

A Photochemical Strategy for Carbon Isotope Exchange with CO₂

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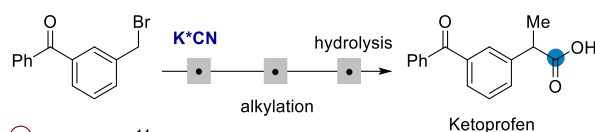
ABSTRACT: A novel photocatalytic approach for carbon isotope exchange is reported. Utilizing [¹³C]CO₂ as primary C1 sources, this protocol allows the insertion of the desired carbon isotope into phenyl acetic acids without the need of structural modifications or pre-functionalization, in one single step.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

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 a major challenge in photocatalysis and, in particular, the valorization of carbon dioxide (CO₂) is drawing much attention. 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 have appeared.^{3,4,5}

Besides valorizing this abundant greenhouse gas, 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.⁶ 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.⁷ While ¹⁴C has traditionally been introduced into biologically relevant target compounds in multi-step fashion (Figure 1A), drawbacks related to the limited available raw materials, their prohibitive costs ([¹⁴C]CO₂: 1600 € per mmol) and the generation of long-lasting waste are standing challenges.⁸

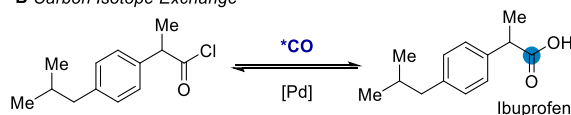
In the last couple of years, late-stage ¹⁴C-labeling has undergone sudden growth.⁹ In particular, carbon isotope exchange (CIE), which allows for ¹²C-¹²C bond cleavage and ¹²C-¹⁴C bond formation in one single step, emerged as privileged strategy (Figure 1B).¹⁰ Mostly focused on [¹²C]/[¹⁴C]CO₂ exchange,^{11,12,13} these methodologies are based on the use of transition metals, which are in some cases even required in stoichiometric amounts.¹⁴ In 2020, our group and Lundgren's independently reported the transition metal-free thermal CIE of phenyl acetic acids (PAA).¹⁵ 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 hrs¹⁵ was required to label a series of well-known Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as Ibuprofen, Fenoprofen, Ketoprofen, Naproxen and Diclofenac.¹⁶ Drastic conditions for an extended period of time are generally unsuitable, and especially when handling of radioactive materials is involved.

A Previous multi-step methods:

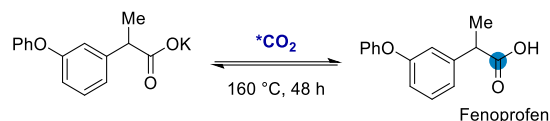


- ⊗ Secondary ^{14}C source (KCN)
- ⊗ Time/Resource consuming
- ⊗ Precursor synthesis

B Carbon Isotope Exchange



- ⊗ Secondary ^{14}C source (CO)
- ⊗ Substrate pre-functionalization



- ✓ Primary ^{14}C source (CO_2)
- ⊗ From the corresponding salt
- ⊗ Harsh conditions

C This work: Photocatalyzed Carbon Isotope Exchange

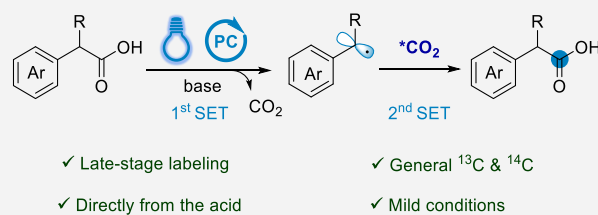


Figure 1: State of the art. (A) Multi-step carbon labeling technologies for the insertion of the isotope into a pharmaceutically relevant PAA. (B) Reported CIE procedures. (C) Photocatalytic CIE. Blue circles represent the positions of isotopically labeled carbon. PC= photocatalyst; SET= single electron transfer.

The invention of a reversible carboxylation process under mild conditions still constitutes a fundamental challenge. Herein, we report the first photocatalytic approach for carbon isotope exchange (Figure 1C). This protocol allows the insertion of the desired isotope into phenyl acetic acids, including non-natural phenyl glycine amino acids, 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.¹⁷

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 47% isotopic enrichment (IE), in presence of the photocatalyst (PC) 4CzIPN (6 mol%), K_3PO_4 and $[^{13}\text{C}]\text{CO}_2$ as a convenient surrogate for $[^{14}\text{C}]\text{CO}_2$ in dry DMF within 6 hours. The reactions were performed employing 0.1 mmol of substrate and 0.3 mmol of $[^{13}\text{C}]\text{CO}_2$ were precisely added using the RC Tritec manifold.¹⁸ 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. This observation is in agreement with previous reports by König and Tunge.¹⁹ Notably, the use of other photocatalysts resulted in low isotope incorporation (SI, 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 Table S4 SI 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). The use of carbonate bases was excluded to avoid isotope dilution, as potential source of unlabeled [¹²C]CO₂.^{5a,5d,20} When the reaction was performed starting from the corresponding potassium carboxylate [¹³C]**1** was obtained in 50% IE and 94% yield (see SI). The use of other polar aprotic solvent such as DMSO provided [¹³C]**1** in 66 % IE, but drastically eroded the yield (entry 6 and Table S2). When [¹³C]CO₂ was replaced by nitrogen complete proto-decarboxylation 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 on non-activated substrate (Table 1, entries 9 and 10).

entry	deviation from std. cdtns.	[¹³ C] 1 : yield (%) ^a / I.E. (%) ^b	yield 2 (%) ^a
1	none	80 (72%) / 47	17
2	4CzIPN (12 mol%)	43 / 62	47
3	4CzBnBN instead of 4CzIPN	82 / 49	17
4	K ₂ CO ₃ instead of K ₃ PO ₄	89 / 32	7
5	CsOAc instead of K ₃ PO ₄	92 / 26	8
6	no base	>90 / 0	0
7	DMSO instead of DMF	21 / 66	n.d
8	N ₂ instead of [¹³ C]CO ₂	traces / 0	85
9	no photocatalyst	>90 / 0	traces
10	no light	>90 / 0	0

2, R = CN, 4CzIPN
3, R = Bn, 4CzBnBN

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 (I.E.) were determined by mass spectrometry. ^c Isolated yield. The temperature of the reaction was to 42 ± 2 °C.

With these optimized conditions in hand, we directed our studies toward the scope (Figure 2). Regardless to the position, in presence of electron donating groups on the aromatic ring, isotopic enrichment was observed in substituted phenyl acetic acids bearing alkyl [¹³C]**4-5** or methoxy [¹³C]**6-9** moieties. It is worth to note that higher incorporation was achieved with *ortho* substitution but a lower isolated yield was obtained ([¹³C]**8**, IE = 71%, 29% yield). Halogen were also tolerated and [¹³C]**10-16** were labeled in 29 to 70% IE and good yields. Only substrate **13** could not be labeled and de-iodination occurred without insertion of ¹³C in the acid. Investigation with stronger electro-withdrawing groups led to successful labeling of various substrates such as trifluoromethyl [¹³C]**17-19** (IE = 33-70%), *m*-nitrile [¹³C]**20** (IE = 64%) and ester derivatives [¹³C]**21** (IE = 63%). Importantly, on this electron poor substrates no background reaction is observed in the absence of PC.^{15b} Labeling of dicarboxylic acids **22-23** required using DMSO in place of DMF, for solubility reasons, and 2 equiv. of base. Interestingly, [¹³C]**22** was selectively labeled in 30% IE, while for [¹³C]**23** only a single label was recovered (IE 15%).

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 minimal exchange ([^{13}C]**32** IE < 7 %). CIE was performed on particularly challenging non-natural protected amino acids [^{13}C]**35-36** and successfully enable the exchange in **39** to 52% IE.

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% yield. Diclofenac **38** and Fenclofenac **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 aniline in *ortho* position to the acid have a deleterious effect on both IE and yield. Fenoprofen **40** was labeled with 68% of IE and a correct isolated yield of 57%. To obtain labeled **41** and **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 [^{13}C]**41** and Naproxen [^{13}C]**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 **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.

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. Implementation of this novel transformation towards radioactive ^{14}C radiolabeling is currently ongoing in our laboratory.

Acknowledgments

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