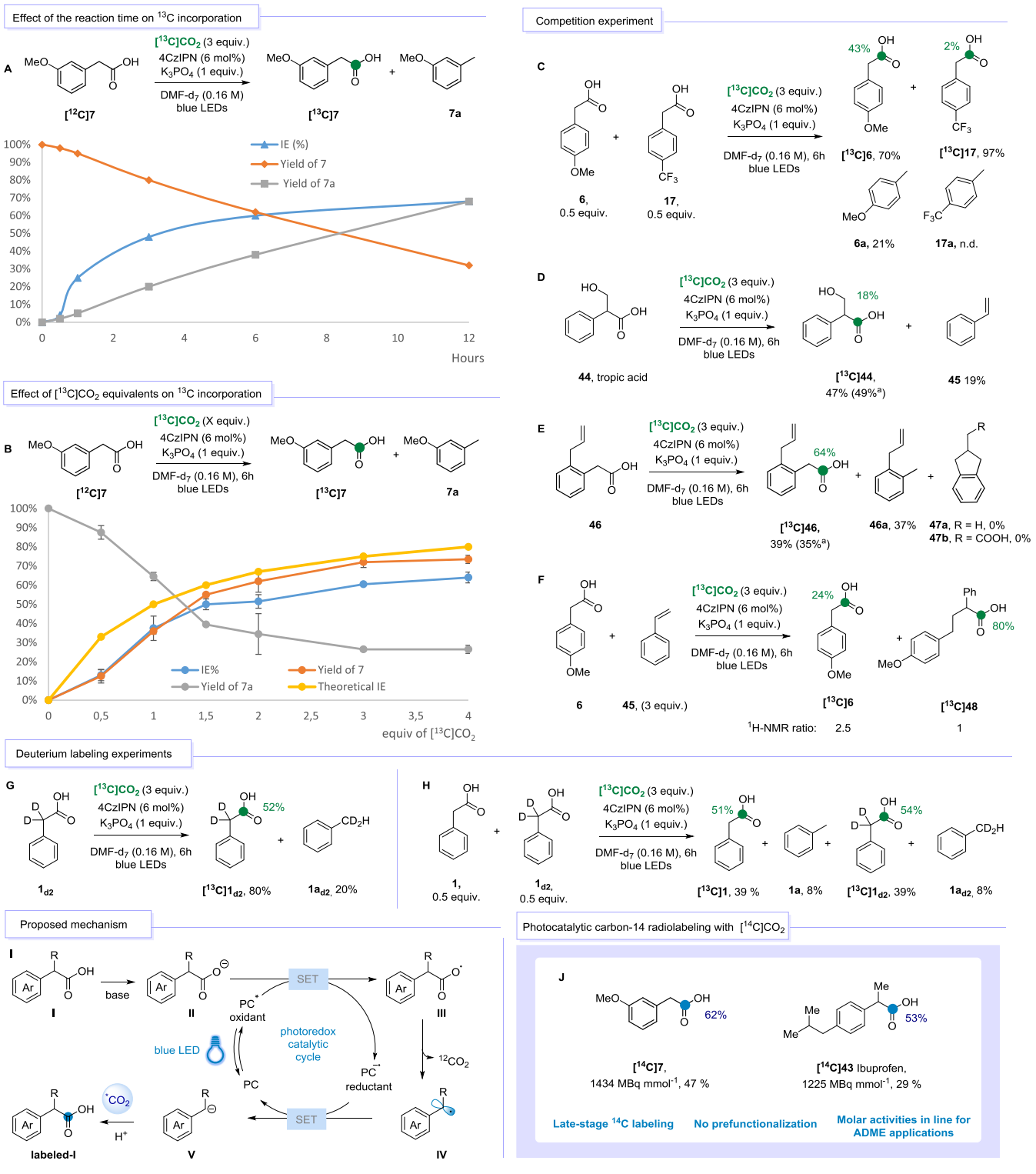

Figure 3. Mechanistic investigations. Green colored circles and numbers denote the positions of the ^{13}C atoms labeled and the percent incorporation of the isotope. Yields were determined from the crude ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. Yields of **7** refer to the inseparable mixture of [^{12}C]**7** and [^{13}C]**7** isotopomers. [a] Isolated yield. (A) Effect of the reaction time on ^{13}C incorporation. (B) Effect of [^{13}C]CO_2 equivalents on ^{13}C incorporation. (C) Competition experiment. (D) E1cB-elimination reaction. (E) Radical clock experiment. (F) Reaction with styrene. (G, H) Deuterium labeling experiments. (I) Proposed mechanism. (J) Photocatalytic CIE radiolabeling with [^{14}C]CO_2. Molar activities for ^{14}C in MBq mmol^{-1}; see the SI for details. Blue colored circles and numbers denote the positions of the ^{14}C atoms labeled and the percent incorporation of the isotope.

isotope incorporation was observed after 6 hours (Figure 3A). Longer reaction times did not provide a significant improvement on the % IE.

Then, the effect of the number of equiv. of [^{13}C]CO_2 on the reaction was monitored. The precise amount of CO_2 required for carboxylation reactions is most often a neglected

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parameter and poorly investigated. As shown in Figure 3B, in the absence of sufficient amounts of $[^{13}C]CO_2$, the protodecarboxylation product **7a** was predominant (up to 0.5 equiv.). When 1 equiv. of electrophile was added, the isotope incorporation observed started to converge toward the expected theoretical value (38% in place of 50% theoretical). Nonetheless, tolyl **7a** was still the major product observed with a 65% yield. Only when more than 1.5 equiv. of $[^{13}C]CO_2$ was added, the yield of **7** was satisfying. When more than 3 equiv. of CO_2 was utilized, the costs of the labeled reagent were not compensated by the limited benefit over IE and yield.[25] Such observations seem to point toward the need for 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 $[^{13}C]CO_2$, the costly limiting reagent of the overall process (see the 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 $[^{13}C]$**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 occurs 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, $[^{13}C]$**44** was isolated in a 49% yield and a moderate IE of 18%, together with 19% of styrene product **45** formed through the E1cB-elimination reaction, thus supporting the formation of a carbanion intermediate in the reaction (Figure 3D).

A radical clock experiment was performed in the presence of allylic acid **46**[28] bearing a terminal olefin at the 5-exo position and provided $[^{13}C]$**46** in a 39% yield and 64% IE, along with tolyl derivative **46a** in a 37% yield (Figure 3E). No traces of the cyclized product **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 the SI for details). This result supports the formation of radicals along the reaction pathway.

Finally, when **6** was subjected to the reaction conditions in the presence of excess of styrene (3 equiv.), the labeled $[^{13}C]$**6** was obtained in a moderate enrichment (24% IE) together with acid $[^{13}C]$**48**, in a 2.5:1 ratio. Interestingly, the product of the radical addition to styrene, $[^{13}C]$**48**, was formed with high enrichment (80% IE) close to the theoretical $^{12/13}CO_2$ ratio. No other products were observed during the reaction, suggesting that **48** was not able to undergo photodecarboxylation 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 $\mathbf{1}_{d2}$ was subjected to standard reaction conditions (Figure 3G), the formation of the desired product $[^{13}C]$-$\mathbf{1}_{d2}$ was observed in the crude mixture with identical efficiency with respect to the unlabeled isotopomer **1** (Table 1).

To confirm this, a competition experiment was performed (Figure 3H). These results in addition to those of the competition experiment in Figure 3C point toward a reaction mechanism that involves a direct nucleophilic attack, of the in situ generated anion, to $[^{13}C]CO_2$ 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 $[^{13}C]CO_2$ 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,H), seem to point against such a parallel mechanism. Nonetheless, substrate dependency cannot be excluded at present.

Photocatalytic Carbon-14 Radiolabeling with $[^{14}C]CO_2$. 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 from 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 ^{14}C radiolabeling. As a first proof-of-concept, **7** was selected as a model substrate. In the presence of exactly 0.3 mmol of $[^{14}C]CO_2$ (3 equiv. cost 580 $), $[^{14}C]$**7** was effectively labeled in a 47% yield and 62% IE, which corresponds to a molar activity (A_m) of 1434 MBq mmol^{-1}, which is fully in line with the possible application of ADME and biodistribution 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 a 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.

CONCLUSIONS

In summary, 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 into the transformation were unveiled and the precise addition of $[^{13}C]CO_2$ showed a strong dependency of reaction outcome in terms of both isotope incorporation and product formation. Finally, it was shown that the implementation of this transformation toward radioactive ^{14}C radiolabeling is possible under safe and cost-sustainable conditions. In the presence of 3 equiv. of $[^{14}C]CO_2$, $[^{14}C]$**7** and ibuprofen $[^{14}C]$**43** were labeled in high molar activities in line with the possible application for ADME studies.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05344.

Photocatalyst synthesis, detailed reaction optimization process, experimental procedures, mechanistic investigations, carbon isotope exchange, determination of isotopic enrichments by HRMS, and computational details of NMR spectra for obtained compounds (PDF)

(PDF)

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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.

Notes

The authors declare no competing financial interest.

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