Carbon Isotope Exchange (CIE) with Labeled Carbon Source

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Apr 23, 2021

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2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

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3 Summary and Outlook

Introduction

1 Introduction

Isotope labeling technology

Non-radioisotope labeling — MS/NMR detection

Radioisotope labeling — ADME studies, PET imaging, etc

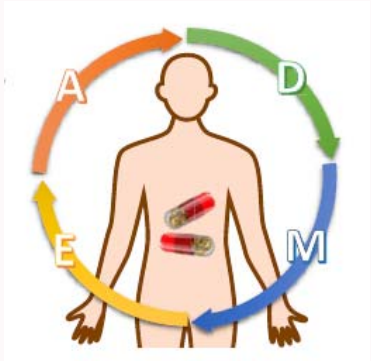
Tracing organic compounds
- Disease diagnosis
- Agrochemicals
- Environmental fate
- Pharmacokinetic studies
- ……

Absorption

Distribution

Metabolism

Excretion



Positron **E**mission **T**omography (PET)

1 Introduction

^{11}C

- radioactive
- $t_{1/2}$ = 20.33 min
- PET imaging

^{12}C

^{13}C

- non-radioactive
- MS/NMR detection

^{14}C

- radioactive
- $t_{1/2}$ = 5730 years
- ADME studies

(Commonly used carbon isotopes)

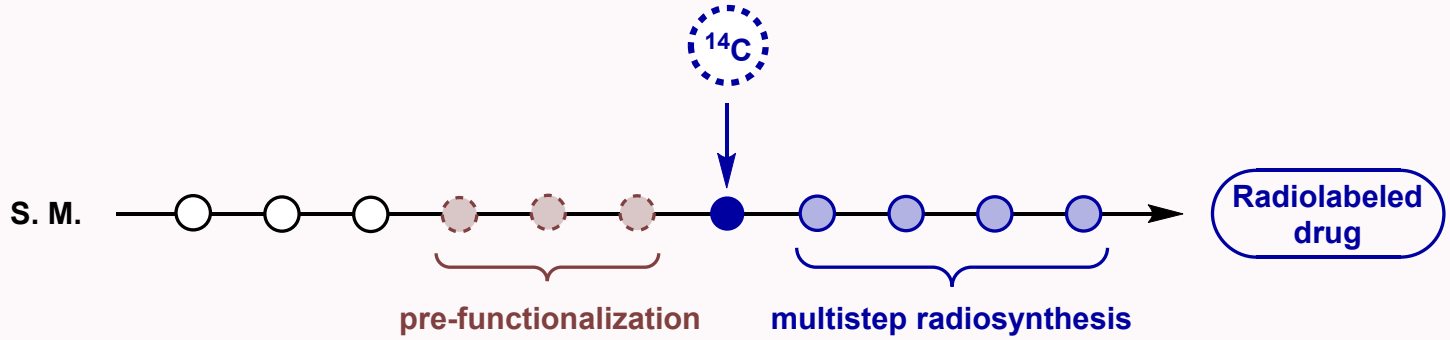
Introduction of carbon isotopes is still challenging, especially radioactive ^{11}C and ^{14}C.

Cost and radioactive waste must be taken into account seriously.

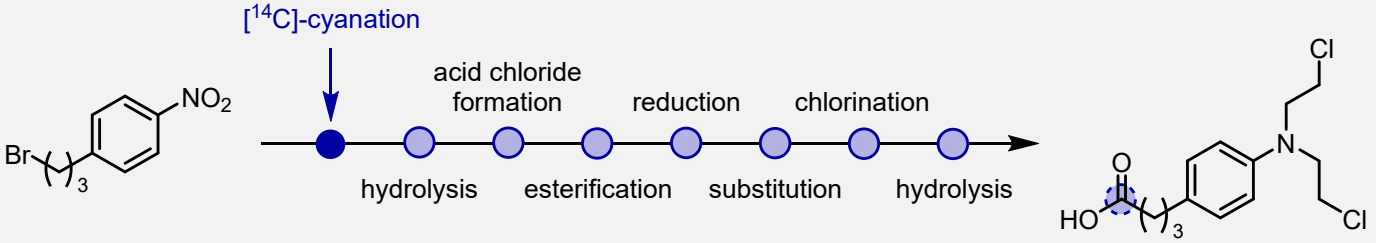
1 Introduction

Traditional approaches for the introduction of carbon isotopes
Take [^{14}C] for example:

(1) *De novo* synthesis



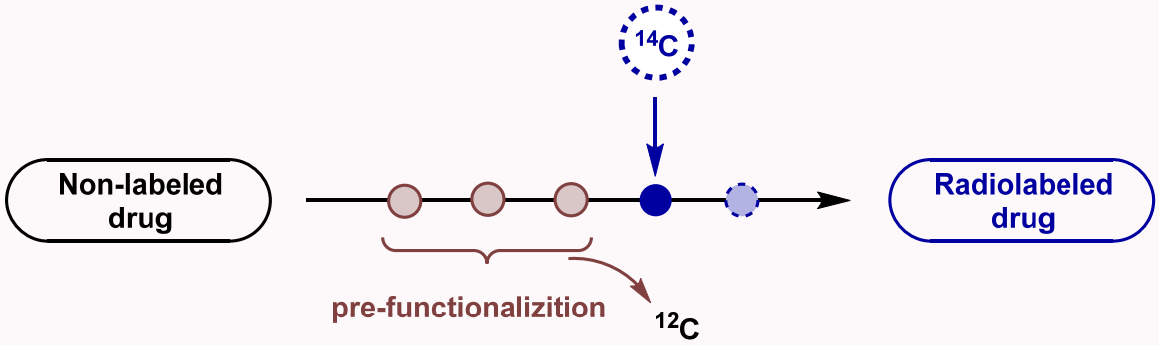
- Time-consuming
- High costs
- Generating large amounts of radioactive waste (extremely difficult and expensive to dispose of)



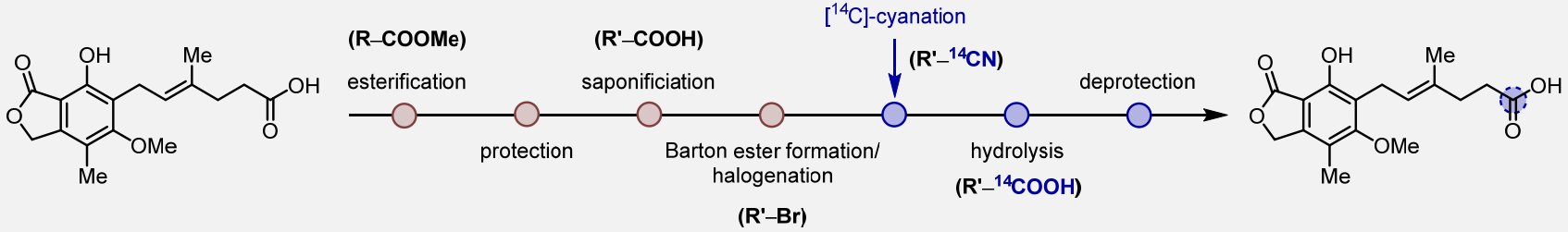
Moreau, J.; Madelmont, J.-C. *J. Labelled Compd.* **1974**, *10*, 271-281.

1 Introduction

(2) Degradation-reconstruction strategy



- Reducing the production of radioactive waste
- Time-consuming

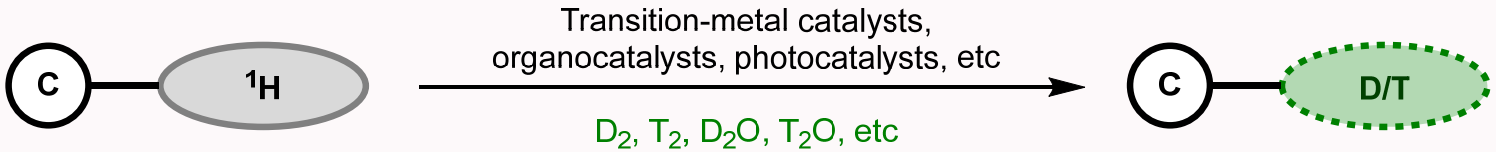


Huang, G. T.; Parnes, H. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 449-456.

1 Introduction

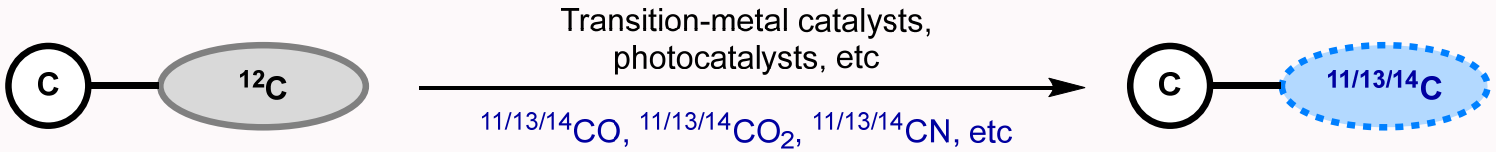
➢ Conceptual development: Carbon Isotope Exchange (CIE)

Hydrogen Isotope Exchange (HIE): well-established



☐ Hundreds of reports
☐ Broad scope of application
☐ Multiple incorporation of isotopes
☐ Mild reaction conditions

Carbon Isotope Exchange (CIE): ?



For selected reviews on HIE, see:
(1) Atzrodt, J.*; Derdau, V.*; Fey, T.*; Zimmermann, J.* *Angew. Chem. Int. Ed.* **2007**, *46*, 7744-7765.
(2) Atzrodt, J.*; Derdau, V.*; Kerr, W. J.*; Reid, M.* *Angew. Chem. Int. Ed.* **2018**, *57*, 3022-3047.

1 Introduction

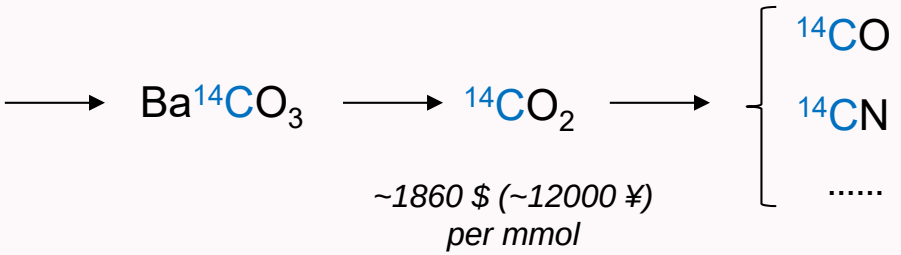
➢ **The challenges of CIE:**

(1) Carbon-carbon bond cleavage *(activation)*

(2) Carbon-carbon bond reconstruction *(avoiding degradation)*

(3) Limited collection of commercially available ^{14}C raw materials

nuclear reactors



Industrial production of [^{14}C] raw materials

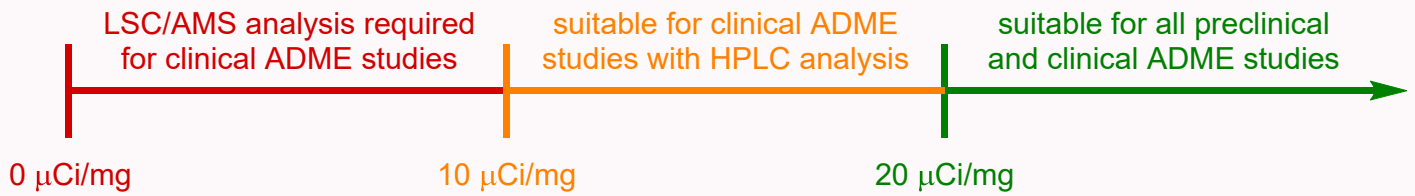
Voges, R.; Heys, J. R.; Moenius, T. *Preparation of compounds labeled with tritium and carbon-14*, Wiley, Hoboken, 2009.

Carbon Isotope Exchange (CIE) with Labeled Carbon Source

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

Instructions before starting

- For ^{14}C labeling:



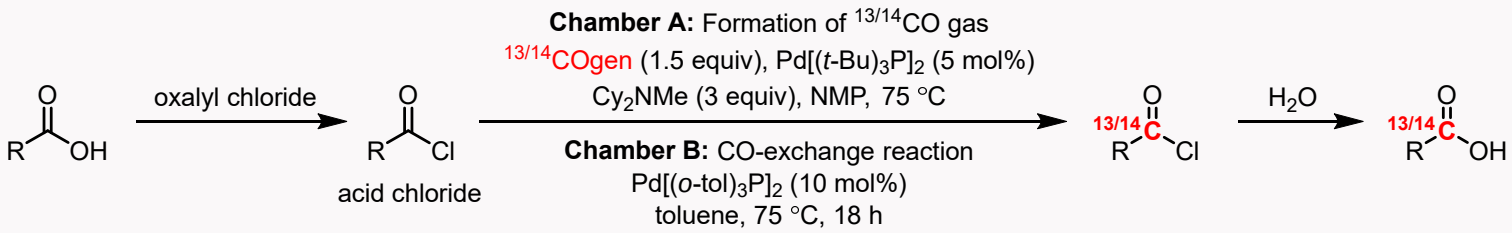
- For optimization and scope studies, [^{13}C] is usually used as a surrogate for precious [$^{11/14}C$].

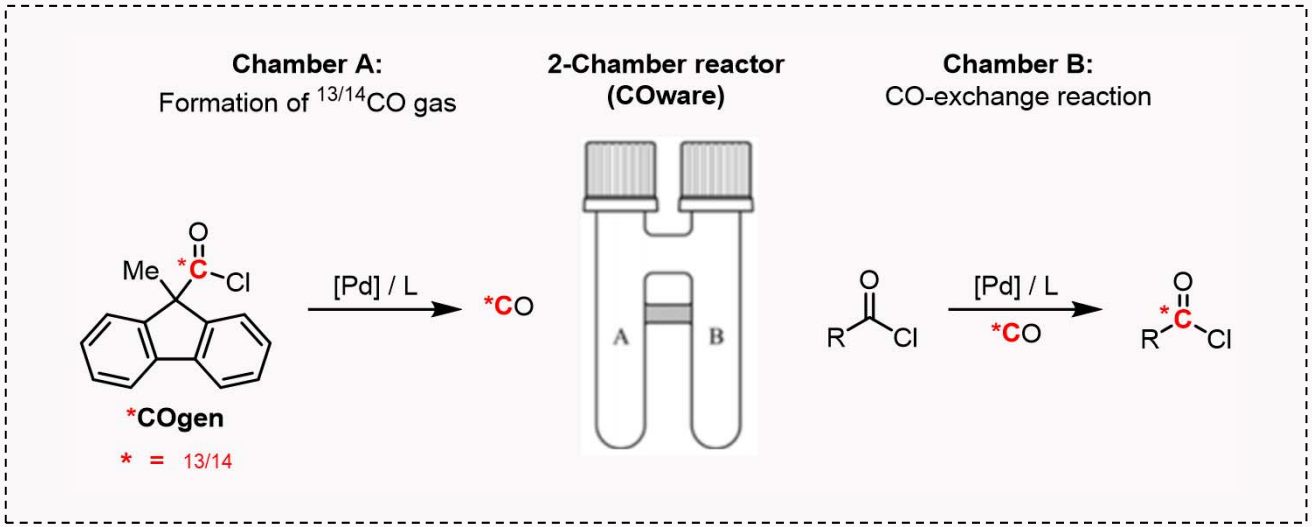
Activity: the number of atoms that a radioactive element or isotope decays per second. Units: bq, Ci (1 bq = 1 s^{-1}, 1 Ci = 3.7 × 10^{10} bq)
Specific activity (SA): radioactivity per unit mass of a stated element or compound. Units: mCi/mmol, μCi/mg, Mbq/mmol, etc.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

2.1 CIE with Labeled CO

Gauthier, Jr., 2018

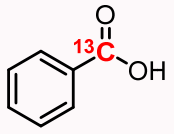




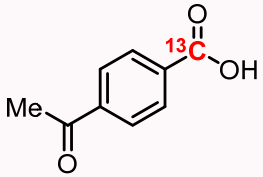
Gauthier, D. R., Jr.* et al. *J. Am. Chem. Soc.* **2018**, *140*, 15596-15600.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

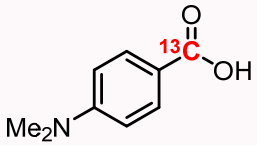
Selected examples:



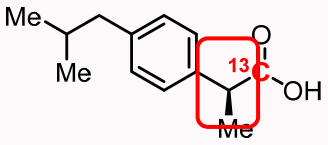
41% (88% yield)



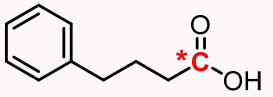
30% (90% yield)



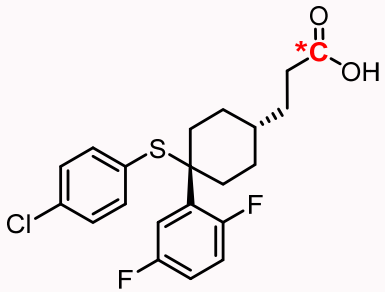
29% (82% yield)



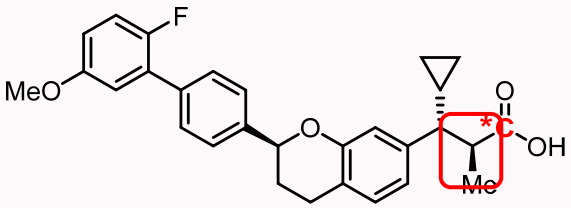
(S)-Ibuprofen (98% ee)
32% (86% yield)



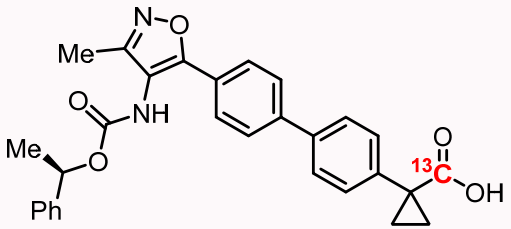
^{13}C: 48% (90% yield)
^{14}C: 27% (16% yield)
SA = 16.8 mCi/mmol



^{13}C: 53% (67% yield)
^{14}C: 37% (20% yield)
SA = 23.3 mCi/mmol



^{13}C: 43% (39% yield)
^{14}C: 40% (24% yield)
SA = 25.2 mCi/mmol

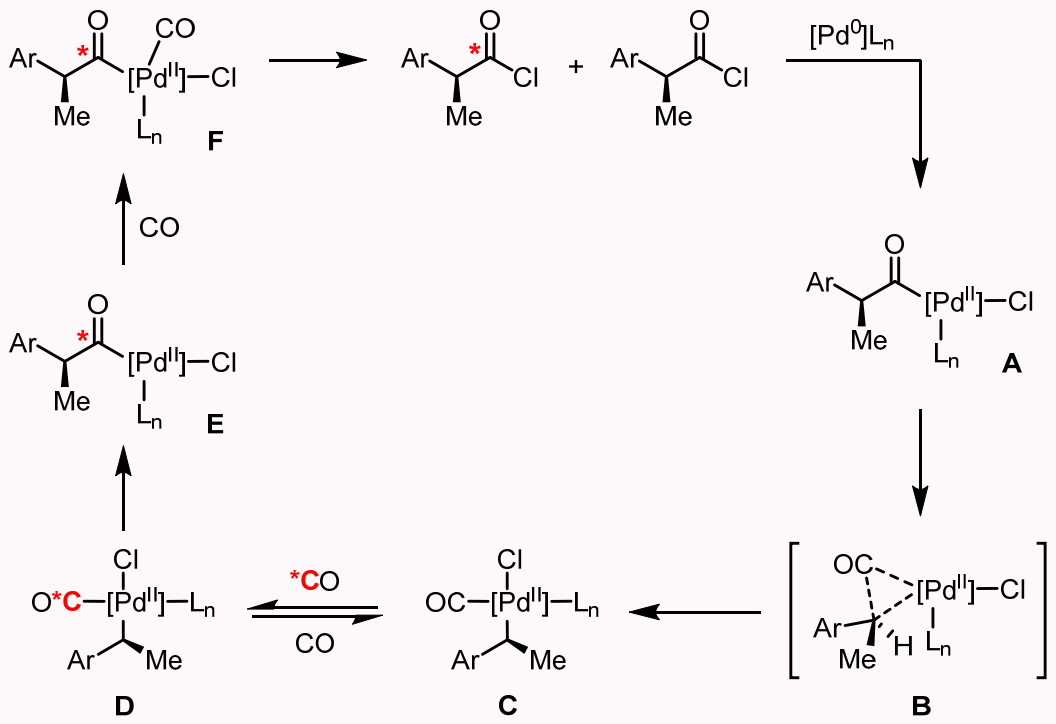


45% (30% yield)

Gauthier, D. R., Jr.* et al. *J. Am. Chem. Soc.* **2018**, *140*, 15596-15600.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

The proposed mechanism:

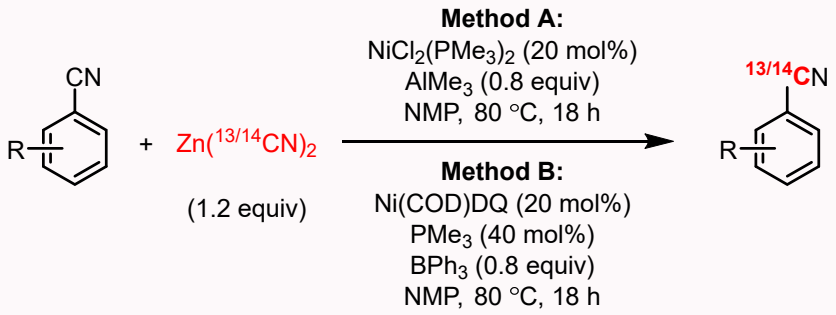


Gauthier, D. R., Jr.* et al. *J. Am. Chem. Soc.* **2018**, *140*, 15596-15600.

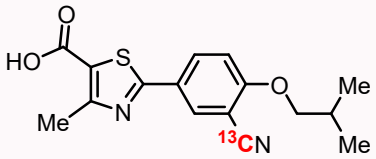
2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

2.2 CIE with Labeled Cyanide

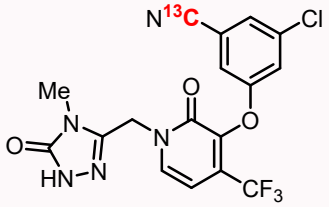
Reilly & Strotman, 2021



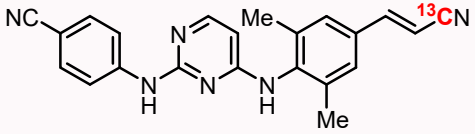
Selected examples:



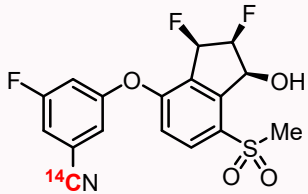
Febuxostat
45% (54% yield)



Doravirine
68% (28% yield)



Rilpivirine
53% (50% yield, *E*/*Z* = 94/6)



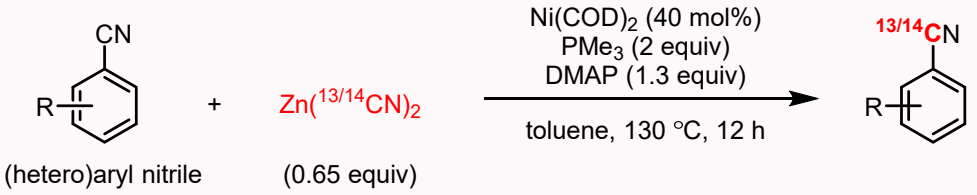
Belzutifan
[^{13}C]: 47% (89% yield)
[^{14}C]: 52%, 31.48 mCi/mmol (72% yield)

Non-labeled Belzutifan: 15 steps
No efficient route to label CN site

Reilly, S. W.*; Strotman, N. A.* et al. *J. Am. Chem. Soc.* **2021**, *143*, 4817-4823.

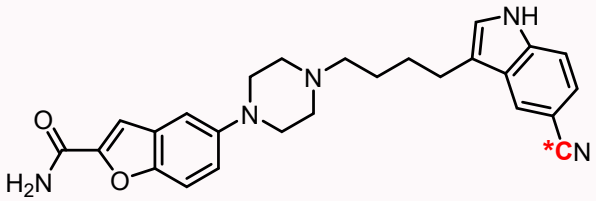
2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

Audisio, 2021



(hetero)aryl nitrile (0.65 equiv)

Selected examples:

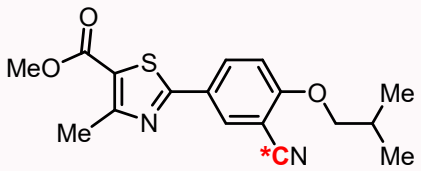


Vilazodone

[^{13}C]: 35% (91% yield)

[^{14}C]: 23%, 540 MBq/mmol (21% yield)

(14.59 mCi/mmol)

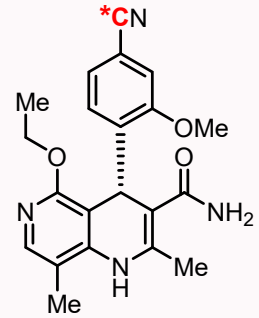


Febuxostat ester

[^{13}C]: 50% (61% yield)

[^{14}C]: 42%, 949 MBq/mmol (39% yield)

(25.65 mCi/mmol)



Finerenone

[^{13}C]: 44% (74% yield)

[^{14}C]: 45%, 1032 MBq/mmol (37% yield)

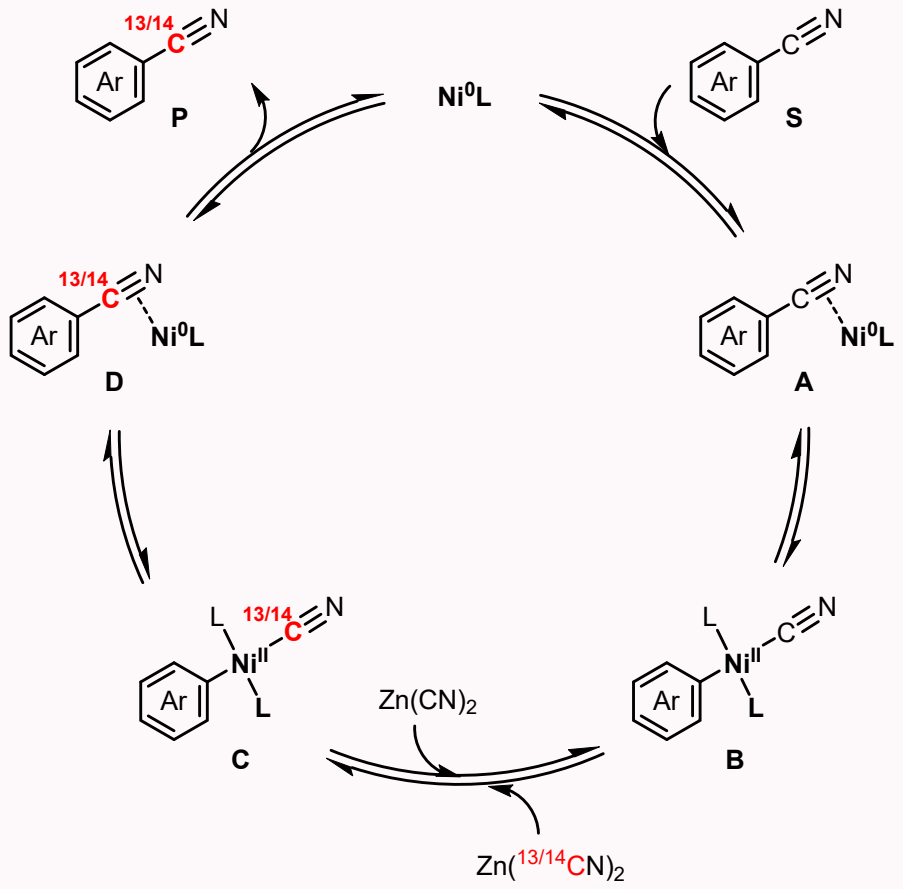
(27.89 mCi/mmol)

Previous report: multistep
117 MBq/mmol
(3.16 mCi/mmol)

Audisio, D.* et al. *J. Am. Chem. Soc.* **2021**, *143*, 5659-5665.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

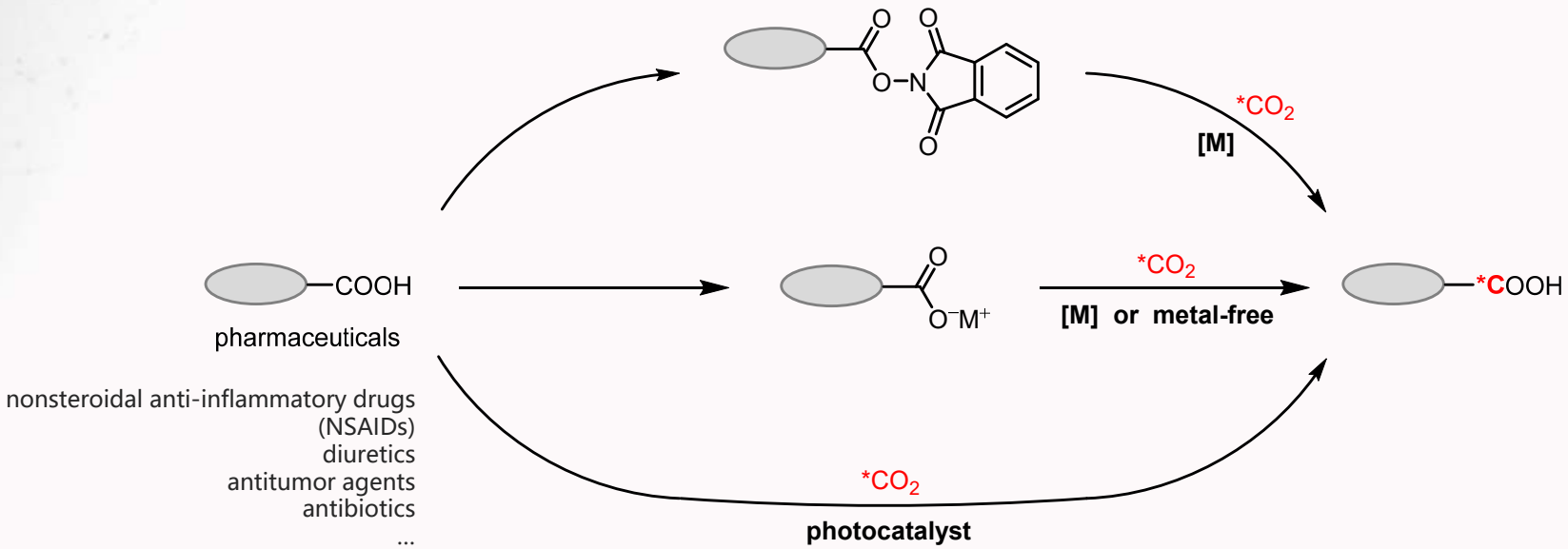
The proposed mechanism:



Audisio, D.* et al. *J. Am. Chem. Soc.* **2021**, *143*, 5659-5665.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

2.3 CIE with Labeled CO_2



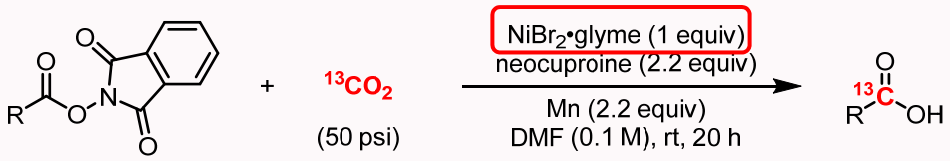
Key: activation of carboxylic acids

- Decarboxylative carboxylation of redox-active esters
- Decarboxylative carboxylation of carboxylates
- Organic photoredox catalysis

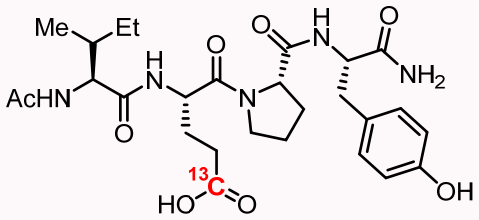
2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

■ Decarboxylative carboxylation of redox-active esters

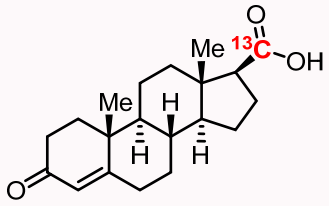
Baran, 2019



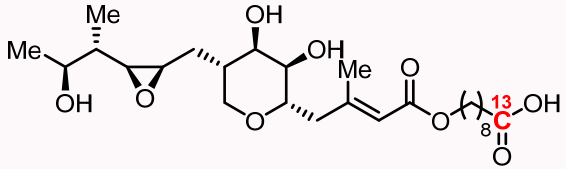
Selected examples:



32% (8% yield)



11% (34% yield)

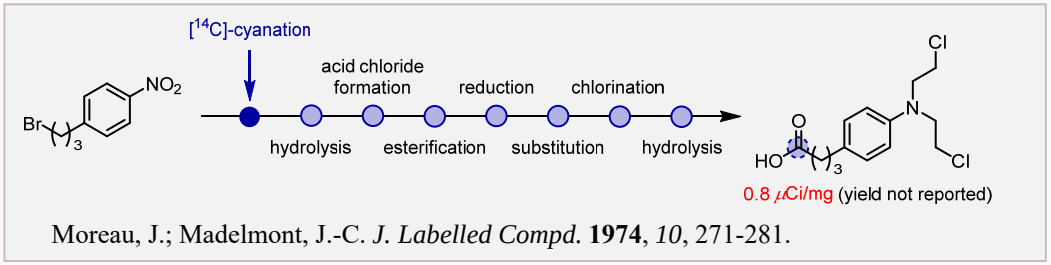


Mupirocin
12% (24% yield over 2 steps)

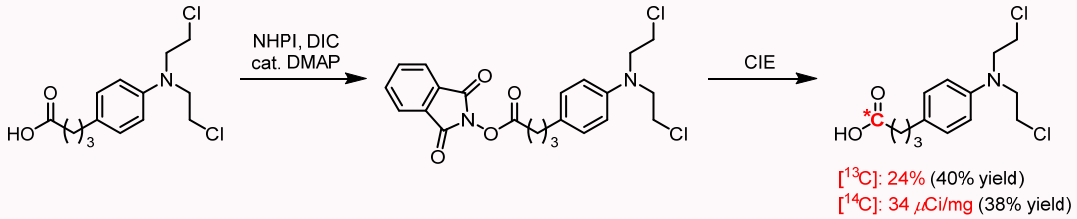
(1 psi = 6.895 kPa, 50 psi = 344.7 kPa = 3.40 atm)

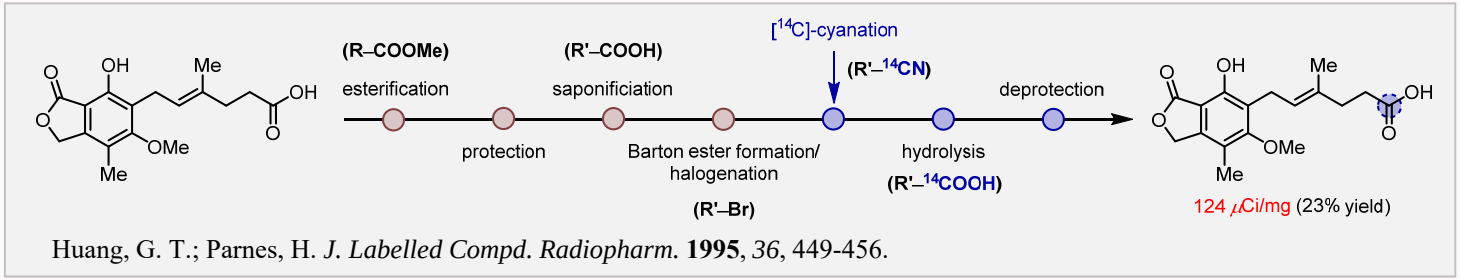
Baran, P. S.* et al. *J. Am. Chem. Soc.* **2019**, *141*, 774-779.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

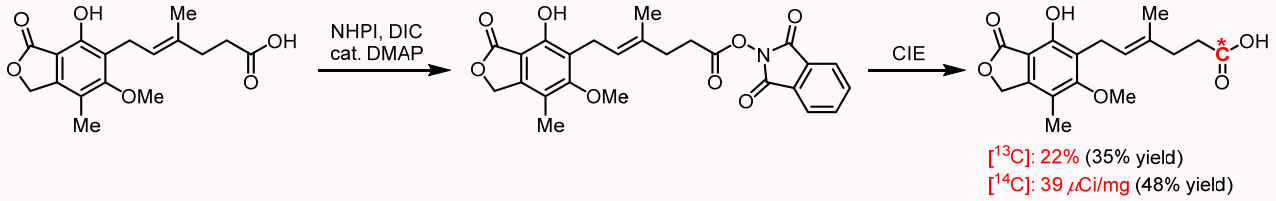


Moreau, J.; Madelmont, J.-C. *J. Labelled Compd.* **1974**, *10*, 271-281.



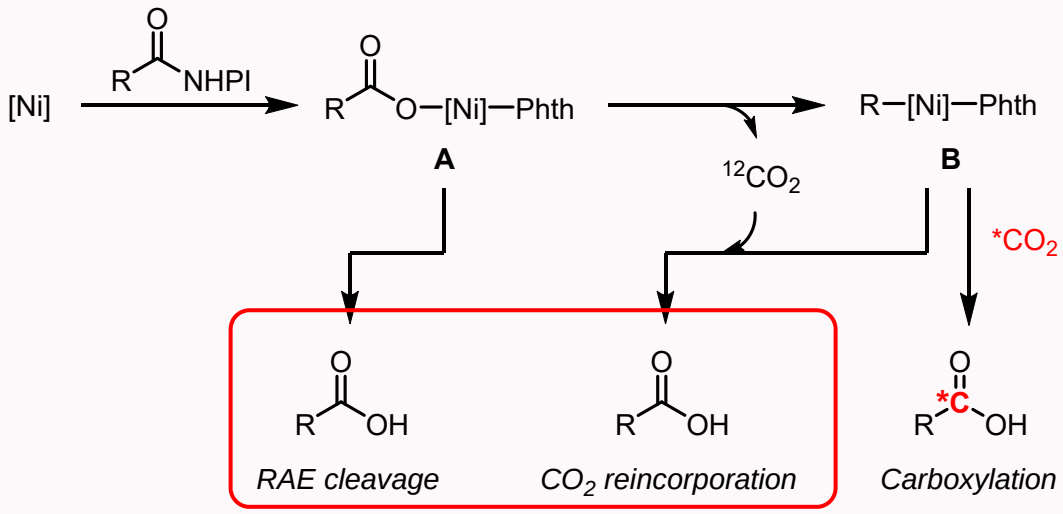


Huang, G. T.; Parnes, H. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 449-456.



Baran, P. S.* et al. *J. Am. Chem. Soc.* **2019**, *141*, 774-779.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

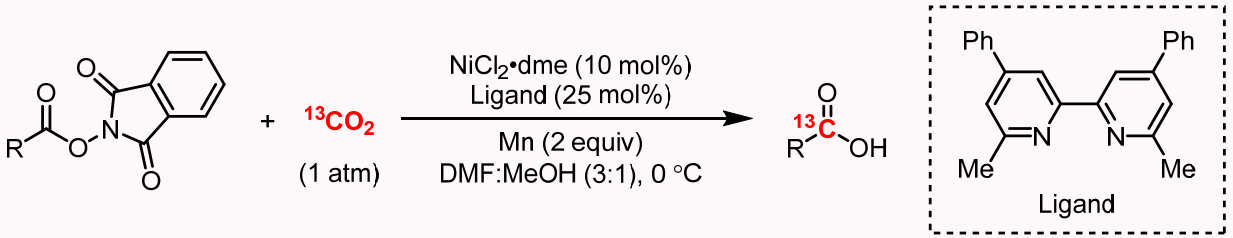


reducing isotope incorporation

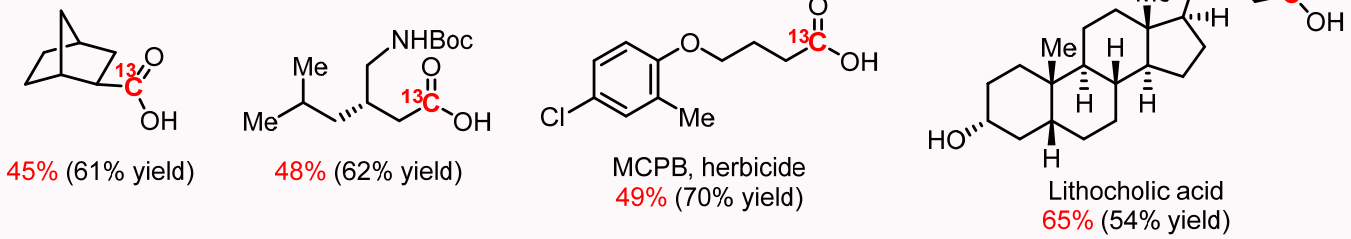
Baran, P. S.* et al. *J. Am. Chem. Soc.* **2019**, *141*, 774-779.

2 Carbon Isotope Exchange (CIE) with Labeled Carbon Source

Martin, 2019



Selected examples:



Martin, R.* et al. *ACS Catal.* **2019**, *9*, 5897-5901.