7 Carbon-11 Labeling Chemistry Based upon [^{11}C]Methyl Iodide

F. Wuest, M. Berndt, T. Kniess

This article is dedicated to Prof. Dr. B. Johannsen on occasion of his 67th birthday.

Abstract. Radiochemistry with the short-lived positron emitter ^{11}C (half-life 20.38 min) represents special challenges in terms of synthesis time and labeling techniques. The recent developments in ^{11}C radiochemistry have steadily expanded the number of ^{11}C labeled compounds. This chapter addresses selected chemical and technical aspects of ^{11}C chemistry based on the readily available labeling precursors [^{11}C]methyl iodide and, to a lesser extent, [^{11}C]methyl triflate. Special emphasis is placed on heteroatom methylation reactions and ^{11}C–C bond formations.

7.1 Radionuclide Production and Carbon-11 Labeling Precursors

The progress of positron emission tomography (PET) as a powerful imaging technique in nuclear medicine and drug research and development is accompanied by an increasing demand for new radiolabeling methods especially for the short-lived positron emitters ^{11}C (half-life 20.4 min) and fluorine-18 (half-life 109.8 min). Compared to the almost 2 h half-life of fluorine-18 the shorter half-life of ^{11}C provides the advantage to perform repeated PET studies while still allowing, to some extent, multi-step radiosynthesis sequences. Moreover, isotopic labeling through substitution of a stable carbon atom with ^{11}C makes the corresponding ^{11}C labeled radiotracers indistinguishable from their stable counterparts within the biological system.

Several nuclear reactions can be used to produce ^{11}C (for reviews see Wolf and Redvantly 1977; Ferrieri and Wolf 1983). Among these processes the $^{14}N(p,\alpha)^{11}C$ nuclear reaction on a nitrogen target gas is by far the most convenient and most commonly used method of producing ^{11}C. The radionuclide can be produced from nitrogen as a non carbon-containing target material, thus providing ^{11}C at high specific radioactivity. Sufficient amounts of radioactivity can be produced within reasonable irradiation times as the $^{14}N(p,\alpha)^{11}C$ nuclear reaction has cross-section of 250 mbarns using a relatively low threshold energy of 3.1 MeV which allows production of ^{11}C on a small biomedical cyclotron. With the addition of oxygen (up to 2%) or hydrogen (5%–10%) to the nitrogen target gas, ^{11}C is obtained in the target either as [^{11}C]carbon dioxide or [^{11}C]methane, respectively, as primary labeling precursor. However, [^{11}C]carbon dioxide is the most important and most versatile primary labeling precursor. Cyclotron-produced [^{11}C]carbon dioxide can directly be used for the ^{11}C labeling of organic molecules. This includes the reaction of [^{11}C]carbon dioxide with primary amines to give [^{11}C]ureas and [^{11}C]isocyanates (Schirbel et al. 1999) and the reaction of [^{11}C]carbon dioxide with organolithium and organomagnesium compounds. In this line, the most important application is the preparation of [1-^{11}C]acetate via carboxylation of Grignard reagents (MeMgCl or MeMgBr) with [^{11}C]carbon dioxide (Kruijer et al. 1995).

The short 20.38 min half-life of ^{11}C imposes major constraints on the synthesis time of ^{11}C-labeled compounds. Hence, methods for the incorporation of this isotope tend to be limited to those based on a few readily available labeling precursors, and the ^{11}C label should be introduced at the latest time possible within the synthesis sequence. The availability of a wide array of different ^{11}C labeling precursors is an important prerequisite for the flexible and position specific radiolabeling of substances.

Starting from [^{11}C]carbon dioxide as the most important and versatile primary labeling precursor a broad spectrum of different ^{11}C-labeled synthetic intermediates as useful secondary labeling precursors can be prepared.

Figure 1 shows a selection of ^{11}C-labeled secondary labeling precursors derived from [^{11}C]carbon dioxide (Langström et al. 1999).

Among the known secondary ^{11}C labeling precursors, [^{11}C]methyl iodide is the most important and most frequently used. [^{11}C]Methyl iodide has been used extensively as an alkylating agent for carbanions and heteroatom nucleophiles. More recently, [^{11}C]methyl iodide was used as electrophile in several palladium-mediated cross-coupling reactions to form distinct ^{11}C–C bonds. Finally, [^{11}C]methyl iodide is needed for the preparation of other labeling precursors such as [^{11}C]methyl lithium, [^{11}C]nitromethane [^{11}C]methyltriphenyl-phosphorane and triphenylarsonium [^{11}C]methylide.

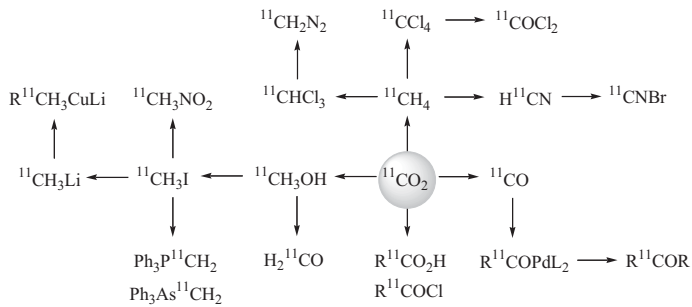


Fig. 1. Selection of ^{11}C-labeled precursors derived from [^{11}C]CO_2

Other important labeling precursors are hydrogen [^{11}C]cyanide and [^{11}C]carbon monoxide. The latter is used for the synthesis of a broad range of carbonyl compounds via palladium- or selenium-mediated reactions (Antoni et al. 2003 and references therein). Recent technical improvements for the handling of [^{11}C]carbon monoxide in carbonylative coupling reactions made this labeling precursor almost equal in importance to [^{11}C]methyl iodide in the synthesis of ^{11}C labeled radiotracers.

In this chapter we wish to give an overview of ^{11}C chemistry based on the readily available labeling precursors [^{11}C]methyl iodide and [^{11}C]methyl triflate. Especial attention is given to heteroatom carbon-11 methylation reactions including recent important technical developments and aspects. Furthermore, recent developments in palladium-mediated ^{11}C–C bond forming reactions with [^{11}C]methyl iodide as an important approach to the position-specific labeling of substances with [^{11}C]methyl groups are discussed.

7.2 Preparation of [^{11}C]Methyl Iodide and [^{11}C]Methyl Triflate

[^{11}C]Methyl iodide as the most versatile ^{11}C labeling precursor can be synthesized via two distinct methods. The so-called ‘wet’ method is based on reduction of cyclotron-produced [^{11}C]carbon dioxide with $LiAlH_4$ in tetrahydrofuran or diethylether (0.05–0.1 M). After evaporation of the solvent hydriodic acid is added and the [^{11}C]methyl iodide formed is distilled off at elevated temperatures in a stream of nitrogen or helium through a $NaOH/P_2O_5$ trap into a reaction vial where the methylation reaction is carried out. This method was developed in the 1970s (Comar et al. 1973; Langström and Lundquvist 1976). Alternatively to hydriodic acid, diphosphorous tetraiodide (Oberdorfer et al. 1985) or triphenylphosphine diiodide (Holschbach et al. 1993) were used to convert [^{11}C]methanol into [^{11}C]methyl iodide. The general reaction sequence to prepare [^{11}C]methyl iodide according to the ‘wet’ chemistry route is outlined in Fig. 2.

The ‘wet’ method is very reliable in terms of radiochemical yields, however, the use of $LiAlH_4$ as reducing agent also has a major draw-

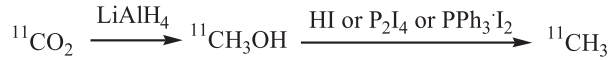


Fig. 2. Synthesis of [^{11}C]methyl iodide via the 'wet' chemistry route

back. $LiAlH_4$ represents the major source of cold carbon dioxide as the most crucial contamination which may cause drastic decrease of specific radioactivity of [^{11}C]methyl iodide and, hence, result in low specific radioactivity of the final ^{11}C labeled radiotracer. Thus, reduction of the amount of $LiAlH_4$ leads to a higher specific radioactivity of the end product (Matarrese et al. 2003). An amount of 5–7 μmol $LiAlH_4$ was shown to be adequate for sufficient trapping of [^{11}C]carbon dioxide whilst providing satisfactory specific radioactivities (2–10 Ci/μmol at the end of synthesis) of the final product (Matarrese et al. 2003).

An alternative method, also referred to as the 'gas phase' method, was developed in the 1990s. This method exploits the conversion of [^{11}C]methane into [^{11}C]methyl iodide by free radical iodination with iodine vapour at elevated temperatures (700–750 °C) in the gas phase (Larsen et al. 1997; Link et al. 1997) (Fig. 3).

[^{11}C]Methane can either be produced directly in the target chamber via the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a 5% or 10% H_2/N_2 target mix (Buckley et al. 2000, 2004) or by hydrogen reduction of cyclotron-produced [^{11}C]carbon dioxide on a nickel catalyst (Larsen et al. 1997, Link et al. 1997).

In order to enable sufficient conversion of [^{11}C]methane into [^{11}C]methyl iodide the gas-phase iodination is performed as a circulation process. The formed [^{11}C]methyl iodide is continuously removed from the circulation process by using a Porapak trap, which is heated afterwards to release [^{11}C]methyl iodide. An alternative gas phase bromination of [^{11}C]methane with bromine at 550 °C to give [^{11}C]methyl bromide in 75% yield was reported by Mock (Mock et al. 1999).

The preparation of [^{11}C]methyl iodide via the 'gas phase' method offers several advantages over the 'wet' chemistry route. Firstly, it cir-

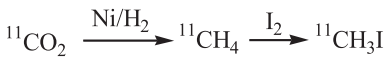


Fig. 3. Synthesis of [^{11}C]methyl iodide via the 'gas phase' method

cumvents the problem associated with the use of $LiAlH_4$, hence leading to higher specific radioactivity. In this respect, the highest specific radioactivities of up to 4,700 GBq/μmol are obtained when [^{11}C]methane is produced in situ in the target chamber and [^{11}C]methyl iodide is synthesised by a single pass iodination procedure in a heated quartz tube (Zhang and Suzuki 2005).

Secondly, avoidance of hydriodic acid prevents tubing and valves from deterioration. Moreover, the 'wet' method using $LiAlH_4$ and hydriodic acid requires intense and time-consuming cleaning and drying procedures of reaction vials and tubings of the ^{11}C methylation apparatus which may limit the number of [^{11}C]methyl iodide preparations possible per day.

Some PET radiotracers were shown to give only moderate or even low radiochemical yields in heteroatom methylation reactions when [^{11}C]methyl iodide is used. Thus, the reactivity of [^{11}C]methyl iodide can be increased by conversion into more reactive [^{11}C]methyl triflate (Jewett 1992).

The use of [^{11}C]methyl triflate as a more reactive methylation agent compared to [^{11}C]methyl iodide provides several advantages. [^{11}C]Methyl triflate is less volatile and thus more easily trapped in small volumes of solvent. Usually heteroatom methylation reactions with [^{11}C]methyl triflate proceed in higher radiochemical yields with shorter reaction times and lower reaction temperatures compared to reactions using [^{11}C]methyl iodide (Nagren et al. 1995a, b; Nagren and Halldin 1998; Lundkvist et al. 1998). Moreover, smaller amounts of desmethyl precursor (<1 mg) are needed which is important for facile final product purification and cost of the precursor.

The synthesis of [^{11}C]methyl triflate is performed as an on-line process by passing [^{11}C]methyl iodide or [^{11}C]methyl bromide (Mock et al. 1999) in a gentle stream of helium or nitrogen through a small column containing silver triflate or silver triflate on graphitised carbon spheres which is preheated at 200–300 °C (Fig. 4).

Typical reaction conditions for heteroatom methylation reactions using [^{11}C]methyl iodide and [^{11}C]methyl triflate are opposed in Table 1 (Elsinga 2002).

Other ^{11}C labeling precursors such as [^{11}C]ethyl iodide (Erikson et al. 2004; Bergström et al. 1998; Schmitz et al. 1995), [^{11}C]propyl iodide

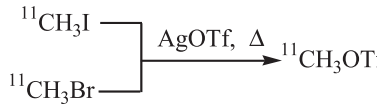


Fig. 4. Synthesis of [^{11}C]methyl triflate

Table 1. Comparison of reaction conditions using [^{11}C]methyl iodide and [^{11}C]methyl triflate (Elsinga 2002)

Reaction condition	[^{11}C]methyl triflate	[^{11}C]methyl iodide
Temperature (°C)	20–60	80–120
Reaction time (min)	1	2–10
Desmethyl precursor (mg)	< 1	1–10

(Ishiwata et al. 1999; Antoni and Langström 1987a) and [^{11}C]formaldehyde (Langer et al. 2005) have also been used in heteroatom alkylation reactions although by far not as frequently as [^{11}C]methyl iodide and [^{11}C]methyl triflate.

Table 2 shows some selected radiotracers and their specific radioactivities reached through heteroatom methylation reactions with [^{11}C]methyl iodide or [^{11}C]methyl triflate. [^{11}C]Methyl iodide was prepared either via the 'wet' method or the 'gas phase' method.

Based on the data summarised in Table 2 it is clear that the 'gas phase' method generally provides ^{11}C-labeled compounds at higher specific radioactivity. Thus, the 'gas phase' method is the method of choice when radiotracers with high specific radioactivity such as receptor ligands or enzyme inhibitors are needed.

Table 2. Examples of specific radioactivities at end-of-synthesis reached in methylation reactions with [^{11}C]methyl iodide and [^{11}C]methyl triflate

Method[a]	Labeling precursor	Radiotracer	SA[b] (GBq/μmol)	Reference
A	[^{11}C]CH_3OTf	[^{11}C]PE2I	29–4	Dolle et al. 2000
A	[^{11}C]CH_3OTf	[^{11}C]HED, [^{11}C]HPED	47–60	van Dort et al. 2000
A	[^{11}C]CH_3I	[^{11}C]DMT, [^{11}C]MPTP, [^{11}C]HED, Dilthiazem, [^{11}C]YM-09151–2	11–74	Iwata et al. 1988
A	[^{11}C]CH_3OTf	[^{11}C]FLB457, [^{11}C]MDL100907, [^{11}C]β-CIT-FE	74–93	Lundkvist et al. 1998
A	[^{11}C]CH_3OTf	[^{11}C]FLB457	78	Sandell et al. 2000
A	[^{11}C]CH_3I	[^{11}C]YM-50001	47–99	Zhang and Suzuki 2002
A	[^{11}C]CH_3I	[^{11}C]MeI	74–175	Crouzel et al. 1987
A	[^{11}C]CH_3OTf	[^{11}C](*R*)MDL-100907	37–370	Matarrese et al. 2003
B	[^{11}C]CH_3I	[^{11}C]MeI	125	Oberdorfer et al. 1985
C	[^{11}C]CH_3I	[^{11}C]β-CPPIT	74–100	Schönbächler et al. 1999
C	[^{11}C]CH_3OTf	[^{11}C]FLB457	126	Sandell et al. 2000
C	[^{11}C]CH_3I	[^{11}C]MeI	370	Larsen et al. 1995
C	[^{11}C]CH_3I	[^{11}C]MHED	444	Link et al. 1997
C	[^{11}C]CH_3I	[^{11}C]MHED	451	Link et al. 1995
C	[^{11}C]CH_3I	[^{11}C]MeI	550	Larsen et al. 1997
C	[^{11}C]CH_3I	[^{11}C] [^{11}C]YM-50001	1810	Zhang et al. 2002
C	[^{11}C]CH_3I	[^{11}C]Flumazenil	2440	Zhang and Suzuki 2005
C	[^{11}C]CH_3I	[^{11}C]Ro15–4513	4700	Noguchi and Suzuki 2003
D	[^{11}C]CH_3OTf	Different compounds[c]	92	Mock et al. 1999

[a] A, "wet" method ($LiAlH_4$/HI); B, "wet method" ($LiAlH_4/P_2I_4$); C, "gas phase" method (iodination); D, "gas phase" method (bromination)

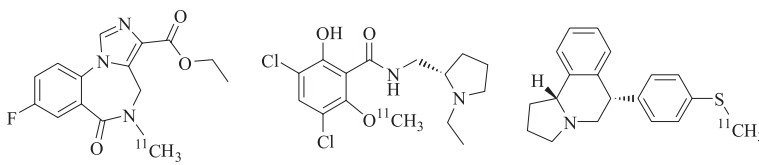
[b] SA=specific radioactivity at end-of-synthesis

[c] Compounds are not explicit specified

7.3 Heteroatom Alkylation Reactions with [^{11}C]Methyl Iodide and [^{11}C]Methyl Triflate

The great majority of carbon-11 labeled compounds has been prepared via *N*-, *O*- and *S*-methylation reactions by using [^{11}C]methyl iodide and [^{11}C]methyl triflate as labeling reagents. Well known examples comprise the synthesis of the PET radiopharmaceuticals [*N*-methyl-^{11}C]flumazenil, [*O*-methyl-^{11}C]raclopride and L[*S*-methyl-^{11}C]McN-5652 (Fig. 5).

The general feature of *N*-, *O*- or *S*-heteroatom ^{11}C methylation reactions is characterized by an extraordinary stoichiometic relationship between the desmethyl precursor and [^{11}C]methyl iodide or [^{11}C]methyl triflate as typically found for radiosyntheses using radionuclides at high specific radioactivity. The corresponding desmethyl precursor is present in an excess of a few orders of magnitude compared to [^{11}C]methyl iodide or [^{11}C]methyl triflate. The resulting stoichiometrical relation can reach a factor of 10^4 : 1. This extraordinary stoichiometry results in a pseudo-first order kinetics of heteroatom methylation reactions with [^{11}C]methyl iodide or [^{11}C]methyl triflate. As a consequence, the conversion rate is highly increased and the radioactive labeling reagent is consumed very rapidly to give satisfactory radiochemical yields within a short reaction time of 5–10 min. Moreover, no problems with polyalkylation occur as otherwise observed when alkylation reactions are performed in stoichiometric amounts of the amine and methyl iodide. The use of trace amounts of compound also simplifies technical handlings such as transfer and purification steps. It also offers the opportunity to



[*N*-methyl-^{11}C]flumazenil [*O*-methyl-^{11}C]raclopride [*S*-methyl-^{11}C]McN-5652

Fig. 5. ^{11}C-labeled radiopharmaceuticals prepared via *N*-, *O*- and *S*-methylation reactions

perform the radiolabeling reaction in small-scale apparatus thus facilitating automation.

Heteroatom alkylation reactions with [^{11}C]methyl iodide and [^{11}C]methyl triflate can either be carried out in solution, on solid-phase support or, more recently, in micro reactors.

The most prominent and most frequently used ^{11}C methylation technique is the execution of the reaction in solution. Commonly used solvents are dimethylsulfoxide (DMSO), dimethylfloride (DMF), acetone and acetonitrile. [^{11}C]Methyl iodide or [^{11}C]methyl triflate is distilled into a vial containing a small amount (0.5–10 mg) of the corresponding desmethyl precursor dissolved in a small volume (<1 ml) of the appropriate solvent. In many cases the use of a base such as K_2CO_3, TBAOH or NaOH is required. The trapping of [^{11}C]methyl iodide in the solution should occur at low temperature (e.g. 0 °C) to enable sufficient trapping. Since trapping of [^{11}C]methyl iodide in solution is not quantitative, insertion of an active charcoal trap attached to the end of waste line is recommended. Trapping of [^{11}C]methyl triflate in solution is usually complete. The vial containing trapped [^{11}C]methyl iodide or [^{11}C]methyl triflate is sealed and heated for a few minutes (1–10 min) for completion of the reaction. The reaction mixture containing the ^{11}C-labeled compound must be subjected onto a semi-preparative HPLC as the almost universal procedure to remove residues of the desmethyl precursor and any other by-products to give a chemically and radiochemically pure compound.

Carbon-11 methylation reactions on a solid support have gained increasing attention over the last years. Reactions on a solid support comprise the use of solid-phase-extraction (SPE) cartridges or a thin tubing loop mounted to the HPLC injector system. Both approaches are characterized by its simple and time-saving operation without significant losses of radioactivity. The simple experimental set-up is easy to automate.

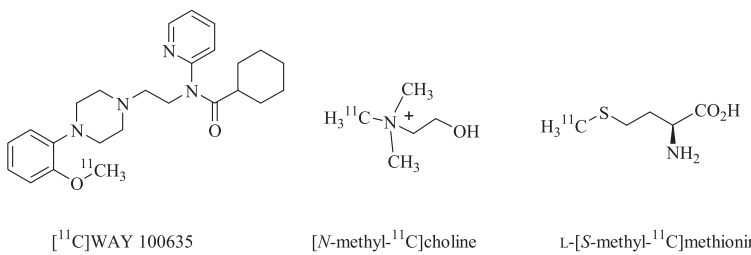
Reactions on SPE cartridges usually make use of disposable C_{18} reverse-phase cartridges which are loaded with a solution (100–200 µl) containing the desired desmethyl precursor and an auxiliary base such as TBAOH or NaOH. [^{11}C]Methyl iodide or [^{11}C]methyl triflate is swept by a gentle stream of nitrogen into the cartridge where the reaction occurs rapidly at ambient temperature. After completion of the reaction the ^{11}C methylated product is removed from the cartridge by an appropriate

solvent. The eluate containing the product can be subjected onto a HPLC injection loop for subsequent conventional HPLC purification.

According to this method, the selective 5-HT_{1A} antagonist [*O*−methyl-^{11}C]-*N*-[2-[4-(-methoxyphenyl)-1-piperazinyl]ethyl-*N*-(2-pyridinyl)cyclohexane carboxamide ([^{11}C]WAY 100635) (Wilson et al. 1995), the amino acid L[*S*-methyl-^{11}C]methionine (Pascali et al. 1999) and [*N*-methyl-^{11}C]choline (Pascali et al. 2000) have been prepared (Fig. 6).

An alternative on-line ^{11}C methylation approach on a solid support was reported by Iwata (Iwata et al. 1992). The key idea of the on-line ^{11}C methylation approach is the incorporation of a short column, which is used as an adsorber, reaction vessel and injection loop, in a HPLC injector. [^{11}C]Methyl iodide is first trapped in the short column containing an appropriate adsorber (e.g. silica gel or Porapak Q) and the coated desmethyl labeling precursor. It was shown that [^{11}C]methyl iodide is almost quantitatively adsorbed by only 30 µl of silica gel. The ^{11}C methylation reaction occurs after DMF as the solvent was introduced into the column. Likewise, a DMF solution of the desmethyl labeling precursor can be added to the short silica gel column after the trapping of [^{11}C]methyl iodide. After heating the column the reaction mixture can easily injected into a HPLC column to purify and isolate the desired ^{11}C-labeled compound.

An advancement of ^{11}C methylation reactions on solid-phase support was achieved by the introduction of the loop method for the automated preparation of ^{11}C-labeled compounds (Watkins et al. 1988; Wilson et al. 2000; Iwata et al. 2001, 2002; Studenov et al. 2004). A stainless steel



[^{11}C]WAY 100635 [*N*-methyl-^{11}C]choline L-[*S*-methyl-^{11}C]methionine

Fig. 6. Carbon-11-labeled radiopharmaceuticals prepared on solid support using a C_{18} SPE cartridge

standard HPLC injection loop or a Teflon loop is coated internally with a thin film of a solution (80–100 μl) containing the desmethyl labeling precursor. [^{11}C]Methyl iodide or [^{11}C]methyl triflate in a gentle stream of nitrogen or helium (flow rate 8–15 ml/min) is passed through the loop for 1–5 min. The content of the loop is injected onto a HPLC column for purification. As no vials, transfer lines, cooling, heating, or sealing valves are required, no transfer losses occur, and the clean-up is minimal. These advantages make the loop method an ideal technique for the convenient preparation of broad range of ^{11}C-labeled radiopharmaceuticals such as [*O*-methyl-^{11}C]raclopride (Wilson et al. 2000; Iwata et al. 2001), [^{11}C]carfentanil (Studenov et al. 2004), [^{11}C]SCH23390 (Wilson et al. 2000; Studenov et al. 2004), [^{11}C]RO5–4864 (Watkins et al. 1988) and [^{11}C]DASB (Wilson et al. 2000) (Fig. 7).

Recently, mircofluidic-based devises have been reported to be capable of performing a wide range of single and multistep synthesis (Ratner et al. 2004). Such continuous-flow microreactors have been used to perform chemical reactions on nanolitre to microlitre scales. This technique proved to be a valuable tool for optimizing synthetic efficiency, particularly when sensitive compounds are used. The distinct advantages of

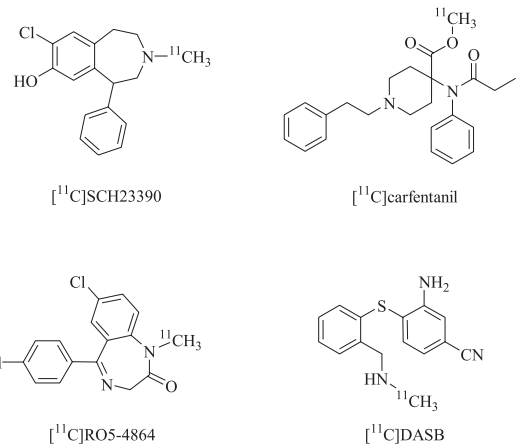


Fig. 7. Carbon-11-labeled radiopharmaceuticals prepared via in-loop radiosynthesis

microfluid technology has also entered the field of PET radiochemistry (Gillies et al. 2006a, 2006b; Lee et al. 2005; Lu et al. 2004). In a proof-of-principle study this technology was applied to the radiosynthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) (Lee et al. 2005). An extention of microreactor technology to ^{11}C chemistry was achieved by the synthesis of ^{11}C-labeled carboxylic esters as depicted in Fig. 8 (Lu et al. 2004).

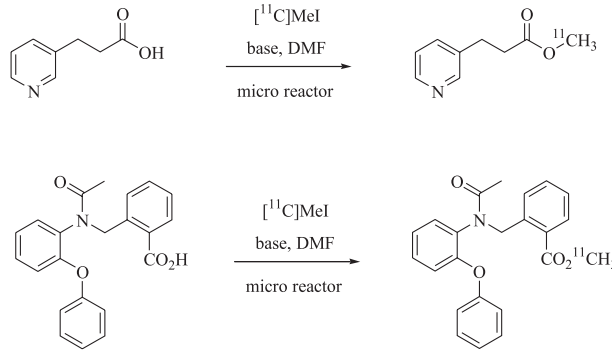


Fig. 8. Carbon-11-labeled esters prepared using microreactor technology

Carbon-11-labeled esters were obtained in radiochemical yields of 56% and 45%, respectively, at an infusion rate of 10 μl/min. Reduction of the infusion rate to 1 μl/min gave increased radiochemical yields of 88% and 65%, respectively.

These promising initial results make mircofluidic-based radiosyntheses a very attractive approach for producing radiotracers for PET. The technology bears many potential advantages (e.g. work with small amounts of compounds, enhanced reactions, rapid reaction optimisation, easy product purification), and it certainly will have an important impact on radiopharmaceutical chemistry in the future.

7.4 Palladium-Mediated ^{11}C–C Bond Formations with [^{11}C]Methyl Iodide

To further expand the number of ^{11}C-labeled compounds as molecular probes for PET the development of novel ^{11}C–C bond forming reactions gains more and more attention. The interest in these reactions stems from the possibility to place the ^{11}C label at a distinct position of a given molecule.

The readily availability of [^{11}C]methyl iodide makes this ^{11}C labeling precursor an ideal reagent for distinct ^{11}C–C bond forming reactions. Several routes for ^{11}C–C bond formations involving [^{11}C]methyl iodide have been developed. Thus, alkylation reactions of stabilized carbanions with [^{11}C]methyl iodide were used to synthesise ^{11}C-labeled amino acids (Antoni and Langström 1987b; Bjurling et al. 1989; Fasth et al. 1988, 1995; Fasth and Langström 1990; Gee and Langström 1991a,1991b; Goethals et al. 1996; Harada et al. 2000; Ikemoto et al. 1999; Mosevich et al. 1996, 1997, 1999; Sasaki et al. 2000; Studenov et al. 2003), nucleoside analogues (Conti et al. 1995; de Vries et al. 2000; Lu et al. 2002), chloride-ion channel blockers (Snyder et al. 1995), methylated thiophenes (Karramkam et al. 2003), dihydroxyvitamin D_3 (Bonasera et al. 2001), oestrogens (Dence et al. 1996) and fatty acids (Hostetler et al. 1998).

Wittig reactions employing [^{11}C]methylenetriphenylphosphorane or triphenylarsonium [^{11}C]methylide afforded [beta-^{11}C]styrene (Kihlberg et al. 1990), 6-[^{11}C]-D-glucose (Grierson et al. 1993) and [2-^{11}C]indole (Zessin et al. 1999). Wittig reaction followed by a Heck coupling led to functionalized olefins (Bjorkman and 2000).

The synthesis of ^{11}C-labeled fatty acids was achieved by conversion of various organocopper compounds with [^{11}C]methyl iodide (Kihlberg and Langström 1994; Neu et al. 1997a, 1997b; Wuest et al. 2000).

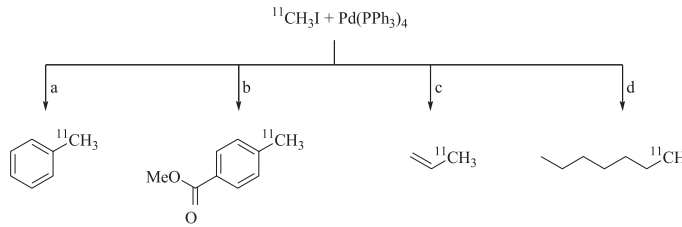
However, the aforementioned methods often require difficult synthetic sequences and they are not compatible with many functional groups. In order to overcome these obstacles, novel technically simple, high-yielding and functional group-tolerating synthetic methods for ^{11}C–C bond formations are of particular interest.

In the last decade, several palladium-mediated cross-coupling reactions have been shown to be effective and very innovative approaches for distinct ^{11}C–C bond formations.

The first application of [^{11}C]methyl iodide in palladium-mediated cross-coupling reactions was reported in 1995 (Andersson et al. 1995). The feasibility of incorporating [^{11}C]methyl groups into arenes, alkenes as well as alkanes was demonstrated by the reaction with the corresponding organostannanes and boranes in Stille and Suzuki cross-coupling reactions (Fig. 9).

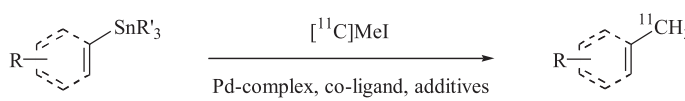
Especially the Stille coupling reaction with [^{11}C]methyl iodide was extensively used in the synthesis of several ^{11}C-labeled compounds (Fig. 10).

The selected palladium complex, the co-ligand and additives have a strong influence on the cross-coupling reaction (Samuelsson and Langström 2003; Suzuki et al. 1997). The generation of the reactive palladium species in situ from $Pd_2(dba)_3$ and a co-ligand is convenient because the type and the amount of co-ligand can be varied. Reaction



a) $PhSnMe_3$, DMSO, 75-85 %; b) Methyl 4-($SnBu_3$)benzoate, DMF or NMP, 30-40 %;
c) Vinyl-$SnBu_3$, DMSO, 75-85 %; d) 9-Hexyl-9-BBN, benzene or dioxane or THF, 60-70 %

Fig. 9. Stille and Suzuki couplings using [^{11}C]methyl iodide



R' = Me, n-B

Fig. 10. Stille cross-coupling reaction

between $Pd_2(dba)_3$ and tri-*o*-tolylphosphine ($P(o\text{-Tol})_3$) as a co-ligand generates the reactive Pd(0) species [$(o\text{-Tol})_3$P-Pd-$P(o\text{-Tol})_3$]. $P(o\text{-Tol})_3$ is superior to other co-ligands because of the large cone angle (194°) which results in the release of steric strain in the transmetalation step. The transmetalation step is considered to be rate determining within the catalytic cycle of the Stille reaction. In many cases addition of CuCl or CuI also results in better yields. After oxidative addition of [^{11}C]methyl iodide into the reactive Pd(0) complex ($Pd[P(o\text{-Tol})_3]_2$) the formed Pd^{II}-complex readily reacts with an organocopper compound which was generated in situ by transmetalation of the stannane with CuCl or CuI.

In a typical reaction [^{11}C]methyl iodide is trapped in a solution containing the Pd-complex (e.g. $Pd_2(dba)_3$) and the co-ligand (e.g. $P(o\text{-Tol})_3$) in DMF. The resulting mixture is transferred into a vial containing the stannane (and CuCl or CuI). After heating the reaction mixture for a couple of minutes, the desired product is subsequently purified by semi-preparative HPLC.

Various PET radiotracers were synthesised by the palladium-mediated reaction of stannanes with [^{11}C]methyl iodide employing Stille reaction conditions as shown in Fig. 11, e.g. serotonin transporter ligands: [^{11}C]citalopram analogue (Madsen et al. 2003), 5-[^{11}C]methyl-6-nitroquipazine (Sandell et al. 2002a, 2002b), [*p*-^{11}C-methyl]-MADAM (Tarkiainen et al. 2001); ligands for metabotropic glutamate subtype 5 receptor: [^{11}C]MPEP (Yu et al. 2005), [^{11}C]M-MTEB (Hamill et al. 2005) [alternatively, [^{11}C]M-MTEB was synthesised using a Suzuki reaction; the Suzuki coupling route gave higher radiochemical yields compared to the Stille reaction (see Fig. 14)]; and glutamate 1 receptor: [^{11}C]JNJ-16567083 (Huang et al. 2005); prostaglandins: [^{11}C]methyl $PGF_{y\alpha}$-analogue (Bjorkman et al. 2000), [^{11}C]TIC methyl esters (Bjorkman et al. 1998; Suzuki et al. 2000, 2004); COX-2 inhibitors: [^{11}C]celecoxib (Prabhakaran et al. 2005), [^{11}C]FMAU (Samuelsson and Langström 2003); tracer for assessment of myocardial sympathetic innervation: 4-[^{11}C]methylmetaraminol (Langer et al. 2003); and ligands for the nicotinic acetyl choline receptor: 5-[^{11}C]methyl-A-85380 (Iida et al. 2004; Karimi and Langström 2002) (Fig. 11). A general protocol for the synthesis of labeled methylalkenes was

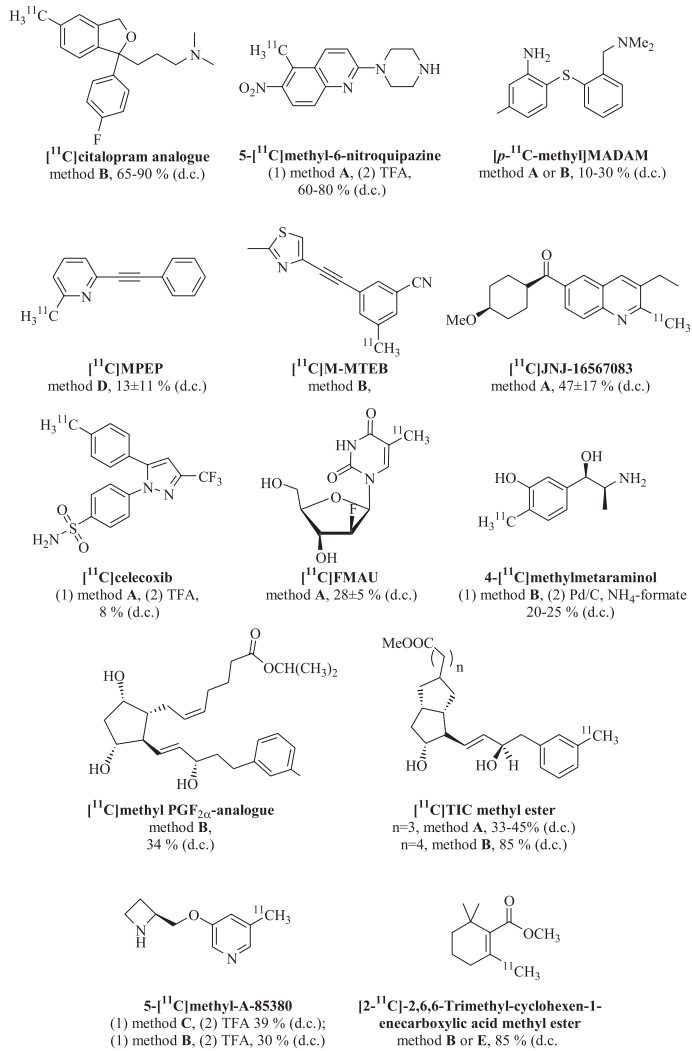


Fig. 11. Carbon-11-labeled radiotracers prepared by Stille reaction (d.c. = decay-corrected). (**A**) $Pd_2(dba)_3$, P(o-Tol)$_3$, DMF. (**B**) $Pd_2(dba)_3$, P(o-Tol)$_3$, CuCl, K_2CO_3, DMF. (**C**) $Pd_2(dba)_3$, P(o-Tol)$_3$, CuCl, K_2CO_3, DMSO. (**D**) $Pd(PPh_3)_4$, toluene. (**E**) $Pd_2(dba)_3$, P(o-Tol)$_3$, CuBr, CsF, DMF

demonstrated by the synthesis of [2-^{11}C]-2,6,6-trimethyl-cyclohexen-1-enecarboxylic acid methyl ester (Hosoya et al. 2006).

Beside the conversion of organostannanes with [^{11}C]methyl iodide the preparation of [^{11}C]monomethyltin reagents (Fig. 12) and their subsequent palladium-mediated reaction with organohalides have been described (Forngren et al. 2004; Huiban et al. 2006). 5-[^{11}C]Methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane was synthesized from the corresponding chloro compound and [^{11}C]methyl lithium (Forngren et al. 2004). The use of the ^{11}C-labeled stannane was demonstrated in palladium-mediated Stille reactions with aromatic, heteroaromatic and vinylic halides to build up [^{11}C]methyl-substituted compounds. An alternative ^{11}C-labeled monomethylstannate was obtained by the conversion of Lappert's stannylene ($Sn[N(TMS)_2]_2$) with [^{11}C]methyl iodide and subsequent activation of the intermediate with tetra-*n*-butyl-ammonium

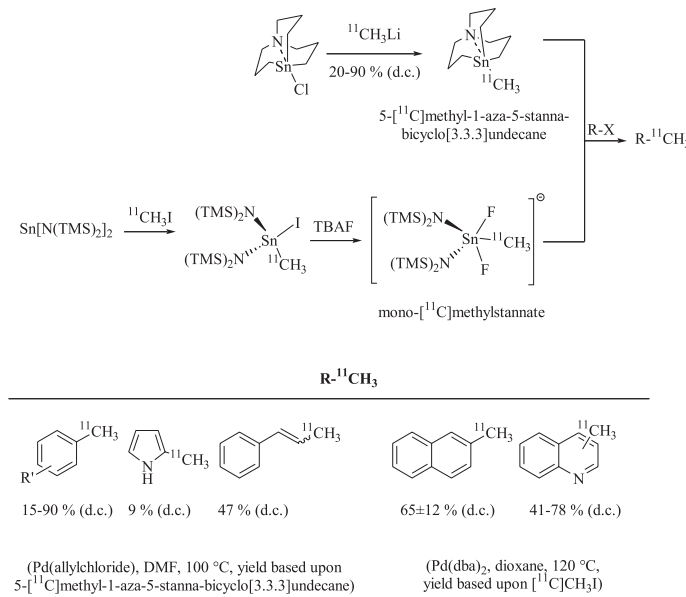


Fig. 12. Carbon-11-labeled monomethyltin reagents in Stille cross-coupling reactions (*d.c.*, decay-corrected)

fluoride (TBAF) (Huiban et al. 2006). Rapid Stille cross-coupling reaction under ligand-free conditions afforded various ^{11}C methylated naphthalenes and quinolines in high radiochemical yields.

However, sometimes toxic tin-containing contaminants are difficult to remove completely from the reaction mixture obtained in Stille cross-coupling reactions. This may limit the application of the Stille reaction especially when pharmaceuticals are synthesized. An alternative to the Stille reaction is the palladium-mediated cross-coupling of boronic acids or boronic esters with electrophiles, also referred to as the Suzuki reaction. Both electron-rich and electron-poor aryl boronic esters and aryl boronic acids bearing a wide range of functional groups were coupled with [^{11}C]methyl iodide in good yields (Hostetler et al. 2005). Thus, several [^{11}C]toluenes could be synthesised via Suzuki cross-coupling reactions (Fig. 13).

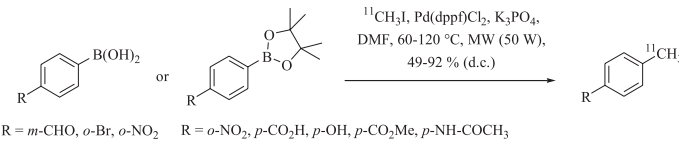


Fig. 13. Preparation of carbon-11-labeled toluenes (*d.c.*, decay-corrected)

First, [^{11}C]methyl iodide was distilled into a solution containing Pd(dppf)Cl_2 in DMF. This mixture was transferred to a vial containing a solution of the aryl boronic acid or ester and K_3PO_4 in DMF. After heating the reaction mixture by microwave (MW) activation (100 °C, 90 s at 50 W) the reaction was quenched by the addition of water. The ^{11}C-labeled toluenes were purified by HPLC.

The glutamate receptor subtype 5 PET radiotracer [^{11}C]M-MTEB could be synthesized effectively starting from a aryl boronic acid and [^{11}C]methyl iodide according to a Suzuki coupling reaction (Hamill et al. 2005; Madsen et al. 2003) (Fig. 14). This synthetic approach was more effective than the Stille reaction using the corresponding trimethylstannane (see Fig. 12).

The coupling of alkyl boranes with [^{11}C]methyl iodide provides a useful excess to ^{11}C-labeled fatty acids (Hostetler et al. 1998). The carboxyl moiety was protected as *tert*-butyl ester or masked as furane (Fig. 15).

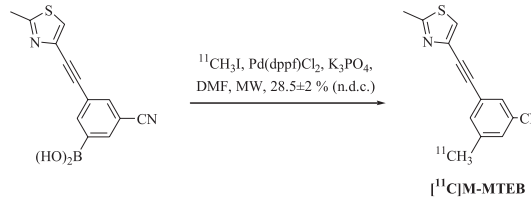


Fig. 14. Synthesis of [^{11}C]M-MTEB employing Suzuki cross-coupling reaction (*n.d.c.*, not decay-corrected)

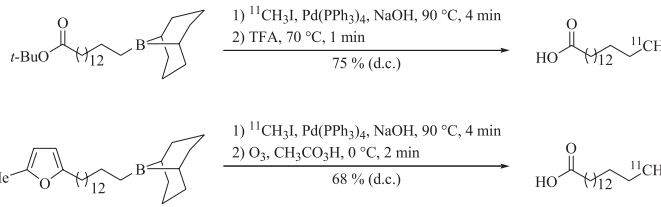


Fig. 15. Carbon-11-labeled fatty acids through Suzuki coupling (*d.c.*, decay-corrected)

Another approach for palladium-mediated ^{11}C–C bond formation with [^{11}C]methyl iodide is the conversion of terminal alkynes according to a Sonogashira cross-coupling reaction. This reaction of a terminal alkynes with [^{11}C]methyl iodide results in the formation of 3′-[^{11}C]prop-1-ynyl-substituted compounds. However, application of the classical Sonogashira reaction conditions is not feasible when [^{11}C]methyl iodide is used as the electrophile. [^{11}C]Methyl iodide will immediately be consumed by the commonly used strong amine base (e.g. triethylamine) used in the classical Sonogashira reaction to form the corresponding quaternary ammonium salt. Consequently, one has to modify the reaction conditions to be compatible with the use of [^{11}C]methyl iodide as the electrophile in the Sonogashira cross-coupling reaction. A combination of $Pd_2(dba)_3$ as palladium complex, $AsPh_3$ as co-ligand and TBAF as activator was shown to give sufficient radiochemical yields of up to 64% (based upon [^{11}C]methyl iodide) of the desired compound (Wuest et al. 2003). After transferring of [^{11}C]methyl iodide into a solution

of $Pd_2(dba)_3$ and $AsPh_3$ in THF, the mixture was heated at 60 °C for 2–3 min. TBAF and the terminal alkyne in THF were added, and the mixture was heated at 60 °C for 3 min. The final product was separated by semi-preparative HPLC (Fig. 16).

A strategy to form ^{11}C-labeled α,α′-dimethyl substituted alkenes comprises the formation of alkenylzirconocenes by the *syn*-insertion of a C–C triple bond into the Zr-H bond of Schwartz reagent [$Cp_2Zr(H)Cl$] followed by palladium-mediated ^{11}C–C bond formation with [^{11}C]methyl iodide under retention of the configuration of the C–C double bond (Wuest and Berndt 2006) (Fig. 17).

The palladium complex $Pd(PPh_3)_4$ proved to be superior to $Pt(PPh_3)_4$ or $Ni(PPh_3)_4$ as a transition metal complex. First, a solution of the alkyne and Schwartz's reagent in THF was stirred for 3 h at ambient temperature, $Pd(PPh_3)_4$ was added, and the mixture was stirred for 5 min. An aliquot of the resulting orange-coloured palladium complex/alkenylzirconocene solution was used for cross-coupling with [^{11}C]methyl iodide which took place on heating the reaction mixture at 60 °C for 5 min. The scope and limitations of the palladium-mediated cross-coupling reaction of alkenyl-zirconocenes with [^{11}C]methyl iodide were tested with various internal alkynes. Radiochemical yields of up to 75% (based upon [^{11}C]methyl iodide) could be achieved.

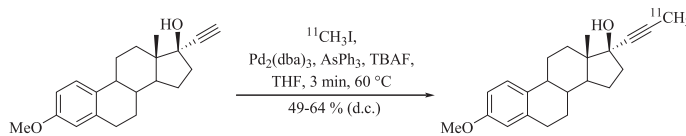


Fig. 16. ^{11}C-C bond formation via a modified Sonogashira cross-coupling (*d.c.*, decay-corrected)

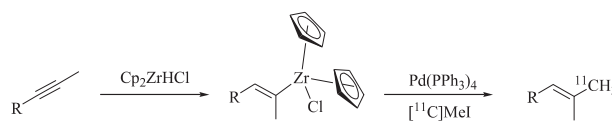


Fig. 17. Synthesis of carbon-11-labeled α,α′-dimethyl alkenes by palladium-mediated cross-coupling alkenylzirconocenes with [^{11}C]methyl iodide

7.5 Conclusion

Among the plethora of ^{11}C-labeling precursors, [^{11}C]methyl iodide is one of the most versatile ^{11}C building blocks for the synthesis of a wide variety of PET radiotracers. [^{11}C]Methyl iodide can easily produced in automated synthesis apparatus in high radiochemical yields and high specific radioactivity. Recent technical improvements and developments have made heteroatom methylation reactions with [^{11}C]methyl iodide a powerful and convenient synthesis route for the preparation of ^{11}C-labeled PET radiotracers for clinical routine and research purposes. Moreover, the scope of [^{11}C]methyl iodide as useful labeling precursor was significantly expanded through the application of transition metal-mediated reactions for distinct ^{11}C–C bond formations. In this line, especially palladium-mediated ^{11}C–C bond formations have proved to be exceptionally valuable to further expand the arsenal of ^{11}C-labeled compounds. Thus, recent developments in ^{11}C radiochemistry are an important prerequisite to further stimulate the progress of PET as a powerful imaging technique in clinical routine and research, and drug research and development.

References

Andersson Y, Cheng AP, Langström B (1995) Palladium-promoted coupling reactions of [^{11}C]methyl-iodide with organotin and organoboron compounds. Acta Chem Scand 49:683–688

Antoni G, Langström B (1987a) Synthesis of racemic [3-^{11}C]-labeled alanine, 2-aminobutyric acid, norvaline, norleucine, leucine and phenylalanine and preparation of l-[3-^{11}C]alanine and l-[3-^{11}C]phenylalanine. J Label Compds Radiopharm 24:125–143

Antoni G, Langström B (1987b) Synthesis of DL-[3-^{11}C]valine using [2-^{11}C]isopropyliodide, and preparation of L-[3-^{11}C]valine by treatment with D-amino acid oxidase. Int J Appl Radiat Isot 655–659

Antoni G, Kihlberg T, Langström B (2003) ^{11}C: Labelling chemistry and labeled compounds. In: Vertes A, Nagy S, Klencsar Z (eds) Handbook of nuclear chemistry, volume 4, radiochemistry and radiopharmaceutical chemistry in life science. Kluwer Academic Publishers, Doedrecht, pp 119–165

Bergström M, Bonasera TA, Lu L, Bergström E, Backlin C, Juhlin C, Langström B (1998) In vitro and in vivo primate evaluation of carbon-11-etomodate and carbon-11-metomidate as potential tracers fot PET imaging of the adrenal cortex and its tumors. J Nucl Med 39:982–989

Bjorkman M, Andersson Y, Doi H, Kato K, Suzuki M, Noyori R, Watanabe Y, Langström B (1998) Synthesis of ^{11}C/^{13}C-labelled prostacyclins. Acta Chem Scand 52:635–640

Bjorkman M, Doi H, Resul B, Suzuki M, Noyori R, Watanabe Y, Langström B (2000) Synthesis of a ^{11}C-labelled prostaglandin F-2 alpha analogue using an improved method for Stille reactions with [^{11}C]methyl iodide. J Label Compds Radiopharm 43:1327–1334

Bjorkman M, Langström B (2000) Functionalisation of ^{11}C -labelled olefins via a Heck coupling reaction. J Chem Soc Perkin Trans 1 3031–3034

Bjurling P, Watanabe Y, Tokushige M, Oda T, Langström B (1989) Syntheses of Beta-^{11}C -Labeled l-Tryptophan and 5-Hydroxy-l-Tryptophan Using a Multi-Enzymatic Reaction Route. J Chem Soc Perkin Trans 1 1331–1334

Bonasera TA, Grue-Sorensen G, Ortu G, Binderup E, Bergström M, Björkling F, Langström B (2001) The synthesis of [26,27-^{11}C]dihydroxyvitamin D-3, a tracer for positron emission tomography (PET). Bioorg Med Chem 9:3123–3128

Buckley KR, Huser J, Jivan S, Chun KS, Ruth TJ (2000) 11C-methane production in small volume, high pressure gas targets. Radiochim Acta 88:201–205

Buckley KR, Jivan S, Ruth TJ. (2004) Improved yields for the in situ production of [11C]CH4 using a niobium target chamber. Nucl Med Biol 31:825–827

Comar D, Maziere M, Crouzel M (1973) Synthesis and metabolism of ^{11}C-chlorpromazine methiodide. Radiopharm Labeled Compd 461–469

Conti PS, Alauddin MM, Fissekis JR, Schmall B, Watanabe KA (1995) Synthesis of 2′-fluoro-5-[^{11}C]-methyl-1-beta-D-arabinofuranosyluracil ([^{11}C]-FMAU) – a potential nucleoside analog for in-vivo study of cellular proliferation with PET. Nucl Med Biol 22:783–789

Crouzel C, Langström B, Pike VW, Coenen HH (1987) Recommendations for practical production of [^{11}C]methyl iodide. Appl Radiat Isot 38:601–603

de Vries EFJ, van Waarde A, Harmsen MC, Mulder NH, Vaalburg W, Hospers GAP (2000) [^{11}C]FMAU and [^{18}F]FHPG as PET tracers for herpes simplex virus thymidine kinase enzyme activity and human cytomegalovirus infections. Nucl Med Biol 27:113–119

Dence CS, Napolitano E, Katzenellenbogen JA, Welch MJ (1996) Carbon-11-labeled estrogens as potential imaging agents for breast tumors. Nucl Med Biol 23:491–496

Dolle F, Bottlaender M, Demphel S, Emond P, Fuseau C, Coulon C, Ottaviani M, Valette H, Loch C, Halldin C, Mauclaire L, Guilloteau D, Maziere B, Crouzel C (2000) Highly efficient synthesis of [^{11}C]PE2I, a selective radioligand for the quantification of the dopamine transporter using PET. J Label Compds Radiopharm 43:997–1004

Elsinga PH (2002) Radiopharmaceutical chemistry for positron emission tomography. Methods 27:208–217

Erikson J, Antoni G, Langström B (2004) Synthesis of [1-^{11}C]ethyl iodide from [^{11}C]carbon monoxide and its application in alkylation reactions. J Label Compds Radiopharm 47:723–731

Fasth KJ, Antoni G, Langström B (1988) Asymmetric synthesis of l-[3-^{11}C]alanine and l-[3-^{11}C]phenylalanine by a phase-transfer alkylation reaction. J Chem Soc Perkin Trans 1 3081–3084

Fasth KJ, Hornfeldt K, Langström B (1995) Asymmetric synthesis of ^{11}C labeled l-amino and D-amino acids by alkylation of imidazolidinone derivatives. Acta Chem Scand 49:301–304

Fasth KJ, Langström B (1990) Asymmetric synthesis of l-[beta-^{11}C]amino acids using a chiral nickel-complex of the Schiff-base of (S)-O-[(*N*-benzylprolyl)-amino]benzophenone and glycine. Acta Chem Scand 44:720–725

Forngren T, Samuelsson L, Langström B (2004) A ^{11}C-methyl stannane (5-[^{11}C]methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane) for use in palladium-mediated [^{11}C]C–C bond forming reactions with organohalides. J Label Compds Radiopharm 47:71–78

Ferrieri RA, Wolf AP (1983) The chemistry of positron emitting nucleogenic (hot) atoms with regard to preparation of labelled compounds of practical utility. Radiochim Acta 34:69–83

Gee A, Langström B (1991a) Synthesis of racemic (S)-(+)-[methyl-^{11}C]amphetamine or (R)-(-)-[Methyl-^{11}C]amphetamine. Acta Chem Scand 45:431–435

Gee AD, Langström B (1991b) The synthesis of alpha-([^{11}C]methyl)phenylalanine and alpha-([^{11}C]methyl)tyrosine from ^{11}C labeled malonic esters. J Chem Soc Perkin Trans 1 215–218

Gillies JM, Prenant C, Chimon GN, Smethurst GJ, Perrie W, Hamblett I, Dekker B, Zweit J (2006a) Microfluidic reactor for the radiosynthesis of PET radiotracers. Appl Radiat Isot 64:325–332

Gillies JM, Prenant C, Chimon GN, Smethurst GJ, Dekker BA, Zweit J (2006b) Microfluidic technology for PET radiochemistry. Appl Radiat Isot 64:333–336

Goethals P, Lameire N, vanEijkeren M, Kesteloot D, Thierens H, Dams R (1996) [Methyl-carbon-11]-thymidine for in vivo measurement of cell proliferation. J Nucl Med 37:1048–1052

Grierson JR, Biskupiak JE, Link JM, Krohn KA (1993) Radiosynthesis of 6-[^{11}C]-D-Glucose. Appl Radiat Isot 44:1449–1458

Hamill TG, Krause S, Ryan C, Bonnefous C, Govek S, Seiders TJ, Cosford NDP, Roppe J, Kamenecka T, Patel S, Gibson RE, Sanabria S, Riffel K, Eng WS, King C, Yang XQ, Green MD, O'Malley SS, Hargreaves R, Burns HD (2005) Synthesis, characterization, and first successful monkey imaging studies of metabotropic glutamate receptor subtype 5 (mGluR5) PET radiotracers. Synapse 56:205–216

Harada N, Nishiyama S, Sato K, Tsukada H (2000) Development of an automated synthesis apparatus for l-[3-^{11}C] labeled aromatic amino acids. Appl Radiat Isot 52:845–850

Holschbach MH, Schüller M (1993) A new simple on-line method for the preparation of n.c.a. [11C]methyl iodide. Appl Radiat Isot 44:779–780

Hosoya T, Sumi K, Doi H, Wakao M, Suzuki M (2006) Rapid methylation on carbon frameworks useful for the synthesis of $^{11}CH_3$-incorporated PET tracers: Pd(0)-mediated rapid coupling of methyl iodide with an alkenyltributylstannane leading to a 1-methylalkene. Org Biomol Chem 4:410–415

Hostetler ED, Fallis S, McCarthy TJ, Welch MJ, Katzenellenbogen JA (1998) Improved methods for the synthesis of [omega-^{11}C]palmitic acid. J Org Chem 63:1348–1351

Hostetler ED, Terry GE, Burns HD (2005) An improved synthesis of substituted [^{11}C]toluenes via Suzuki coupling with [^{11}C] methyl iodide. J Label Compds Radiopharm 48:629–634

Huang YY, Narendran R, Bischoff F, Guo NN, Zhu ZH, Bae SA, Lesage AS, Laruelle M (2005) A positron emission tomography radioligand for the in vivo labeling of metabotropic glutamate 1 receptor: (3-ethyl-2-[^{11}C]methyl-6-quinolinyl) (cis-4-methoxycyclohexyl)methanone. J Med Chem 48:5096–5099

Huiban M, Huet A, Barre L, Sobrio F, Fouquet E, Perrio C (2006) Methyl transfer reaction from monomethyltin reagent under palladium(0) catalysis: a versatile method for labelling with carbon-11. Chem Commun 97–99

Iida Y, Ogawa M, Ueda M, Tominaga A, Kawashima H, Magata Y, Nishiyama S, Tsukada H, Mukai T, Saji H (2004) Evaluation of 5-^{11}C-methyl-A-85380 as an imaging agent for PET invesvigations of brain nicotinic acetylcholine receptors. J Nucl Med 45:878–884

Ikemoto M, Sasaki M, Haradahira T, Yada T, Omura H, Furuya Y, Watanabe Y, Suzuki K (1999) Synthesis of l-[beta-^{11}C]amino acids using immobilized enzymes. Appl Radiat Isot 50:715–721

Iwata R, Ido T, Ujiie A, Takahashi T, Ishiwata K, Hatano K, Sugahara M (1988) Comparative study of specific activity of [^{11}C]methyl iodide: a search for the source of carrier carbon. Appl Radiat Isot 39:1–7

Iwata R, Pascali C, Yuasa M, Yanai K, Takahashi T, Ido T (1992) On-line [^{11}C]methylation using [^{11}C]methyl iodide for the automated preparation of ^{11}C-radiopharmaceuticals. Appl Radiat Isot 43:1083–1088

Ishiwata K, Ishii SI, Shinoda M, Maekawa S, Senda M (1999) Automated synthesis of radiochemically pure ^{11}C-labelled ethyl, propyl and butyl iodides. Appl Radiat Isot 50:693–697

Iwata R, Pascali C, Bogni A, Miyake Y, Yanai K, Ido T (2001) A simple loop method for the automated preparation of [^{11}C]raclopride from [^{11}C]methyl triflate. Appl Radiat Isot 55:17–22

Iwata R, Pascali C, Bogni A, Yanai K, Kato M, Ido T, Ishiwata K (2002) A combined loop-SPE method for the automated preparation of [^{11}C]doxepin. J Label Compd Radiopharm 45:271–280

Jewett DM (1992) A simple synthesis of [^{11}C]Methyl triflate. Appl Radiat Isot 43:1383–1385

Karimi F, Langström B (2002) Synthesis of 3-[(2S)-azetidin-2-ylmethoxyl-5-[^{11}C]-methylpyridine, an analogue of A-85380, via a stille coupling. J Label Compds Radiopharm 45:423–434

Karramkam M, Demphel S, Hinnen F, Trognon C, Dolle F (2003) Methylation of the thiophene ring using carbon-11-labelled methyl iodide: formation of 3-[^{11}C]methylthiophene. J Label Compds Radiopharm 46:255–261

Kihlberg T, Gullberg P, Langström B (1990) [^{11}C]Methylenetriphenylphosphorane, a New ^{11}C Precursor, Used in a One-Pot Wittig Synthesis of [Beta-^{11}C]Styrene. J Label Compds Radiopharm 28:1115–1120

Kihlberg T, Langström B (1994) Cuprate-Mediated ^{11}C-C Coupling Reactions Using Grignard-Reagents and ^{11}C Alkyl Iodides. Acta Chem Scand 48:570–577

Kruijer PS, ter Linden T, Mooij R, Visser FC, Herscheid JDM (1995) A practical method for the preparation of [^{11}C]acetate. Appl Radiat Isot 46:317–321

Langer O, Krcal A, Schmid A, Abrahim A, Minetti P, Celona D, Roeda D, Dolle, F, Kletter K, Müller M (2005) Synthesis of 1,1′[^{11}C]-methylene-di-(2-naphthol) ([^{11}C]ST1859) for PET studies in humans. J Label Compds Radiopharm 48:577–587

Langer O, Forngren T, Sandell J, Dolle F, Langström B, Nagren K, Halldin C (2003) Preparation of 4-[^{11}C]methylmetaraminol, a potential PET tracer for assessment of myocardial sympathetic innervation. J Label Compds Radiopharm 46:55–65

Langström B, Lunquvist H (1976) The preparation of [^{11}C]methyl iodide and its use in the synthesis of [^{11}C]methyl-L-methionine. Int J Appl Radiat Isot 27:357–363

Langström B, Kihlberg T, Bergstrom M, Antoni G, Bjorkman M, Forngren BH, Forngren T, Hartvig P, Markides K, Yngve U, Ogren M (1999) Compounds labelled with short-lived beta(+)-emitting radionuclides and some applications in life sciences. The importance of time as a parameter. Acta Chem Scand 53:651–669

Larsen P, Ulin J, Dahlstrom K (1995) A new method for production of ^{11}C-labelled methyl iodide from [^{11}C]methane. J Label Compds Radiopharm 37:73–75

Larsen P, Ulin J, Dahlstrom K, Jensen M (1997) Synthesis of [^{11}C]Iodomethane by iodination of [^{11}C]methane. Appl Radiat Isot 48:153–157

Lee CC, Sui G, Elizarov A, Shu CJ, Shin YS, Dooley AN, Huang J, Daridon A, Wyatt P, Stout D, Kolb HC, Witte ON, Satyamurthy N, Heath JR, Phelps ME, Quake SR, Tseng HR (2005) Multistep synthesis of a radiolabeled imaging probe using integrated microfluidics. Science 310:1793–1796

Link JM, Clark JC, Larsen P, Krohn KA (1995) Production of [^{11}C]methyl iodide by reaction of [^{11}C]CH_4 with I_2. J Label Compds Radiopharm 37:76–78

Link JM, Krohn KA, Clark JC (1997) Production of [^{11}C]CH_3I by single pass reaction of [^{11}C]CH_4 with I_2. Nucl Med Biol 24:93–97

Lu L, Samuelsson L, Bergström M, Sato K, Fasth KJ, Langström B (2002) Rat studies comparing ^{11}C-FMAU, ^{18}F-FLT, and ^{76}Br-BFU as proliferation markers. J Nucl Med 43:1688–1698

Lu SY, Watts P, Chin FT, Hong J, Musachio JL, Briard E, Pike VW (2004) Syntheses of ^{11}C- and ^{18}F-labeled carboxylic esters within a hydrodynamically-driven micro-reactor. Lab Chip 4:523–525

Lundkvist C, Sandell J, Nagren K, Pike VW, Halldin C (1998) Improved synthesis of the PET radioligands [^{11}C]FLB 457, [^{11}C]MDL 100907 and [^{11}C]β-CIT-FE, by the use of [^{11}C]methyl triflate. J Label Compds Radiopharm 41:545–556

Madsen J, Merachtsaki P, Davoodpour P, Bergström M, Langström B, Andersen K, Thomsen C, Martiny L, Knudsen GM (2003) Synthesis and biological evaluation of novel carbon-11-labelled analogues of citalopram as potential radioligands for the serotonin transporter. Bioorg Med Chem 11:3447–3456

Matarrese M, Soloviev D, Todde S, Neutro F, Petta P, Carpinelli A, Brüssermann M, Kienle MG, Fazio F (2003) Preparation of [^{11}C]radioligands with high specific radioactivity on a commercial PET tracer synthesizer. Nucl Med Biol 30:79–83

Mock BH, Mulholland GK, Vavrek MT (1999) Convenient gas phase bromination of [^{11}C]methane and production of [^{11}C]methyl triflate. Nucl Med Biol 26:467–471

Mosevich IK, Kuznetsova OF, Fedorova OS, Korsakov MV (1996) Synthesis of [beta-^{11}C]-L-3,4-dihydroxyphenylalanine. Key stage of the syn-

thesis: Asymmetric alkylation with 3,4-dimethoxybenzyl halides of the nickel complex of the Schiff base derived from glycine and *S*-2-*N*-(*N′*-benzylprolyl)aminobenzophenone. Radiochemistry 38:511–515

Mosevich IK, Kuznetsova OF, Fedorova OS, Korsakov MV (1997) Synthesis of [beta-^{11}C]-l-3,4-dihydroxyphenylalanine. Automated synthesis of the intermediate alkylating agent, [alpha-^{11}C]-3,4-dimethoxybenzyl bromide. Radiochemistry 39:552–554

Mosevich IK, Kuznetsova OF, Vasil'ev DA, Anichkov AA, Korsakov MV (1999) Automated synthesis of [3-^{11}C]-L-alanine involving asymmetric alkylation with (CH_3I)-^{11}C of the nickel complex of the Schiff base derived from glycine and (*S*)-2-*N*-(*N′*-benzylprolyl)aminobenzophenone. Radiochemistry 41:273–280

Nagren K, Halldin C (1998) Methylation of amide and thiol functions with [^{11}C]methyl triflate, as exemplified by [^{11}C]NMSP, [^{11}C]Flumazenil and [^{11}C]Methionine. J Label Compds Radiopharm 41:831–841

Nagren K, Müller L, Halldin C, Swahn CG, Lehikoinen P (1995a) Improved synthesis of some commonly used PET radioligands by the use of [^{11}C]methyl triflate. Nucl Med Biol 22:235–239

Nagren K, Halldin C, Muller L, Swahn CG, Lehikoinen P (1995b) Comparison of [^{11}C]methyl triflate and [^{11}C]methyl iodide in the synthesis of PET radioligands such as [^{11}C]beta-CIT and [^{11}C]beta-CFT. Nucl Med Biol 22:965–979

Neu H, Kihlberg T, Langström B (1997a) Synthesis of [18-^{11}C/(^{13}C)]linoleic acid. J Label Compds Radiopharm 39:607–619

Neu H, Kihlberg T, Langström B (1997b) Synthesis of saturated fatty acids ^{11}C (^{13}C)-labelled in the omega-methyl position. J Label Compds Radiopharm 39:509–524

Noguchi J, Suzuki K.(2003) Automated synthesis of the ultra high specific activity of [^{11}C]Ro15–4513 and its application in an extremely low concentration region to an ARG study. Nucl Med Biol 30:335–343

Oberdorfer F, Hanisch M, Helus F, Maier-Borst W (1985) A new procedure for the preparation of ^{11}C-labelled methyl iodide. Int J Appl Radiat Isot 36:435–438

Pascali C, Bogni A, Iwata R, Decise D, Crippa F, Bombardieri E. (1999) High efficiency preparation of L-[S-methyl-11C]methionine by on-column [11C]methylation on C18 Sep-Pak. J Label Compds Radiopharm 42:715–724

Pascali C, Bogni A, Iwata R, Cambie M, Bombardieri E. (2000) [11C]Methylation on a C18 Sep-Pak cartridge: A convenient way to produce [*N*-methyl-11C]choline. J Label Compds Radiopharm 43:195–203

Prabhakaran J, Majo VJ, Simpson NR, Van Heertum RL, Mann JJ, Kumar JSD (2005) Synthesis of [^{11}C]celecoxib: a potential PET probe for imaging COX-2 expression. J Label Compds Radiopharm 48:887–895

Ratner DM, Adams EW, Disney MD, Seeberger PH (2004) Tools for glycomics: mapping interactions of carbohydrates in biological systems. Chembiochem 5:1375–1383

Samuelsson L, Langström B (2003) Synthesis of 1-(2′-deoxy-2′-fluoro-beta-D-arabinofuranosyl)-[Methyl-^{11}C]thymine ([^{11}C]FMAU) via a Stille cross-coupling reaction with [^{11}C]methyl iodide. J Label Compds Radiopharm 46:263–272

Sandell J, Halldin C, Sovago J, Chou YH, Gulyas B, Yu MX, Emond P, Nagren K, Guilloteau D, Farde L (2002a) PET examination of [^{11}C]5-methyl-6-nitroquipazine, a radioligand for visualization of the serotonin transporter. Nucl Med Biol 29:651–656

Sandell J, Yu MX, Emond P, Garreau L, Chalon S, Nagren K, Guilloteau D, Halldin C (2002b) Synthesis, radiolabeling and preliminary biological evaluation of radiolabeled 5-methyl-6-nitroquipazine, a potential radioligand for the serotonin transporter. Bioorg Med Chem Lett 12:3611–3613

Sandell J, Langner O, Larsen P, Dolle F, Vaufrey F, Demphel S, Crouzel C, Halldin C (2000) Improved specific radioactivity of the PET radioligand [^{11}C]FLB 457 by use of the GE Medical Systems PETtrace MeI MicroLaB J Label Compds Radiopharm 43:331–338

Sasaki E, Ikemoto M, Mutoh M, Haradahira T, Tanaka A, Watanabe Y, Suzuki K (2000) Automatic synthesis of l-[beta-^{11}C]amino acids using an immobilized enzyme column. Appl Radiat Isot 52:199–204

Schirbel A, Holschbach MH, Coenen HH (1999) N.C.A.[11C]CO2 as a safe substitute for phosgene in the carbonylation of primary amines. J Label Compds Radiopharm 42:537–551

Schmitz F, Del Fiore G, Plenevaux A, Lemaire C, Aerts J, Luxen A (1995) [1-^{11}C]Bromoethane: an alternative to use of [1-^{11}C]idoethane. J Label Compds Radiopharm 37:111–112

Schönbächler R, Ametamey SM, Schubiger PA (1999) Synthesis and [^{11}C]-radiolabelling of a tropane derivative lacking the 2β-ester group: a potential PET-tracer for the dopamine transporter. J Label Compds Radiopharm 42:447–456

Snyder SE, Kume A, Jung YW, Connor SE, Sherman PS, Albin RL, Wieland DM, Kilbourn MR (1995) Synthesis of Carbon-11-Labeled, Fluorine-18-Labeled, and Iodine-125-Labeled Gaba(a)-Gated Chloride-Ion Channel Blockers – Substituted 5-Tert-Butyl-2-Pheny1–1,3-Dithianes and 5-Tert-Butyl-2-Pheny1–1,3-Dithiane-Oxides. J Med Chem 38:2663–2671

Studenov AR, Szalda DE, Ding YS (2003) Synthesis of no-carrier-added ^{11}C labeled d- and l-enantiomers of phenylalanine and tyrosine for comparative PET studies. Nucl Med Biol 30:39–44

Studenov AR, Jivan S, Adam MJ, Ruth TJ, Buckley KR (2004) Studies of the mechanism of the in-loop synthesis of radiopharmaceuticals. Appl Radiat Isot 61:1195–1201

Suzuki M, Doi H, Bjorkman M, Andersson Y, Langström B, Watanabe Y, Noyori R (1997) Rapid coupling of methyl iodide with aryltributylstannanes mediated by palladium(0) complexes: A general protocol for the synthesis of $(CH_3)-^{11}$C-labeled PET tracers. Chem Eur J 3:2039–2042

Suzuki M, Doi H, Hosoya T, Langström B, Watanabe Y (2004) Rapid methylation on carbon frameworks leading to the synthesis of a PET tracer capable of imaging a novel CNS-type prostacyclin receptor in living human brain. TrAC, Trends Anal Chem 23:595–607

Suzuki M, Doi H, Kato K, Bjorkman M, Langström B, Watanabe Y, Noyori R (2000) Rapid methylation for the synthesis of a ^{11}C-labeled tolylisocarbacyclin imaging the IP2 receptor in a living human brain. Tetrahedron 56:8263–8273

Tarkiainen J, Vercouille J, Emond P, Sandell J, Hiltunen J, Frangin Y, Guilloteau D, Halldin C (2001) Carbon-11 labelling of MADAM in two different positions: a highly selective PET radioligand for the serotonin transporter. J Label Compds Radiopharm 44:1013–1023

Van Dort ME, Tluczek L (2000) Synthesis and carbon-11 labelling of the stereoisomers of meta-hydroxyephedrine (HED) and meta-hydroxyspeudoephedrine. J Label Compds Radiopharm 43:603–612

Watkins GL, Jewett DM, Mulholland GK, Kilbourn MR, Toorongian SA (1988) A captive solvent method for rapid *N*-[^{11}C]methylation of secondary amides: Application to the benzodiazepine, 4‘-chlorodiazepam (RO5-4864). Appl Radiat Isot 39:441–444

Wilson AA, DaSilva JN, Houle S (1995) Solid-phase synthesis of [^{11}C]WAY 100635. J Label Compds Radiopharm 38:149–154

Wilson AA, Garcia A, Jin L, Houle S (2000) Radiotracer synthesis from [^{11}C]-iodomethane: A remarkable simple captive solvent method. Nucl Med Biol 27:529–532

Wolf AP, Redvantly CS (1977) Carbon-11 and radiopharmaceuticals. Int J Appl Radiat Isot 28:29–48

Wuest FR, Berndt M (2006) ^{11}C-C bond formation by palladium-mediated cross-coupling of alkenylzirconocenes with [^{11}C]methyl iodide. J Label Compds Radiopharm 49:91–100

Wuest F, Dence CS, McCarthy TJ, Welch MJ (2000) A new approach for the synthesis of [^{11}C]-labeled fatty acids. J Label Compds Radiopharm 43:1289–1300

Wuest F, Zessin J, Johannsen B (2003) A new approach for ^{11}C-C bond formation: synthesis of 17 alpha-(3′-[^{11}C]prop-1-yn-1-yl)-3-methoxy-3,17 beta-estradiol. J Label Compds Radiopharm 46:333–342

Yu MX, Tueckmantel W, Wang XK, Zhu AJ, Kozikowski AP, Brownell AL (2005) Methoxyphenylethynyl, methoxypyridylethynyl and phenylethynyl derivatives of pyridine: synthesis, radiolabeling and evaluation of new PET ligands for metabotropic glutamate subtype 5 receptors. Nucl Med Biol 32:631–640

Zessin J, Steinbach J, Johannsen B (1999) Synthesis of triphenylarsonium [^{11}C]methylide, a new ^{11}C-precursor. Application in the preparation of [2-^{11}C]indole. J Label Compds Radiopharm 42:725–736

Zhang MR, Haradahira T, Maeda J, Okauchi T, Kawabe K, Noguchi J, Kida T, Suzuki K, Suhara T (2002) Synthesis and pharmacological evaluation of two potent antagonists for dopamine D4 receptors: [^{11}C]YM-50001 and *N*-[2-[4-(4-chlorophenyl)-piperizin-1-yl]ethyl]-3-[^{11}C]methoxybenzamide. Nucl Med Biol 29:233–241

Zhang MR, Suzuki K (2005) Sources of carbon which decrease the specific activity of [^{11}C]CH_3I synthesized by the single pass I_2 method. Appl Radiat Isot 62:447–450