Radiolabeling with [11C]HCN for Positron Emission Tomography

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Abstract

Hydrogen cyanide (HCN) is a versatile synthon for generating carbon-carbon and carbon-heteroatom bonds. Unlike other one-carbon synthons (*i.e.*, CO, CO_2), HCN can function as a nucleophile (as in potassium cyanide, KCN) and an electrophile (as in cyanogen bromide, (CN)Br). The incorporation of the –CN motif into organic molecules generates nitriles, hydantoins and (thio)cyanates, which can be converted to carboxylic acids, aldehydes, amides and amines. Such versatile chemistry is particularly attractive in PET radiochemistry where diverse bioactive small molecules incorporating carbon-11 in different positions need to be produced. The first examples of making [11C]HCN for radiolabeling date back to the 1960s. During the ensuing decades, [11C]cyanide labeling was popular for producing biologically important molecules including 11C-labeled α-amino acids, sugars and neurotransmitters. [11C]cyanation is now reemerging in many PET centers due to its versatility for making novel tracers. Here, we summarize the chemistry of [11C]HCN, review the methods to make [11C]HCN past and present, describe methods for labeling different types of molecules with [11C]HCN, and provide an overview of the reactions available to convert nitriles into other functional groups. Finally, we discuss some of the challenges and opportunities in [11C]HCN labeling such as developing more robust methods to produce [11C]HCN and developing rapid and selective methods to convert nitriles into other functional groups in complex molecules.

Graphical Abstract

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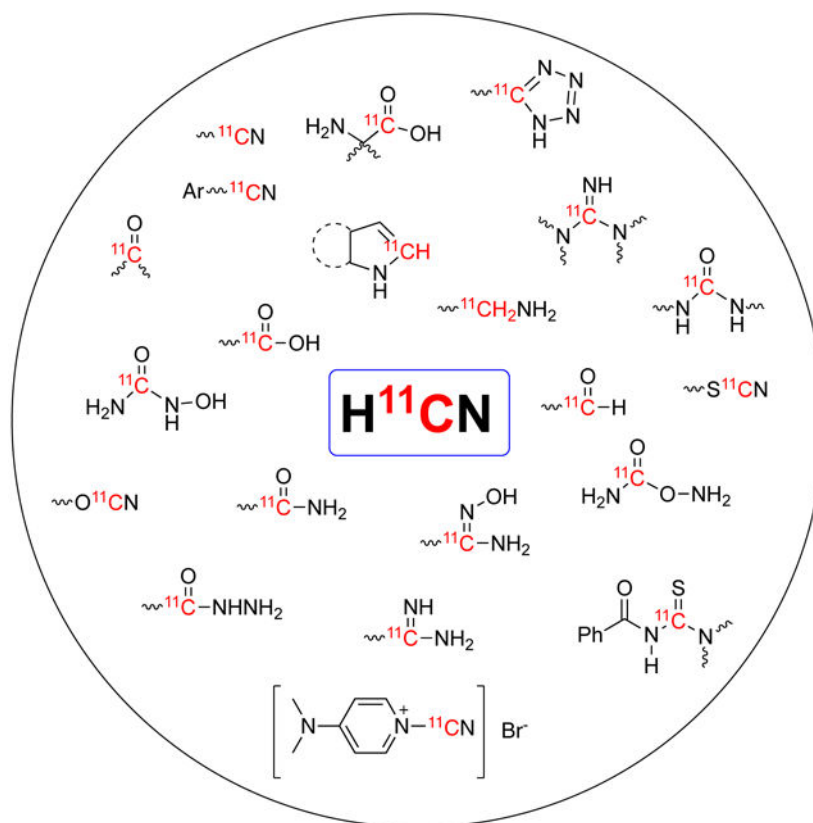
Keywords

carbon-11; radiolabeling; [^{11}C]HCN; radiopharmaceuticals; amino acids; sugars

1. Introduction

Positron emission tomography (PET) is a molecular imaging technique that allows imaging the location of radiolabeled molecules inside living subjects. Unlike other molecular imaging techniques, PET can image deep inside the body as it relies in the detection of gamma rays generated by the annihilation of a positron emitted by the radiolabeled molecule and an electron of the surroundings. This feature, combined with its fully quantitative nature, makes PET a powerful tool for probing biological processes in live subjects, which can provide valuable information for disease diagnoses and drug development[1–5]. In order to reap the benefits of PET, radiotracers labeled with positron emitting isotopes are essential. In the case of small molecule radiotracers, the most common PET isotopes are fluorine-18 ($t_{1/2}$ = 110 min)[6–8] and carbon-11 ($t_{1/2}$ = 20.3 min)[9–11]. While the longer half-life of fluorine-18 offers the opportunity to produce multiple doses from one batch production and distribute them to nearby hospitals, carbon-11 offers other advantages such as the opportunity to label molecules that do not contain fluorine and the opportunity to scan the same subject twice on the same day. Furthermore, the recent developments of Time-of-Flight (TOF) PET technology and the total-body PET scanner require shorter scan times and lower doses of radiotracer and are expected to make ^{11}C-labeled radiotracers even more useful[12–13,14].

Currently, the most common method for labeling small molecules with carbon-11 is carbon-11 methylation using [^{11}C]methyl iodide or [^{11}C]methyl triflate. However, ^{11}C-methylation is mainly used for producing compounds bearing -Me, -OMe, -SMe, or -NRMe groups[9, 11, 15–17]. When introducing methyl is not possible or desirable, labeling with ^{11}CO, ^{11}CO$_2$, H^{11}CN and other ^{11}C-synthons offer the opportunity to synthesize a variety of radiolabeled molecules (Fig. 1). Methods for labeling with ^{11}CO and ^{11}CO$_2$ have been extensively reviewed recently[9–11, 15, 17–28]. However, H^{11}CN labeling methods have only been covered succinctly in several more general reviews about ^{11}C-labeling[9, 11, 15, 17, 21, 26, 29] as well as a recent review on isotope cyanation chemistry focused on ^{14}C, ^{13}C and ^{11}C cyanation reagents and applications[30]. Given the versatility of this synthon in PET radiochemistry and to facilitate and promote its use in radiopharmaceutical synthesis, here we present a comprehensive review of labeling with H^{11}CN.

2. Properties of hydrogen cyanide

Hydrogen cyanide is a liquid at room temperature (bp. 25.6 °C) which, as discussed in the Section 3 (H^{11}CN Production), makes it challenging to transfer within radiochemistry synthesizers. Hydrogen cyanide is slightly acidic (pK_a 9.2) and partially ionizes in water to give cyanide ion (CN$^-$). Cyanide can react with alkaline metals to generate salts (*e.g.,* NaCN, KCN, etc) and with transition metals to generate coordination compounds (*e.g.,* Prussian blue, Fe$^{III}_4$[Fe^{II}(CN)$_6$]$_3$). Cyanide is a good nucleophile and can react with organic molecules containing electrophilic carbons to generate nitriles and cyanohydrins. Nitriles can be hydrolyzed to carboxamides (R(C=O)NH$_2$) and carboxylic acids (RCOOH), reduced to primary amines (R$_2$CH$_2$NH$_2$) and aldehydes (RCHO) as well as alkylated. Cyanohydrins are common precursors to amino acids. In addition, metal cyanides can be reacted with halogens such as bromine to generate cyanogen bromide (CNBr). Cyanogen bromide is a common reagent in organic syntheses that contains an electrophilic carbon and is prone to nucleophilic attack. All these properties make hydrogen cyanide an attractive synthon for radiolabeling.

3. H^{11}CN production

Carbon-11 hydrogen cyanide (H^{11}CN) was first reported by Dubrin and colleagues in 1964.[31] H^{11}CN was produced by bombarding nitrogen gas or nitrogen oxides (N$_2$O, NO or NO$_2$) with ^{11}C ions generated through the neutron stripping of a ^{12}C ion beam produced by a Heavy Ion Accelerator (Fig. 2A). These ^{11}C ions reacted with gas molecules in the target chamber to produce a mixture of ^{11}CO and ^{11}CN$^•$ radical. Given the unstable nature of the ^{11}CN$^•$ radical, hydrocarbons like ethylene were used to quench the radical which produced H^{11}CN through hydrogen abstraction. In 1966, Ache and Wolf showed that H^{11}CN was the main product of the proton bombardment,^{14}N(p,α)^{11}C reaction, of a gas mixture containing 89.5% N$_2$ and 10.5% ethane (C$_2$H$_6$) which also occurred via ^{11}CN$^•$ radical formation and hydrogen abstraction (Fig. 2B).[32] In 1971, another two methods were described for the preparation of ^{11}C cyanide.[33] The first method involved the recoil synthesis, NaCN → Na^{11}CN, via the ^{14}N(p,α)^{11}C and ^{12}C(p,pn)^{11}C reactions (Fig. 2C). The second method used the recoil synthesis, B$_2$O$_3$ → ^{11}CO + ^{11}CO$_2$, via the ^{11}B(p,n)^{11}C, which after full

oxidation to $^{11}CO_2$, was converted to $K^{11}CN$ through the reaction: $^{11}CO_2 + K + NH_3 \rightarrow$ $K^{11}CN$ (Fig. 2D). These methods use non-standard liquid targets, suffer from low molar activity and require moisture and air sensitive reagents, which promoted the development a simple and reliable flow method for routine production of no-carrier-added, high-activity $H^{11}CN$ for radiopharmaceutical labeling by Christman and colleagues in 1973.[34–35] This method consisted on reacting cyclotron-produced methane ($^{11}CH_4$) with ammonia gas (NH_3) in a effluent stream over a platinum catalyst at 1,000 °C. A typical run produced 74 GBq (2 Ci) of no-carrier-added $H^{11}CN$ from a 45 min irradiation with a current of 30 μA of focused 25 MeV protons (Fig. 2E). In 1983, a method for producing $H^{11}CN$ using microwave discharge was reported by Niisawa et al (Fig. 2F).[36] This method produces no-carrier added $H^{11}CN$ by the direct microwave discharge of cyclotron-produced $^{11}CO_2$, with H_2 and N_2 gas mixture. This method typically yielded *ca.* 7.4 GBq (200mCi) of $H^{11}CN$ in *ca.* 20% radiochemical yield with molar activity of 7.33 GBq/μmol (199 mCi/μmol) within 20min of synthesis time.

Currently, the most common method to generate $H^{11}CN$ for radiopharmaceutical synthesis consists in the stepwise conversion of cyclotron-produced $^{11}CO_2$ to $^{11}CH_4$ and then to $H^{11}CN$ by reacting H_2 gas over a nickel catalyst at 400 °C followed by reaction with NH_3 gas over a platinum catalyst at 1000 °C as previously described (Fig. 2). This process is typically carried out in an automated flow reactor. While the chemistry is reproducible careful attention has to be paid to the flowrate and the dryness of NH_3 in the effluent. Furthermore, when using these systems, it is imperative to use high purity anhydrous NH_3 and an inline desiccant since moisture causes the formation $NH_4^{11}CN$ which tends adsorb to the walls of the delivery lines. Also, since HCN has a boiling point of 25.6 °C it can easily condense in the transfer lines making its transfer inefficient.

4. [^{11}C]Cyanation of aliphatic compounds

4.1. Nucleophilic substitution reactions

Cyanide, CN^-, is a very good nucleophile. The nucleophilic substitution reaction is the most direct method of introducing ^{11}CN group into organic molecules to form [^{11}C]nitriles. These [^{11}C]nitriles can readily be generated by reaction of an alkyl electrophile with a cyanide salt ($Na^{11}CN$, $K^{11}CN$ or $NH_4^{11}CN$). These reactions typically proceed under mild conditions and give the excellent radiochemical yields.

4.1.1. Bisulfite, -SO$_3$Na, as leaving group—The *in situ* reactions of aldehyde or ketone with sodium bisulfite, $NaHSO_3$, give the corresponding bisulfite adduct. Although sodium bisulfite, -SO$_3$Na, is not a commonly used leaving group, it is a good precursor for the synthesis of [^{11}C]α-substituted carboxylic acids (*e.g.*, [^{11}C]α-amino acid and [^{11}C]α-hydroxy acid). This reaction has been used to produce several biologically important molecules including [^{11}C]dopamine (**3**) and [^{11}C]norepinephrine (**4**) (Fig. 3).

Dopamine is a hormone and a neurotransmitter that plays important roles in the brain and body. [^{11}C]dopamine hydrochloride (**3**) was first reported by Chrisman et al at 1970[37]. In this first report, precursor **1** was prepared by the reaction of sodium bisulfite with 3,4-dihydroxybenzaldehyde in water and used without isolation. The addition of carrier-added

Na[11]CN generated intermediate **2**. This was then reacted with hydrogen gas over palladium catalyst and hydrochloric acid to generate [^{11}C]dopamine hydrochloride (**3**). The molar activity was 0.23 MBq/μmol (0.0062 mCi/μmol) calculated to end of bombardment (EoB).

Since the molar activity of **3** prepared from carrier-added Na[11]CN was very low and limited its biological application, the same research group developed the synthesis [^{11}C]dopamine hydrochloride (**3**) from no-carrier-added H[11]CN later[38]. Using no-carrier added Na[11]CN, **3** was prepared with high molar activity of 383 GBq/μmol (10.3 Ci/μmol). One year later, Fowler et al reported the preparation of [^{11}C]norepinephrine hydrochloride (**4**) in 2.5% decay-corrected radiochemical yield using a similar no-carrier-added method.[39]

The iodo- derivative of dopamine, [^{11}C]6-iododopamine hydrochloride (**7**), was also prepared using similar no-carrier-added method. In this case, precursor **5** was prepared by the *in situ* reaction of 6-iodo-3,4-dihydroxybenzaldehyde with sodium bisulfite. Further substitution of -SO_3Na by [11]CN^{−} yielded intermediate **6**, which was then reduced to produce [^{11}C]6-iododopamine hydrochloride (**7**) in 11% TLC-based radiochemical yield.[40] This represents a good example of a selective reduction to remove the hydroxyl group while preserving the nitrile group.

[^{11}C]2-N-Phenethylaminoalkanenitriles were synthesized using a similar method.[41] The corresponding *in situ* prepared aldehyde-sodium bisulfite addition adducts was reacted with phenethylamine and carrier added Na[11]CN to give [^{11}C]2-N-phenethylaminoalkanenitrile (**9**). Further acidification gave the corresponding hydrochloride salt (**10**), which was used for biodistribution studies. The synthesis times were 51–66 min and 0.22–1.30GBq (6–35 mCi) of products were obtained.

In 1987, Iwata et al reported the use of sodium bisulfite precursors to produce several amino acids labeled at the carboxylic carbon (Fig. 4). Specifically, they reported the synthesis of no-carrier-added phenylalanine, valine, isoleucine and others via [^{11}C]aminonitriles intermediates.[42] The precursors for labeling, amino sulfites (**12a-12i**), were prepared by the reaction between ammonium hydroxide with the corresponding aldehyde or ketone bisulfite adducts (**11a-11i**). The following [^{11}C]cyanation and nitrile-hydrolysis lead to the corresponding racemic [^{11}C]amino acids (**14a-14i**) in good radiochemical yields. As such, this chemistry makes the synthesis and purification of [^{11}C]amino acids simple and suitable for automation. In 1990, Takahashi et al reported the synthesis of DL-[^{11}C]alanine from H[11]CN using this method[43]. Starting from sodium 1-hydroxyethanesulfite, DL-[^{11}C]alanine was obtained in 75% decay-corrected radiochemical yield within 40 min.

In 1995, a new on-column synthesis system was developed for the synthesis of 1-aminocyclopentane-1-[^{11}C]carboxylic acid ([^{11}C]ACPC, **14i**) from H[11]CN using the same chemistry.[44] This on-column method greatly simplifies the synthesis procedure and enables the automation for routine synthesis of PET tracers. This compound, also known as cycloleucine, is a metabolically stable amino acid used for oncologic imaging.[45] The preparation has been successfully accommodated to routine production of [^{11}C]ACPC. The on-column synthesis method could generate [^{11}C]ACPC in over 60% decay-corrected radiochemical yield in 40 min and >98% of radiochemical purity.

Although this chemistry produces a mixture of the *D* and *L* amino acids, Bjurling and colleagues were able to prepare optically pure *L*-amino acids by combining this method with enzymatic reactions. Specifically, they could convert racemic [1-^{11}C]alanine (**16**) to [1-^{11}C]pyruvate (**17**) with D-amino acid oxidase (D-AAO) and further convert **17** to optically pure L-[^{11}C]alanine (**16b**) with glutamic-pyruvic transaminase (GPT)[46]. In addition, they could also use **17** to generate L-[^{11}C]tyrosine (**18**) and L-[^{11}C]3,4-dihydroxyphenylalanine (**19**, L-[^{11}C]DOPA) with β-tyrosinase as well as L-[^{11}C]tryptophan (**20**) and [^{11}C]5-hyroxy-L-tryptophan (**21**) with tryptophanase. These products were generated in 45–60% decay-corrected radiochemical yield, >99% of enantiomeric purity and molar activity 0.41–2.00 GBq/μmol (0.011–0.054 Ci/μmol) in 45 – 50 min synthesis time.

In the same year, the same group also reported the synthesis of L-1-[^{11}C]lactic acid (**22**) from the corresponding racemic 1-[^{11}C]alanine (**16**) using similar enzyme catalyzed reactions (Fig 5).[47] Racemic 1-[^{11}C]alanine (**16**) was converted to 1-[^{11}C]pyruvic acid (**17**) by D-amino acid oxidase (D-AAO)/catalase and glutamic-pyruvic transaminase (GPT). Finally, **17** was reduced to L-[1-^{11}C]lactic acid (**22**) by L-lactic dehydrogenase (L-LDH). The total synthesis time was *ca.* 40 min and the decay-corrected radiochemical yields were ca. 70%. In 2006, Drandarov et al reported a nonenzymatic automated synthesis method of D- and L-[1-^{11}C]lactic acid (**22**) from the same precursor (**15**).[48] In this case, direct conversion from 16 to 22 under acidic conditions produced the two [^{11}C]lactic acid enantiomers which were separated by chiral ligand-exchange chromatography. This fully automated radiosynthesis resulted in >80% decay-corrected radiochemical yield in 45min of synthesis time. The products were obtained in >99% radiochemical, chemical and enantiomeric purity. The molar activity at the end of the synthesis was *ca.* 370.30 GBq/μmol (10.8 Ci/μmol).

Octopamines are neurotransmitters from invertebrate animals used clinically as adrenergic drugs. The synthesis of p- and m-[^{11}C]octopamine hydrochloride (**27a** and **27b**) were reported in 1990 (Fig. 5).[49] 3- and 4-hydroxybenzaldehyde (**25a** and **25b**) were reacted with sodium bisulfite and [^{11}C]HCN to generate **26a** and **26b**. Alternatively, **26a** and **26b** were also produced by enzymatic conversion using mandelonitrile lyase. **26a** and **26b** were reduced using borane-THF to give final products (**27a** and **27b**). The enantiomeric pure chiral isomer of p- and m-octopamine were separated using chiral column chromatography. This complex procedure which required ether extraction and drying under a stream of argon of the intermediate yielded the p- and m-octopamine in 1.2% and 2.3% non-decay-corrected isolated yields in *ca.* 40–60 min.

Enantiomerically pure [^{11}C]tyrosine (Tyr, **32**) and phenylalanine (Phe, **14d**) were prepared in 2003 by Studenov *et al* using nonenzymatic conversions (Fig. 6).[50] Starting from sodium bisulfite adducts of the aldehydes (**29** and **11d**), the corresponding ^{11}C-labeled amino acids were produced by reacting with ammonia and ^{11}CN$^-$, followed by basic hydrolysis. The solid-phase extraction and chiral HPLC allowed individual enantiomers to be separated in 12–16% decay-corrected radiochemical yields within 40 – 45 min of total synthesis time. Enantiomeric excess of each isomer was >98% with the molar activity was 74–111 GBq/μmol (2–3 Ci/μmol).

Levetiracetam (LEV), (S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, is a widely used epilepsy and central nervous system (CNS) disorder drug that binds to synaptic vesicle protein 2A (SV2A). [^{11}C]levetiracetam **38** was reported in 2014 as PET tracer for SV2A expression (Fig. 7).[51] The bisulfite adduct of propionaldehyde reacted with ammonia to give the precursor amino sulfonate **34**, which further reacted with H^{11}CN yielding **35** in aqueous solution. The intermediate **35** was converted to final product **38** by first reacting it with 4-chlorobutyryl chloride followed by hydrolysis or *vice versa*. Both approaches resulted in low radiochemical yield (~1.0%) of [^{11}C]LEV within 1 hour of synthesis time. Given the low radiochemical yield, a modified multistep one-pot reaction based using H^{11}CN addition to carbonyl addition reaction was later developed (see Section 4.2.2).

4.1.2. Triflate, -OTf, as leaving group—Triflate is an excellent leaving group for cyanation. However, its use in radiochemistry has been limited due the instability of many triflate precursors. Nevertheless, a triflate precursor was used to synthesize an important compound in radiochemistry: 2-deoxy-*D*-[1-^{11}C]glucose (**43**).

It was the pioneer work by Sokoloff and colleagues using 2-deoxy-D-glucose labeled with carbon-14 the late 1960s and 70s that established the foundation for PET imaging. Following his autoradiography studies, Sokoloff sought to collaborate with radiochemists Alfted Wolf and Joanna Fowler at Brookhaven National Lab to develop derivatives of 2-deoxy-D-glucose that could be imaged noninvasively in humans. This led to the development of 2-deoxy-2-[^{18}F]fluoro-D-glucose, [^{18}F]FDG, the most important and widely used PET tracer today. Soon after the ^{11}C analogue, 2-deoxy-D-[1-^{11}C]glucose, was developed (Fig. 8).[52–54] The reaction of precursor **40** with H^{11}CN gave intermediate 2,3:4,5-di-O-isopropylidene-D-arabinononitrile (**41**). 2-Deoxy-D-[1-^{11}C]glucose (**42**) was synthesized by the reduction-hydrolysis of intermediate **41**. 2-Deoxy-D-[1-^{11}C]glucose was obtained in 25–40% decay-corrected radiochemical yield with a synthesis time of 45–50 min according to different reports.[55–56] Later in 1982, a remote semiautomated radiochemical synthesis system for 2-deoxy-D-[1-^{11}C]glucose was reported.[57] The system consists five flasks, two chromatography columns, a flow-through gamma detector, and a sterilization unit. A typical run could produce 0.74–1.30 GBq (20–35 mCi) of sterile, pyrogen-free 2-deoxy-D-[1-^{11}C]glucose dose within a synthesis time of 50 min with radiochemical purity of greater than 98% and decay-corrected radiochemical yields of 25–30%.

4.1.3. Halides as leaving group—Halides, specifically iodide, bromide, and chloride, are among the most widely used leaving groups in organic chemistry. Many halide precursors are benchtop stable and widely available. Consequently, numerous ^{11}CN$^-$ based nucleophilic substitution reactions have been developed. In the following paragraphs (figures 9–14), we review examples for making amino acids, sugars, aliphatic diamines, fatty acids and Pt(II) based anticancer drugs via ^{11}C-cyanation of halide precursors.

[3-^{11}C]β-Alanine (**46**) was first synthesized from the chloride precursor by Elias et al in 1972.[58] 2-Chloroacetic acid (**44**) was reacted with carrier-added Na^{11}CN or K^{11}CN yielding 2-isocyanoacetic acid (**45**) (Fig. 9). Subsequently, **45** was hydrogenated over PtO$_2$ to generate [3-^{11}C]β-alanine (**46**) in 35% chemical yield and 4.5% radiochemical yield.

In 1977, Mestelan *et al* reported the synthesis and biodistribution of [^{11}C]3,4-dimethoxyphenethylamine (**50**).[59] No-carrier-added H^{11}CN was reacted with precursor 3,4-dimethoxybenzylchloride (**48**) in DMSO yielding intermediate **49**, which was then reduced with borane to produce [^{11}C]3,4-dimethoxyphenethylamine (**50**) in ca. 40% decay-corrected radiochemical yield.

In 1985, two research groups independently reported the optimized methods for 2-deoxy-D-[1-^{11}C]glucose (**42**).[60–61] Both papers describe the same new and bench stable labeling precursor, 1-deoxy-2,3:4,5-di-O-isopropylidine-1-iodo-D-arabitol (**51**). Stone-Elander *et al* used diethyl ether as solvent and diisobutylaluminium hydride (DIBAH) for the reduction of the intermediate (**41**).[60] After the reduction, sulfuric acid and formic acid were used to hydrolyze the imine-aluminum complex and deprotect -OH groups. The decay-corrected radiochemical yield was ca. 20% the synthesis time around 50 min. van Haver *et al* purified the nitrile intermediate (**41**) by HPLC before reducing it with Raney nickel in formic acid[61]. The final product 2-deoxy-D-[1-^{11}C]glucose (**42**) was isolated by ion exchange chromatography. The decay-corrected radiochemical yield was also around 20% and the synthesis time 50–55 min. The molar activity the final product (**42**) was 0.55–0.61 GBq/μmol (14.8–16.5 mCi/μmo) corresponding to a specific activity of 3.33–3.7 GBq/mg (90–100 mCi/mg).

In 1980, several ^{11}C-labeled aliphatic diamines (**54a-54c** and **57a-57c**) including putrescine (**54a**) and cadaverine (**54b**) were reported (Fig. 10).[62] These diamines were synthesized from the reactions between the carrier-added Na^{11}CN and the corresponding bromonitriles (**52a-52c**, n = 2, 3, and 4) or dibromoalkanes (**55a-55c**, n = 5, 6, and 7) followed by reduction with borane and acidification with hydrochloric acid. The decay-corrected radiochemical yields of these ^{11}C-labeled aliphatic diamine were between 57% to 84%. Five years later, the synthesis of no-carrier-added [^{11}C]putrescine was reported using a similar method.[63] In this case, the decay-corrected radiochemical yield was 20% radiochemical yield and the synthesis time around 50–60 min. In 1989, the synthesis of L-[5-^{11}C]ornithine was reported.[64] The reaction of the bromo precursor **58** with K^{11}CN gave intermediate **59**, which was further reduced and deprotected yielding [5-^{11}C]ornithine (**6** in 25–40% decay-corrected radiochemical yield with the <u>molar</u> activity of >77.7 GBq/μmol (>2.1 Ci/μmol). The total synthesis and purification time was 50 min (EOB).

The platinum(II) complex based anticancer drug, (ethylenediamine) (1-[^{11}C]malonate)platinum(ll) ([^{11}C]Ptenmal, [^{11}C]EDMAL, or [^{11}C]JM4O, **64**), was also prepared using H^{11}CN labeling.[65] The labeling precursor bromoacetate (**62**) was reacted with H^{11}CN to yield [^{11}C]cyanoacetate (**45**), which was then converted to [^{11}C]malonic acid (**63**) via hydrolysis. The resulting [^{11}C]malonic acid was coordinated to Pt(II) diethylenediamine anion to give the desired final product **64** in 17–40% decay-corrected radiochemical yield within one hour after EoB. The <u>molar</u> activity was *ca.* 7.4 GBq/μmol (200 mCi/μmol).

Using a similar method, [1-^{11}C]oxalic acid, **68** and [2-^{11}C]2,3-dihydroxyquinoxaline, **69**, were synthesized in 1993.[66] Methyl chloroformate was reacted with no-carrier-added H^{11}CN to give the intermediate [^{11}C]methylcyanoformate, which was then

converted to [1-^{11}C]diethyl oxalate in ethanolic HCl solution. Subsequent hydrolysis of [^{11}C]diethyl oxalate yielded [^{11}C]oxalic acid (**68**). The time of synthesis was 6–7 min using combined microwave and thermal treatment. The radiochemical conversions of [^{11}C]cyanide to [^{11}C]diethyl oxalate and [^{11}C]oxalic acid were ca. 80% and ca. 70%, respectively. The further reaction of phenylenediamine with [^{11}C]oxalic acid gave [^{11}C]-2,3-dihydroxyquinoxalin (**69**) in ca. 90% of radiochemical conversion.

Takahashi *et al* reported the synthesis of ^{11}C-labeled multiple linear and branched fatty acid from H^{11}CN in 1990 (Fig. 12).[67] This method has several advantages over ^{11}CO$_2$ carboxylation via Grignard reaction such as not requiring absolutely anhydrous solvents, not being sensitive to ambient CO$_2$ and being highly reproducible. The direct reaction of alkyl bromides (**72a**-**72f**) with K^{11}CN in DMSO gave the corresponding [^{11}C]alkyl nitriles intermediates (**73a**-**73f**). The hydrolysis of these intermediates with hydrochloric acid yielded the corresponding [^{11}C]fatty acid (**74a**-**74f**). Four straight chain [1-^{11}C]fatty acids (**74a**-**74d**) were synthesized in 70%-83% radiochemical yields and four branched chain ones (**74e**-**74f**) in 33%-42% decay-corrected radiochemical yields. The total synthesis times were 47–67 min from the EOB.

The ^{11}C-labeling of Busulfan, 1,4-bis(methanesulfonoxy)butane, a chemotherapy drug used for chronic myelocytic leukemia, was reported in 1991 (Fig. 13).[68] The reaction of no-carrier-added NH$_4$^{11}CN with 3-bromopropanol (**75**) followed by acid hydrolysis yielded the intermediate [1-^{11}C]γ-butyrolactone, which was isolated using solid phase extraction and reduced to [1-^{11}C]1,4-butanediol (**78**) with lithium aluminum hydride. Dimesylation of the ^{11}C-labeled diol with methanesulfonyl chloride gave the final product [1-^{11}C]busulfan (**79**) in 47% of decay-corrected isolated yield within a total synthesis and HPLC purification time of 65–75 min. Starting from no-carrier-added H^{11}CN, several ^{11}C labeled compounds, including ethyl [1-^{11}C]glycolate (**82**), [1-^{11}C]glycolic acid (**83**), [1-^{11}C]ethylene glycol (**85**), [2-^{11}C]2-aminoethanol (**84**) were prepared by Thorell and colleages in 1994.[69] The reaction of H^{11}CN with chloromethyl pivalate generated the intermediate nitrile [^{11}C]cyanomethyl pivalate (**81**), which was subsequently converted to **82**-**85** under the corresponding conditions shown in Fig. 13. The use of microwave reactions enabled the synthesis of the products in less than 3 min in ca. 90% conversions.

The radiolabeling of γ-vinyl-γ-aminobutyric acid (GVG, Vigabatrin, **88**) using H^{11}CN was reported by Zhang et al in 2001.[70] Vigabatrin inhibits the breakdown of GABA in the brain and it is used in the treatment of epilepsy and other psychiatric diseases. The precursor 5-bromo-3-(carbobenzyloxy)amino-1-pentene (**86**) was reacted with no-carrier-added H^{11}CN, trapped with K$_2$CO$_3$ and K$_{222,}$ to generate intermediate **87**. This compound was further hydrolysed to afford [1-^{11}C]GVG (**88**) in $27 \pm 9\%$ (n=6, not optimized) of decay-corrected radiochemical yield. This one-pot, two-step radiosynthesis was completed with a synthesis time of 45min.

The synthesis of [^{11}C]indole was first developed in 2015 using the nucleophilic cyanation method (Fig. 14).[71] The ^{11}C-cyanation of 2-nitrobenzyl bromide (**89**) with base-trapped H^{11}CN gave 2-(2-nitrophenyl)-[1-^{11}C]acetonitrile (**90**) as intermediate. The temperature and pH control of this reaction is crucial as high temperature or pH results in undesired side

product 2,3-bis(2-nitrophenyl)-[1-^{11}C]propanenitrile (**92**). The reductive cyclization of **90** catalyzed by Raney nickel yielded the desired product [2-^{11}C]indole (**91**) in 21 ± 2.2% (n = 5, ranging from 18–24%) of decay-corrected radiochemical yield within 50–55 min of synthesis and HPLC purification time. The molar activity of [2-^{11}C]indole was 176.12 ± 24.79 GBq/μmol (4.76 ± 0.67 Ci/μmol) (n = 5, ranging from 3.81–5.51 GBq/μmol).

^{11}C-labeled L-glutamine was also prepared using a similar method.[72] The iodination of L-homoserine gave the labeling precursor **93**, which was then reacted with base-trapped H^{11}CN to form intermediate **94**. Hydrolysis of intermediate under acidic condition yielded the final product L-[5-^{11}C]-glutamine (**95**) with a decay-corrected radiochemical yield of 63.8 ± 8.7 % (range from 51 to 74 %, n = 10), >90 % enantiomeric purity, and 7.03 ± 1.48 GBq/μmol (0.19 ± 0.04 Ci/μmol) of molar activity. The total synthesis and purification time was 40–50 min from the end of bombardment.

4.1.4. Carboxylate as leaving group—L-2,4-Diamino[4-^{11}C]butyric acid is a natural nonproteinogenic amino acid that participates in amino acid metabolism and has been proposed as a potential tumor marker. L-2,4-Diamino[4-^{11}C]butyric acid (DAB, **99a**) was synthesized from H^{11}CN using carboxylate as leaving group (Fig. 15).[73] The enzyme (β-cyano-L-alanine synthase, BCas) catalyzed reaction of carrier-added (0.1 μmol KCN) H^{11}CN with O-acetyl-L-serine to give the intermediate β-[^{11}C]cyano-L-alanine (**97a**). This was then reduced to L-2,4-diamino[4-^{11}C]butyric acid (98% e.e.) in 30–40% of decay-corrected radiochemical yield, 96% of radiochemical purity and 32 min of synthesis time. The purified product was studied in vivo but it was less favorable for tumor imaging than other amino acids.

In 2001, the same group reported the preparation of L-[4-^{11}C]aspartate (**98a**) and L-[5-^{11}C]glutamate (**98b**) using a similar method.[74] The intermediates, β-[^{11}C]cyano-L-alanine (**97a**) and γ-[^{11}C]cyano-α-amino-L-butyric acid (**97b**) were obtained by the reaction of O-acetyl-L-serine and O-acetyl-L-homoserine with carrier-added H^{11}CN (0.1 μmol) using O-acetyl-L-serine sulfhydrylase and O-acetyl-L-homoserine sulfhydrylase as enzymes. The final products **98a** and **98b** were generated by alkaline hydrolysis of corresponding intermediates in 65% and 55% decay-corrected radiochemical yields. The molar activitiy was *ca.* 29.6 GBq/μmol (0.8mCi/μmol) and the enantiomeric purities were greater than 97.5%. The total reaction times were 50–55 min.

4.1.5. Amine as leaving group—In 2011, ^{11}C labeled 3-indolylacetic acid ([^{11}C]IAA), the most common naturally occurring plant hormone, was synthesized by Reid et al using the reaction of H^{11}CN with a precursor bearing a dimethyl amine leaving group (Fig. 16).[75] The reaction of gramine (**100**) with H^{11}CN gave the intermediate 3-indolyl[1-^{11}C]acetonitrile (**101**). This intermediate was purified using HPLC and then hydrolysed with NaOH solution to give corresponding amide (**102**) side product and carboxylic acid (**103**). 3-indolyl[1-^{11}C]acetic acid (**103**) was isolated in 28% of overall decay-corrected radiochemical yield after a second HPLC purification and 68 min of synthesis and purification time. The molar activity was 25.9 GBq/μmol (0.7 Ci/μmol). Three years later, the same group lead by Joanna Fowler reported an improved synthesis procedure of the same compound.[76] This method utilized a streamlined semi-remote controlled

production system which resulted in 61.0 ± 0.3 % (n = 10) decay-corrected radiochemical yield and 82.51 ± 36.26 GBq/μmol (2.23 ± 0.98 Ci/μmol) molar activity. The total synthesis time was 81.8 ± 3.0 minutes (n = 10). Finally, in 2015, they reported a one-pot synthesis procedure. To accomplish that they changed the solvent to tetraethylene glycol and both cyanation and hydrolysis reactions were performed without an intermediate purification step. The total synthesis time was reduced to 55 min. The decay-corrected radiochemical yield was 33 ± 9.5% of and the molar activity 47.36 ± 12.58 GBq/mmol (1.28 ± 0.34 Ci/mmol).[77]

4.2. Nucleophilic addition reaction

The nucleophile $^{11}CN^-$ can also attack electron-deficient centers of unsaturated compounds (e.g. C=O, electron-withdrawing group bearing C=C bond) leading to nucleophilic additions.

4.2.1. Bucherer-Strecker reaction—Bucherer-Strecker technique is a conventional method used for amino acid synthesis starting from cyanide. The reaction first generates the hydantoins, which are further hydrolyzed to generate the corresponding amino acids. Although amino acid synthesis by Bucherer-Strecker technique requires long reaction times, the reaction conditions can be optimized to shorten the reaction time making it suitable for ^{11}C chemistry. (i.e., by increasing reaction temperature and pressure). ^{11}C-labeled amino acids are of interest in oncologic imaging.

The Bucherer-Strecker technique was first used by Hayes et al to produce $[^{11}C]$1-aminocyclopentanecarboxylic acid synthesis in 1976 (Fig. 17).[78] In this report, ^{11}C was produced by using a boron trioxide (B_2O_3) target as described in Section 3. $H^{11}CN$ was trapped by NaOH and then introduced into the reaction mixture containing clclopentanone, $(NH_4)_2CO_3$, NH_4Cl, and KCN. The reaction of carrier-added $H^{11}CN$/KCN with cyclopentanone (105) generated the corresponding hydantoin intermediate which was subsequently hydrolyzed to $[1-^{11}C]$1-aminocyclopentanecarboxylic acid (14i) (also known as cycloleucine). The decay-corrected radiochemical yield was ca. 40% with 1h synthesis time.

Later in 1978, the same group optimized and expanded the Bucherer-Strecker technique to several ^{11}C-labeled neutral and basic α-amino acids. Starting from different cyclic ketones (104-107) they were able to generate the corresponding cyclic amino acids (108, 14i, 14h, 107a). Using this method they also reported the synthesis of DL-valine (14e), and DL-tryptophan (20).[79] All of these reactions required ca. 20 min for synthesis and an 25 min for purification. Decay-corrected radiochemical yields ranged from 10–70%. In 1985, Sambre *et al* reported the routine production of 1-$[^{11}C]$aminocyclopentanecarboxylic acid (14i) for medical use.[80] This system allowed them to carry out 30 preparations per year with 60 ± 2% of decay-corrected radiochemical yield, which is significantly improved compared to the original report.

In 1981, Casey et al reported a method for the preparation of optically pure α-amino acid (D- and L-$[^{11}C]$phenylalanine).[81] The enatiomeric mixture of ^{11}C-labeled DL-Phenylalanine (14a, 13.88 GBq (375 mCi)) was produced in 40 minutes and 65% decay-corrected radiochemical yield using the Bucherer-Strecker reaction. Subsequently, optically pure D-

phenylalanine (yield 0.703 GBq (19mCi)) and L-phenylalanine (yield 1 GBq (27 mCi)) were separated by oxidative deamination using immobilized L- and D-amino acid oxidase in 35 min, respectively. Comparison of the uptake of the two amino acids in the pancreas (relative to liver) suggested that the natural L-amino acid accumulated over time whereas the other did not.

The synthesis of optically pure L-[^{11}C]leucine was reported in 1983 by Barrio et al.[82] Starting from the corresponding aldehyde **112**, the enantiomeric mixture DL-[^{11}C]leucine **14f** was synthesized using a modified Bucherer-Strecker reaction. The L-isomer was obtained by using a D-amino acid oxidase/catalase enzyme complex immobilized on a Sepharose support with a decay-corrected radiochemical yield of 25%. The synthesis was fully automated and the production time was 30–40 min. As reviewed in Section 4.1.1, compound class **14**, were also produced via cyanation of sodium bisulfite precursors with higher radiochemical yields.

[^{11}C]α-aminoisobutyric acid ([^{11}C]AIB, **107a**) was also prepared by Bucherer-Strecker reaction.[83] Since AIB is a non-metabolizable amino acid, it is a good candidate to study the amino acid transport *in vivo* without interference by radiolabeled metabolic products. Starting from acetone, ammonium carbonate, and carrier-added K^{11}CN, [^{11}C]AIB was prepared in 35 – 60 % decay-corrected radiochemical yields in 70–80 min of synthesis and purification time. The carrier-added synthesis gave the molar activity of 11.1 GBq/mmol (0.3 Ci/mmol).

Applying the same method and starting from formaldehyde, ammonium carbonate and H^{11}CN, [^{11}C]glycine (**114**) was prepared. The synthesis and chromatographic purification time was 30–35 min and the decay-corrected radiochemical yield was 35%. [^{11}C]glycine was used together with [^{68}Ga]EDTA and L-[methyl-^{11}C]methionine for imaging anaplastic astrocytoma using PET.[84]

In 1984, L-[1-^{11}C]lactic acid **22**, was prepared by addition of ^{11}CN$^-$ to acetaldehyde.[85] This reaction produced racemic DL-[^{11}C]alanine **16** which was then converted to [1-^{11}C]pyruvic acid **17** and L-[1-^{11}C]lactic acid **22** by enzymatic transformation as described in Section 4.1.1 (Fig. 5). The synthesis and purification time was 35–40 min and the decay-corrected radiochemical yields were 25% for L-[1-^{11}C]lactic acid, 29% for [1-^{11}C]pyruvic acid, and 20% for L-[1-^{11}C]alanine). Finally, in 1991, Fissekis et al reported a remote-control apparatus for the routine synthesis of [^{11}C]carboxy-labelled α-amino acids using modified Bucherer-Strecker method.[86] The apparatus has been used for the synthesis of several α-amino acids including DL-valine, DL-leucine, DL-isoleucine, α-amino-isobutyric acid, and 1-amino-cyclopentane-1-carboxylic acids. The apparatus allows the sequential batch-production of two different ammo acids in average 1.48–2.59 GBq (40–70 mCi) with average molar activates of 92.5 GBq/mmol (2.5 Ci/mmol).

4.2.2. Addition to C=O—The nucleophilic additions of ^{11}CN$^-$ to carbonyl compounds (mainly aldehydes) give cyanohydrins, which can be further converted to aldehydes (sugars), amines, and carboxyl acids with one carbon atom chain extended.

The Kiliani-Fischer synthesis is a widely-used method of extending the carbon atom chain of pentopyranoses. In this reaction, the addition of cyanide to a pentopyranose and subsequent hydrolysis yields the corresponding hexopyranose.

In 1985, the synthesis of [1-^{11}C]-D-glucose (**118**) and [1-^{11}C]-D-mannose (**119**) from carrier added Na^{11}CN was reported by Shiue and Wolf (Fig. 18).[87] H^{11}CN was trapped in NaCN/AcOH solution at pH = 8 to give carrier added Na^{11}CN. This was further reacted with D-arabinose (**116**) yielding intermediate [1-^{11}C]-aldononitrile (**117**). [1-^{11}C]-D-glucose (**118**) and [1-^{11}C]-D-mannose (**119**) were obtained by reducing **117** with Raney alloy in 30% formic acid. The ratio of [1-^{11}C]-D-glucose (**118**) and [1-^{11}C]-D-mannose (**119**) was pH dependent and these two products could be separated by HPLC. The decay-corrected radiochemical yield of **118** was ca. 15% with a total synthesis and purification time of 70 min. Using a similar method, [1-^{11}C]-D-galactose (**122**) which was synthesized from D-lyxose (**120**) with a decay-corrected radiochemical yield of ca. 30% and a synthesis and purification time of 70 min.

In 1988, [^{11}C]phenylethanolamine (**125**) was prepared using no-carrier-added H^{11}CN.[88] The enzyme-catalyzed addition of H^{11}CN to benzaldehyde gave the intermediate [^{11}C]cyanohydrin (**124**), which was then reduced to produce [^{11}C]phenylethanolamine (**125**) in 2–4% of radiochemical yields. The synthesis and purification took 50–60 min and the enantiomeric purities were dependent on the reducing reagent. NaBH$_4$-CoCl$_2$ reduction gave 60% e.e. while borane-THF reduction gave 80% e.e.

In 1982, D-[1-^{11}C] glucopyranose (**133**) and D-[1-^{11}C] galactopyranose (**134**) were also prepared using Kiliani-Fischer synthesis (Fig. 19).[89] The reaction of D-arabinopyranose (**127**) / D-Lyxopyranose (**128**) with K^{11}CN in the presence of base gave **131**/**132** via intermediates **129**/**130**. **131**/**132** were further reduced by diborane yielding D-[1-^{11}C] glucopyranose (**133**) and D-[1-^{11}C] galactopyranose (**134**), which were purified by HPLC. The radiochemical yields of D-glucopyranose (**133**) and D-[1-^{11}C] galactopyranose (**134**) were 17% and 50%, respectively. The total synthesis and purification time of **133**/**134** was ca. 60 min. In 1994, a fully automatic synthesis system of [1-^{11}C]labelled aldoses, such as [1-^{11}C]-D-glucose, and [1-^{11}C]galactose, based on modified Kiliani-Fischer method was described.[90] The system described had the ability of supplying reagents, performing the synthesis, purifying the ^{11}C-labeled aldose, and preparing an injectable solution. In a typical run, 0.048 GBq (1.3 mCi, 11.9% of decay-corrected radiochemical yield) of [1-^{11}C]-D-glucose was obtained in 49 min

In Section 4.1.1, the radiochemical synthesis of [^{11}C]levetiracetam (**38**) via nucleophilic substitution of bisulfite by [^{11}C]cyanide was described (Fig. 20). Since this method gave low radiochemical yield an improved method of synthesis based on the nucleophilic addition of [^{11}C]cyanide to carbonyl was developed. In this method, propionaldehyde was reacted with ammonia and H^{11}CN to yield intermediate **35**, which was then reacted with 4-chlorobutyryl chloride and followed by hydrolysis to give [^{11}C]levetiracetam. After purification by chiral HPLC the decay-corrected radiochemical yield was $8.3 \pm 1.6\%$ (n = 8) in 50 ± 5.0 min, which is significantly better than the previous method (< 1% radiochemical yield).

Nucleophilic addition of [^{11}C]cyanide to carbonyl has also been applied in synthesis of ^{11}C-labeled amino acids: [^{11}C]methionine (**138**), [^{11}C]glycine (**114**), and [^{11}C]-N-phenylglycine (**139**).[91] Using this method, the non decay-corrected radiochemical yields were 5%, 14%, and 2%, respectively. The molar activities were 46.62 GBq/μmol (1.26 Ci/μmol), 55.5 GBq/μmol (1.5 Ci/μmol), and 569.8 GBq/μmol (15.4 Ci/μmol), respectively. The protocol was fully automated using a commercially available radiochemistry synthesis module.

In 2016, the endogenous redox pair, [^{11}C]ascorbic acid (vitamin C) and [^{11}C]dehydroascorbic acid, were synthesized and used for sensing reactive oxygen species using PET.[92] Aqueous solution of L-xylosone (**140**) was reacted with no-carrier-added or carrier-added H^{11}CN/KCN to generate the addition cyanohydrin, which underwent cyclization upon reaction with HCl at 150°C to give the desired product [^{11}C]ascorbic acid (**141**). [^{11}C]ascorbic was completely oxidized to [^{11}C]dehydroascorbic acid (**142**) in 10 min by bubbling O_2 in the presence of activated charcoal. [^{11}C]ascorbic (**141**) was produced in 14.3 ± 10.4% of decay-corrected radiochemical yield and 9.88 ± 5.48 GBq/μmol (267 ± 148 mCi/μmol) molar activity using no-carrier-added H^{11}CN and in 29.7 ± 8.8 % to 45.4 ± 1.2 % of decay-corrected radiochemical yields and 0.148 ± 0.044 to 0.33 ± 0.137 GBq/μmol (4.0 ± 1.2 to 9.0 ± 3.7 mCi/μmol) of molar activity using carrier added H^{11}CN.

4.2.3. Addition to C=C (Michael addition)—[^{11}C]Cyanide can also react with the electron-withdrawing groups bearing α,β-unsaturated compounds via Michael addition reactions. These methods have been employed in the synthesis of [1-^{11}C]putrescine (**144**) and γ-amino[4-^{11}C]butyric acid (GABA, **146**) (Fig. 21).

In 1985, a synthetic method of no-carrier-added [1-^{11}C]putrescine (**144**) using Michael addition was reported by McPherson et al.[63] No-carrier-added H^{11}CN was trapped in 1% KOH solution and reacted with acrylonitnile (**143a**) for 5 min at 65°C to give the intermediate succinonitrile (**143b**). This was then reduced to [1-^{11}C]putrescine (**144**) using the same method reported previously (Section 4.1.3) in 20% radiochemical decay-corrected yield. The synthesis time was around 50 min.

In 1990, a silica gel based H^{11}CN trap was developed by Somawardhana et al for the synthesis of base and moisture sensitive ^{11}C-labeled compounds.[93] The trap consisted on either coating silica gel particles directly with the substrate or adding KOH to the silica gel. The later version was employed for the synthesis of succinonitrile (**143b**) synthesis. After trapping the [^{11}C]HCN in the silica-KOH, acrylonitrile was added to the column, the column was sealed and placed in a boiling water bath. Using this method the reaction time was reduced from 5 to 2 min and the decay-corrected radiochemical yield was increased to 73.9% to 84.7%. One year later, the same research group applied this method in the synthesis of [1-^{11}C] putrescine.[94] This method yielded [1-^{11}C] putrescine in 53±4% decay-corrected radiochemical yield in 40 min of synthesis and purification time. The moisture-free semi-automated method allowed better radiochemical yields (53% vs. 20%), fewer side products and shorter synthesis time (40 vs. 50 min) compared to the previous report.[63] It will be interesting to see whether this method can be applied to other reactions with [^{11}C]HCN.

A one-pot synthesis of γ-amino[4-^{11}C]butyric acid (GABA, **146**) starting with H^{11}CN based on Michael addition reaction was first reported by Antoni and Långström in 1989.[95] No-carrier-added H^{11}CN was first trapped in tetrahydrofuran/potassium hydroxide in the presence of Kryptofix 2.2.2. and then reacted with ethyl acylate to give intermediate **145b**. This was further selectively reduced and hydrolyzed to yield [4-^{11}C]GABA in 60–65% decay-corrected radiochemical yield. The total synthesis and purification time was ca. 40 min. Similar to previously described nucleophilic substitution methods, Michael addition can result in aliphatic amines although it may be less favorable for generating secondary and tertiary amines.

4.3. Ring opening reaction

The attack of the electrophilic center in aziridines by H^{11}CN leads to ring-opening reaction, as reported by Gillings et al in 2001.[96] In this example, the reaction of N-(tert-butoxycarbonyl)aziridine-2-isopropyl carboxylate (**147**) with H^{11}CN gave intermediate DL-[4-^{11}C]β-cyanoalanine (**148**). This was subsequently hydrolyzed or reduced-hydrolyzed to generate DL-[4-^{11}C]asparagine (**149a**), DL-[4-^{11}C]aspartic acid (**149b**), and DL-2,4-diamino[4-^{11}C]butyric acid (**149c**) in 30–40% decay corrected radiochemical yield within 30 min. The racemization occurred during the ring-opening of racemic precursor **171** yield the racemic mixture products, which were resolved by chiral HPLC. It will be interesting to see if this ring opening reaction would work for other ring structures.

4.4. Oxidation reaction

The oxidation of H^{11}CN gives the KO^{11}CN, which can be further transferred to urea, (iso)hydroxyurea, and other related compounds. In 1978, [^{11}C]hydroxyurea (**150a**), [^{11}C]isohydroxyurea (**150b**) and [^{11}C]urea (**151**) were synthesized from H^{11}CN via [^{11}C]cyanate (Fig. 23).[97] H^{11}CN was exchanged with KCN in aqueous solution giving carrier-added K^{11}CN, which was then oxidized by KMnO$_4$ and Cu(OH)$_2$ yielding KO^{11}CN in 37 min with 78.9% decay-corrected radiochemical yield. The further reaction of KO^{11}CN with hydroxylamine-HCl gave the mixture of [^{11}C]hydroxyurea (**150a**) and [^{11}C]isohydroxyurea (**150b**) in 72% overall decay-corrected radiochemical yield and a total synthesis time of 124 min.

Using a no-carrier added method, the synthesis of ^{11}C-labeled urea (**151**) was reported by Emran et al in 1983 (Fig. 23).[98] KO^{11}CN, obtained through the oxidization of K^{11}CN, was reacted with NH$_4$OH to generate NH$_4$O^{11}CN intermediate. Heating of the intermediate yielded [^{11}C]urea in 85 ± 5% decay-corrected radiochemical yield. The total synthesis time was less than 20 min. Two years later, the same research group reported several modifications which increased the decay-corrected radiochemical yield to 95 ± 2.5% and reduced the total synthesis time was reduced to 16±1 min. The molar activity of [^{11}C]urea after the improvements was 129.5 ± 29.6 GBq/μmol (3.5 ± 0.8 Ci/μmol).[99–101]

5,5-diphenylhydantoin (DPH, phenytoin) is a widely prescribed anticonvulsant that works by blocking sodium channels in the brain. A ^{11}C-labeled version of phenytoin (**153**) was synthesized by Emran et al via [^{11}C]urea intermediate.[102] [^{11}C]urea was prepared from no-carrier added H^{11}CN as previously described and reacted with a saturated alcoholic/

aqueous benzil (1,2-diphenylethane-1,2-dione) KOH solution to generate [2-^{11}C]-5,5-diphenylhydantoin (**153**). **153** was purified by preparative HPLC in an overall 30–35% decay-corrected radiochemical yield with high molar activity (118.4 ± 11.1 GBq/μmol; 3.2 ± 0.3 Ci/μmol) in 55–60 min. Prolonged reaction time resulted the dissociation of [^{11}C]DPH to [^{11}C]diphenylhydantoic acid ([^{11}C]DPHA, **154**), which could further undergo decarboxylation to generate diphenylglycine(DPG) and [^{11}C]carbonate.

4.5. The reactions of [^{11}C]cyanogen bromide (^{11}CN$^+$ reagent)

Through the reaction of H^{11}CN with bromine, [^{11}C]cyanogen bromide (^{11}CN)Br can be made. This reaction converts the nucleophilic carbon center of cyanide, ^{11}CN$^−$, to an electrophilic carbon center cyanogen, ^{11}CN$^+$. Nucleophiles can attack the electrophilic carbon in [^{11}C]cyanogen leading to very different chemical reactions compared with ^{11}CN$^−$.

In 1993, a new ^{11}C-electrophilic labeling reagent, [^{11}C]cyanogen bromide (^{11}CN)Br, based on H^{11}CN was developed by Westerburg *et al* (Fig. 24).[103] H^{11}CN was reacted with bromine in triethylenglycol dimethyl ether to give (^{11}CN)Br in 70–80% decay-corrected radiochemical yield in 9–11 min. (^{11}CN)Br (b.p. 61.5 °C) was separated from bromine (b.p. 137.8 °C) via distillation for further reactions. A typical run, which started from 20.35 GBq (550 mCi) of ^{11}CO$_2$, could yielded 10.14 GBq (274 mCi) of (^{11}CN)Br. (^{11}CN)Br was tested in the reaction with (thio)phenols, amines, pyridine, and disulfide compounds which yielded the corresponding [^{11}C](thio)cyanates (**156a-d**), [^{11}C]cyanamide (**158**-**160**), [1-^{11}C]cyanopyridninium bromide (**157**), and [^{11}C]thiocyanate (**161**) in 12–98% of radiochemical yields in 13–27 min from (^{11}CN)Br production.

A second flow production system of (^{11}CN)Br using solid pyridinium bromide perbromide instead of elemental bromine was developed in 1997.[104] This simplified method produced (^{11}CN)Br in 95% radiochemical yield (decay-corrected) within 3 min from the end of bombardment.

In 1994, Långström's research group reported the synthesis of 1,3-di(2-tolyl)-[^{11}C]guanidine (**164**) from o-toluidine and (^{11}CN)Br.[105] 1,3-Di(2-tolyl)-[^{11}C]guanidine was obtained in 87 % decay-corrected radiochemical yield within 31–33 min of synthesis time. The molar radioactivity of **164** was 118.4 GBq/μmol (3.2 Ci/μmol). *In vitro* autoradiographic studies showed specific binding of **164** on rat brain sections. However, in vivo PET imaging of Rhesus monkey suggested very low brain uptake, indicating that the 1,3-di(2-tolyl)-[^{11}C]guanidine did not cross the blood-brain barrier. Very recently, Scott, Shao and co-workers reported the automated radiosynthesis of [^{11}C]guanidines using (^{11}CN)Br.[106] The method was found to tolerate unprotected -OH and -NH groups and have broad substrate scope. Using this method they were able to prepare [^{11}C]3F-PHPOG (**167**) which was found to have good cardiac uptake and heart retention in rabbits.

A similar method using (^{11}CN)Br was reported for the synthesis [^{11}C]polysaccharides in high molar radioactivity.[107] The reaction of dextran and hyaluronan with (^{11}CN)Br in basic solution gave the corresponding labeled products in 30–47% decay-corrected radiochemical yields. The synthesis times were 24–26 min and the molar activity activities were 4.44–

114.7 GBq/μmol (0.12–3.1 Ci/μmol). The isolated fraction of [^{11}C]hyaluronan (**169**) with 98% radiochemical purity was used for the biodistribution study in rats using PET imaging which suggested a rapid and displaceable uptake in liver.

4.6. Other reactions

H^{11}CN can be directly reduced to [^{11}C]methylamine (Fig. 25). This was accomplished by the hydrogenation-reduction of H^{11}CN using Adams catalyst with H$_2$ gas in diluted sulfuric acid solution. [^{11}C]methylamine was synthesized in 50–70% decay-corrected radiochemical yield. The synthesis and purification time was 25 min.[108]

In 1980, Jay et al reported the -CN exchange of the radiolabeled potassium cyanide with solvent acetonitrile in the present of crown ether (Fig. 25).[109] Even though the exchange rate was slow this has implications in the choice of solvent for radiocyanations.

A method of synthesis ^{11}C-labeled dialkyl ketones using H^{11}CN was developed based on the reaction of H^{11}CN with organoboranes by Kothari et al in 1986.[110] The labeling precursor di-n-octylthexylborane (**178**) was synthesized by the reaction of 1-octene, tetramethylethylene, and BH$_3$-THF. **178** was reacted with K^{11}CN to give the adduct intermediate **179**, which was further rearranged and oxidized to give 9-[^{11}C]heptadecane-9-one (**180**) in in 50–70% overall decay-corrected radiochemical yield. The reaction and purification time was 55–60 min from the end of bombardment (EoB).

Similar to the oxidative reactions, the reaction of H^{11}CN with S$_8$ and KOH yields potassium [^{11}C]thiocyanate, KS^{11}CN, a heavier analogue of potassium cyanate, KO^{11}CN. The myeloperoxidase inhibitor AZD3241 (**184**), a candidate drug for neurodegenerative brain disorders, can be synthesized via KS^{11}CN labeling[111]. KS^{11}CN was reacted with benzoyl chloride to generate benzoyl [^{11}C]isothiocyanate (**181**), which was further converted to [^{11}C]AZD3241 (**184**) via the reaction with ethyl 3-(2-isopropoxyethylamino)-1H-pyrrole-2-carboxylate and subsequent base-catalyzed cyclization. A typical synthesis gave 0.71 ± 0.29 GBq (19.19 ± 7.95 mCi) (mean ± SD, n = 7) of [^{11}C]AZD3241 within 60 min with molar activity of 8.88 ± 4.07 GBq/μmol (0.24 ± 0.11 Ci/μmol) and 98% radiochemical purity. This compound was utilized for PET microdosing studies in cynomolgus monkeys.

5. [^{11}C]cyanation of aromatic compounds

5.1. S$_N$Ar reaction with Cr(CO)$_3$ activated arenes

The first example of an aromatic [^{11}C]cyanation was first reported in a meeting abstract in 1986 by Balatoni, *et. Al.*[112] with additional details published in the related paper by the same group in 1989.[113] Nucleophilic displacement of arene chromium tricarbonyl complexes had previously been reported for [^{12}C]cyanation conditions. The coordination to chromium helps withdraw the electron density from the ring making the nucleophilic displacement possible. This electron removal effect is similar to an aryl nitro group, commonly used in nucleophilic aromatic substitutions. Synthesizing an arene chromium tricarbonyl complex can be completed in milder conditions than the synthesis of aryl nitro derivatives in most cases.[112]

In 1986, one example of nucleophilic substitution by defluorination is reported (Fig. 26).[112] No-carrier-added H[11]CN was bubbled into a solution of NaOH, dried, and then used under inert conditions to radiolabel η^6-fluorobenzenetricarbonylchromium in DMSO at 150 °C for 5 min. A decay-corrected radiochemical yield of ~50% was obtained after HPLC purification.[112] The authors noted that under these conditions, the decomplexation also occurs so an additional step is not needed. A control experiment using fluorobenzene produced no [11C]benzonitrile under the otherwise same conditions.[112]

In 1989, the scope of the defluorination by nucleophilic displacement of arene chromium tricarbonyl complexes was expanded to four substrates (Fig. 27).[113] Carrier-added Na[11]CN was used under inert conditions to radiolabel the aryl chromium tricarbonyl complexes in DMSO at 135 °C for 10 min. The radiochemical yields after HPLC purification ranged from 19–35%.[113] Control experiments using the uncomplexed arenes provided no product under than same labeling conditions.

5.2. Palladium-Mediated [11C]cyanation

In 1991, a symposium abstract published the first example of combining the previously developed radiolabeling arenetricarbonyl chromium complexes by nucleophilic displacement [11C]cyanide and the carbon-carbon bond formation reactions using palladium(0) to obtain aryl nitriles.[114] The nucleophilic displacement of aryl halides was investigated with arene chromium complexes with and without palladium(0) catalyst (Fig. 28). It was found for the aryl fluorine substrates, the conditions without palladium(0) gave product as observed previously. Aryl chlorides could also undergo the cyanation reaction, whereas aryl bromides gave no product without palladium(0) present. Interestingly, the trend is reversed when palladium(0) is added. Aryl fluorides give no product while aryl chlorides and aryl bromides give high yields.

Starting with the aryl halides and palladium(0) catalyst, a similar trend was observed when both arene chromium complexes and palladium(0) were used: aryl fluorides and aryl chlorides gave poor yields while aryl bromides and aryl iodides gave high yields (Fig. 29). Typical conditions used K[11]CN in DMSO at 135 °C for 5 min (with palladium(0) present) or 10 min (without palladium(0) present), followed by purification via Sep-Pak cartridge to obtain decay-corrected radiochemical yields of 49–80%, decay-corrected.[114] The authors also found that decomplexation of the chromium complex were not necessary under these conditions.

In 1994, the relationship between reaction conditions (palladium(0) assisted, nucleophilic substitution of chromium complexes or a combined approach) and the leaving group were explored.[115] In the Pd(0) assisted reactions, it was found that aryl iodides were the best substrates, followed by aryl bromides. Aryl chlorides gave a lower yield and aryl fluorides were not reactive (Fig. 30).[115] The control reaction without Pd(0), gave no desired product. High yields were obtained when the Pd(0) complex was added as a solid in the last possible time in the synthetic procedure. Using a solution of the metal complex, prepared in advance, gave a decreased RCY, likely due to the rapid oxidation of the Pd(0) complex.[115] This limitation could be circumvented if the reaction was performed under argon in an anaerobic conditions.

The halogen leaving group for the nucleophilic substitution of arene(tricarbonyl)chromium complexes was found to have the opposite trend of the Pd(0) assisted reactions. Aryl fluorides provided the best results, followed by aryl chlorides, and no product was determined with the aryl bromides (Fig. 31).[115] Optimization led to an improvement of the original report of [11C]benzonritile (74% versus 35%).[113] The decomplexation of the chromium complex was observed during the reaction conditions. The chromium complexes are known to be stable in crystalline form, but unstable in solution. It is probable that performing these reaction under anaerobic conditions would increase the yield, but then the decomplexation step would be required; therefore increasing the overall time of the reaction and likely not significantly improving the overall yield.[115] Combining arene (tricarbonyl)chromium complexes with Pd(0) assisted reactions increased the yield of the reaction by facilitating the oxidative addition (Fig. 31 in parenthesis). This approach could lead to high yield products with the stable aryl chloride substrates.[115]

Aryl nitriles can be converted into other useful functional groups including amides under 11C-labeling conditions in an one-pot procedure (Fig. 32).[116] In anhydrous conditions the Pd(0) [11C]cyanation step could be performed rapidly (<2 min) with good yields in the presence of sodium percarbonate. The hydrolysis could be performed in the same pot by the addition of water to dissolve the sodium percarbonate which releases hydrogen peroxide. This method allows the authors to synthesize the three targeted compounds in useful yields of 45–66% decay-corrected yield in 25–35 min.[116]

Benzamide (**213**), methoxybenzamide (**214**), aminobenzamide (**215**), and nicotinamide (**216**) are known to be potent inhibitors of poly (ADPribose) synthetase (Fig. 32), a common target for anticancer drugs and could be used to evaluate the amount DNA damage that occurs during treatments with radiotherapy or chemotherapy.[116] Compounds **214**, **215**, and **216** were studied *in vivo* in a rhesus monkey model. Purification optimization to remove Pd(0) from the reaction mixture was analyzed by ICP-AES. The preliminary studies investigated the initial distribution and kinetics of the potential tracers. It was found that the blood-clearance was too rapid, the brain uptake was too low, and there was rapid fixation with high uptake in the liver, kidney and lymph nodes with slow washout.

In 2015, a modified Pd(0) method was investigated where the active catalyst is generated *in situ* using biaryl phosphine ligands.[117] These biaryl phosphine ligands offer several advantages from the traditional ligands, such as milder conditions, shorter reaction times, ideal solvents, and reduced addition of base.[117] There are three general steps the reaction needs to undergo to form the desired product: oxidative addition (OA), transmetalation I, and reductive elimination (RE). Previous [11C]cyanation methodologies performed all three transformations after the 11CN− has been introduced to the reaction resulting in higher temperatures and longer reaction times (Fig. 33, pathway a).[115–116] Biaryl phosphine ligands (L) allow the reaction to be performed at ambient temperature in under 5 min (Fig. 33, pathway b).[117] While using a biaryl phosphine ligand offered some iprovements on the current procedures, the Pd(0) catalyst and ligand were added separately, required to form the active complex and perform OA after end of bombardment (EOB) while the 11CN− was in solution. These steps were independent of the 11CN− and it was proposed that they could occur prior to EOB to save on the overall reaction time (Fig. 33, pathway c).[117]

Complex **A** is a stable intermediate that can be isolated for some simple aryl groups, but this isolation can be tedious. This work generates complex **A** *in situ* prior to EOB, without the requirement to isolate complex **A** (Fig. 33, pathway d).[117] Pathways **c** and **d** allow for the OA to occur before EOB resulting in an unnecessary loss of radioactivity. Then the TM and RE can occur post EOB resulting in a more efficient timeline.

Optimization lead to the conditions of a preformed Pd(0)-L complex, aryl halide or pseudohalides in THF or toluene at room temperature for 30 min then $H^{11}CN$ in THF was added to the mixture and allowed to react for 1–5 min. The crude yields of reaction was found to be robust for common functional group, such as phenols, amides, and heterocycles, and small amounts of water. Commercial $Pd(PPh_3)$ could be used with K_2CO_3 in DMF at 100 °C for 5 min, but lower yields were observed in most cases.[117] To show the versatility of this method, three known [^{11}C]radiolabeled pharmaceuticals (**217**-**219**) were isolated in good non-decay corrected (ndc) RCY (10–20%) in 12–23 min with good molar activity (Fig. 34). This method is an improvement upon earlier Pd(0) methods in terms of yield, overall reaction time, and breadth of scope. A limitation is the Pd(0) catalyst used has to be synthesized prior and stored in an inert atmosphere at −20 °C due to their susceptibility to oxygen and moisture.

In 2017, the same group applied this new method development to label unprotected peptides with [^{11}C]cyanide.[118] The two approaches prior to this method was either to attach a prosthetic group that could be radiolabeled later or radiolabel the prosthetic group and then conjugate to the peptide. The method reduces the previous two step approaches to a one step, avoiding the need for a prosthetic group. Using conditions similar to the initial publication,[117] a [^{11}C]benzonitrile group can be installed on a cysteine reside in the presence of other nucleophilic functional groups (**220** and **221**).[118]

In 2018, the substrate scope was extended to include arylboron compounds using Pd(II) complexes.[119] The optimal conditions consisted of $NH_4^{11}CN$ with excess NH_3 and $PdCl_2(PPh_3)_2$ in DMF at 100 °C for 5 min. These conditions were used to label a range of arylboronic acids and arylboronic esters with good RCC. The reaction was automated to produce [^{11}C]Cetrozole (**224**) and [^{11}C]YM511 (**225**) in 45% and 33% decay corrected RCY, respectively, in 28 min from the generation of $^{11}CH_4$ (Fig. 35). All reagents are bench-stable and readily available. Using $NH_4^{11}CN$ as the cyanide source eliminates the need to remove the excess NH_3, saving time in the synthesis. This method uses a relatively large amount of starting precursor (20 μmol compared to <10 μmol of related methods) which can be difficult to achieve for some complex structures.[119]

The general Pd-mediated [^{11}C]cyanation reaction conditions that were developed in 1994 by Andersson and co-workers has been used in many imaging studies (Fig. 36).[115] These general conditions consisted of an aryl halide (X = I or Br), $Pd(PPh_3)_4$ in DMF or DMSO at relatively high temperatures (>100 °C) for ~5 min. In 1998, [^{11}C]MK-801 (**226**) was synthesized from an aryl iodide precursor in an overall 37% DCY in 32 min from end of bombardment (Fig. 36).[120] [^{11}C]MK-801 (**226**) was used in an *in vitro* investigation of rat brain to analyze the specific and high-affinity binding to the *N*-methyl-D-aspartate (NMDA) receptor. An *in vivo* experiment in a Rhesus monkey did not show an improvement over

the known $[^{18}F]$methyl-MK-801 and the preliminary data was not sufficient to validate $[^{11}C]$MK-801 (**226**) as a useful tracer for studying the NMDA receptor.[120]

In 1999, $[^{11}C]$NAD-299 (**227**) was synthesized over two steps in 20–40% DCY in 40–45 min (Fig. 36). The benzonitrile intermediate was synthesized from the aryl triflate with $Pd_2(dba)_3CHCl_3$ complex with extra dppf ligand in NMP at 80 °C for 3 min.[121] When the conventional $Pd(PPh_3)_4$ catalyst was used, the benzonitrile intermediate had a 20% incorporation of $[^{11}C]$cyanide as opposed to a nearly quantitive yield when $Pd_2(dba)CHCl_3$ with dppf was used.[121] In 1999, $[^{11}C]$NAD-299 (**227**) was found *in vitro* to demonstrate high binding to the 5-HT$_{1A}$ receptors using human brain postmortem analyzed by autoradiography techniques.[121] In 2002, the same group analyzed $[^{11}C]$NAD-299 (**227**) in a cynomolgus monkey for metabolite evaluation. After 45 min post injection, 49% of radioactivity was from unchanged radioligand, a much slower metabolism than the currently used [*carbonyl*-^{11}C]WAY-100635 which has 25% remaining at the same time point.[122]

In 2008, a new radioligand investigated the imaging of cannabinoid subtype-1 (CB$_1$) receptors *in vivo* with PET.[123] This radioligand, later commonly referred to as (±)-$[^{11}C]$SD5024 (**228a**, Fig. 36), was synthesized as a racemic mixture in a 36% DCY in an overall time of 30 min using $Pd(PPh_3)_4$ in DMSO at 110 °C from the aryl bromide precursor. When attempting to isolate the higher affinity enantiomer from the enantiomerically pure precursor, complete racemization was observed likely due to KOH used in K^{11}CN formation.[123] They found exchanging the base to KH_2PO_4 allowed for both enantiomers to be isolated in high e.e. All three isomers were analyzed in a cynomolgus monkey and it was found that the binding assays matched the studies conducted with the naturally abundant isotope. Namely, the racemic compound had a mixture of specific and non-specific binding, the high affinity isomer ($[^{11}C]$SD5024 (**228**)) was responsible for the specific and the enantiomer (+) was the result of the non-specific binding.[123] In 2014, the compound was compared *in vitro* and *in vivo* to other known CB$_1$ receptor ligands previously used in humans.[124] The dissociation constant and lipophilicity was measured *in vitro* in the human brain. Specific binding was measured *in vivo* in monkeys. Studied the kinetics in healthy subjects. $[^{11}C]$SD5024 (**228**) had favorable or improved results the other known CB$_1$ receptors in all sections analyzed.[124] In 2016, $[^{11}C]$SD5024 (**228**) was used to analyze the efficacy of three drug candidates in non-human primate brain *in vivo*.[125]

In 2009, a high-affinity aromatase inhibitor, letrozole, was labelled with carbon-11 (Fig. 36).[126] $[^{11}C]$Letrozole (**229**) was synthesized from the aryl bromide precursor with $Pd(PPh_3)_4$ in DMSO at 110 °C for 5 min with an overall synthesis of 60 min. $[^{11}C]$Letrozole (**229**) was not a promising PET radiotracer for brain aromatase due to the lack of specific binding and saturability in regions known to have a high concentration of aromatase.

In 2009, compound **230** (Fig. 36) was synthesized as a potent and selective antagonist of the dopamine D$_3$ receptor.[127] Compound **230** was synthesized from the aryl iodide precursor with Pd_2dba_3, dppf ligand, and $KHCO_3$ as the base in either NMP at 80 °C for 3 min or in DMF at 110 °C for 5 min. Analysis in a non-human primate model showed no specific signal for the dopamine D$_3$ receptor.[127]

In 2010, multiple tuberculosis chemotherapeutics were ^{11}C-labeled using Pd-mediated method (Fig. 36) and analyzed in baboons *in vivo*.[128] [^{11}C]isoniazid (INH) was synthesized in three steps starting from the iodopyridine with Pd(PPh$_3$)$_4$ in DMSO for 5 min to give [^{11}C]cyanopyridine in 90% crude RCC. The final product, [^{11}C]INH (**231**) was synthesized in a 45–50% DCY in 50 min over three steps. [^{11}C]pyrazinamide (PZA, **232**) was synthesized with the same conditions as [^{11}C]INH (**231**) to provide an overall 50–55% DCY in 45 min. The preliminary kinetics and metabolites for the potential radiotracers were analyzed in baboons.[128]

In 2012, a known effective high-affinity and selective radioligand for imaging metabotropic 5 receptors (mGluR5), [^{18}F]SP203, was labelled with carbon-11 (Fig. 36).[129] Both aryl bromides and aryl iodides were used to synthesize the desired product with Pd(PPh$_3$)$_4$ in THF at 80 °C for 4 min. Aryl bromide precursor gave poor reproducibility (20–52% DCY) while the aryl iodide provides a nearly quantitive decay-corrected yield.[129] The imaging study showed similar results for the new [^{11}C]SP203 (**233**) compared to the known [^{18}F]SP203 in terms of uptake and stability. For metabolites, a known metabolic pathway is the defluorination where the fluorine-18 is labelled, indicated by bone uptake, a process avoids radioactivity accumulation in bone.[129] In 2017, another mGluR5 ligand FPEB was labelled with carbon-11 and compared with [^{11}C]SP203 (**233**) (Fig. 36). The same trend was observed with [^{11}C]FPEB (**235**) having more favorable binding and kinetic results than [^{11}C]SP203 (**233**).[130]

In 2013, another selective mGluR5 antagonist, [^{11}C]AZD9272 (**236**, Fig. 36), was prepared from an aryl bromide precursor with Pd(PPh$_3$)$_4$ in DMSO at 135 °C for 5 min to give an overall DCY of 50% in 45 min.[131] *In vivo* analysis in non-human primates provided favorable results and additional studies shown an improvement upon the known mGluR5 antagonists.[131–134]

In 2013, [^{11}C]LY2795050 (**237**) was synthesized and evaluated as selective κ-opioid receptor (KOR) antagonist (Fig. 36).[135] [^{11}C]LY2795050 (**237**) was synthesized over two steps from the aryl iodide precursor with Pd$_2$dba$_3$ in DMF at 80 °C for 5 min, followed by hydrolysis to give an overall 12% RCY. [^{11}C]LY2795050 (**237**) was found to have favorable imaging properties in non-human primates.[135] In 2014, the derivative [^{11}C]LY2459989 (**238**) was synthesized in similar conditions to [^{11}C]LY2795050 (**237**) and found to have a higher binding affinity for KOR *in vitro* and *in vivo* (Fig. 36).[136]

Aside from methodology development publications, there were several examples of Pd-mediated [^{11}C]cyanation that were not used in an imaging study or investigated further after the initial study. Two examples, shown in Fig. 36, were made with the standard Pd-mediated method developed in 1994 using Pd(PPh$_3$)$_4$. In 2008, [^{11}C]Ximelagatran (**239**) intermediate was synthesized in DMSO at 135 °C for 4 min to yield the Ar-[11]CN compound. Further elaboration let to the final compound in an overall decay-corrected yield of 27% in 45 min.[137] In 2001, the two step [^{11}C](*Z,Z*)-BABCH (**240**) was synthesized in a 55% RCY in 55 min via Pd-mediated [^{11}C]cyanation.[138]

5.3. Copper-Mediated [^{11}C]cyanation

A reoccurring limitation for the previous sections is the requirement for inert and anhydrous conditions. Additionally, palladium has a lower allowable amount (10 μg/day) when compared to other first row metals such as chromium and copper (parenteral 1070 μg/day and 340 μg/day, respectively).[139] While copper(II) salts are known to be sensitive to atmospheric oxygen, the reaction conditions are generally more forgiving than the related palladium-mediated methods.

In 1997, the first example of a copper(I)-mediated [^{11}C]cyanation was reported.[140] This method adapted the known Rosenmund-von Braun reaction to carbon-11 by synthesizing a Cu^{11}CN. Cu(I) salts are known to not require an inert atmosphere and/or anhydrous conditions. Additionally, these salts are known to react with other aromatic nucleophilic substitutions and have been used with other isotopes, including PET and SPECT radiopharmaceutics. This long history and versatility made it a new approach when extending from palladium-mediated methods. Cu^{11}CN was generated *in situ* by adding an aqueous solution of CuSO$_4$ to H^{11}CN and headed at 60 °C for 5 min. Next, the precursor was added in DMF and heated at 180 °C for 5 min (Fig. 37). The benzonitrile products were converted into tetrazoyls, benzamides, or benzoic acids in conditions that were amenable to carbon-11. The authors found that trapping H^{11}CN without a base present, gave more optimal yields than trapping with KOH to make K^{11}CN. It was hypothesized that the excess KOH needed, disrupted the Cu reaction that needed to occur. This reaction worked well for a variety of substrates and the benzonitriles were able to be converted into other function groups with modified conditions (Fig. 37).[140]

This method was used in a one-pot, four steps method from H^{11}CN via Cu^{11}CN to radiolabel [tetrazoyl-^{11}C]irbesartan (**241**), a non-peptidic angiotensin II antagonist (Fig. 38).[141] Due to the lengthy synthesis, a relatively low RCY was obtained (<1% non-decay corrected) in 39 min. A preliminary study was performed in dogs and it was found this radiotracer was not suitable for studying myocardial angiotensin II receptors with PET.[141]

In 2017, a copper-mediated [^{11}C]cyanation of arylboronic acids was developed (Fig. 38, reaction a).[142] The following year, this method was extended further to include other arylboron derivates and arylstannanes (Fig. 38, reaction b).[143] These methodologies improved the limitation with the previous Cu(I) method of generating Cu^{11}CN *in situ* prior to introducing the precursor, saving time in the overall reaction.[140] Additionally, using more active organometallic reagents as precursors help the conditions to be more mild and higher yielding than using aryl halides as the starting materials. The optimal conditions for both methodologies were similar the general format of copper source, base, DMF-type solvent, water, and >100 °C for 5 min (Fig. 38). The substrate scope was similar for both conditions with high yields observed. Both methods were able to be automated and the desired product isolated.[142–143]

The 2018 [^{11}C]cyanation method, developed by the Sanford/Scott group, was used to radiolabel [^{11}C]LY2795050 (**243**) for clinical PET imaging (Fig. 39).[143] Previous methods to synthesize [^{11}C]LY2795050 (**243**) used Pd(0) catalysts. This approach is a complementary method that avoids using expensive catalyst that require inert and anhydrous

conditions to obtain high yields. The authors were able to the final product in 6% RCY, non-decay corrected and were able to perform preclinical studies in rodents and in nonhuman primates. This method was able to be initiated into clinical imaging studies.[143–144]

There have been several potential tracers synthesized with Cu[11]CN. In 2001, [^{11}C](Z,Z)-BABCH (**244**), a serine protease inhibitor was synthesized with Cu[11]CN as a first attempt.[138] A RCY of 46% was obtained and could not be improved with further optimization (Fig. 40, **244**). Higher yields were obtained with Pd(PPh$_3$)$_4$ (see above). In 2006, a potential glutamate 5 receptor (mGluR5) antagonist, [^{11}C]LY2232645 (**245**), was synthesized using Cu[11]CN in a RCY of 2.5% in 26 min (Fig. 40, **245**).[145] In 2013, a series of [^{11}C]methyl- and [^{11}C]cyano-substrates were evaluated as potential orexin receptors ligands *in vitro* in rat models.[146] Fig. 40, **246** was synthesized via Cu[11]CN in 2.8% decay-corrected radiochemical yield in 34 min since end of bombardment. In 2021, PET tracer [^{11}C]MTP38 (**247**) for phosphodiesterase 7 was synthesized using similar method with 99.4% radiochemical purity and molar activity of 38.6 ± 12.6 GBq/μmol.[147] [^{11}C]MTP38 was used for evaluating PDE7 expression in the brain of rodents and monkeys.

5.4. Other aromatic [^{11}C]cyanation methodology

In 1990, a method based on Reissert-Kaufmann Reaction was developed to extend [^{11}C]cyanation reactions to functional groups that were base-sensitive by trapping the H[11]CN on a silica gel column.[93] This trapping method, avoiding using NaOH or KOH which could hinder later reactions. The method was used to synthesize methyl 2-[^{11}C]-cyano-isonicotinate (**249**) in a 32% RCY via a Reissert-Kaufmann Reaction (Fig. 41). The following year, the same research group used the solid-state support method to synthesize 2-[^{11}C]cyano-isonicotinic acid hydrazide (**250**) in 10% RCY in 35 min from end of bombardment.[148] This compound is a potential radiotracer to diagnose tuberculoma.

6. Summary and outlook

In summary, numerous organic molecules, including biologically important molecules such as [^{11}C]α-amino acids (e.g. [^{11}C]alanine, [^{11}C]tyrosine [^{11}C]methionine, [^{11}C]glycine), [^{11}C]sugars (e.g. 2-deoxy-D-[1-^{11}C]glucose, D-[1-^{11}C]glucose, D-[1-^{11}C]mannose), neurotransmitters (e.g. [^{11}C]dopamine, [^{11}C]norepinephrine, [^{11}C]GABA) have been synthesized from H[11]CN in useful radiochemical yields. ^{11}C-cyanation reactions can be classified in three broad categories. In the first category (Fig. 42), ^{11}C-cyanide is incorporated into organic molecules to produce [^{11}C]nitriles, which can be further modified to generate [^{11}C]amines, [^{11}C]aldehydes, [^{11}C]indoles, [^{11}C]carboxylic acids, [^{11}C]amides, [^{11}C]hydrazides, [^{11}C]amidoximes, [^{11}C]imidamides and [^{11}C]tetrazoles. Some of the conditions used for the secondary transformations have poor chemoselectivity and require judicious selection of reagents, protecting groups and reaction conditions.

In the second category, ^{11}C cyanide is incorporated into organic molecules to generate other types of ^{11}C-labeled intermediates different from nitriles (Fig. 43). For example, the reaction of H[11]CN with ketones in the presence of ammonium carbonate generates [^{11}C]hydantoins which can be hydrolyzed to produce amino acids. Or the reaction of

$H^{11}CN$ with dialkylthexylborane generates the cyanide adduct which upon further chemical transformation produces the corresponding $[^{11}C]$dialkylketone.

In the third category, $[^{11}C]$cyanide is first transferred to a secondary ^{11}C synthon (e.g. $[^{11}C]$cyanate, $[^{11}C]$thiocyanate, and $[^{11}C]$cyanogen bromide) (Fig. 44). Starting from these secondary synthons, the ^{11}C labeled N-substituted (thio)urea, (thio)cyanate esters, and guanidines can be obtained by the reactions of $[^{11}C]$(thio)cyanate and $[^{11}C]$cyanogen bromide with corresponding precursors.

These reactions and their products illustrate the versatility of $H^{11}CN$ to generate diverse radiolabeled molecules. Nevertheless, many opportunities and challenges remain in order to harness the full potential of $H^{11}CN$ labeling in PET radiochemistry, such as for example:

1. In our experience, the production of $H^{11}CN$ is not as robust and reproducible as the production of $^{11}CO_2$ $^{11}CH_4$ and $^{11}CH_3I$. Variability in the dryness and flow of NH_3 gas can result in poor conversion from $^{11}CH_4$ to $H^{11}CN$ and the transfer of the $H^{11}CN$ through gas lines can also be problematic. Advances in instrumentation to reliably produce $H^{11}CN$ with high molar activity would greatly facilitate the future use of $H^{11}CN$ in PET radiochemistry.

2. Many ^{11}C-cyanations developed in 20th century to produce labeled amino acids and sugars employed carrier-added $^{11}CN^-$. These methods may need to be further optimized to produce no carrier added tracers.

3. Many ^{11}C-cyanation publications prior to 1960s reported only the radiochemistry and did not include the evaluation of the radiolabeled compounds *in vitro* or *in vivo*. Further, evaluation of some of these compounds may result in useful tracers.

4. Even though this review described several examples of multistep reactions in which the nitrile group is further converted into other groups such as amine, amide or carboxylic acid, etc, it remains challenging to do this selectively in complex molecules containing other reactive functional groups. As such, advances in organic chemistry that allow efficient, selective and fast conversion of nitriles into other functional groups would further the utility of $H^{11}CN$ in PET tracer radiochemistry.

Finally, we believe that the rapid growth of PET radiopharmaceuticals is generating a demand for rapid development of new radiolabeled compounds. This field could greatly benefit from the increased use of $H^{11}CN$ labeling and therefore we are optimistic to witness increased use and development of ^{11}C-cyanation in coming years.

Acknowledgement

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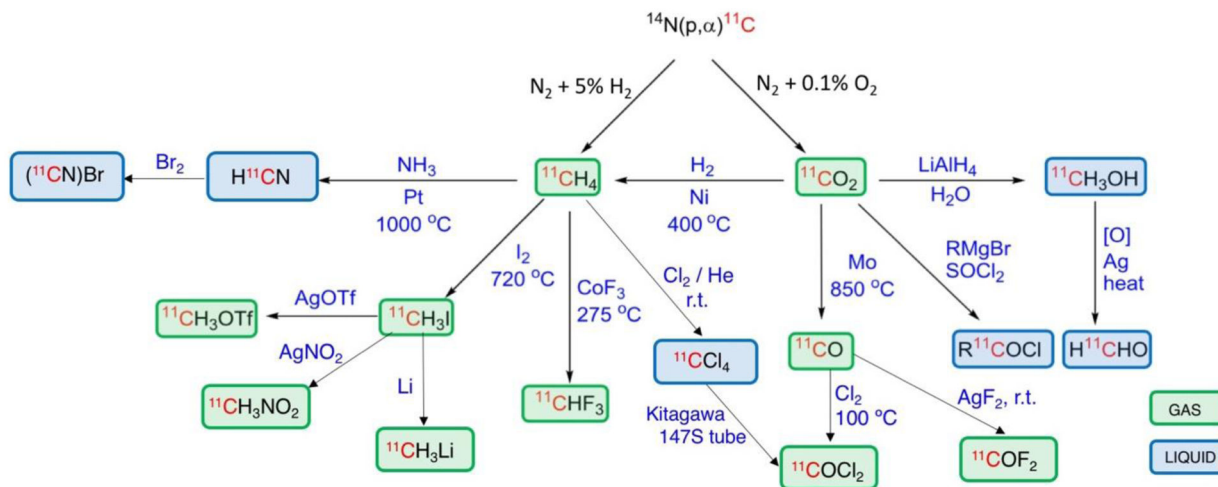
Fig. 1.
Carbon-11 reagents available for radiolabelin (original image courtesy of V. W. Pike and colleagues at NIMH, modified by the authors).

$$^{12}C \xrightarrow{\text{neutron stripping}} {}^{11}C \xrightarrow{N_2 \text{ or } N_xO_y} {}^{11}CN\cdot \xrightarrow{\text{hydrocarbons}} H^{11}CN \quad \textbf{(A)}$$

$$N_2 \text{ and } C_2H_6 \xrightarrow{{}^{14}N(p,\alpha)^{11}C} H^{11}CN \quad \textbf{(B)}$$

$$NaCN \xrightarrow{{}^{14}N(p,\alpha)^{11}C \ / \ {}^{12}C(p,pn)^{11}C} Na^{11}CN \quad \textbf{(C)}$$

$$B_2O_3 \xrightarrow{{}^{11}B(p,n)^{11}C} {}^{11}CO \text{ and } {}^{11}CO_2 \xrightarrow{\text{oxidation}} {}^{11}CO_2 \xrightarrow{K \text{ and } NH_3} K^{11}CN \quad \textbf{(D)}$$

$$N_2 \text{ and } H_2 \xrightarrow{{}^{14}N(p,\alpha)^{11}C} {}^{11}CH_4 \xrightarrow{NH_3, \text{ Pt(cat.)}} H^{11}CN \quad \textbf{(E)}$$

$$N_2 \text{ and } O_2 \xrightarrow{{}^{14}N(p,\alpha)^{11}C} {}^{11}CO_2 \xrightarrow[\text{microwave discharge}]{N_2 \text{ and } H_2} H^{11}CN \quad \textbf{(F)}$$
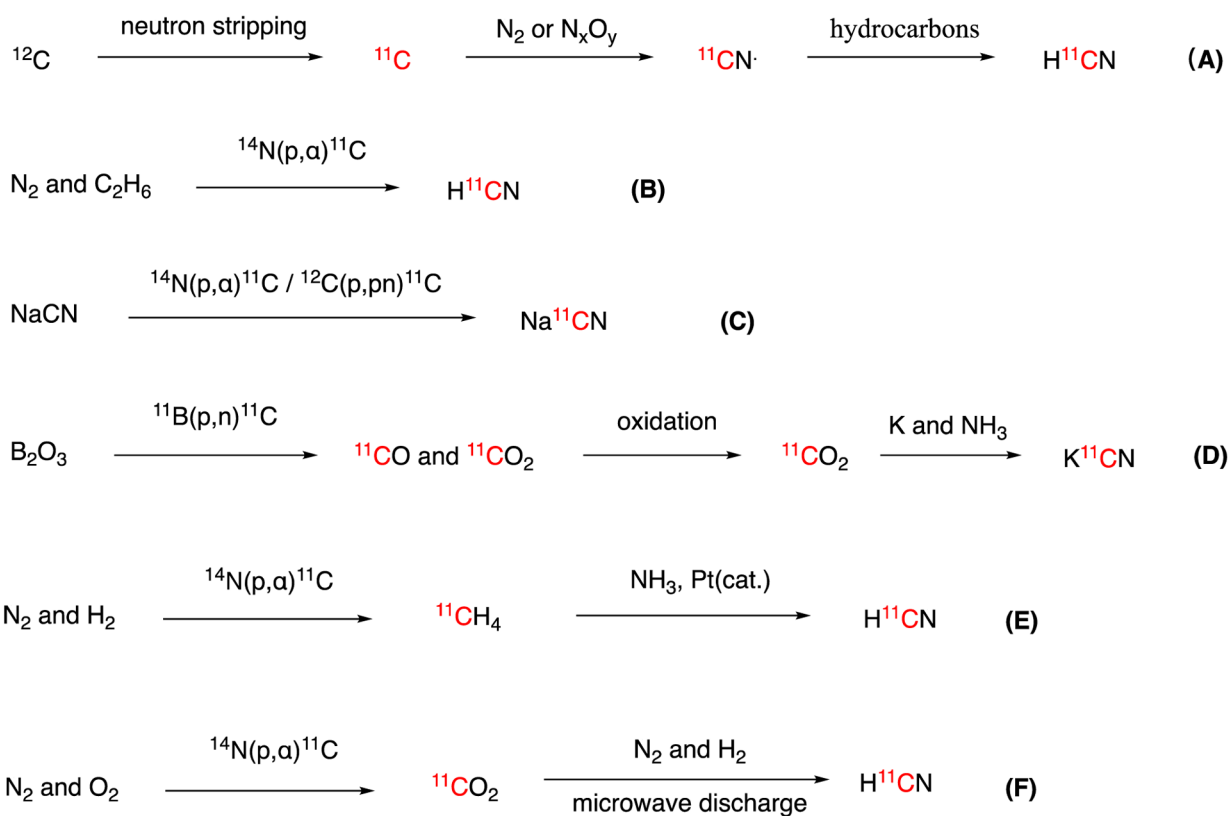
Fig. 2.
Summary of the H^{11}CN/M^{11}CN production methods.
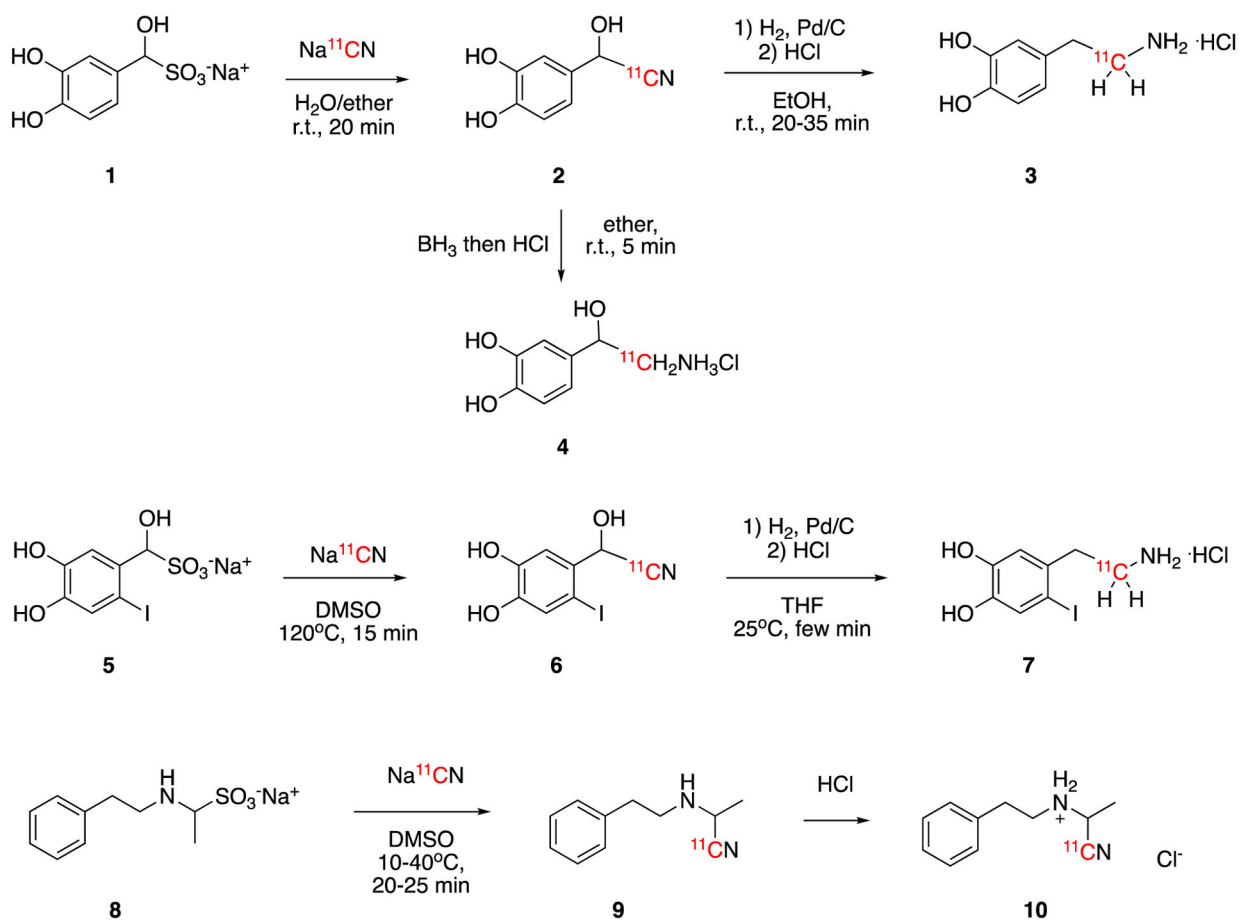
Fig. 3.
Synthesis of [^{11}C]dopamine hydrochloride (**3**), [^{11}C]norepinephrine hydrochloride (**4**), [^{11}C]6-iododopamine hydrochloride (**7**), and [^{11}C]2-N-benzylaminobutanenitrile hydrochloride (**10**).
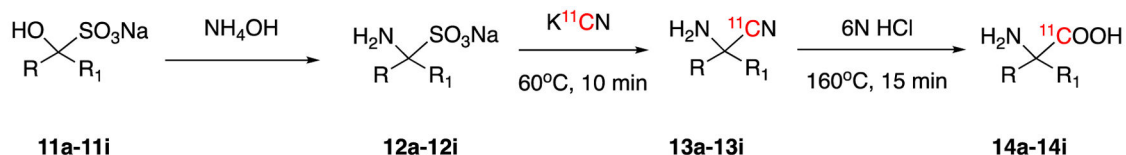
a: R = phenyl, R$_1$ = H;
b: R = phenyl, R$_1$ = methyl;
c: R = cyclohexyl, R$_1$ = H;
d: R = benzyl, R$_1$ = H;
e: R = isopropyl, R$_1$ = H;
f: R = isobutyl, R$_1$ = H;
g: R = n-butyl, R$_1$ = H.
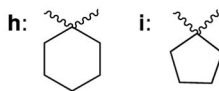
Radiochemical yields:
14a: phenylglycine, 16%;
14b: α-methylphenylglycine, low;
14c: cyclohexylglycine, 45%;
14d: phenylalanine, 56%;
14e: valine, 49%;
14f: leucine, 35%;
14g: norleucine, 63%;
14h: aminoclyclohexanecarboxylic acid, 43%;
14i: aminocyclopentanecarboxylic acid, 34%.
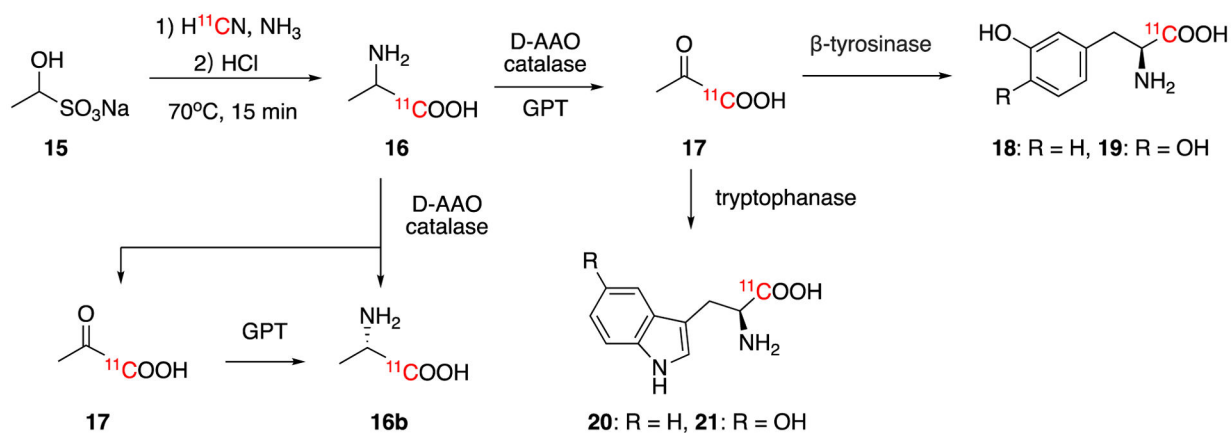
D-AAO: D-amino acid oxidase
GPT: Glutamate-Pyruvate Transaminase

Fig. 4.
Synthesis of [^{11}C]α-amino acids (**14a-14i**), L-[^{11}C]alanine(**16b**), L-[^{11}C]tyrosine (**18**), L-[^{11}C]DOPA (**19**), L-[^{11}C]tryptophan (**20**) and [^{11}C]5-hyroxy-L-tryptophan (**21**).

D-AAO: D-amino acid oxidas; GPT: Glutamate-Pyruvate Transaminase; L-LDH: L-Lactate Dehydrogenase

a: R_1 = OH, R_2 = H;
b: R_1 = H, R_2 = OH
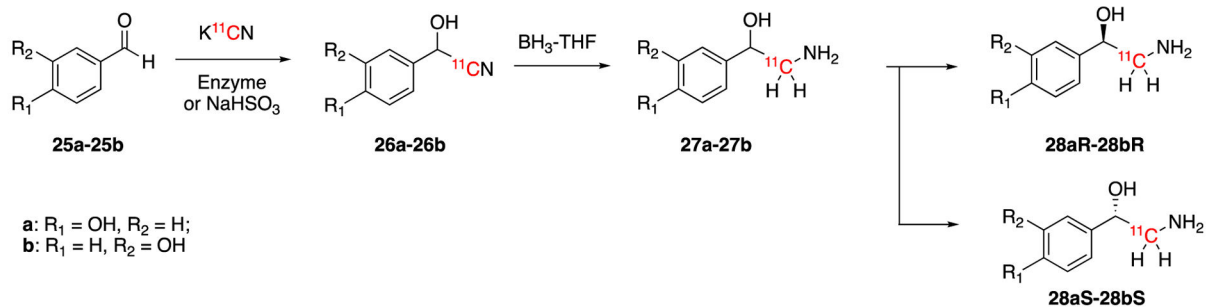
Fig. 5.
Synthesis of L-[1-^{11}C]lactic acid (**22**), p-[^{11}C]octopamine (**28aR** and **28aS**), and m-[^{11}C]octopamine (**28bR** and **28bS**).
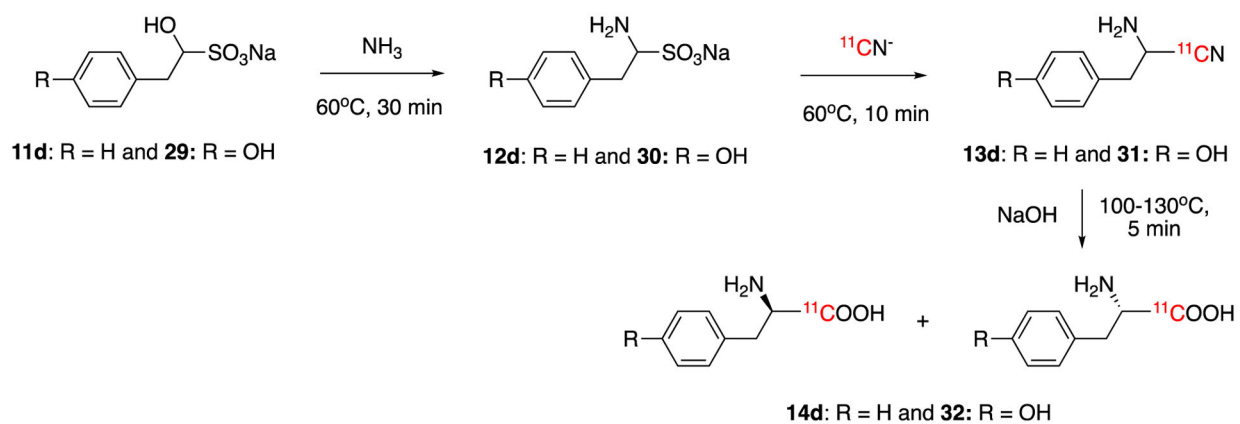
Fig. 6.
Synthesis of enantiomerically pure [^{11}C]tyrosine (Tyr, **32**) and phenylalanine (Phe, **14d**).
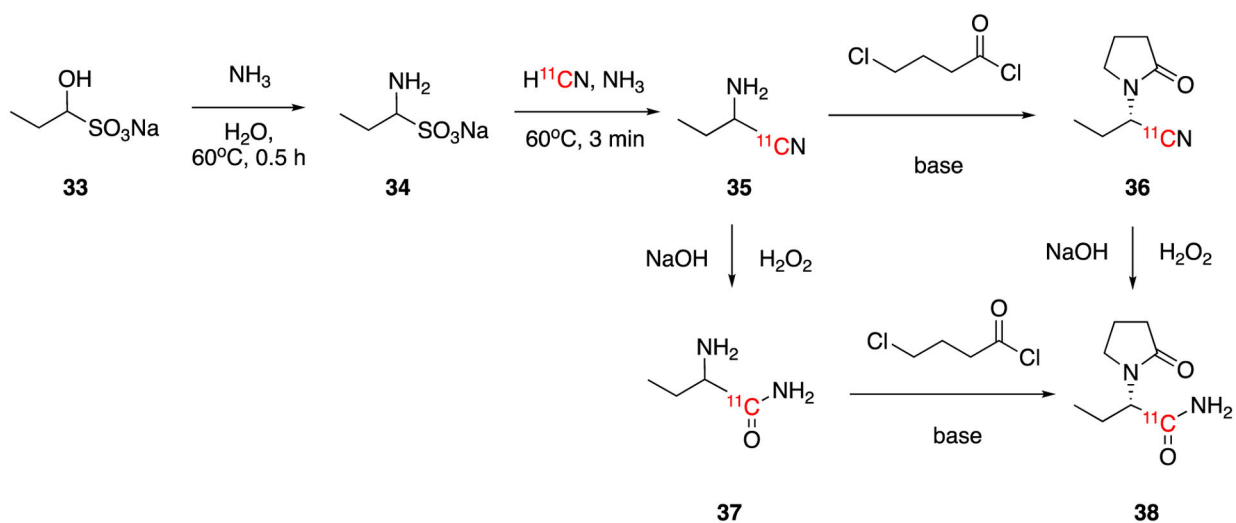
Fig. 7.
Synthesis of [^{11}C]levetiracetam **38**.
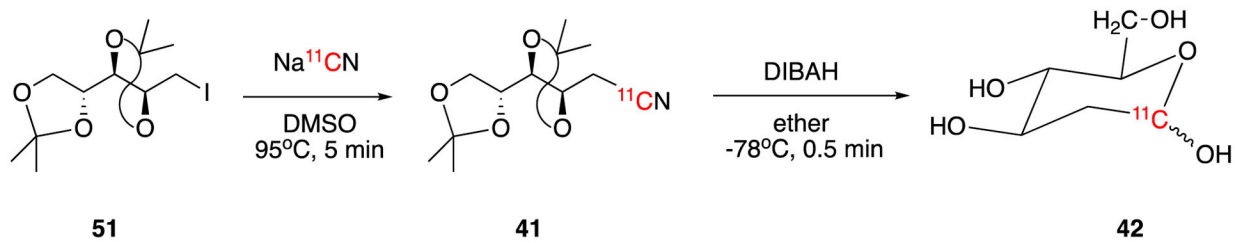
DIBAH = Diisobutylaluminium hydride

Fig. 8.
Synthesis of 2-deoxy-D-[1-^{11}C]glucose (**42**).
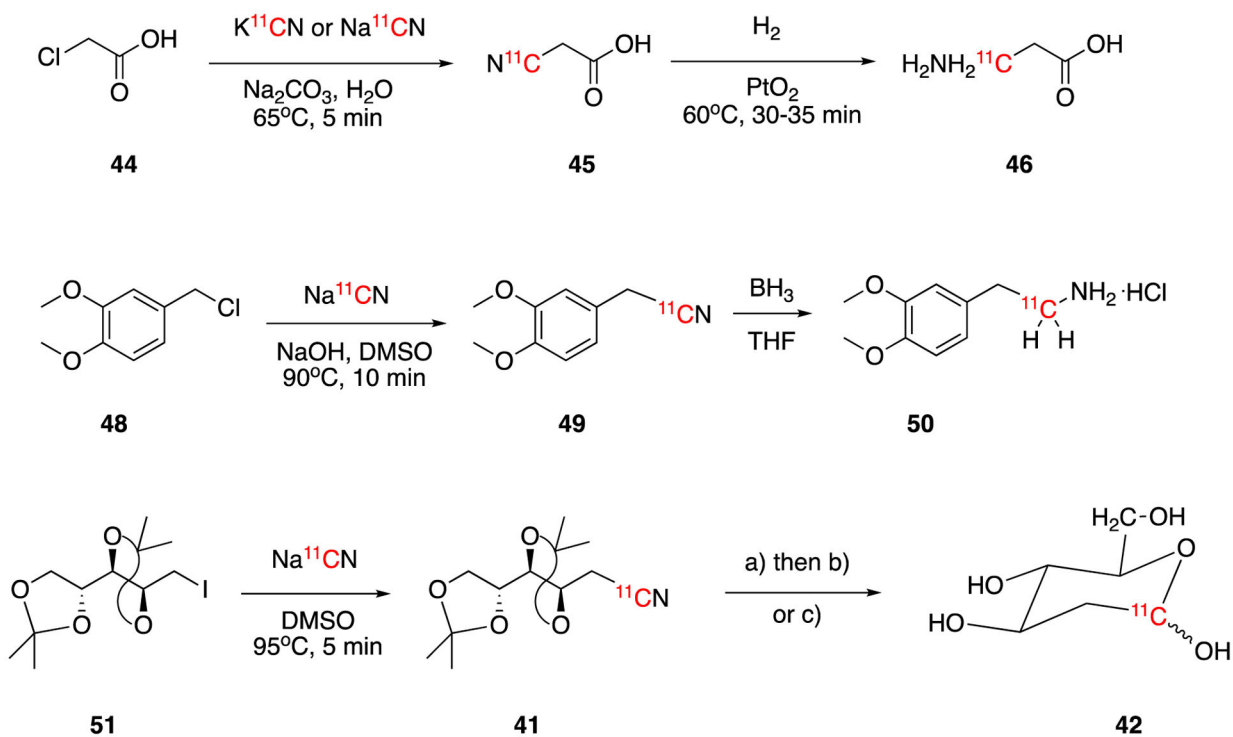
DIBAH = Diisobutylaluminium hydride
a: DIBAH, ether, -78°C, 0.5 min; b: H$_2$SO$_4$, 10 min, then HCOOH, 75°C, 5 min
c: Al/Ni alloy, HCOOH, 100°C, 10 min

Fig. 9.
Synthesis of [3-^{11}C]β-Alanine (**46**), [^{11}C]3,4-dimethoxyphenethylamine (**50**), and 2-deoxy-D-[1-^{11}C]glucose (**42**).
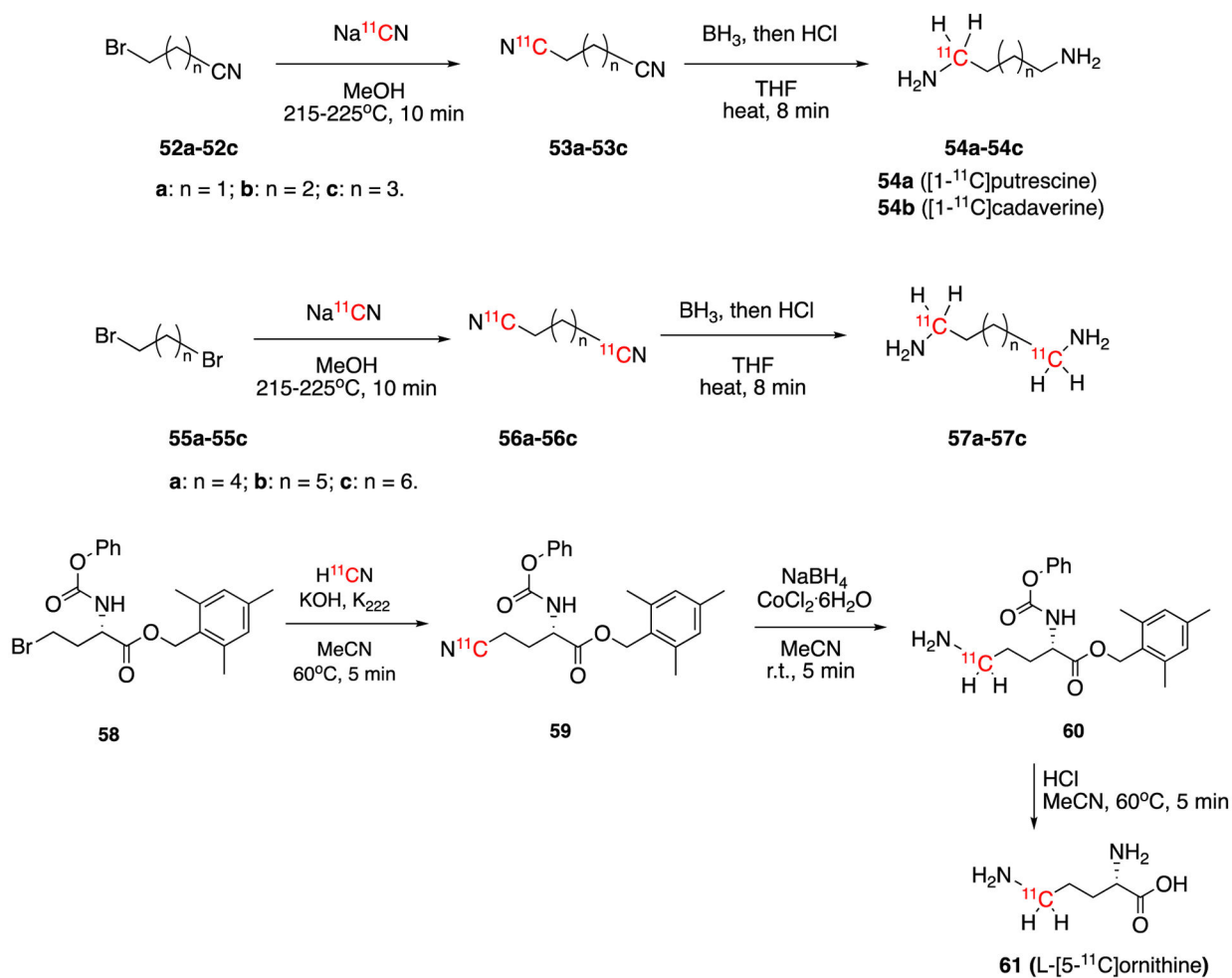
Fig. 10.
Synthesis of ^{11}C labeled aliphatic diamines (**54a**-**54c** and **57a**-**57c**) and [5-^{11}C]ornithine
(**61**).
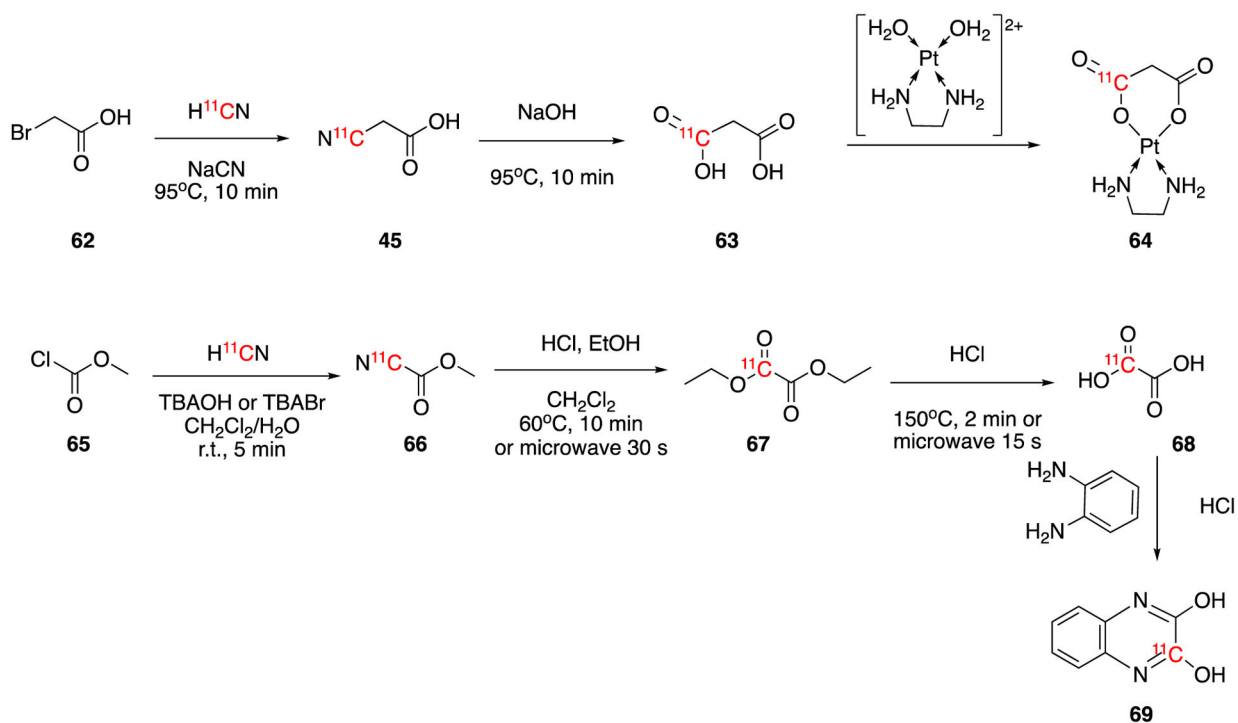
Fig. 11.
Synthesis of (ethylenediamine)(1-[^{11}C]malonate)platinum(ll) (**64**), [^{11}C]oxalic acid (**68**), and [^{11}C]-2,3-dihydroxyquinoxalin (**69**).
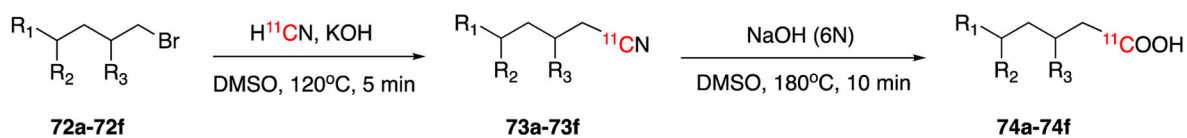
a: R_1 = $C_{10}H_{21}$, R_2 = H, R_3 = H; b: R_1 = $C_{11}H_{23}$, R_2 = H, R_3 = H; c: R_1 = $C_{12}H_{25}$, R_2 = H, R_3 = H; d: R_1 = $C_{13}H_{27}$, R_2 = H, R_3 = H;
e: R_1 = $C_{12}H_{25}$, R_2 = H, R_3 = Me; f: R_1 = $C_{12}H_{25}$, R_2 = Me, R_3 = H.

Fig. 12.
Synthesis of [1-^{11}C]fatty acids (**74a**-**74d**).
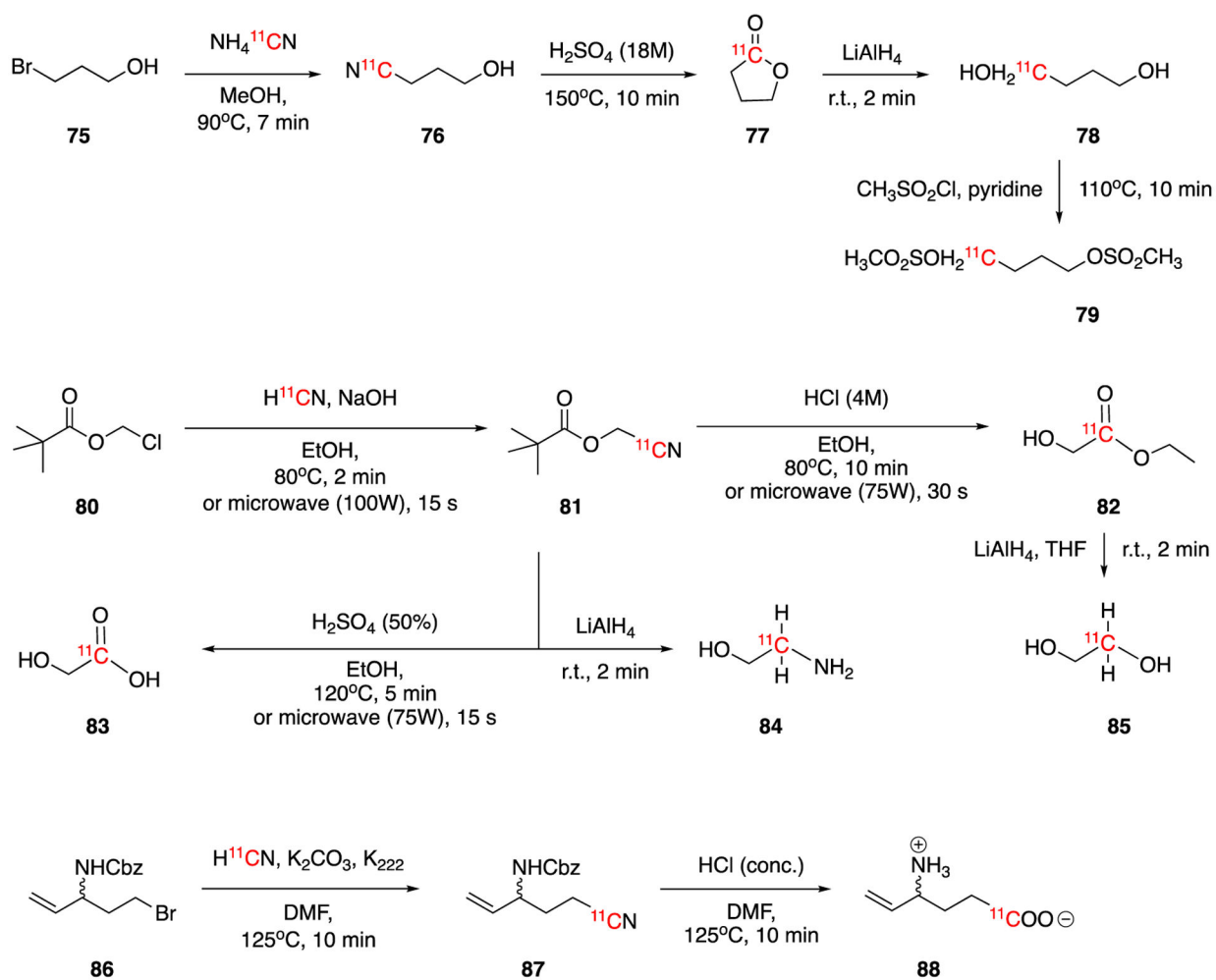
Fig. 13.
Synthesis of [1-^{11}C]busulfan (**79**), ethyl [1-^{11}C]glycolate (**82**), [1-^{11}C]glycolic acid (**83**), [1-^{11}C]ethylene glycol (**85**), [2-^{11}C]2-aminoethanol (**84**) and [1-^{11}C]γ-vinyl-γ-aminobutyric acid (**88**).
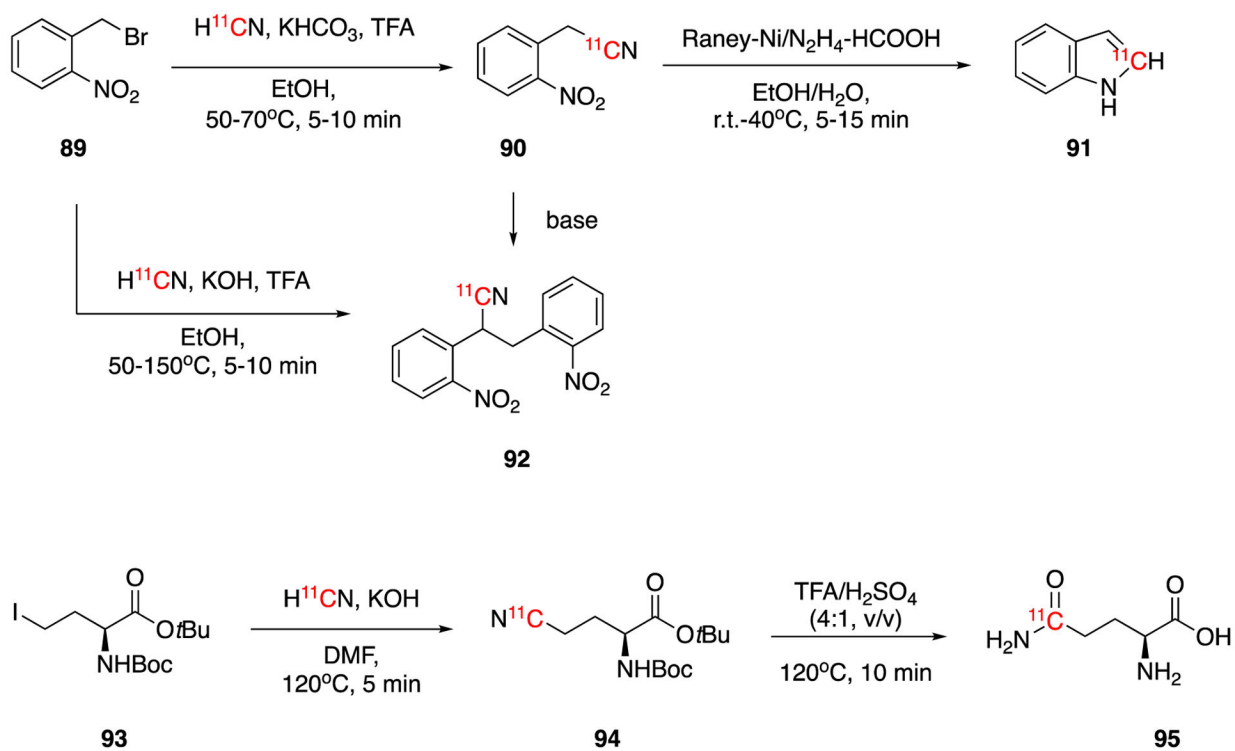
Fig. 14.
Synthesis of [2-^{11}C]indole (**91**) and [5-^{11}C]-glutamine (**95**).
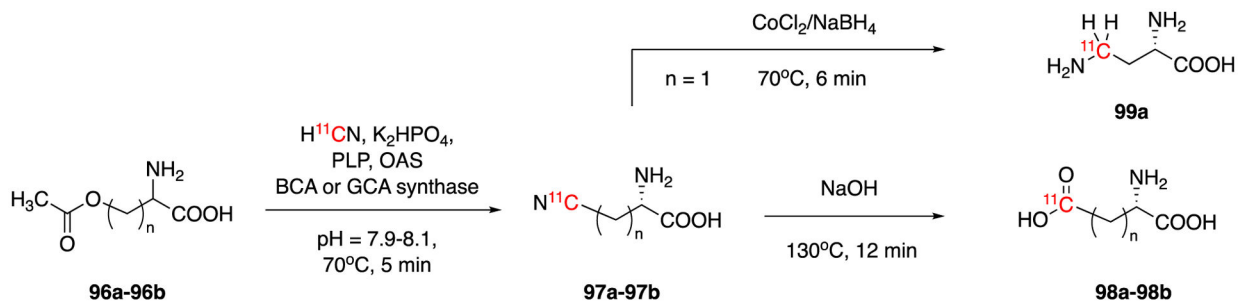
Fig. 15.

Synthesis of L-2,4-Diamino[4-^{11}C]butyric acid (DAB, **99a**), L-[4-^{11}C]aspartate (**98a**) and L-[5-^{11}C]glutamate (**98b**).

Fig. 16.
Synthesis of 3-indolyl[1-^{11}C]acetic acid (**103**).

Fig. 17.
Synthesis of [^{11}C]α-amino acid *via* Bucherer-Strecker reactions and the synthesis of L-[1-^{11}C] lactic acid (**22**).
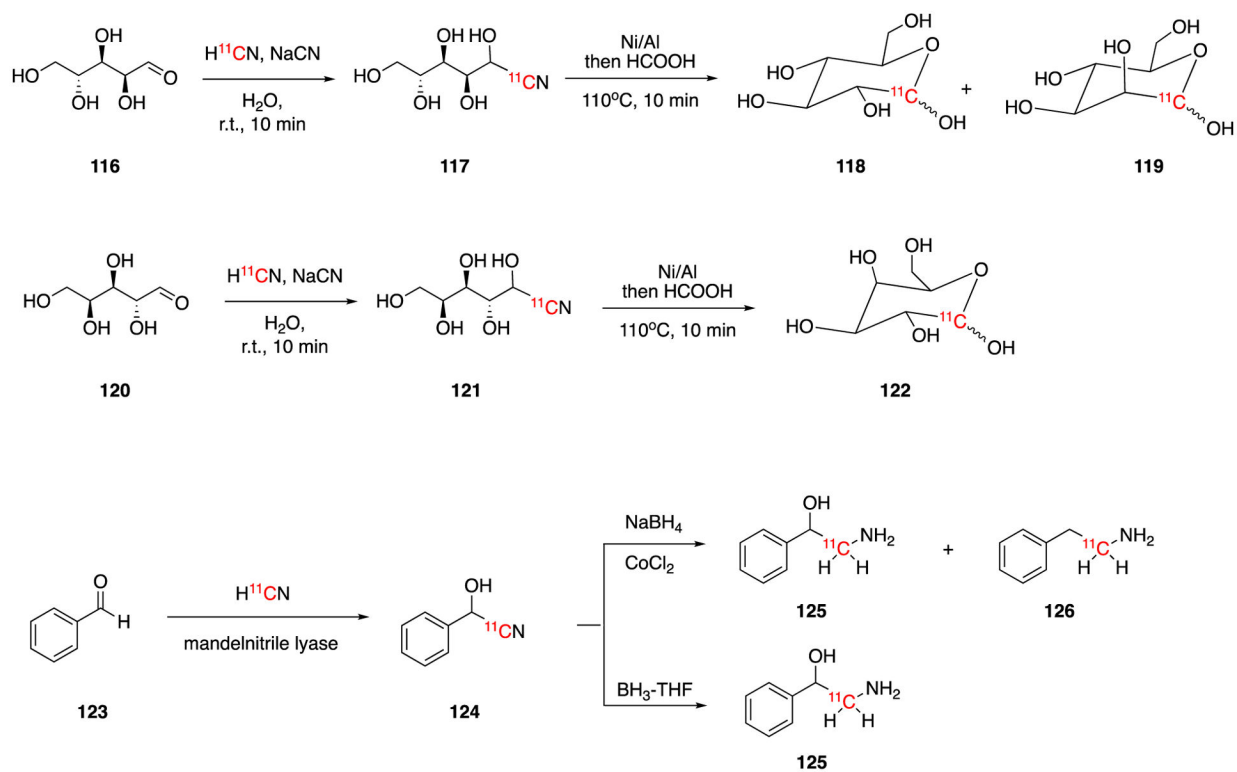
Fig. 18.
Synthesis of [1-^{11}C]-D-glucose (**118**), [1-^{11}C]-D-mannose (**119**), [1-^{11}C]-D-galactose (**122**), and [^{11}C]phenylethanolamine (**125**).

Fig. 19.
Synthesis of D-[1-^{11}C] glucopyranose (**133**) and D-[1-^{11}C] galactopyranose (**134**).
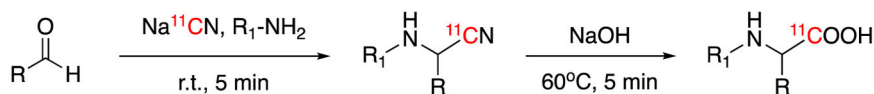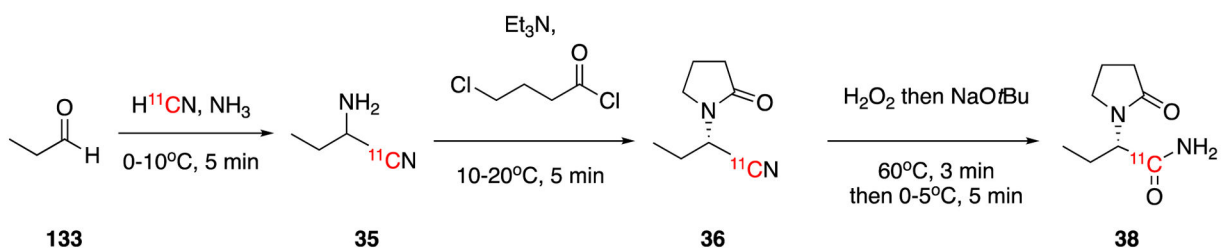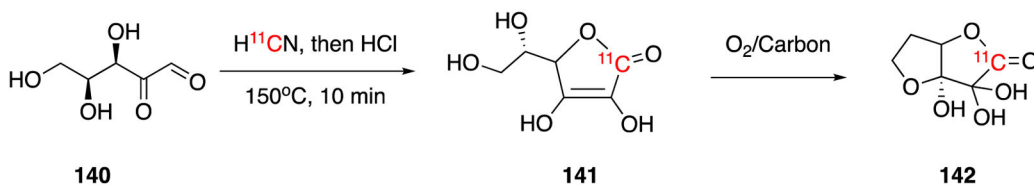
Fig. 20.
Synthesis of [^{11}C]levetiracetam (**38**), [^{11}C]methionine (**138**), [^{11}C]glycine (**114**), [^{11}C]-N-phenylglycine (**139**), [^{11}C]ascorbic (**141**) and [^{11}C]dehydroascorbic acid (**142**).
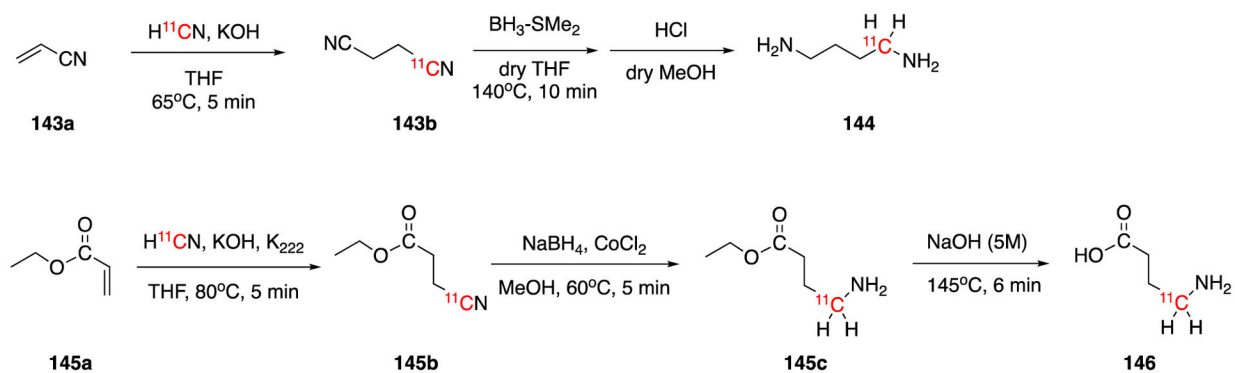
Fig. 21.
Synthesis of [1-^{11}C]putrescine (**144**) and γ-amino[4-^{11}C]butyric acid (GABA, **146**).
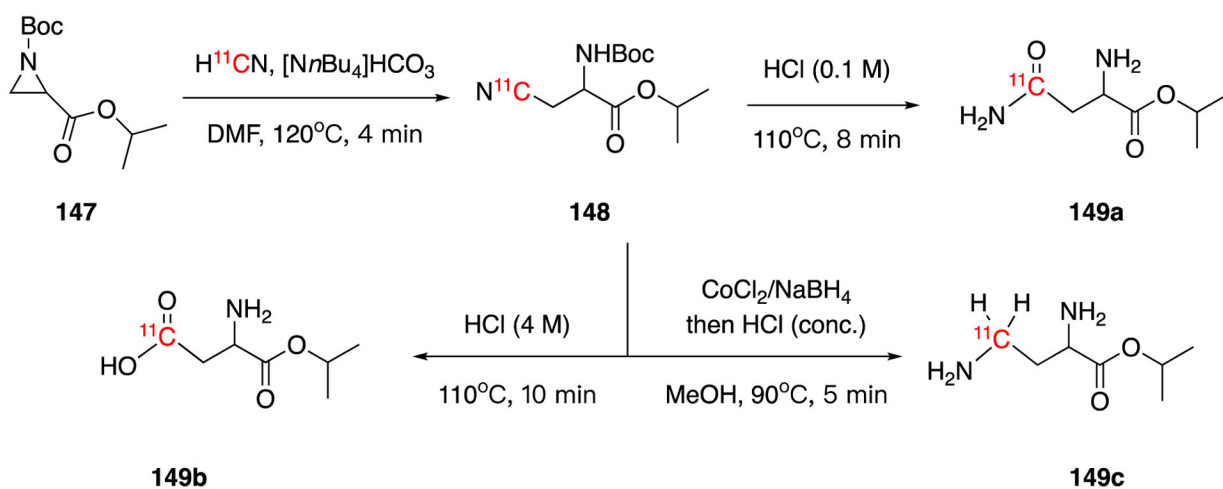
Fig. 22.
Synthesis of DL-[4-^{11}C]asparagine (**174**), DL-[4-^{11}C]aspartic acid (**175**), and DL-2,4-diamino[4-^{11}C]butyric acid (**176**).
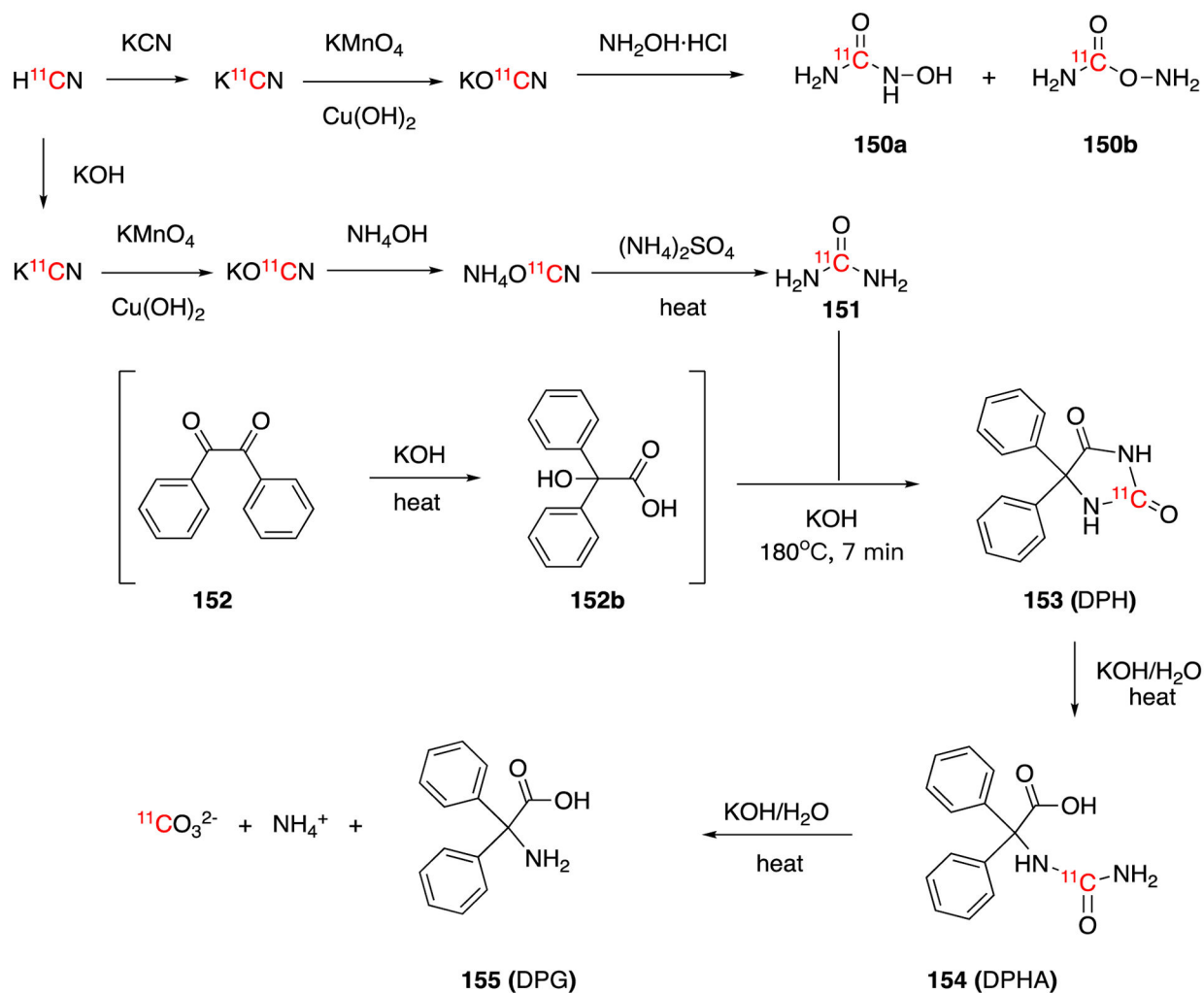
Fig. 23.
Synthesis of [^{11}C]hydroxyurea (**150a**), [^{11}C]isohydroxyurea (**150b**), [^{11}C]urea (**151**), and [2-^{11}C]5,5-diphenylhydantoin (DPH, **153**).
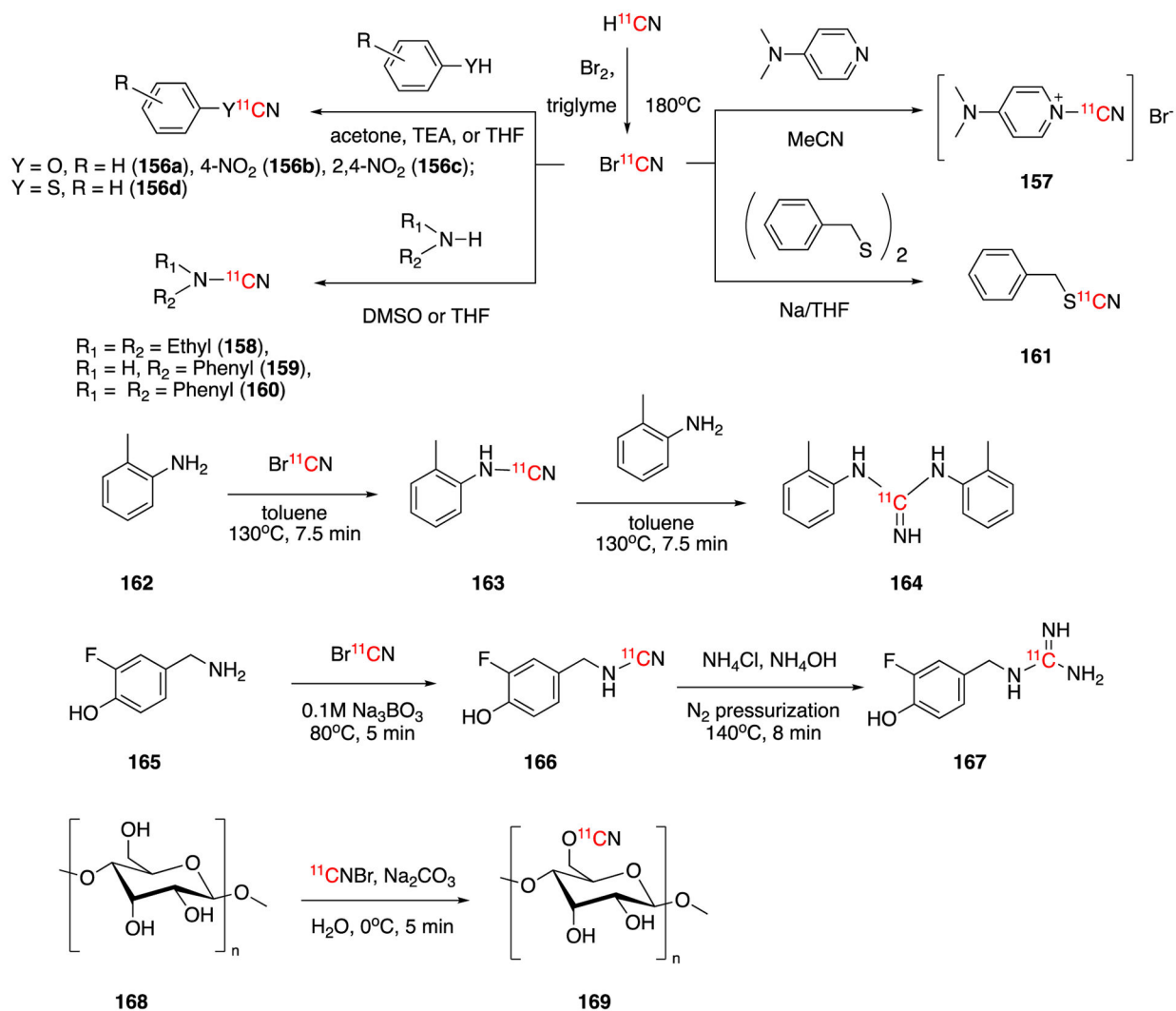
Fig. 24.
Radiochemistry of [^{11}C]cyanogen bromide.
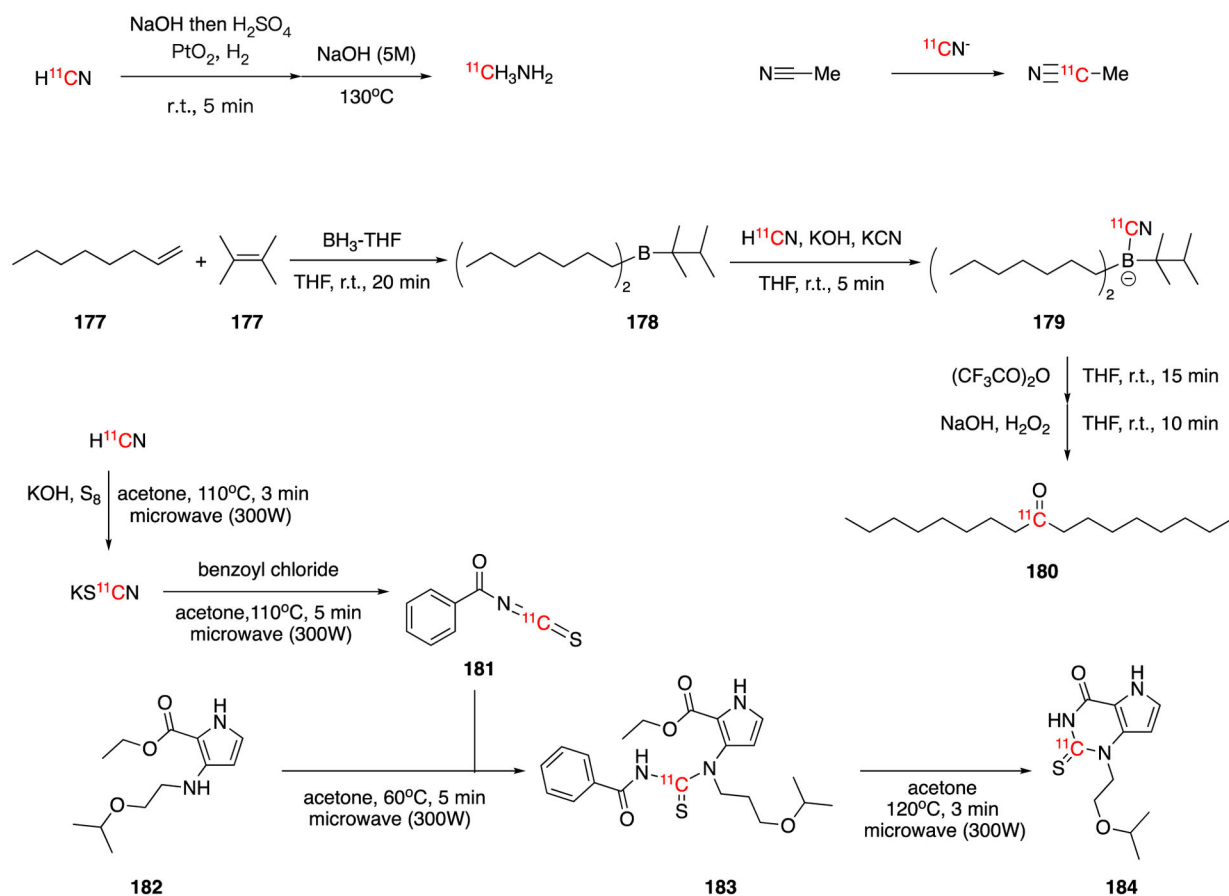
Fig. 25.
Synthesis of [^{11}C]methylamine and 9-[^{11}C]heptadecane-9-one (**180**) and cyanide exchange in acetonitrile.
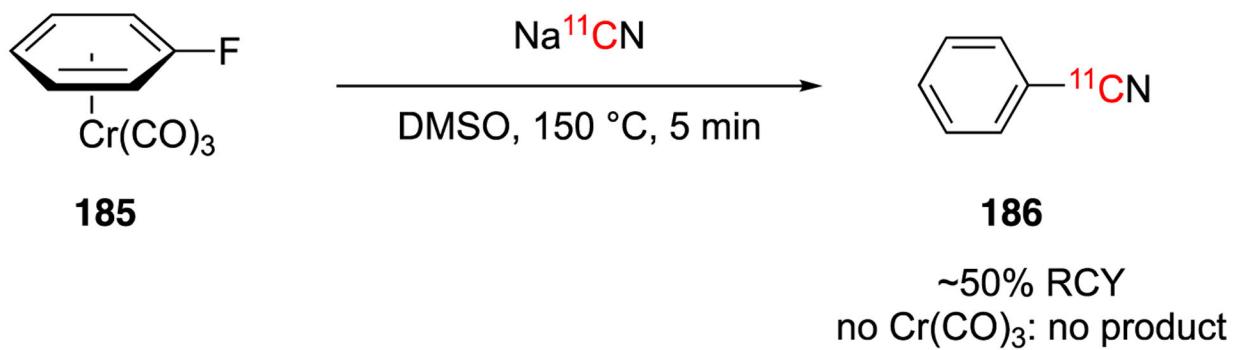
Fig. 26.
First example aromatic [^{11}C]cyanation using arenechromium tricarbonyl complexes.
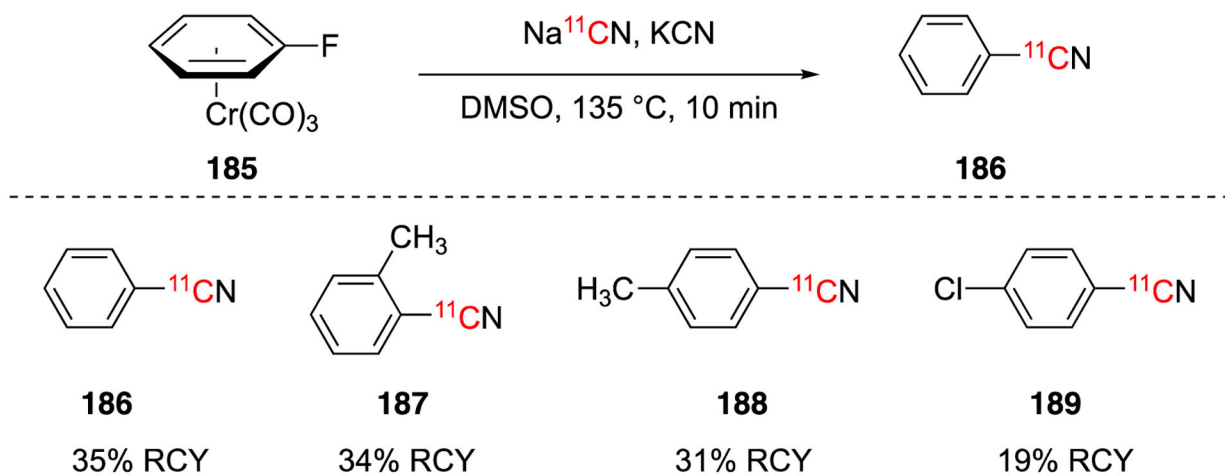
Fig. 27.
Expanded scope of aromatic [^{11}C]cyanation using arenechromium tricarbonyl
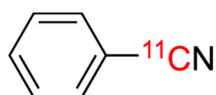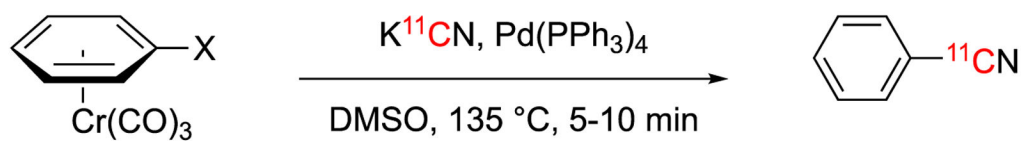
Fig. 28.
Substrate scope using arene chromium complex substrates and with (or without) palladium(0) catalyst.
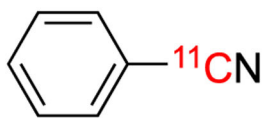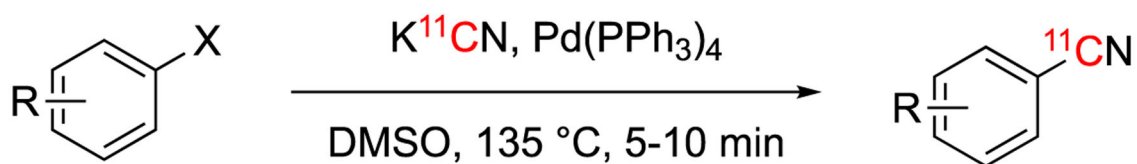
Fig. 29.
Substrate scope using aryl halide substrates and with palladium(0) catalyst.
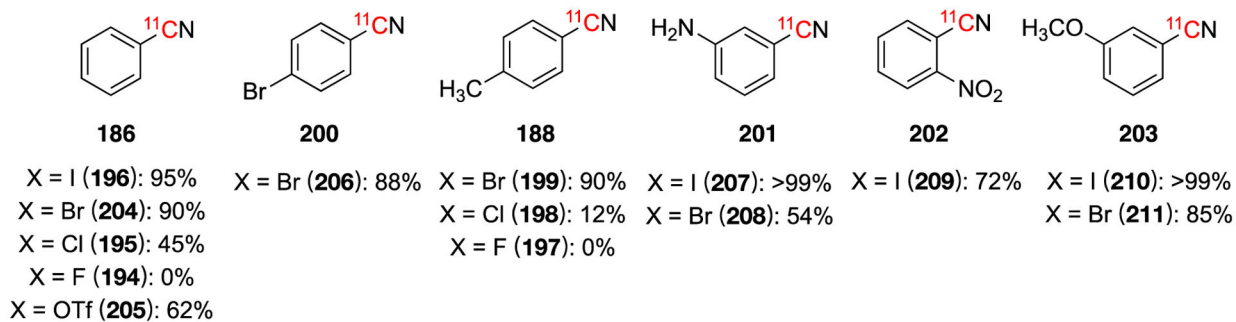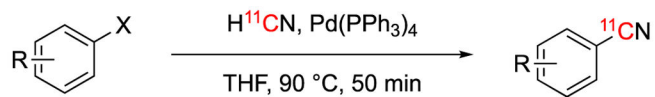
Fig. 30.
Palladium(0)-mediated [^{11}C]cyanation of aromatic compounds.
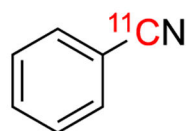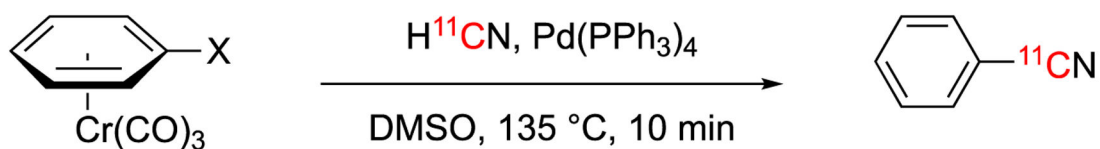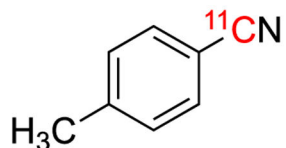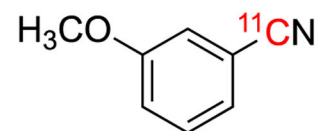
Fig. 31.
[^{11}C]Cyanation on tricarbonylchromium complexes of arenes (with Pd(PPh$_3$)$_4$).
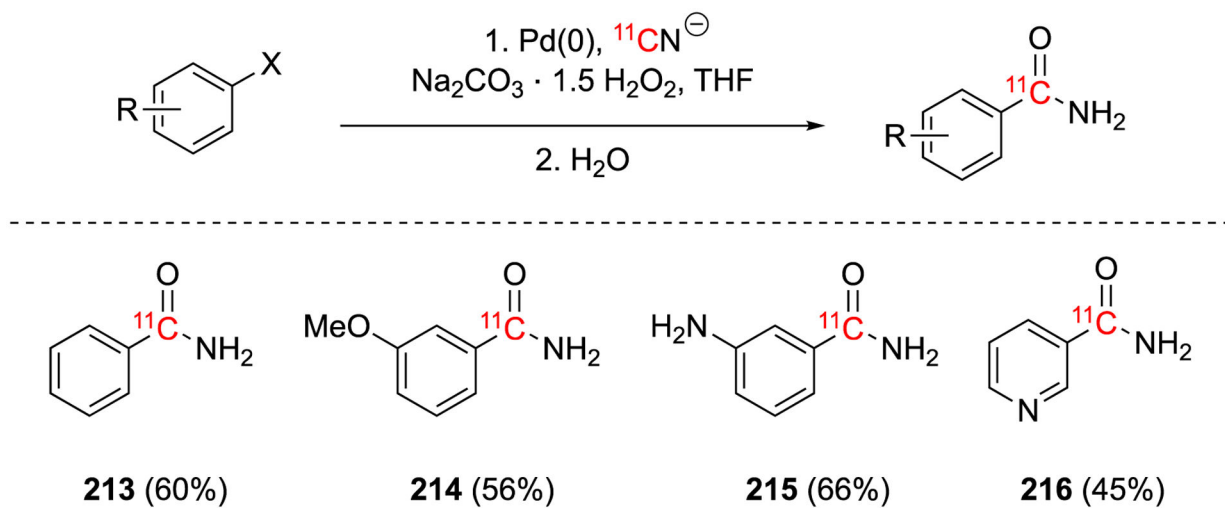
Fig. 32.
[^{11}C]Cyanation of benzamide compounds as potential radiotracers.

(a)   Ar-X, Pd(0)/L
      L = PPh$_3$ or dppf

☐, base

(b)   Ar-X, Pd(0)/L1

H^{11}CN

(c)   L$_1$–Pd$\overset{Ar}{\underset{X}{|}}$ (**A**)

(d) Ar-X
    Pd(0)/L1 $\left[\text{L}_1\text{–Pd}\overset{Ar}{\underset{X}{|}} \right]$
    (**A**)

Ar-^{11}CN
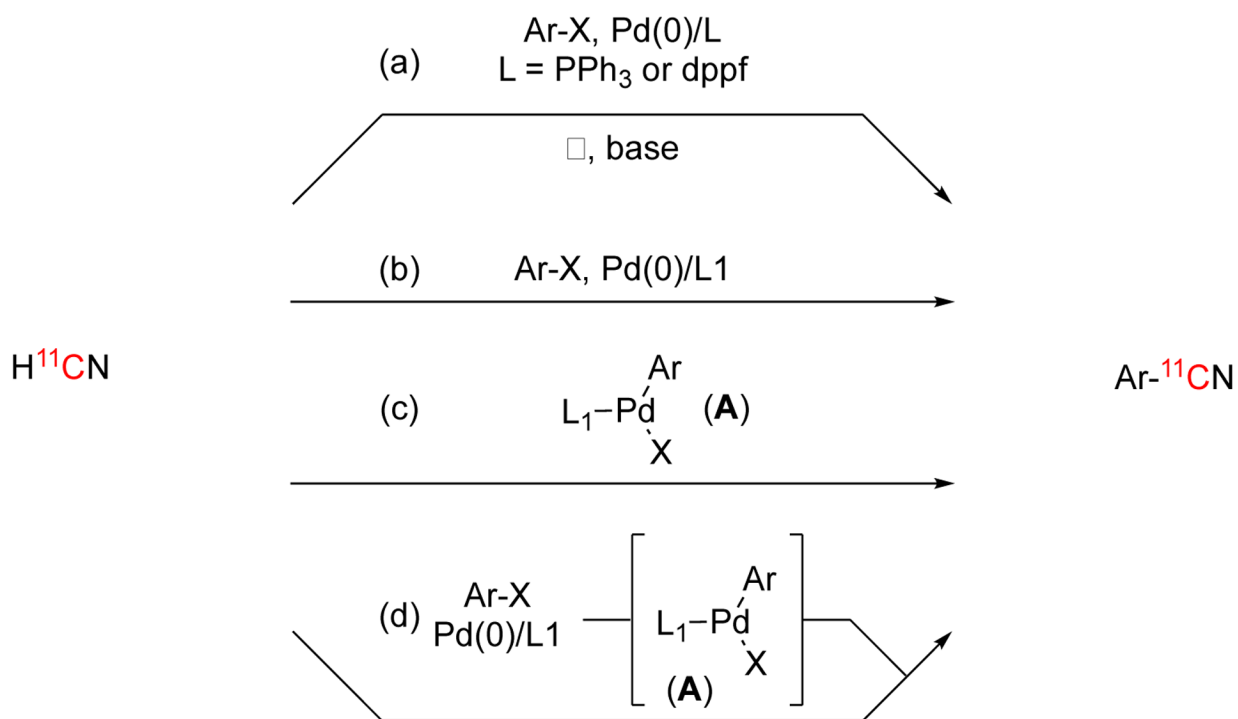
Fig. 33.
Synthetic strategies for Pd(0) mediated [^{11}C]cyanation.

[11C]vilazodone (**217**)
19% RCY in 16.5 min

precursor to [11C]LC2795050 (**218**)
21% RCY in 12.4 min

[11C]perampanel (**219**)
10% RCY in 22.5 min

220

221
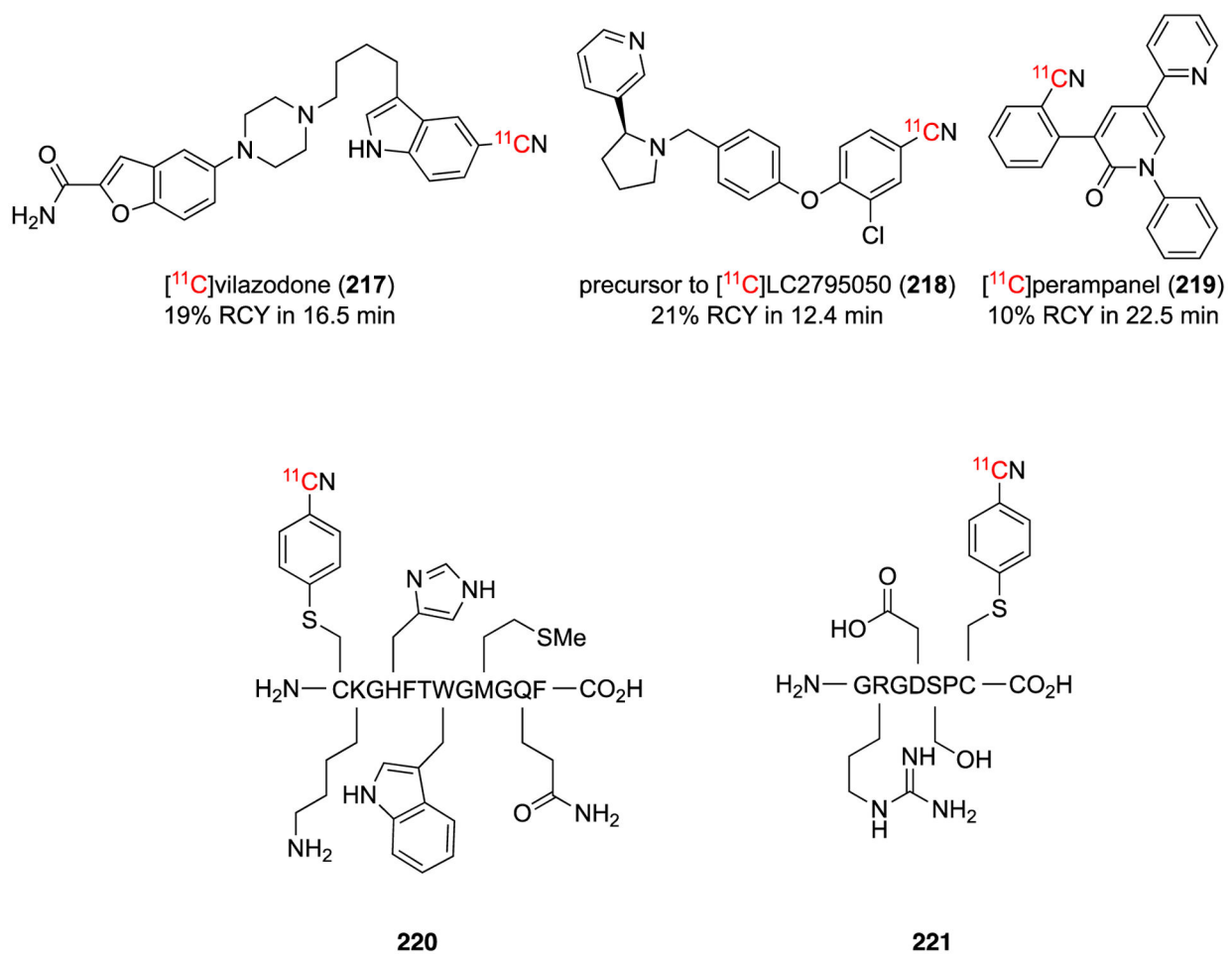
Fig. 34.
Synthesis of [11C]radiolabeled pharmaceuticals and peptides via Pd(0) method.

R = Me (**222**), Br (**223**)

[11C]NH4CN, NH3
PdCl2(PPh3)2, K2CO3

DMSO, 100 °C, 5 min

R = Me (**224**), [11C]cetrozole: 85%
R = Br (**225**), [11C]YM511: 73%
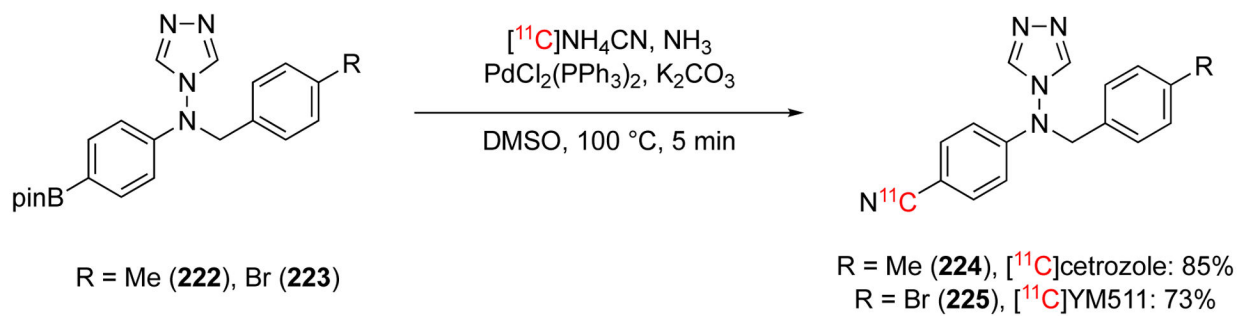
Fig. 35.
Automated synthesis [11C]cetrozole and [11C]YM511.
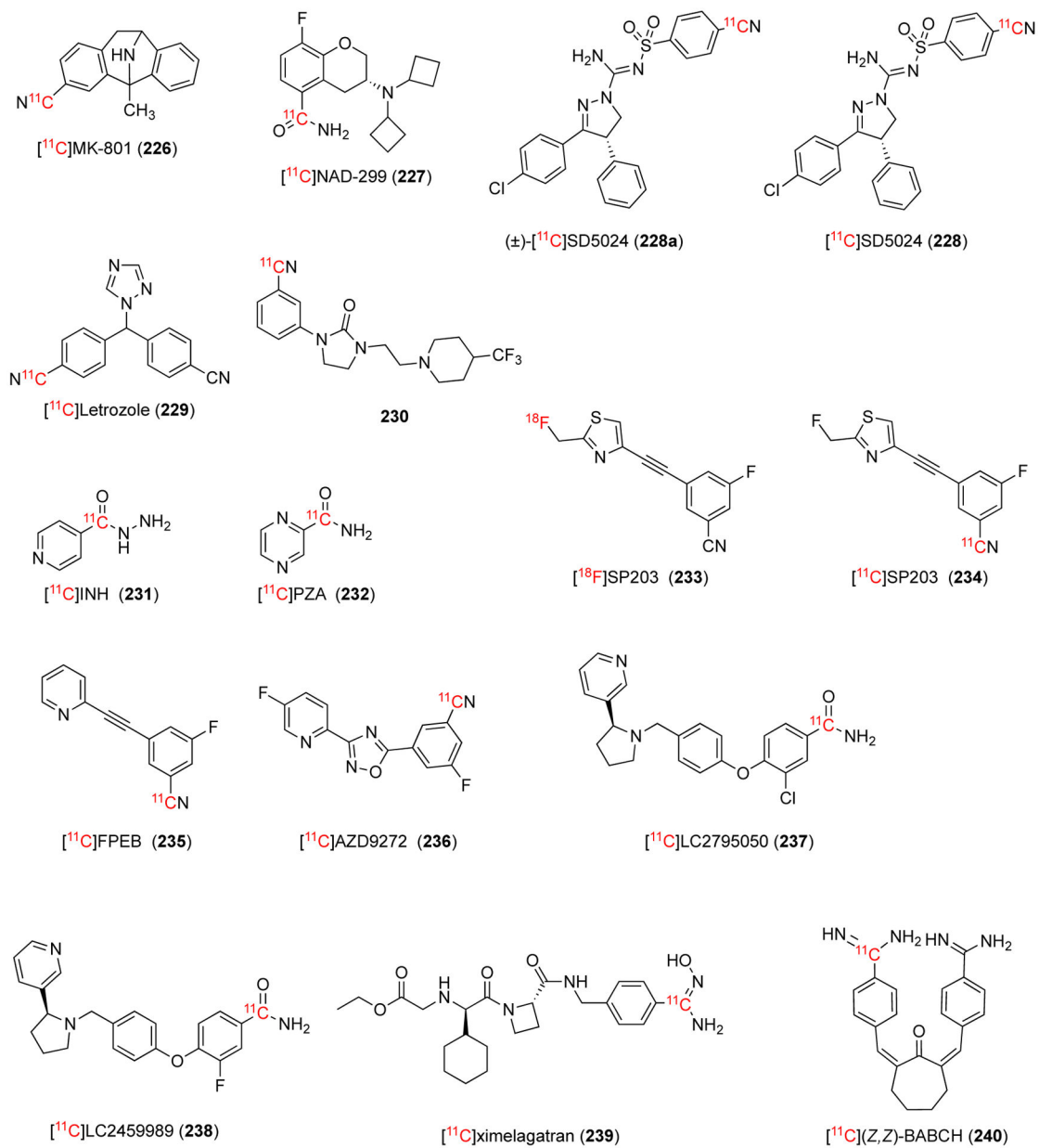
Fig. 36.
Radiotracers developed based on Pd-mediated cyanation.
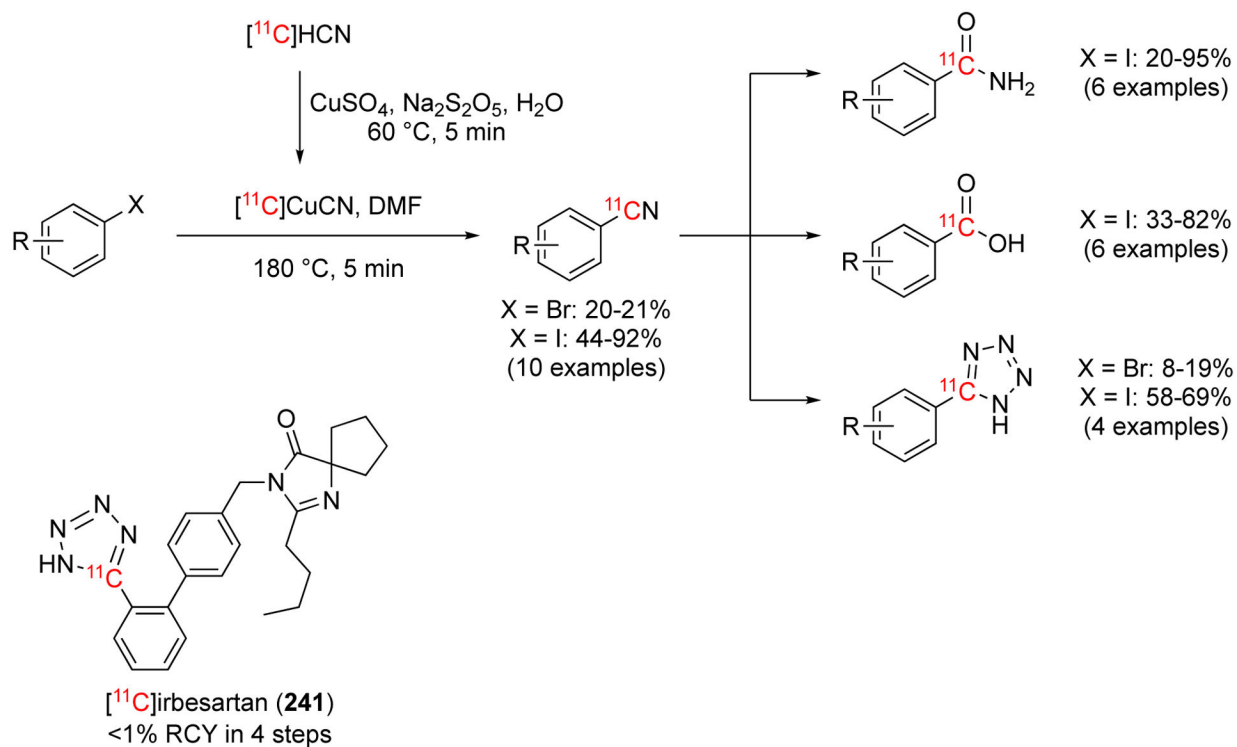
Fig. 37.
[¹¹C]Cyanation using Cu¹¹CN with representative decay-corrected yields.

(a)

$$R\text{—}C_6H_4\text{—}B(OH)_2 \quad \xrightarrow[\text{DMF/H}_2\text{O (3:1), 150 °C, 5 min}]{\text{Cs}^{11}\text{CN, CuI, DMEDA}} \quad R\text{—}C_6H_4\text{—}^{11}\text{CN}$$

8-70% RCC
(12 examples)

(b)

$$R\text{—}C_6H_4\text{—[M]} \quad \xrightarrow[\text{DMA/H}_2\text{O (9:1), 100 °C, 5 min}]{\text{K}^{11}\text{CN, Cu(OTf)}_2\text{, pyridine}} \quad R\text{—}C_6H_4\text{—}^{11}\text{CN}$$

[M] = B(OH)$_2$, BF$_3$K,
Bpin, SnBu$_3$

5-93% RCC
(36 examples)
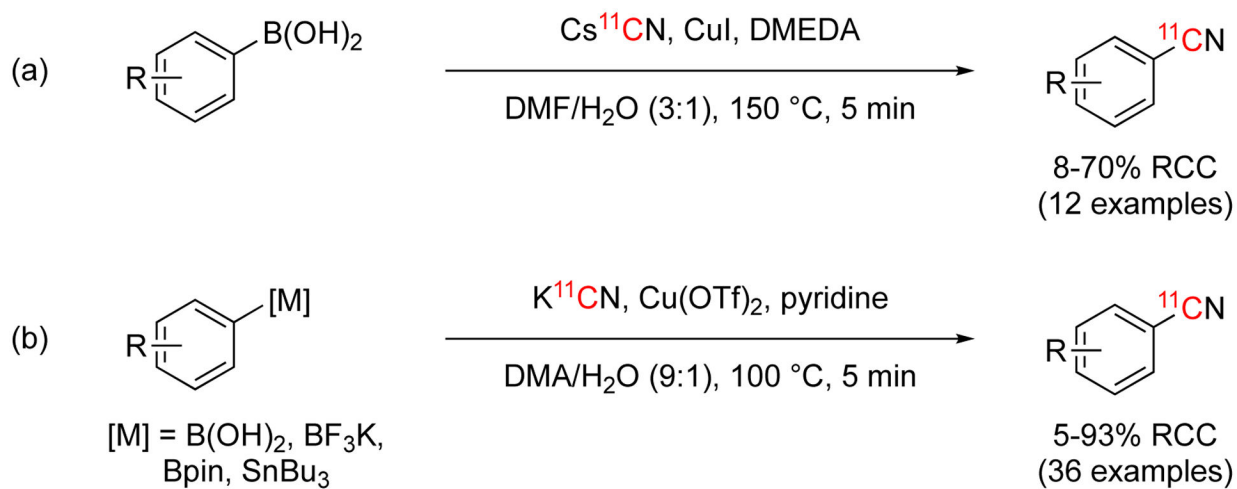
Fig. 38.
Copper-mediated [^{11}C]cyanation of arenes using organometallic reagents.
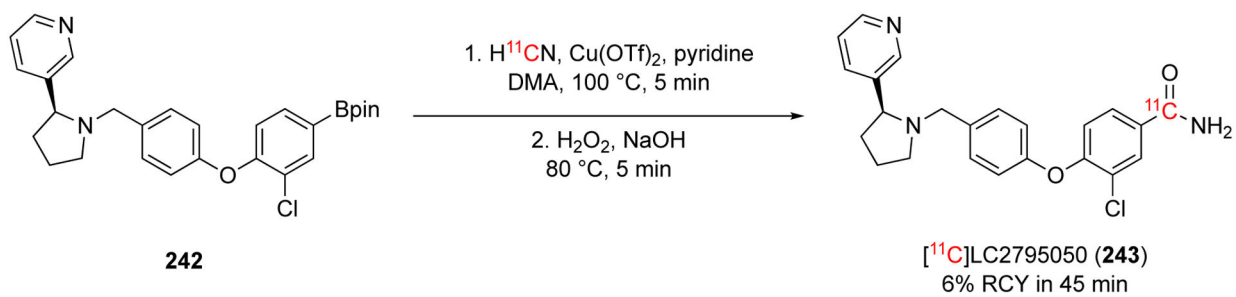
Fig. 39.
Synthesis of [^{11}C]LY2795050 (**243**).
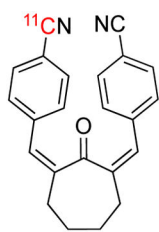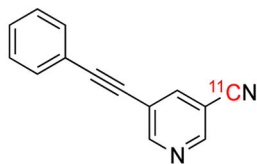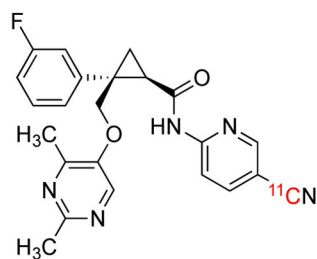
Fig. 40.
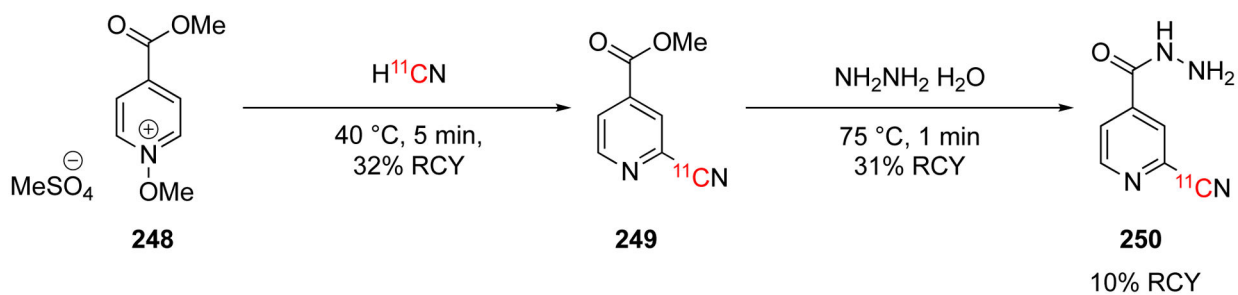[^{11}C]CuCN used to synthesize potential radiotracers.

Fig. 41.
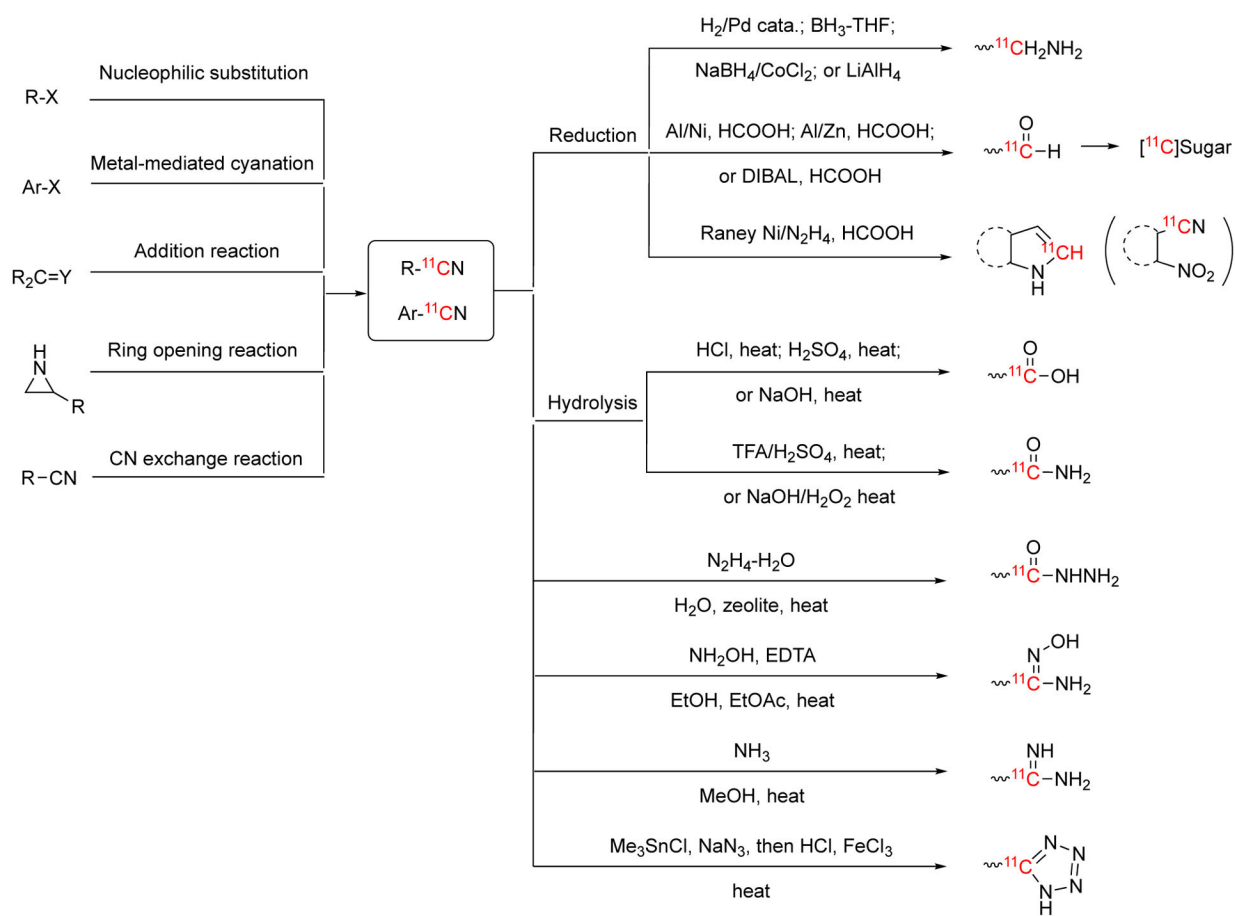Synthesis of 2-[^{11}C]cyano-isonicotinic acid hydrazide via a solid-state support.
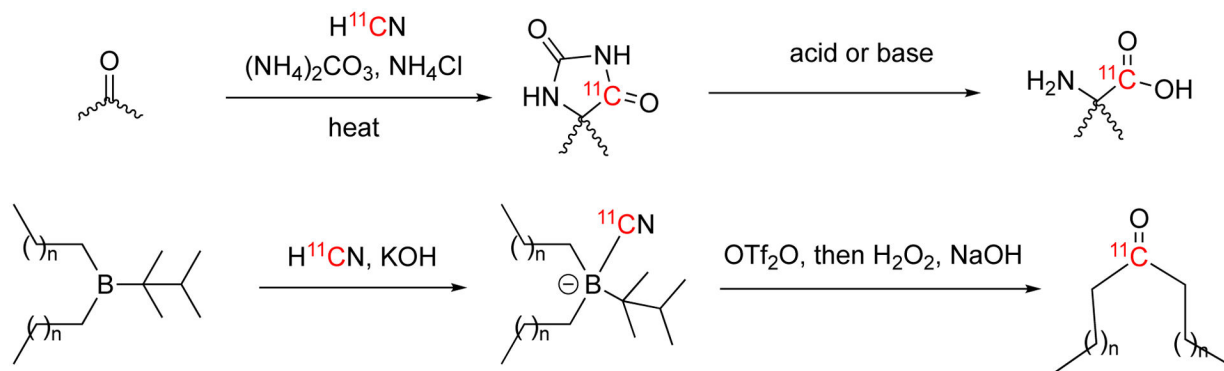
Fig. 42.
H^{11}CN reactions via [^{11}C]nitriles

Fig. 43.
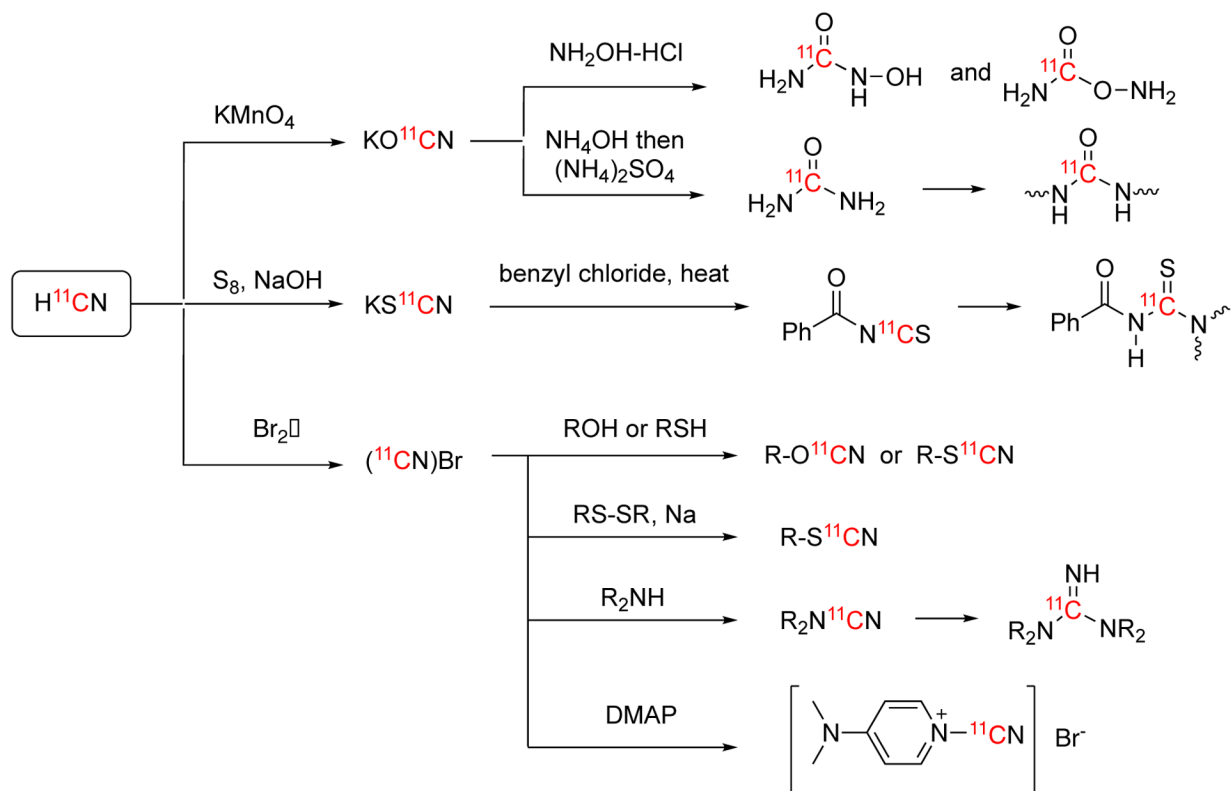Reactions via [^{11}C]hydantoins and [^{11}C]cyanide

Fig. 44.
Summary of [^{11}C]cyanations and related reactions (continue).