



HAL
open science

Transition-Metal-Free Carbon Isotope Exchange of Phenyl Acetic Acids

Gianluca Destro, Kaisa Horkka, Olivier Loreau, David-Alexandre Buisson, Lee Kingston, Antonio del Vecchio, Magnus Schou, Charles Elmore, Frédéric Taran, Thibault Cantat, et al.

► **To cite this version:**

Gianluca Destro, Kaisa Horkka, Olivier Loreau, David-Alexandre Buisson, Lee Kingston, et al.. Transition-Metal-Free Carbon Isotope Exchange of Phenyl Acetic Acids. *Angewandte Chemie International Edition*, 2020, 59 (32), pp.13490-13495. 10.1002/anie.202002341 . cea-02559747

HAL Id: cea-02559747

<https://cea.hal.science/cea-02559747>

Submitted on 30 Apr 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Transition-Metal-Free Carbon Isotope Exchange of Phenyl Acetic Acids

Gianluca Destro,^{[a],[b]} Kaisa Horkka,^[c] Olivier Loreau,^[a] David-Alexandre Buisson,^[a] Lee Kingston,^[e] Antonio Del Vecchio,^[a] Magnus Schou,^{[c],[d]} Charles S. Elmore,^[e] Frédéric Taran,^[a] Thibault Cantat,^[b] Davide Audisio^{[a]*}

Abstract: A transition-metal-free carbon isotope exchange procedure on phenyl acetic acids is described. Utilizing the universal precursor CO₂, this protocol allows the carbon isotope to be inserted into the carboxylic acid position, with no need of precursor synthesis. This procedure enabled the labeling of 15 pharmaceuticals and was compatible with carbon isotopes [¹⁴C] and [¹³C]. A proof of concept with [¹¹C] was also obtained with low molar activities valuable for distribution studies.

Radiolabeling with long-lived β⁻ emitters carbon-14 (¹⁴C) and tritium (³H) plays a critical role in drug discovery and development.¹ These techniques allow the determination of key data such as the absorption, distribution, metabolism, and excretion (ADME), both for human and veterinary drug development.^{2,3}

In this context, technologies allowing the direct incorporation of carbon and hydrogen labels onto organic molecules are of critical importance. Over the last decade, hydrogen isotope exchange (HIE)⁴ has emerged as the most effective way to introduce ³H and ²H into organic molecules. Despite recent progress on HIE, risks for potential tritium loss due to metabolic instability in biological media, such as cytochrome P450-mediated oxidative cleavage of the C-³H bonds, limit the use of tritiated radiotracers to early drug discovery and preclinical phase.⁵ On the other hand, due to the higher metabolic stability of C-C bonds, the utilization of ¹⁴C is strongly recommended by regulatory agencies for advanced human ADME studies, new drug submission and it is almost exclusive for human food safety and environmental fate studies.

Nonetheless, ¹⁴C radiosynthesis remains a significant challenge: ¹⁴C is generated in nuclear reactors as Ba[¹⁴C]CO₃ and

converted into [¹⁴C]CO₂.^{6,7} Consequently, ¹⁴C syntheses rely on [¹⁴C]CO₂ as sole basic starting material⁸ and, in the end, all ¹⁴C-labeled compounds have to be built up from ¹⁴CO₂. The whole labeling procedures are multi-step and time-consuming. In addition, costs associated to this building block ([¹⁴C]CO₂: 1600 € per mmol) and the generation of long-lived radioactive waste (half-life 5730 years) affect even further the radiosynthesis. More advanced building blocks are commercially available, but they are often highly expensive and still a bottleneck when planning an actual synthesis.⁹

Recent breakthroughs in late-stage ¹⁴C labeling have challenged this traditional approach and showcased direct access to complex scaffolds from [¹⁴C]CO₂.¹⁰ In addition, the first examples of transition-metal-catalyzed carbon isotope exchange (CIE) have recently emerged.¹¹ Such technology enable selective replacement of molecular moieties into complex organic molecules, by reversible molecular deconstruction/reconstruction thus providing access to ¹⁴C labeled compounds in a single operation, directly from the end-use molecules. We described a copper-catalyzed decarboxylative-carboxylation of (hetero)aromatic carboxylic acid salts with [¹⁴C]CO₂.¹² In 2019, Baran¹³ and Martin¹⁴ independently reported a nickel-catalyzed approach utilizing [¹⁴C]CO₂. Gauthier *et al.* developed a palladium-catalyzed decarboxylative-carboxylation CIE¹⁵ of acid chlorides, using *in situ* generated [¹⁴C]CO.¹⁶ While these complementary approaches are particularly attractive, novel developments in CIE are highly desirable.

Phenyl acetic acids (PAA) are important scaffolds for carbon labeling.¹⁷ This pharmacophore is quintessential in Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and largely found in anti-muscarinics, anti-narcoleptics, analgesic opioids, agrochemicals, and plant protection products (Scheme 1A).¹⁸

While carbon labeling of PAA at the carbonyl position is metabolically stable and suitable for biological studies, no general procedures are available.¹⁹ The most utilized is the ¹⁴C-cyanation of the benzyl halides (Scheme 1B),²⁰ which requires the prior synthesis of tailored precursors: a time-consuming and often non-trivial task, especially for poly-functionalized PAAs. The work by Gauthier *et al.* on carbon monoxide CIE has shown promise. Examples of PAAs were labeled from the parent compound, after prior carboxylic acid activation (Scheme 1B). Unfortunately, [¹⁴C]CO is a less convenient ¹⁴C reagent because of the requirement that it is freshly generated from ¹⁴COgen. The price of this precursor, which is obtained in two radiochemical steps from [¹⁴C]CO₂, and the inherent toxicity of this poisonous radioactive gas somewhat limits the immediacy for its implementation. In 1979, Parnes reported an exchange procedure using strong basic conditions (LDA) in presence of HMPA and ¹⁴CO₂.¹⁹ Since this seminal publication, only one

[a] Dr. G. Destro, O. Loreau, D.-A. Buisson, Dr. Del Vecchio, Dr. F. Taran, Dr. D. Audisio
Université Paris-Saclay, CEA, Service de Chimie Bio-organique et de Marquage, 91191, Gif-sur-Yvette, France
E-mail: davide.audisio@cea.fr

[b] Dr. G. Destro, Dr. T. Cantat
Université Paris-Saclay, CEA, CNRS, NIMBE, 91191, Gif-sur-Yvette, France

[c] K. Horkka, Dr. M. Schou
Karolinska Institutet, 17176 Stockholm, Sweden

[d] Dr. M. Schou
PET Science Centre, Precision Medicine, Oncology R&D, AstraZeneca, Karolinska Institutet, 17176 Stockholm, Sweden

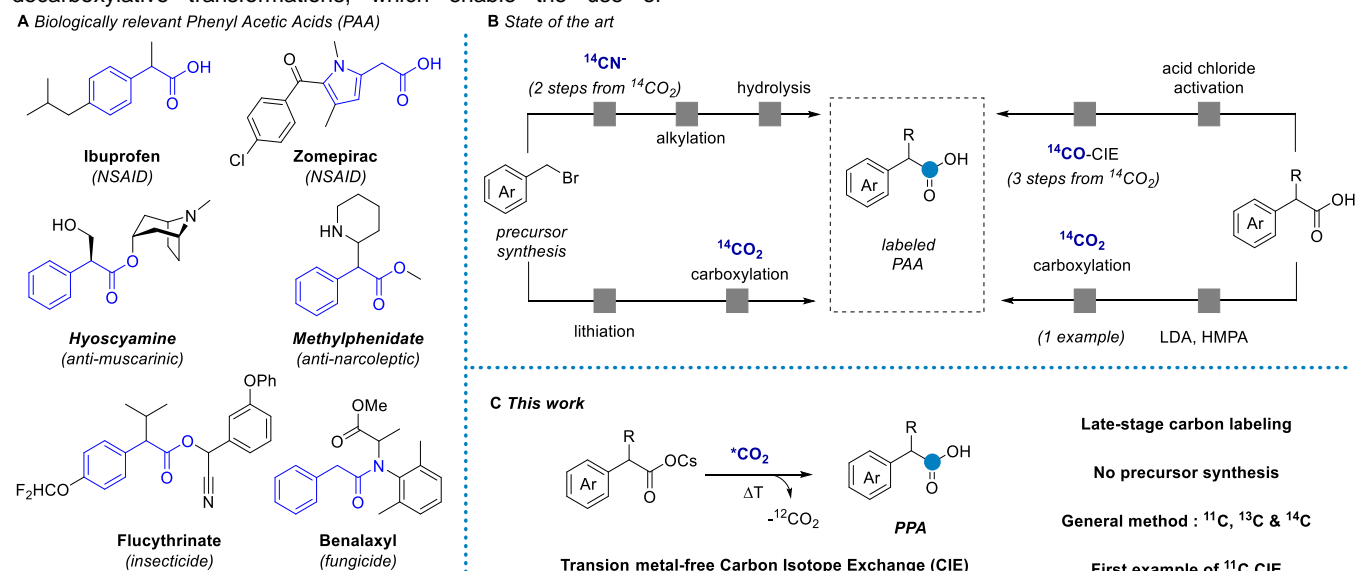
[e] L. Kingston, Dr. C. S. Elmore
Early Chemical Development, Pharmaceutical Sciences, R&D, AstraZeneca, Gothenburg, Sweden

example of PAA was labeled by this method, probably due to poor functional group compatibility.

As part of our interest in carbon isotope labeling, we report a transition-metal-free carbon isotope exchange on PAA (Scheme 1C). Our protocol allowed the labeling of a variety of PAA derivatives, including pharmaceuticals, with $[^{13}\text{C}]\text{CO}_2$ and $[^{14}\text{C}]\text{CO}_2$ without need for substrate pre-functionalization. The procedure allowed application of CIE to short-lived positron emitting ^{11}C radioisotope, for the first time.

Recent years have witnessed the development of catalytic decarboxylative transformations, which enable the use of

carboxylic acids as versatile handles for a variety of high-value functionalisations.²¹ In particular, the use of PAA salts in decarboxylative cross-coupling transformations has been reported by Liu,²² Zhu²³ and others.²⁴ Recently, the group of Lundgren have shown that electron deficient aryl acetates decarboxylate under thermal conditions, in the absence of Pd-catalysts.²⁵ The authors suggested that aryl acetate decarboxylation generates a basic benzylic anion species which can deprotonate another aryl acetate partner.²⁶



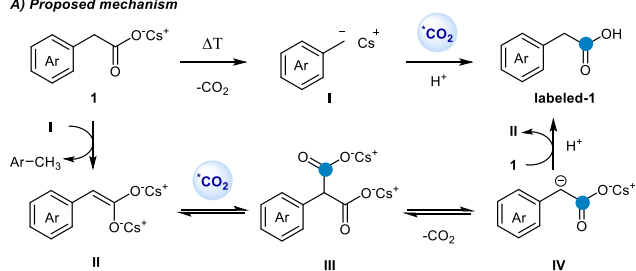
Scheme 1: Carbon isotope labeling of PAA. A) Examples of biologically relevant PAA. B) Previous methodologies towards the introduction of ^{14}C . C) Transition-metal-free CIE for PAA.

After the cross-coupling and C-C bond formation, the carbonyl group would spontaneously decarboxylate. Inspired by this hypothesis, it was reasoned that after decarboxylation, anion **I** might either react directly with CO_2 or, alternatively, generate *in situ* a dienolate species **II** (Scheme 2A). Intermediate **II** could undergo nucleophilic attack onto isotopically labeled carbon dioxide, thus forming a malonate derivative (**III**). Subsequent decarboxylation would afford the carbon-enriched material (**IV**), which might either act as a base, deprotonating another substrate or, after protonation, deliver the enriched PAA (**labeled-1**).

To test our hypothesis, we selected 4-methoxyphenylacetate cesium salt **2** as a model substrate (Scheme 2C). Temperature, time, and solvent screening was initially conducted with $[^{13}\text{C}]\text{CO}_2$ gas as a convenient and readily handled $[^{14}\text{C}]\text{CO}_2$ surrogate. All of the reactions were performed under standard conditions employing 0.1 mmol of substrate in dry DMF with 3 equiv. of $[^{13}\text{C}]\text{CO}_2$.²⁷ The extent of isotopic exchange was determined after 2 hours using mass spectroscopy. For model substrate **2**, the best conditions were found to be 1 hour 150 °C in DMSO; $[^{13}\text{C}]\mathbf{2}$ was isolated in 43% yield and with 48% isotopic enrichment (IE).^{28,29} Next, we examined the scope of the reaction. A series of electron-rich derivatives were screened: labeled PAAs $[^{13}\text{C}]\mathbf{2}$ - $[^{13}\text{C}]\mathbf{8}$ were isolated in 32% to 98% yields and 29% to 55% IE. The presence of steric hindrance in the *ortho* position on the ring, slightly affected the efficiency of the CIE, as $[^{13}\text{C}]\mathbf{4}$ and $[^{13}\text{C}]\mathbf{7}$ were labeled in 39% and 34% IE, respectively. The presence of di- and

tri-methoxy groups is well tolerated, hence compound $[^{13}\text{C}]\mathbf{5}$ could be obtained with 29% IE and 98% yield. In addition, $[^{13}\text{C}]\mathbf{9}$ bearing a *p*-naphthamide moiety was labeled with 35% IE (56% yield), and the presence of a secondary amide did not affect the transformation. Electron-donating thioether $[^{13}\text{C}]\mathbf{10}$ was labeled in 70% IE (40% yield). Finally, heterocyclic derivatives such as oxazole and thiophene were obtained: $[^{13}\text{C}]\mathbf{11}$ in 57% yield (63% IE) and $[^{13}\text{C}]\mathbf{12}$ in 40% yield (50% IE). When standard conditions were applied to *p*-nitro PAA **13**, complete decarboxylation was observed. After optimization, it was found that time and temperature reduction to 5 minutes and 80 °C, allowed to isolate $[^{13}\text{C}]\mathbf{13}$ in 39% yield and 46% IE. The presence of the methyl group in *alpha* to the carboxylic acid was tolerated and $[^{13}\text{C}]\mathbf{14}$ was isolated in 42% yield with 45% IE. For other electron poor derivatives, we found that optimal isotope incorporation was substrate dependent. For example, 130 °C and 1 hour were necessary for derivatives *p*- CF_3 -**15** and *o*- CF_3 -**16**: $[^{13}\text{C}]\mathbf{15}$ and $[^{13}\text{C}]\mathbf{16}$ could be obtained in 53% IE and 64% IE, respectively. On the other hand, for *p*-Cl-**17** 2 hours and 150 °C were utilized and $[^{13}\text{C}]\mathbf{17}$ obtained with 43% IE.

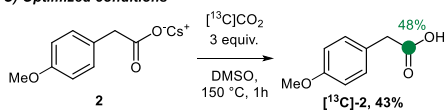
A) Proposed mechanism



B) Challenge

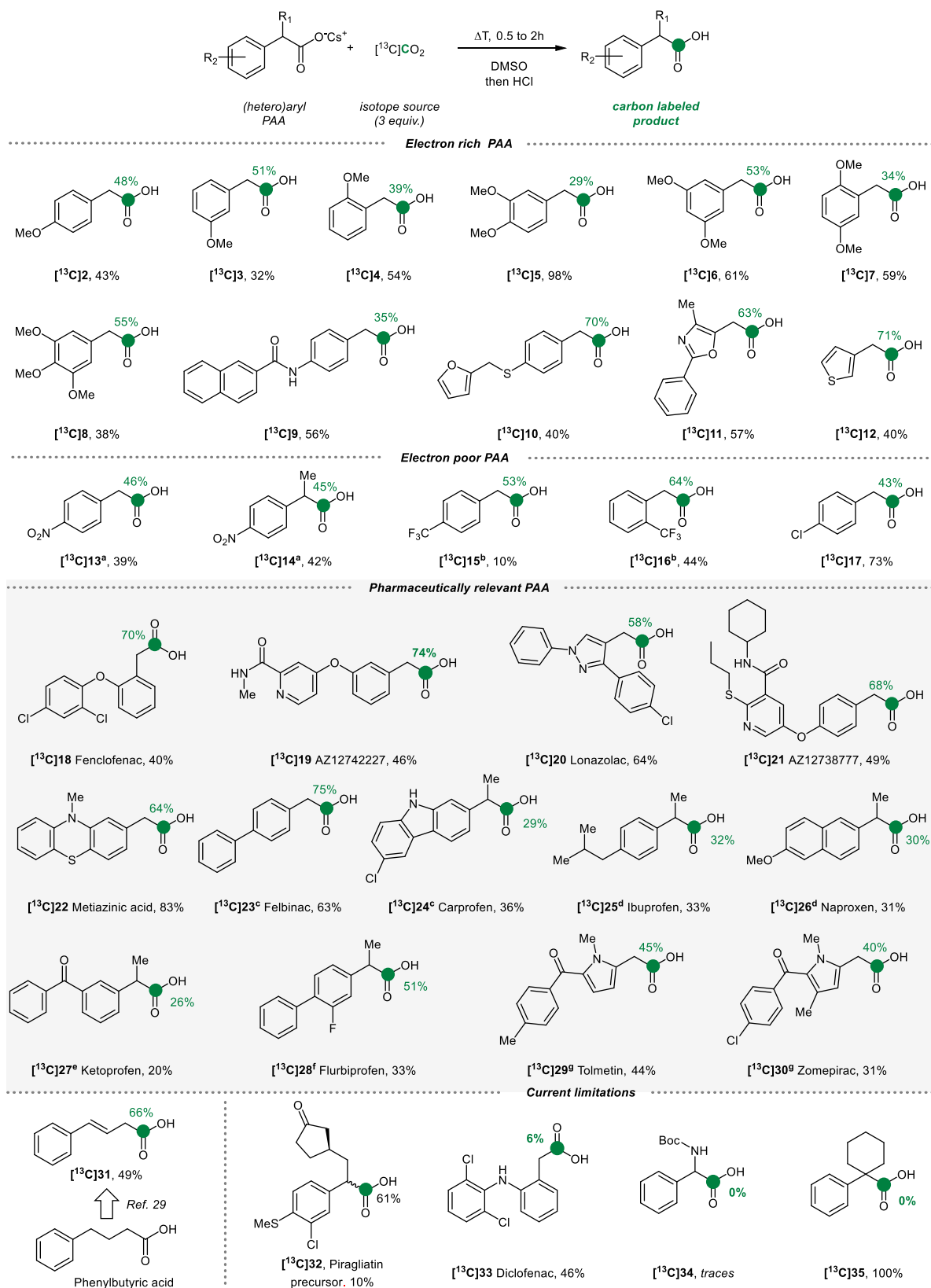
^{13}C
 $\text{O}=\text{C}=\text{O}$
 primary isotope source
 poor electrophile
 high cost (1600 € mmol⁻¹)

C) Optimized conditions



Scheme 2: A) Potential mechanisms for transition-metal-free CIE. B) Hurdles in ¹³C radio-synthesis. C) Optimized conditions for substrate 2. Colored circles and numbers denote the positions of the carbon atoms labeled and the percent incorporation of the carbon isotope. DMSO, dimethyl sulfoxide.

Next, we explored the labeling of pharmaceuticals. Pleasingly, Fenclofenac (**18**), AZ12742227 (**19**), Lonazolac (**20**), AZ12738777 (**21**), and Methiazinic acid (**22**) reacted under standard conditions in 40% to 83% yields and 56% to 75% IE.

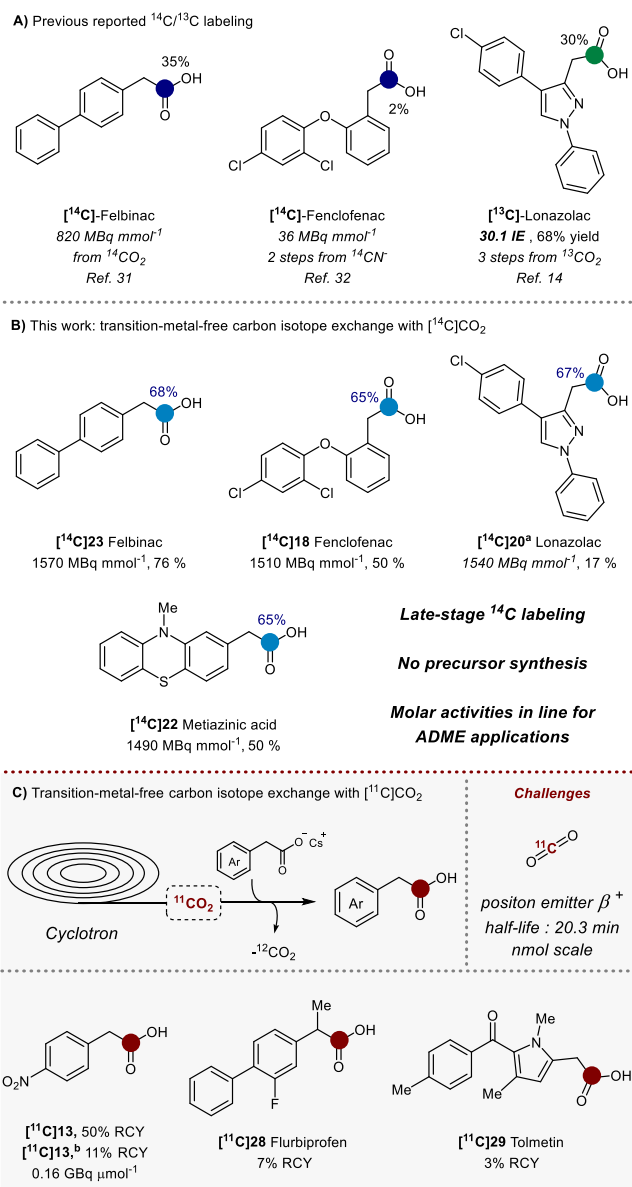


Scheme 3: ¹³C-labeling of PAA. The green colored circles and numbers denote the positions of the atoms labeled and the percent incorporation of the isotope. Reaction conditions: substrate (0.1 mmol, 1 equiv.), ¹³CO₂ (3 equiv.), DMSO (0.5 mL), temperature 150 °C, time 2 h. DMSO, dimethyl sulfoxide. ^a Reaction time 5 minutes, temperature 80 °C. ^b Reaction time 1h, temperature 130 °C. ^c Reaction time 4h. ^d Reaction time 6h, temperature 190 °C. ^e Reaction time 3.5h, temperature 190 °C. ^f Reaction time 0.5h, temperature 190 °C. ^g Reaction time: 5 minutes.

Notably, [^{13}C]18 (70% IE, 40% yield) and [^{13}C]20 (58% IE, 64% yield) were isolated without any traces of de-halogenation. PAAs displaying structural complexity such as [^{13}C]19 and [^{13}C]21 were obtained in high levels of ^{13}C incorporation in 74% IE (48% yield) and 68% IE (49% yield). Felbinac (**23**) and Carprofen (**24**) required longer reaction time (4h). Nonetheless, [^{13}C]23 was obtained with 75% IE (63% yield) and [^{13}C]24, bearing an unprotected carbazole core, with 29% IE (36% yield). The current protocol was successfully applied to anti-inflammatory drugs such as Ibuprofen (**25**), Naproxene (**26**), and Ketoprofen (**27**), though a higher temperature (190 °C) was necessary to achieve reasonable carbon-13 incorporations (26% to 32% IE). Flurbiprofen (**28**) did not perform effectively under standard conditions; further optimization allowed to label [^{13}C]28 in 51% IE (33% yield) at 190 °C in only 30 minutes. Finally, when pyrrole derivatives Tolmetin (**29**) and Zomepirac (**30**) were tested, full decarboxylation was observed. Thus, the reaction was shortened to 5 minutes and [^{13}C]29 and [^{13}C]30 were obtained in 45% and 40% IE. Next, we explored the reactivity of allyl carboxylate **31**. Gladly, cesium carboxylate **31** smoothly underwent CIE yielding [^{13}C]31 in 49% yield and 66% IE. Notably, under previously reported hydrogenation conditions, [^{13}C]31 can be directly converted into phenylbutyric acid (Scheme 3),³⁰ a histone deacetylase inhibitor that displays anticancer activity.³¹

An inherent limitation of the method is the loss of chiral information, Piragliatin precursor [^{13}C]32 was obtained with isotopic enrichment of 61% (in a 1:1 diastereomer ratio). In this context, it is worth noting that NSAIDs are known to racemize *in vivo* and are generally administered as racemic mixtures.³² Diclofenac **33** and amino acid **34** were not productive.³³ Finally, *alpha* disubstituted carboxylate **35** was fully recovered without any isotope incorporation.

Next, a series of pharmaceuticals were labeled using [^{14}C]CO₂ under otherwise identical conditions (Scheme 4). [^{14}C] Felbinac was previously labeled by Bruce and co-workers on the same position, for ADME studies,³⁴ from the Grignard precursor, affording [^{14}C] Felbinac with a molar activity (A_m) of 820 MBq mmol⁻¹. The current approach provided [^{14}C]23 in 76% yield and 1570 MBq mmol⁻¹ A_m (68% IE). Similarly, [^{14}C] Felclofenac was prepared for ADME studies with an A_m of 36 MBq mmol⁻¹.³⁵ This procedure allowed the radiolabeling of [^{14}C]18 Fenclufenac in 50% yield and 1510 MBq mmol⁻¹ (65% IE). An advantage of this methodology is its operational simplicity that is convenient for implementation in radiochemistry. In addition, compared to concurrent CIE, the absence of transition-metal catalyst is attractive, as no residual metal traces are released in the transformation. A relevant point for safety in animal and human ADME studies. The preparation of the cesium salts and the use of a glovebox (to reduce moisture) might still be a hurdle for its proliferation. To avoid it, we tested compound **20** under modified conditions: out of the glovebox and adding 0.3 equiv. of anhydrous K₃PO₄: [^{14}C]20 was obtained in 1540 MBq mmol⁻¹ (67% IE).²⁷ Lonazolac was previously labeled by means of CO CIE with carbon-13. Comparatively, we obtained the ^{14}C radioisotopomer in a higher IE and a more cost-effective manner, without need for radiolabeled ^{14}C -carbon monoxide. Finally, [^{14}C]22 Metiazinic acid was obtained in A_m of 1490 MBq mmol⁻¹.



Scheme 4: Transition-metal-free CIE ^{14}C - and ^{11}C -labeling of pharmaceuticals. A) Methods previously reported. B) CIE with [^{14}C]CO₂. Molar activities for ^{14}C in MBq mmol⁻¹. C) CIE with [^{11}C]CO₂. Molar activities for ^{11}C in GBq μmol^{-1} . ^a Potassium salt prepared *in situ* and reaction performed out of the glovebox. ^b Preparative run, isolated yield.

While CIE has been so far reported on long-lived ^{14}C , to the best of our knowledge, there are no examples on carbon-11 (^{11}C).³⁶ [^{11}C]CO₂ is a primary source of ^{11}C , but its use has been hampered by difficulties associated with the high energy β^+ emission, the minute concentrations of [^{11}C]CO₂ produced in the cyclotron and its short half-life (20.33 min).³⁷ During the optimization, we observed that some compounds underwent CIE in short reaction time, compatible with this isotope. Pleasingly, a proof-of-concept was obtained on substrate [^{11}C]13, which was labeled with only minimal optimization in a promising 50% RCY. In a preparative experiment, [^{11}C]13 was isolated in 11% RCY and a A_m of 0.16 GBq μmol^{-1} . Although this A_m is unsuitable for receptor binding studies with high affinity radioligands, it is valuable for studying *in vivo* organ distribution of druglike

molecules in drug development. [¹¹C]Flurbiprofen (**28**) was obtained under modified conditions as 150 °C in 10 minutes with 7% RCY, and [¹¹C]Tolmetin (**29**) was labeled, under non-optimized conditions, with 3% RCY. These preliminary results open new perspectives in ¹¹C isotope labeling.³⁸

In conclusion, a transition-metal-free procedure enabling carbon isotope exchange with all carbon isotopes was developed. This technology utilizes the universal precursor [¹⁴C]CO₂, [¹³C]CO₂, and [¹¹C]CO₂ allowing the insertion, in one single step, of the desired carbon tag into phenyl acetic acids, with no need of structural modifications or precursor synthesis. The practical utility of the method was showcased on the labeling of a variety of pharmaceuticals.

Acknowledgements

This work was supported by CEA and by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement N°675071. The authors thank Amélie Gaudet and Sabrina Lebrequier for the excellent analytical support. Dr. Fabien Caillé and Dr. Antoine Sallustrau are acknowledged for helpful discussions.

Keywords: Isotope labeling • Carbon-14 • Carbon-11 • Isotope exchange • Carbon dioxide

- [1] a) E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol.* **2009**, *25*, 532–542. b) C. S. Elmore, R. A. Bragg, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 167–171. c) P. H. Marathe, W. C. Shyu, W. G. Humphreys, *Curr. Pharm. Des.* **2004**, *10*, 2991–3008.
- [2] a) B. D. Maxwell, C. S. Elmore, Eds. *Radiosynthesis for ADME studies*; 461–471 (John Wiley & Sons, Inc: Hoboken, 2012). b) C. S. Elmore, *Ed. Annu. Rep. Med. Chem.* **2009**, *44*, 515–534.
- [3] N. Penner, L. J. Klunk, C. Prakash, *Biopharm. Drug Dispos.* **2009**, *30*, 185–203.
- [4] a) R. Pony Yu, D. Hesk, N. Rivera, I. Pelczar, P. J. Chirik, *Nature*, **2016**, *529*, 195–199. b) Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies, D. W. C. MacMillan, *Science*, **2017**, *358*, 1182–1187. c) A. Palazzolo, S. Feuillastre, V. Pfeifer, S. Garcia-Argote, D. Bouzouita, S. Tricard, C. Chollet, E. Marcon, D.-A. Buisson, S. Cholet, F. Fenaille, G. Lippens, B. Chaudret, G. Pieters, *Angew. Chem. Int. Ed.* **2019**, *58*, 4891–4895; *Angew. Chem.* **2019**, *131*, 4945–4949. d) M. Valero, R. Weck, S. Güssregen, J. Atzrodt, V. Derau, *Angew. Chem. Int. Ed.* **2018**, *57*, 8159–8163; *Angew. Chem.* **2018**, *130*, 8291–8295.
- [5] J. A. Krauser *J. Label. Compd. Radiopharm* **2013**, *56* 441–446.
- [6] R. Voges, J. R. Heys, T. Moenius, *Preparation of Compounds Labeled with Tritium and Carbon-14* (John Wiley & Sons, 2009).
- [7] N. Zwiebel, J. Turkevich, W. W. Miller, *J. Am. Chem. Soc.*, **1949**, *71*, 376–377.
- [8] a) M. Aresta, *Carbon dioxide as chemical feedstock* (John Wiley & Sons, 2010). b) R. A. Bragg, M. Sardana, M. Artelsmair, C. S. Elmore, *J. Label. Compd. Radiopharm.* **2018**, *61*, 934–948.
- [9] Besides [¹⁴C]CO₂, other secondary building blocks are K[¹⁴C]CN and [¹⁴C]CO. For recent examples see: a) O. Loreau, N. Camus, F. Taran, D. Audisio, *Synlett* **2016**, *27*, 1798–1802. b) F. Song, R. Salter, L. Chen, *J. Org. Chem.* **2017**, *82*, 3530–3537.
- [10] a) A. Del Vecchio, F. Caillé, A. Chevalier, O. Loreau, K. Horkka, C. Halldin, M. Schou, N. Camus, P. Kessler, B. Kuhnast, F. Taran, D. Audisio, *Angew. Chem. Int. Ed.*, **2018**, *57*, 9744–9748; *Angew. Chem.* **2018**, *130*, 9892–9896. b) P. Gotico, A. Del Vecchio, D. Audisio, A. Quaranta, Z. Halime, W. Leibl, A. Aukauloo, *ChemPhotoChem* **2018**, *2*, 715–719.
- [11] K. Hinsinger, G. Pieters, *Angew. Chem. Int. Ed.* **2019**, *58*, 9678–9680; *Angew. Chem.* **2019**, *131*, 9780–9782.
- [12] a) D. Audisio, T. Cantat, G. Destro, EP18305407 (**2018**); WO 2019/193068 A1. b) G. Destro, O. Loreau, E. Marcon, F. Taran, T. Cantat, D. Audisio. *J. Am. Chem. Soc.* **2019**, *141*, 780–784.
- [13] C. Kingston, M. A. Wallace, A. J. Allentoff, J. N. deGruyter, J. S. Chen, S. X. Gong, Jr., S. Bonacorsi, P., S. Baran. *J. Am. Chem. Soc.* **2019**, *141*, 774–779.
- [14] A. Tortajada, Y. Duan, B. Sahoo, F. Cong, G. Toupalas, A. Sallustrau, O. Loreau, D. Audisio, R. Martin, *ACS Catal.* **2019**, *9*, 5897–5901.
- [15] Jr. D. R. Gauthier, N. L. Rivera, Y. Yang, D. M. Schultz, C. S. Shultz, *J. Am. Chem. Soc.* **2018**, *140*, 15596–15600.
- [16] P. Hermange, R. Lindhardt, R. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061–6071.
- [17] W. Smalley, W. Ray, J. Daugherty, *Am. J. Epidemiol.* **1995**, *141*, 539–545.
- [18] For recent synthetic methodological reports on PAA, see: a) Q.-Y. Meng, T. E. Schirmer, A. L. Berger, K. Donabauer, B. König, *J. Am. Chem. Soc.* **2019**, *141*, 11393–11397. b) F. Mandrelli, A. Blond, T. James, H. Kim, B. List, *Angew. Chem. Int. Ed.* **2019**, *58*, 11479–11482; *Angew. Chem.* **2019**, *131*, 11603–11606. c) M. Valero, D. Becker, K. Jess, R. Weck, J. Atzrodt, T. Bannenberg, V. Derau, M. Tamm, *Chem. Eur. J.* **2019**, *25*, 6517–6522. d) N. Ishida, Y. Masuda, Y. Imamura, K. Yamazaki, M. Murakami, *J. Am. Chem. Soc.* **2019**, *141*, 19611–19615.
- [19] H. Parnes, *J. Label. Compd. Radiopharm.* **1979**, *16*, 771–775.
- [20] a) Y. Horio, Y. Torisawa, S. Ikegami. *Chem. Pharm. Bull.* **1985**, *33*, 5562–5564. b) P. J. Hayball, R. L. Nation, F. Bochner, J. L. Newton, R. A. Massy-Westropp, D. P. G. Hamon, *Chirality*, **1991**, *3*, 460–466. c) J. E. T. Corrie, V. R. N. Munasinghe, *J. Label. Compd. Radiopharm.* **2005**, *48*, 231–233. d) D. M. Shackelford, P. J. Hayball, G. D. Reynolds, D. P. Hamon, A. M. Evans, R. W. Milne, R. L. Nation, *J. Label. Compd. Radiopharm.* **2001**, *44*, 225–234.
- [21] For a non-comprehensive series of reviews in the field, see: a) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120. *Angew. Chem.* **2008**, *120*, 3144–3164. b) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048. c) T. Patra, D. Maiti, *Chem. Eur. J.* **2017**, *23*, 7382–7401. d) Y. Wei, P. Hu, M. Zhang, W. Su, *Chem. Rev.* **2017**, *117*, 8864–8907. e) M. Font, J. M. Quibell, G. J. P. Perry, I. Larrosa, *Chem. Commun.* **2017**, *53*, 5584–5597. f) J. Schwarz, B. König, *Green Chem.* **2018**, *20*, 323–361. g) P. J. Moon, R. J. Lundgren, *ACS Catal.* **2020**, *10*, 1742–1753.
- [22] a) R. Shang, Z. Huang, L. Chu, Y. Fu, L. Liu, *Org. Lett.* **2011**, *13*, 4240–4243. b) R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 14391–14393.
- [23] Z. Xu, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 3272–3276; *Angew. Chem.* **2013**, *125*, 3354–3358.
- [24] a) S. R. Waetzig, J. Tunge, A. *J. Am. Chem. Soc.* **2007**, *129*, 14860–14861. b) P. J. Moon, A. Fahandj-Sadi, W. Qian, R. J. Lundgren, *Angew. Chem. Int. Ed.* **2018**, *57*, 4612–4616; *Angew. Chem.* **2018**, *130*, 4702–4706.
- [25] D. Kong, P. Moon, W. Qian, R. Lundgren, *Chem. Commun.* **2018**, *54*, 6835–6838.
- [26] For a recent example of Pd-catalyzed cross-coupling of dienolates, see: S.C. Sha, J. Zhang, P.J. Walsh, *Org Lett.* **2015**, *17*, 410–413.
- [27] See supporting information for experimental details.
- [28] Isotopic Enrichment was determined by mass spectrometry. In this study, the maximum theoretical IE is: 3 equiv. *CO₂ / (3 equiv. *CO₂ + 1 equiv. ¹²CO₂ substrate) × 100 = 75%.
- [29] To the best of our knowledge, an example of isotope exchange was reported, under extremely harsh, pyrolytic conditions (290–440 °C): A. Szabolcs, J. Szammer, L. Noszkó, *Tetrahedron* **1974**, *30*, 3647–3648.
- [30] J. B. Arterburn, M. Pannala, A. M. Gonzalez, R. M. Chamberlin, *Tetrahedron Lett.* **2000**, *41*, 7847–7849.

-
- [31] P. S. Kolb, E. A. Ayaub, W. Zhou, V. Yum, J. G. Dickhout, K. Ask, *Int. J. Biochem. Cell Biol.* **2015**, *61*, 45–52.
- [32] I. Ali, V. K. Gupta, H. Y. Aboul-Enein, P. Singh, B. Sharma, *Chirality*, **2007**, *19*: 453-463.
- [33] When Fmoc protected **34** was utilized, cleavage of the protecting group was observed. This is in agreement with previous literature: S. Höck, R. Marti, R. Riedl, M. Simeunovic *CHIMIA* **2010**, *64*, 200-202.
- [34] L. B. Turnbull, C. J. Johnson III, Y. H. Chen, L. F. Sancilio, R. B. Bruce, *J. Med. Chem.* **1974**, *17*, 45-48.
- [35] M. V. Marsh, J. Caldwell, T. P. Sloan, R. L. Smith, *Xenobiotica*, **1983**, *13*, 233-240.
- [36] For examples of isotope exchange with positron emitter ^{18}F , see: a) R. Schirmacher, G. Bradtmöller, E. Schirmacher, O. Thews, J. Tillmanns, T. Siessmeier, H. G. Buchholz, P. Bartenstein, B. Wängler, C. M. Niemeyer, K. Jurkschat, *Angew. Chem. Int. Ed.*, **2006**, *45*, 6047-6050; *Angew. Chem.* **2006**, *118*, 6193–6197. b) Z. Liu, M. Pourghiasian, M. A. Radtke, J. Lau, J. Pan, G. M. Dias, D. Yapp, K. Lin, F. Bénard, D. M. Perrin, *Angew. Chem. Int. Ed.*, **2014**, *53*, 11876-11880; *Angew. Chem.* **2014**, *126*, 12070–12074. c) Z. Liu, K.-S. Lin, F. Bénard, M. Pourghiasian, D. O. Kiesewetter, D. M. Perrin, X. Chen, *Nat. Protoc.* **2015**, *10*, 1423-1432. d) K. Chansaenpak, H. Wang, M. Wang, B. Giglio, X. Ma, H. Yuan, S. Hu, Z. Wu, Z. Li *Chem. Eur. J.* **2016**, *22*, 12122 – 12129. e) H. Hong, L. Zhang, F. Xie, R. Zhuang, D. Jiang, H. Liu, J. Li, H. Yang, X. Zhang, L. Nie, Z. Li, *Nat. Commun.* **2019**, *10*, 989-996.
- [37] a) B. H. Rotstein, S. H. Liang, J. P. Holland, T. L. Collier, J. M. Hooker, A. A. Wilson, N. Vasdev, *Chem. Commun.* **2013**, *49*, 5621-5629. b) B. H. Rotstein, S. H. Liang, M. S. Placzek, J. M. Hooker, A. D. Gee, F. Dollé, A. A. Wilson, N. Vasdev, *Chem. Soc. Rev.* **2016**, *45*, 4708-4726. c) X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson, S. H. Liang, *Angew. Chem. Int. Ed.* **2019**, *58*, 2580-2605; *Angew. Chem.* **2019**, *131*, 2604–2631.
- [38] After this manuscript was submitted, a related work focused only on stable ^{13}C was reported by the group of Lundgren: D. Kong, P. Moon, E. K. J. Lui, O. Bsharat, R. Lundgren, (2020): ChemRxiv. Preprint. <https://doi.org/10.26434/chemrxiv.11899755.v1>.
-