Production of ^{11}C-Labeled Radiopharmaceuticals

Part 2

Contents of Lecture

- [^{11}C]Carbon monoxide chemistry
- Labeling agents from cyclotron-produced [^{11}C]methane
- Ring labeling of arenes

[^{11}C]Carbon Monoxide

– Preparation

Zn at 390 °C
or Mo at 850 °C

$^{11}CO_2$ ⟶ ^{11}CO

Preparation time:	5 min
Production efficiency:	~ 90%
Applications:	^{11}CO insertion reactions
	Preparation of other labeling agents

[^{11}C]Carbon Monoxide

- Practical considerations

• Carbon monoxide has low solubility in most organic solvents

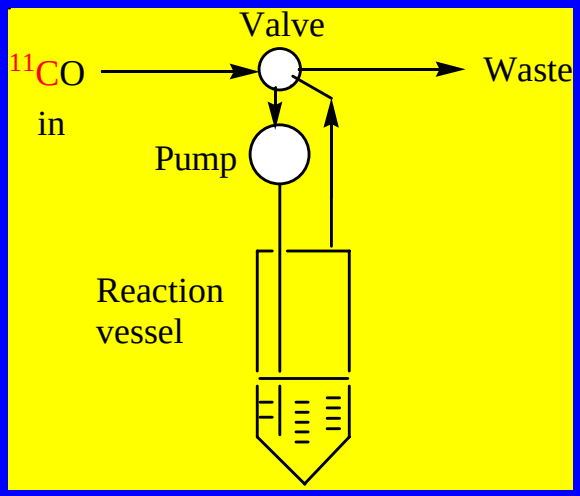
This problem may be countered by:
• Recirculation of the [^{11}C]carbon monoxide through the reaction
or
• Use of a high pressure micro-autoclave

• Carbon monoxide is generally considered to be unreactive

• Reactivity is inducible by Pd(0) species

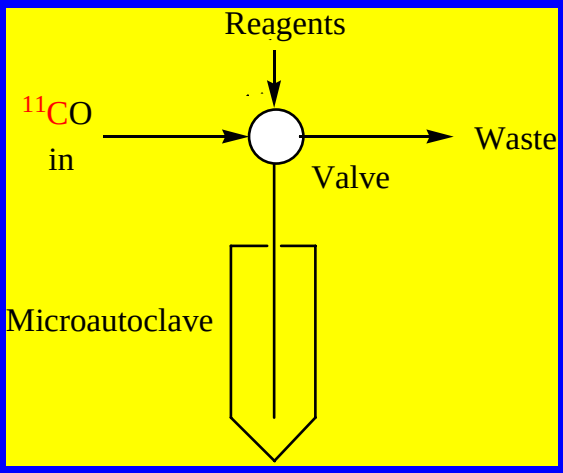
[^{11}C]Carbon Monoxide

- Recirculation method



[^{11}C]Carbon Monoxide

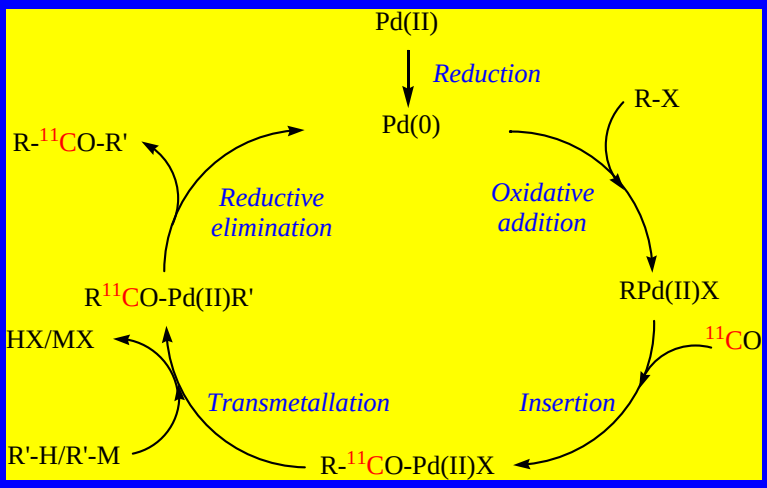
- Microautoclave method



Use of high pressure allows solvents to be used at high temperature
e.g. diethyl ether at 200 °C

[^{11}C]Carbon Monoxide

- *Pd(0)-mediated insertion (between R and R')*

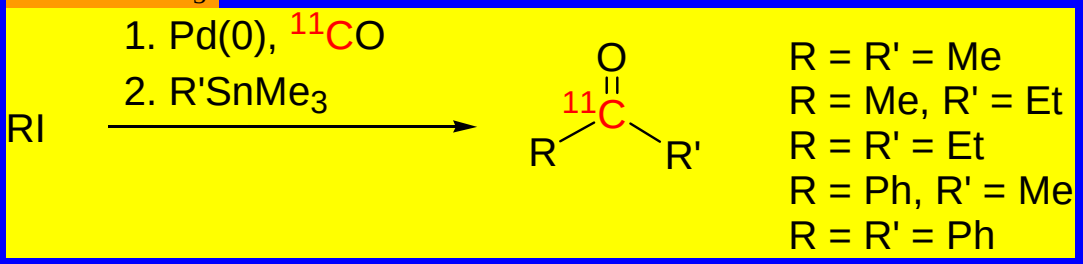


• R and R'can vary greatly.

[^{11}C]Carbon Monoxide

- *For preparation of ^{11}C-labeled ketones from iodides (1)*

M = $SnMe_3$



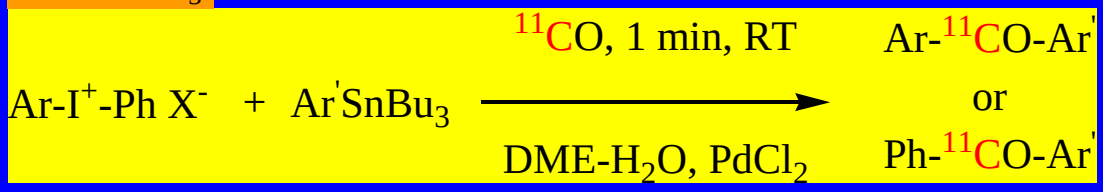
• Radiochemical yields in DMSO are 62-82% within 30 min from EOB

• Iodoarenes react rapidly (1 min) in 1,2-dimethoxyethane-water at RT; yields are 58-82%

[^{11}C]Carbon Monoxide

- For preparation of ^{11}C-labeled ketones from iodonium salts (2)

M = $SnBu_3$

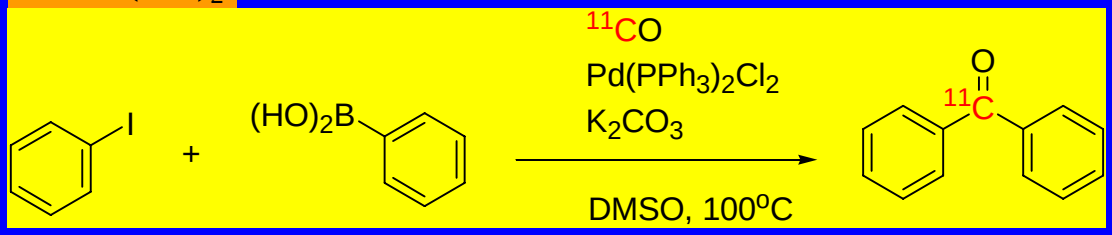


- For Ar' = Ph, decay-corrected radiochemical yields are generally very high (> 96%)
- Me, MeO, CF_3 and F substituents are known to be tolerated

[^{11}C]Carbon Monoxide

- For preparation of ^{11}C-labeled ketones from boron compounds (3)

M = $B(OH)_2$



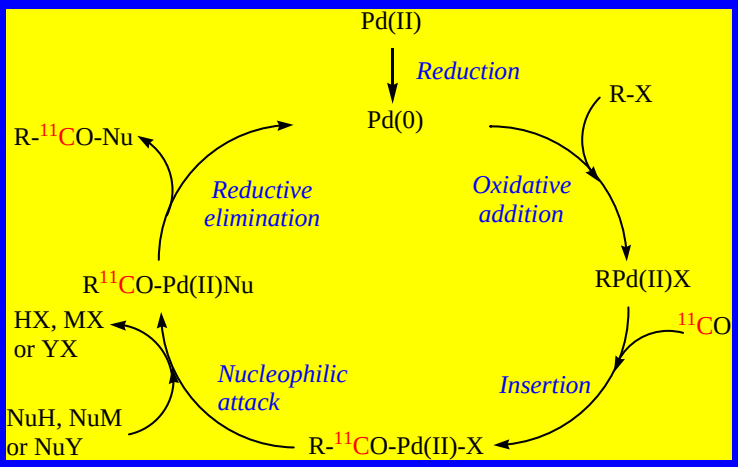
- Method is widely tolerant of functional groups *e.g.* Cl, amido, ether

[^{11}C]Carbon Monoxide

- *Pd(0)-mediated insertion (between R and Nu)*

$$R\text{-}X + {}^{11}CO + NuH/Y/M \xrightarrow[XH/Y/M]{Pd(0)} R^{11}CONu$$

Nu = nucleophile



• R and Nu can vary greatly.

[^{11}C]Carbon Monoxide

- *For preparation of ^{11}C-labeled acids*

NuY = $HO^-N^+R_4$

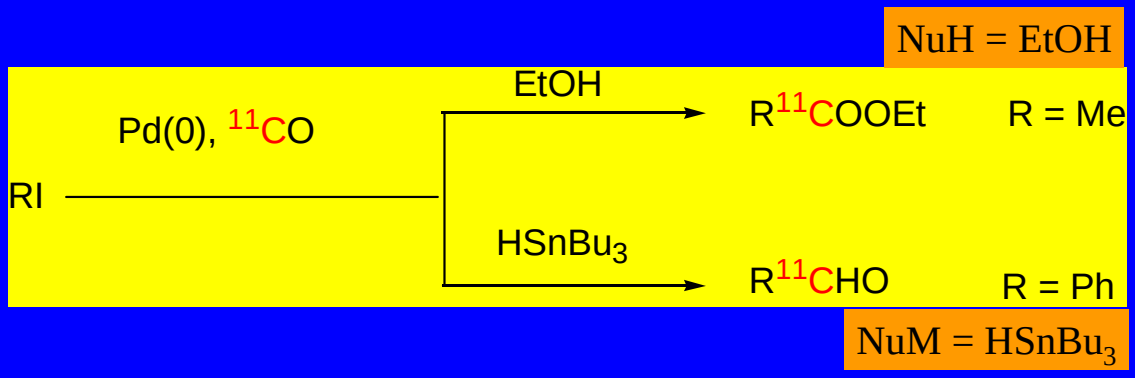
RX + tetrabutylammonium hydroxide or trimethylphenylammonium hydroxide $\xrightarrow[THF,\ 180\text{-}190^oC]{Pd(O),\ {}^{11}CO}$ $R^{11}COOH$

RX = aryl halide
aryl triflate or
benzyl halide

- Radiochemical yields: 20-85%, decay-corrected
- Preparattion time: 25 min
- Specific radioactivity: ~ 20 Ci/μmol

[^{11}C]Carbon Monoxide

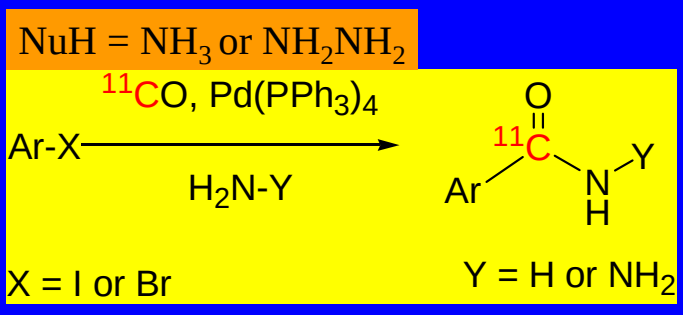
- For preparation of ^{11}C-labeled esters or aldehydes



- No yields reported

[^{11}C]Carbon Monoxide

- For preparation of ^{11}C-labeled primary amides or hydrazides

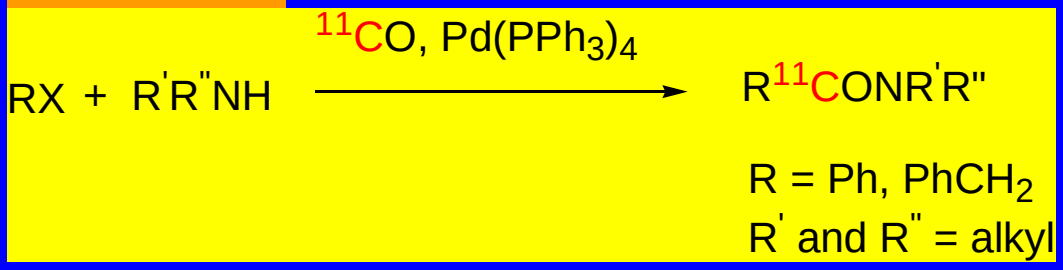


- The method is tolerant of wide functionality (MeO, NO_2, Cl)
- Radiochemical yields are generally very high (40-90%)
- Specific radioactivity is up to 45 Ci/μmol

[^{11}C]Carbon Monoxide

- For preparation of ^{11}C-labeled secondary or tertiary amides

NuH = R'R"NH

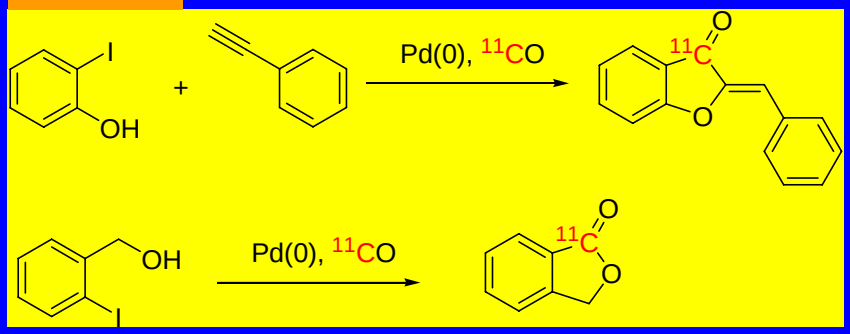


- Radiochemical yields are good to almost quantitative
- Specific radioactivities are up to 25 Ci/μmol
- A wide range of substituents/groups are tolerated (*e.g.* Ar-Cl, tertiary amine, quaternary amine)

[^{11}C]Carbon Monoxide

- In ring closure reactions

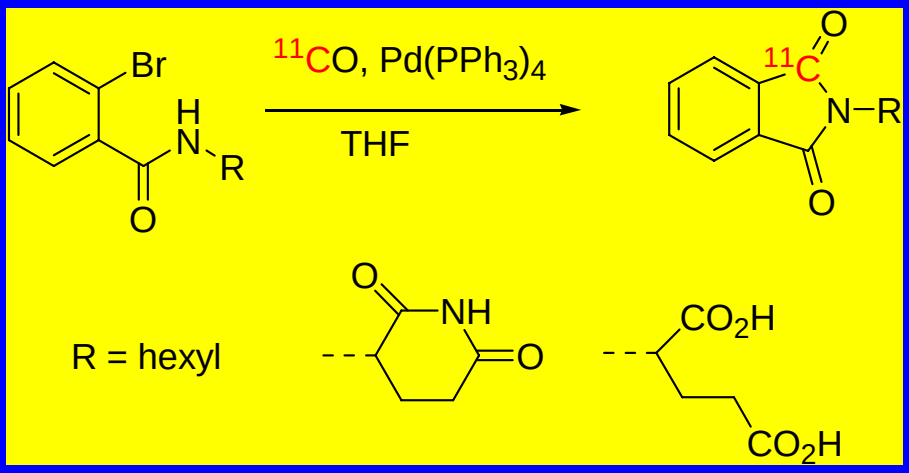
Nu = OH



- Radiochemical yields are high (70-95%)

[^{11}C]Carbon Monoxide

- For preparation of ^{11}C-labeled imides



- Radiochemical yields are nearly quantitative
- High specific radioactivity is obtained (~ 15 Ci/μmol)

[^{11}C]Carbon Monoxide

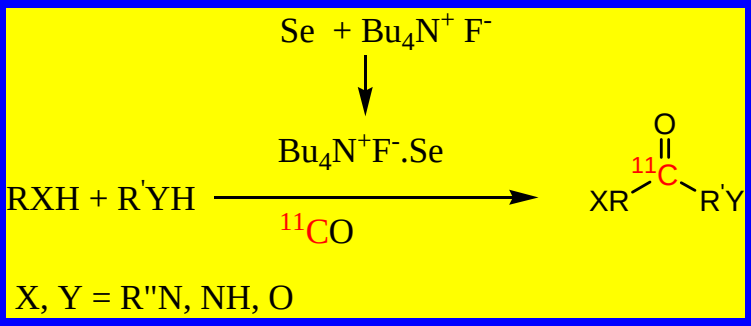
- Conclusions on Pd(0)–mediated reactions

- Pd(0)–mediated reactions are generally highly efficient processes for introducing [^{11}C]carbonyl groups into a wide variety of structures
- The method is very tolerant of functionality
- The method can provide high specific radioactivity

The method is not easily applicable to aryl halides having hydrogen on an *sp*^{3} carbon in β-position – because of a competing elimination reaction

[^{11}C]Carbon Monoxide

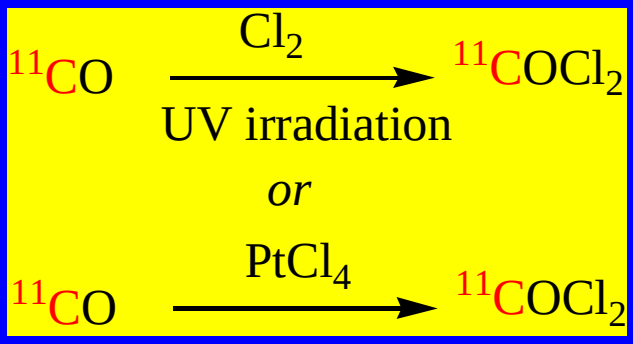
- Labeling of ^{11}C-carbamoyl compounds



• Radiochemical yields range from low to almost quantitative

[^{11}C]Phosgene

- From [^{11}C]carbon monoxide



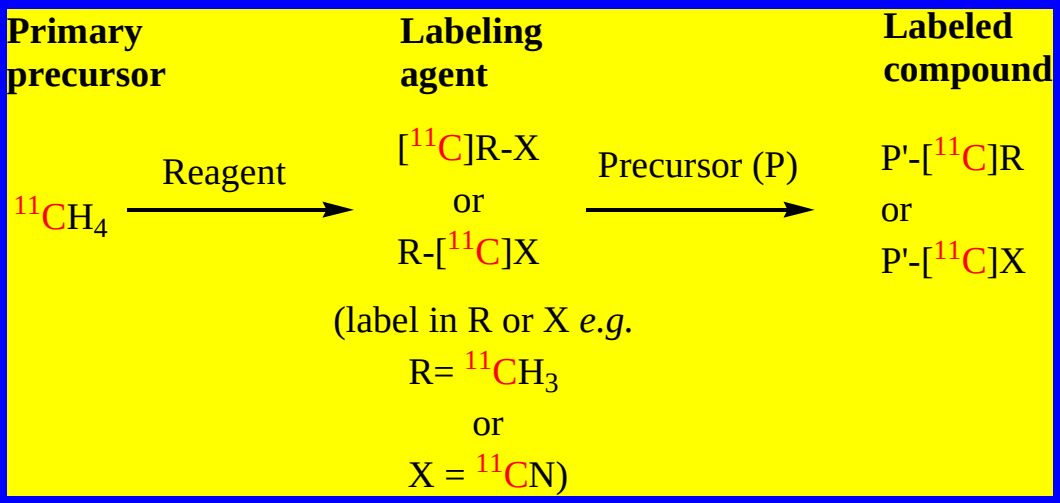
• Specific radioactivity is low by either method

Comparison of [^{11}C]Methane and [^{11}C]Carbon Dioxide as Primary Cyclotron-produced Precursors

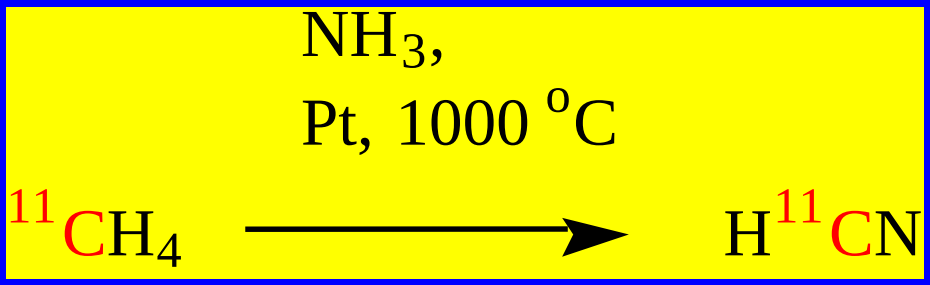
Ease of production:	Same by $^{14}N(p,\alpha)^{11}C$ reaction
Radioactivity obtainable:	Same by $^{14}N(p,\alpha)^{11}C$ reaction
Specific radioactivity:	Higher for [^{11}C]methane
Reactivity:	[^{11}C]Carbon dioxide > [^{11}C]Methane

[^{11}C]Methane generally delivers higher specific radioactivity and provides scope for simple gas phase production of secondary labeling agents

Use of [^{11}C]Methane to Produce Monofunctional Labeling Agents



[^{11}C]Hydrogen Cyanide - Preparation



Preparation time:	~ 5 min
Production efficiency:	~ 80%

H^{11}CN can be trapped in basic solution to give nucelophilic ^{11}CN^{-} ion

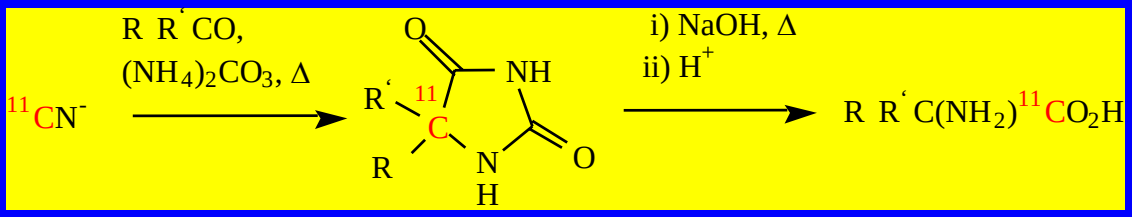
[^{11}C]Hydrogen Cyanide

- Applications

- Synthesis of [^{11}C]amino acids
- Nucleophilic substitution reactions
- Michael addition reactions
- Preparation of other labeling agents

[^{11}C]Hydrogen Cyanide

- [^{11}C]Amino acid synthesis (1)

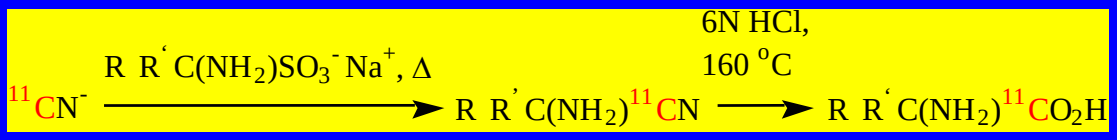


- Note racemic [^{11}C]amino acids are produced
- Natural (Val, Ala, Phe, Try, Leu..) and cyclic amino acids may be produced

Known as Bucherer-Strecker technique

[^{11}C]Hydrogen Cyanide

- [^{11}C]Amino acid synthesis (2)



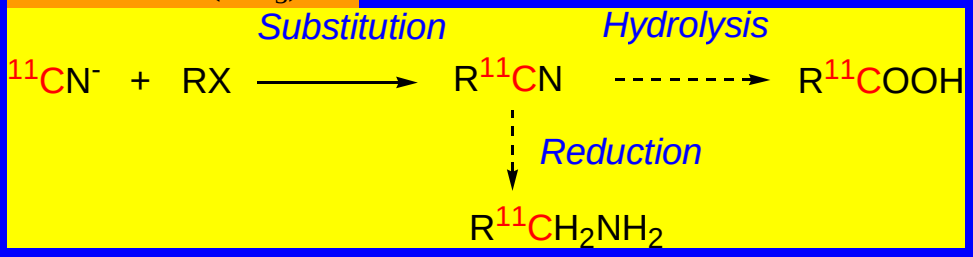
- Note racemic [^{11}C]amino acids are produced *e.g.* Val, Leu, DOPA

The reaction is a nucleophilic subsitition of bisulfite by [^{11}C]cyanide ion

[^{11}C]Hydrogen Cyanide

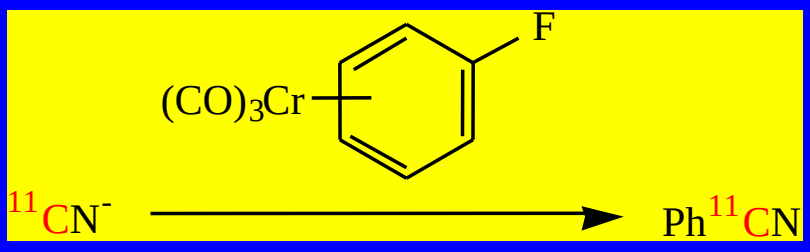
- Other aliphatic nucleophilic substitution reactions

R = Br, Cl, $(Me_3)N^+$



[^{11}C]Hydrogen Cyanide

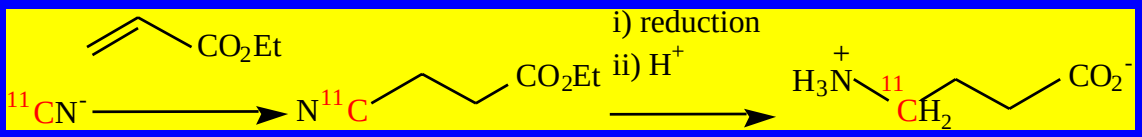
- Preparation of [^{11}C]aryl nitriles



- Decomplexation is simultaneous with substitution
- Direct nucleophilic substitution can be achieved on aryl halides with [^{11}C]CuCN

[^{11}C]Hydrogen Cyanide

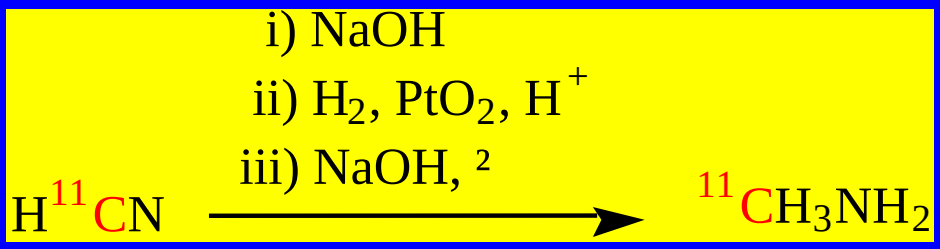
- Michael addition



- Initial reaction is equivalent to addition [^{11}C]hydrogen cyanide to double bond
- Other electron withdrawing groups may serve in place of CO_2Et

[^{11}C]Methylamine

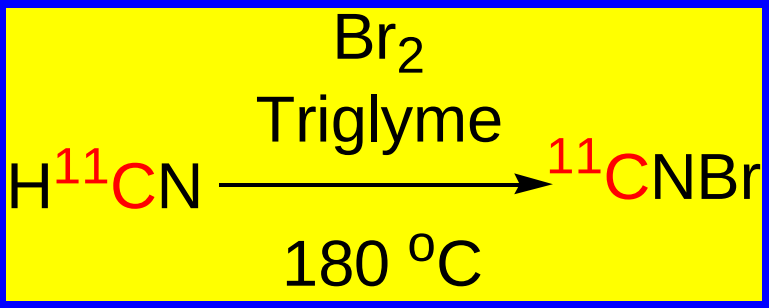
- From [^{11}C]hydrogen cyanide



Preparation time: ~ 20–25 min.
Production efficiency: ~ 20–35%
Applications: Labeling methylamino functions
Potential for labeling through Mannich-type reactions.
Not widely used

[^{11}C]Cyanogen Bromide

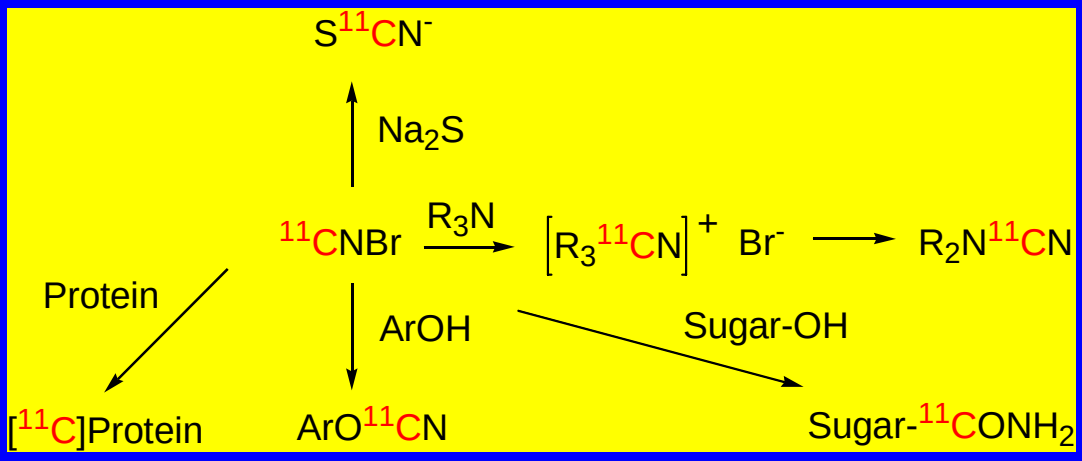
- Preparation from [^{11}C]hydrogen cyanide



- Radiochemical yield: 70-80%
- Preparation time: ~10 min
- The [^{11}C]cyanogen bromide can be trapped in a variety of solvents for further reaction

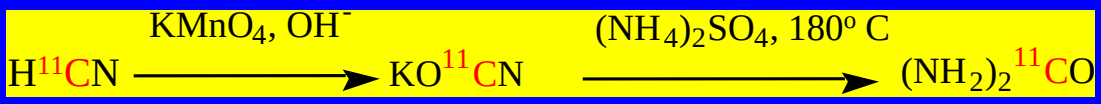
[^{11}C]Cyanogen Bromide

- Applications



[^{11}C]Urea

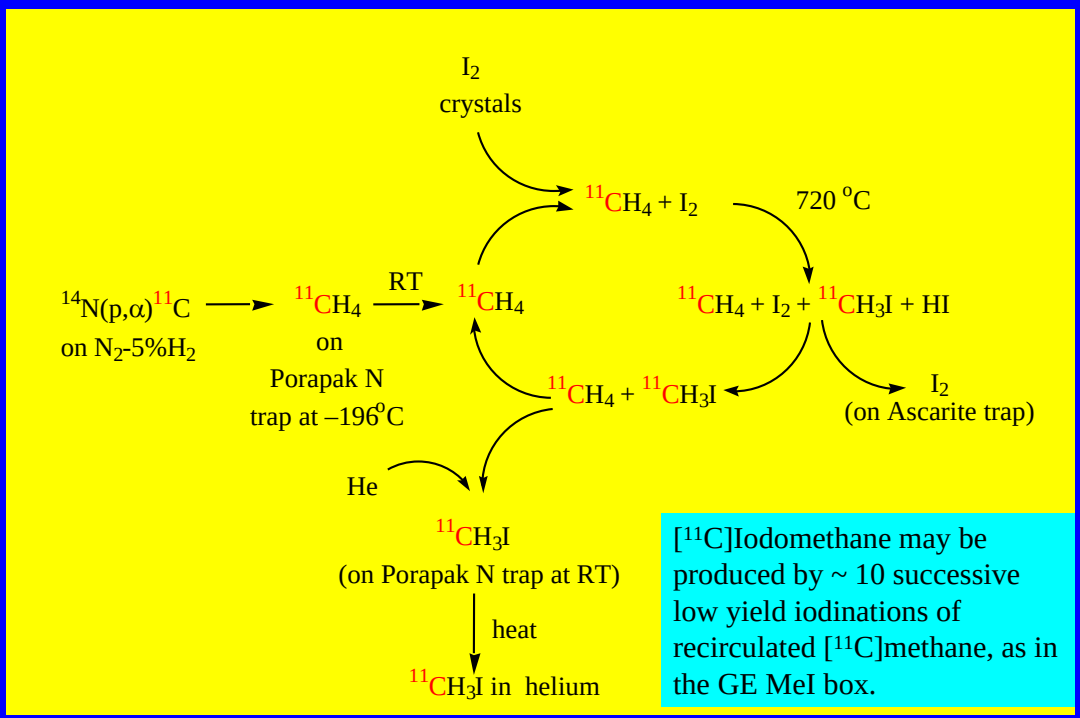
- From [^{11}C]hydrogen cyanide



- Radiochemical yield from [^{11}C]cyanide; 95%
- Synthesis time: 16 min

[^{11}C]Iodomethane

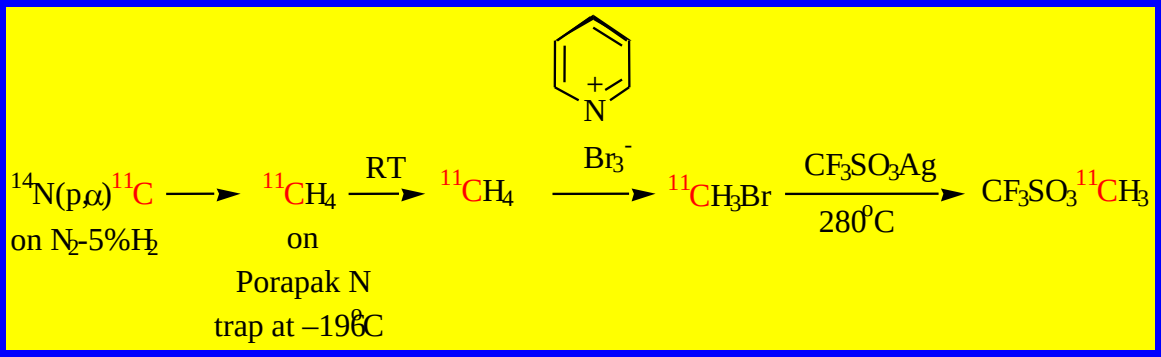
- From [^{11}C]methane



[^{11}C]Iodomethane may be produced by ~ 10 successive low yield iodinations of recirculated [^{11}C]methane, as in the GE MeI box.

[^{11}C]Methyl Triflate

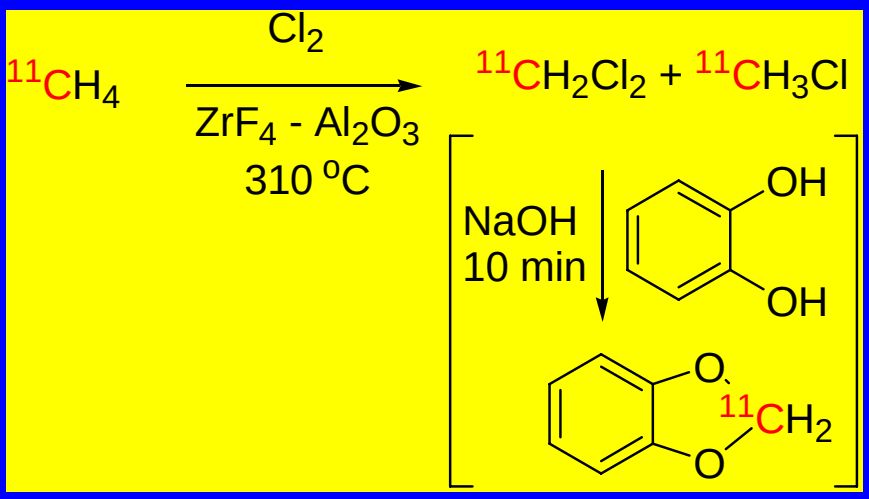
- From [^{11}C]methane



- Radiochemical yield: 60 %
- Preparation time: 20 min
- Specific radioactivity: 20 Ci/μmol

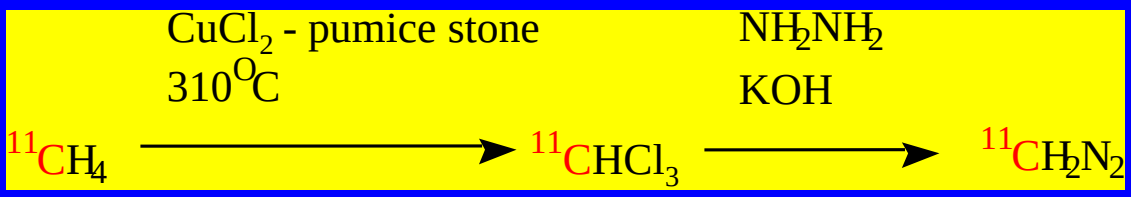
Monobromination is easily controlled

[^{11}C]Dichloromethane



- Radiochemical yield of [^{11}C]dichloromethane: 30-35%

[^{11}C]Diazomethane

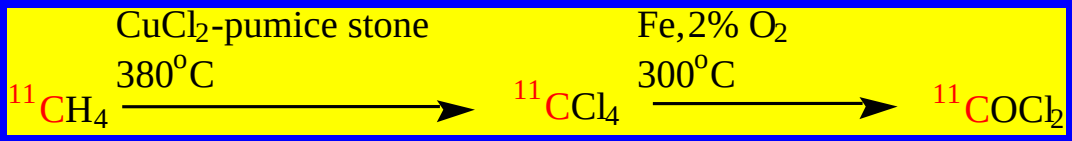


Preparation time:	~ 10 min
Production efficiency:	~ 22%
Applications:	Preparation of [^{11}C]ethers

Not widely used

[^{11}C]Phosgene

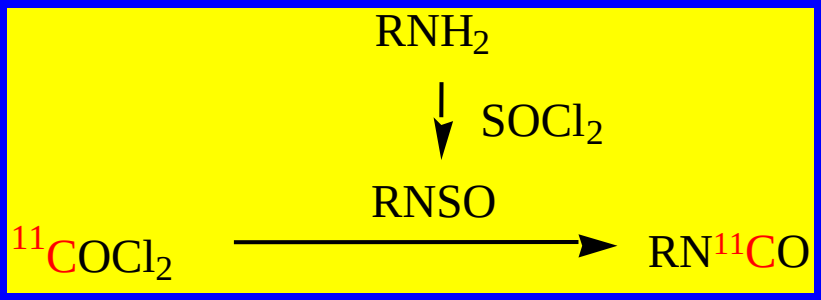
- Preparation from [^{11}C]methane



- This route gives high specific radioactivity and a useful radiochemical yield
- [^{11}C]Phosgene is mainly useful for labeling by reaction with nitrogen and oxygen nucleophiles
- [^{11}C]Phosgene is also useful for preparing other labeling agents
- An important application is the labeling of the β-receptor radioligand, (*S*)-CGP 12177, in the carbonyl carbon, by cyclisation of the parent aromatic diamine

[^{11}C]Phosgene

- For preparation of alkyl [^{11}C]isocyanates



Preparation time:	20 min
Production efficiency:	15-30%

- Alkyl [^{11}C]isocyanates are useful labeling agents in their own right

[^{11}C]Phosgene

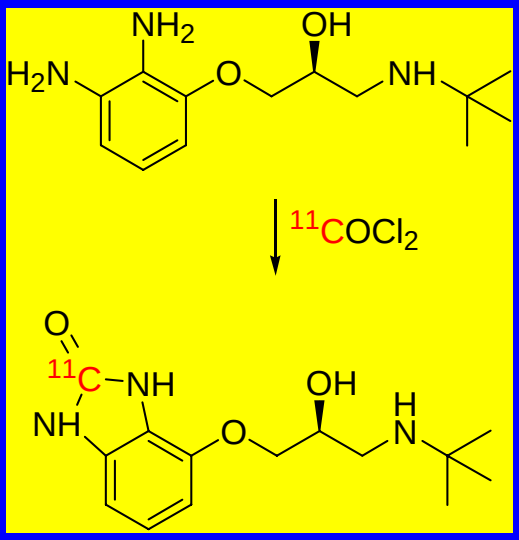
- For prepartion of [^{11}C]alkyl chloroformates and [^{11}C]dialkyl carbonates

R = Me or Et

- Reactions with oxygen nucleophiles, such as those in methanol and ethanol, afford the mono- or di-alkoxides respectively, depending on reaction conditions
- [^{11}C]Alkyl chloroformates and [^{11}C]dialkoxides are useful labeling agents in their own right *e.g.* in ring closure reactions

[^{11}C]Phosgene

- Preparation of [^{11}C](S)-CGP 12177



[^{11}C](*S*)-CGP 12177 is a β_2/β_2 adrenoceptor radioligand

[^{11}C]Urea

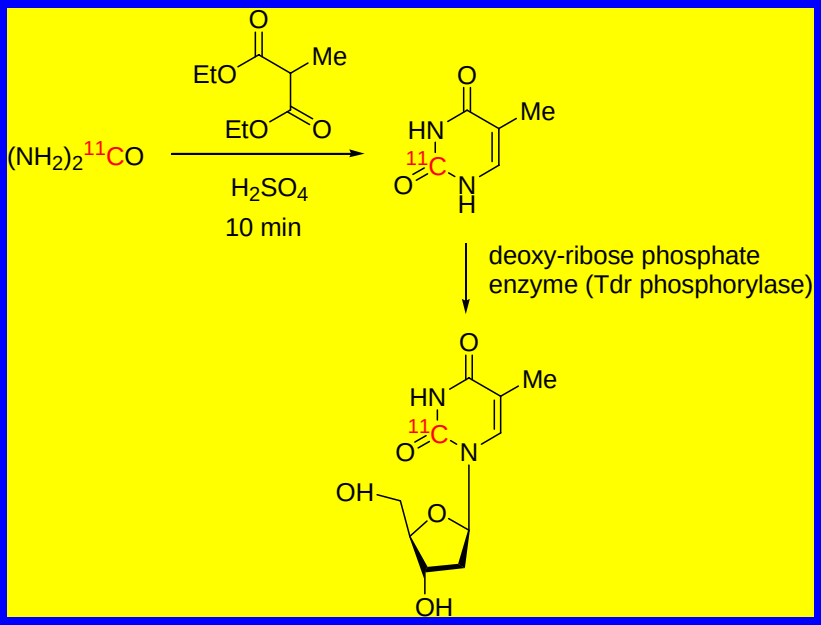
- from [^{11}C]phosgene

$$^{11}COCl_2 \xrightarrow{aq.\ NH_4^+\ OH^-} (NH_2)_2{}^{11}CO$$

- Preparation time: 30 min
- Radiochemical yield: 15% decay corrected from cyclotron-produced [^{11}C]carbon dioxide

[^{11}C]Urea

- For preparation of [2-^{11}C]thymidine

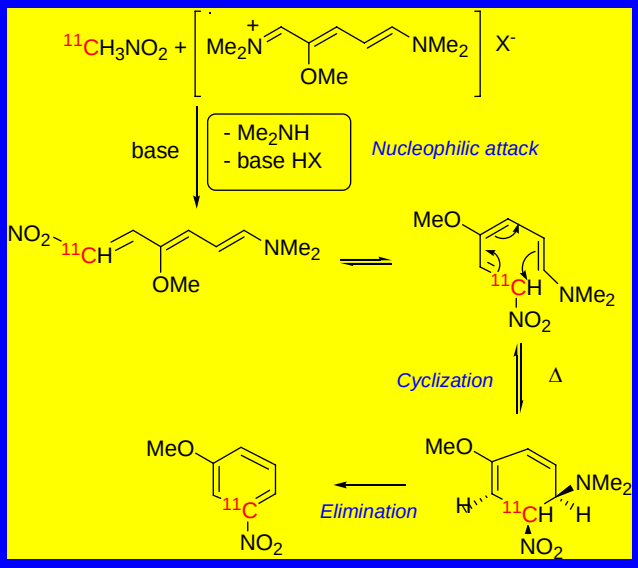


Labeling of Arenes

- Labeling of benzenoid compounds
- Labeling of indoles
- Labeling of pyridines

Labeling of Arenes

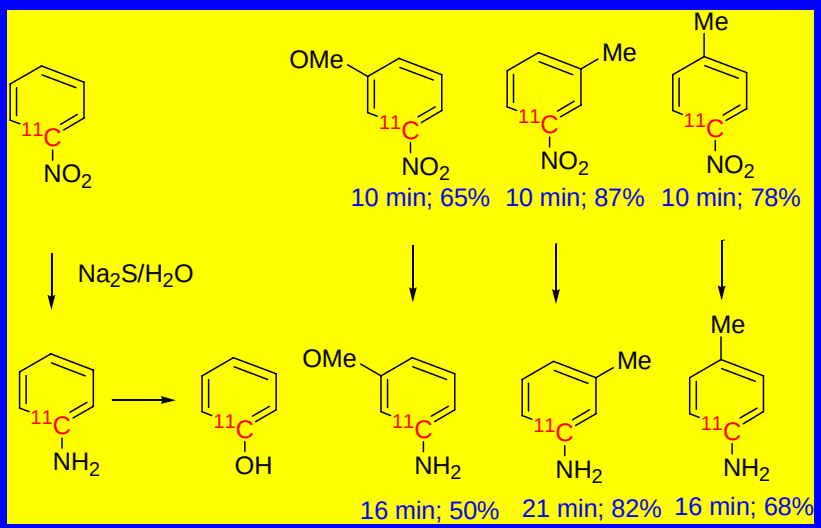
- Preparation of [3-^{11}C]3-nitro-anisole



- Radiochemical yield: ~ 60%
- Preparation time: 10 min
- Specific radioactivity: 1 Ci/μmol.

Labeling of Arenes

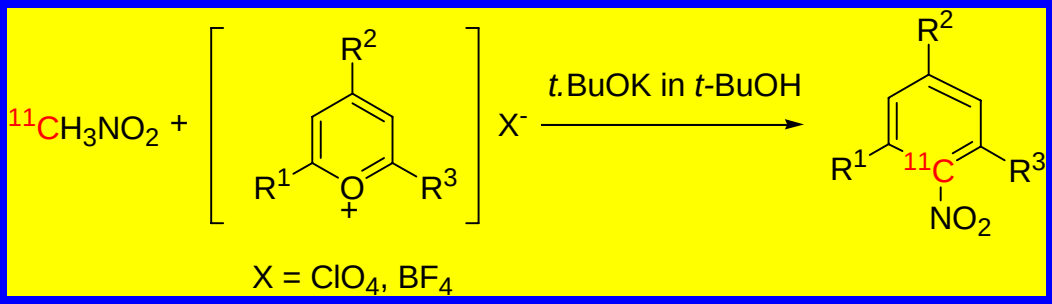
- Other [^{11}C]benzenoid compounds



- Radiochemical yields are from [^{11}C]nitromethane

Labeling of Arenes

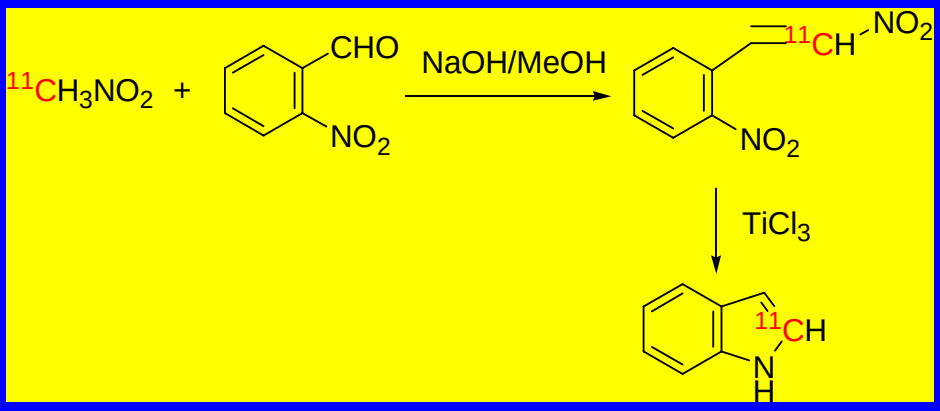
- Preparation of [1-^{11}C]nitrobenzenes from [^{11}C]nitrobenzene and pyrilium salts



- Radiochemical yield: ~ 29% (Rs = Me)-77 % (Rs = H)
- Preparation time: 20 min
- Specific radioactivity: 0.8 Ci/μmol

Labeling of Arenes

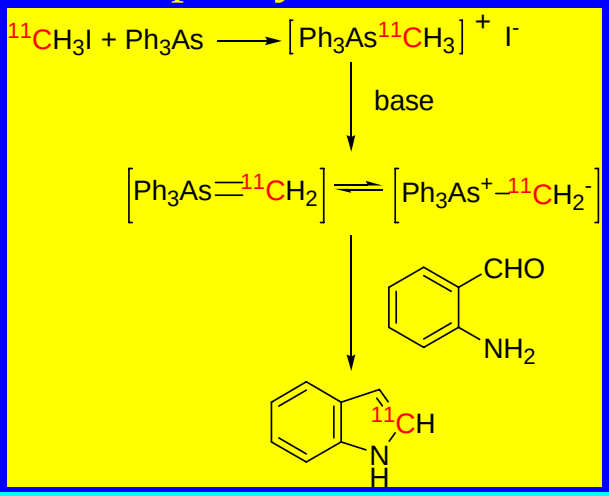
- Preparation of [2-^{11}C]indole from [^{11}C]nitromethane



- Radiochemical yield: ~ 10%
- Preparation time: 22 min

Labeling of Arenes

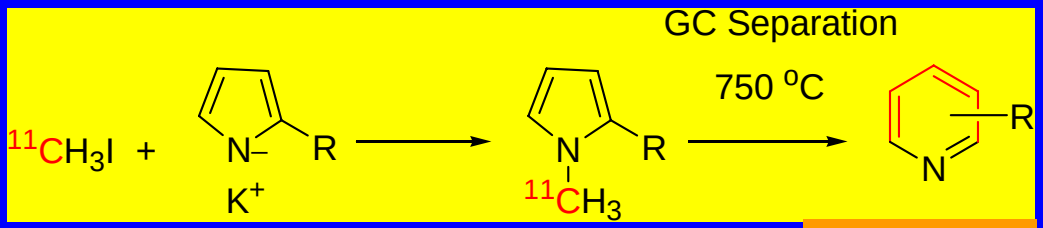
– Preparation of [2-^{11}C]indole from [^{11}C]triphenylarsonium methylide



- Radiochemical yield: ~ 23-27%
- Preparation time: 15 min
- Specific radioactivity: 1 Ci/μmol

Labeling of Arenes

- Preparation of [^{11}C]pyridine



R = H or CN

- Decay-corrected radiochemical yield: 18% (NCA; R = H)
- Decay corrected radiochemical yield: 79% (CA; R = H)
- Preparation time ~ 20 min

Conclusions

- A vast array of NCA ^{11}C-labeling agents can be prepared, in many cases efficiently, from either cyclotron-produced [^{11}C]carbon dioxide or [^{11}C]methane.
- This array of labeling agents offers a multitude of methods for labeling drug-like molecules and endogenous compounds.
- A major challenge is to exploit the potential for higher specific radioactivity.