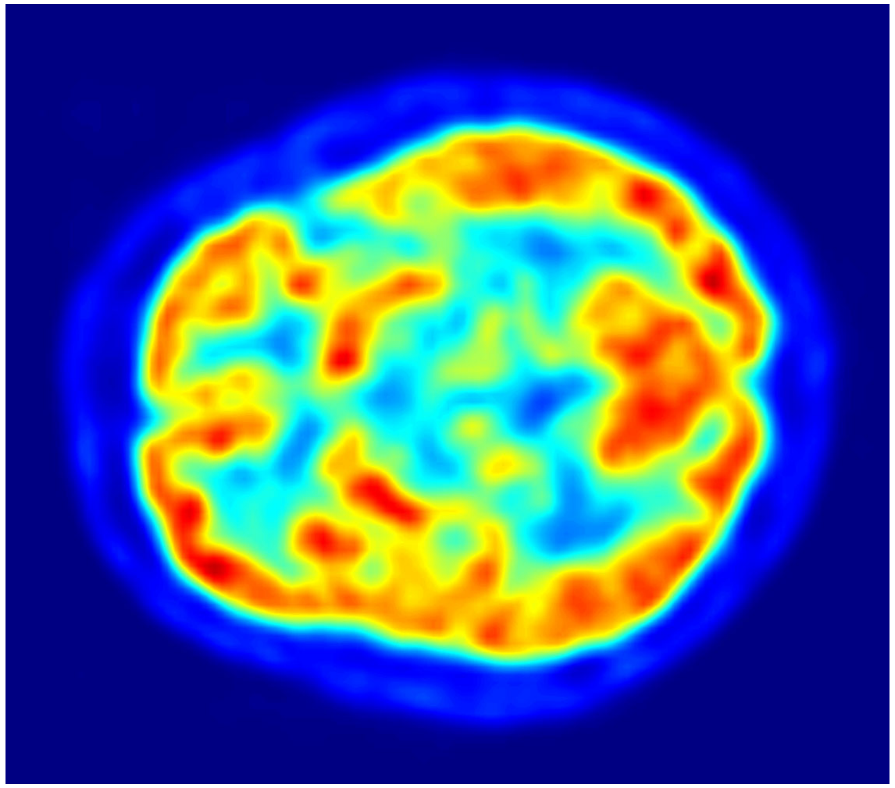
Carbon-11 Chemistry for Positron Emission Tomography

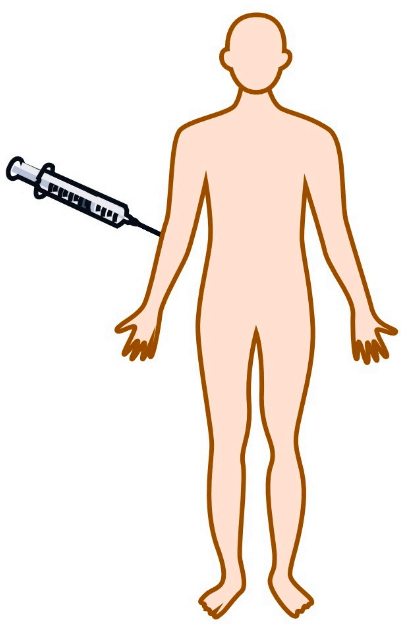


Yongliang Zhang

2020.05.28

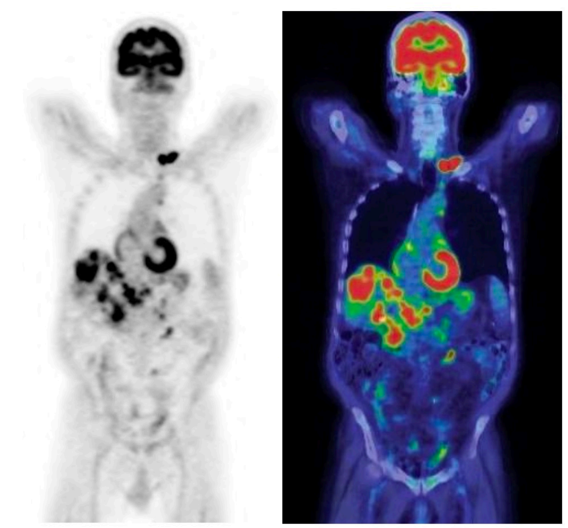
Introduction —— Positron Emission Tomography

Positron Emission Tomography (PET): a molecular imaging technique which utilizes positron-emitting radiotracers, often used to observe *in vivo* metabolic processes as an aid to diagnose various diseases.



Radiotracer delivery

PET scanning

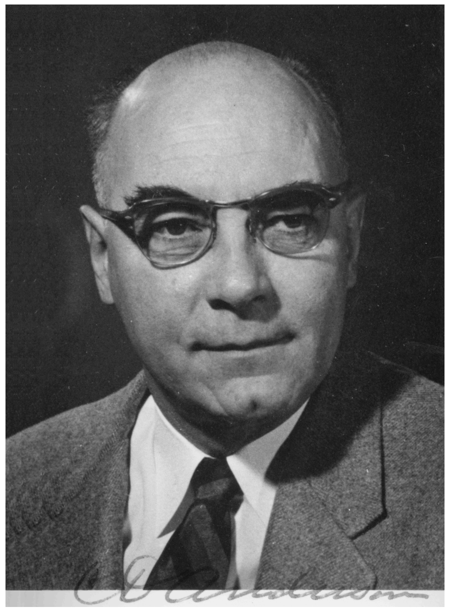


PET image with CT overlay

An estimated 2,200,800 clinical PET scans were performed in U.S. in 2019

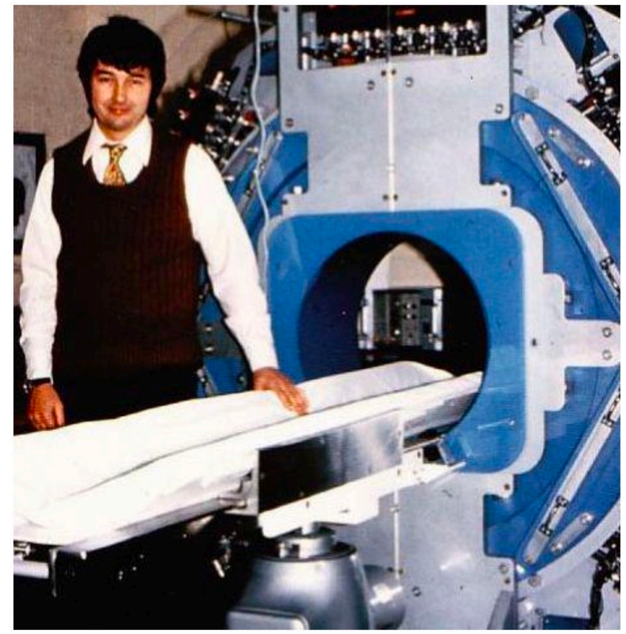
IMV Medical Information Division. 2020 PET Imaging Market Summary Report. Des Plaines, IL.

History of Positron Emission Tomography

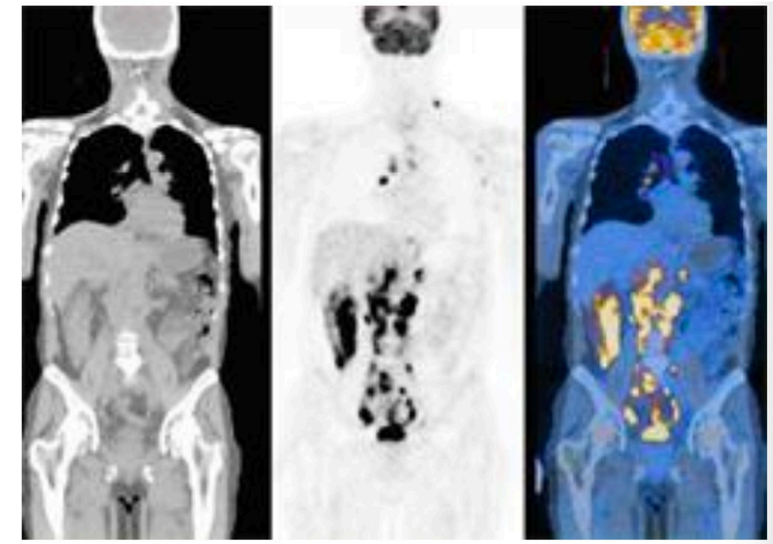


Chung-Yao Chao (1930)

1932: First observation of positrons by Carl Anderson (1936 Nobel Prize)



1975: First clinically used PET scanner developed



2000: First PET-CT prototype developed

1976: the synthesis of [11C]methyl iodide

1936: development of the cyclotron

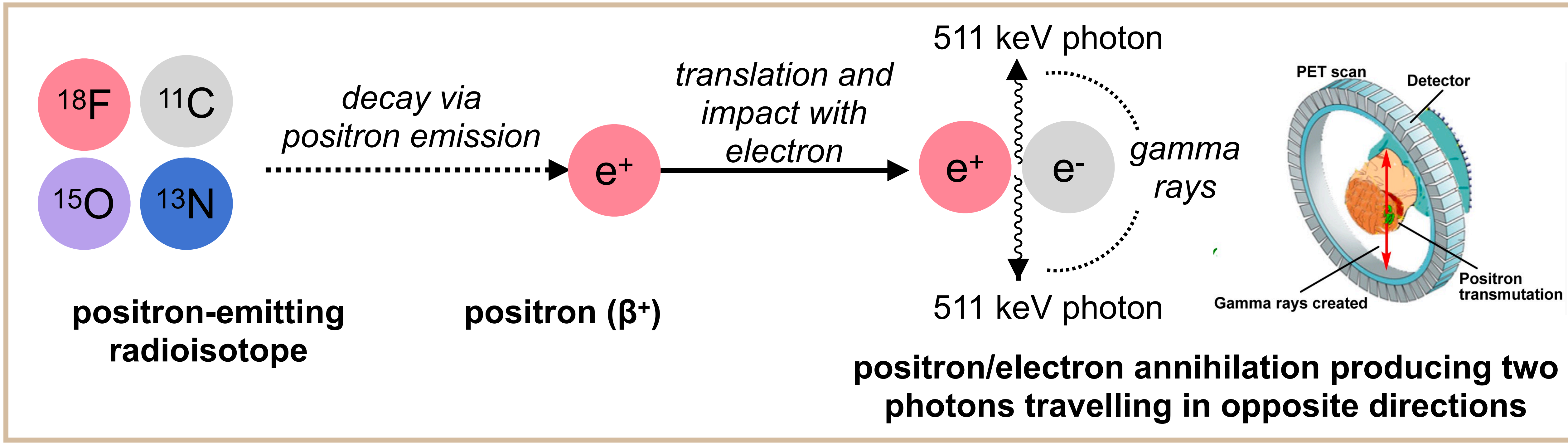
1945: first use of β+-emitting nuclides in humans using [11C]-carbon monoxide

1973: X-ray Computed Tomography (CT) developed

1997: first PET-MRI prototype developed

Portnow, L. H.; Vaillancourt, D. E.; Okun, M. S. *Neurology* **2013**, *80*, 952.

Introduction of Positron Emission Tomography

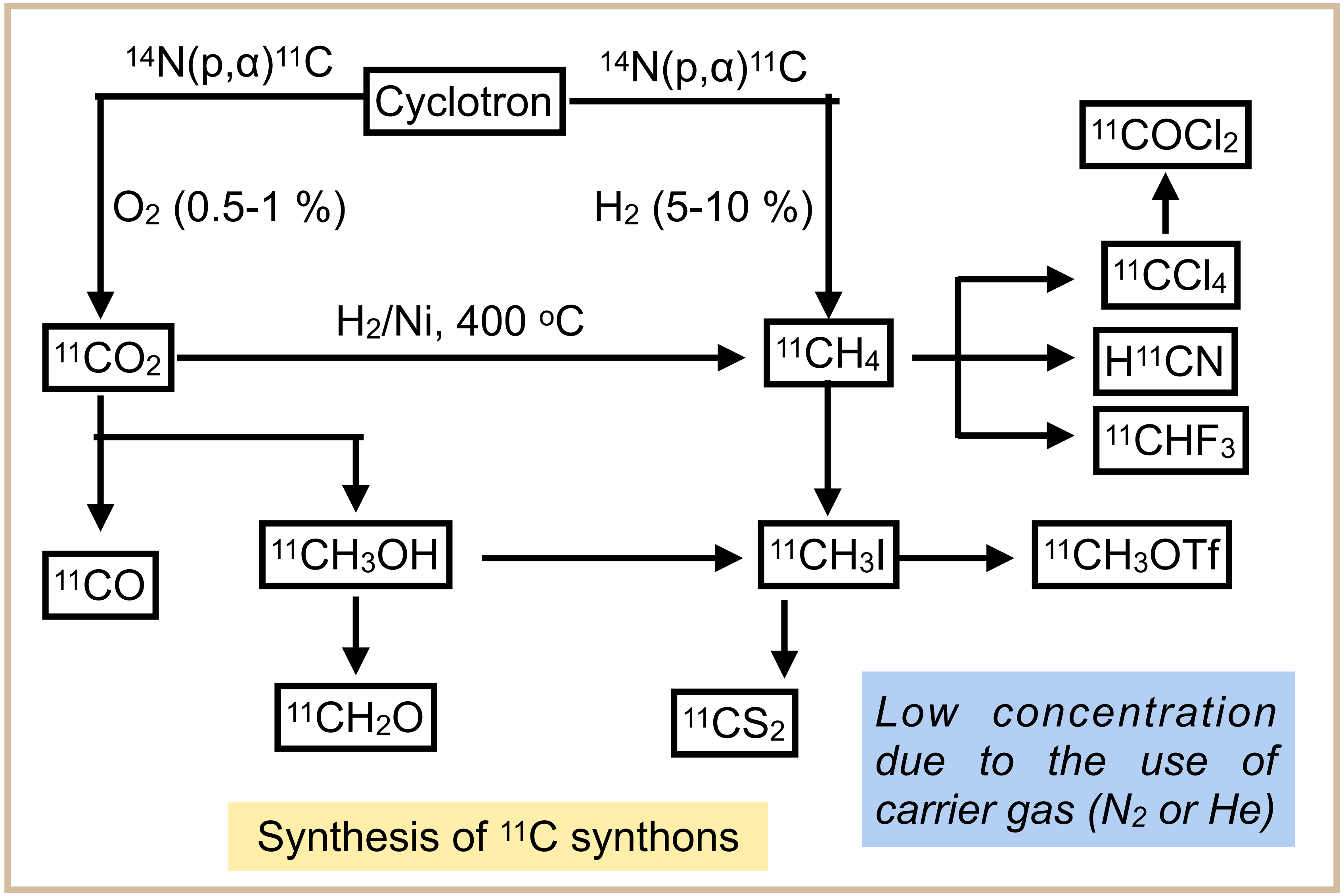


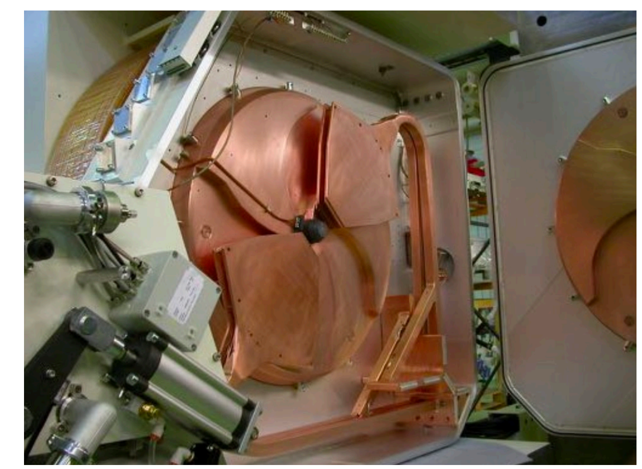
PET utilizes these generated photons to observe the location of the radionucleotide in a given system

nuclide	half-life	β^+ efficiency
^{18}F	110 min	96.7%
^{11}C	20.4 min	99.8%
^{13}N	10 min	99.8%
^{15}O	2.0 min	99.9%

Piel, M.; Vernaleken, I.; Rösch, F. *J. Med. Chem.* **2014**, *57*, 9232.

Carbon-11 of Positron Emission Tomography





The cyclotron in UChicago

The key aspects to an effective strategy for ^{11}C-based radiosynthesis:

- Introducing the carbon-11 atom as late as possible in the reaction sequence
- Minimizing the synthesis time (^{11}C, $t_{1/2}$ = 20.4 min)
- Minimizing isotopic dilution

Taddei, C., Pike, V. W. *EJNMMI radiopharm. chem.* **2019**, *4*, 25.

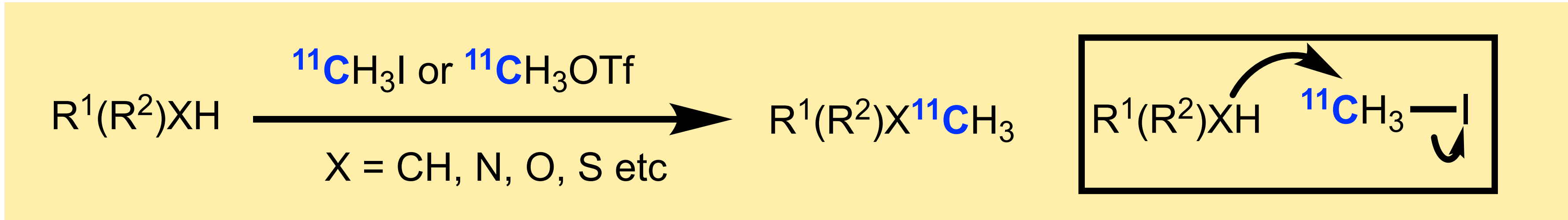
$^{11}CH_3X$ Chemistry (X = I or OTf)

$$^{11}CO_2 \xrightarrow{Ni/H_2} {}^{11}CH_4 \xrightarrow[720\text{–}740\ °C]{I_2} {}^{11}CH_3I \xrightarrow[200\ °C]{AgOTf} {}^{11}CH_3OTf$$

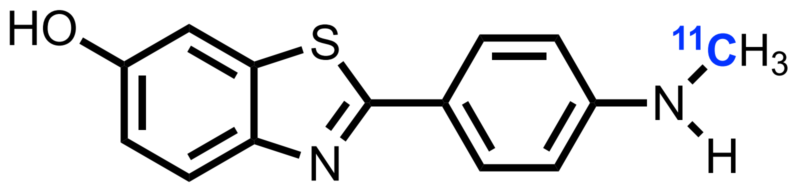
$^{11}CH_3I$ is by far the most frequently used ^{11}C-labeling agent

$^{11}CH_3X$ Chemistry (X = I or OTf)

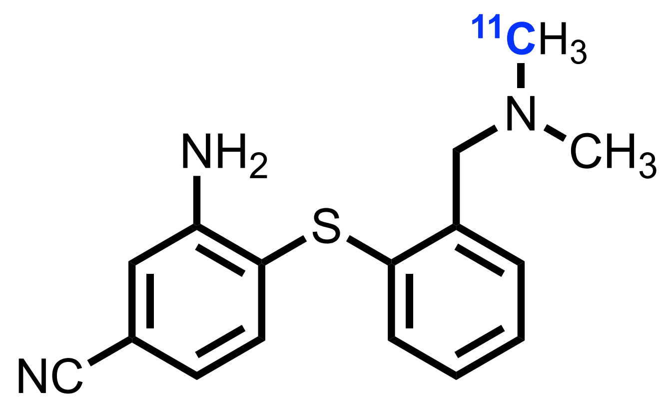
^{11}C-Methylation via nucleophilic substitution



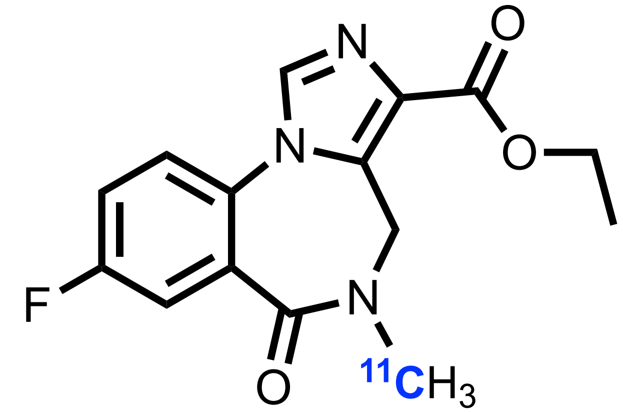
Examples



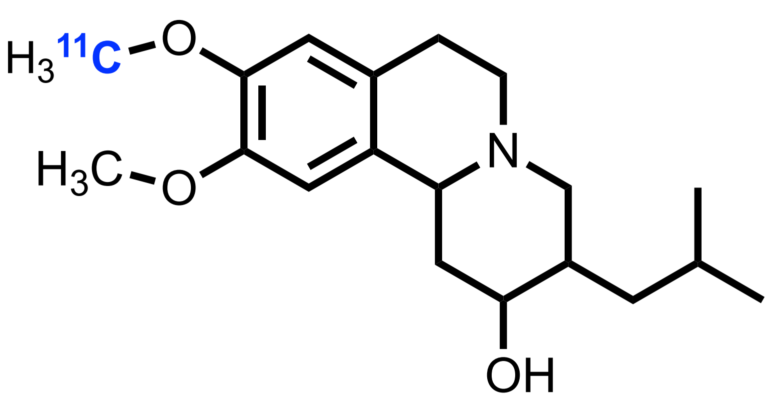
[^{11}C]PIB



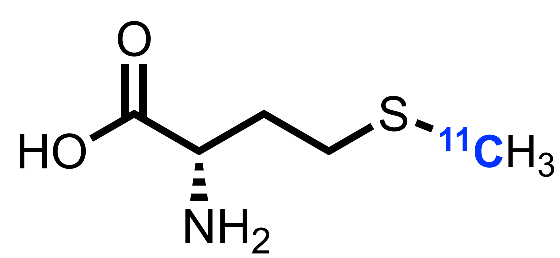
[^{11}C]DASB



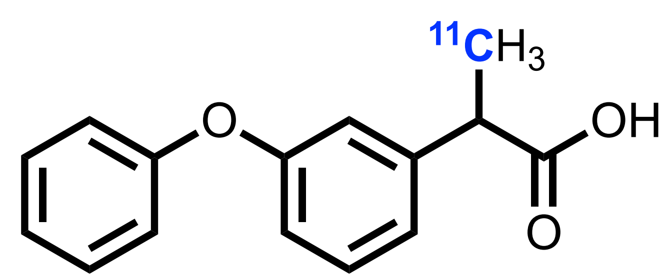
[^{11}C]flumazenil



[^{11}C]DTBZ



[^{11}C]MET

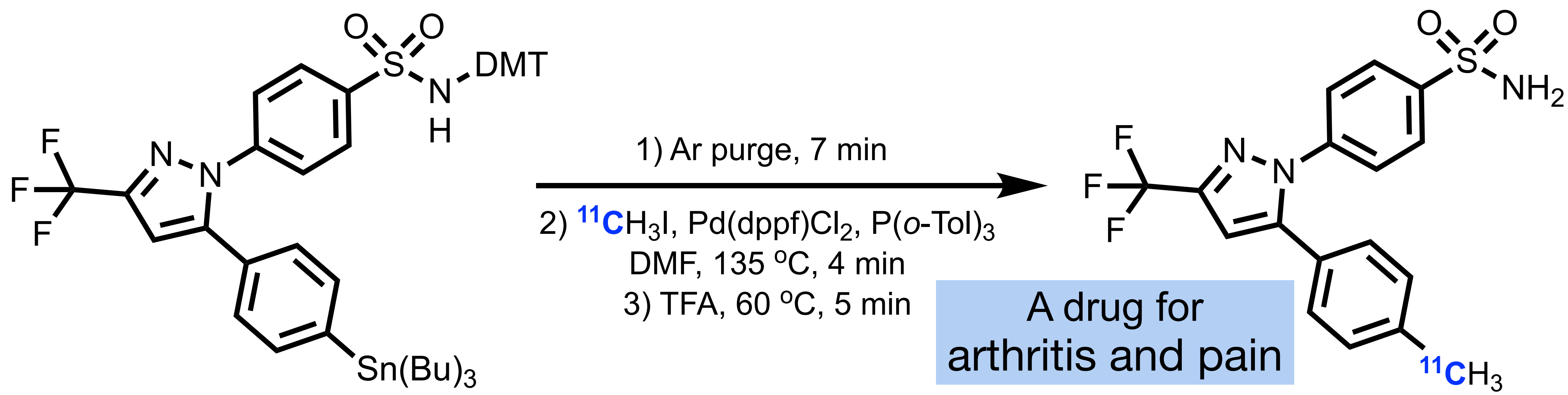


[^{11}C]fenoprofen

Wilson, A. A.; Garcia, A.; Chestakova, A.; Kung, H.; Houle, S.
J. Labelled Compd. Radiopharm. **2004**, *47*, 679.

$^{11}CH_3X$ Chemistry (X = I or OTf)

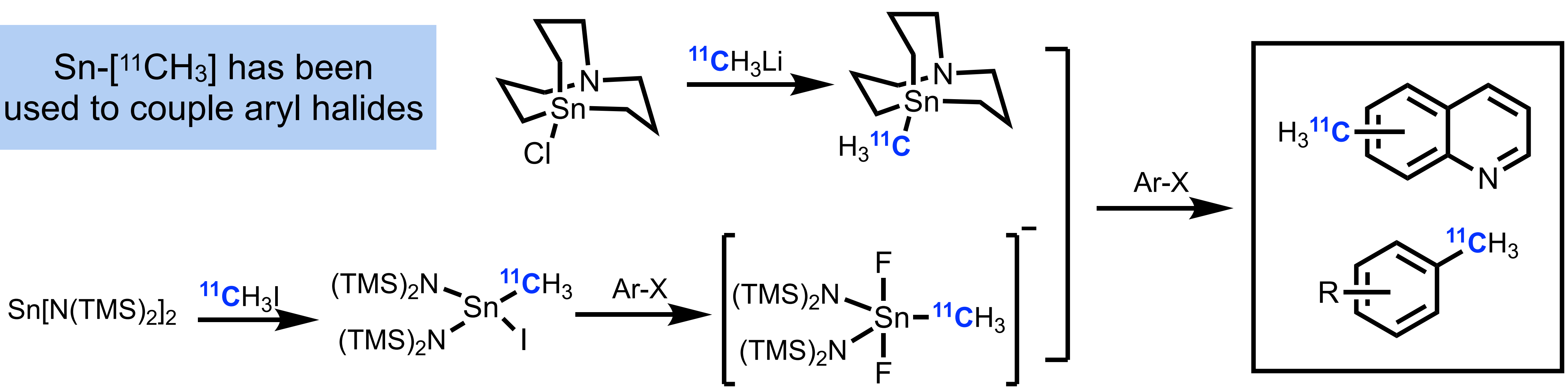
^{11}C-Methylation via Stille coupling



[^{11}C]celecoxib, 8 %

Most commonly used method for aryl-[$^{11}CH_3$] installation

Sn-[$^{11}CH_3$] has been used to couple aryl halides

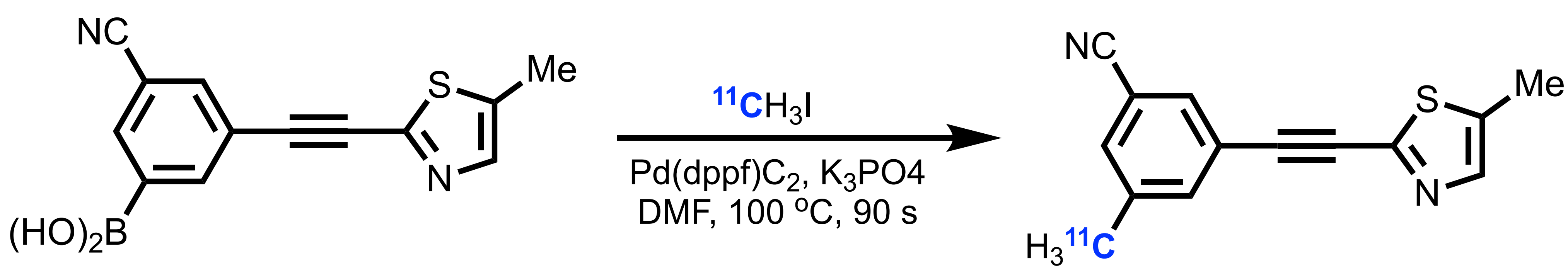


Prabhakaran, J. et. al. *J. Label Compd. Radiopharm.* **2005**,*48*, 887.
Li, Z.; Conti, P. S. *Advanced Drug Delivery Reviews.* **2010**, *62*, 1031.

$^{11}CH_3X$ Chemistry (X = I or OTf)

^{11}C-Methylation via Suzuki coupling

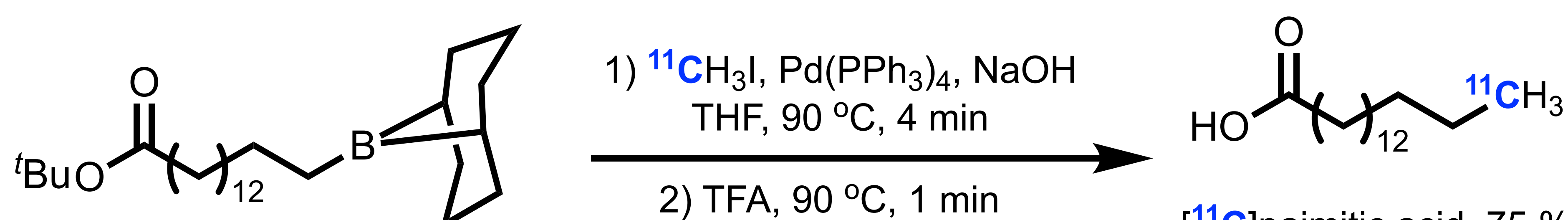
^{11}C-Methylation with arylboronic acids



- Other examples include phenylboronic acid derivatives
- Aryl pinacol boronates also suitable coupling partners

[^{11}C]-M-MTEB, 29 %

^{11}C-Methylation with alkylboronates



alkyl borane precursor

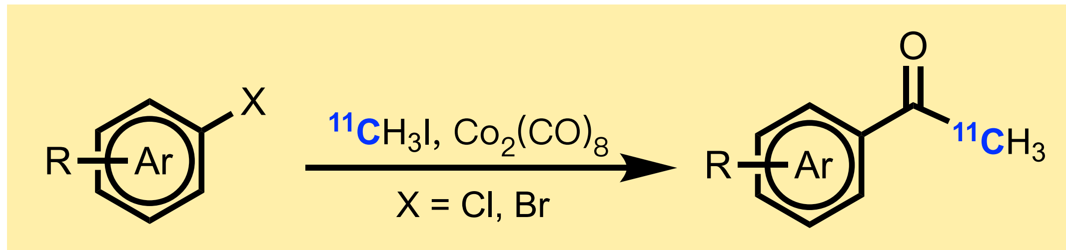
[^{11}C]paimitic acid, 75 %

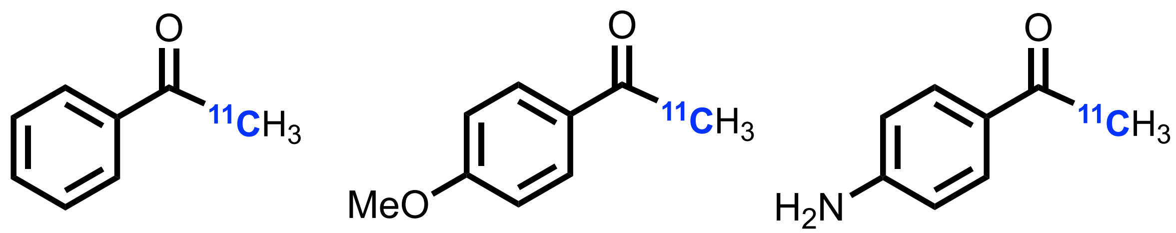
Tracer to evaluate the rate of fatty acid metabolism

Hamill, T. G. et. al. *Synapse*. **2005**, *56*, 205.
Hostetler, E.D. et. al. *J. Org. Chem.* **1998**, *63*, 1348.

$^{11}CH_3X$ Chemistry (X = I or OTf)

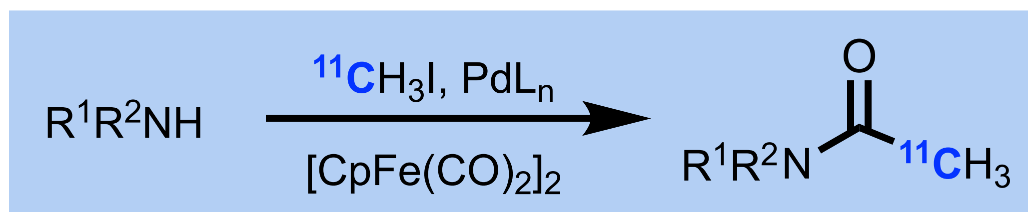
^{11}C-Acetylation



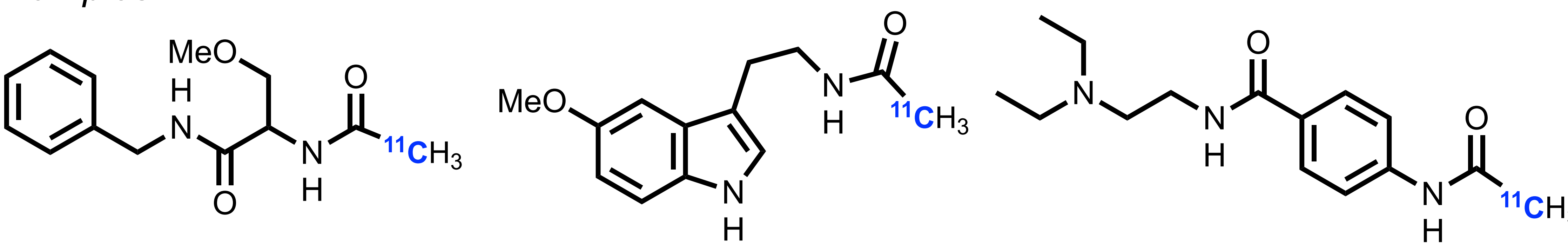


43 % RCY | 47 ± 2 % RCC | 46 ± 1 % RCC

building blocks to pharmacologically active molecules



Examples



[^{11}C]lacosamide
52 ± 2 % RCC

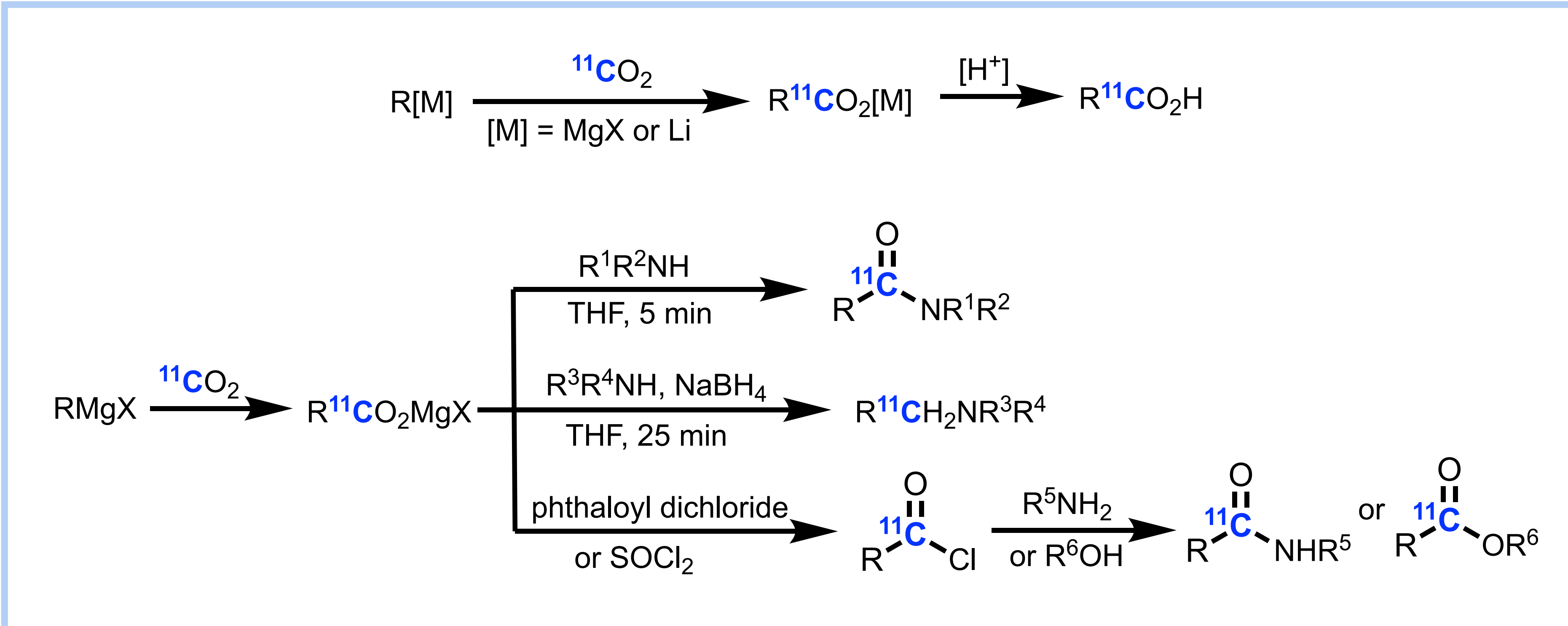
[^{11}C]melatonin
55 ± 1 % RCC

[^{11}C]acecainide
44 ± 1 % RCC

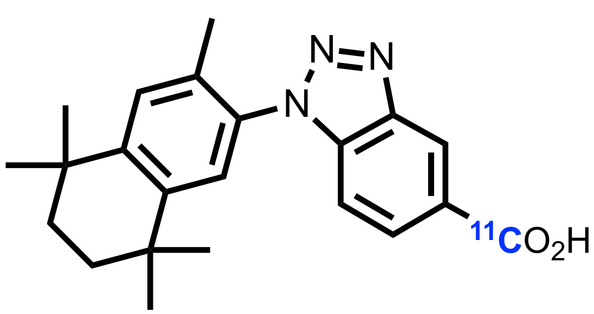
Dahl, K.; Schou, M.; Halldin, C. *Eur. J. Org. Chem.* **2016**, 2775.
Dahl, K.; Nordeman, P. *Eur. J. Org. Chem.* **2017**, 5785.

$^{11}CO_2$ Chemistry

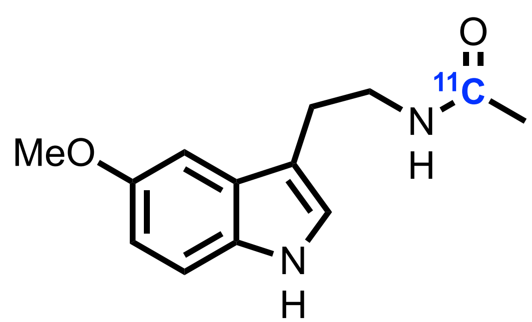
^{11}Carboxylic acid derivatives from organometallics



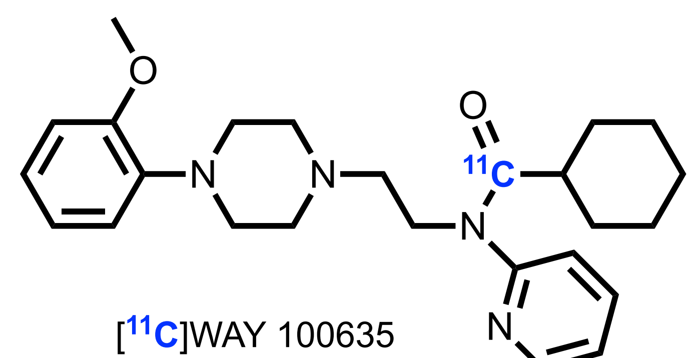
Examples



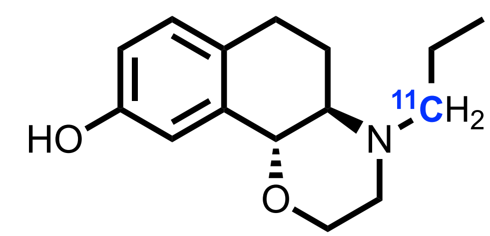
[^{11}C]RXR-partial agonist
0.33 % RCY



[^{11}C]melation
13 % RCY



[^{11}C]WAY 100635
15.5 % RCY

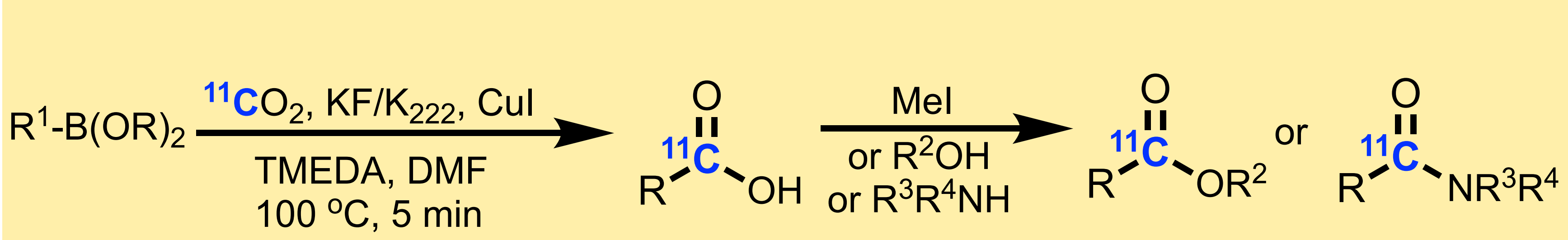


(+)-[^{11}C]PHNO
8.2 % RCY

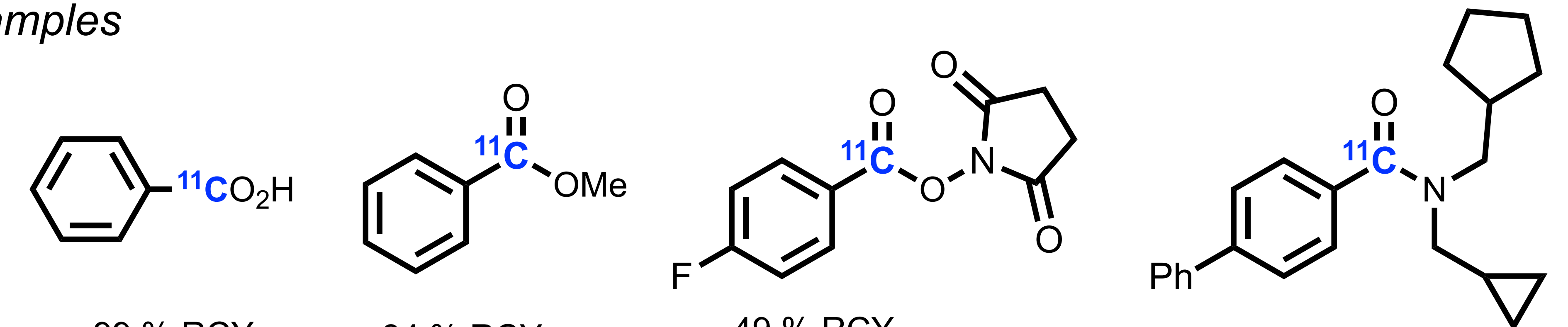
Rotstein, B. H. et al. *Chem. Soc. Rev.* **2016**, *45*, 4708.
Shibahara, O. et al. *J. Med. Chem.* **2017**, *60*, 7139.
Mossine, A. V. et al. *Bioconjugate Chem.* **2016**, *27*, 1382.

$^{11}CO_2$ Chemistry

^{11}Carboxylic acid derivatives from boronates



Examples

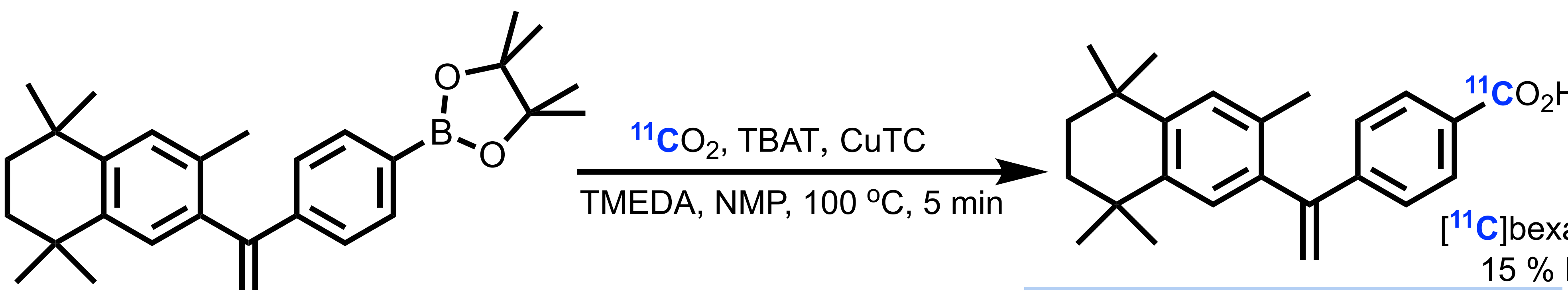


99 % RCY

84 % RCY

49 % RCY

[^{11}C]oxytocin receptor ligand
20 % RCY



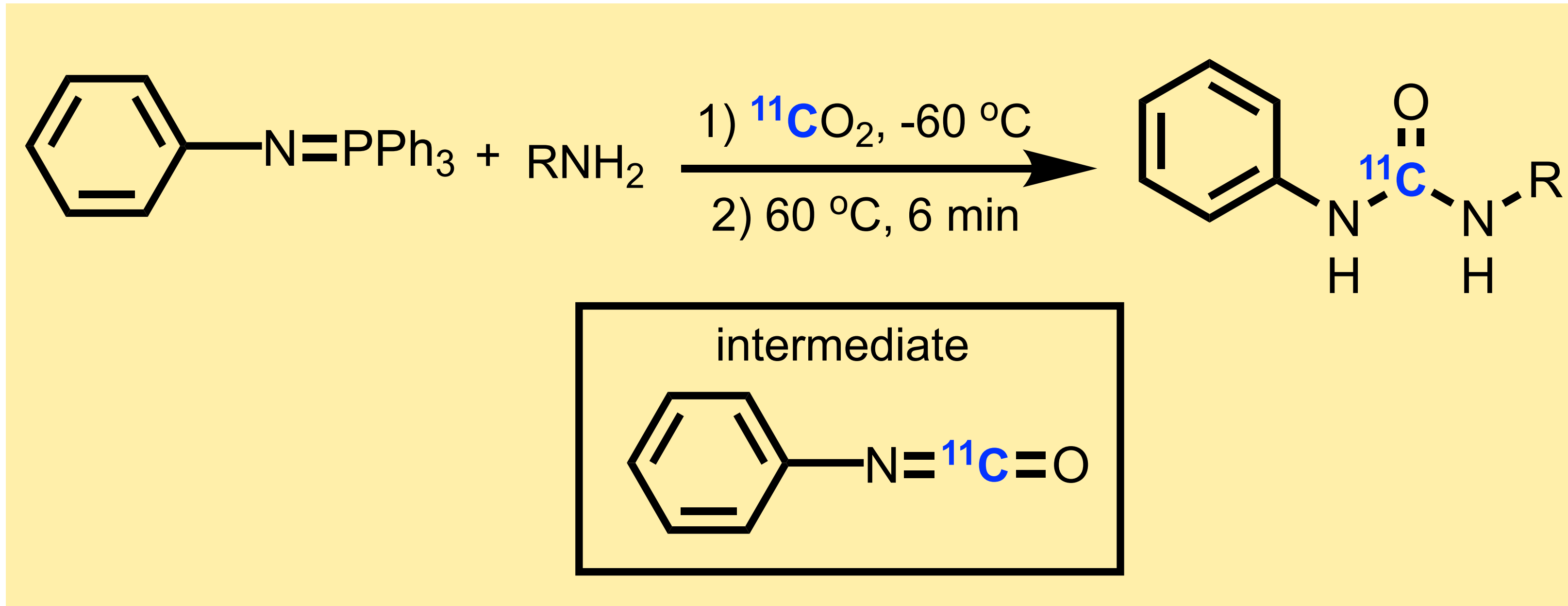
[^{11}C]bexarotene
15 % RCY

Nonhuman primates
PET-MR imaging studies

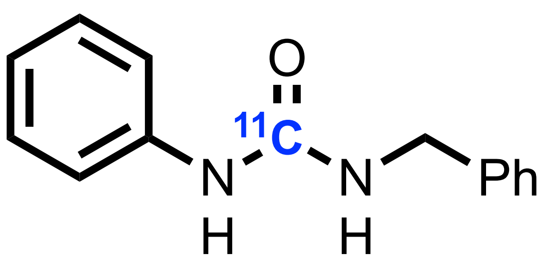
Riss, P. J.; Lu, S.; Telu, S.; Aigbirhio, F. I.; Pike, V. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 2698.
Rotstein, B. H. et al. *ACS Med. Chem. Lett.* **2014**, *5*, 668.

$^{11}CO_2$ Chemistry

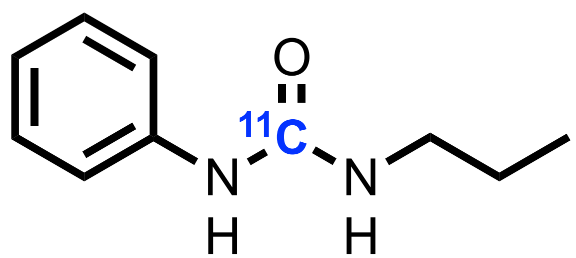
^{11}Ureas from triphenylphosphinimines and amides



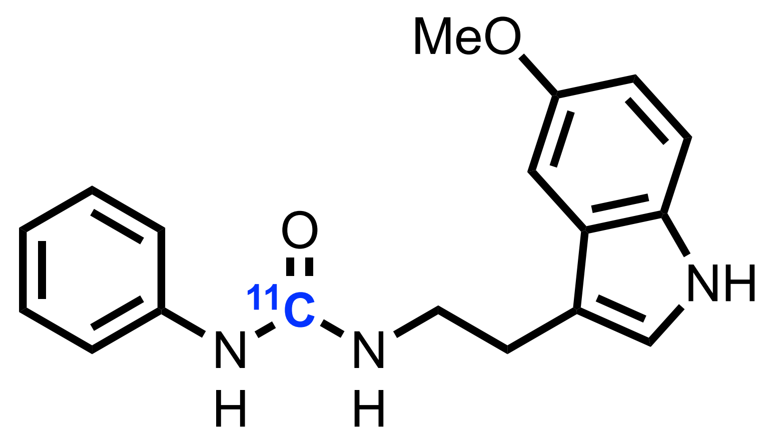
Examples



46 % RCY



49 % RCY

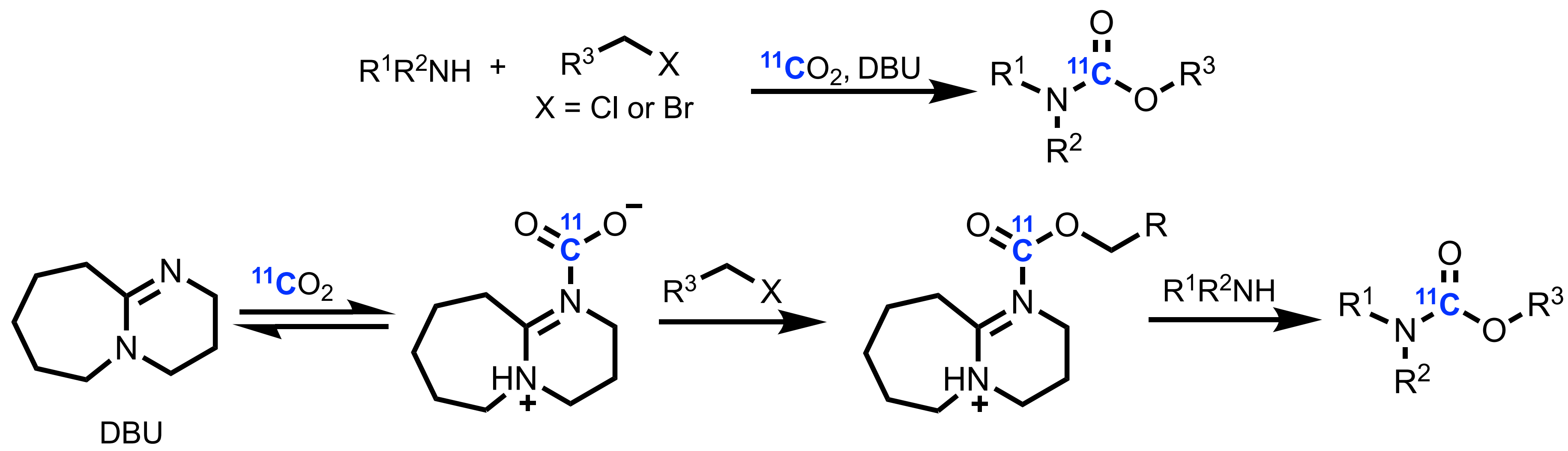


45 % RCY

van Tilburg, E. W.; Windhorst, A. D.; van der Mey, M.; Herscheid, J. D.
J. Labelled Compd. Radiopharm. **2006**, *49*, 321.

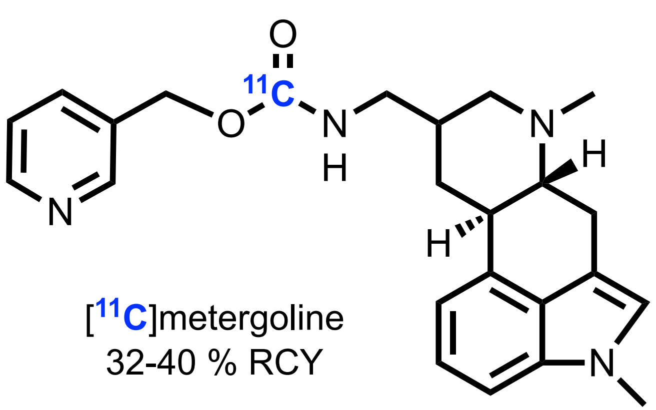
$^{11}CO_2$ Chemistry

^{11}Carbamates from amines

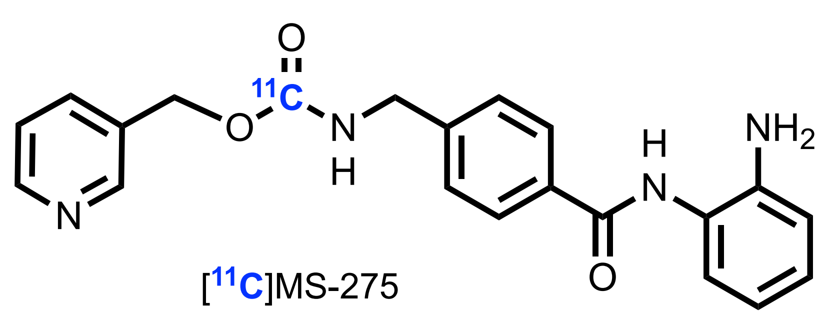


Organic amines DBU act as organomediator by activating $^{11}CO_2$ prior to the covalent bond formation

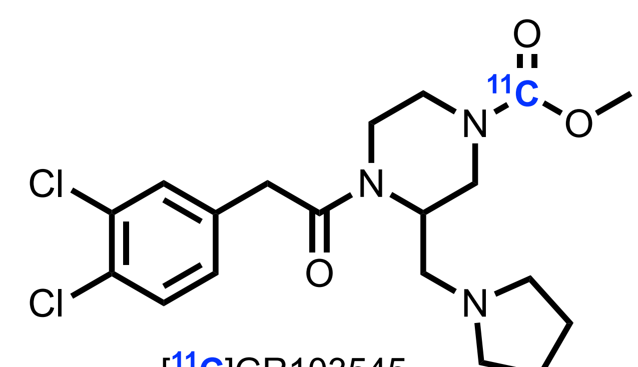
Examples



[^{11}C]metergoline
32-40 % RCY



[^{11}C]MS-275
25 % RCY



[^{11}C]GR103545

Hooker, J. M.; Reibel, A. T.; Hill, S. M.; Schueller, M. J.; Fowler, J. S.
Angew. Chem. Int. Ed. **2009**, *48*, 3482.

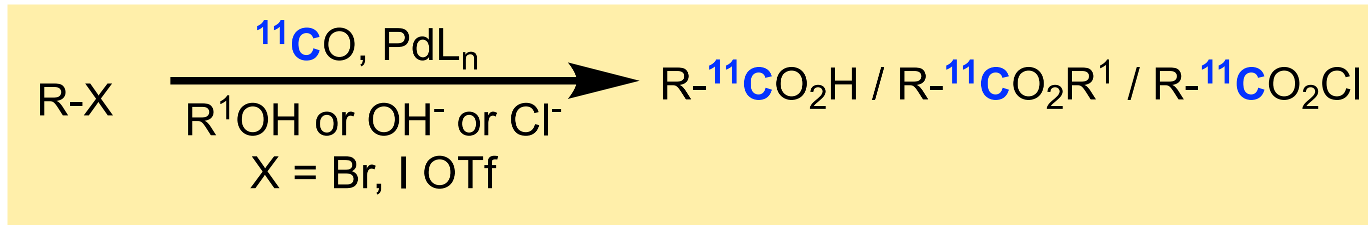
^{11}CO Chemistry

$$^{11}CO_2 \xrightarrow[\text{or Mo, 850 }^{o}\text{C}]{\text{Zn, 400 }^{o}\text{C}} {}^{11}CO$$

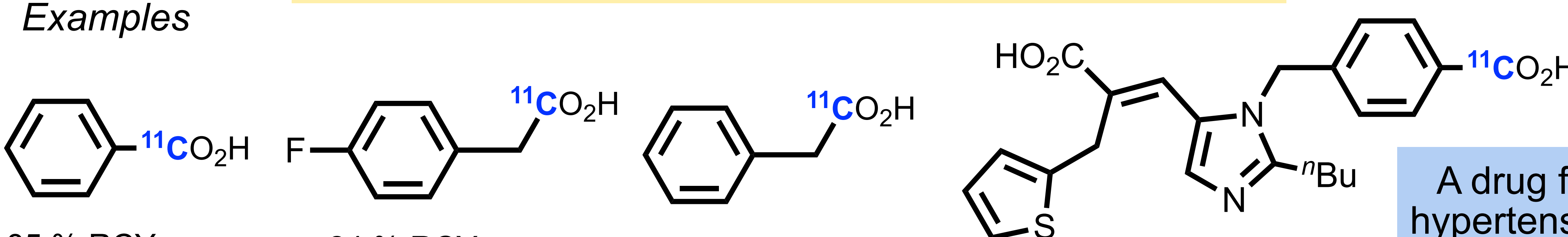
^{11}CO was used as a tracer to study interactions with red blood cells *in vivo* in 1945, which was the first human application of a ^{11}C-labelled compound.

^{11}CO Chemistry

^{11}C-carbonyl-labeled carboxylic acids, esters and acyl chlorides



Examples



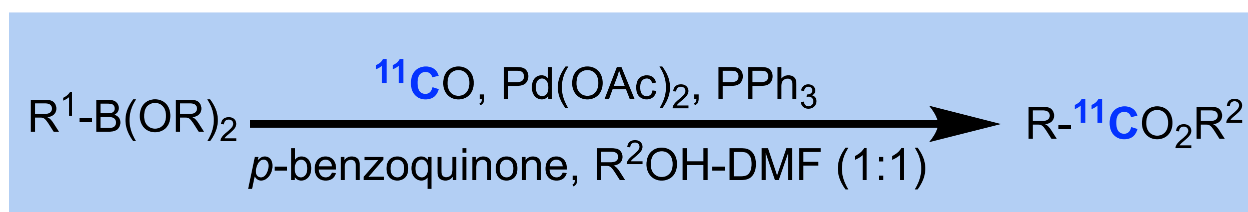
85 % RCY

24 % RCY

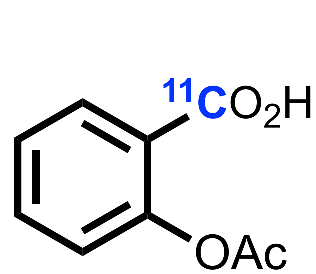
10 % RCY

[^{11}C]eprosartan
37-54 % RCY

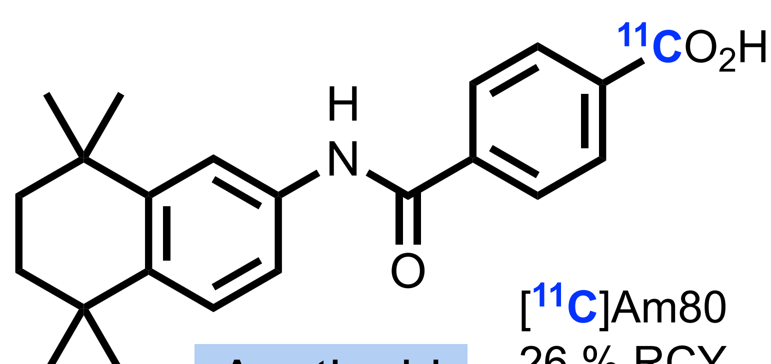
A drug for hypertension



Examples



[^{11}C]aspirin
15 % RCY



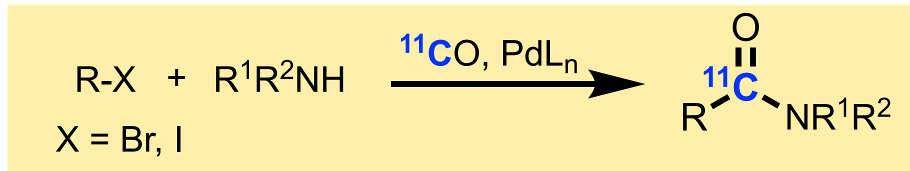
A retinoid compound

[^{11}C]Am80
26 % RCY

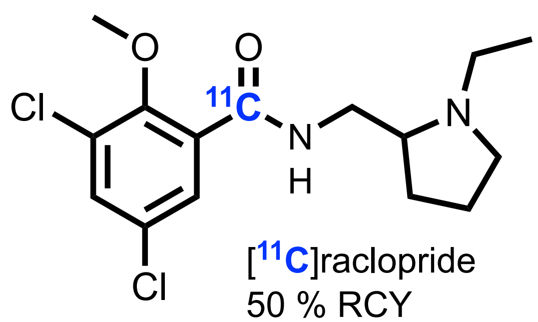
Lu, S. et al. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 548.
Kealey, S. et al. *Org. Biomol. Chem.* **2011**, *9*, 3313.
Ishii, H.; Minegishi, K.; Nagatsu, K.; Zhang, M.-R. *Tetrahedron* **2015**, *71*, 1588.

^{11}CO Chemistry

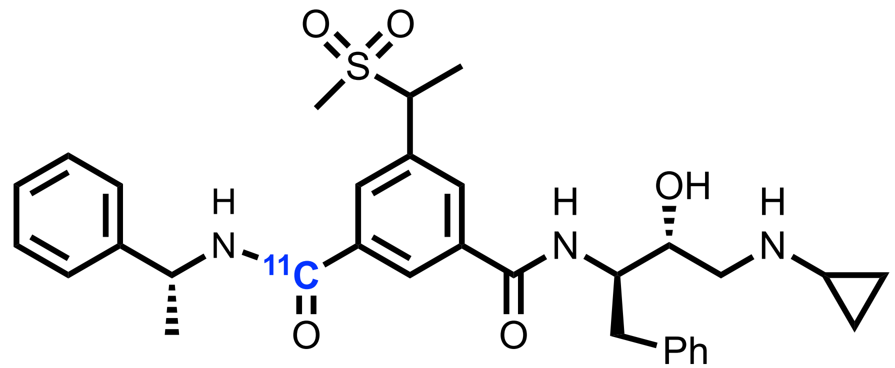
^{11}C-carbonyl-labeled amides



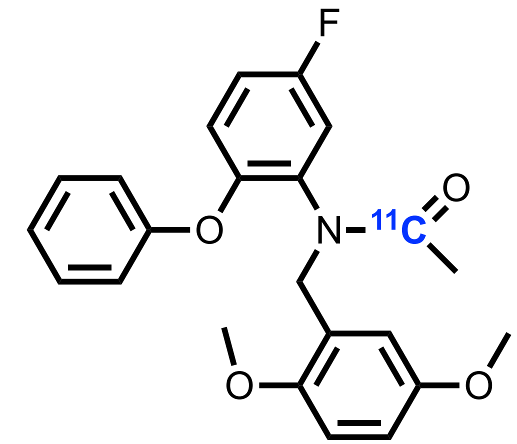
Examples



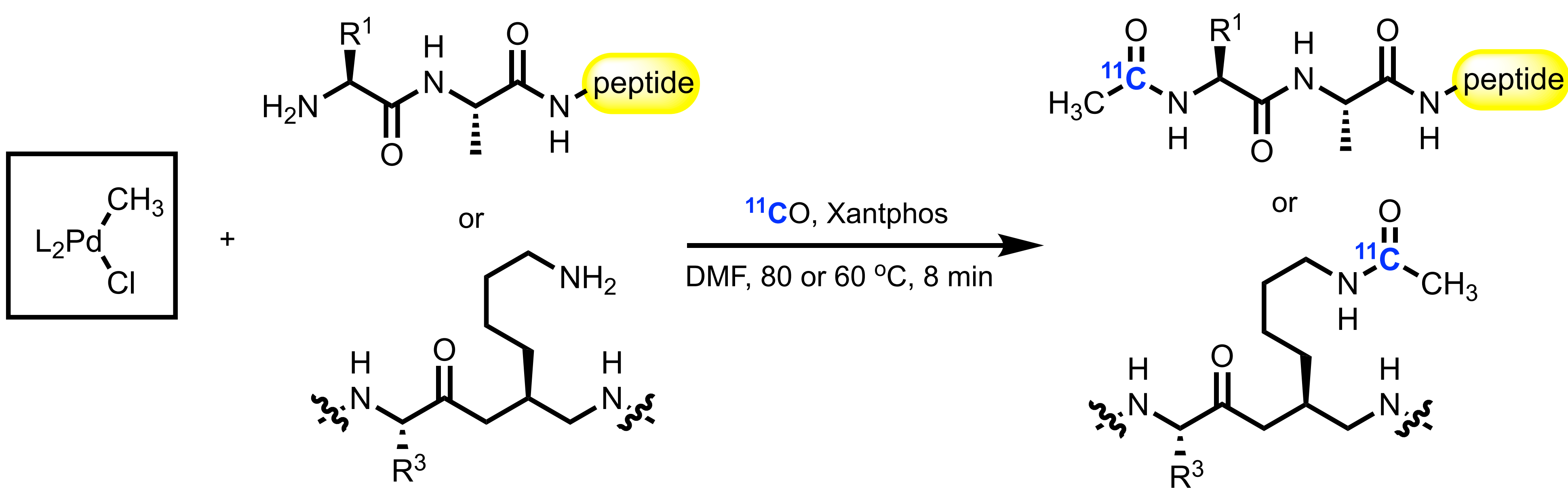
[^{11}C]raclopride
50 % RCY



[^{11}C]BSI-IV
29 % RCY



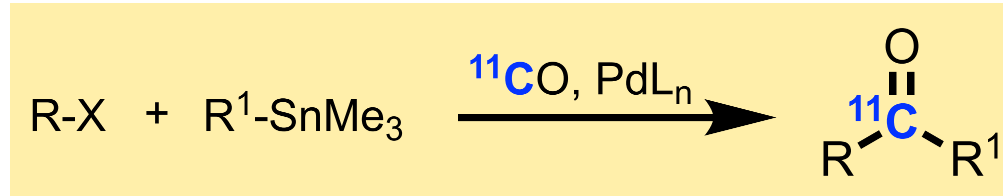
[^{11}C]DAA1106
10-55 % RCY



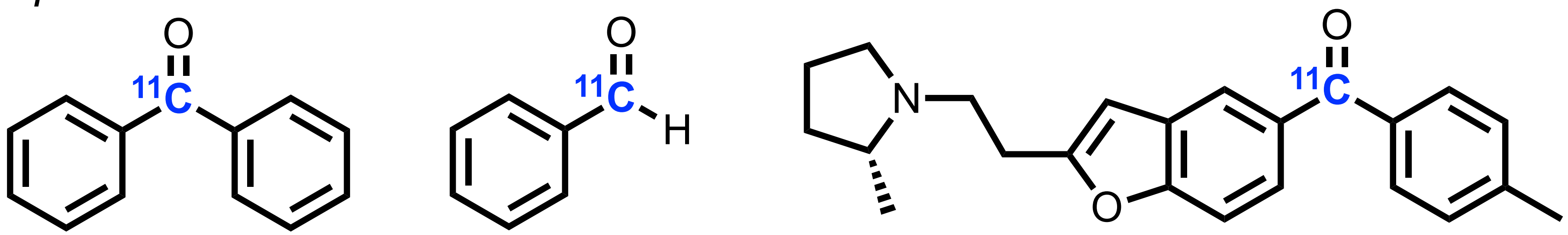
Taddei, C.; Gee, A. D. *J. Labelled Compd. Radiopharm.* **2018**, *61*, 237.
Andersen, T. L. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 4549.

^{11}CO Chemistry

Stille coupling



Examples



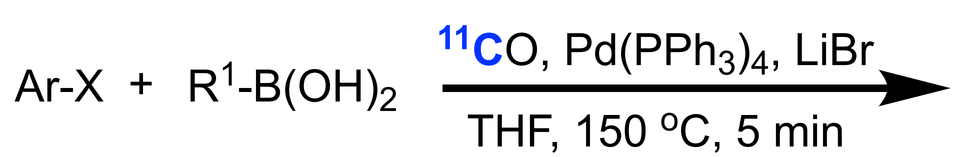
52-58 % RCY

73 % RCY

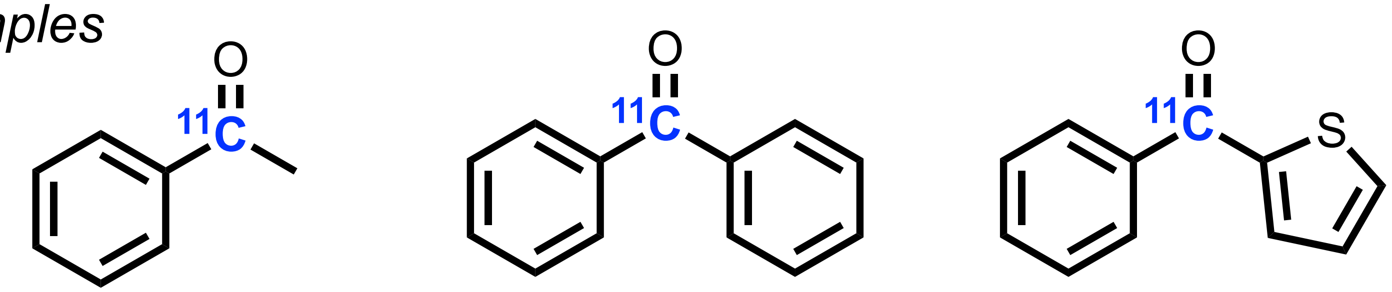
6.8 % RCY

A potential PET radioligand for histamine subtype 3 receptors

Suzuki coupling



Examples



30 % RCY

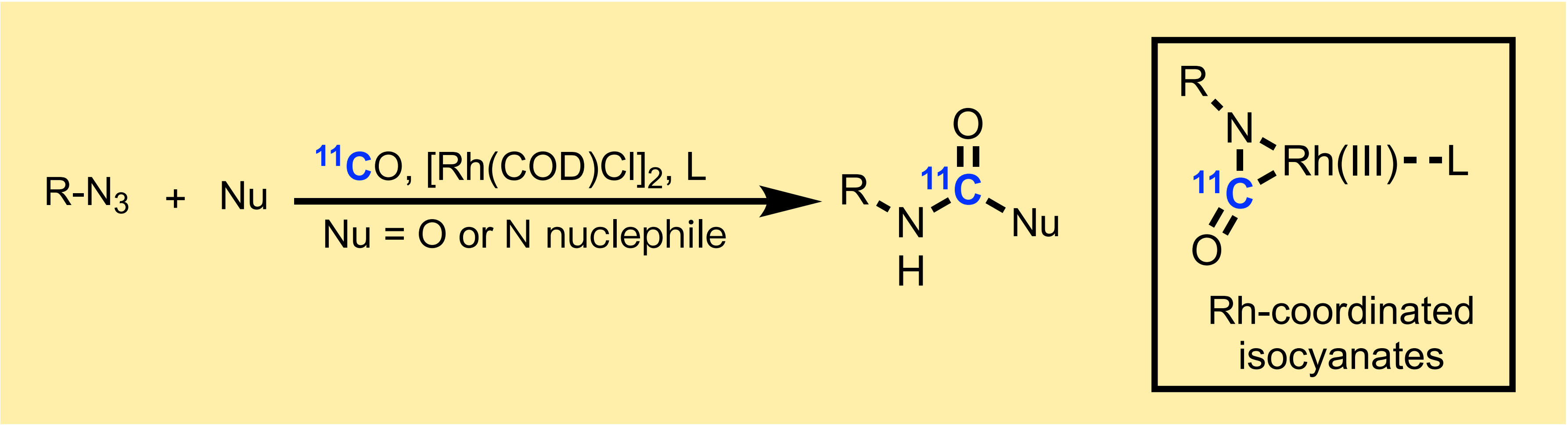
64 % RCY

39 % RCY

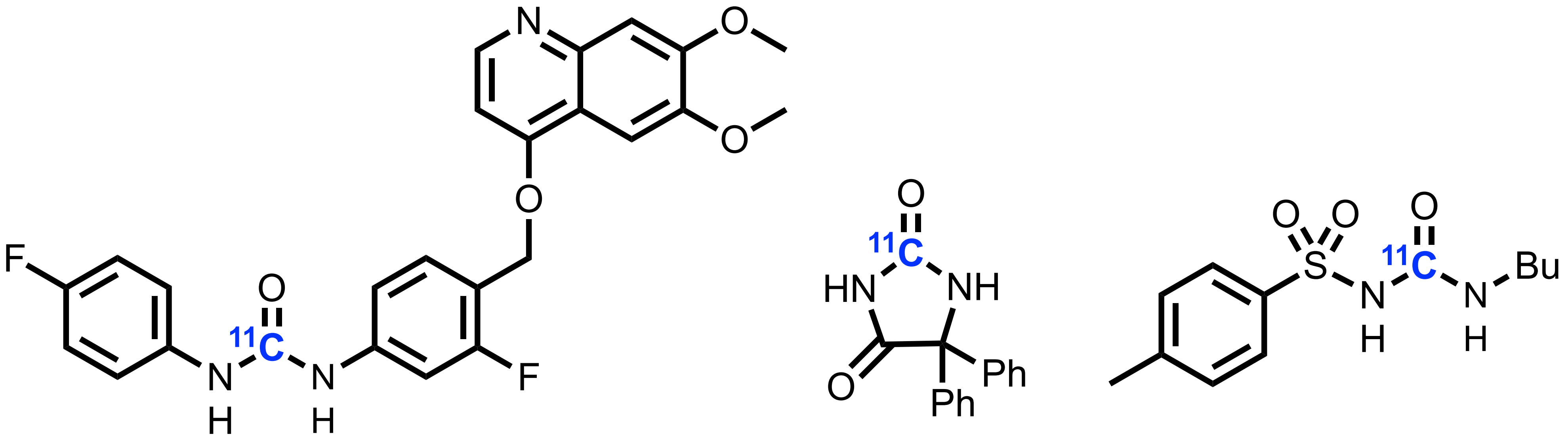
Siméon, F. G.; Culligan, W. J.; Lu, S.; Pike, V. W. *Molecules* **2017**, *22*, 792.
Rahman, O.; Kihlberg, T.; Lågström, B. *Eur. J. Org. Chem.* **2004**, 474.

^{11}CO Chemistry

^{11}C-carbonyl-labeled ureas and carbamates



Examples



[^{11}C]VEGFR-2/PDGFR-β dual inhibators
38-81 % RCY

[^{11}C]phenytoin
22 % RCY

83 % RCY

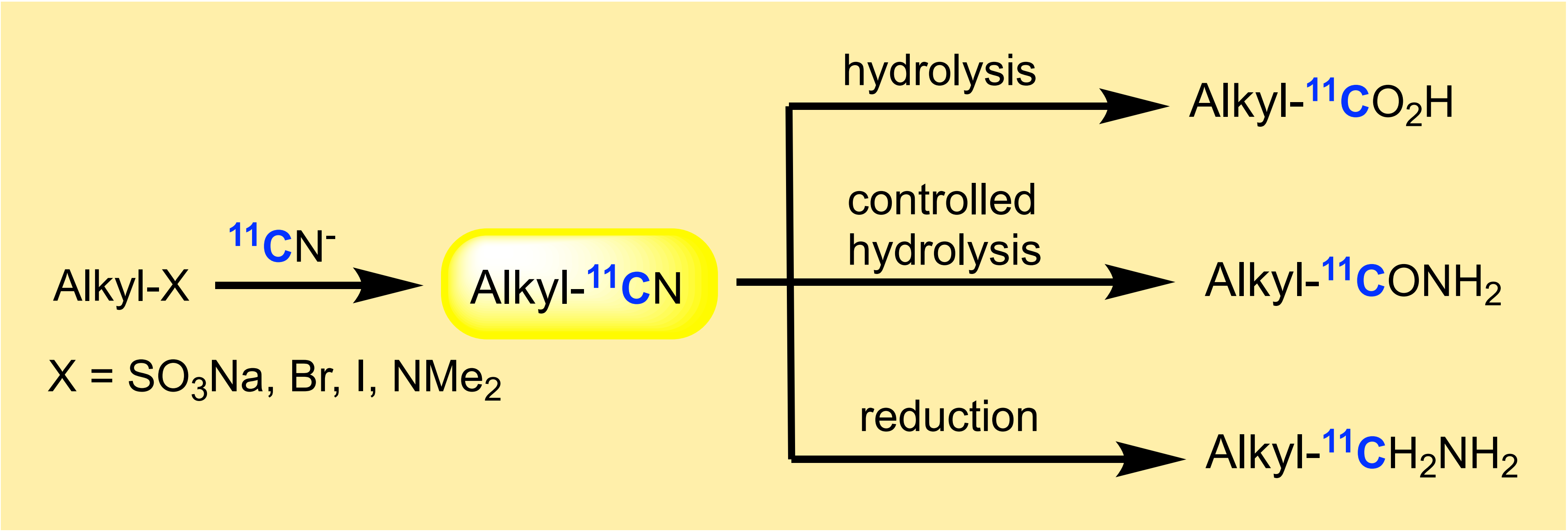
Doi, H.; Barletta, J.; Suzuki, M.; Noyori, R.; Watanabe, Y.; Lågström, B.
Org. Biomol. Chem. **2004**, *2*, 3063.

$^{11}CN^{-}$ Chemistry

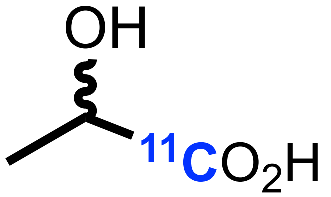
$$^{11}CO_2 \xrightarrow{Ni/H_2} {}^{11}CH_4 \xrightarrow[950\ ^\circ C]{Pt/NH_3} NH_4{}^{11}CN \xrightarrow{PyBr} Br^{11}CN$$

$^{11}CN^-$ Chemistry

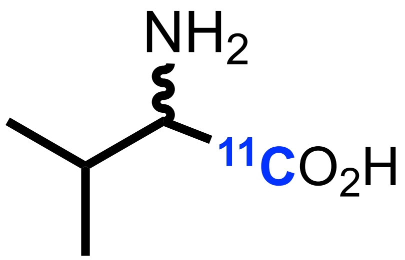
Alkyl-^{11}CN and its derivatives



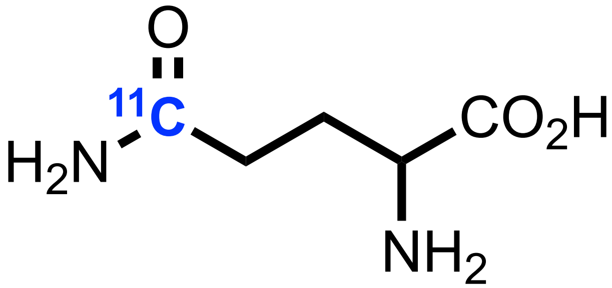
Examples



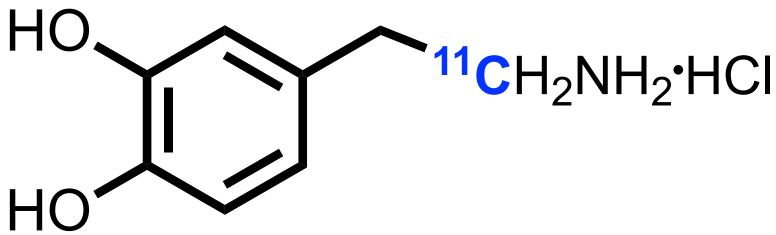
[^{11}C]lactic acid
53.5 % RCY



[^{11}C]valine
49 % RCY



L-[^{11}C]glutamine
25-40 % RCY

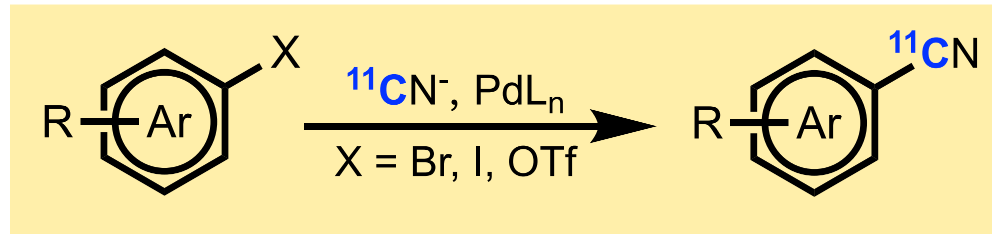


[^{11}C]dopamine•HCl
53.5 % RCY

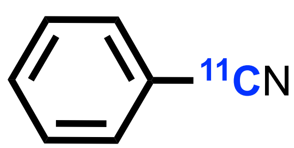
Deng, X.; Rong, J.; Wang, L.; Vasdev, N.; Zhang, L.; Josephson, L.; Liang, S.
Angew. Chem. Int. Ed. **2019**, *58*, 2580.

$^{11}CN^-$ *Chemistry*

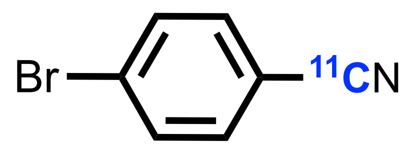
Pd-mediated alkyl-^{11}CN formation



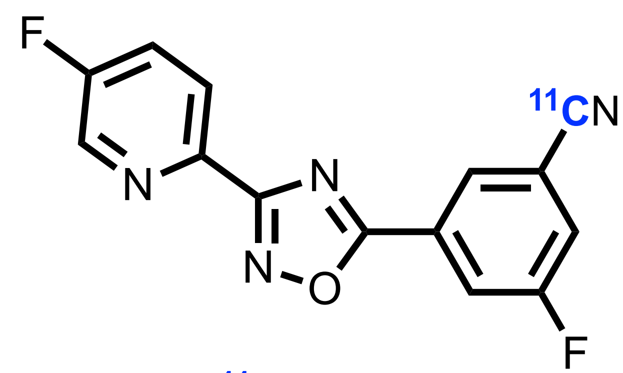
Examples



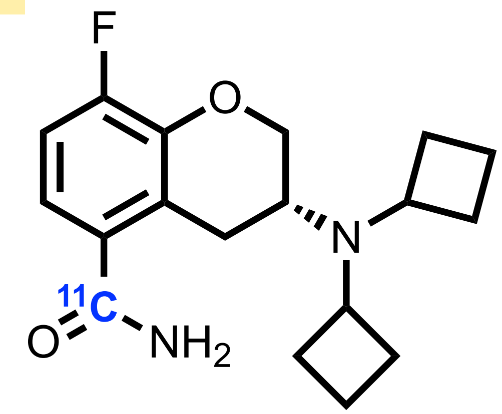
90 % RCY



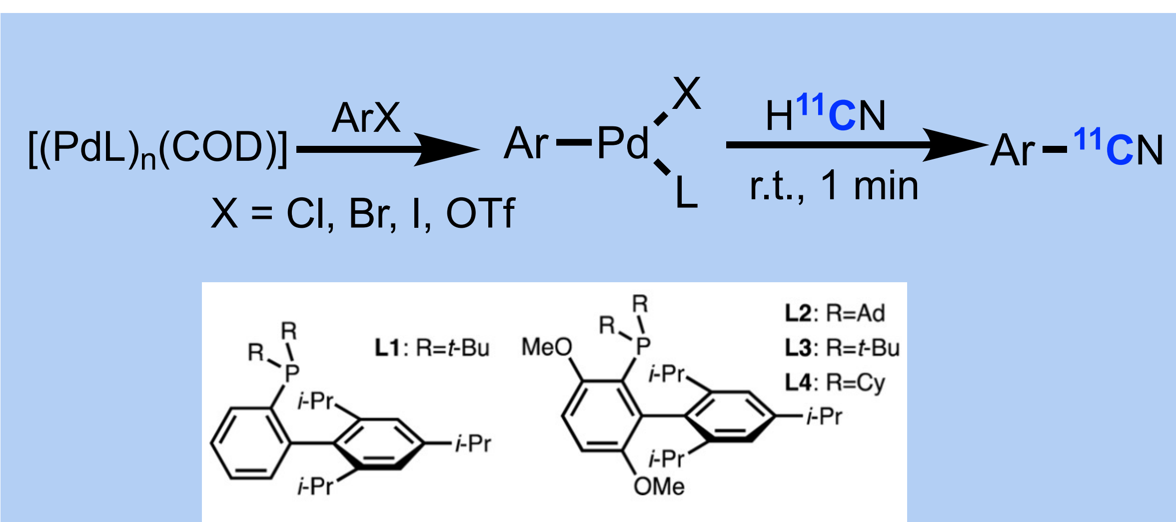
62 % RCY



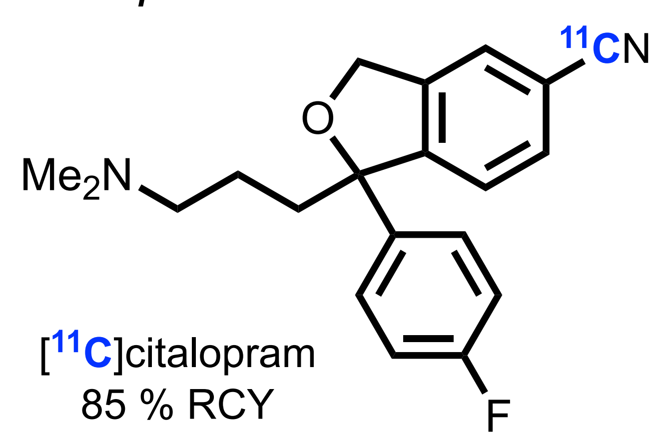
[^{11}C]AZD9272
>50 % RCY



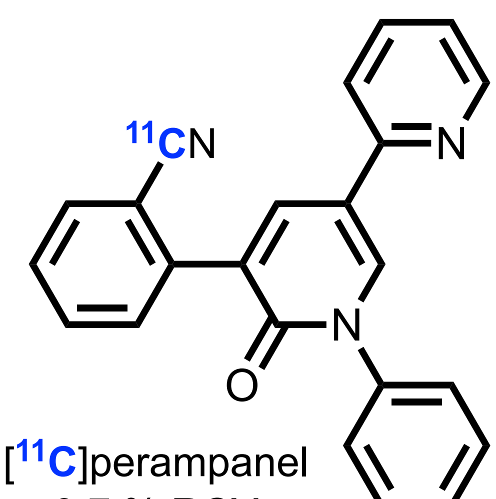
[^{11}C]NAD-299
20-40 % RCY



Examples



[^{11}C]citalopram
85 % RCY

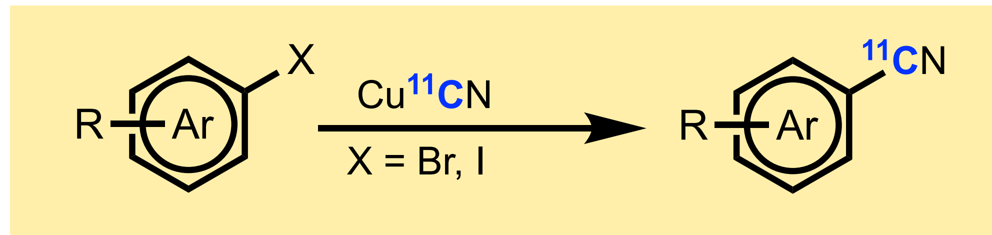


[^{11}C]perampanel
9.7 % RCY

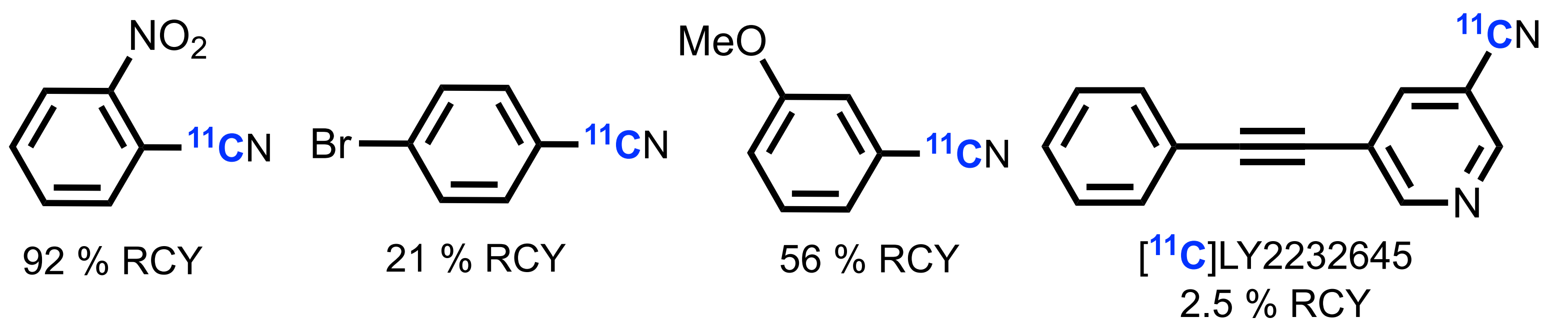
Rotstein, B. H. et al. *Chem. Soc. Rev.* **2016**, *45*, 4708.
Lee, H. G.; Milner, P. J.; Placzek, M. S.; Buchwald, S. L.; Hooker, J. M.
J. Am. Chem. Soc. **2015**, *137*, 648.

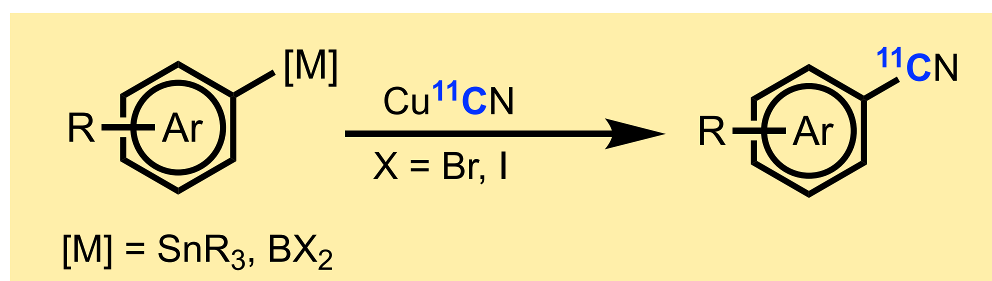
$^{11}CN^-$ Chemistry

Cu-mediated alkyl-^{11}CN formation

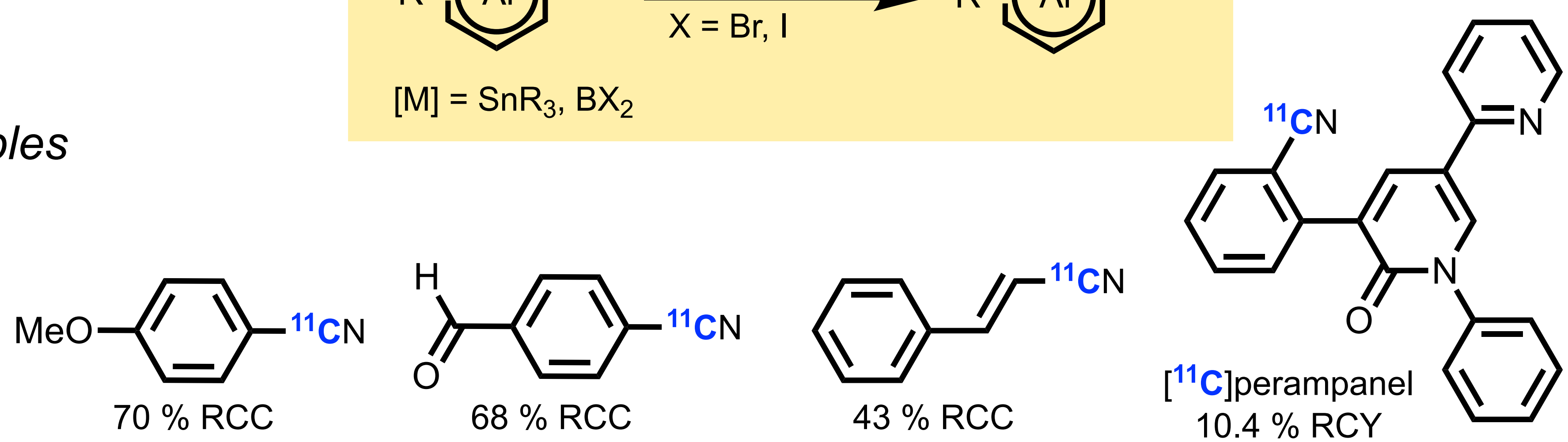


Examples



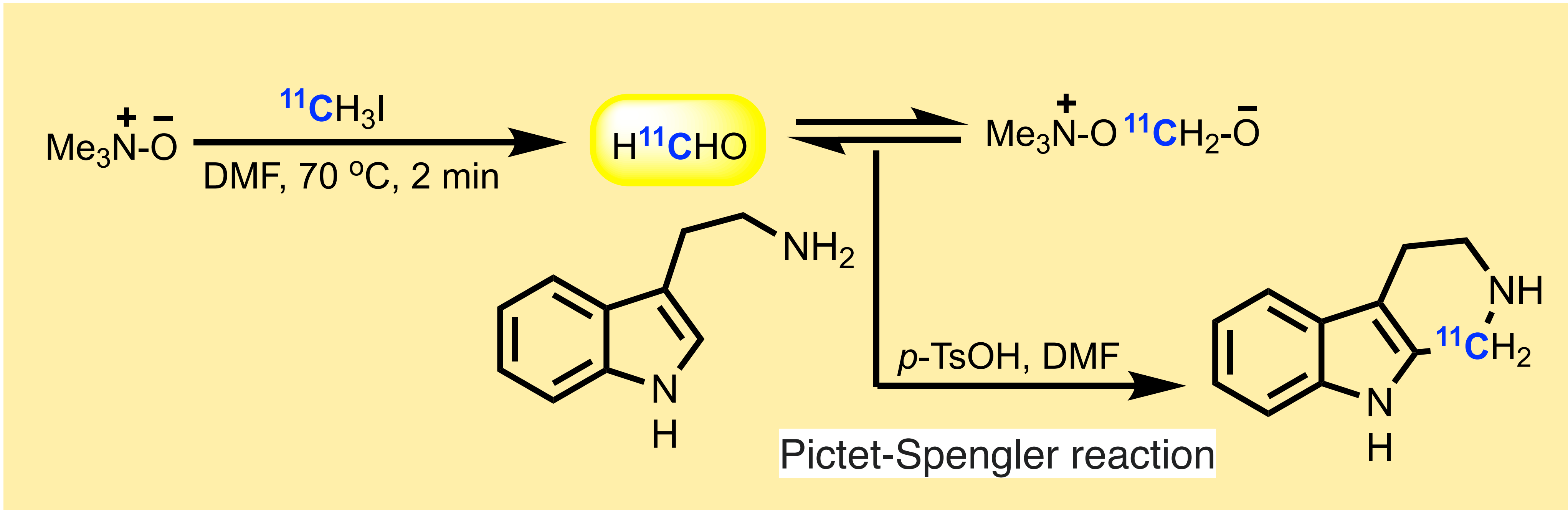


Examples

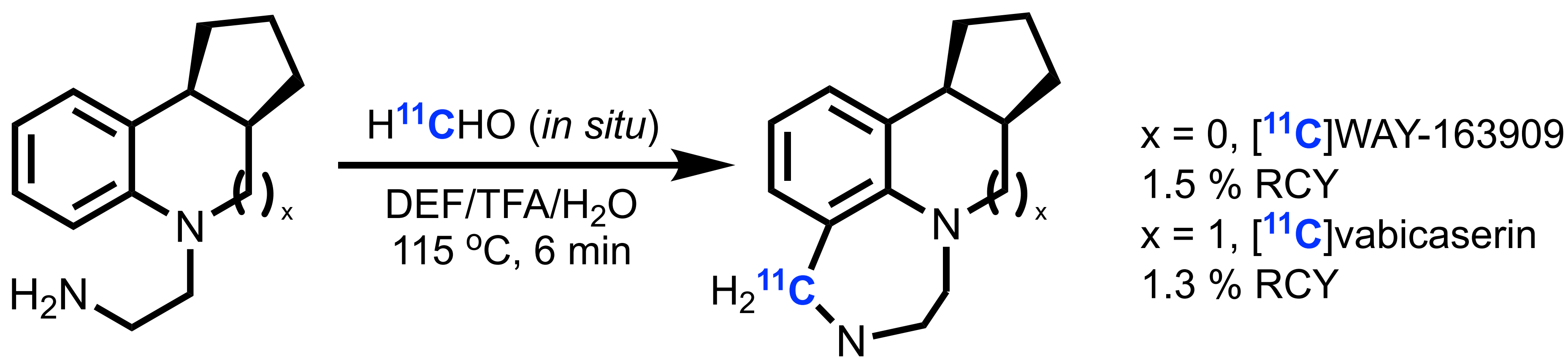


Ma, L.; Placzek, M. S.; Hooker, J. M.; Vasdev, N.; Liang, S. H. *Chem. Commun.* **2017**, *53*, 6597.
Makaravage, K. J.; Shao, X.; Brooks, A. F.; Yang, L.; Sanford, M. S.; Scott, P. J. *Org. Lett.* **2018**, *20*, 1530.

H¹¹CHO Chemistry



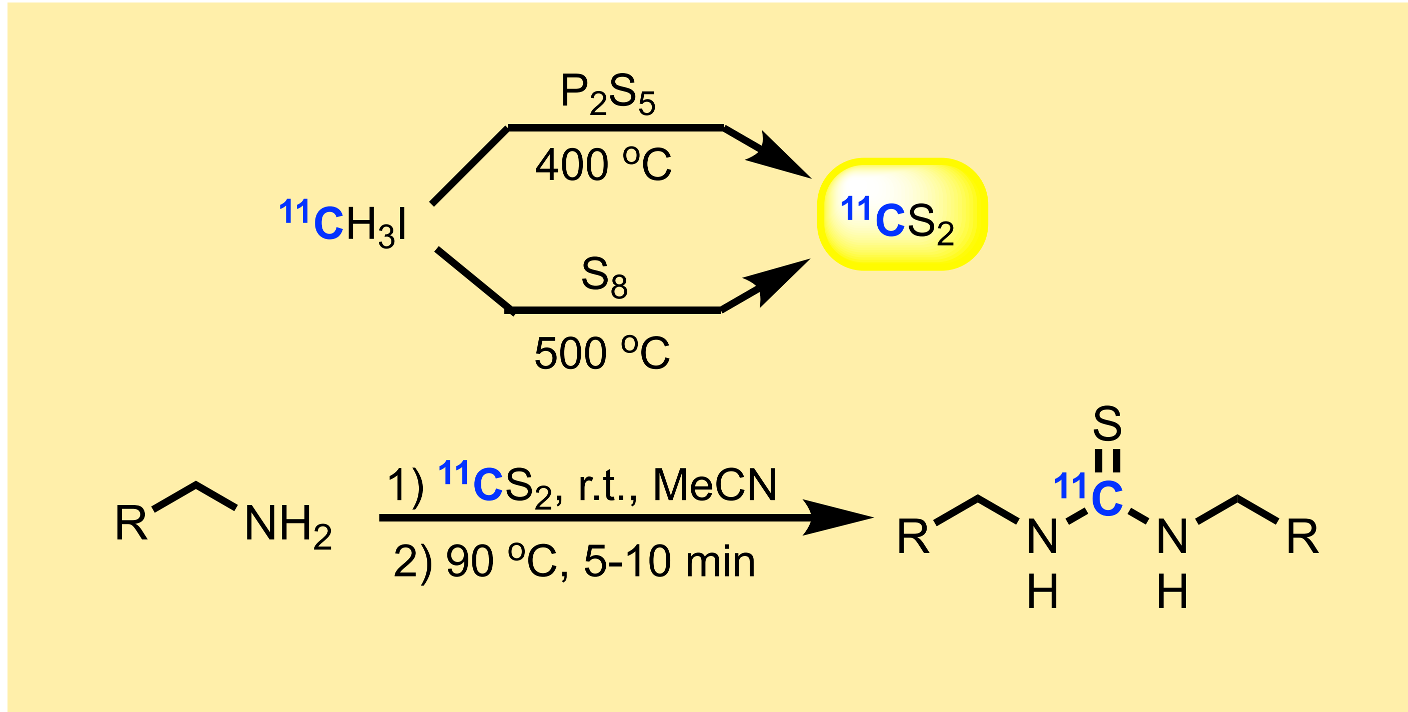
Examples



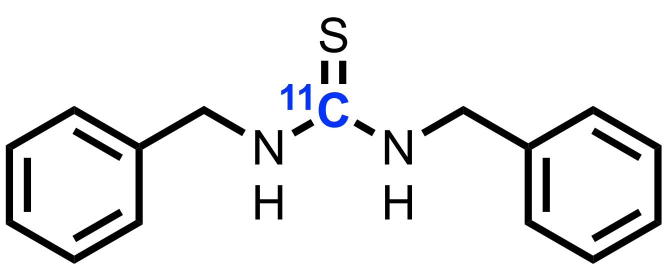
Emerging drug target to treat several disorders of the human central nervous system

Hooker, J. M.; Schönberger, M.; Schieferstein, H.; Fowler, J. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 5989.
Neelamegam, R.; Hellenbrand, T.; Schroeder, F. A.; Wang, C. Hooker, J. M.
J. Med. Chem. **2014**, *57*, 1488.

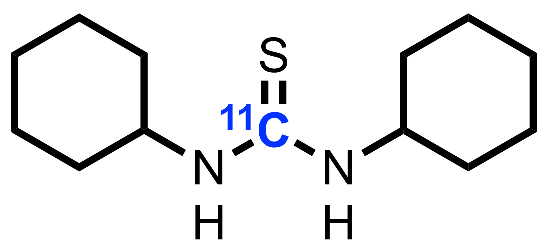
^{11}CS Chemistry



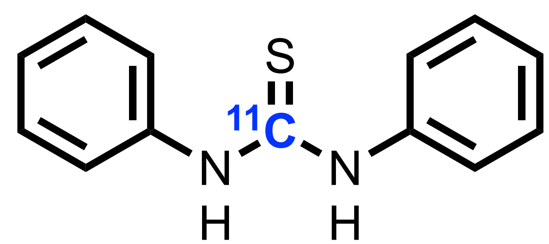
Examples



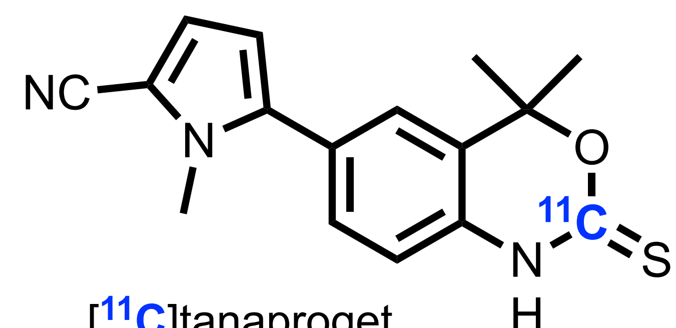
> 99 % RCC



> 99 % RCC



> 99 % RCC



[^{11}C]tanaproget
> 75 % RCY

progesterone receptor agonist

Haywood, T.; Kealey, S.; Sánchez-Cabezas, S.; Hall, J. J.; Allott, L.; Smith, G.; Plisson, C.; Miller, P. W. *Chem. Eur. J.* **2015**, *21*, 9034.

Conclusion

$^{11}CH_3X$

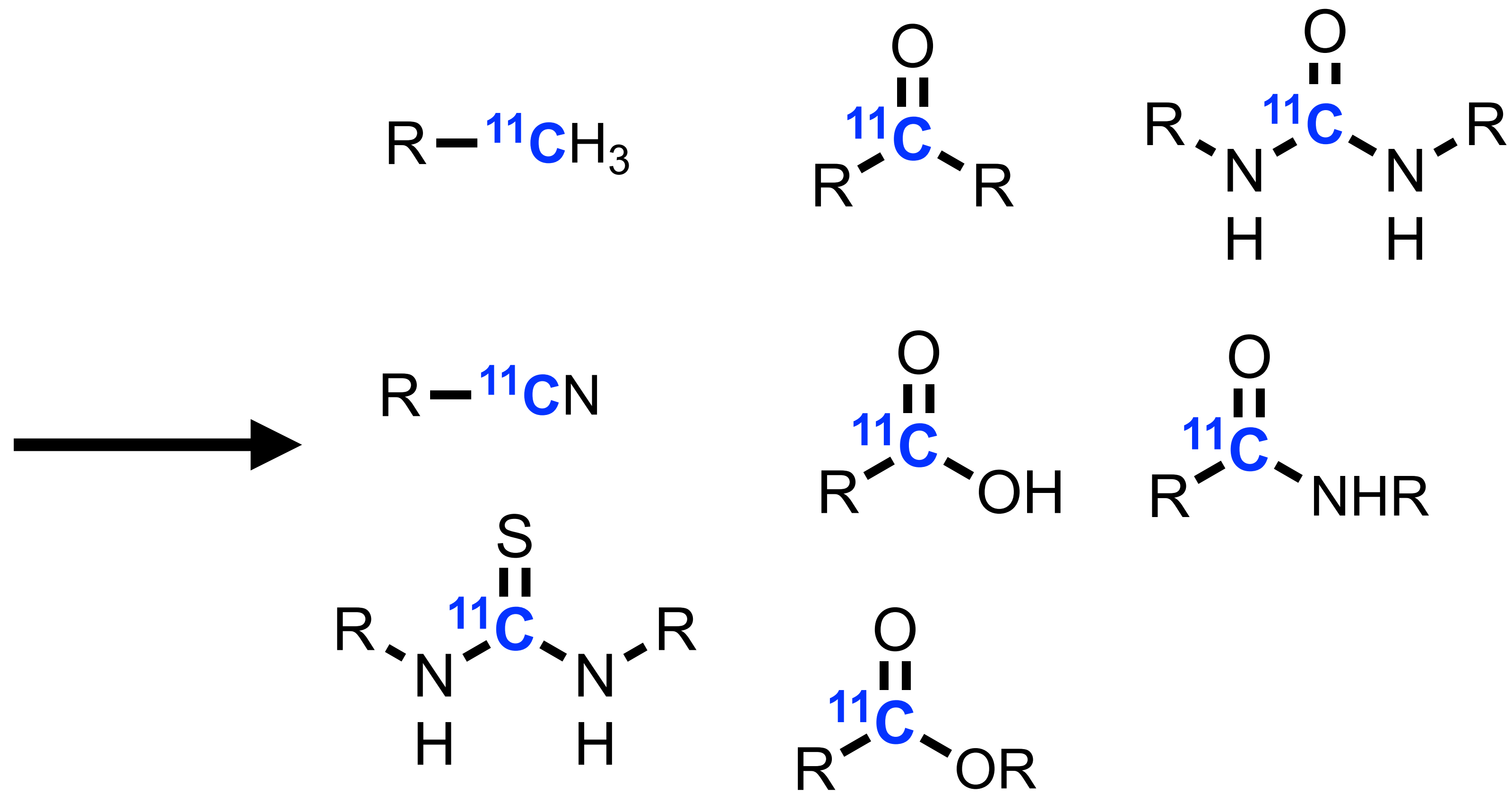
$^{11}CO_2$

^{11}CO

$^{11}CN^-$

$H^{11}CHO$

$^{11}CS_2$



The carbon-11 chemistry for PET is far more to be developed !!!

More labeled positions
More reaction types
Automatic synthesis

→

Cancer visualization
Disease diagnosis
Drug research & development

Thank You!