Synthetic Isotopic Labeling

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Content

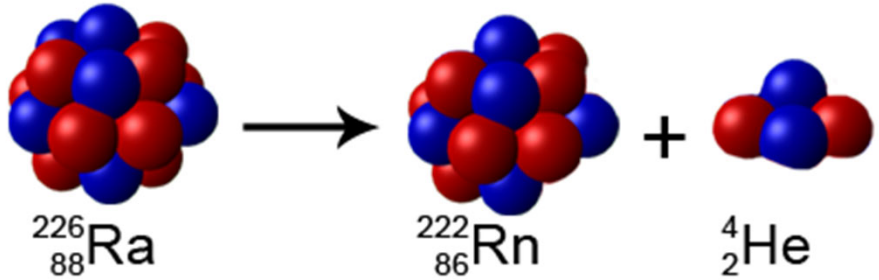
Isotope

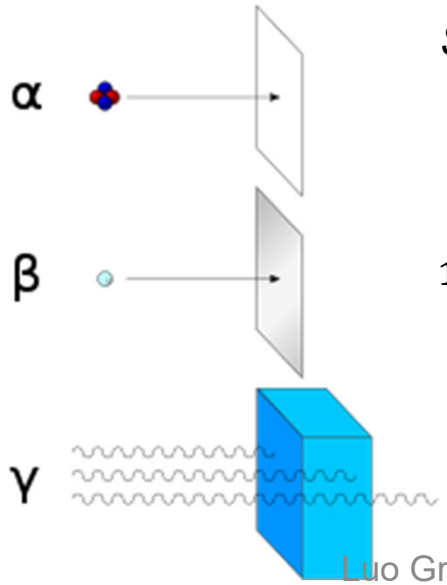
- *Isotope: atoms with same atomic number*
  - *From Greek roots: "isos" (equal) & "topos" (place)*

$${}^{A}_{Z}E$$

Frederick Soddy (1877-1956)
1921 Nobel Prize in Chemistry

- *Unstable isotope (radioactive isotopes)*





Smoke detector: $^{241}AmO_2$ ($t_{1/2}$ = 432.2 y)

$${}^{241}_{95}Am \rightarrow {}^{237}_{93}Np + {}^{4}_{2}He$$

Fast energetic electron or positron

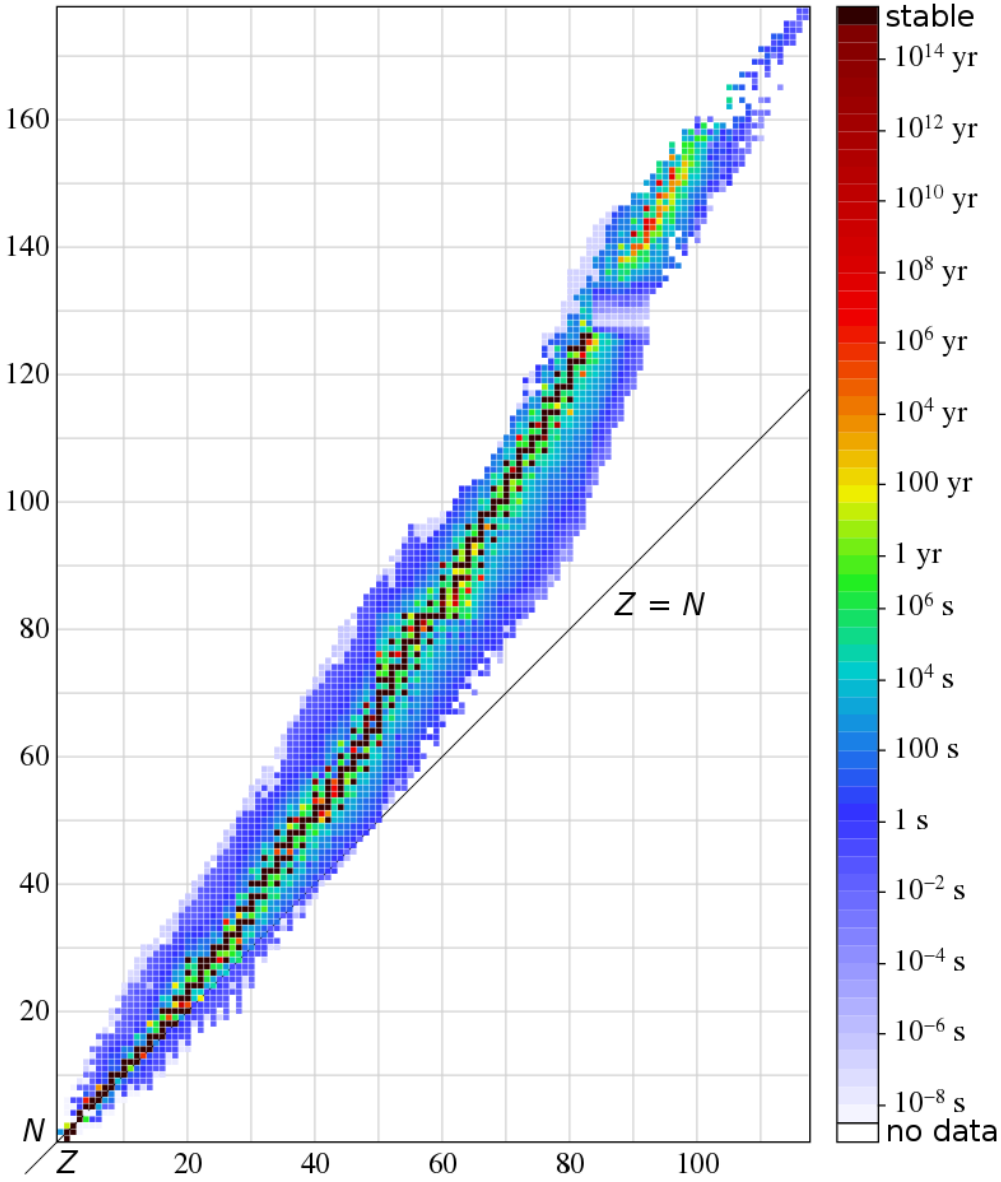
$${}^{14}_{6}C \rightarrow {}^{14}_{7}N + {}^{0}_{-1}e + \nu_e$$ ($t_{1/2}$ = 5730 y)

$\lambda < 10^{-10}$ m, E >1.24 eV

Isotope

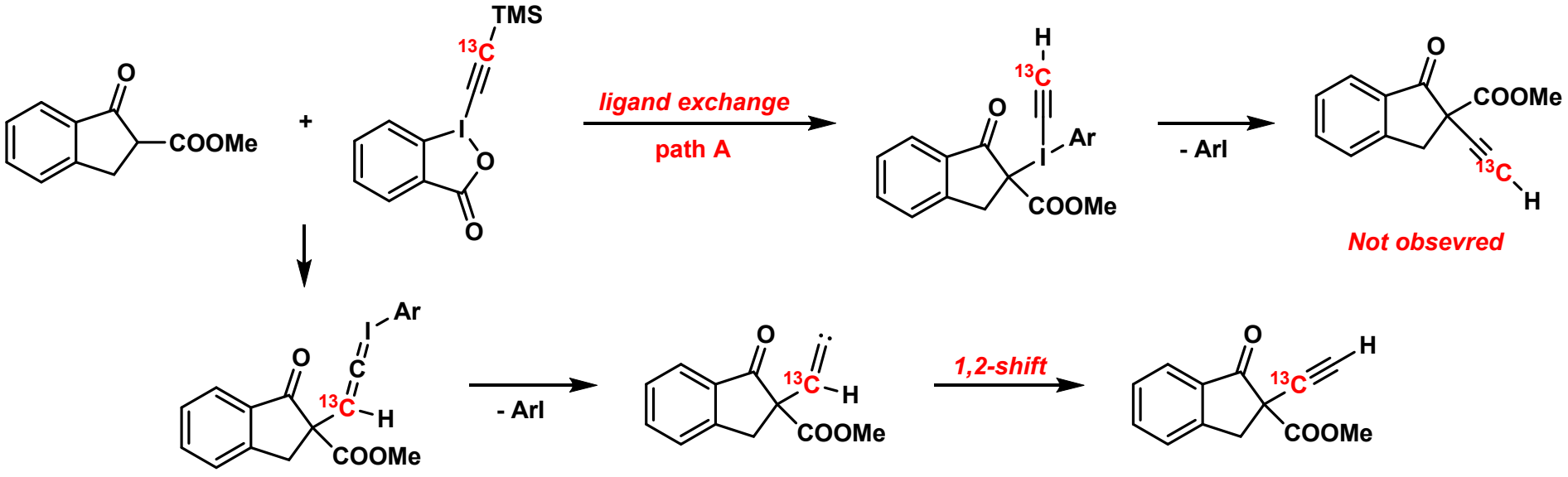
➢ *Stable isotope*

Nuclide	Natural abundance	Spin
^{1}H	[0.99972, 0.99999]	1/2
^{2}H (D)	[0.00001, 0,00028]	1
^{12}C	0.9893(8)	0
^{13}C	0.0107(8)	-1/2
^{14}C	trace	0
^{14}N	0.99636(20)	1
^{15}N	0.00364(20)	-1/2
^{16}O	0.99757(16)	0
^{17}O	0.00038(1)	5/2
^{18}O	0.00205(14)	0
^{19}F	1.0000	1/2



Synthetic Isotopic Chemistry

- *Strategy for isotopic labeling (long half-life & stable isotope)*
  - *Exchange ~ Late stage derivatization* (P → P*)
  - *Construction ~ Total synthesis* (A → B* → C* → P*)
  - *Reconstruction ~ Semi-synthesis* (P → A → B* → A* → P*)
- *Usage*
  - *NMR solvent: $CDCl_3$, C_6D_6, THF-d_8, etc…*
  - *Mechanism study: KIE, isotope tracer*

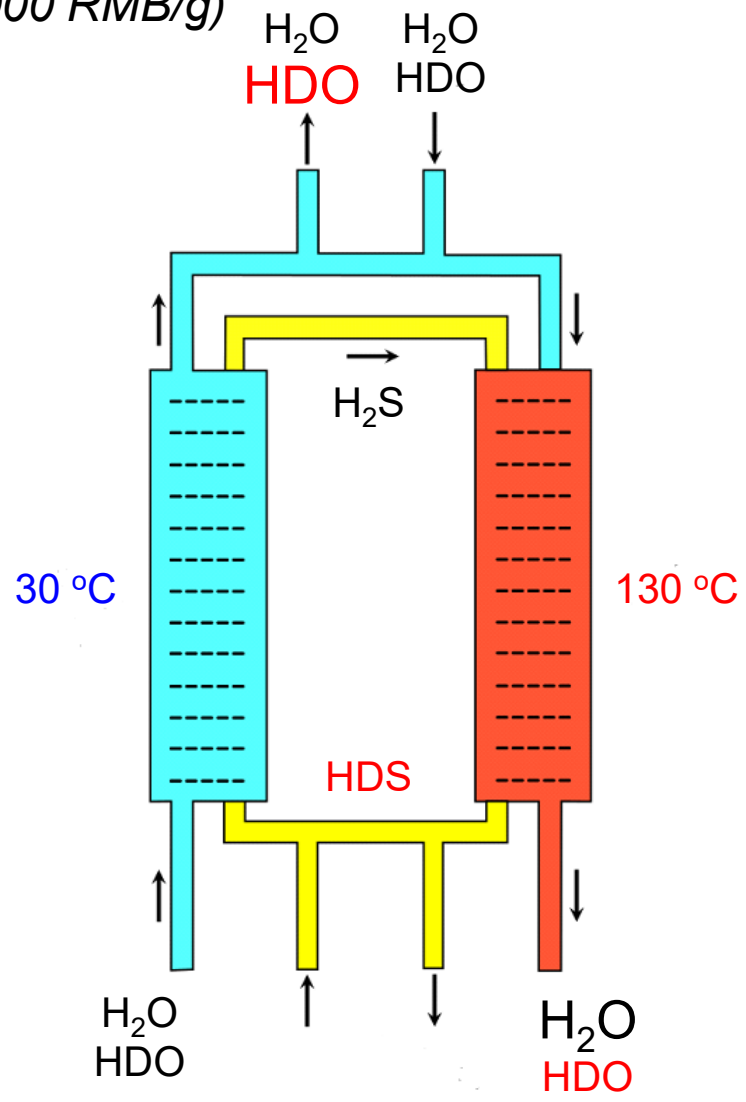


- *Biological tracing: metabolic pathway, PET-CT, SILAC*
- *…*

Overview of ^2H (D)

- *Source: all D-labelled compounds come from D_2O (~ 10 RMB/g)*
  - *All ^{18}O-labelled compounds come from $H_2{}^{18}O$ (~ 2000 RMB/g)*

	H_2O (light water)	HDO (semiheavy water)	D_2O (heavy water)
B. P.	100 °C	100.7 °C	101.4 °C
pH (25 °C)	7.0	7.266 (pHD)	7.44 (pD)
U°	1.230 V	-	1.240 V
abuandance	1	1/3200	-



- *Gridler sulfide process (invented in 1943)*
  - *Enrichment process*

$$H_2O + HDS \rightleftarrows HDO + H_2S$$

K = 2.33 (30 °C), K = 1.82 (130 °C)

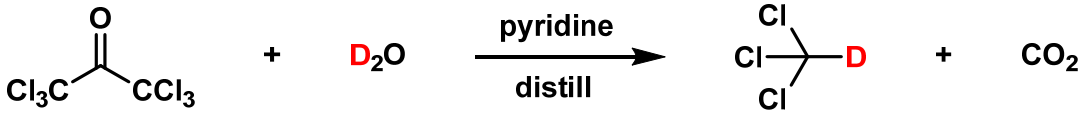
28% more D each cycle (ideally)
Water is enriched to 15-20% D_2O

- *Distillation to get reactor gread D_2O (> 99%)*

D-Labelled Solvent

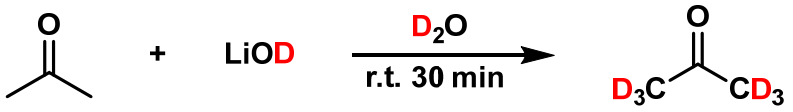
- *Chloroform-d (~ 1.6 RMB/g)*

up to 97% D
w/ several runs

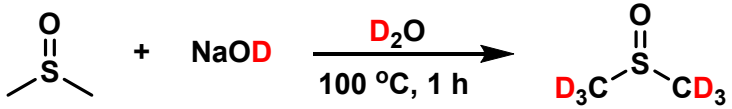


99.3% D

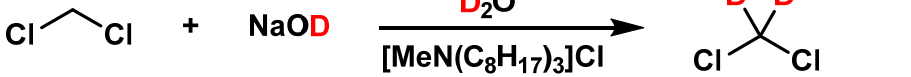
- *Via basic H-D exchange*



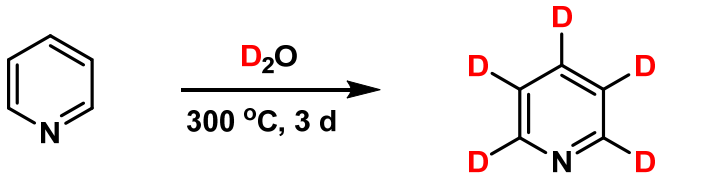
99.5% D after 4 runs
~ 20 RMB/g



~ 20 RMB/g



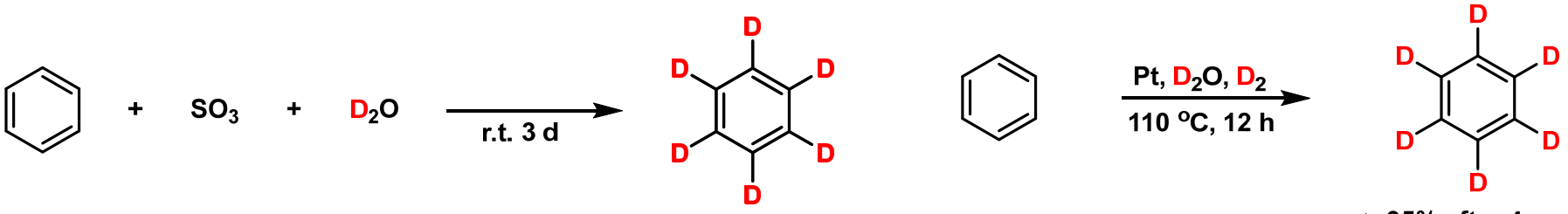
98.7% D after 2 runs
~ 50 RMB/g



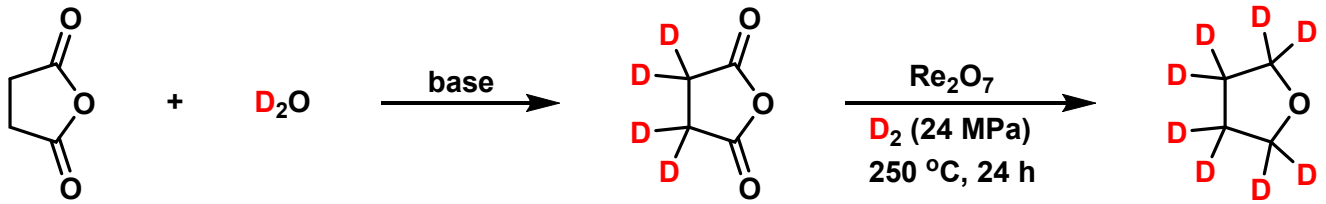
95% D at each site
~ 80 RMB/g

D-Labelled Solvent

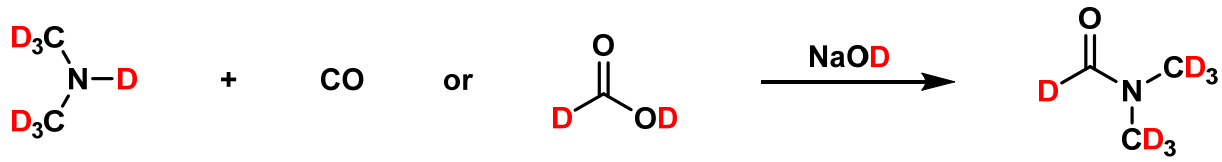
- *Benzene-d_6 (~ 40 RMB/g)*



- *THF-d_8 (~ 200 RMB/g)*

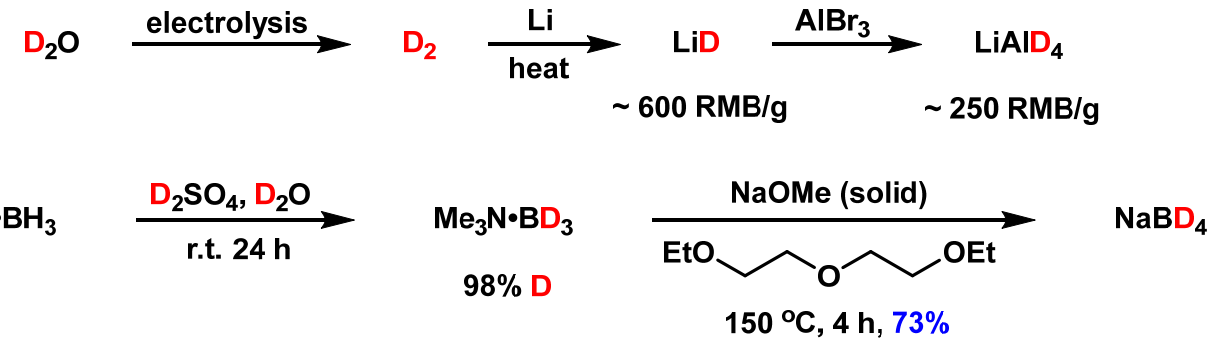


- *DMF-d_7 (~ 400 RMB/g)*

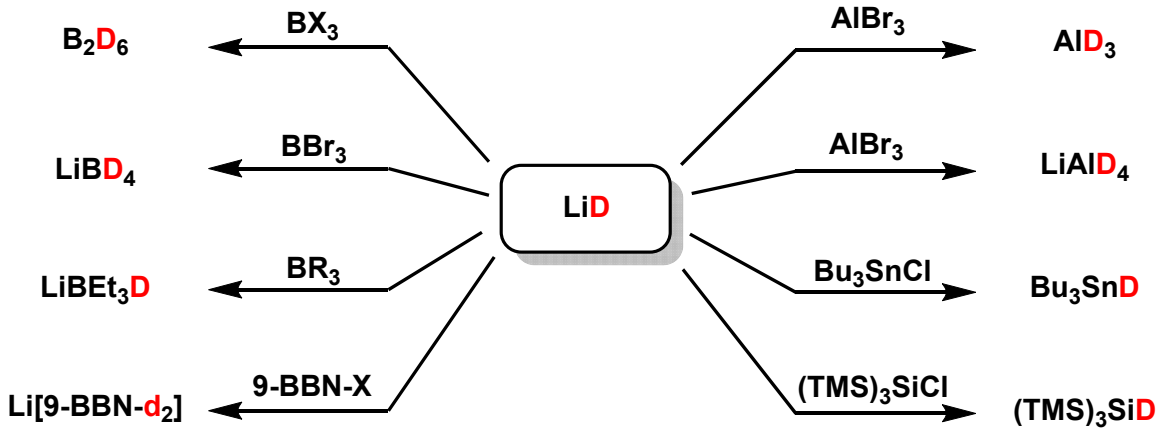


D-Labelled Hydrides

- *Electrolyzed D_2O*

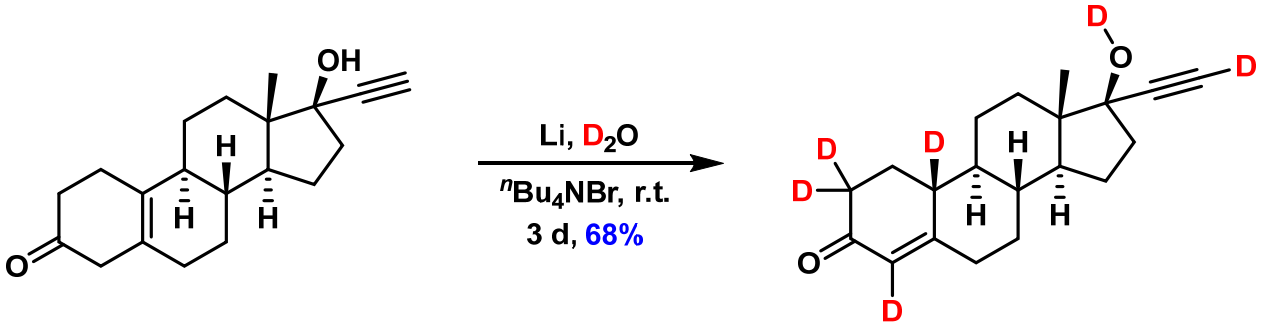


- *Other D-hydrides*



D-Labeling in Synthesis

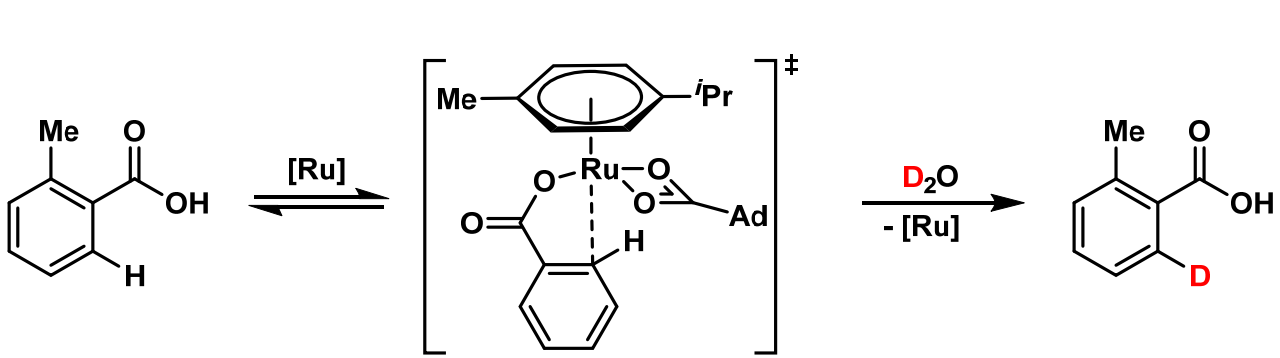
- *H/D exchange*

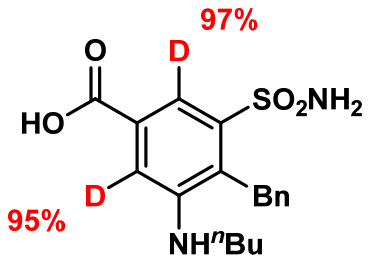


	d_4	d_5	d_6
Li	21.9	38.9	28.9
Na	23.6	30.8	23.0

Journal of Labelled Compounds, **1989**, *27*, 629-633.

- *H/D exchange: via C-H activation*



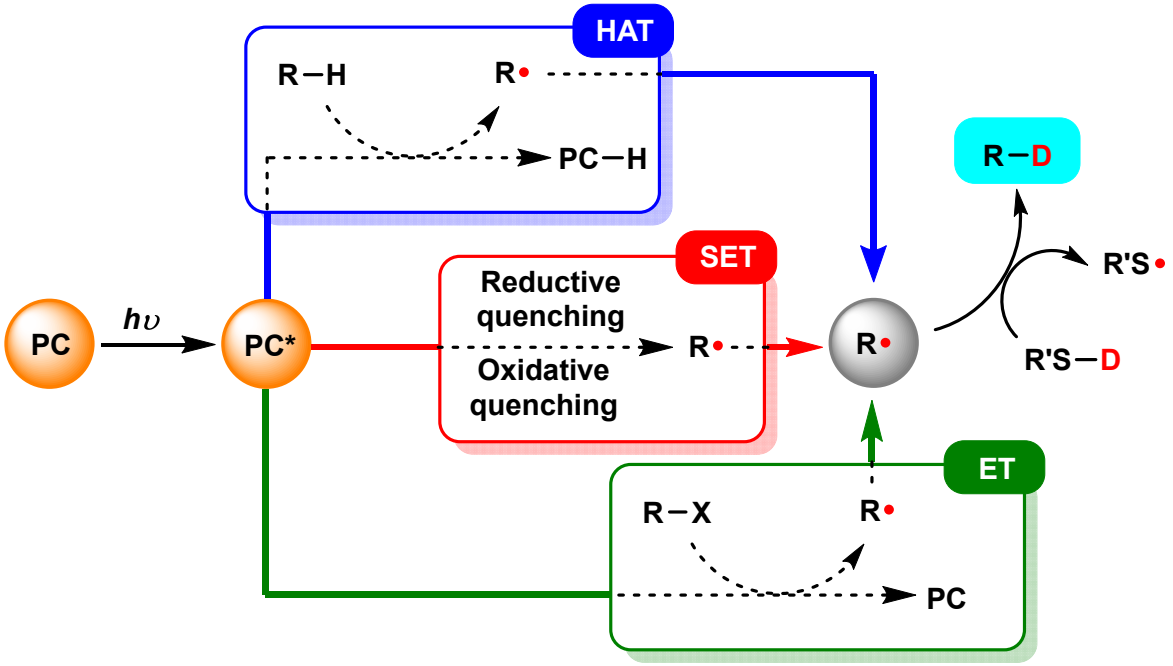


Bumetanide
Bumex®

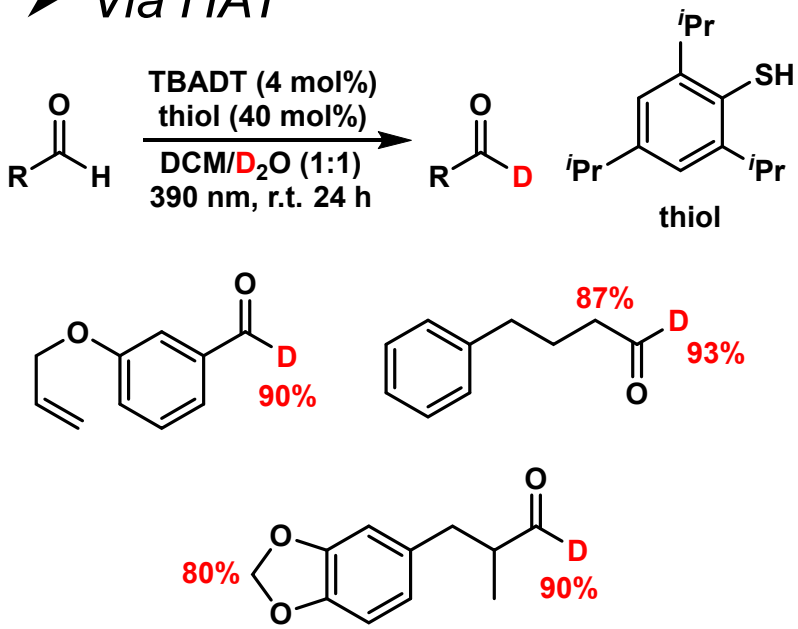
Chem. Cat. Chem, **2020**, *12*, 100-104.

D-Labeling in Synthesis

➢ *D quenched carbon radical*

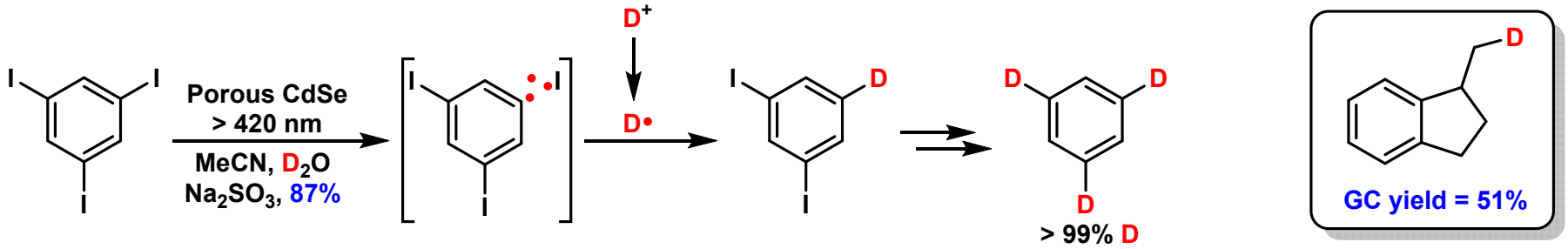


➢ *Via HAT*



Chem. Sci., **2020**, *11*, 1026-1031.

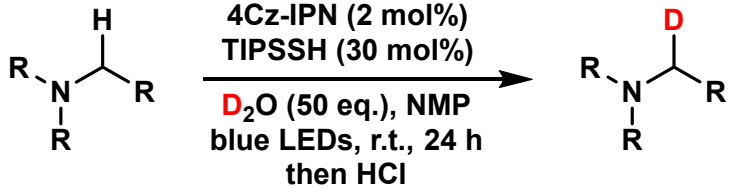
➢ *Via ET*

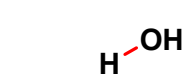


Nat. Commun. **2018**, *9*, 80.

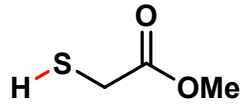
D-Labeling in Synthesis

- *Via SET*

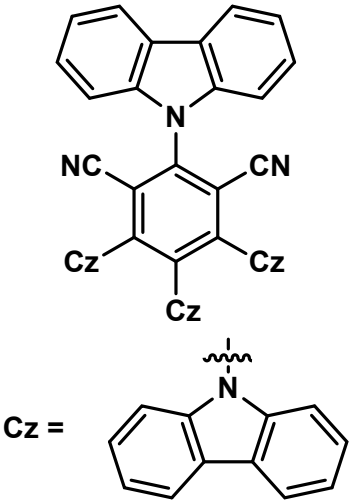


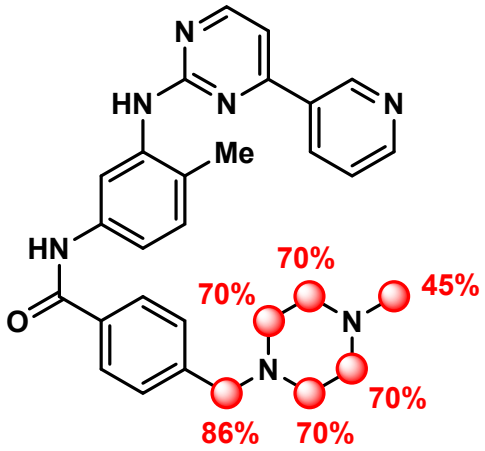


BDE = 119 kcal/mol
pKa (DMSO) = 32.0



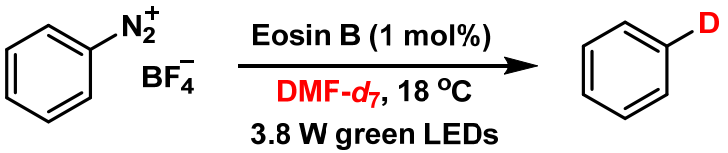
BDE = 87 kcal/mol
pKa (DMSO) = 14.1

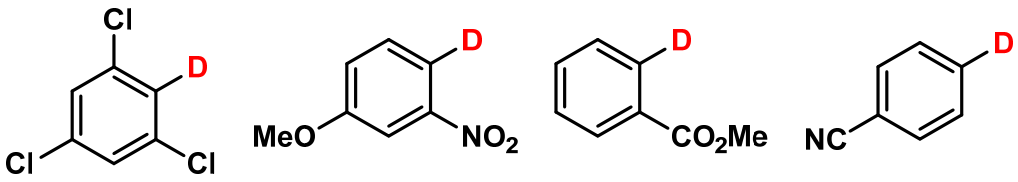




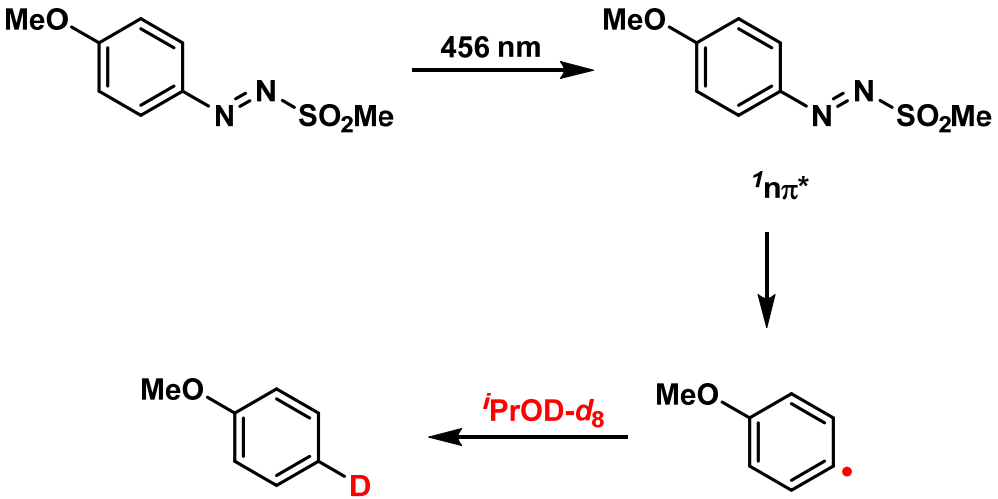
Imatinib, 59%
8.66 D/molecule

Science **2017**, *358*, 1182-1187.





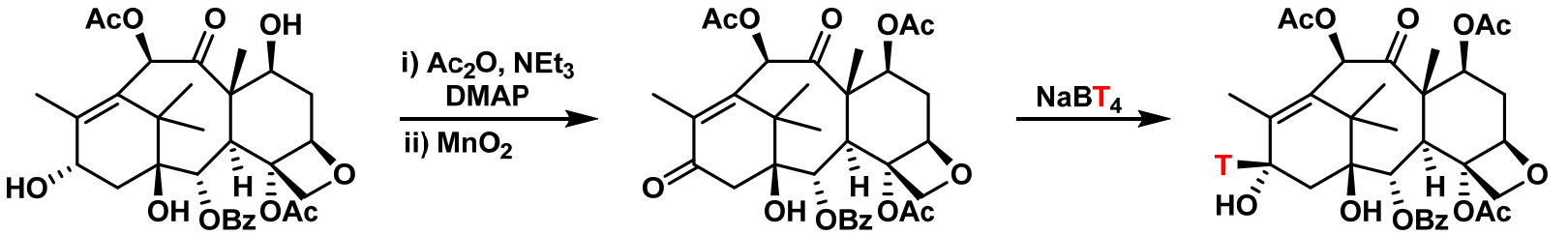
Chem. Eur. J., **2015**, *21*, 4518–4522.



Molecules, **2019**, *24*, 2164-2173.

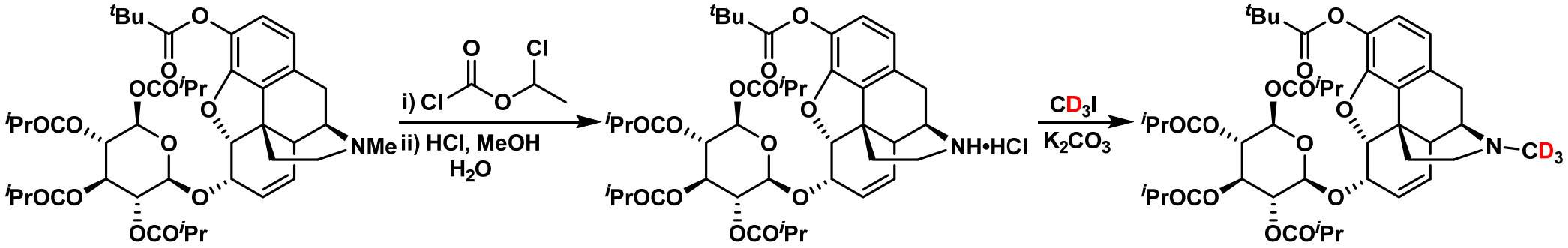
D-Labeling in Synthesis

- *Via reconstruction* (P → B → A* → B* → P*)
  - *Baccatin III*



J. Nat. Prod. **2010**, *73*, 151–159.

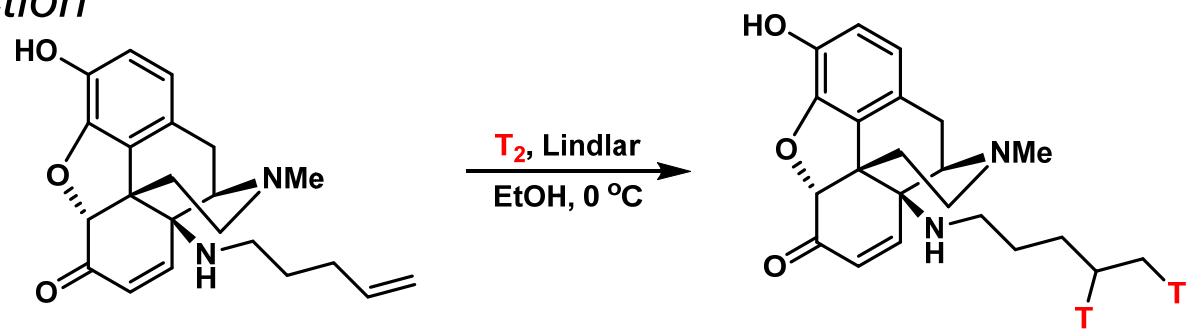
- *Morphine-6-b-D-glucuronide*



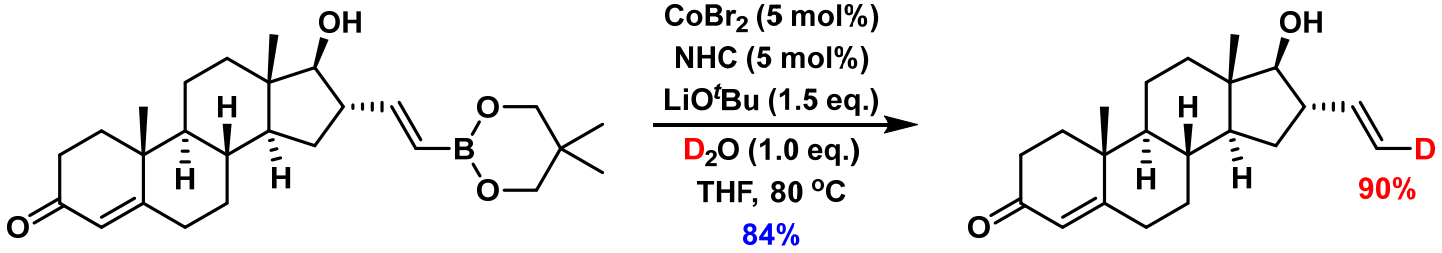
J Label Compd Radiopharm **2002,** *45,* 107–113.

D-Labeling in Synthesis

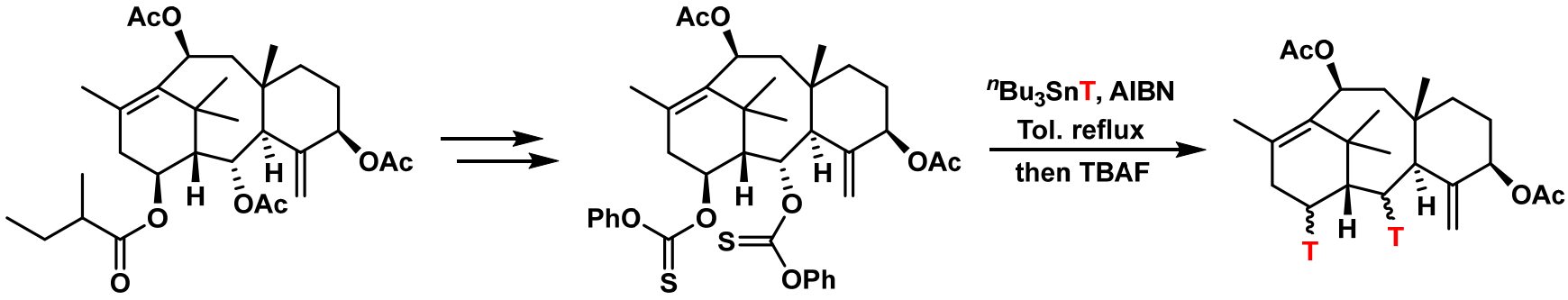
- *Via construction*



J Radioanal Nucl. Chem. **2020,** *326,* 1727–1732.



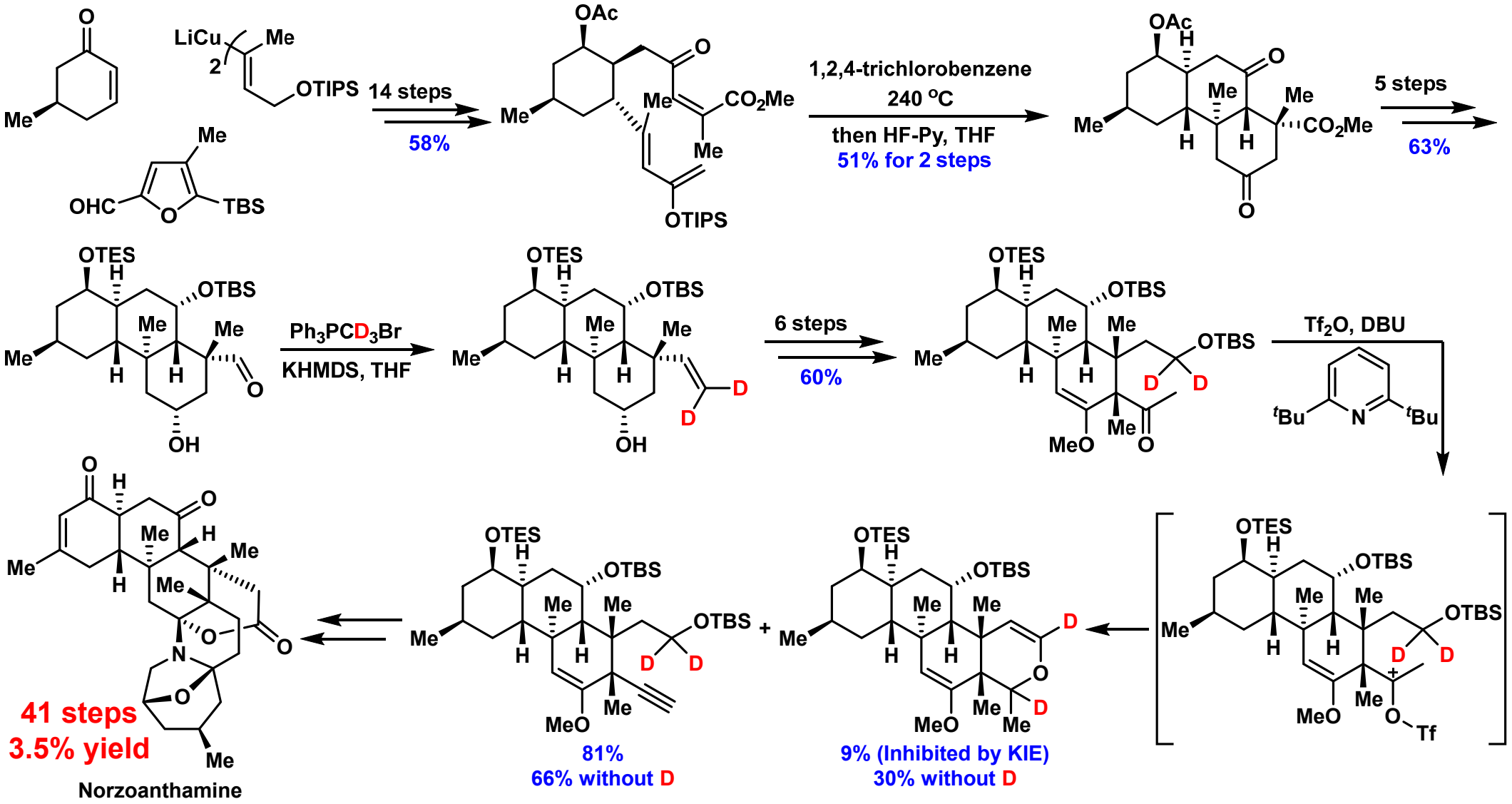
J. Org. Chem. **2021**, *86*, 1972−1979.



J Label Compd Radiopharm **2008,** *51, 325*–328.

D-Labeling in Synthesis

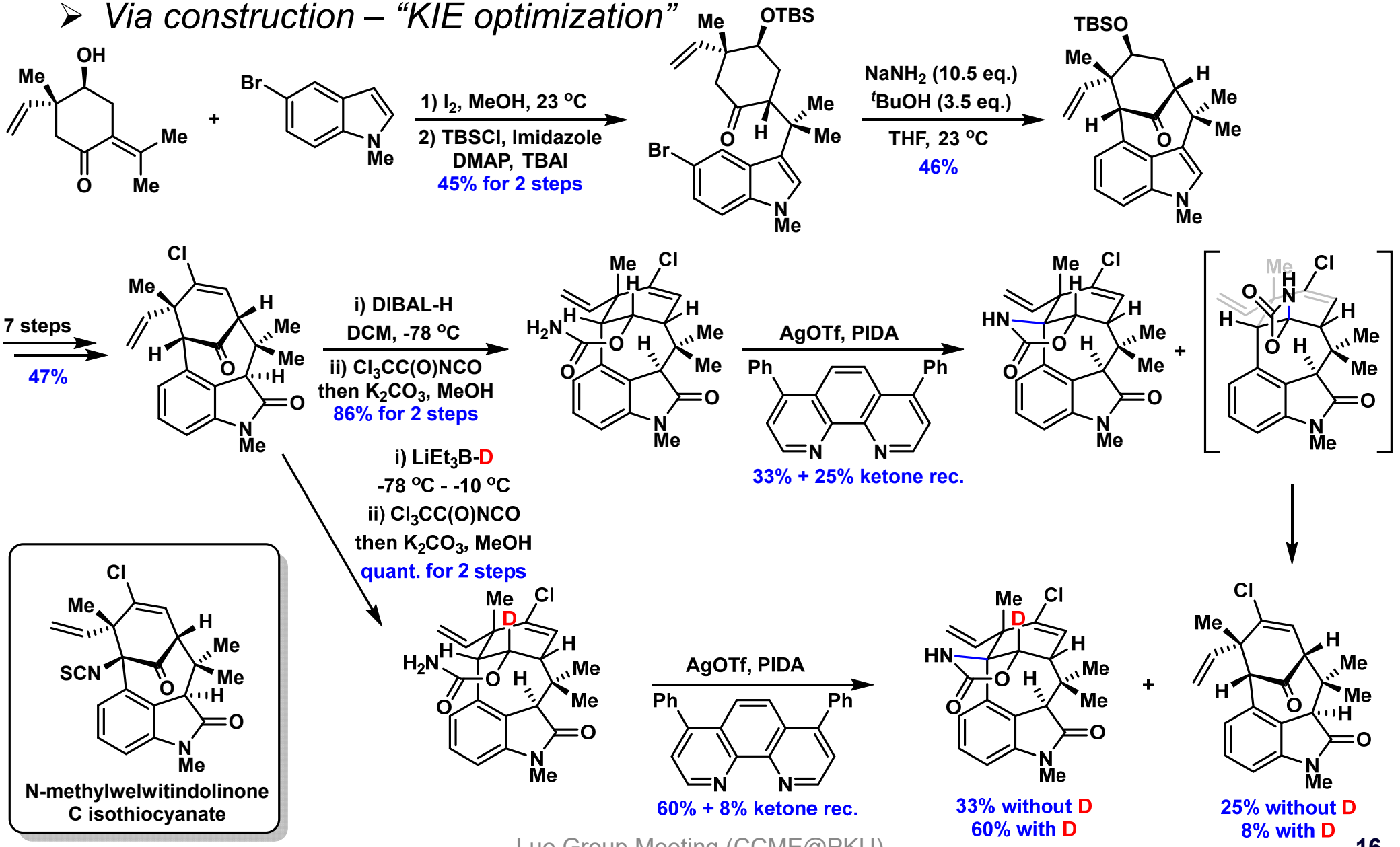
- *Via construction – "KIE optimization"*



Science **2004**, *305*, 495-499

D-Labeling in Synthesis

➢ *Via construction – "KIE optimization"*

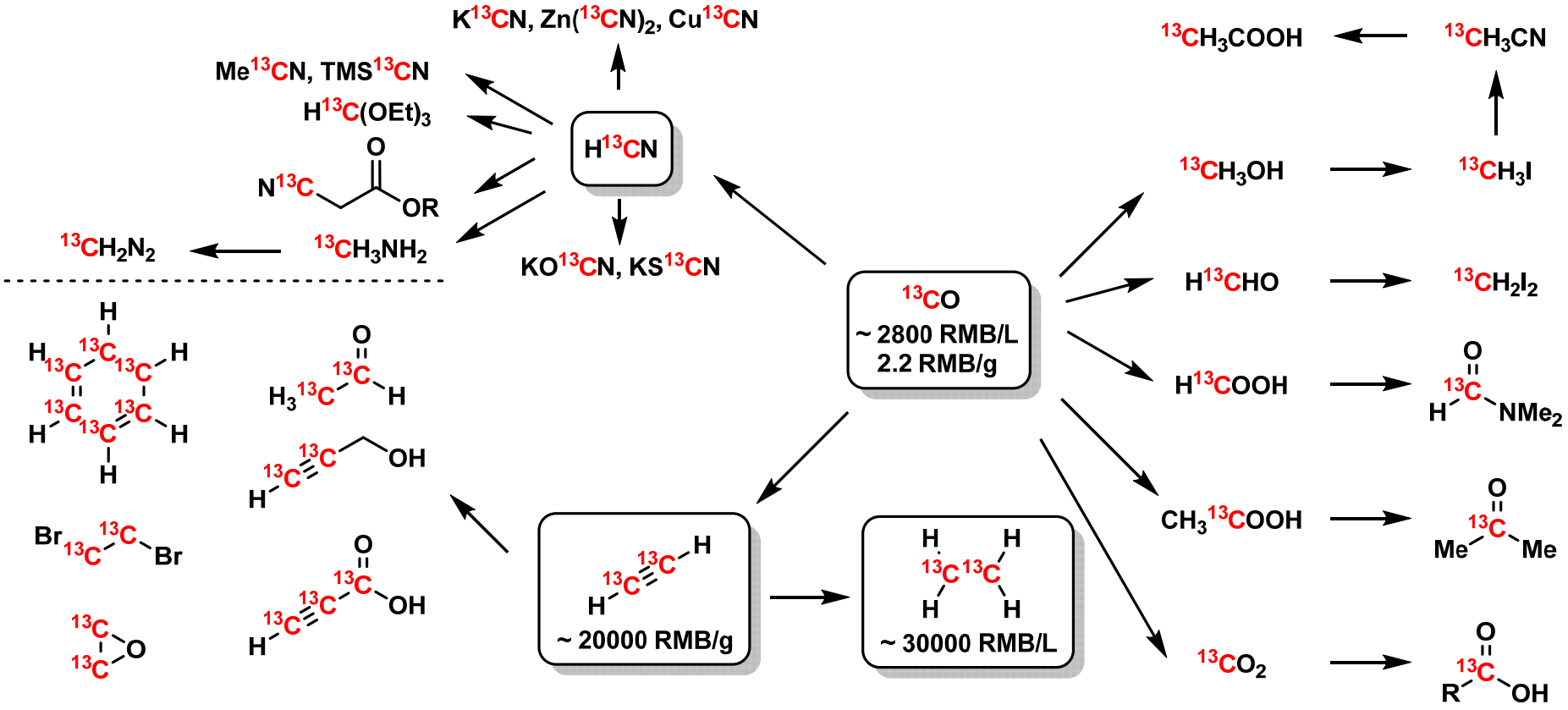


J. Am. Chem. Soc. **2011**, *133*, 15797–15799. **2012**, *134*, 1396−1399.

Overview of ^{13}C & ^{14}C

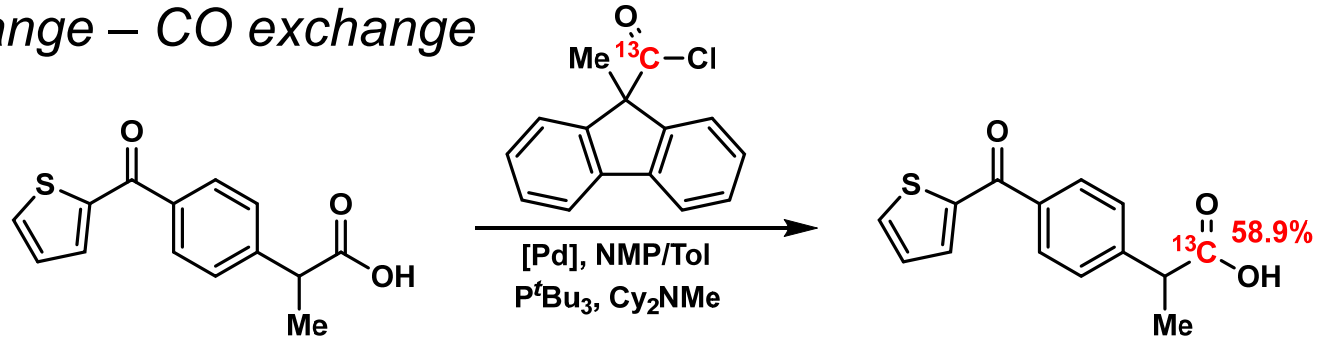
Isotope	Abundance	Commercial	Half-life	Preparation	Decay
^{13}C	1%	^{13}CO	-	-	-
^{14}C	10^{-12}	^{14}CO	5730 y	$^{14}N + {}^{1}n \rightarrow {}^{14}C + {}^{1}p^{+}$	$^{14}C \rightarrow {}^{14}N + e^{-}$

- *All ^{13}C compounds come from ^{13}CO (~ 3800 RMB/L, isolated via cryo-distillation)*



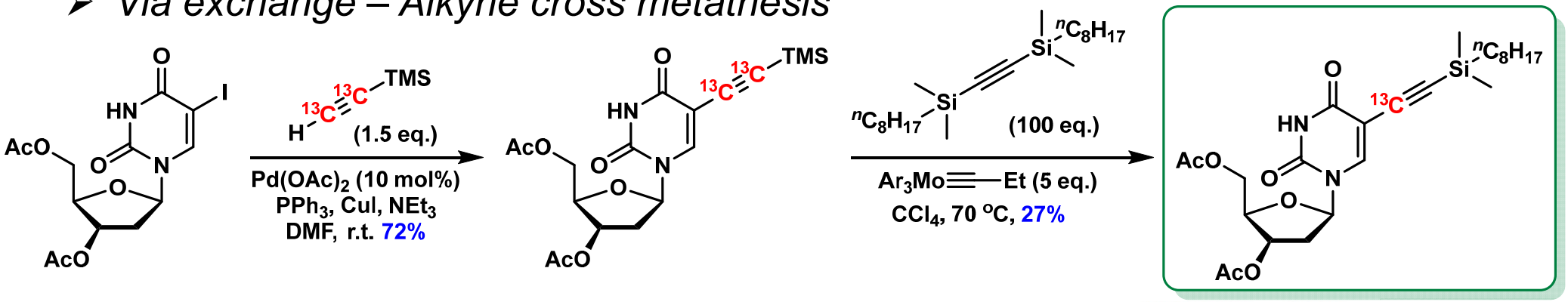
^{13}C-Labeling

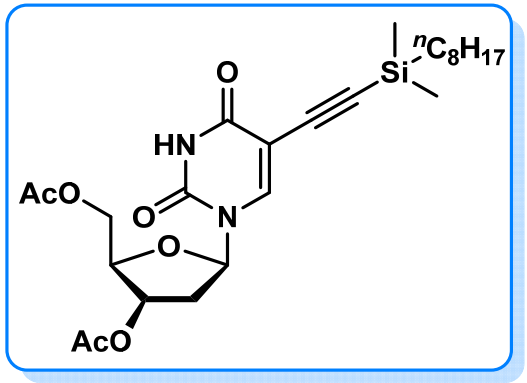
- *Via exchange – CO exchange*

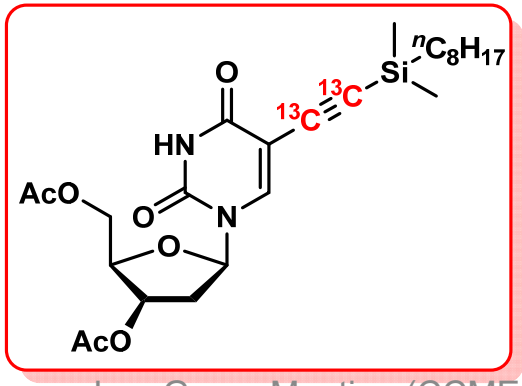


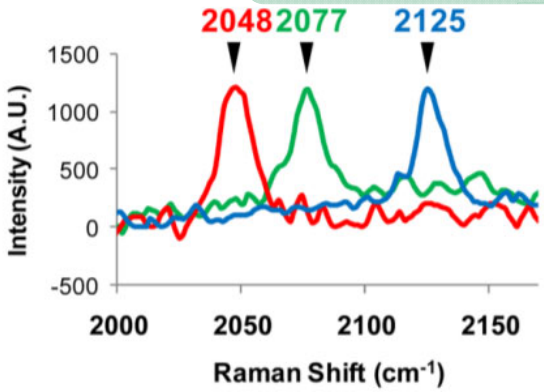
J. Am. Chem. Soc. **2018**, *140*, 15596−15600.

- *Via exchange – Alkyne cross metathesis*





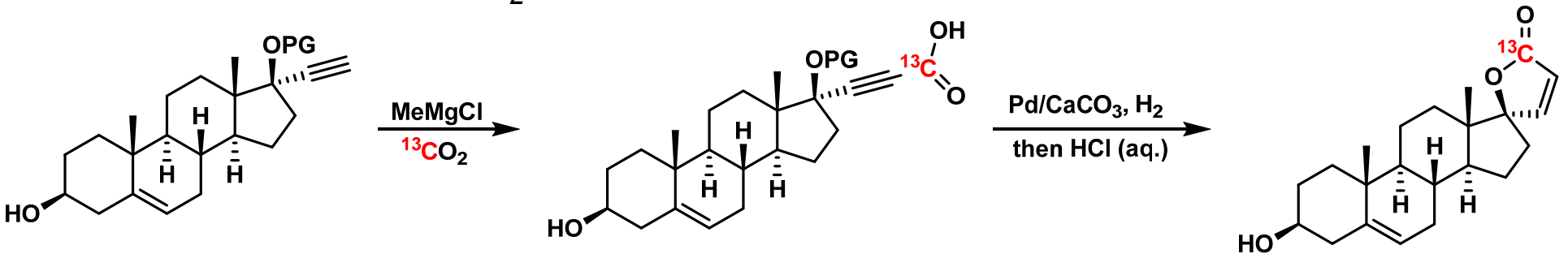




J. Am. Chem. Soc. **2014**, *136*, 8027−8033.

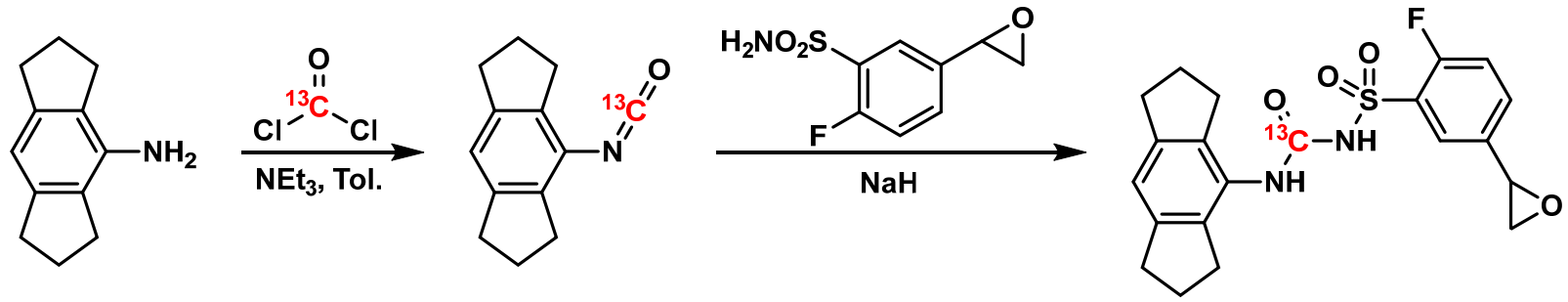
^{13}C-Labeling

- *Via construction – $^{13}CO_2$*



J Label Compd Radiopharm **1988,** *25, 515–529.*

- *Via construction – $^{13}COCl_2$*

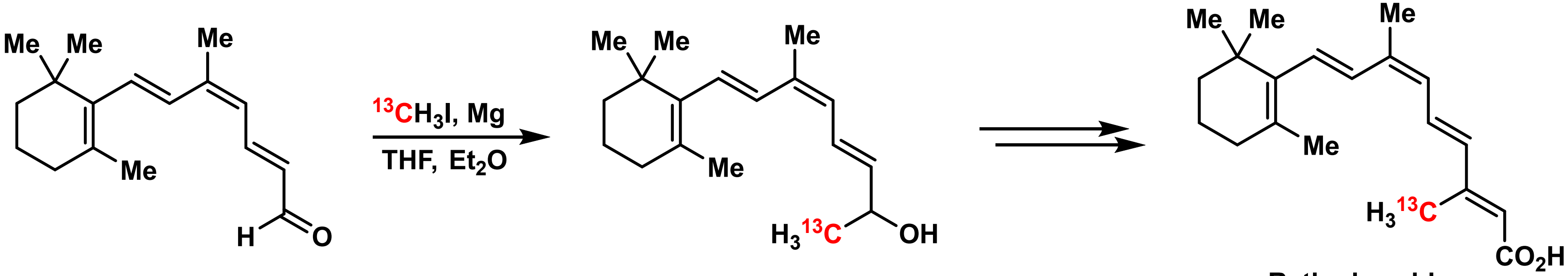


J Label Compd Radiopharm **2002,** *45, 785–794.*

- *H^{13}CHO, $^{13}CH_3I$, $BrCH_2{}^{13}COCl$, etc…*

^{13}C-Labeling

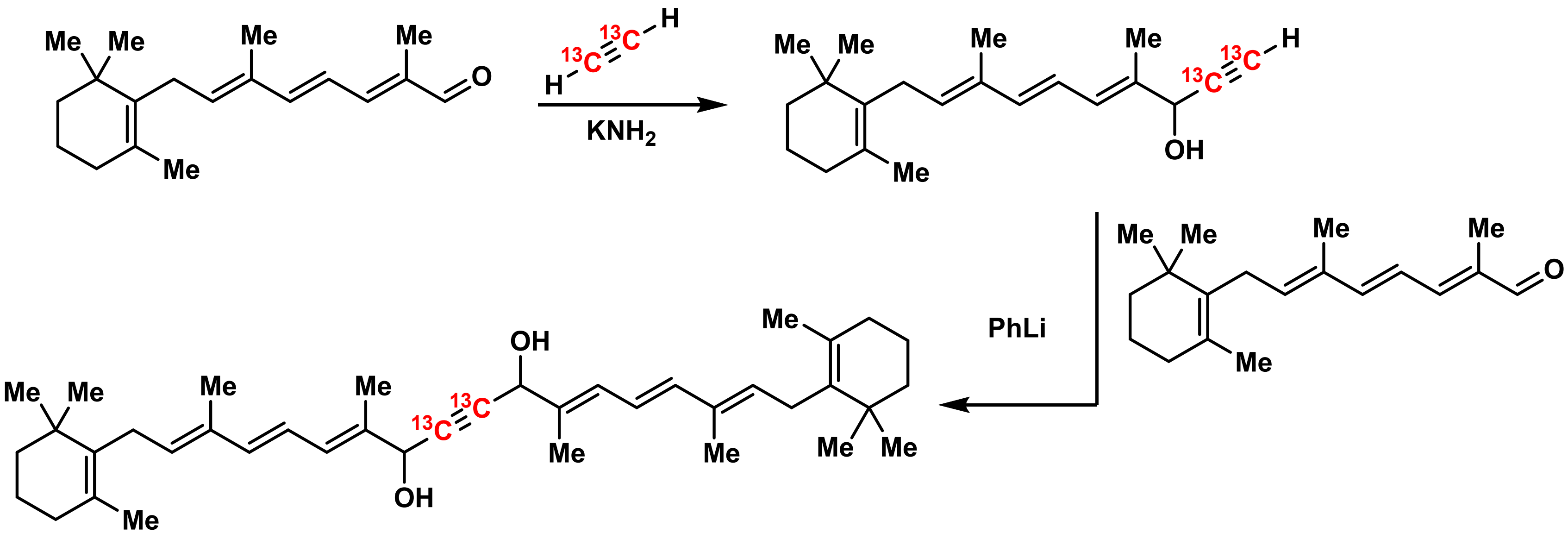
- *Via construction – $^{13}CH_3I$*



Retinoic acid

Pure & Appl. Chem. **1985,** *57, 753–762.*

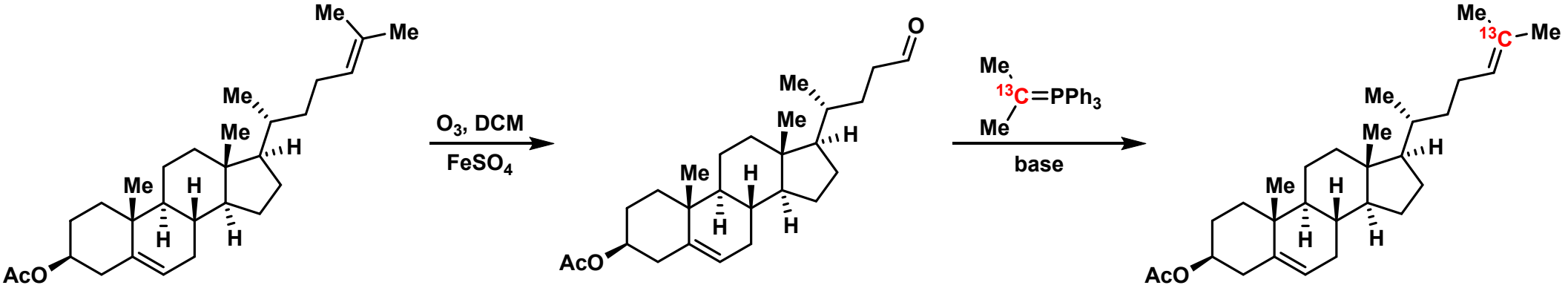
- *Via construction – $H^{13}C^{13}CH$*

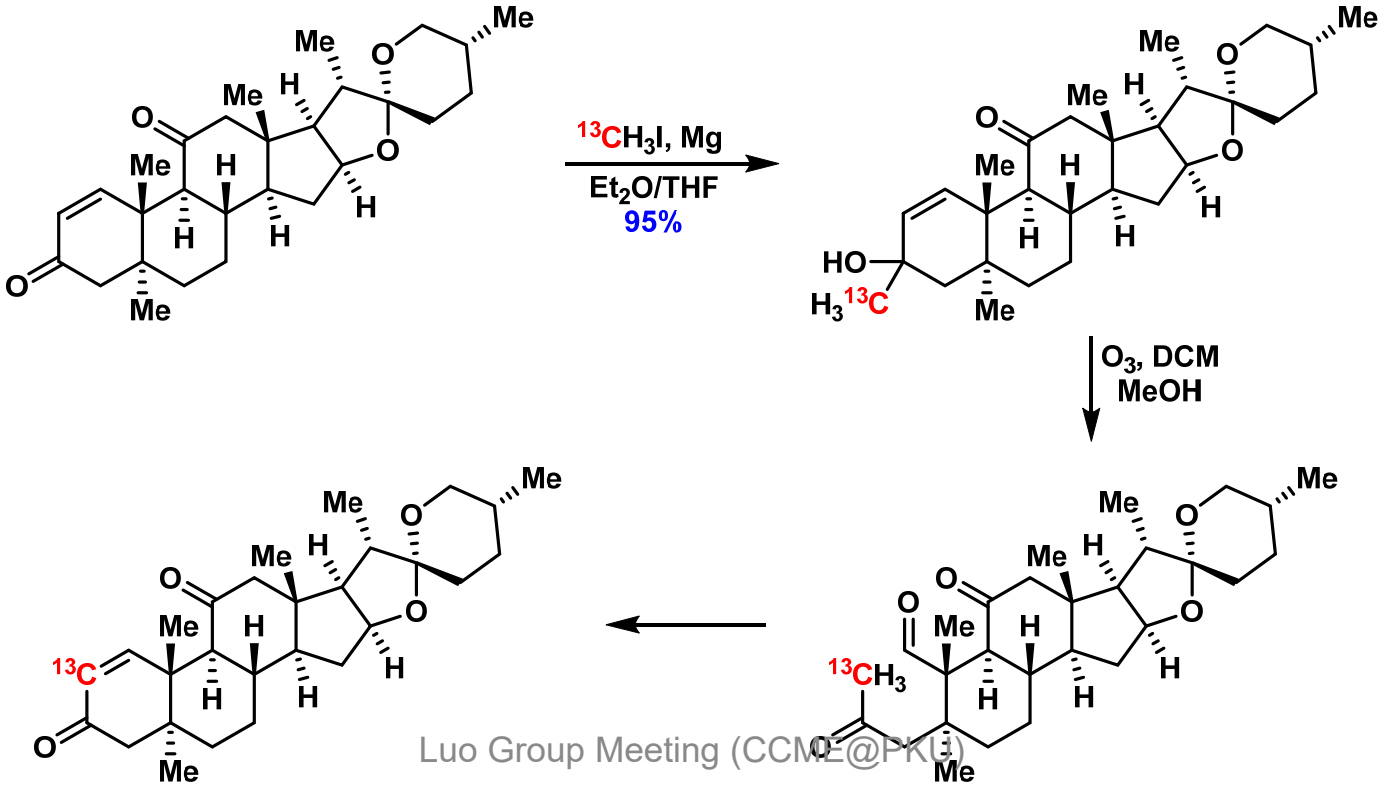


- *$^{13}CH_2N_2$, TMS^{13}CN, etc…*

^{13}C-Labeling

- *Via reconstruction*





Unstable Isotope

- *Radioactivity*
  - *Nuclear reaction equation:* $^{40}_{19}K \rightarrow {}^{40}_{20}Ca + {}^{0}_{-1}e + \nu_e$ ($t_{1/2}$ = 10^9 y)
  - *Unit:*
    - *Activity:* Becquerel (贝克勒尔) : 1 Bq = 1 decay/s
      Curie (居里) (1 g ^{226}Ra) : 1 Curie = 37G Bq
    - *Dose:* Sievert (西弗) : 1 Sv = 1 J/Kg

	1 banana	1 h plane	X-Ray	Natural	Safe dose	Disease	Death
Dose (mSv)	0.0001	0.01	0.02	2.4 /year	1 /year	2000-4000	> 4000

- *Short half-life isotope*
  - *^{18}F (110 min), ^{11}C (20 min), ^{13}N (10 min), ^{15}O (2 min), ^{131}I (8 h)*
  - *^{32}P (14 days), ^{35}S (87 days)*
  - *Not commercial available*
  - *Fast chemical reaction*
  - *Late stage functionalization*

Overview of ^{18}F

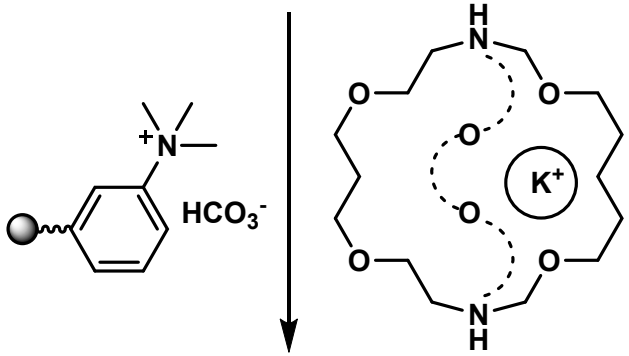
Isotope	Commercial	Half-life	Preparation	Decay
^{18}F	-	110 min	$^{18}O + p\ (15\ MeV) \rightarrow {}^{18}F + n$ $^{20}Ne + {}^{2}D^{*} \rightarrow {}^{18}F + {}^{4}He$	$^{18}F \rightarrow {}^{18}O + e^{+}$ $e^{+} + e^{-} \rightarrow 2\ \gamma\ (511\ keV)$

- *In hospital ^{18}F-FDG synthesis*
  - *High energy proton generation (Cyclotron)*
  - *$^{18}F^{-}$ synthesis*

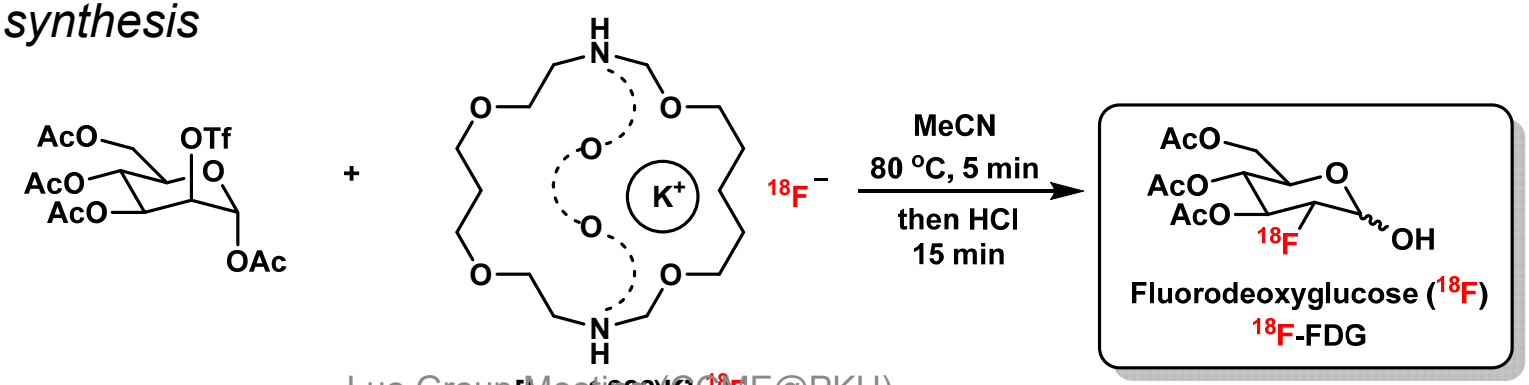
$$H_2{}^{18}O + p^{+}\ (15\ MeV) \rightarrow H^{+} + H{}^{18}F \cdot n(H_2{}^{18}O) + n$$

(~ 2000 RMB/g)

- *Anhydrous extraction*



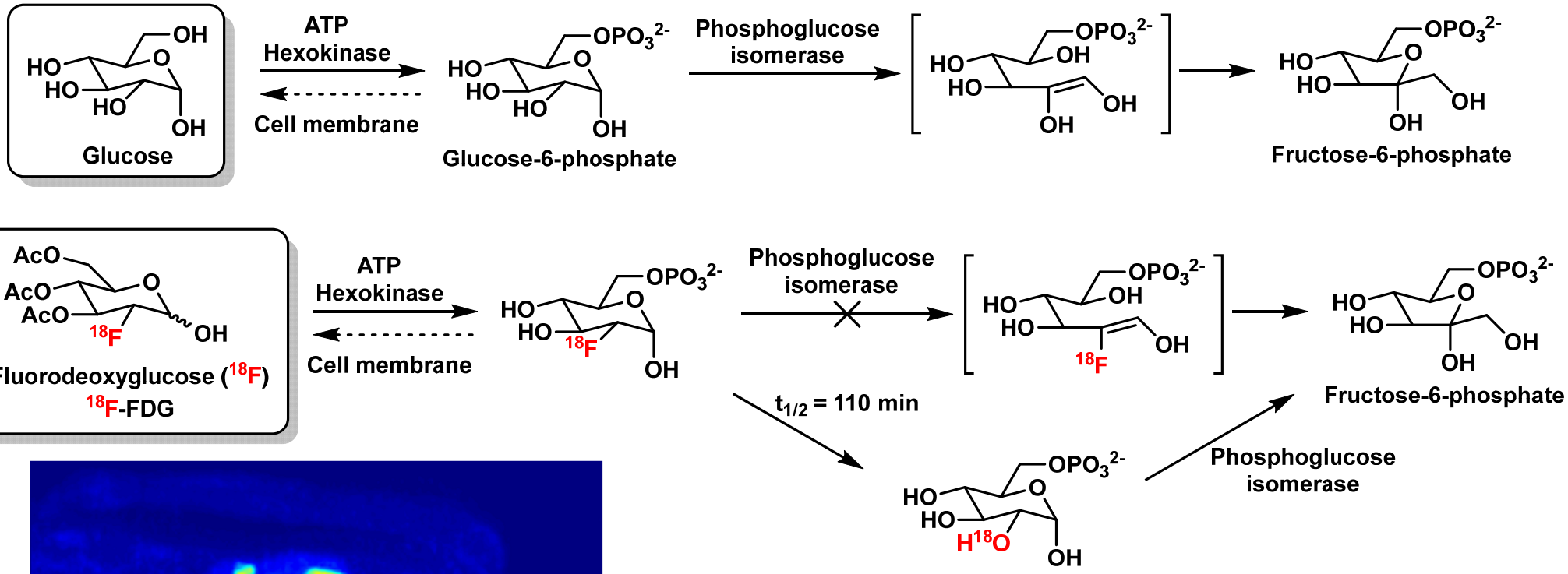
- *Organic synthesis*

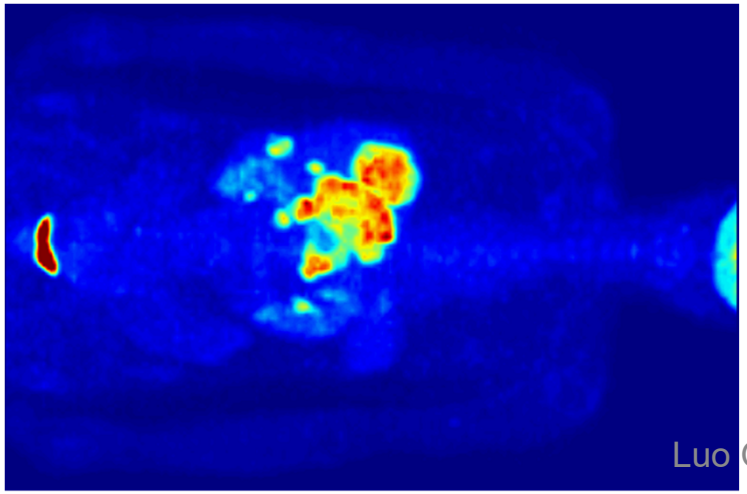


[(crypt-222)K]^{18}F

^{18}F-FDG & PET-CT

- *PET-CT*
  - *Fasting for at least 12 h, blood sugar test*
  - *Injection of ^{18}F-FDG (30 mSv, 8 MBq/kg) (Full body CT: 15 mSv)*



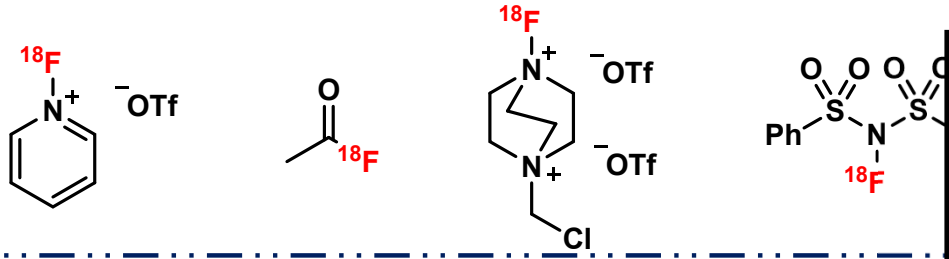


High-glucose-using cells: brain, kidney, and cancer cells.
Diagnosis, staging, and monitoring treatment of cancers.
Colorectal, breast cancer, and lung cancer.

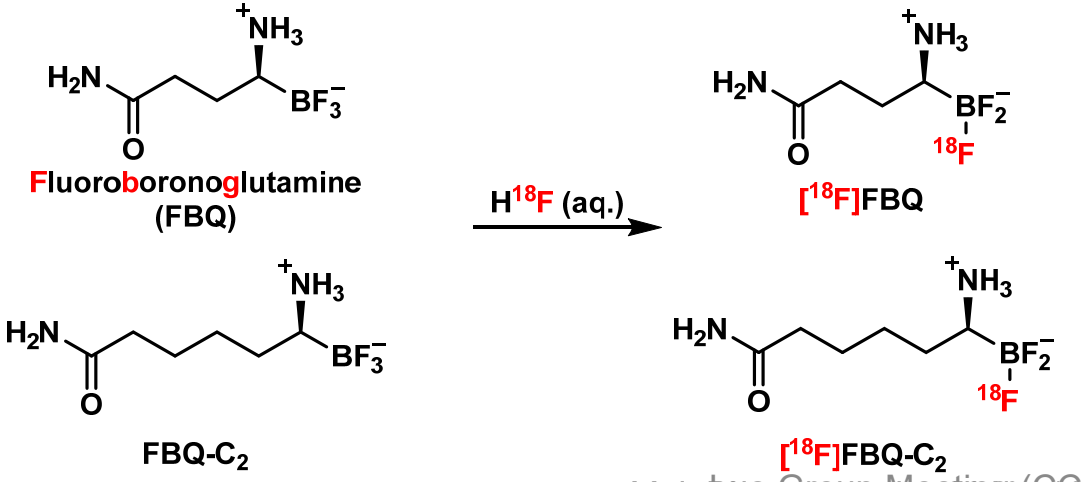
^{18}F-Labeling

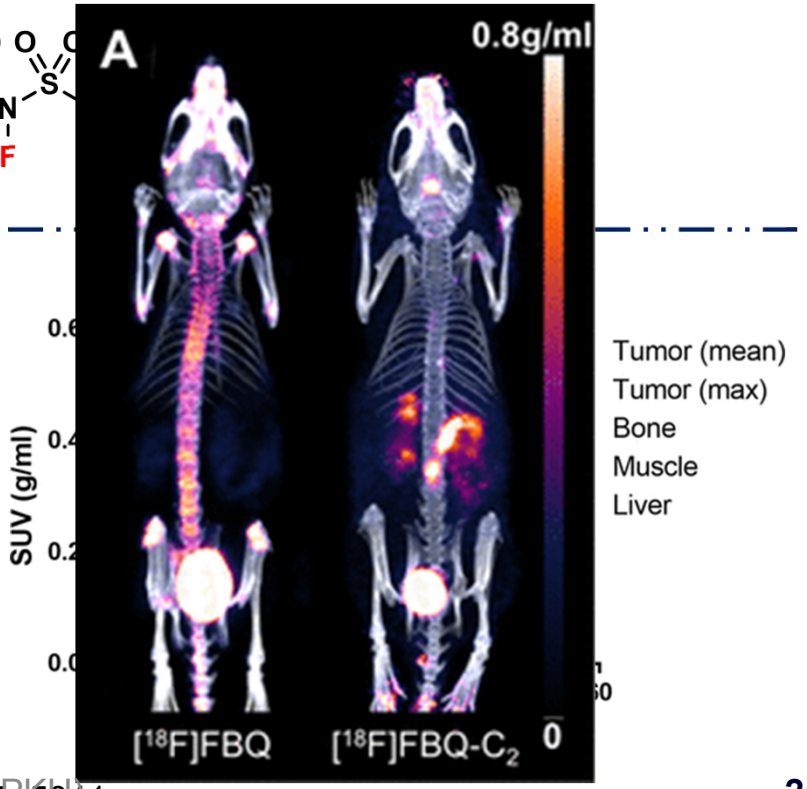
- *Other ^{18}F source*

Nuclear reaction	^{20}Ne → ^{18}F	^{18}O → ^{18}F	^{18}O → ^{18}F
Target	^{20}Ne (200 μmol of F_2)	$^{18}O_2$, Kr (50 μmol of F_2)	$H_2{}^{18}O$
Product	[^{18}F]F_2	[^{18}F]F_2	[^{18}F]fluoride
Specific activity (GBq/μmol)	0.04 – 0.40	0.35 – 2.00	4 x 10^4



- *R-BF_3^-: ^{18}F exchange*





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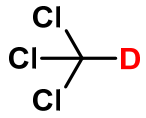
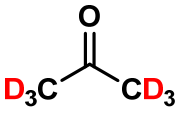
Summary

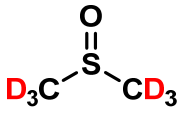
- ^{2}H (D)-Labelled solvent



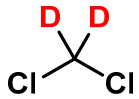
1.6 RMB/g



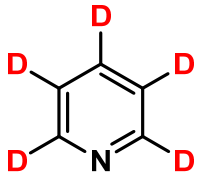
~ 20 RMB/g



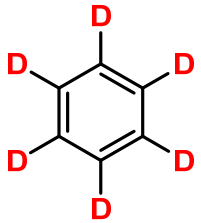
~ 20 RMB/g



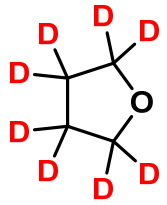
~ 50 RMB/g



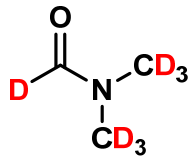
~ 80 RMB/g



~ 40 RMB/g



~ 200 RMB/g



~ 400 RMB/g

- Synthetic 2H (D)-Labeling strategies
- ^{13}C-labelled reagent