HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2020 February 04.

Published in final edited form as:

J Am Chem Soc. 2019 January 16; 141(2): 774–779. doi:10.1021/jacs.8b12035.

Direct Carbon Isotope Exchange Through Decarboxylative Carboxylation

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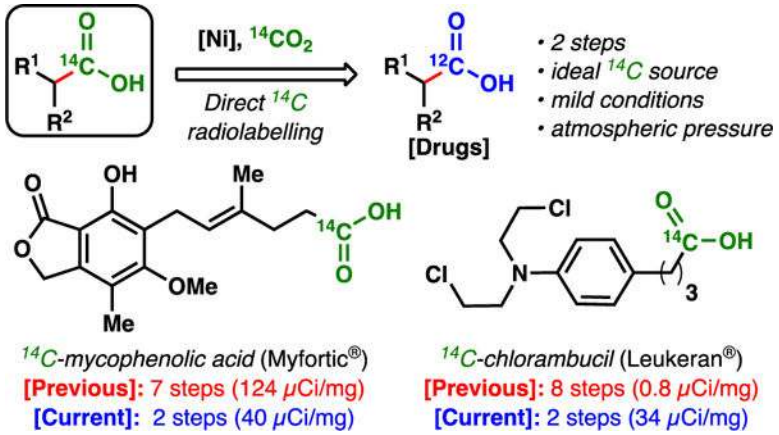
Abstract

A two-step degradation-reconstruction approach to the carbon-14 radiolabeling of alkyl carboxylic acids is presented. Simple activation via redox-active ester formation was followed by nickel-mediated decarboxylative carboxylation to afford a range of complex compounds with ample isotopic incorporations for drug metabolism and pharmacokinetic studies. The practicality and operational simplicity of the protocol was demonstrated by its use in an industrial carbon-14 radiolabeling setting.

Graphical Abstract



Successful execution of the metabolic and pharmacokinetic studies required in a modern drug development campaign is often predicated on the ability to access useful quantities of radiolabeled lead analogues.[1] The demand for ever more advanced radiolabeling techniques is illustrated by the recent reports describing the tritiation of arene-, azaarene-, amine-,

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The authors declare no competing financial interest.

amide- and thioether-containing compounds through efficient hydrogen isotope exchange (HIE) processes (Figure 1A, I).[2] As the more metabolically-stable radiolabel, carbon-14 is heavily relied upon during all stages of drug development, including (pre)clinical absorption, distribution, metabolism, and excretion (ADME) studies.[3] In contrast to tritium, the synthetic methods for introduction of this isotope have remained relatively inefficient due to the difficulties associated with C–C bond formation.[4] Still, the ubiquity of carboxylic acids in nature has made them a prime target for carbon-14 radiolabeling, particularly in the synthetically favorable degradation-reconstruction strategies that begin from the unlabeled target compound (Figure 1A, II).[1a,5] However, current approaches rely on harsh conditions to facilitate the common activation/substitution/hydrolysis sequence, thereby severely limiting their application.[6] Inspired by the synthetic utility of HIE, we set out to invent a method to radiolabel alkyl carboxylic acids through direct carbon isotope exchange, wherein the isotope is incorporated in the final step. We envisaged an expedient sequence consisting of mild formation of a redox-active ester[7] (RAE) followed by a chemoselective nickel-mediated reductive decarboxylative carboxylation (Figure 1A, III).[8] As a further advantage, the use of carbon-14 labeled CO_2 would maximize the radiochemical yields and minimize the handling of radioactive intermediates.[9] A concern with the use of RAE substrates is the undesired partial reformation of the unlabeled target compound via cleavage or incomplete $^{12}CO_2/^{14}CO_2$ exchange (Figure 1B). However, while mechanistically limiting the specific activity, the levels of incorporation should be more than sufficient for practical use in ADME studies.[10]

The desire to evaluate the proposed methodology using cheap and readily available $^{12}CO_2$ uncovered an interesting problem: how does one quantify product formation in the presence of an identical byproduct? Different mechanistic solutions (Scheme 1A) were evaluated to address this issue. Whereas methods relying upon diastereomeric inversion (Scheme 1A, I)[7l] and nickel chain-walking[11] (Scheme 1A, II) afforded irreproducible results and no product formation, respectively, the use of cyclopropylmethyl substrate **7** enabled reproducible differentiation between the carboxylated and hydrolyzed products **9** and **10** via radical-induced ring opening (Scheme 1A, III). With a proof-of-concept in hand, RAE **11** was chosen as a model substrate and subjected to carboxylation by non-radioactive $^{13}CO_2$ as a surrogate for $^{14}CO_2$ (a summary of reaction optimization is depicted in Scheme 1B). Some initial difficulties encountered using a traditional pressure vessel were circumvented by switching to Unchained Labs deck screening pressure reactor, which provided reliable and reproducible results (see the Supporting Information for further details). Screening of the reaction parameters led to the formation of acid **[^{13}C]-12** in 42% yield with 19% $^{13}CO_2$ incorporation (entry 1).[12] If this level of incorporation could be realized using $^{14}CO_2$, a specific activity of 66 μCi/mg would be achieved. Lowering both the pressure and the nickel/ligand loading had a deleterious effect upon the isotopic incorporation (entries 2–3) and control reactions showed the nickel source, ligand and reductant were all essential for product formation and/or $^{13}CO_2$ incorporation (entries 4–6). Photoinduced electron transfer processes were also investigated but failed to provide the product in meaningful yields and isotopic incorporations (see the Supporting Information).

With an optimized set of conditions in hand, the scope of the reaction was explored with a series of primary, secondary, and tertiary RAEs (Scheme 2A). To gauge the potential application of the methodology for preclinical and clinical ADME studies, the observed $^{13}CO_2$ incorporations were converted to the theoretical specific activities which would result from using $^{14}CO_2$. With the recent advent of ultrasensitive analytical techniques, the bottleneck for specific activity in radiolabeling clinical human ADME studies has shifted to analysis of radiochemical purity. Industrial standard HPLC with in-line radioactivity detection requires 10 μCi/mg or higher to allow for sufficient disintegrations per minute for precise radiochemical analysis while maintaining column performance.[13] Lower isotopic incorporations can be analyzed by liquid scintillation counting, microplate scintillation or accelerator mass spectrometry, but these are more resource-intensive techniques. In general, higher incorporations over 20 μCi/mg are required for early preclinical animal ADME studies.[14] Gratifyingly, primary and secondary RAEs generated from acids **14**–**22** bearing a variety of functional groups including ketone, ester, protected amines and amides and a phenol were all well tolerated, with excellent isotopic incorporations suitable for all preclinical and clinical ADME studies. In the case of such radiolabeling studies, isolated chemical yields are less important than the speed of preparation and cost of the isotope source. Chemoselectivity of the process is also critical so as to avoid extra functional group/protecting group manipulations on radioactive material. Thus, the mild degradation-reconstruction approach described here in which the unlabeled target compound is readily available from preliminary scale-up is ideal. Compound **23** bearing additional functionality in an epoxide and free alcohols was formed with isotopic incorporation that would be sufficiently high for in-line HPLC purity analysis for use in carbon-14 clinical ADME studies. While secondary acids **19**, **21**[15] and **22** were formed with excellent isotopic incorporations, no incorporation was observed for tertiary acid **24**.

With the scope and practicality of the reaction established, it was implemented in an industrial radiosynthetic setting using $^{14}CO_2$. Although only a small amount of pressure was required under the optimized conditions with $^{13}CO_2$, efforts to further increase operational simplicity, cost effectiveness and safety were made through consideration of Henry's law.[16] Gratifyingly, implementation of an initial temporary cryogenic period provided a balance of CO_2 solubility and chemical reactivity at atmospheric pressure. This facilitated the development of a practical laboratory setup using standard vacuum manifold techniques to allow safe application of $^{14}CO_2$ to the process (see the Supporting Information for further details). Using only 5.5–32 equivalents of $^{14}CO_2$ (depending on the use of an ampule or *in situ* formation from [^{14}C]-$BaCO_3$), a selection of RAEs underwent decarboxylative carboxylation to afford the carbon-14 radiolabeled products with sufficient levels of isotopic incorporation for general use in preclinical and clinical ADME studies (Scheme 2B). Interestingly, the inverted α-diastereomer of **21** was isolated with a significantly higher specific activity than the corresponding β-product, presumably due to the intermediacy of a radical species (as proposed in Scheme 1A, I). To further explore the advantages of this methodology, it was compared to two previous radiosyntheses of biologically important compounds (Scheme 3). Parnes and co-workers previously reported a seven-step degradation-reconstruction approach to [^{14}C]-mycophenolic acid **25** which relied upon a decarboxylative halogenation/[^{14}C]-cyanation sequence to introduce the radiolabel in the

antepenultimate step.[17] In stark contrast, the developed procedures for $^{13}CO_2$ and $^{14}CO_2$ both afforded the product in just two steps, one (radio)labeled, with sufficient isotopic incorporation for all ADME studies. In the synthesis of [^{14}C]-chlorambucil **26**, Madelmont and co-workers introduced the radiolabel in the first step of an eight-step sequence via [^{14}C]-cyanation of alkyl bromide **27** using low specific activity K^{14}CN.[18] In contrast, decarboxylative carboxylation afforded the product in an expedient two-step sequence with excellent $^{13}CO_2$/$^{14}CO_2$-incorporation. The results bode well for the widespread adoption of this method for carbon-14 radiosynthesis of ubiquitous alkyl carboxylates.[19]

In summary, a decarboxylative carboxylation method has been developed for the efficient carbon-14 radiolabeling of carboxylic acid containing compounds. Conceptually analogous to H/D and H/T isotopic exchange, the ^{12}C/^{13}C and ^{12}C/^{14}C isotopic exchange represents an expedient and operationally simple alternative to existing radiosynthetic methods that rely on inconvenient multi-step strategies. The utility of the method is self-evident through its field testing in an established radiosynthetic pharmaceutical setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Financial support for this work was provided by Bristol-Myers Squibb and NSF GRFP (J.N.D.). We are grateful to Dr. Dee-Hua Huang and Dr. Laura Pasternack (TSRI) for assistance with nuclear magnetic resonance spectroscopy. We also thank Dr. Byron K. Peters and Dr. Yu Kawamata for helpful advice and discussion.

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19. An elegant Pd-catalyzed approach to direct carbon isotope exchange was reported as this work was submitted: Gauthier DR Jr.; Rivera NR; Yang H; Schultz DM; Shultz CS Palladium-Catalyzed Carbon Isotope Exchange on Aliphatic and Benzoic Acid Chlorides. J. Am. Chem. Soc 2018, DOI: 10.1021/jacs.8b09808. Orthogonal to our process, the method is broad in scope providing access to labeled alkyl and benzoic acids. However, it relies upon activation of expensive carbon monoxide precursors ($962/g for 13COgen as compared to $3.5/g for 13CO2 from Sigma Aldrich).

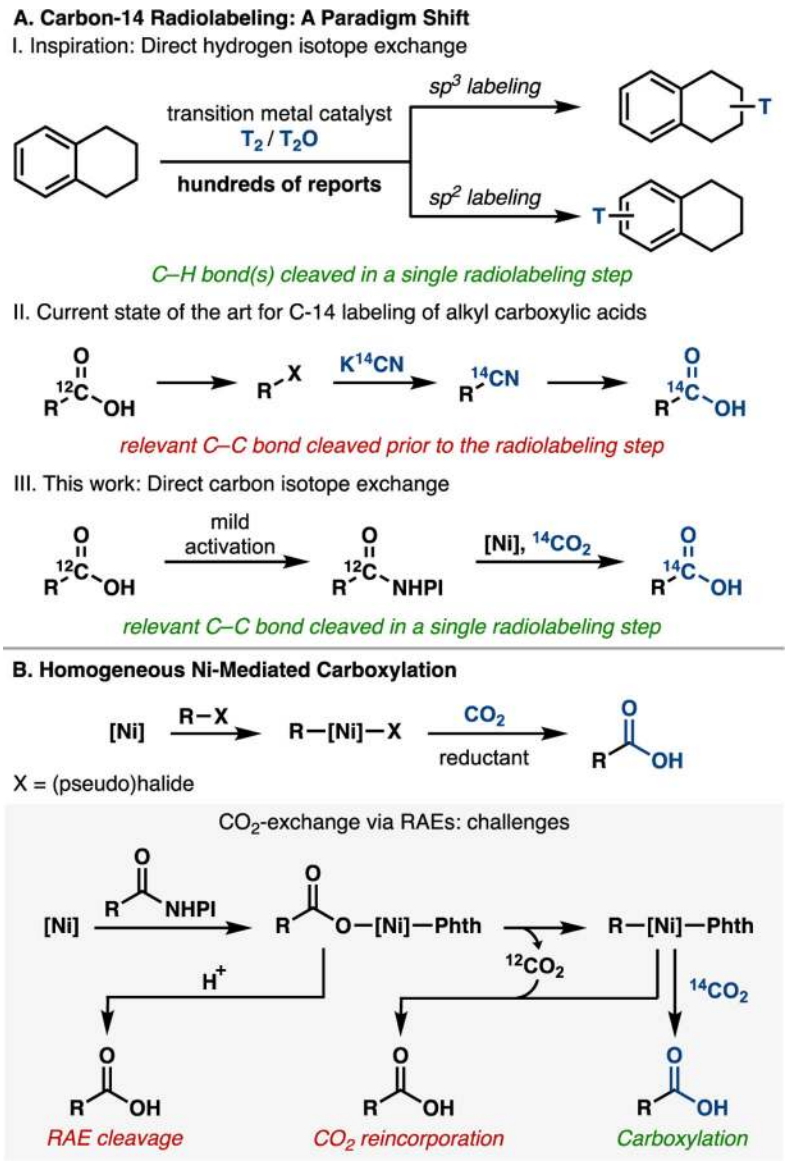
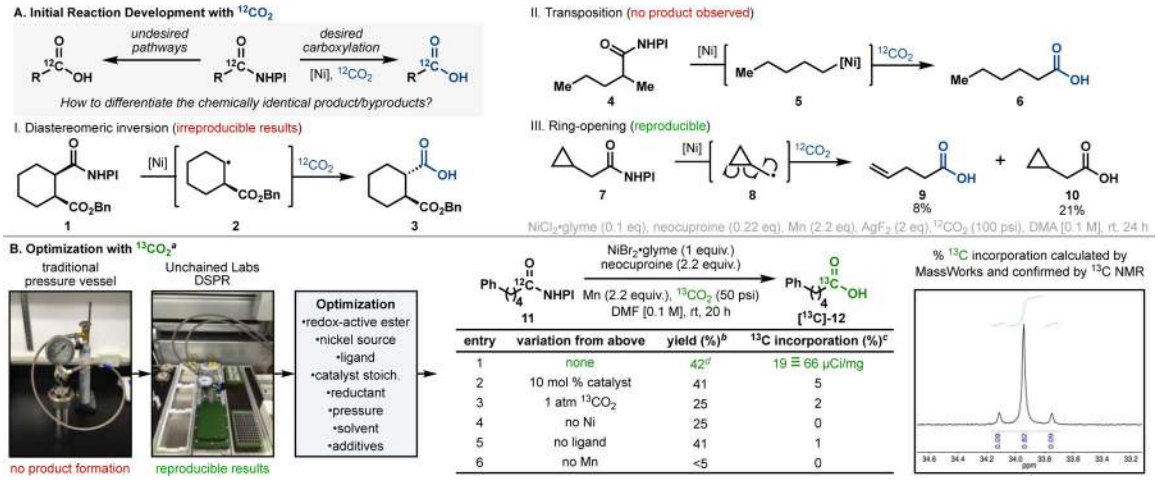


Figure 1.

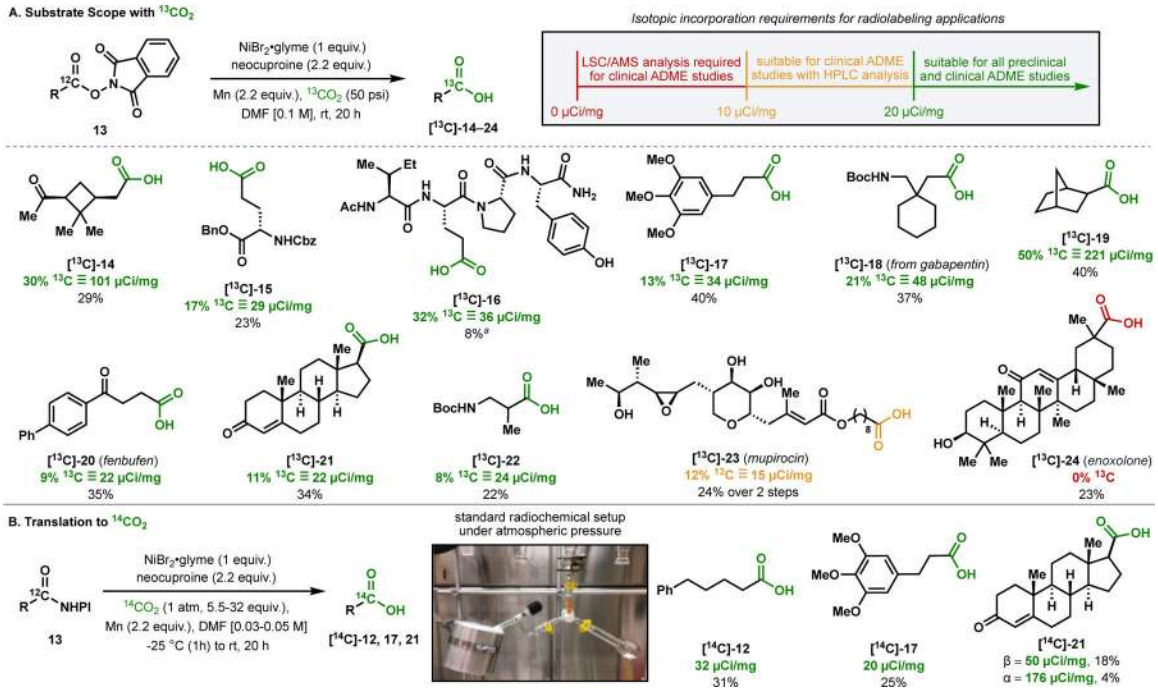
(A) A new approach to carbon-14 radiolabeling inspired by hydrogen isotope exchange. NHPI = N-hydroxyphthalimide. (B) Potential pitfalls of Ni-mediated carboxylation of redox-active ester substrates.



entry	variation from above	yield (%)[b]	^{13}C incorporation (%)[c]
1	none	42[d]	19 ≡ 66 μCi/mg
2	10 mol % catalyst	41	5
3	1 atm $^{13}CO_2$	25	2
4	no Ni	25	0
5	no ligand	41	1
6	no Mn	<5	0

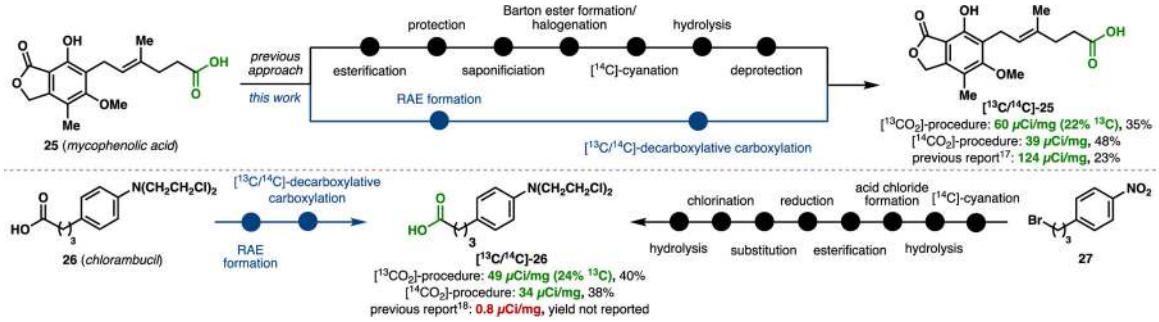
Scheme 1.

(A) Initial investigation with $^{12}CO_2$. (B) Development, optimization and analysis with $^{13}CO_2$. [a]0.1 mmol. [b]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [c]Calculated from high-resolution mass spectrometry data in MassWorks (Cerno Bioscience) and confirmed by ^{13}C NMR. [d]Isolated yield. DSPR = deck screening pressure reactor.



Scheme 2.

(A) Scope of the Ni-mediated decarboxylative carboxylation with $^{13}CO_2$. Reaction conditions: RAE (1.0 equiv.), NiBr$_2$•glyme (1.0 equiv.), neocuproine (2.2 equiv.), Mn (2.2 equiv.), $^{13}CO_2$ (50 psi), DMF (0.1 M), rt, 20 h. [a]^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. LSC = liquid scintillation counting, AMS = accelerator mass spectrometry, HPLC = high-performance liquid chromatography. (B) Translation to a $^{14}CO_2$ radiochemistry setup. Reaction conditions: RAE (1.0 equiv.), NiBr$_2$•glyme (1.0 equiv.), neocuproine (2.2 equiv.), Mn (2.2 equiv.), $^{14}CO_2$ (1 atm, 5.5–32 equiv.), DMF (0.03–0.05 M), −25° C (1h) to rt, 20 h.



Scheme 3.

Comparative studies on the synthesis of biologically-relevant compounds. Reactions conditions as in Scheme 2.