Imaging Methods

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Synthesis of ^{11}C, ^{18}F, ^{15}O, and ^{13}N Radiolabels for Positron Emission Tomography

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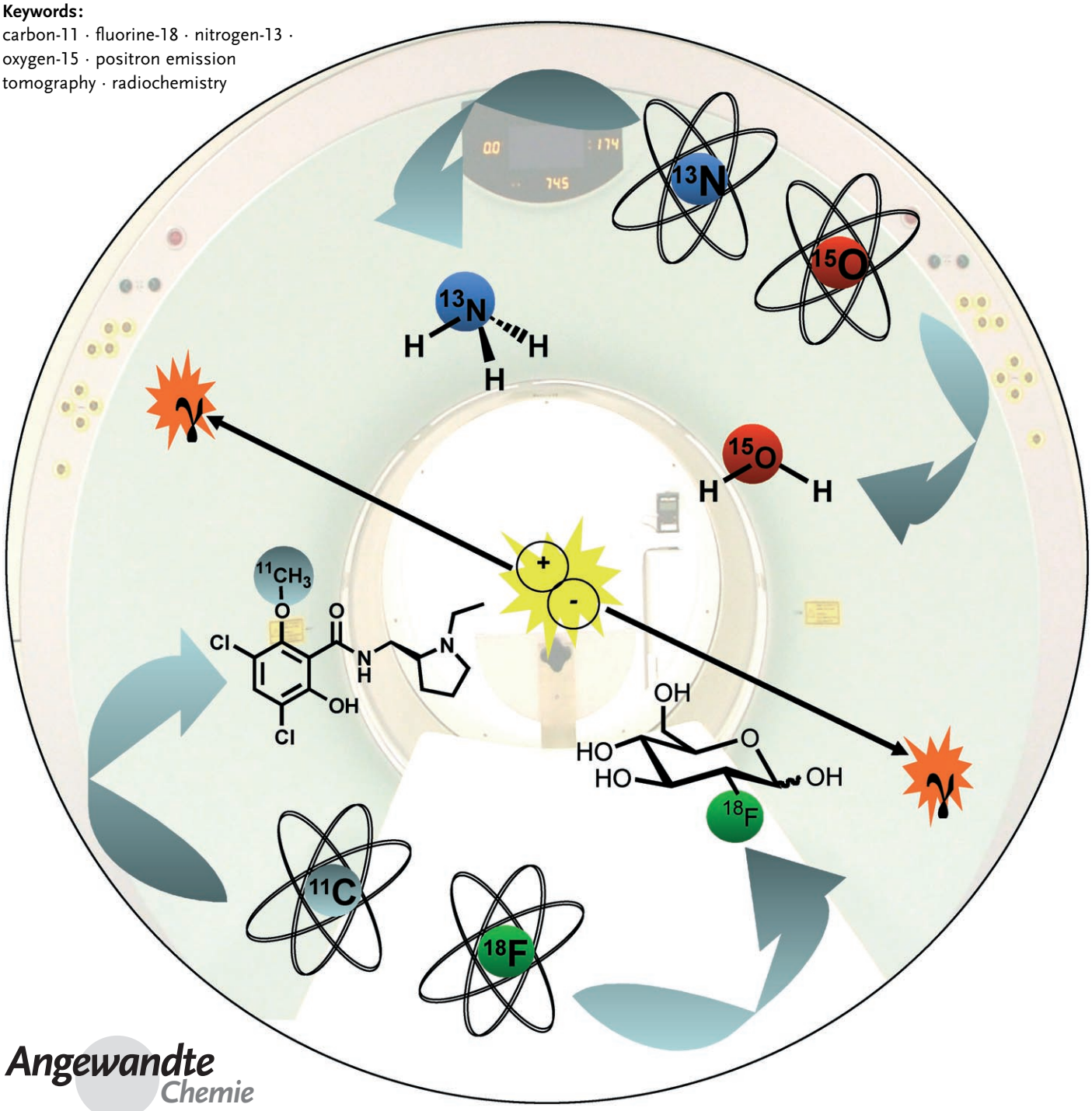
Keywords:
carbon-11 · fluorine-18 · nitrogen-13 · oxygen-15 · positron emission tomography · radiochemistry



Positron emission tomography (PET) is a powerful and rapidly developing area of molecular imaging that is used to study and visualize human physiology by the detection of positron-emitting radiopharmaceuticals. Information about metabolism, receptor/enzyme function, and biochemical mechanisms in living tissue can be obtained directly from PET experiments. Unlike magnetic resonance imaging (MRI) or computerized tomography (CT), which mainly provide detailed anatomical images, PET can measure chemical changes that occur before macroscopic anatomical signs of a disease are observed. PET is emerging as a revolutionary method for measuring body function and tailoring disease treatment in living subjects. The development of synthetic strategies for the synthesis of new positron-emitting molecules is, however, not trivial. This Review highlights key aspects of the synthesis of PET radiotracers with the short-lived positron-emitting radionuclides ^{11}C, ^{18}F, ^{15}O, and ^{13}N, with emphasis on the most recent strategies.

From the Contents

1. Introduction	8999
2. Radiolabeling with Carbon-11	9003
3. Radiolabeling with Fluorine-18	9013
4. Radiolabeling with Oxygen-15 and Nitrogen-13	9026
5. Conclusions and Outlook	9027

1.1. Positron Emission Tomography: Principles, Instrumentation, and Applications

1. Introduction

The ability to image and monitor molecular events in vivo and in real time is of great value to unveil a detailed picture of fundamental biochemical and physiological processes in living organisms. This in turn is essential for the development of novel approaches for the early detection of disease and for the design of new drugs. As a consequence, there is a continuous need to develop imaging techniques with better sensitivity, spatial resolution, selectivity, and tissue specificity.

Imaging techniques such as magnetic resonance imaging (MRI), X-rays, or ultrasound (US) provide valuable information on anatomy (namely, structural imaging), but give limited or no information at all on metabolic or molecular events. Therefore, for the in vivo detection of disease, these imaging methods can be restricted to those malfunctions associated with structural abnormalities. In contrast, techniques such as positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) have the ability to monitor metabolic processes in living patients. These imaging techniques rely on the use of exogenous radioactive probes which provide a detectable signal. These "reporter" probes can be designed to be tissue- or receptor-specific and provide a detailed picture of the targeted structure or biological processes under study.

Despite the great wealth of information that such probes can provide, the development of the exogeneous probes is far from trivial and represents an important challenge for synthetic chemists. In this Review we provide an overview of the most common chemical approaches for the synthesis of PET-labeled molecules, highlighting the most recent developments and trends, and also the problems and challenges currently faced. In addition to showing the synthetic aspects of the area, we will provide examples of the use of PET-labeled molecules for biomedical imaging and drug development.

1.1. Positron Emission Tomography: Principles, Instrumentation, and Applications

PET is a non-invasive molecular imaging technique that is used to study and visualize human physiology by the detection of positron-emitting radiopharmaceuticals. An important advantage of PET as an imaging technique is that it provides metabolic information that cannot be generated with techniques confined to determining the physical structure of the organ (for example, X-ray or ultrasound). Furthermore, since some of the positron-emitting radionuclides are low atomic mass elements (for example, C, N, and O) found in biomolecules it is possible to directly label molecules of interest without interfering with their biological activity. This ability differentiates PET from other techniques, where the imaging "handle" is a relatively large molecule which, when attached to the targeting species, can modify its bioactivity. Several good reviews have appeared in the literature that highlight the principles of PET and its instrumentation.[1–3]

One of the main challenges of PET for chemists is the development of rapid synthetic methods for introducing these short-lived positron-emitting isotopes into the molecule of interest. The labeled probe has to be synthesized, purified, analyzed, and formulated usually within minutes. A timescale of roughly three isotope half-lives is loosely applied for the total synthesis time so as to ensure there is enough radiolabeled material to administer to a subject undergoing the PET scan. The extremely short half-lives of the isotopes shown in Table 1 necessitate that the labeled probes be

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Table 1: The most commonly used short-lived radionuclides in PET, their half-lives, nuclear reactions, target products, and decay products.

Radionuclide	Half-life, $t_{1/2}$ (min)	Nuclear reaction	Target	Product	Decay product
^{11}C	20.4	$^{14}N(p,\alpha)^{11}C$	$N_2(+O_2)$	$[^{11}C]CO_2$	^{11}B
			$N_2(+H_2)$	$[^{11}C]CH_4$	
^{13}N	9.97	$^{16}O(p,\alpha)^{13}N$	H_2O	$[^{13}N]NO_x$	^{13}C
			$H_2O + EtOH$	$[^{13}N]NH_3$	
^{15}O	2.04	$^{15}N(d,n)^{15}O$	$N_2(+O_2)$	$[^{15}O]O_2$	^{15}N
^{18}F	110	$^{20}Ne(d,\alpha)^{18}F$	$Ne(+F_2)$	$[^{18}F]F_2$	^{18}O
		$^{18}O(p,n)^{18}F$	$[^{18}O]H_2O$	$^{18}F^-$	

prepared in proximity to where the isotopes are produced and used almost immediately after their synthesis. A number of modern PET facilities house cyclotrons (for radioisotope production), radiosynthetic laboratories, and PET scanners under one roof to allow efficient production and transport of short-lived PET probes from the laboratory to the scanner.

Inhalation or more commonly intravenous injection is required to administer the PET probe to the subject (animal or human). The PET radionuclide decays in the body by positron emission (Scheme 1). The emitted positron (β^+) is not detected directly, but travels a short distance (0.5–2.0 cm, depending on its characteristic kinetic energy) and collides with an electron in the surrounding tissue. This collision of matter and antimatter results in an annihilation event that produces two gamma ray photons (γ) of 511 keV that travel at 180° to each other (Figure 1). It is the simultaneous detection of these two gamma ray photons that travel out through the body along a "line of coincidence" that allows the annihilation events, and hence the approximate location of the PET probe in the body, to be located. The PET scanner typically consists of a series of detectors arranged in a circular ring

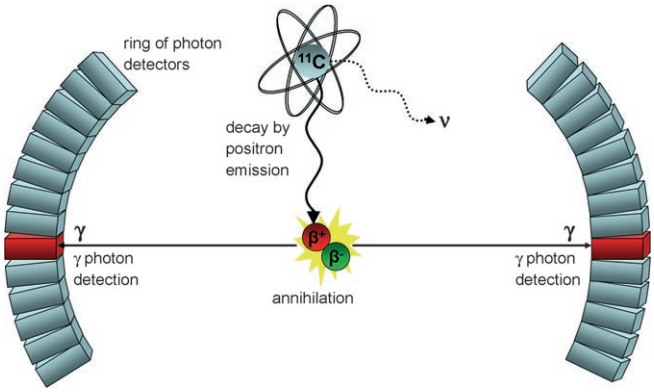

Figure 1. Schematic representation of the principle behind PET showing the positron decay and annihilation which produces two γ quanta of 511 keV.

$$^{11}C \longrightarrow {}^{11}B + \beta^+ + \nu$$

Scheme 1. Decay of an ^{11}C isotope by positron emission results in the formation of a ^{11}B atom, a positron (β^+), and a neutrino (ν).

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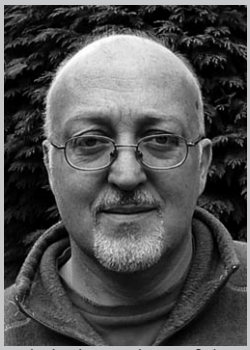

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around the subject, with each detector connected in a coincidence circuit with a detector located on the opposite side of the ring (Figure 2). Many millions of individual annihilation events are required to give enough data to construct a PET image. An important advance in scanner technology has been the integration of PET and CT into one device.[4,5] The combined PET/CT technique allows the matching of functional information on the PET scan to the detailed anatomical images from the CT scan.[6]

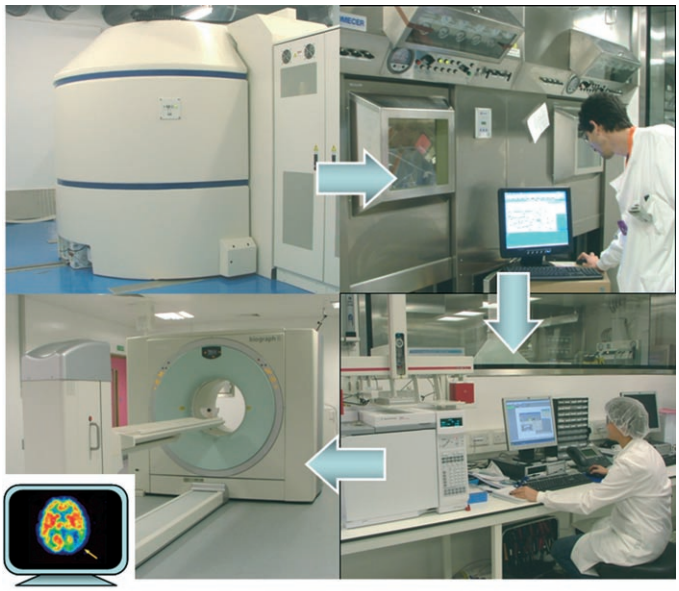


Figure 2. "Bench-to-bedside": the process of PET radiotracer production begins at a cyclotron and ends at the PET scanner; the whole process typically takes a few hours. From top left: a commerically available biomedical cyclotron; an automated radiolabeling system controlled from outside the hot cell; analysis and quality-control laboratory; a combined PET/CT scanner (Siemens); and a processed PET image (bottom left).

PET is a truly quantitative technique. Important information about physiological and biochemical events may be obtained by monitoring the distribution and concentration of the labeled probe in the body over time. PET has been widely used in oncology[7–9] for the diagnosis of tumors by looking at the accumulation and metabolism of certain PET probes within the tumor. In the field of cardiology,[10–12] PET has been developed as a clinical tool for myocardial perfusion imaging as a means of characterizing and diagnozing coronary heart disease. In neurology,[13–17] PET has been used for the characterization of early stage neurological disorders (such as Alzheimer's and Parkinson's disease), abnormal neurotransmitter activity, movement disorders, stroke, epilepsy, and neurooncology. It is expected that PET—as an in vivo pharmacological imaging tool—will play an increasingly important role in drug development.[18–21] It is anticipated that PET studies will improve the selection of potential drug candidates at an earlier stage of development, give a greater understanding of a drug's mechanism of action, and aid in guiding dose selection.

1.2. Synthesis with Short-Lived PET Isotopes

There is an array of challenges facing the radiochemist when attempting to label a compound with short-lived radioisotopes for PET.[22] Radioisotope production begins in a cyclotron[23,24]—a compact particle accelerator which is capable of producing proton or deuteron beams of the required energy range to generate ^{11}C, ^{13}N, ^{15}O, and ^{18}F species. The beam is directed onto a target system at the exit of the cyclotron which contains the target material suitable for the production of the required radioisotope (Table 1). Dealing with high-energy short-lived radioactive compounds safely and effectively is a priority; traditional bench-top synthetic chemistry is clearly not an option. State-of-the-art PET radiosynthesis laboratories use "hot cells", which are basically enclosed lead-lined versions of a fumehood with lead glass windows many inches thick, to carry out radiolabeling procedures. The basic radiolabeled product (or synthon) from the cyclotron target is transferred to the hot cell (usually under an inert gas stream) where it is converted by a series of chemical steps into the final radiolabeled product. Typically, computer-controlled robotic or automated systems are used for such labeling reactions to restrict, as much as possible, exposure of the user to radiation (see Figure 2).

As mentioned above, the three isotope-half-life rule-of-thumb imposes a rough guideline to the timeframe for the synthesis of a PET sample. The maximum time for the preparation of a ^{11}C compound, including synthesis and purification, should not exceed 60 minutes from the EOB (end of bombardment of the target material with a proton or deuteron beam in the cyclotron). A range of new technologies, including microwaves, microfluidics, ultrasound, and solid-phase extraction, have been adapted to enhance the speed, reproducibility, and efficiency of radiolabeling reactions and their purification. Additionally, "on-line" conversion (as opposed to batchwise synthesis) of radioactive species is commonly used. For example, the conversion of $[^{11}C]CO_2$ into $[^{11}C]CO$ can be achieved almost instantaneously by passage of $[^{11}C]CO_2$ in a stream of helium over a heated zinc or molybdenum catalyst.

The difficulties of working with short-lived PET radioisotopes are further exacerbated by the minuscule amounts of radioisotopes produced by the cyclotron (typically on the picomolar to nanomolar scale). Dealing with such tiny amounts of material, barely comprehensible to the traditional synthetic chemist, has led to increasingly specialized and miniaturized apparatus for reacting and manipulating radiolabeling reactions on such a small scale. Since PET labeling reactions are performed with low nanomolar amounts of radioisotopes, there is normally a vast stoichiometric excess of "cold" reagents which results in pseudo-first-order reaction kinetics with respect to the radioisotope concentration. Advantageously, reactions which may normally need hours or days to reach completion on a macroscopic scale can often be performed in minutes or seconds using PET radioisotopes. It is also worth noting that even minor impurities found in

pure solvents and reagents can become significant when performing such small-scale reactions.

Before a PET radiotracer can be administered to a patient, there is the further requirement to produce a compound that is of pharmaceutical quality. Care must be taken to ensure that the radiotracer is suitably and rapidly characterized, purified, formulated (typically as a saline solution), and sterilized. Producing such tiny amounts of radiolabeled compounds poses characterization problems; for example, usual characterization techniques, such as NMR spectroscopy, can not be applied. PET radiotracers are often characterized by using a combination of HPLC, thin-layer chromatography, and gas chromatography in conjunction with suitable radioactivity and mass detectors. Quality control procedures for radiotracers and radiopharmaceuticals[25,26] are similar to those applied to nonradioactive pharmaceuticals. There are two categories for quality control tests: physiochemical tests and biological tests. Physiochemical tests give the level of radioisotope and radiochemical impurities, chemical impurities,[27] pH value, ionic strength, osmolality, and physical state of the sample, while the biological tests determine the sterility, apyrogenicity, and toxicity of the sample.

The radiochemist has to further consider the radiochemical yield (RCY) of the radiosynthesis and the specific activity (SA) of the final radiolabeled compound. The RCY is a function of both the chemical yield and half-life of the radioisotope and is expressed as a fraction of the radioactivity originally present in the sample following a radiochemical separation; the value is often quoted as being either nondecay corrected or decay corrected. (Decay-corrected figures are mathematically adjusted measurements that take into account radioactive decay that has occurred between two different times to give a single value.) It is desirable, but not always essential, to have a high RCY as it is a useful gauge to measure the efficiency of the radiolabeling procedure. The specific activity is a measure of the radioactivity per unit mass of the labeled compound, commonly expressed as giga-Becquerel per micromol ($GBq\,\mu mol^{-1}$) or Curies per micromol ($Ci\,\mu mol^{-1}$). The theoretical maximum values of the specific activity are never reached for radiolabeled compounds because of unavoidable isotopic dilution by the naturally occurring stable isotope. This effect is particularly apparent when a "carrier" is added to assist with the physical or chemical transfer of the radionuclide through the labeling process. The carrier is often the stable isotope, as is the case for the production of $^{18}F[F_2]$ for electrophilic fluorinations. Specific activities can be much lower because of isotopic dilution resulting from the added carrier or from side reactions with the naturally occurring isotopes in the environment. Typical specific activities of PET-labeled products are in the order of 50–500 $GBq\,\mu mol^{-1}$ (ca. 1–15 $Ci\,\mu mol^{-1}$). Since a small amount of radioactivity can lead to a good quality PET image, only very low amounts (tracer dose) of compound need to be administered—typically in the low or sub-microgram level. This implies that the fate of labeled molecules can be studied in vivo without perturbing the biological system being measured and that very potent or toxic compounds can be studied in human at subpharmacological or subtoxicological doses.

1.3. Choice of PET Radionuclide

The half-life of the radionuclide used for labeling the radiotracer should be commensurate with the timescale of the biological process to be studied. A process with a short biological half-life, for example, blood flow, can be quite adequately studied with the two-minute half-life of the ^{15}O nuclide. In fact ^{15}O-labeled water is commonly used to study cerebral blood flow in PET studies. An ^{18}F- or possibly ^{11}C-labeled tracer would be more appropriate for the study of protein synthesis or amino acid utilization, since an ^{15}O radiolabel would have mostly decayed by the time the labeled molecule had reached the biological target.

1.4. Metabolism

1.4.1. Position of the Label

An understanding of the metabolic fate of a radiotracer can be crucial to its successful design and an important factor in determining the best position for labeling the tracer molecule. There is often a choice of positions within the molecule for radioisotope labeling, and metabolic information can be useful in determining the best labeling position. If the labeled compound is broken down in the body, undesired labeled metabolites may arise that can result in an unwanted background signal in the organ under study during the PET scan (effectively decreasing the signal to noise ratio). Alternatively, and possibly more worrying, undesired labeled metabolites may have active pharmacology that confound the useful signal at the biological target under study. The blood–brain barrier (BBB) in the central nervous system is poorly permeable to compounds that are hydrophilic (assuming that these hydrophilic compounds are not subject to an active or facilitated transport system). Often, PET radiotracers for studying brain biochemistry are labeled at a metabolically labile position in the molecule (for example, an *N*-[^{11}C]methyl group) to produce hydrophilic radiolabeled metabolites in the peripheral organs which are not able to cross over the BBB, thus leaving an intact parent radiolabeled tracer signal within the brain tissue.

1.4.2. Metabolic Trapping

In some cases, knowledge of the metabolic route of a labeled compound may be useful in simplifying the interpretation of the PET data obtained. An example of this is the metabolism of the glucose derivative [^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG). This compound behaves in a similar manner to glucose in vivo: it is transported from plasma to tissue by the glucose transporter and then phosphorylated in tissue by the hexokinase enzyme to give [^{18}F]FDG-6-phosphate. Further metabolism of [^{18}F]FDG-6-phosphate is inhibited because the 2-O atom in glucose has been replaced by an ^{18}F atom, thus preventing it from acting as a substrate for the subsequent degradative enzymatic pathway. This results in accumulation of [^{18}F]FDG-6-phosphate in cells, which reflects blood–tissue transport and hexokinase activity, and thus provides regional imaging of energy metabolism. Labeling

an exact copy of the glucose molecule (with, for example, ^{11}C or ^{15}O) would result in its progression through the Krebs cycle to produce many different radiolabeled metabolites that would be difficult to differentiate in the PET scan.

1.5. Stereochemistry

The use of enantiomerically pure labeled compounds is usually required for PET studies. In many cases preexisting chirality can be built onto a target molecule prior to the labeling step; however, a number of syntheses have been developed (for example, of amino acids) where asymmetric induction has been achieved using chiral handles, stereoselective enzymes, or chiral resolution. In some cases a biological question can be answered elegantly by the successive study of labeled enantiomers in the same subject. For example, the specific binding of rolipram to the enzyme phosphodiesterase-4 in the central nervous system (CNS) is almost exclusively observed using the [^{11}C]*R*(−)rolipram enantiomer, whereas the [^{11}C]*S*(+)rolipram enantiomer exhibits homogeneous binding in the brain. Since there is no discrete region in the brain which is devoid of phosphodiesterase-4, the [^{11}C]*S*(+)rolipram enantiomer can be used to estimate the free and nonspecifically bound component of its biologically active antipode.[28]

1.6. Nonspecific Binding

Nonspecific binding is the binding of a labeled compound to a nonsaturable component in tissue, and is thought to relate to the propensity of a molecule to interact nonspecifically with membrane structures. In practical terms, a high background nonspecific binding signal can result in the reduction of the PET signal contrast when probing a specific receptor or enzyme with a labeled probe. The failure of a PET radiotracer to target a particular receptor or enzyme is most commonly associated with the labeled molecule having a high nonspecific binding signal in vivo. A highly lipophilic molecule might be expected to interact extensively with the fatty acid residues in membrane bilayers in preference to the molecular target of interest. In terms of the selection and design of a suitable radiotracer, a rule of thumb is used which suggests that PET radiotracers should have a lipophilicity (typically measured as the logarithum of the octanol/water partition coefficient, log*P*)) of less than 3. For brain radiotracers, a certain degree of lipophilicity may be required to enable the labeled molecule to cross the blood–brain barrier. In this case it is generally thought that a log*P* value between 1.5 and 3 is optimal. In silico estimates of log*P* values (often termed clog*P*) can be useful as a guide; however, these values should be treated with caution as they can often be inaccurate. As the log*P* value does not take into account the effect of charge at the physiological pH value, the partitioning is often measured at pH 7.4 and termed the log*D* value. This value is the preferred gold standard measure of lipophilicity for the screening of radiotracer candidates.

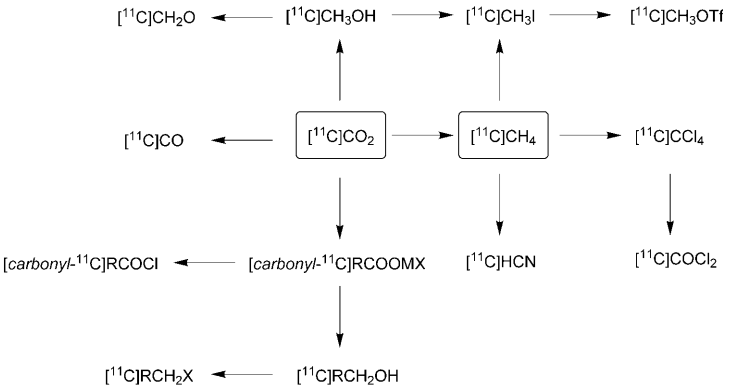
Many useful radiotracers have a log*P* value of less than 3; however, there are also many exceptions to this rule of thumb. A recent study has shown that ab initio estimates of the interaction energy between a single candidate molecule and a single phospholipid molecule is a better predictor of nonspecific binding in vivo than the measured log*P* value.[29] This finding underlines the view that our understanding of the nonspecific binding process on a molecular and biological level is at best primitive. Recent work in this area has suggested that the phenomenon of nonspecific binding may be related to the ability of a molecule to hydrolyze the phospholipid membrane bilayer.[30]

Another factor that affects the magnitude of nonspecific binding is the affinity of the radiolabeled molecule for the molecular target of interest. Typically, useful radiotracers have low- or sub-nanomolar affinity. In principle, the higher the affinity of a probe for its intended molecular target, the higher the signal-to-noise ratio of the PET tracer. To find the optimal affinity of a probe, the density of the molecular target should be taken into consideration, in addition to the degree of reversibility of its binding. The latter is an important consideration for the quantitation of a PET tracer binding signal in vivo.

2. Radiolabeling with Carbon-11

The ubiquitous presence of carbon in natural products and drug compounds makes carbon-11 an attractive and important positron-emitting isotope for labeling molecules of biological interest. Advantageously, ^{11}C-labeled molecules will behave the same, chemically and biologically, as their unlabeled equivalents. This is particularly important since it removes any doubts about the effect of introducing an "artificial" PET tag (such as introducing an ^{18}F atom; see Section 3) may have on the biological properties of the compound of interest. Although the half-life of carbon-11 is only 20.4 minutes and multistep syntheses are not generally used for the synthesis of ^{11}C-containing molecules, a diverse array of reactions has been applied and developed for the introduction of ^{11}C into target molecules. One restriction in the synthesis of ^{11}C-labeled compounds for PET is the limited range of ^{11}C-labeled precursors. A small number of simple ^{11}C precursors are available that can be used directly in synthesis or converted into more reactive secondary precursors prior to the final radiolabeling step.

Cyclotron-generated carbon-11 is mainly produced by the proton bombardment of nitrogen-14, which emits an α particle to give ^{11}C ($^{14}N(p,\alpha)^{11}C$). The two major ^{11}C precursors used in synthesis are $^{11}CO_2$ and $^{11}CH_4$, which are formed, respectively, when either small amounts of oxygen or hydrogen are present in the target. Almost all ^{11}C-labeled compounds for PET are made from these two major synthons (Scheme 2). The challenges for the synthesis of ^{11}C labels are in the development of rapid, reliable, and versatile labeling techniques to incorporate the ^{11}C isotope into the molecular target using the available ^{11}C precursors. Besides the development of new chemical syntheses for PET, the development of technology has had, and will have, an equally important role.



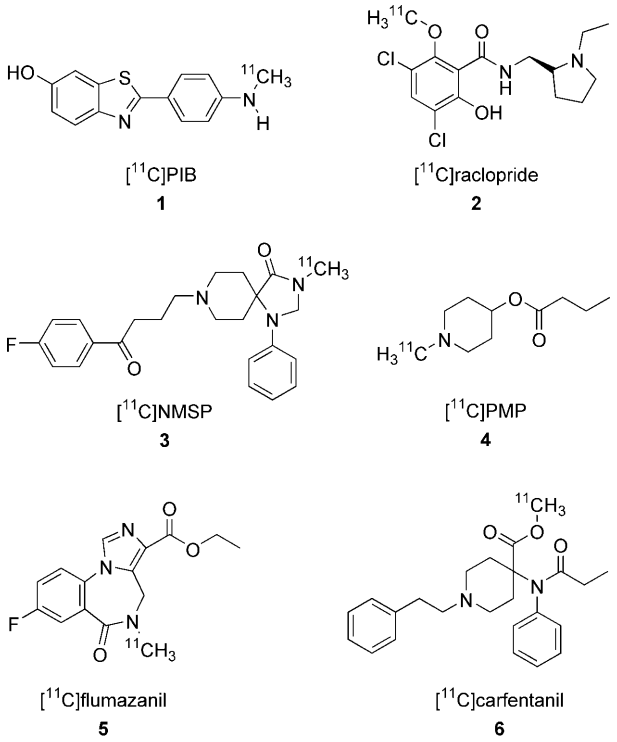
Scheme 2. The most important ^{11}C precursors used in the synthesis of ^{11}C-labeled compounds produced from either $[^{11}C]CO_2$ or $[^{11}C]CH_4$.

The use of synthesis modules (for example, GE Tracerlab),[31,32] microwave reactors,[33,34] microfluidic reactors,[35] high-pressure reactors,[36,37] supercritical fluids,[38] solid-phase synthesis,[39] and automated "loop" synthesis[40,41] combined with HPLC purification have enhanced the speed, efficiency, reliability, and safety of radiosyntheses.

2.1. ^{11}C-Methylation Reactions

^{11}C Methylation leads to the incorporation of a $[^{11}C]CH_3$ methyl group into a target compound; it is by far the most frequently used method for the introduction of ^{11}C into organic molecules. $[^{11}C]$Methyl iodide, the most widespread methylating agent, can be prepared by a wet method by reducing $[^{11}C]CO_2$ using $LiAlH_4$ followed by reaction with hydroiodic acid[42] or by the gas–solid iodination reaction of $[^{11}C]CH_4$ at high temperature.[43,44] The alternative methylating agent $[^{11}C]$methyl triflate ($[^{11}C]CH_3OTf$) has become more important and more widely used in recent years because of its greater reactivity and volatility;[45] these properties make it ideally suited to rapid methylation reactions.[46–50] $[^{11}C]$Methyl triflate is prepared by passing gaseous $[^{11}C]$methyl iodide through a column of silver triflate at 200 °C.[51] The ^{11}C-alkyating agents $[^{11}C]$ethyl iodide, $[^{11}C]$propyl iodide, $[^{11}C]$butyl iodide, and $[^{11}C]$benzyl iodide have also been developed for labeling procedures.[52,53]

The introduction of the $[^{11}C]CH_3$ group into a target molecule is generally carried out by so-called N-, O-, and S-methylation reactions. These are nucleophilic substitution reactions of methyl iodide with a precursor amine, alcohol, or thiol group to form the labeled primary or secondary amine, ether, or thioether. The simplicity and speed of this reaction has made it the primary method for the production of ^{11}C-labeled compounds. The synthetic methods used to carry out methylation reactions are relatively straightforward and usually involve simply trapping $[^{11}C]CH_3I$ in a solution of the target precursor and heating for a short time (typically < 5 min). Many ^{11}C-methylation procedures are reported in the literature[54] and the method is used for the production of the key ^{11}C tracers (Scheme 3): Pittsburg Compound B ($[^{11}C]$PIB, **1**) for imaging amyloid plagues in Alzheimer's



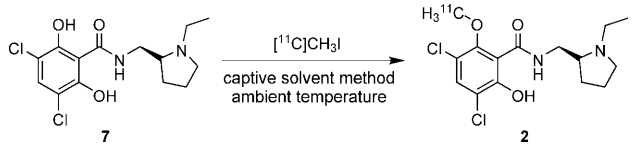
Scheme 3. A selection of key ^{11}C tracers prepared by ^{11}C-methylation reactions of N or O atoms.

disease,[17,50,55,56] raclopride (**2**)[57,58] and $[^{11}C]$*N*-methylspiperone[59] ($[^{11}C]$NMSP, **3**) for imaging of the dopamine receptor,[60] $[^{11}C]$*N*-methylpiperidin-4-yl propinoate ($[^{11}C]$PMP, **4**) for mapping acetylcholinesterase activity in patients with Alzheimer's disease,[61] $[^{11}C]$flumazanil (**5**) for imaging benzodiazepine receptors,[62] and the opioid receptor ligand $[^{11}C]$carfentanil (**6**).[21,63,64] In recent years the use of transition-metal-mediated methylation reactions has become more widespread for ^{11}C radiolabeling, especially notable is the use of palladium catalysts for the formation of a C–^{11}C bond by adapted Stille and Suzuki coupling reactions. The following section will focus on recent methods used to prepare $[^{11}C]CH_3$-labeled compounds.

2.1.1. Nucleophilic ^{11}C-Methylation Reactions

Reproducibility and versatility are two requirements for successful radiolabeling protocols. The development of so-called "captive solvent" methods, where the radioactive synthon (for example, $[^{11}C]CH_3I$) is trapped in a solution of the target precursor epitomises this. Automated continuous flow reaction and purification systems using narrow-bore stainless-steel or plastic/polymer loops as reaction chambers have found increased use in simple ^{11}C-methylation reactions because of their ease of use and versatility. These so-called "loop" methods involve coating the inside surface of the loop with micromolar amounts of reagent precursor in a suitable solvent and then passing a gaseous stream of $[^{11}C]CH_3I$ or $[^{11}C]CH_3OTf$ through the loop. These methods have been used to label a variety of biological compounds, including

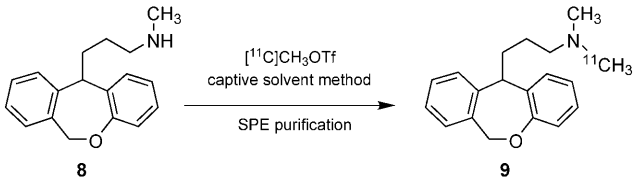
[^{11}C]raclopride (**2**)[40] (Scheme 4), with [^{11}C]methyl groups in good radiochemical yields, purities, and in short reaction times that were either equal to or better than conventional methods. The efficiency of such simple methods is surprising



Scheme 4. O-Selective ^{11}C methylation of **7** to form [^{11}C]raclopride (**2**), which is used to image dopamine D2/D3 receptors.

considering the relatively low surface areas of the reaction loops and the fact that they can be carried out without cooling (to aid the trapping of [^{11}C]CH_3I) or heating. Such loop systems minimize the use of solvent and precursor material (in many cases this can be expensive) which may contribute to the increased efficinecy of the reactions. In addition, minimal losses of labeled product occur as a result of transfers when the system is integrated with HPLC apparatus for purification.

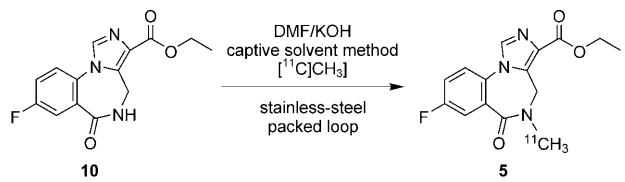
Combined automated loop and solid-phase extraction (SPE) methods have been reported for the synthesis of [^{11}C]doxepin (**9**, Scheme 5) by exploiting the more reactive [^{11}C]methyl triflate.[65,66] The gaseous [^{11}C]CH_3OTf was passed



Scheme 5. N-Selective ^{11}C methylation of nordoxepin (**8**) to form [^{11}C]doxepin (**9**), a histamine H1 receptor antagonist and antidepressant.

through a teflon loop that had been internally coated with a film of the precursor solution. Products were then flushed from the loop onto a SPE column, concentrated, and injected onto a semipreparative HPLC column. This method allowed the production of [^{11}C]doxepin (**9**) in 40% RCY and with high radiochemical purity (99%) within 40 minutes from EOB. ^{11}C-Methylation loop reactions have more recently been applied to the synthesis of [^{11}C]carfentanil,[67,68] [^{11}C]-L-[methyl]methionine,[69] [^{11}C]gefitinib,[70] and, by using a column microreactor, to the labeling of [^{11}C]flumazanil (**5**, Scheme 6).[71]

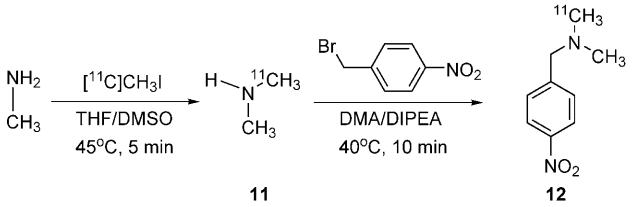
[^{11}C]Dimethylamine (**11**)[72] provides an attractive alternative method for the preparation of [^{11}C]methyl compounds with dimethylamine functional groups that avoids the direct use of [^{11}C]methyl iodide. The dimethylamine group is found in a number of drug molecules (for example, [^{11}C]doxepin (**9**)). Although direct labeling may be achieved using [^{11}C]methyl iodide and the monomethylamine, an indirect method using [^{11}C]dimethylamine and bromide precursors



Scheme 6. N-Selective ^{11}C methylation of **10** to form [^{11}C]flumazanil (**5**), a benzodiazepine antagonist that prevents the enhancement of GABA activity.

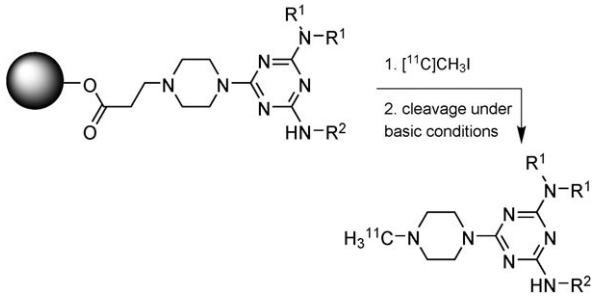
(Scheme 7) provides certain advantages over precursor behavior and product purification.

Solid-supported methods of synthesis have been used in the synthesis of ^{11}C-labeled compounds either as a means of



Scheme 7. Radiosynthesis of [^{11}C]dimethylamine (**11**) and reaction with bromomethyl-4-nitrobenzene to form [^{11}C]dimethyl-4-nitrobenzylamine (**12**).

rapid purification by SPE[73] methods or more interestingly using polymer supports to carry out reactions. Polymer-supported ^{11}C-methylation reactions using the so-called "safety-catch" linker method have been found to give high purity ^{11}C compounds without the need for HPLC purification.[74] Moreover, this method is based on standard combinatorial synthesis methods and could potentially be used for the rapid preparation of a vast number of ^{11}C-labeled compounds for screening. The development of such a library of compounds, ready for use in PET applications, could allow the selection and optimization of tracer molecules. Traditionally, however, excess reagents are usually required with combinatorial methods to drive the reaction. Such conditions are not possible with the preparation of PET markers, since only nanomolar amounts of the isotope are produced. In this method, a precursor molecule is attached to a solid support through the "safety-catch" linker and then treated with a radiolabeling reagent ([^{11}C]CH_3I), which then results in the release of the labeled target compound (Scheme 8). A vast excess of the polymer-linked precursor relative to the [^{11}C]CH_3I ensures that the reaction goes to completion. The unlabeled precursor remains attached to the resin and thus simplifies purification; only the labeled compound can be eluted from the polymer. REM and Kenner linkers were evaluated in the study, initially using nonradioactive CH_3I. Both resins were found to be almost completely alkylated within 15 minutes, with rapid cleavage of the alkylated product achieved within 1 minute, thus making the method suitable for the synthesis of PET markers. The use of substoichiometric amounts of CH_3I was tested to mimic the

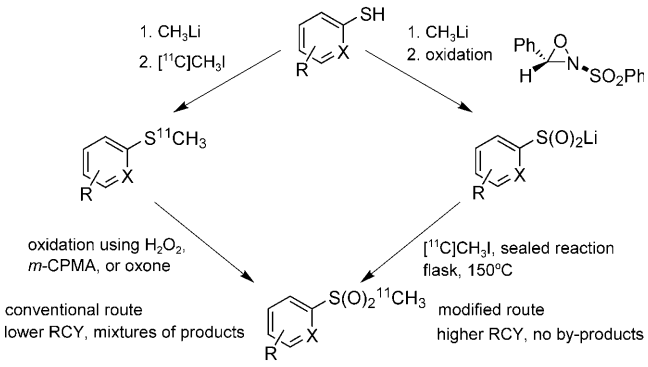


Scheme 8. ^{11}C Methylation of the resin-attached precursor molecule followed by release of the labeled molecule under basic conditions.

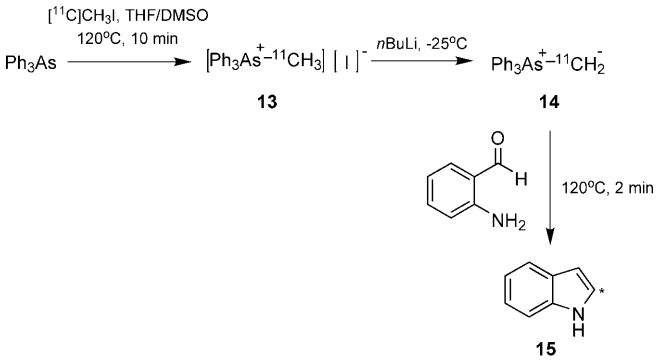
conditions of a PET reaction, and found to give lower but acceptable yields (30–50%). The system was applied to the synthesis of a small PET library of compounds and was focused on a triazine molecule. Decay-corrected RCYs were low (5–10%; 2–5% when the resin was recycled), but sufficient for microPET studies in vivo on small animals. One significant advantage of this method was the high level of RCP (95%) without the use HPLC purification. The selected triazine molecule has the possibility to be varied extensively to generate many hundreds of possible labeled PET molecules in a combinatorial fashion.

An improved radiosynthesis of [^{11}C]sulfones by S alkylation of lithiated sulfones has recently been reported.[75] This method uses the mild oxidation agent *N*-sulfonylaziridine to oxidize the lithium thiolate prior to the ^{11}C-alkylation step, thus allowing the introduction of the [^{11}C]alkyl radiolabel at a later stage in the synthesis compared to other reported procedures (Scheme 9). Although good RCYs (55–67%) were obtained for a range of simple aryl and heteroaryl sulfone molecules, this method has yet to be applied to biologically relevant sulfone molecules.

^{11}C-Labeled indole rings have been prepared using [^{11}C]methyl-labeled triphenyl arsonium ylides through their rapid reaction with 2-aminobenzoyl compounds (Scheme 10).[76] This method is similar to the application of [^{11}C]phosphonium ylides for the synthesis [^{11}C]alkenes.[77] [^{11}C]Methyltriphenylarsonium iodide was prepared by the reaction of $^{11}CH_3I$ with triphenylarsine. The highly reactive



Scheme 9. Synthesis of [^{11}C]alkyl-labeled sulfones by conventional S-selective ^{11}C alkylation and the improved lithium thiolate S-selective ^{11}C-alkylation method. X = N or C; R = H, 4-F, or 2-CO_2CH_3.



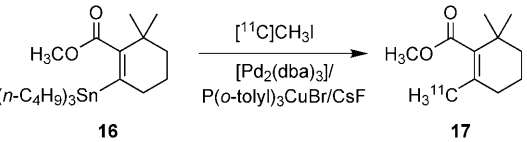
Scheme 10. The synthesis of [2-^{11}C]indole (**15**) via [^{11}C]methyltriphenyl arsonium ylide (**14**). * indicates the labeling position.

ylide, [^{11}C]triphenylarsoniummethylide (**14**), was then generated following the reaction of [^{11}C]methyltriphenylarsonium iodide (**13**) with *n*-butyllithium. The reaction of **14** with 2-aminobenzaldehyde gave the corresponding [2-^{11}C]indole (**15**) in 27% decay-corrected RCY.

2.1.2. *Palladium-Mediated ^{11}C Methylation*

Palladium-catalyzed reactions for C–C bond formation are currently finding wider application in the synthesis of ^{11}C compounds for PET. This is, in part, due to the vast developments in traditional synthetic chemistry where palladium catalysts are used for the formation of C–C, C–O, and C–N bonds. The term "palladium-mediated reaction" is preferred over the term "palladium-catalyzed reaction" for radiosynthesis because of the vast stoichiometric excess of the palladium complex compared to the ^{11}C precursor.

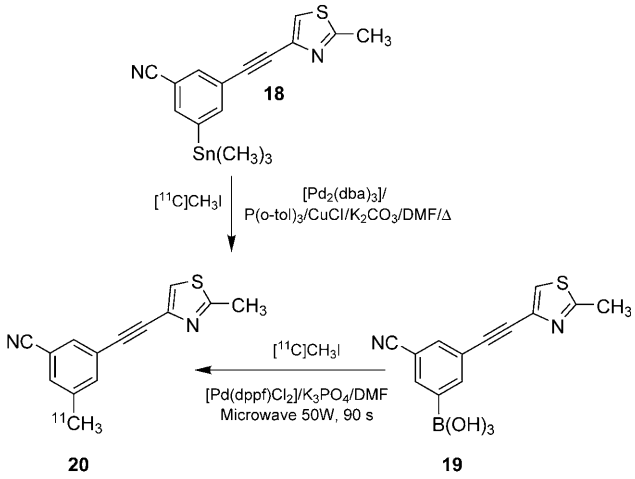
Palladium(0)-mediated Stille-type coupling reactions have been the most widely studied of the palladium coupling reactions for the introduction of [^{11}C]methyl groups into organic molecules. Some of the benefits of using stannanes include good functional group tolerances and low polarity, which can facilitate rapid chromatographic separation of the labeled product from the vast excess of the stannane starting material. One caveat of using stannanes in these coupling reactions is their inherent toxicity, which may pose problems for the production of labeled compounds for in vivo use. A recent study[78] has reported the rapid palladium-mediated methylation of a series of alkenyltributylstannanes to give methylated alkenes and the further application of this method to the synthesis of $^{11}CH_3$-labeled analogues of 1-methylalkene (**17**; Scheme 11). Under optimized reaction conditions (solvent, base, Pd precursor, phosphine ligand) reactions could be carried out in 5 minutes at 60 °C, thus making the reaction



Scheme 11. Stille cross-coupling reaction for the formation of ^{11}C-labeled alkenes using [^{11}C]CH_3I.

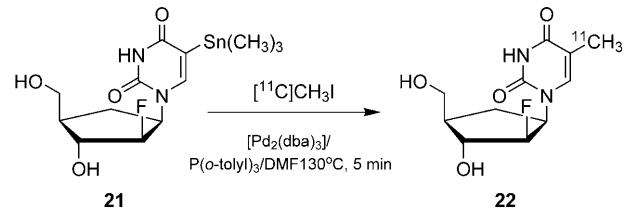
suitable for the synthesis of PET markers. The order in which reagents are added together was found to be important to give reproducible yields. Methyl iodide should first be added to the palladium complex, followed by the stannane precursor and base.

The [^{11}C]diaryl alkyne M-MTEB ([^{11}C]3-methyl-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]benzonitrile, **20**) radioligand, which is used for imaging metabotropic glutamate receptors (mGluR5), has been synthesized by palladium-mediated Suzuki and Stille cross-coupling reactions[79] (Scheme 12). The Suzuki method, in which microwave radiation is used, was found to give superior RCYs in shorter reaction times than the Stille method.



Scheme 12. Radiosynthesis of [^{11}C]M-MTEB (**20**) by Suzuki or Stille reactions.

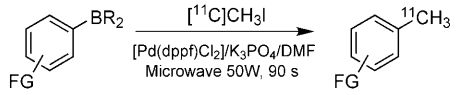
The palladium source and phosphine ligand used in [^{11}C]CH$_3$I Stille cross-coupling reactions has been shown to have a marked effect on the RCYs of the obtained products. A recent study showed that the bulky phosphine ligand P(*o*-tolyl)$_3$ and the palladium(0) complex [Pd$_2$(dba)$_3$] proved the best combination for the formation of 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)[methyl-^{11}C]thymine ([^{11}C]FMAU, **22**)[80] by a Stille coupling reaction (Scheme 13). Other phosphine ligands such as PPh$_3$, dppp, AsPh$_3$, and TFP gave no labeled product over a reaction time of 5 minutes. P(*o*-tolyl)$_3$ is thought to be most effective ligand because of its large cone angle, which enhances the transmetalation step of the cycle by relieving steric strain. The use of the preformed catalyst [Pd(P(*o*-tolyl)$_3$)$_2$] resulted in slightly lower RCYs. The



Scheme 13. Synthesis of [^{11}C]FMAU (**22**) by palladium-mediated [^{11}C]CH$_3$I Stille cross-coupling reactions.

reaction was also dependent on the solvent, with DMF proving best by acting as both a trapping and reaction medium for [^{11}C]CH$_3$I.

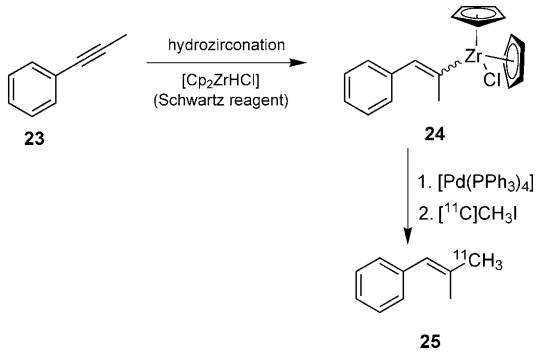
The palladium-mediated Stille reaction of [^{11}C]CH$_3$I has been exploited for the synthesis of other biological molecules, such as [^{11}C]prostaglandins[81,82] and the selective serotonin transporter (5-HTT) radioligand *N*,*N*-dimethyl-2-(2-amino-[^{11}C]4-methylphenylthio)benzylamine ([^{11}C]MADAM).[83] The desire for alternative synthetic methods for ^{11}C–C coupling other than the Stille reaction, because of the formation of toxic tin by-products and purification difficulties, has led to the development of palladium-mediated Suzuki coupling reactions to give [^{11}C]CH$_3$–C compounds. Suzuki coupling of [^{11}C]CH$_3$I to aryl boronic acids or esters is an arguably better alternative to the Stille reaction. Test reactions using a range of simple aryl halides with different functional groups have been carried out[84] with good RCYs (49–92%) by using [Pd(dppf)Cl$_2$] as the catalyst (in several minutes reaction time, 100°C, microwave irradiation; Scheme 14). Again, the order of reagent addition for these



Scheme 14. Palladium-mediated Suzuki coupling of [^{11}C]CH$_3$I with aryl boronic acids or esters. FG = aldehyde, halide, nitro, ester, alcohol, carboxylic acid, or amide.

coupling reactions was found to be crucial in obtaining consistent and high RCYs. [^{11}C]CH$_3$I must be added first to the palladium catalyst (to form the oxidative addition product), followed by the aryl boronic species and base; similar observations were also made for the palladium-mediated Sonogashira coupling reaction of terminal alkynes with [^{11}C]CH$_3$I.[85]

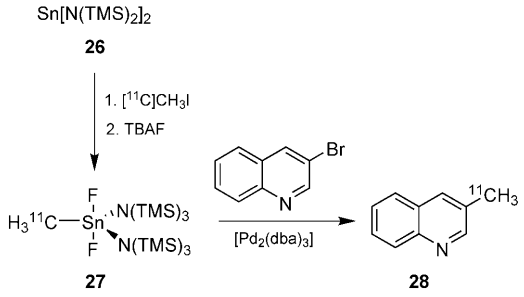
Palladium-mediated ^{11}C–C coupling reactions of alkenylzirconocenes with [^{11}C]CH$_3$I have been reported recently.[86] Alkynes were first converted into alkenylzirconocenes and then treated with [Pd(PPh$_3$)$_4$] in a transmetalation step. The resulting complex was then treated with [^{11}C]CH$_3$I to form the ^{11}C-labeled product. This reaction is particularly useful for the generation of the 3,3-dimethylallyl group (Scheme 15), which



Scheme 15. The synthesis of [^{11}C]2-methylpropenylbenzene (**25**) from prop-1-ynyl-benzene (**23**) by reaction with an alkenylzirconocene (**24**), [Pd(PPh$_3$)$_4$], and [^{11}C]CH$_3$I.

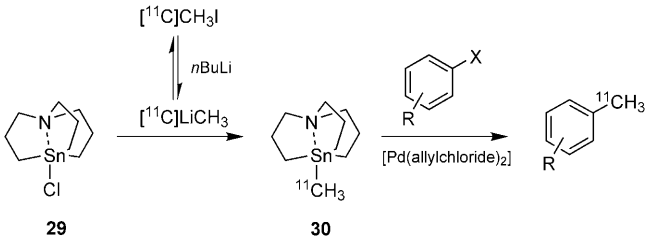
is an important building block in many natural products. The synthesis of [^{11}C]2-methylpropenylbenzene (**25**) was investigated as a model reaction. The ^{11}C-labeling step was carried out in 6 minutes at 60 °C and gave **25** in 70 % RCY. A range of different methyl-substituted alkynes were tested to investigate the scope of this coupling reaction. Moderate to good RCYs (50–75 %) were obtained for phenyl ether, *tert*-butyl, *n*-propyl, silyl ether, and alcohol alkyne starting materials. Readily reducible groups such as esters and nitro groups were found to be incompatible with the Schwartz reagent for the hydrozirconation step. This type of reaction has been under exploited, but may find wider application with regards to labeling with [^{11}C]CH_3I or [^{11}C]CO.[87]

The preparation of organostannane precursors for the synthesis of target molecules is not always straightforward. The use of a generic tin-based methyl transfer reagent avoids the difficulties of preparing individual bespoke organostannane precursors by allowing a general route for the introduction of methyl groups into more readily available aryl and vinyl halides. Fluoride-activated monoorganotin reagents have been demonstrated to be very reactive in the Stille coupling reaction and allow the transfer of vinyl, allyl aryl, and benzyl groups onto aryl and vinyl halides, thus avoiding the preparation of stannane precursors. The [^{11}C]methyl transfer reagent [^{11}C]monomethylstannate ([^{11}C]CH_3SnF_2[N(TMS)$_2$]$_2$, **27**), has recently been demonstrated to couple its [^{11}C]CH_3 group to a series of aryl iodides and bromides in the presence of a palladium catalyst (Scheme 16).[88] The conversion of [^{11}C]CH_3I into the [^{11}C]methyl tin reagent was achieved in quantitative yields and then coupled with an aryl halide under ligand-free palladium-catalyzed conditions at the optimized conditions of 120 °C for 5 minutes in dioxane. This reaction was applied to the ^{11}C methylation of a series of bromoquinolines and gave good radiochemical yields ranging from 41 to 78 % depending on the substrate used.



Scheme 16. Synthesis of the methyl transfer reagent **27** and reaction with 3-bromoquinoline to give [^{11}C]3-methylquinoline (**28**).

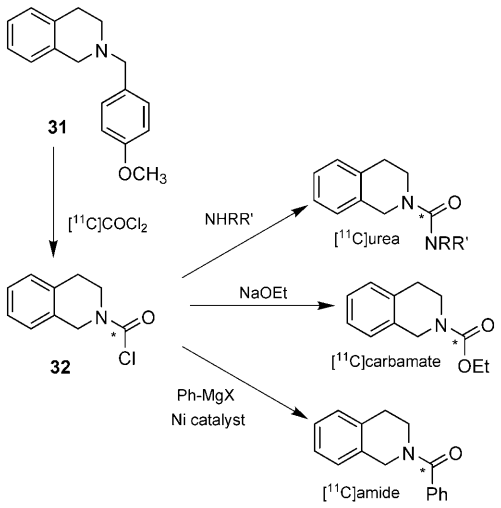
Other tin-based methyl-transfer reagents include 5-[^{11}C]methyl-1-aza-5-stanna-bicyclo[3.3.3]undecane (**30**),[89] which has been used to couple [^{11}C]CH_3 to a range of aryl and vinyl halides (Scheme 17). The preparation of this methyl-transfer reagent requires the generation of [^{11}C]$LiCH_3$ from [^{11}C]CH_3I and *n*-butyllithium followed by reaction with 5-chloro-1-aza-5-stanna-bicyclo[3.3.3]undecane (**29**). Coupling reactions of aryl and vinyl halides were found to give the highest RCYs within 2 minutes when carried out in the presence of a palladium–allyl catalyst at temperatures above 100 °C. However, the RCYs varied widely and were highly dependent on the aryl halide substrate. One drawback of this system is the difficulty associated with the preparation of [^{11}C]$LiCH_3$, which may be responsible for inconsistent RCYs.



Scheme 17. Preparation of the [^{11}C]methyl transfer reagent **30** and Stille cross-coupling reaction with aryl or vinyl halides.

2.2. [^{11}C]Phosgene Reactions

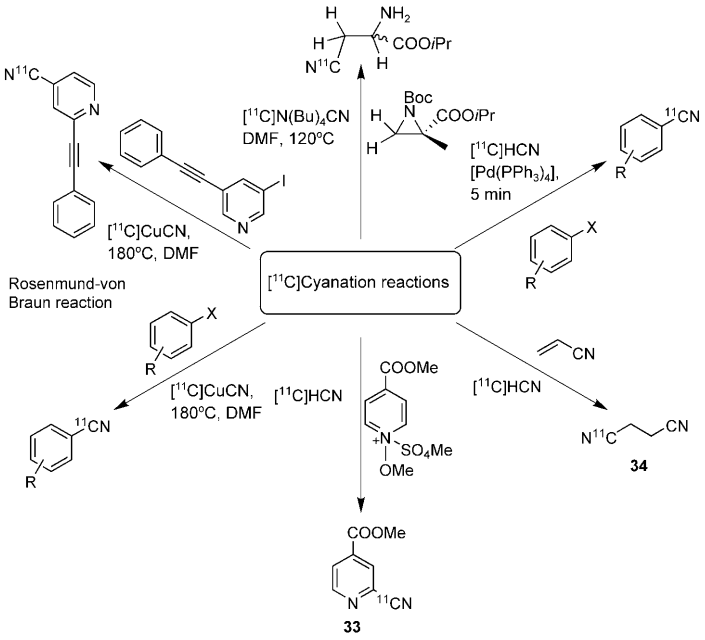
Phosgene ($COCl_2$) is a highly reactive molecule which potentially makes it an ideal synthon for use in the ^{11}C labeling of compounds for PET studies. Although the synthesis of [^{11}C]phosgene[90,91] has been well developed, there are still technical difficulties with regards to its reliable and reproducible production which have prevented its widespread use in the field. [^{11}C]Phosgene has been used for the synthesis of a range of symmetrical and unsymmetrical ^{11}C-labeled urea derivatives.[92–94] The synthesis of [^{11}C]carbamoyl chlorides (Scheme 18) has also been achieved[95] by the [^{11}C]phosgene-promoted debenzylation of tertiary amines. The reaction of the *N*-4-methoxybenzylamine tetrahydroisoquinoline (**31**) with [^{11}C]phosgene was optimized to give a decay-corrected RCY of 74 % for the [^{11}C]carbamoyl chloride (**32**) after a reaction time of 16 minutes. The [^{11}C]carbamoyl chloride could then be transformed into ^{11}C-labeled urea, carbamate, or amide derivatives (Scheme 18).



Scheme 18. Synthesis of [^{11}C]isoquinoline ureas, carbamates, and amides from [^{11}C]isoquinoline carbamoyl chloride (**32**), prepared from [^{11}C]phosgene.

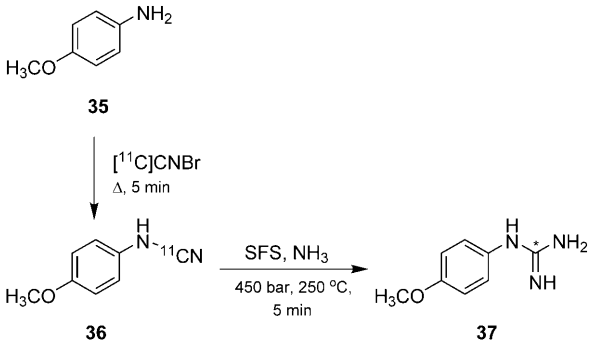
2.3. ^{11}C-Cyanation Reactions

The nitrile group is found in a number of important drug molecules and biologically interesting compounds, which makes it a natural target for ^{11}C-labeling reactions. [^{11}C]HCN is the starting material for ^{11}C-cyanation reactions and is usually prepared by the reduction of [^{11}C]CO_2 to [^{11}C]CH_4, using H_2 over nickel, and then converted into [^{11}C]HCN by reaction with NH_3 over platinum.[96] [^{11}C]HCN can be used directly, for example, in the formation of [^{11}C-*cyano*]methyl-2-cyanoisonicotinate (**33**) and [^{11}C-*cyano*]1-succinonitrile (**34**)[97] as well as for the ring-opening of N-activated aziridine-2-carboxylates for the synthesis of the amino acids[98] (Scheme 19). [^{11}C]HCN may also be used to introduce the [^{11}C]CN group into a target through palladium-mediated cyanation reactions[99,100] (Scheme 19). Additionally, [^{11}C]HCN may be converted into [^{11}C]CuCN[101] and reacted with aryl halides through the Rosenmund–von Braun reaction[101–103] (Scheme 19). Palladium-mediated reactions may become a more favored [^{11}C]cyanation route because of the increased number of palladium-catalyzed cyanations in the mainstream literature.[104]



Scheme 19. Summary of ^{11}C-cyanation reactions.

Once the [^{11}C]cyano group has been introduced into the target molecule there is potential to convert it into a wide range of other functional groups, such as carboxylic acids, amides,[100] tetrazoles,[101] and amidines.[103] [^{11}C]Cyanogen bromide has been used for the synthesis of ^{11}C-labeled guanidines[38] in supercritical ammonia. Amines were first converted into cyanamides, by reaction with [^{11}C]CNBr, then injected into the supercritical fluid synthesis system, and converted into the corresponding guainidines at high pressures and temperatures (Scheme 20). The radiochemical yields for [^{11}C]cyanamide formation were higher for aliphatic amines (70–98%) than for aromatic amines; the latter required activation with electron-donating groups to obtain high RCYs. However, overall aromatic amines afforded labeled guanidines with higher RCYs than did aliphatic amines.



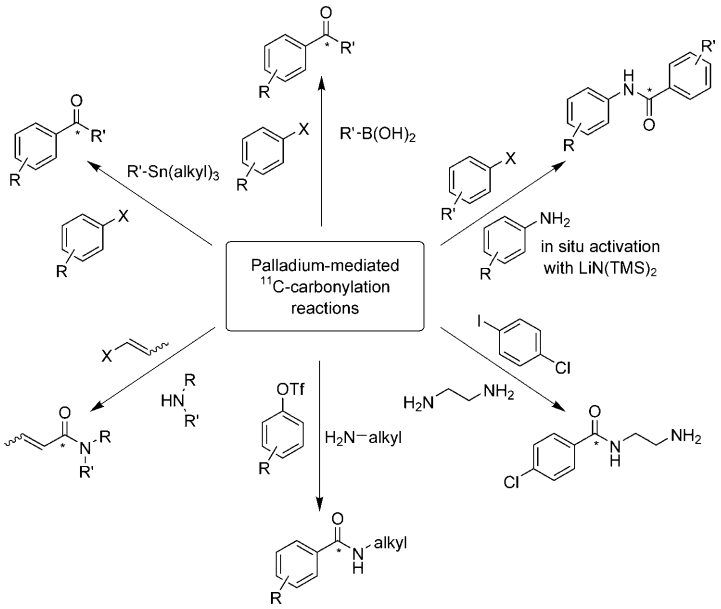
Scheme 20. Conversion of 4-methoxyaniline (**35**) into [^{11}C-*cyano*]4-methoxyphenylcyanamide (**36**) using [^{11}C]CNBr, and reaction of the [^{11}C]cyanamide under supercritical ammonia to produce the corresponding [^{11}C]guanidine (**37**) in 83% RCY under optimized conditions.

2.4. ^{11}C-Carbonylation Reactions

The drive to label target molecules with [^{11}C]CO[105] has come about for two reasons: 1) The wide variety of carbonyl-containing biologically interesting molecules that have the potential to be synthesized through carbonylation reactions; and 2) the readily available route to the [^{11}C]CO unit through the reduction of [^{11}C]CO_2 over zinc[106] or molybdenum.[107] The most widely applied ^{11}C-carbonylation method is the palladium-mediated carbonylation reaction. This method has been developed most effectively by Långström and co-workers to label a range of biological molecules including imides, ketones, amides, and acrylamides.[36,108–110] Palladium-catalyzed carbonylation reactions proceed through a three-step catalytic cycle: oxidative addition of an aryl halide species to the in situ generated palladium(0) catalyst, insertion–migration of carbon monoxide to form the palladium–acyl complex, and finally nucleophilic attack and reductive elimination to form the carbonylated product. The rate of this reaction can be limited by the CO insertion step because of the poor reactivity of carbon monoxide as a result of its low solubility in organic solvents at low CO pressures. This problem is even more apparent when using [^{11}C]CO at high isotopic dilution, where the partial pressure exerted by [^{11}C]CO will be extremely low. One solution to this problem has been to recirculate the [^{11}C]CO gas through the reaction mixture.[110] This method has been superseded by the use of high-pressure reaction systems (HPLC micro-autoclave)[36,37] to increase the [^{11}C]CO pressure and enhance the CO insertion step.

Suzuki-type ^{11}C-carbonylation reactions have been studied for the synthesis of [*carbonyl*-^{11}C]ketones under lower pressures[107] and by using the micro-autoclave reactor system.[111,112] Aryl and alkyl boronic acids were treated with

aryl triflate electrophiles and [^{11}C]CO in the presence of a palladium catalyst to prepare the [*carbonyl*-^{11}C]biaryl or [*carbonyl*-^{11}C]aryl benzyl ketones (Scheme 21). The radiochemical yields were found to be improved when an organic

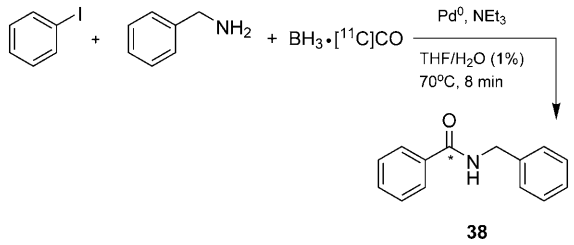


Scheme 21. Selected palladium-mediated ^{11}C-carbonylation reactions using Långström's high-pressure microautoclave. X = I, Br, or triflate. * indicates the ^{11}C position.

base such as *tert*-butylammonium fluoride (TBAF), *t*BuO$^-$, or TEA was added to the reaction. In a similar approach, the Stille coupling reaction with the coordinatively unsaturated palladium(0) species [Pd(P(*o*-tolyl)$_3$)$_2$] has been applied to the synthesis of [*carbonyl*-^{11}C]ketones[108] (Scheme 21). A series of [*carbonyl*-^{11}C]benzophenones have been obtained with high RCYs at low pressures by palladium-mediated [^{11}C]carbonylative cross-coupling reactions using diphenyl iodonium salts with phenyltributylstannane.[113] However, potential drawbacks to this system include a low trapping efficiency of [^{11}C]CO in the DME/H$_2$O solution[114] and the formation of mixtures of ^{11}C-radiolabeled compounds when iodonium salts with different substituents are used.

The synthesis of [*carbonyl*-^{11}C]amides by palladium-mediated carboxyaminations with [^{11}C]CO has been studied extensively by Långström and co-workers,[109,115–119] who used the micro-autoclave reactor system (Scheme 21). ^{11}C-Carboxyamination reactions can also be carried out with less basic amines, such as aniline and indole derivatives, by in situ activation using lithium bis(trimethylsilyl)amide[117] and 1,2,2,6,6,-pentamethylpiperidine[118] to improve the RCYs. Aryl triflates have been used, as alternative organic electrophiles, to widen the scope of [*carbonyl*-^{11}C]amide synthesis.[119] The more easily synthesised triflates can be used as an alternative to aryl halides for these reactions, although the reactivity of the triflates can be lower than aryl iodides. Good radiochemical yields were obtained by reaction optimization and through the use of LiBr as an additive.

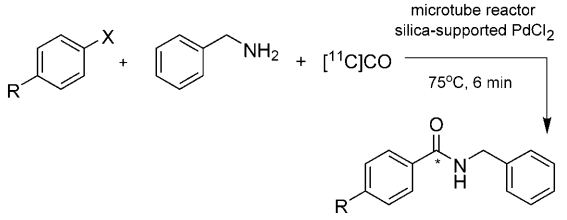
Effective palladium-mediated ^{11}C-carbonylation methods at normal pressures have been developed, and include the use of a borane·THF solution for sequestering and solubilizing [^{11}C]CO in the form of a BH$_3$·[^{11}C]CO adduct.[120] The trapped [^{11}C]CO was concentrated into a smaller volume and could be used for palladium-mediated cross-coupling reactions of aryl halides with amine or alcohol nucleophiles to form [*carbonyl*-^{11}C]amide or [^{11}C-*carbonyl*]ester, respectively. The best RCYs (47%) were obtained for the formation of the model compound [*carbonyl*-^{11}C]*N*-benzylbenzamide (**38**) when a 1% water/THF solution was used at reaction temperatures above 70°C (Scheme 22).



Scheme 22. Synthesis of **38** by palladium-mediated carbonylation using the BH$_3$·[^{11}C]CO adduct.

Palladium-mediated ^{11}C carbonylation of aryl halides for [^{11}C-*carbonyl*]amide formation at normal pressure has also been achieved by using a microtube reactor with a palladium support.[121] This device was prepared by packing a silica-supported palladium catalyst into 1 mm diameter PTFE tubing. The high surface area/volume ratio of the catalyst generated within the reactor was suggested to improve the contact between the gaseous [^{11}C]CO and liquid aryl halide/amine reagents, thus enhancing the ^{11}C-carbonylation reaction. This system was used to label four different benzylbenzamide molecules in the carbonyl position in short reaction times (6 min), with RCYs ranging from 33 to 79% depending on the aryl substrate used (Scheme 23). This method provides a simple and effective route to [*carbonyl*-^{11}C]amide molecules without the need for sophisticated equipment. Additionally, the microtube reactor loops could be reused for successive labeling reactions provided the same substrate molecules were used, and can provide more improved and rapid purification procedures.

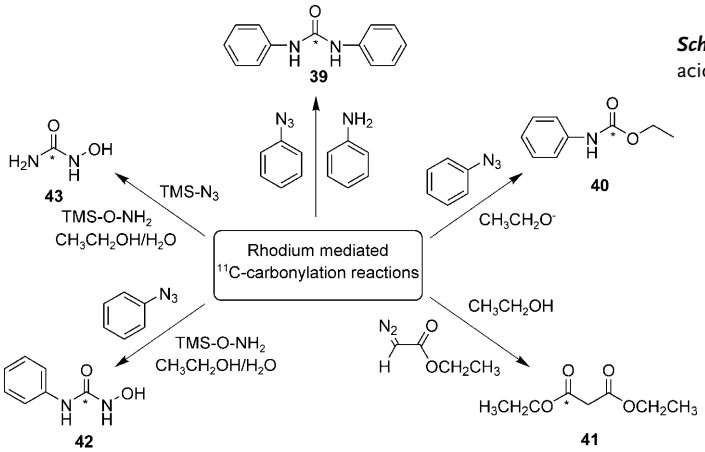
Rhodium-mediated carbonylation[122–124] reactions provide an alternative route for the introduction of [^{11}C]CO into organic molecules. ^{11}C-labeled malonates,[123] hydroxyur-



Scheme 23. Synthesis of a series of [*carbonyl*-^{11}C]*N*-benzylbenzamides by palladium-mediated carbonylation in a microtube reactor with a palladium support. X = I or Br; R = H, CF$_3$, CN, or OCH$_3$.

eas,[122] carbamates,[124] and diphenylureas[124] have been synthesized using [RhCl(cod)/phosphine] (cod = cyclooctadiene) catalysts. The rhodium catalyst mediates [^{11}C]CO insertion and the subsequent formation of either rhodium-coordinated [^{11}C]isocyanate or [^{11}C]ketene intermediates, which are then presumed to undergo either direct reaction with a nucleophile or reductively eliminate from the rhodium complex prior to nucleophilic attack.

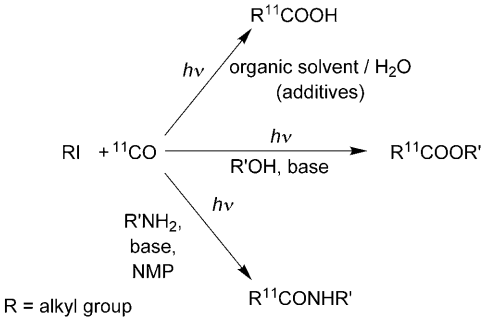
Rhodium-mediated ^{11}C carbonylation of phenylazide in a micro-autoclave forms the reactive [^{11}C]isocyanate intermediate which can then be treated with either aniline or ethoxide nucleophiles to form [*carbonyl*-^{11}C]diphenylurea (**39**) or [^{11}C-*carbonyl*]ethylphenyl carbamate (**40**), respectively[124] (Scheme 24). The one-pot procedure for the synthesis of



Scheme 24. Summary of rhodium-mediated ^{11}C-carbonylation reactions leading to the formation of [*carbonyl*-^{11}C]urea and carbamate compounds in a micro-autoclave.

[*carbonyl*-^{11}C]diethyl malonate (**41**)[123] from the stable α-diazoesters and [^{11}C]CO has also been reported using a rhodium-mediated micro-autoclave[123] (Scheme 24). In this reaction system a mixture of the Rh^{I} catalyst, diazoacetate, and ethanol (added later to the reaction mixture) were injected into the micro-autoclave reactor that had been previously charged with [^{11}C]CO. This reaction proceeds by the complexation of ethyl diazoacetate to the active Rh species with a concerted loss of N_2 gas that results in the formation of the [^{11}C]rhodium–carbenoid complex. [^{11}C]CO insertion and migration gives the [^{11}C]rhodium–ketenyl complex. A subsequent nucleophilic attack of ethanol either directly on the [^{11}C]rhodium–ketenyl complex or on the [^{11}C]ketene forms diethyl [*carbonyl*-^{11}C]malonate in 25% RCY (Scheme 24). A similar reaction protocol is employed for the two-step synthesis of [*carbonyl*-^{11}C]hydroxyureas **42** and **43**. A solution of trimethylsilylazide (or phenylazide), rhodium catalyst, and *o*-trimethylsilylhydroxylamine in THF was heated at 120 °C for 5 minutes in a micro-autoclave reactor charged with [^{11}C]CO (Scheme 24). Following a deprotection step, [*carbonyl*-^{11}C]hydroxy urea **42** or **43** was obtained.

Free-radical photoinitiated ^{11}C-carbonylation reactions have very recently been used to synthesize ^{11}C-labeled long- and short-chain aliphatic carboxylic acids,[125,126] esters,[126–128] and amides[129] (Scheme 25). This method is of particular interest because of the high tolerance to functional groups such as carboxylic acids and hydroxy groups, compared to, for



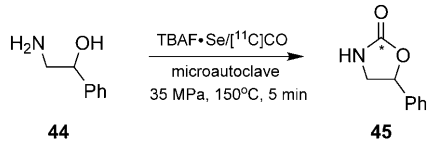
Scheme 25. Synthesis of [*carbonyl*-^{11}C]-labeled aliphatic carboxylic acids, esters, and amides by photoinitiated carbonylation reactions.

example, the Grignard synthesis of carboxylic acids (using [^{11}C]CO_2, see Section 2.5), which requires addition protection/deprotection steps. In contrast to the palladium-mediated ^{11}C-carbonylation reactions, which are restricted mainly to aryl halide and benzylic halide starting materials, because of the problems associated with β-hydride elimination, the photoinitiated route can introduce [^{11}C]CO into aliphatic molecules; this is something that has previously proven difficult to accomplish.

The reported photoinitiated ^{11}C-carbonylation reactions were carried out in a modified micro-autoclave equipped with a sapphire window to allow penetration of UV light.[125] [^{11}C]Carboxylic acids, esters, and amides could be prepared from a mixture of the corresponding alkyl iodides, ketone sensitizer (acetone or benozophenone), nucleophile (water, alcohol, or amine), and [^{11}C]CO pressurized to 40 MPa and with UV (280–400 nm) irradiation. The polarity of the solvent was shown to have a marked effect on the synthesis of the [*carbonyl*-^{11}C]amide. Polar solvents such as DMSO and DMF gave better RCYs than the less polar acetone; however, they also produced significant amounts of side products. These polar solvents are thought to stabilize the [^{11}C]acyl radicals and facilitate the acylation step of the reaction. Conversions of [^{11}C]CO were also found to be dependent on stirring, the concentration of alkyl iodide, pressure, and intensity of UV irradiation.

^{11}C-Carbonylation reactions of amines, alcohol amines, and alcohols have led to the synthesis of [*carbonyl*-^{11}C]ureas, carbamates, and carbonates in high RCYs by high-pressure selenium-mediated synthesis.[130] It is thought that a carbonyl selenide is initially formed on reaction of carbon monoxide with selenium which then reacts with the amine or alcohol to form a carbamoselenoate intermediate. Subsequent elimination of hydrogen selenide then generates an isocyanate. Nucleophilic attack of this isocyanate with the amine or alcohol gives a urea or carbamate, respectively. This procedure has been shown to work most effectively for the synthesis of cyclic [*carbonyl*-^{11}C]ureas and carbamates with

almost quantitative RCYs. A soluble form of selenium is required to enhance the reactivity of [^{11}C]CO and also to make it easier to transfer solutions through narrow capillaries of the apparatus. The use of TBAF as a base gave the best results as it forms a complex with selenium and results in greater solubility in polar solvents such as THF (Scheme 26).

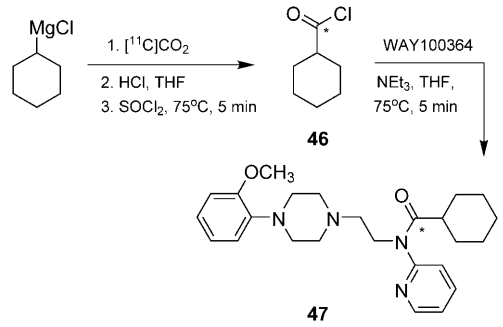


44 45

Scheme 26. Synthesis of the cyclic carbamoyl compound [*carbonyl*-^{11}C]5-phenyl-oxazolidin-2-one (**45**) by a selenium-mediated ^{11}C-carbonylation reaction.

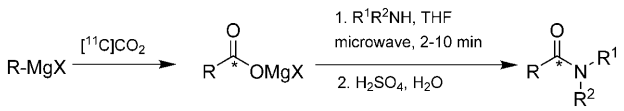
2.5. Synthesis with [^{11}C]Carbon Dioxide

[^{11}C]CO_2 can be treated with organometallic Grignard reagents to form [^{11}C]carboxymagnesium halides and then transformed into [^{11}C]carboxylic acids. These can then be converted into the more reactive acid chloride species and treated with amines to form [*carbonyl*-^{11}C]amides. This method has been used for ^{11}C labeling at the carbonyl position of the important $5HT_{1A}$ receptor ligand WAY100635 (**47**) (Scheme 27).[131,132] The complex biological molecule



Scheme 27. One-pot synthesis of [*carbonyl*-^{11}C]WAY100635 (**47**) by reaction of [*carbonyl*-^{11}C]cyclohexyl acid chloride (**46**) with WAY100634.

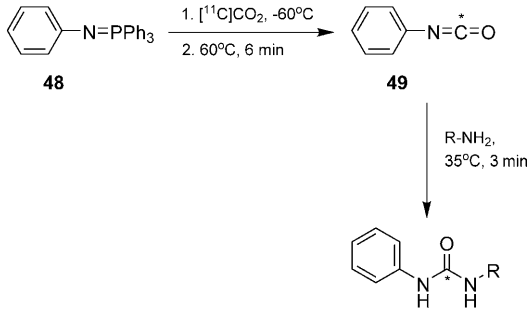
BAY 59-8862, a taxane derivative of interest as an oncology biomarker, has also been labeled in a similar way through reaction of its lithium precursor with [^{11}C]acetyl chloride; the latter species was prepared from the reaction of [^{11}C]CO_2 with methyl magnesium bromide and phthaloyl dichloride.[133] The synthesis of [*carbonyl*-^{11}C]amides has been achieved directly from [^{11}C]carboxymagnesium halides[134,135] and enhanced further by using microwave heating[136] (Scheme 28). Associated challenges with the direct reaction of [^{11}C]CO_2 with organometallic reagents include contamination with atmospheric CO_2, which adversely affects the specific activity of the produced tracer, and the sensitivity of the organometallic reagents to hydrolysis.



Scheme 28. Synthesis of [*carbonyl*-^{11}C]amides from [^{11}C]carboxymagnesium halides with amines using microwave heating.

[^{11}C]Acetate, used in the evaluation of myocardial oxygen metabolism[137] and diagnosis of prostate cancer,[138] has been produced from the ^{11}C carboxylation of Grignard reagents by using automated captive solvent methods with reaction loops.[41,139,140] Methyl magnesium bromide was coated onto the internal surface of the loop and then [^{11}C]CO_2 passed through, thereby forming the [1-^{11}C]acetate magnesium bromide which was then quenched and neutralized to form the [1-^{11}C]acetate. A high RCY (65%) of [1-^{11}C]sodium acetate can be achieved in reaction times of 5 minutes.[140]

A one-pot method for the synthesis of unsymmetrical ^{11}C-labeled ureas has recently been developed using triphenylphosphinimines and [^{11}C]CO_2.[141] [^{11}C]Phenylisocyanate (**49**) is initially formed from the reaction of triphenylphosphinimine (**48**) and [^{11}C]CO_2 (Scheme 29). Subsequent reaction of



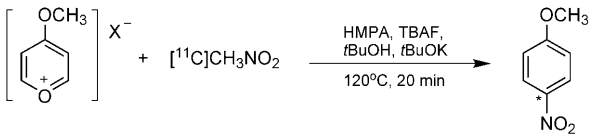
Scheme 29. Synthesis of unsymmetrical [^{11}C]ureas by reaction of triphenylphosphinimine (**48**) with [^{11}C]CO_2 to form [^{11}C]phenylisocyanate (**49**) followed by reaction with an amine. R = Ph, Bn, *n*Pr, or 5-methoxyltryptamine.

the [^{11}C]phenylisocyanate with amines gave [^{11}C]ureas in short reaction times (3 min). The best RCYs were obtained when more basic primary amines were used (45–49%), a low RCY of 8% was obtained when the aromatic amine aniline was used. This method is particularly interesting since it uses the readily available [^{11}C]CO_2 for the preparation of [^{11}C]urea, and thus avoids using the more sophisticated reagents [^{11}C]phosgene or [^{11}C]CO. Additionally, there is the possibility to synthesize a wide range of [^{11}C]ureas by varying both the phosphinimines and the amines. The utility of this reaction system may, however, be limited due to the range of phosphinimines that may be prepared because of their air and moisture sensitivity.

2.6. Miscellaneous ^{11}C Reactions

Pyrylium salts, which consist of a cyclic conjugated oxonium cation and a counterion, have been used as precursors for the formation of ring-positioned ^{11}C-labeled benzenoid compounds.[142] The condensation reaction of the pyryilium salt **50** with [^{11}C]nitromethane, prepared by the

reaction of [^{11}C]methyl iodide with silver nitrite, gives methoxy-4-nitro-[4-^{11}C]benzene (**51**; Scheme 30). An auxiliary base, TBAF, and a solvent mixture of HMPT and *tert*-butanol were needed for an efficient reaction. The RCY of



Scheme 30. Direct labeling of aromatic rings using a pyrylium salt and [^{11}C]CH_3NO_2. * indicates the position of the ^{11}C label. X = ClO_4 or BF_4.

this reaction was found to be dependent on the addition of the bases for the trapping of [^{11}C]nitromethane in the pyrylium solvent mixture. Addition of TBAF to the mixture of the pyrylium salt in the solvent (HMPT), followed by the trapping of [^{11}C]CH_3NO_2 and then addition of the *t*BuOK in *t*BuOH and heating to 120 °C for 20 minutes gave an RCY of 77 % (Scheme 30). These optimized conditions were, however, limited to only one pyrylium salt; the RCYs were significantly lower when other R groups were attached to the ring.

3. Radiolabeling with Fluorine-18

Fluorine-18 ($t_{1/2}$ = 110 min) is the most widely used radionuclide in PET. The development and widespread use of the most commonly used PET tracer 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG, **53**) to image, diagnose, and tailor cancer treatments spurred the increasing global interest in PET imaging. ^{18}F is often referred to as the "radionuclide of choice" because of its favorable physical and nuclear characteristics: a short but manageable 110 minute half-life which allows sufficient time for multistep synthetic labeling reactions, and a short positron linear range in tissue (2.3 mm) which gives the highest resolution PET images of all the available positron emitters. The half-life of the ^{18}F isotope is long enough to allow transportation of doses to sites several hours away. For example, transporting a 1 GBq dose of ^{18}F tracer gives a 250 MBq dose at a site four hours away. A further advantage of ^{18}F-labeled compounds is that multiple patients can be scanned from a single dose; for example, one delivery per day of [^{18}F]FDG to a PET center is usually sufficient for a full day's scanning.

There are two evident disadvantages of using the ^{18}F radioisotope in labeling PET molecules: 1) the relatively small pool of biologically active fluoroorganic target molecules; and 2) the unknown effects of introducing an "unnatural" fluorine atom may have on the biological properties[143] of the newly labeled compound and the difficulties of making direct comparisons between the biological properties of the nonfluorous parent molecule, which may have been studied in detail, and the ^{18}F-labeled counterpart. In recent years, however, there has been an increase in the number of biologically active fluoroorganic drugs.[144–147] The reason for this is directly due to the beneficial effects of simple substitution of an H atom by an F atom on the physical and/or biological properties of the molecule.

The aim of this section is to highlight the current methods for ^{18}F labeling, drawing on both the established ^{18}F-fluorination methods and examples from recent literature. Several general[148,149] and more in-depth reviews[150–152] on the topic of ^{18}F labeling exist in the literature, to which the reader is directed.

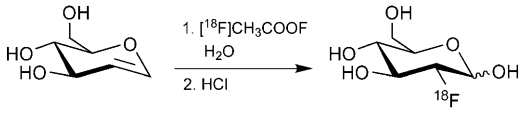
3.1. Strategies for ^{18}F Radiolabeling

The variety of chemical methods by which the ^{18}F isotope can be introduced into target molecules is, by comparison to ^{11}C-labeling strategies, rather limited. The main synthetic strategies behind ^{18}F labeling can be crudely divided into two distinct areas: 1) direct fluorination, where the ^{18}F isotope is introduced "directly" into the target molecule of interest in one step; and 2) indirect fluorination which exploits so-called ^{18}F prosthetic groups and requires a multistep synthetic approach. These prosthetic groups are typically small ^{18}F-labeled alkyl or aryl groups that have reactive functional groups. They are used to react with more complex biological molecules which may not be suitable or stable enough to tolerate direct fluorination methods. The direct ^{18}F-labeling strategies can be subdivided into two main areas of fluorination: nucleophilic and electrophilic. Of these two methods, nucleophilic ^{18}F-fluorination reactions have dominated in importance because of their greater selectivity and capability to give highly specific radioactive compounds suitable for true tracer methods in PET.

3.2. Electrophilic Fluorine-18 Labeling Reactions

Electrophilic ^{18}F fluorinations are less favored nowadays for two reasons: 1) they generally give labeled products with low specific activity because of the carrier-added method of [^{18}F]F_2 production; and 2) labeling with electrophilic reagents such as [^{18}F]F_2 is generally unspecific and can result in mixtures of ^{18}F-labeled products. Considerable steps usually need to be taken to control the very reactive [^{18}F]F_2 species. This has led to the development of softer and more selective electrophilic [^{18}F]fluorination reagents, such as the recently developed [^{18}F]-*N*-fluorobenzenesulfonimide[153] used in the preparation of labeled fluorinated ketones and allylic fluorides. Although nucleophilic fluorination is currently the most common synthetic approach for ^{18}F radiolabeling, electrophilic fluorination has played an important and historic role in the development of ^{18}F-labeled molecules for PET imaging. For example, the first synthesis of the hugely important PET tracer [^{18}F]FDG (**53**) was carried out by electrophilic fluorination (Scheme 31).[154] Other more recent examples of important PET tracers, which still rely on electrophilic ^{18}F-fluorination methods of synthesis, include [^{18}F]fluoro-L-DOPA and 2-L-[^{18}F]fluorotyrosine.

The most common reagent for electrophilic fluorination is [^{18}F]F_2, which is obtained from the nuclear reactions of ^{20}Ne(d,α)^{18}F or ^{18}O(p,n)^{18}F, and can be used as it is or



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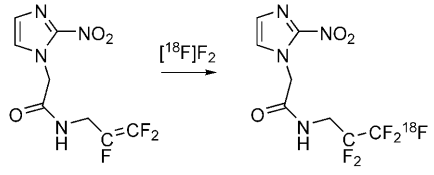
Scheme 31. Electrophilic ^{18}F fluorination using [^{18}F]acetyl hypofluorite for the preparation of [^{18}F]FDG.

converted into the less reactive derivative acetyl hypofluorite ($CH_3COO[^{18}F]F$). Other derivatives that have been used as electrophilic fluorinating reagents are [^{18}F]fluoropyridones[155–157] and [^{18}F]fluoro-*N*-sulfonamides.[158] These reagents can be used to fluorinate electron-rich substrates (such as alkenes and aryl compounds) by either direct electrophilic substitution or by demetalation reactions using organometallic reagents such as organomercury and organotin reagents. Examples of these two reactions are discussed in the next two sections.

3.2.1. Direct Electrophilic ^{18}F Fluorination

As stated above, the first synthesis of [^{18}F]FDG was based on a direct electrophilic substitution. This molecule is a glucose mimic which has been employed successfully in neurological, cardiovascular, and oncology investigations. When FDG is transported intracellularly (using similar pathways to glucose) it can be phosphorylated to FDG-6-phosphate by hexokinase. In contrast to phosphorylated glucose, FDG-6-phosphate is not a significant substrate for further reactions and therefore it accumulates in cells reflecting blood–tissue transport and hexokinase activity, thereby providing regional imaging of energy metabolism. The information obtained can then be employed to identify and characterize diseases related to alterations in the metabolism of glucose. For example, experimental and clinical studies have shown that the uptake of FDG in cancer cells (with increased levels of glycolysis) correlates with the rate of tumor growth and degree of metastasis. Therefore, [^{18}F]FDG is a powerful imaging agent for locating a tumor and determining its response to therapy.

There is ongoing interest in the development of molecular probes that can detect tissue hypoxia, since the latter has important biological and clinical implications in various pathological states. It has been found that certain 2-nitroimidazoles such as, 2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide (EF5, **55**; Scheme 32) can be used to detect hypoxia, since the rate of their bioreductive



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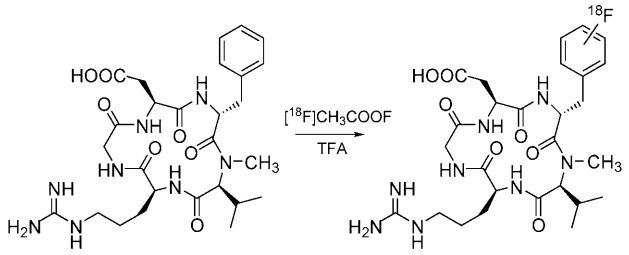
Scheme 32. Formation of the hypoxia biomarker [^{18}F]EF5 (**55**) by direct electrophilic substitution using [^{18}F]F_2.

metabolism is inversely dependent on the oxygen partial pressure. An example of this type of marker is [^{18}F]EF5, which can be obtained by direct fluorination of the corresponding allyl precursor (**54**, Scheme 32).[159]

Another reagent commonly used for electrophilic fluorinations is acetyl hypofluorite ([^{18}F]CH_3COOF). This reagent has been used in, for example, the radiofluorination of a cyclic RGD peptide for PET imaging of tumors.[160] Arg-Gly-Asp (RGD) peptides are recognized by integrins, a family of transmembrane glycoproteins that mediate cell adhesion to extracellular matrix proteins and other cells. Since the adhesiveness of tumor cells correlates with their metastatic ability, it has been suggested that molecular probes that interact with integrin receptors (such as cyclic RGD peptides) could be used to image tumors. Scheme 33 shows the electrophilic radiofluorination of the phenylalanine residue of one of these cyclic RGD peptides (**56**) by acetyl hypofluorite. The reaction yielded different mono- and difluorinated products (**57**), some of which were purified by chromatography and used successfully to image integrin receptors.



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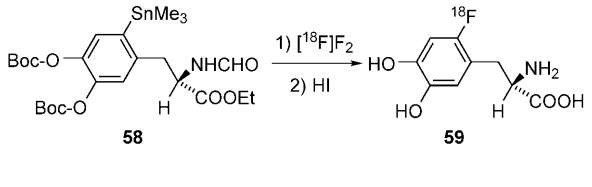
Scheme 33. Electrophilic ^{18}F fluorination of cyclic RGD peptides using [^{18}F]CH_3COOF.

3.2.2. Fluorination by Demetalation of Organometallic Intermediates

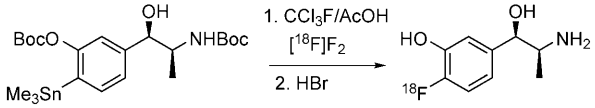
In this type of reaction, organometallic intermediates are produced and subsequently treated with the corresponding fluorinating agent. An early example of this type of reaction was the synthesis of [^{18}F]fluoro-L-DOPA (**59**) from an organotin precursor (**58**, Scheme 34).[161] A similar demetalation approach has been more recently employed to prepare 2-[^{18}F]fluoro-L-tyrosine (**61**, Scheme 34).[162] This amino acid is known to incorporate into newly synthesized proteins and, therefore, it could be employed as a tracer to image protein metabolism in vivo by PET.[163,164]

Electrophilic aromatic ^{18}F substitution of organometallic compounds has been used to prepare [^{18}F]metaraminol derivatives, which are used as cardiac sympathetic innervation tracers. Initial synthetic approaches were based on electrophilic aromatic substitution of an acetoxymercury group with [^{18}F]acetyl hypofluorite.[165] This approach produced tracers with low specific activity and, therefore, limited use for human PET studies. A more recent study has shown that it is possible to prepare [^{18}F]metaraminol derivatives (more specifically (1*R*,2*S*)-4-[^{18}F]fluorometaraminol, **63**) with



Scheme 34. Synthesis of [^{18}F]fluoro-L-DOPA (**59**) and 2-[^{18}F]fluoro-L-tyrosine (**61**) from their corresponding organotin precursors by direct fluorination with [^{18}F]F_2.

higher specific activity.[166] This synthetic route is based on the reaction between an organotin reagent (**62**) and [^{18}F]F_2 (Scheme 35). As pointed out by the authors of this study,

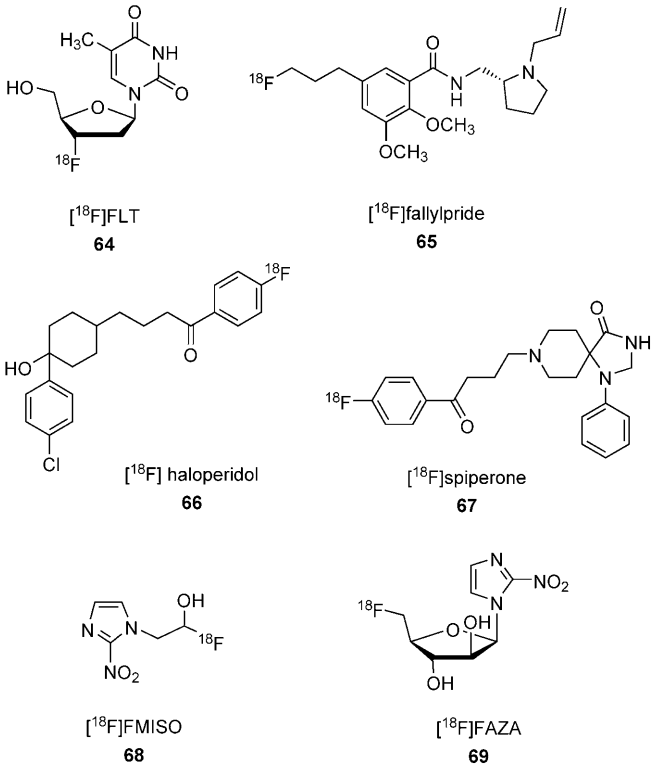


Scheme 35. Preparation of **63**, with improved specific activities, by reaction of the corresponding organotin reagent with [^{18}F]F_2.

the main radiosynthetic difference to earlier electrophilic fluorination syntheses, was the use of high specific activity [^{18}F]F_2 gas produced with a "post-target" method (previously developed by Bergman and Solin[167]). This led to a 1000-fold improved specific activity of the tracer.

3.3. Nucleophilic ^{18}F-Substitution Reactions

Nucleophilic ^{18}F-fluorination reactions are routinely used to efficiently produce some of the most important ^{18}F PET radiotracers (Scheme 36): [^{18}F]FDG (**53**) and 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT, **64**)[168–170] widely used in oncology investigations; [^{18}F]fallypride (**65**),[171,172] [^{18}F]haloperidol (**65**),[173] and [^{18}F]spiperone (**66**)[174,175] used in dopamine receptor studies;[60] and [^{18}F]fluoroazomycinarabinofuranoside ([^{18}F]FAZA, **67**)[176] and [^{18}F]Fluoromisonidazole ([^{18}F]FMISO, **68**)[177,178] for imaging tissue hypoxia.[179,180] Nucleophilic $^{18}F^-$ is commonly produced by the nuclear reaction $^{18}O(p,n)^{18}F$ from enriched [^{18}O]H_2O. $^{18}F^-$ from the target is then trapped on an ion-exchange column which allows the recovery of [^{18}O]H_2O. The trapped $^{18}F^-$ is then eluted from the ion-exchange resin using potassium carbonate in a water/acetonitile solution. The aqueous fluoride obtained is, however, a poor nucleophile because of its high degree of solvation. The addition of the phase-transfer reagent kryptofix-222 (K_{222}), followed by the removal of water has proven to be crucial in improving the reactivity of the [^{18}F]fluoride ion for nucleophilic substitution reactions. The azacryptand K_{222} (Figure 3) forms a strong



Scheme 36. A selection of key ^{18}F tracers.

complex with the potassium cation and leaves the fluoride ion exposed ("naked") and highly nucleophilic when dissolved in a polar nonprotic solvent such as DMF, DMSO, or acetonitrile.

A routinely used alternative to [^{18}F]KF·K_{222} is [^{18}F]tetrabutylammonuim fluoride ([^{18}F]TBAF), which is prepared by trapping $^{18}F^-$ on an ion-exchange column and eluting with tetrabutylammonium hydrogencarbonate.[181] Comparisons between the reactivity of "cold" KF·K_{222} and in situ generated anhydrous TBAF demonstrate that TBAF gives greater yields of fluorinated products in short reaction times (< 10 min).[182] Recently, [^{18}F]TBAF has been used as a highly effective fluorinating reagent in protic *tert*-alcohol media for the synthesis of [^{18}F]FLT (**64**), [^{18}F]FMISO (**68**), and [^{18}F]FP-CIT.[183–185]

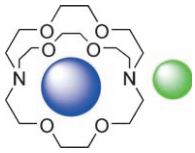


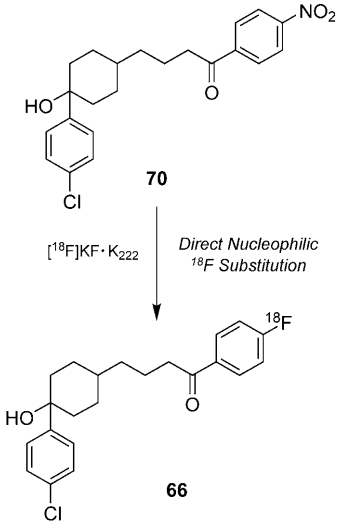
Figure 3. Complexation of a potassium ion (blue) by the azacryptand kryptofix-222 (K_{222}); green: fluoride ion.

In addition to [^{18}F]fluoride activation, the reacting precursor molecule is required to have a suitable leaving group, and in the case of aromatic rings be suitably activated. Direct ^{18}F nucleophilic labeling can be subdivided into two categories: aliphatic ^{18}F-labeling and aromatic ^{18}F-labeling strategies.

3.3.1. Aromatic ^{18}F Nucleophilic Reactions

Direct nucleophilic substitution reactions with ^{18}F provide a simple one-step pathway to a wide range of labeled aromatic

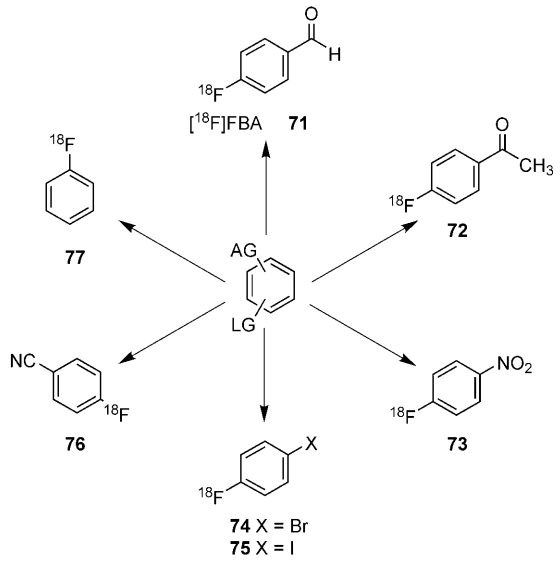
compounds provided that the aromatic ring is suitably activated by an electron-withdrawing group (nitro, cyano, or acyl) on the *ortho* or *para* positions to be a good leaving group. Common leaving groups used in nucleophilic ^{18}F-fluorination reactions include nitro, trialkylamine, halogen, mesylate, tosylate, or triflate. This is often the method of choice for obtaining high radiochemical yields and specific activities of ^{18}F-labeled compounds by a simple one-pot method. One example is the synthesis of [^{18}F]haloperidol (**66**)[173] (Scheme 37).



Scheme 37. Direct synthesis of [^{18}F]haloperidol (**66**) from the corresponding nitro precursor **70**.

Direct ^{18}F-fluorination methods are not always suitable for the synthesis of ^{18}F target compounds because of the harsh reaction conditions (high reaction temperatures and polar organic solvents). More often, milder indirect ^{18}F-labeling methods are used to obtain the labeled compounds through the use of small ^{18}F-labeled reactive precursors that can form part of the intrinsic structure of the molecule (as for receptor ligands) or act as a "prosthetic tag" to the molecule of interest (as in the case of larger biomolecules such as proteins). For example, [^{18}F]fluoroaromatic groups that have a reactive functional group can be used as ^{18}F precursor molecules or as prosthetic tags by reacting rapidly and under mild conditions after the initial direct ^{18}F-fluorination step. The synthesis of a range of [^{18}F]fluoroaromatic precursor molecules is now well established and includes: 4-[^{18}F]fluorobenzaldehyde ([^{18}F]FBA, (**71**)), 4-[^{18}F]fluorophenylethanone (**72**), 4-[^{18}F]fluoronitrobenzene (**73**), 1-bromo-4-[^{18}F]fluorobenzene (**74**), 1-[^{18}F]fluoro-4-iodobenzene (**75**), 4-[^{18}F]fluorobenzonitrile (**76**), and [^{18}F]fluorobenzene (**77**) (Scheme 38).

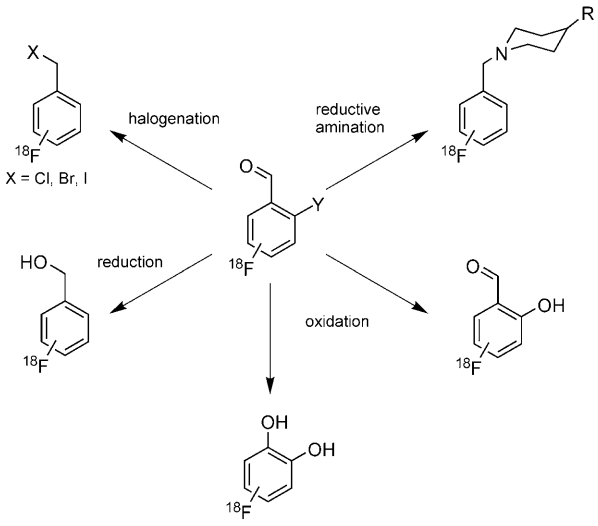
Nitrobenzene derivatives are the most widely used precursors in the preparation of simple [^{18}F]fluoroaromatic compounds. The nitro group is both an activating group (in the *ortho* or *para* positions) and a leaving group under the right conditions. Additionally, the nitro group may be reduced to an amine and reacted further to form tertiary amines, piperazines, and anilinoquinazolines, as well as a range of



Scheme 38. Synthesis of simple [^{18}F]fluoroaromatic precursors by direct nucleophilic ^{18}F substitution. AG = activating group (NO_2, nitrile, or carbonyl). LG = leaving group (NO_2, halide, triflate, tosylate, mesylate, trialkylamonium halide, or iodonium salt). X = halide I or Br.

other labeled compounds such as alcohols, hydrazines, sulfonyl chorides, and chlorides via formation of an intermediate diazonium salt.

[^{18}F]Fluorobenzaldehydes can be readily prepared in good radiochemical yield from their nitro or trimethylammonium triflate precursors by direct ^{18}F fluorination using the [^{18}F]KF/K_{222} method when the leaving groups are sufficiently activated by an acyl group on the *ortho* or *para* positions. [^{18}F]Fluorobenzaldehydes (Scheme 39) can be further converted into benzyl alcohols through reduction, and then halogenated to form the corresponding Cl, Br, or I benzyl halides. ^{18}F-Labeled phenols and catechols may be obtained by oxidation of [^{18}F]fluorobenzaldehyde derivatives; how-



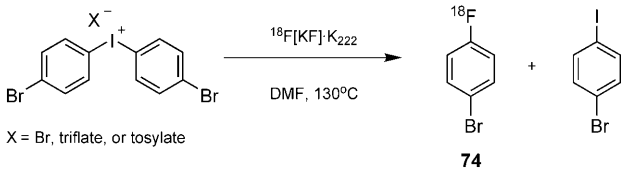
Scheme 39. Reactions of simple [^{18}F]fluorobenzaldehydes. ^{18}F is positioned on the *ortho* or *para* ring positions. Y = MEM protecting group or H.

ever, extra protection and deprotection steps are required. [^{18}F]Fluorobenzylamines[150] may also be prepared from [^{18}F]fluorobenzaldehyde by reductive amination (Scheme 39).

[^{18}F]Fluoroaryl ketones can be synthesized in a similar way as [^{18}F]fluorobenzaldehydes by the direct substitution of the NO_2 or other suitable leaving group when the aryl ring is activated by the carbonyl group. The activating effect of the ketone carbonyl is lower than that of an NO_2 or nitrile group which results in lower but none-the-less good RCYs. The trimethyl ammonium triflate leaving group has been found to give the best RCYs for the synthesis of [^{18}F]fluoroaryl ketones,[186] although a chloride has also found to be an effective leaving group for the synthesis of [^{18}F]fluorospiperone and [^{18}F]haloperidol.[187,188]

The strongly electron withdrawing nature of the nitrile group can be exploited to obtain high RCYs of [^{18}F]fluorobenzonitrile precursors from the corresponding trimethyl ammonium starting materials.[189] The nitrile group can then be transformed into reactive groups such *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide for the ^{18}F labeling of peptides and oligonucleotides (see Section 3.5.1).[190]

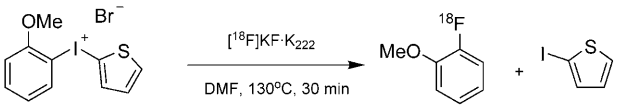
The increased use and versatility of palladium-catalyzed cross-coupling reactions in mainstream organic chemistry (Heck, Stille, Suzuki–Miyaura, Negishi, Sonogashira, and Buchwald–Hartwig reactions) has had an equally important knock-on effect in the field of radiochemistry.[123,124,191–194]) The rapid and high-yielding synthesis of labeled [^{18}F]fluorohaloaryl compounds is important for the current and future exploitation of these palladium cross-coupling reactions for radiolabeling strategies. The synthesis of relatively simple [^{18}F]fluorohalobenzene precursors has, until recently, been surprisingly quite problematic. Traditional synthetic methods for the preparation of [^{18}F]fluoroaromatic compounds are reliant on the use of activated aryl groups to achieve good radiochemical yields in reasonably short reaction times. This, however, limits the range of [^{18}F]fluoroaromatic compounds available from simple one-step methods to those rings which have electron-withdrawing substituents. The use of iodonium salts as precursors[195,196] in nucleophilic ^{18}F-substitution reactions is an extremely useful alternative for the synthesis of a range of simple [^{18}F]fluoroaromatic compounds in good RCYs and in short reaction times that would be otherwise unobtainable by traditional methods. A recent study[197] has compared literature examples of the commonly used methods for the one-pot synthesis of 1-bromo-4-[^{18}F]fluorobenzene (**74**) and compared nucleophilic pathways. The use of the symmetrical bis(4-bromophenyl)iodonium salts gave the highest RCY of 1-bromo-4-[^{18}F]fluorobenzene (Scheme 40), and no formation of other ^{18}F by-products were observed when the unsymmetrical (4-bromophenyl)phenyliodonium salts were used.



Scheme 40. One-step synthesis of **74** from bis(4-bromophenyl)iodonium salts.

The first use of iodonium salts as a general route for the no-carrier-added (NCA) synthesis of unactivated [^{18}F]fluoroaromatic compounds with high specific activity was reported by Pike and Aigbirhio.[198] The reliability and versatility of the procedure has since been improved greatly for the production of unactivated or electron-rich [^{18}F]fluoroaromatic compounds. Further studies on the ^{18}F fluorination of iodonium salts describe the optimum reaction conditions, temperature, choice of anion, and solvent. Pike and co-workers[199] described the reaction of aryl iodonium salts with [^{18}F]fluoride at 80 °C in acetonitrile to generate labeled aryl fluorides. The regioselectivity of this reaction was found to be controlled electronically as well as by the steric bulk of the *ortho* substituents (*ortho* effect). The *ortho* effect can be a dominant factor for the preferential nucleophilic attack in which the electron-rich rings are fluorinated. *Ortho*-substituted aryl fluorides can be selectively produced by using unsymmetrical diaryl iodonium salts. Nucleophilic attack of fluoride proceeds at the most activated ring for unsymmetrical diaryliodonium salts. It was found that [^{18}F]fluorobenzene was the sole product when the iodonium salts contained a phenyl group and an electron-rich aryl ring (alkyl or alkoxy substituents).

The use of heteroaromatic iodonium salts containing the electron-rich 2-thienyl ring has recently been reported[200] as a way of directing the ^{18}F nucleophilic substitution to the less-electron-rich aryl ring. The reaction of the 2-methoxyphenyl(2-thienyl)iodonium salt **78** with [^{18}F]fluoride for the synthesis of *ortho*-[^{18}F]fluoroanisole (**79**) was studied as a model reaction system (Scheme 41). This study investigated the role of steric effects on the reaction kinetics and RCY by



Scheme 41. Synthesis of *ortho*-[^{18}F]fluoroanisole (**79**) using the heteroaromatic iodonium salt **78**.

varying the position of the methoxy group at the 2-, 3-, and 4-positions. The role of the anion and the solvent were also studied. DMF gave superior RCYs in the model reaction compared to DMSO, acetonitrile, and dimethylacetamide (DMA) which all gave low or very low RCYs. The effect of temperature in these reactions was important; the optimal temperature was found to be 130 °C, above this the RCYs decreased, probably because of thermal decomposition of the iodonium salt. The anions of iodonium salts are known to have a significant influence on their reaction with nucleophiles. Bromide salts were found to give the best RCYs; however, the organic triflate anion displayed the fastest reaction kinetics in the first 5 minutes of the radiolabeling reaction. Nucleophilic $^{18}F^-$ attack on the unsymmetrical iodonium salt was found, as expected, to be dependent on

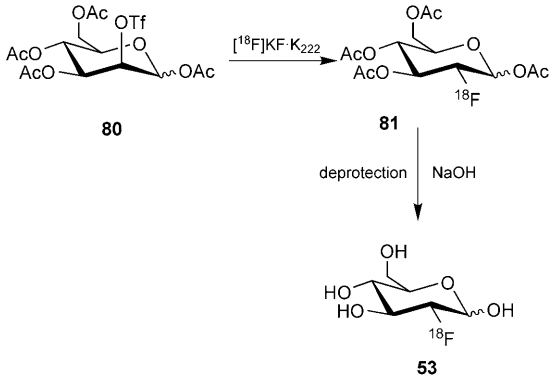
the electronic character of the aryl groups of the salt. The very electron rich 2-thienyl group does not undergo nucleophilic attack by $^{18}F^-$, but instead directs nucleophilic attack to the less electron rich ring in the salt, thus forming only one ^{18}F-labeled compound. Generally it was found that RCYs increased with weaker electron-donating substituents on the ring. The exception to this was the model reaction of **78**, which showed a high RCY of 61% as a result of the *ortho* effect of the methoxy group. The sterically demanding *ortho* substituents have been previously found to take-up the equatorial positions of the trigonal bipyramidal iodine intermediate on nucleophilic attack which favors the introduction of the $^{18}F^-$ into this ring.[199]

3.3.2. Heteroaromatic ^{18}F Nucleophilic Substitution Reactions

Strategies to synthesize ^{18}F-labeled heteroaromatic compounds[201] are receiving increased levels of interest because of the wide array of biological pyridyl molecules, particularly those that have been found to bind to nicotinic receptors. Initial model reactions of [^{18}F]fluoride with pyridines substituted with *ortho*-leaving groups were investigated using both conventional heating and microwave irradiation.[202] Nucleophilic substitution reactions of 2-nitro and 2-trimethylammonium pyridines with [^{18}F]KF·K_{222} gave the highest RCYs in the shortest reaction times. Excellent RCYs of 2-[^{18}F]fluoropyridine were obtained by microwave heating a solution of the 2-trimethylammonium pyridine in DMSO for one minute. The reactions proceeded faster when microwave heating was used; microwave irradiation for 2 minutes gave comparable RCYs as conventional heating at 180 °C for 10 minutes. Nucleophilic ^{18}F-substitution reactions of 4-nitropyridine can be efficiently carried out in short reaction times to form 4-[^{18}F]fluoropyridine; however, the 3-[^{18}F]fluoropyridine analogue could not be synthesized by using these methods.[203] Substitution at the *meta* position is possible if electron-withdrawing substituents are present at the *ortho* or *para* positions to activate the *meta* leaving groups.[204] Heteroaromatic nucleophilic ^{18}F-substitution reactions at the *ortho* position of the pyridyl groups is the most efficient route to ^{18}F-labeled fluoropyridyl derivatives when using [^{18}F]KF·K_{222}. Additional activating groups, which are required for homoaromatic compounds, are not usually required for nucleophilic ^{18}F substitution of pyridyl groups at the *ortho* or *para* positions, the only requirement is to have a good leaving group. The radiochemical yields are generally moderate to good with conventional heating to 100–180 °C in DMSO for 10–20 minutes or with microwave irradiation for 1–2 minutes at 100 W.

3.3.3. Aliphatic ^{18}F Nucleophilic Substitution Reactions

Direct aliphatic nucleophilic ^{18}F reactions are generally straightforward and are commonly used for the introduction of ^{18}F into a range of molecules. Unlike aromatic substitution reactions, activating groups are not required. The only requirement for aliphatic nucleophilic ^{18}F reactions is a good leaving group, such as triflate, tosylate, mesylate, iodo, or bromo. The main drawback of this method—similar to the direct aromatic ^{18}F-fluorination reactions—is the need to protect any potentially competing sites of nucleophilic attack in the molecule (principally acid, alcohol, or amine groups). This results in additional synthesis and purification steps, which can result in longer synthesis times. A good example of aliphatic nucleophilic ^{18}F substitution is the synthesis of [^{18}F]FDG (**53**)[205,206] in which the acetyl-protected sugar tetra-*O*-acetyl-2-triflate-β-mannose (**80**) is used during the direct ^{18}F-fluorination step (Scheme 42). A deprotection of the ester

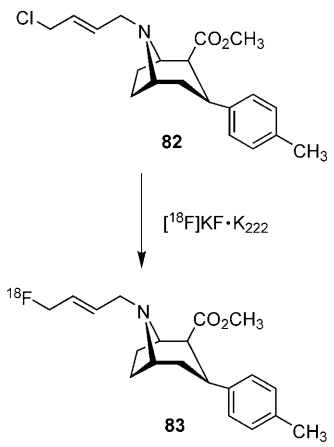


Scheme 42. Synthesis of [^{18}F]FDG (**53**) following deprotection of the protected [^{18}F]sugar **81**.

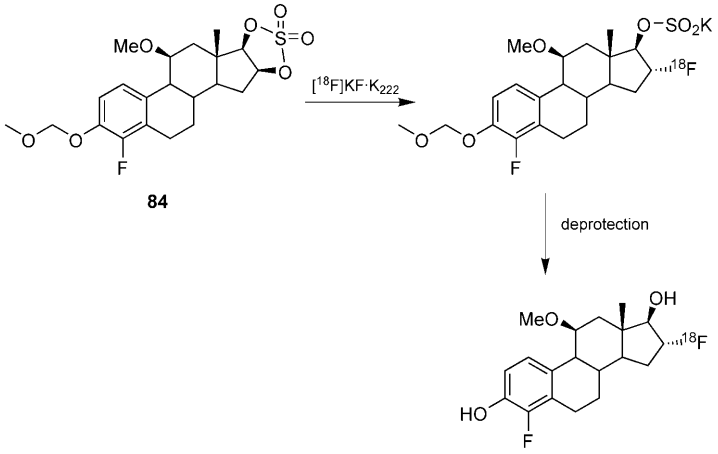
groups completes the synthesis of [^{18}F]FDG. The production of [^{18}F]FDG is now fully automated, with a range of commercial units available which exploit polymer-supported reagents to trap the $^{18}F^-$ ion for the nucleophilic substitution reaction with the protected sugar. These methods also allow easier recovery of the valuable ^{18}O-enriched water, used for the production of ^{18}F, and aid rapid purification of [^{18}F]FDG. The synthesis of [^{18}F]FDG can now be achieved in approximately 30 minutes with radiochemical yields greater than 70%. A newer method for the synthesis of [^{18}F]FDG involves a protected sugar supported on a resin that is liberated when treated with [^{18}F]KF·K_{222} in acetonitrile for 2–4 minutes.[207] Following deprotection, [^{18}F]FDG was obtained in high RCY (73%) and with high chemical purity.

Aliphatic ^{18}F reactions have been used to effectively label a number of complex organic molecules in either one step (where no protecting groups are necessary) or two synthetic steps (which involve a deprotection).[150] Some recent examples include the one-step preparation of selective dopamine transporter ligands such as [^{18}F]LBT-999 (**83**, Scheme 43)[208] and other related analogues such as [^{18}F]FP-CIT.[209] Two-step preparations, in a similar fashion to [^{18}F]FDG synthesis, include the preparation of [^{18}F]estradiol derivatives, for breast cancer imaging, such as 16α-[^{18}F]fluoroestradiol ([^{18}F]FES)[210,211] and more recently 4F-M[^{18}F]FES (**85**, Scheme 44)[212] which rely on the use of protected cyclic sulfonate derivatives.

An alternative method to the [^{18}F]KF·K_{222} labeling procedure in aprotic solvents is the use of [^{18}F]TBAF in tertiary alcohols. Protic solvents, such as alcohols, are generally not used for nucleophilic substitution reactions because of their ability to solvate the nucleophile and retard

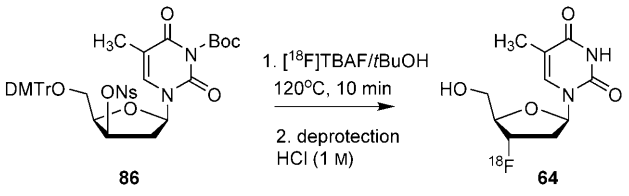


Scheme 43. One-step synthesis of [^{18}F]LBT-999 (**83**) from the chloro precursor **82**.



Scheme 44. Two-step synthesis of the [^{18}F]estradiol derivative 4F-M[^{18}F]FES (**85**) from the protected cyclic sulfonate precursor **84**.

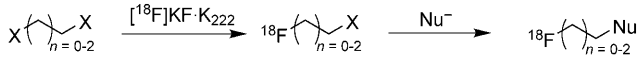
its reactivity. However, the beneficial effects of using tertiary alcohols as solvents has recently been reported for nucleophilic ^{19}F and ^{18}F reactions.[183–185,213] The protic medium is reported to suppress the formation of by-products and increase the rate of nucleophilic fluorination. For example, remarkable improvements in RCYs (65%) have been reported for the synthesis of [^{18}F]FLT (**64**, Scheme 45) compared to previously reported literature methods (15%).



Scheme 45. Synthesis of [^{18}F]FLT (**64**) by reaction of the protected precursor **86** with [^{18}F]TBAF in *tert*-butyl alcohol.

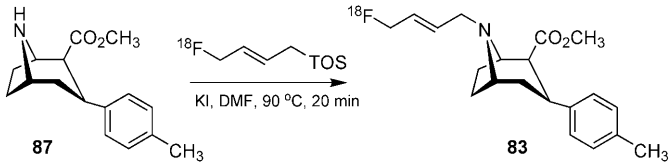
3.3.4. *Simple [^{18}F]Fluoroaliphatic Derivatives*

[^{18}F]Fluoroaliphatic derivatives are important synthetic precursors for the introduction of [^{18}F]fluoroalkyl groups into target molecules that would be otherwise difficult to synthesize under the reaction conditions used for direct nucleophilic ^{18}F fluorination. Simple [^{18}F]fluoroalkyl derivatives are prepared by the reaction of nucleophilic [^{18}F]fluoride with dihalo or disulfonate alkyl starting materials; the vast excess of the alkyl starting material compared to the $^{18}F^-$ allows exclusive formation of the mono[^{18}F]fluoroalkyl halide or sulfonate. A range of [^{18}F]fluoroalkylating agents have been prepared with methyl, ethyl, and propyl carbon backbones together with suitable leaving groups for reaction with nucleophilic species (Scheme 46).[214–218] Simple mono[^{18}F]fluoroalkyl halide/sulfonate groups provide an alternative synthetic pathway to label target biological compounds such as the dopamine transporter ligands [^{18}F]LBT-999 (**83**, Scheme 47)[219] and the related [^{18}F]FP-CIT analogue.[220]



X = Br, I, or tosylate

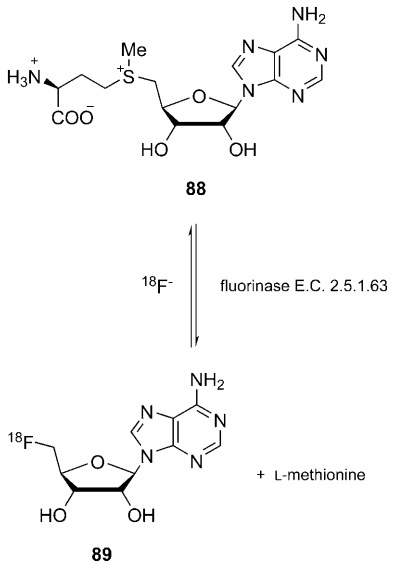
Scheme 46. Synthesis and reaction of simple [^{18}F]fluoroaliphatic derivatives.



Scheme 47. Synthesis of [^{18}F]LBT-999 (**83**) using the reactive (*E*)-[^{18}F]fluoro-4-tosyloxybut-2-ene group and the secondary amine precursor **87** (see Scheme 43).

3.3.5. *[^{18}F]Fluorinase Reactions*

The formation of C–F bonds in biological systems is a very rare occurrence. The use of the fluorinase enzyme, from the bacterium *Streptomyces cattleya*, as a method for the direct introduction of ^{18}F into organic molecules presents a powerful breakthrough in the field of radiolabeling. Recent work by the research group of O'Hagan[221,222] into the isolation and over-expression of the fluorination enzyme has led to its utilization for the highly selective formation of C–F bonds and its application in ^{18}F radiolabeling. Initial reports using the wild-type enzyme gave low RYCs of about 1%,[223] but provided proof-of-principle. A recent study of ^{18}F labeling using the over-expressed fluorinase enzyme brought about a major improvement, with [^{18}F]-5′-fluoro-5′-deoxyadenine ([^{18}F]5′-FDA, **89**) synthesized in 95% RCY within two hours.[224] The fluorination reaction was found to be in equilibrium (Scheme 48), and to give a good RCY this equilibrium must be shifted towards [^{18}F]5′-FDA (**89**) by using a coupled fluorinase-oxidase enzyme system. The oxidase

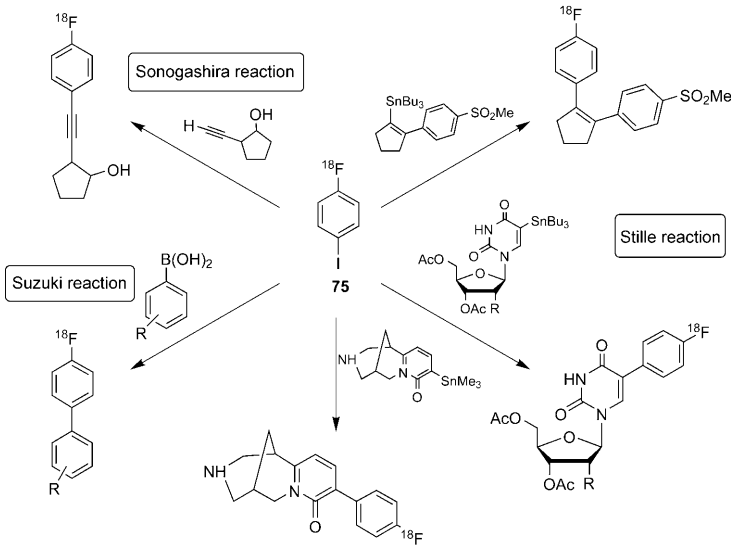


Scheme 48. Fluorinase-oxidase reaction for the synthesis of [^{18}F]-5′-fluoro-5′-deoxyadenine ([^{18}F]5′-FDA).

removes the L-methionine from the reaction and shifts the equilibrium to the right, thereby improving both the rate of the reaction and overall conversion. Other coupled enzyme systems also proved to be successful for the synthesis of the labeled derivatives [^{18}F]-5′-fluoro-5′-deoxyinosine ([^{18}F]-5′-FDI; RCY 75%, 4 h) and the free sugar [^{18}F]-5-fluoro-5-deoxy-D-ribose ([^{18}F]-5-FDR; RCY 45%, 4 h). Although the incubation times for these enzymatic reactions are long (2–4 h) on the timeframe of PET labeling, rapid evolutionary techniques are expected to improve such enzymes and greatly enhance reaction rates. The major limitation to this technique is the specificity of the fluorinase enzyme, which restricts its use as a general fluorination method. However, as the authors have already demonstrated, it is possible to label a range of derivatives using additional enzyme coupled systems and hydrolysis reactions. Research into the specificity of modified adenine and ribose substrates will further extend the range of ^{18}F-labeled compounds and the versatility of this method. Such enzymatic methods of radiolabeled compounds are particularly attractive because of their high chemospecificity and the formation of few side products, which can simplify purification. The use of biotransformations for the synthesis of short-lived radiolabeled compounds is, without question, challenging, but with foresight and innovation, as we have seen, extremely impressive results can be produced.

3.4. Indirect ^{18}F Labeling using [^{18}F]Fluorohalobenzenes

1-Bromo-4-[^{18}F]fluorobenzene (**74**) and 1-[^{18}F]fluoro-4-iodobenzene (**75**) have been used as ^{18}F precursors in palladium-mediated cross-coupling for the synthesis of complex ^{18}F-labeled target molecules. 1-[^{18}F]Fluoro-4-iodobenzene (**75**) can be prepared by the thermal decomposition of 4,4′-diiododiphenyliodonium triflate in the presence of ^{18}F (see Section 3.3.1). Removal of the excess diiodobenzene by-product can be achieved by automated solid-phase extraction.[225] The Suzuki reaction has been investigated as a method to couple together simple [^{18}F]fluoroaryl derivatives to form a series of [^{18}F]fluorobiphenyls (Scheme 49).[225] The reaction of **75** with *p*-tolylboronic acid was used as a model reaction to screen the effectiveness of different palladium complexes, bases, and solvents. The optimum coupling conditions to give the highest RCYs were found to be [$Pd_2(dba)_3$], Cs_2CO_3, and acetonitrile at 60 °C for 5 minutes. These conditions were then applied to the synthesis of a series of ^{18}F-labeled biphenyls. A range of functional groups are tolerated in this reaction including esters, OMe, SMe, methanesulfonyl groups, hydroxy, and nitro groups; carboxylic acid groups were less well tolerated and gave lower RCYs. Both boronic acid and boronic ester starting materials were found to couple efficiently in model reactions. Similar coupling reactions have been reported for the palladium-mediated Stille reaction of trialkyl tin precursors with **75** to form selective COX-2 inhibitors.[226] Optimization of the reaction conditions by catalyst and solvent screening showed that a high RCY of 93% could be obtained with [$Pd_2(dba)_3$]/P(*o*-tol)$_3$/CuI in a DMF/toluene mixed solvent system at 65 °C.

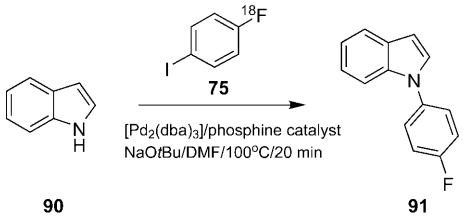


Scheme 49. Synthesis of [^{18}F]fluorocompounds by palladium-mediated reactions of 1-[^{18}F]fluoro-4-iodobenzene (**75**).

The Stille reaction has also been used for the synthesis of nucleotides (Scheme 49).[227] The best RCYs were obtained with a 1:1:1 mixture of [$Pd_2(dba)_3$]/CuI/$AsPh_3$ catalyst system in a DMF/dioxane solvent mixture at 65 °C for 20 minutes. The Stille reaction has also been reported for the synthesis of ^{18}F-labeled cytisine alkaloids by using 1-bromo-4-[^{18}F]fluorobenzene (**74**); good RCYs were obtained (68%) in short reaction times of 10–15 minutes.[228] Wüst and Kniess[229] have also described the use of palladium-mediated Sonogashira coupling of **75** to form a range of terminal

alkynes (Scheme 49) that were found to be tolerant of the hydroxy functional group.

The palladium-mediated N-arylation reaction of **75** with indole **90** has been investigated[230,231] (Scheme 50). The highest RCYs were obtained using CuI/1,2-ethylenediamine and the precatalyst $[Pd_2(dba)_3]$/2,9-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (81–90% with sodium *tert*-butoxide as base in toluene at 100 °C for 20 minutes). Direct ^{18}F fluorination of the aromatic rings in these compounds is not possible because they are not sufficiently activated by electron-withdrawing groups, thus the indirect coupling method is the only available ^{18}F-labeling route.



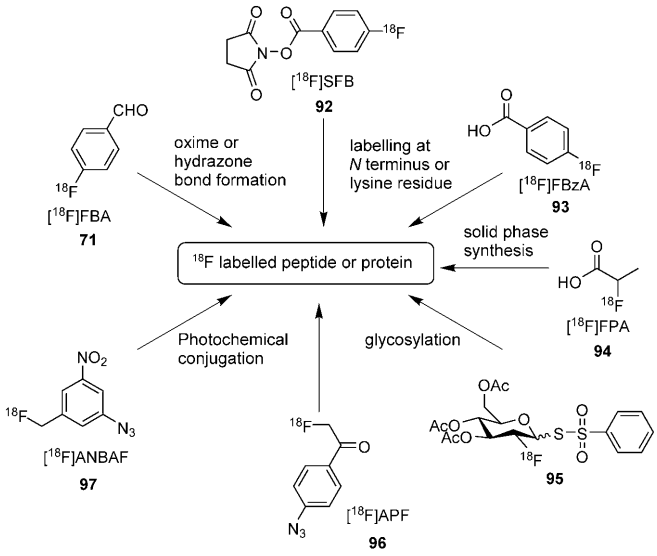
Scheme 50. N Arylation of 1-iodo-4-[^{18}F]fluorobenzene (**75**) to form the 4-[^{18}F]fluorophenylindole **91**.

3.5. ^{18}F Labeling of Biomolecules

Isotopic labeling of biomolecules (oligonucleotides, peptides, and proteins) for applications in PET is becoming more important because of the increasing interest in using these compounds for the treatment of diseases and diagnosis. The direct labeling of most peptides and proteins using nucleophilic [^{18}F]fluoride is not appropriate because the harsh reaction conditions (high temperatures, basic conditions, and organic solvents) required to achieve good RCYs would destroy the molecule. The labeling of proteins and peptides for PET relies on the indirect introduction of the ^{18}F radioisotope by reaction with suitable prosthetic ^{18}F groups under mild reaction conditions (room temperature and aqueous solution). Additionally, the reaction of the prosthetic group should be chemoselective and have no adverse effects on the biological properties of the biomolecule. The area of peptide-based radiopharmaceuticals for imaging has recently been reviewed[232] and the synthesis of ^{18}F-labeled peptides was reviewed in 2001,[233] while the application of labeled oligonucleotides as radiopharmaceuticals was reviewed in 2002.[234] This section focuses on the more recent development of the radiolabeling of peptides and biomolecules with ^{18}F.

3.5.1. Common ^{18}F Reagents for Labeling Peptides

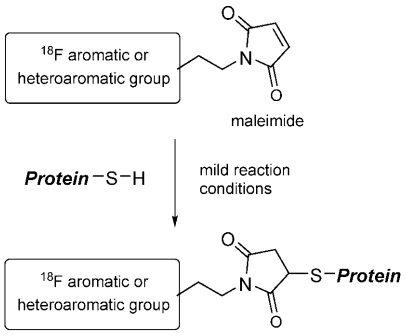
A range of prosthetic ^{18}F groups have been developed for peptide labeling (Scheme 51)—each has its own strengths and weaknesses in terms of ease of synthesis and reactivity with the target peptide. There is no general protocol for the synthesis of labeled peptides for PET, and often several labeling procedures need to be explored and optimized to find the best method for a particular peptide. The majority of



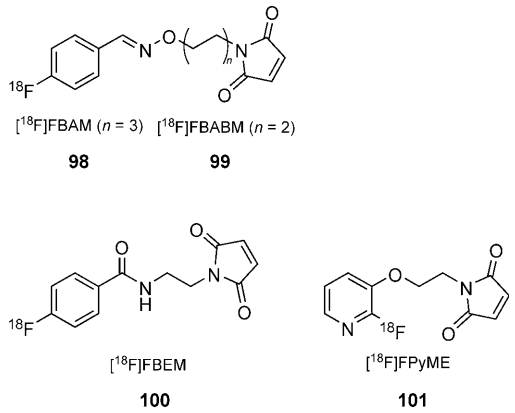
Scheme 51. Reagents for the ^{18}F labeling of proteins, peptides, and oligonucleotides.

peptide-labeling strategies focus on prosthetic ^{18}F reagents that target amino, carboxylic acid, or sulfhydryl functional groups within the peptide. Primary amino groups at the N-terminus or lysine residues in proteins or peptides have, to date, received the greatest attention. The most commonly used ^{18}F-labeling reagent for this is the active ester *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB, **92**), which is conjugated to a peptide through an acylation reaction. Although the preparation of [^{18}F]SFB is well reported,[235] it requires a time-consuming three-step synthesis. Recently, however, significant advances have been taken to automate its synthesis.[236] 4-[^{18}F]Fluorobenzaldehyde ([^{18}F]FBA, **71**) has also proven to be a versatile labeling reagent that is significantly easier to prepare than [^{18}F]SFB. Chemoselective ^{18}F labeling, with high RCYs and under mild reaction conditions, of peptides which have an aminooxyl functional group (via the formation of an oxime group) can be achieved using [^{18}F]FBA.[237] Photochemical conjugation reactions using 4-azidophenacyl[^{18}F]fluoride ([^{18}F]APF, **96**),[235] for peptide labeling, and 3-azido-5-nitrobenzyl[^{18}F]fluoride ([^{18}F]ANBF, **97**),[238] for oligonucleotide labeling, have also been reported.

The reaction of peptides or proteins containing a free thiol group with [^{18}F]maleimide reagents (Scheme 52), such as [^{18}F]FBAM (**98**), [^{18}F]FBABM (**99**), *N*-[2-(4-[^{18}F]fluorobenzamido)ethyl]maleimide ([^{18}F]FBEM, **100**), or 1-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl]pyrrole-2,5-dione ([^{18}F]FpyME, **101**; Scheme 53), with formation of a thioether bond, is a chemoselective labeling technique that gives high RCYs under mild reaction conditions. Since most proteins contain cysteine residues, or can be engineered to do so, these prosthetic [^{18}F]maleimide groups have the potential for labeling a wide range of peptides, proteins, and/or oligonucleotides. [^{18}F]Maleimides can be obtained efficiently (within 60 min) in two steps (via formation of an oxime) by the reaction of an aminooxymaleinimide with [^{18}F]FBA (**71**) to form [^{18}F]FBABM (**99**)[239] or [^{18}F]FBAM (**98**).[240,241] Cou-



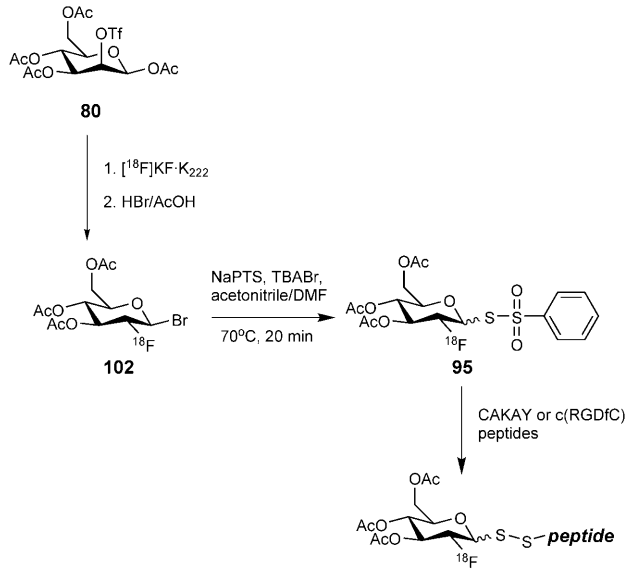
Scheme 52. Synthesis of ^{18}F-labeled proteins by reaction of [^{18}F]maleimides and free thiol groups.



Scheme 53. [^{18}F]Malemide reagents that react with thiol groups for peptide and protein labeling.

pling of [^{18}F]SFB (**92**) with *N*-(2-*a*minoethyl)maleimide to form the amide [^{18}F]FBEM (**100**)[242] is an alternative route to [^{18}F]malenimides; however, the overall synthesis takes a relatively long time (150 min). The three-step preparation of the pyridylmaleimide reagent [^{18}F]FpyME (**101**),[243] exploits the use of heteroaromatic nucleophilic substitution reactions to efficiently introduce ^{18}F into the *ortho* position of the pyridyl ring. The above prosthetic [^{18}F]maleimide groups have been used to conjugate efficiently with free thiol groups in peptides or proteins, thereby achieving high RCYs for the final conjugation step.

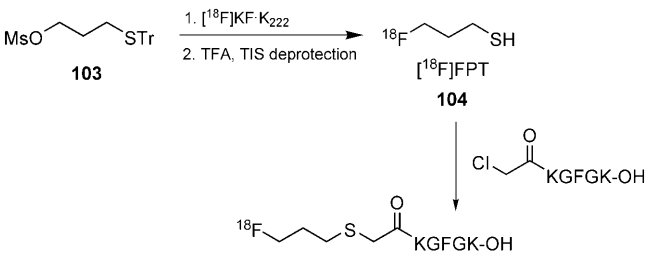
^{18}F-Glycosylation reactions of amino acids[244,245] and peptides[246] using a novel chemoselective derivative of [^{18}F]FDG has been reported to be an effective way of introducing an ^{18}F label. This method combines O glycosylation, which may enhance bioavailability and BBB permeability, with ^{18}F labeling of the target compound in one step. Model reactions were initially carried out using the Fmoc-protected amino acids serine and threonine glycosyl acceptors with the tetra-O-acetylated 2-deoxy-2-[^{18}F]fluoropyranoside. The deprotected ^{18}F-glycosylated amino acids were obtained in modest 25% and 12% RCYs, respectively, using BF_3 as a promoter. This method was further adapted by using the 3,4,6-tri-*O*-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranosyl bromide (**102**) under Koenigs–Knorr conditions to improve the RCY to 67% for protected serine derivatives.[245] More recently, the new ^{18}F glycosyl donor 3,4,6-tri-*O*-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranosyl phenylthiosulfonate (Ac_3-[^{18}F]FGlc-PTS, **95**) was developed for the ^{18}F glycosylation of cyclic RGD peptides.[246] The reagent was obtained in 33% RCY after three steps and purified using semipreparative HPLC. This strategy combines chemospecific ^{18}F labeling and glycosylation of a cysteine residue in the target peptide, and gave an excellent RCY of 95% within 15 minutes for the final conjugation step (Scheme 54).



Scheme 54. ^{18}F Glycosylation of peptides using Ac_3-[^{18}F]FGlc-PTS (**95**).

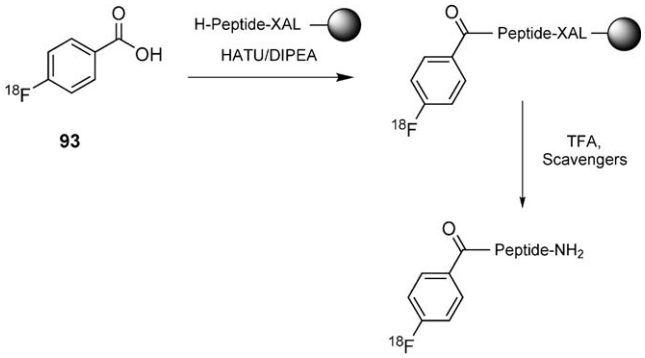
Simple [^{18}F]fluorothiol reagents, such as 3-[^{18}F]fluoropropane-1-thiol ([^{18}F]FPT, **104**), have been reported recently as a new approach for obtaining labeled peptides for PET.[247] Although the RCYs of the ^{18}F-labeled peptides are not as impressive as the other more powerful oxime methods described above, it nevertheless proved to have high chemoselectivity towards the labeling of a chloroacetylated model peptide at the N terminus. Three new [^{18}F]fluorothiols were developed by reaction of mesylated protected thiols with [^{18}F]KF·K_{222}, followed by deprotection (Scheme 55). Excellent analytical RCYs of labeled peptides were obtained; however, the isolated RCYs (1–32%) were poor.

Solid-phase methods are particularly useful in radiosyntheses because their integration with automated systems



Scheme 55. Preparation of [^{18}F]FPT (**104**) from the protected thiol **103** and reaction with *N*-chloroacetylated model peptide $ClCH_2C(O)$-KGFGKOH.

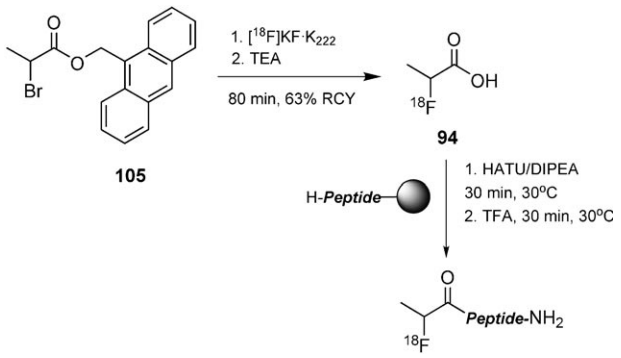
allows rapid synthesis and easier product separation. Solid-phase methods have been used very effectively for the synthesis of ^{18}F-labeled peptides using 4-[^{18}F]fluorobenzoic acid ([^{18}F]FBzA, **93**)[248,249] and 2-[^{18}F]fluoropropionic acid ([^{18}F]FPA, **94**).[39] The synthesis of 4-[^{18}F]fluorobenzoyl peptides has been achieved in two steps (Scheme 56), starting



Scheme 56. Solid-phase method for the ^{18}F labeling of peptides using [^{18}F]FBzA (**93**).

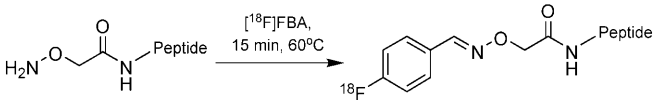
from the synthesis of [^{18}F]FBzA from the 4-trimethylammonium triflate ethylbenzoate salt. In the presence of HATU/DIPEA ^{18}F labeling with [^{18}F]FBzA was complete within two minutes; cleavage from the polyethylene glycol/polystyrene resin and deprotection of the side chain was achieved within seven minutes. 4-[^{18}F]Benzoyl peptides were synthesized with a radiochemical purity of greater than 99% and decay-corrected RCY of greater than 90% after HPLC.

[^{18}F]FPA (**94**) represents an alternative labeling group to the commonly used [^{18}F]FBzA (**95**) or [^{18}F]SFB (**92**) prosthetic groups for the synthesis of ^{18}F-labeled peptides. The small [^{18}F]FPA group has been purported to have a minimal impact on the biological properties (such as lipophilicity) of proteins[235] compared to labeling with [^{18}F]FBzA. [^{18}F]FPA was prepared in a solid-phase peptide synthesis by the reaction of [^{18}F]KF·K_{222} with 9-methylanthranyl-2-bromopropionate (**105**) and treated with a protected peptide attached to a range of resin supports (Scheme 57). ^{18}F-Labeled peptides could be obtained in a total reaction time of 175 minutes, with RCYs ranging from 6–16% depending on the peptide, resin, and conjugation conditions used.



Scheme 57. Preparation of [^{18}F]FPA (**94**) and its use in the solid-phase synthesis of peptides.

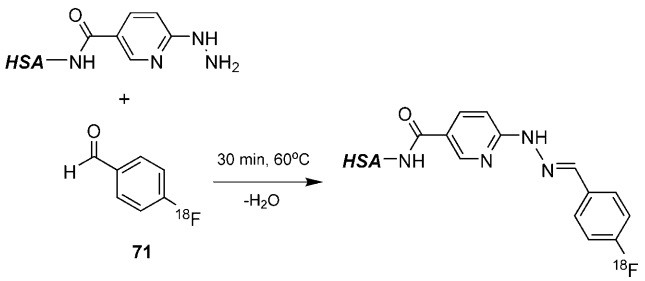
The formation of a chemoselective hydrazone bond through conjugation of hydrazine-functionalized precursors with the [^{18}F]FBA (**71**) prosthetic group is a common route to ^{18}F-labeled peptides and proteins. Peptide conjugation can be achieved in excellent RCYs by using this method;[250,251] however, the main drawback is the necessary preparation of hydrazine-functionalized peptides. Human serum albumin (HSA) has recently been labeled by using this method[252] by conjugating hydrazinonicotinic acid (HYNIC) first with HSA and then treating with [^{18}F]FBA (Scheme 58). The conjuga-



Scheme 58. The preparation of [^{18}F]HSA using HSA-HYNIC coupling and [^{18}F]FBA (**71**) through formation of a hydrazone bond.

tion efficiency was between 25 and 99%, and found to be highly dependent on the reaction conditions. The optimum conditions were achieved at higher concentrations of the protein (3 mg/1.5 mL), incubation times of 30 minutes, and a reaction temperature of 60°C. Comparisons can be made between the oxime-formation reactions (see below) and hydrazone formation.

The rapid and efficient chemoselective formation of the ^{18}F-labeled RGD peptides Tyr^3-octreotate (TOCA) and octreotide analogues by oxime formation[237,253] can be achieved in short reaction times, with high RCYs obtained using unprotected precursors in aqueous media. For example, a chemoselective oxime bond can be formed between an unprotected aminooxy-functionalized peptide precursor and [^{18}F]FBA (**71**, Scheme 59). The RCYs of *N*-4-

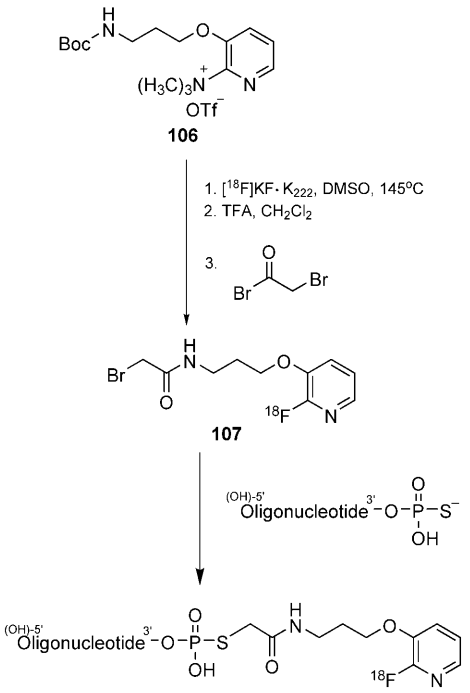


Scheme 59. Synthesis of ^{18}F-labeled peptides through oxime formation by using [^{18}F]FBA (**71**).

[^{18}F]fluoro(benzylidene)oximes are found to be dependent on reaction time, temperature, peptide concentration, and pH value. Labeling efficiencies of 60–80% were achieved at low peptide concentrations (0.5 mmol L^{-1}) within 15 minutes at 60°C and pH 2–3. The overall yields for the two steps (preparation of [^{18}F]FBA and conjugation) were 40% from EOB. Such straightforward and rapid labeling of peptides may allow for the routine production of tracers on a large scale for clinical use. The specificity of the [^{18}F]FBA reaction with the aminooxy group was proven by incubation experiments with competing amino acids (cysteine, lysine, arginine,

histidine, and serine) in the presence and absence of 2-aminooxyacetic acid. [^{18}F]FBA was found to react with cysteine in the absence of 2-aminooxyacetic acid; however, in its presence the RCY of 4-[^{18}F]fluorobenzylideneaminooxy acetic acid was 93%, thus proving the high specificity for oxime formation.

The new [^{18}F]fluoropyridine-based bromoacetamide reagent 2-bromo-*N*-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl]acetamide ([^{18}F]FpyBrA, **107**) has recently been reported for oligonucleotide labeling.[254] The pyridyl group allows efficient incorporation of ^{18}F into the *ortho* position by a standard nucleophilic substitution of a trimethyl ammonium triflate group. The bromoacetamide functional group of [^{18}F]FpyBrA ensures efficient alkylation of a phosphorothioate monoester group of single-stranded oligonucleotides (Scheme 60). [^{18}F]FpyBrA (**107**) could be regioselectively



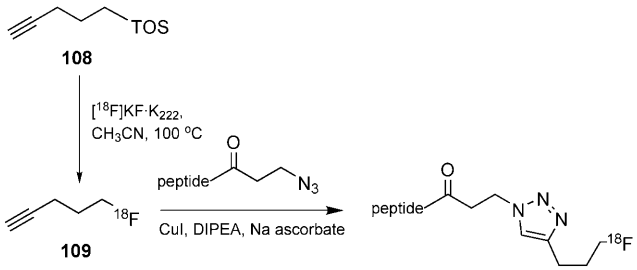
Scheme 60. Synthesis of [^{18}F]FpyBrA (**107**) from the Boc-protected precursor **106** and subsequent ^{18}F labeling of oligonucleotides (9- or 18-mer).

conjugated with 9-mer and 18-mer single-stranded oligonucleotides at the 3′ end. The optimal reaction conditions for the conjugation reaction were a reaction time of 15 minutes, MeOH/0.1M PBS, pH 7.4, and 120°C. The total time for the whole radiosynthetic procedure, including HPLC purification and formulation, was 140–160 minutes.

[^{18}F]FPyBrA provides a valuable alternative to the *N*-(4-[^{18}F]fluorobenzyl)-2-bromoacetamide ([^{18}F]FBBA),[190] [^{18}F]SFB (**92**),[255] and 3-azido-5-nitrobenzyl-[^{18}F]fluoride ([^{18}F]ANBF, **97**)[238] prosthetic groups for the labeling of oligonucleotides. The main drawback of the [^{18}F]FpyBrA prosthetic group is the three-step reaction required for its production which takes 85 minutes.

3.5.2. ^{18}F Labeling Using the Click Reaction

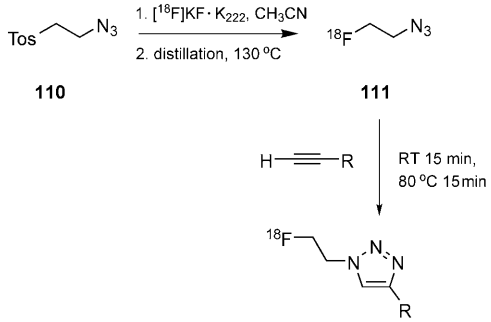
The rapid formation of triazole rings by the 1,3-dipolar Huisgen cycloaddition of alkynes to azides (click chemistry) has recently been exploited for the synthesis of ^{18}F-labeled biomolecules. The click reaction is a particularly amenable reaction for adaptation to radiosynthetic methods because of its speed, selectivity, and simplicity under mild reaction conditions. The click reaction was first adopted by Marik, Sutcliffe et al.[39] for the preparation of ^{18}F-labeled peptide fragments. ^{18}F-Labeled alkynes were prepared by the ^{18}F$^-$ nucleophilic substitution reaction of an alkyne tosylate (Scheme 61). Traditionally, copper(I)-catalyzed 1,3-dipolar



Scheme 61. Formation of a simple [^{18}F]fluoroalkyne **109** from the tosylate **108** followed by ^{18}F labeling of peptides through the click reaction.

cycloadditions of azides and alkynes require reaction times of several hours to obtain high yields, and thus may appear unsuitable for rapid syntheses of PET markers. However, the vast stoichiometric excess of the Cu^{I} catalyst and azide compared to the [^{18}F]alkyne results in good to excellent RCYs (54–99%) for the conjugation step within 10 minutes at room temperature under basic conditions. The labeled compounds were obtained in high purity by using a simple purification method—extraction on a C18 Sep-Pak cartridge followed by evaporation of the eluent solvent and excess [^{18}F]fluoroalkyne.

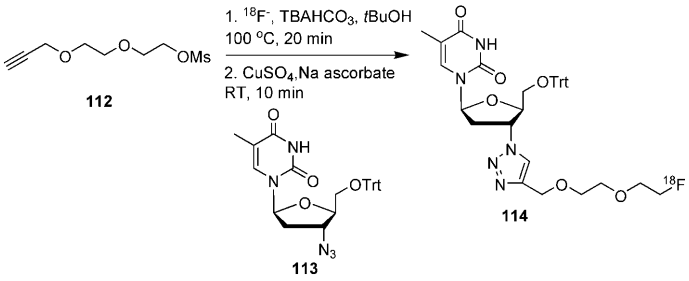
The preparation of 2-[^{18}F]fluoroethylazide (**111**) and its copper(I)-catalyzed Huisgen cycloaddition reaction with a library of terminal alkynes has recently been reported (Scheme 62).[256] Reactions were carried out for 15 minutes under ambient conditions followed by 15 minutes of heating



Scheme 62. ^{18}F labeling of terminal alkynes by the click reaction using 2-[^{18}F]fluoroethylazide (**111**).

in a buffered solution (pH 6.0, water/acetonitrile/DMF) in an inert atmosphere in the presence of excess copper(I). The RCYs of the labeled products ranged from 15 to 98%, and were markedly dependent on the alkyne substrate and the catalytic system used. The mild reaction conditions employed and the high functional group tolerance (acids, amides, alcohols, and primary amines, etc) make this reaction suitable for labeling more complex biomolecules. 2-[^{18}F]Fluoroethylazide (**111**) was found to be suitable for the labeling of a model alkyne peptide, with a 92% decay-corrected RCY in high purity (>99%) achieved for the cycloaddition step under mild reactions within 15 minutes.

[^{18}F]Glycoalkynes and [^{18}F]glycoazides have recently been used as precursers for the ^{18}F labeling of small biological molecules such as monosaccarides, amino acids, and oligonucleotides,[257] as well as the much larger RGD peptides[258] by the click reaction. In the case of oligonucleotide labeling, a simplified reaction procedure was used which enabled both the ^{18}F fluorination of the mesylate precursor **112** and cycloaddition to the azide **113** (with formation of the ^{18}F-labeled compound **114**) to be conducted in one pot without the need to change solvent systems (Scheme 63). The 1,3-cycloaddition reaction, using $CuSO_4$/Na ascorbate, was found to be almost



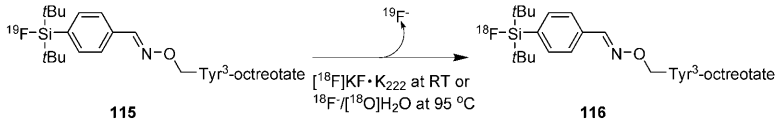
Scheme 63. One-pot ^{18}F labeling of an oligonucleotide through the click reaction.

complete after only 5 minutes and complete reaction was observed within 10 minutes. Reactions were complete within 40 minutes from EOB, and RCYs exceeded 90% for the [^{18}F]alkyne–azide reactions.

The click reaction provides an efficient and mild ^{18}F-labeling route, and will certainly find wider application and interest as a method for introducing PET isotopes into target molecules. A possible limitation of this method is that the copper catalyst can decompose under acidic conditions. Furthermore, the biological effect of including triazole rings into biomolecules has not been investigated, and may significantly alter their chemical and biological properties.

3.6. Miscellaneous ^{18}F-Labeling Reactions

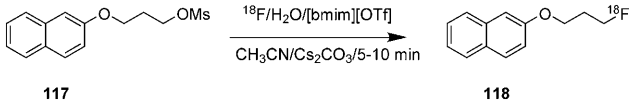
Aryl fluoroborate and alkyl fluorosilicate functionalized biotin molecules have recently been used as novel precursors for aqueous-phase ^{18}F labeling followed by subsequent targeting of the glycoprotein avidin.[259] A related method enables an effective one-step ^{18}F labeling of the peptide Tyr^3-octreotate which was achieved by isotopic exchange of ^{19}F for ^{18}F by using an organosilane fluoride acceptor directly bound to the target peptide (**115**).[260] This method is technically more straightforward way, compared to the multistep peptide-labeling reactions (for example, oxime formation), of introducing ^{18}F into a peptide molecule under mild reaction conditions without time-consuming HPLC purification. Selective ^{18}F labeling was carried out in acetonitrile within 15 minutes at room temperature by using the [^{18}F]KF·K$_{222}$ method (Scheme 64). Alternatively, commercially available aqueous $^{18}F^-$ could be used effectively when the reaction



Scheme 64. Synthesis of the labeled peptide [^{18}F]Tyr^3-octreotate (**116**) by isotopic ^{19}F/^{18}F exchange using a fluoroorganosilane tag.

temperature was increased to 95 °C, with RCYs of 70–90% being achieved within 30 minutes. The major drawback of this method is the production of relatively low specific activities (3–5 GBq μmol^{-1}), which could limit its use in the production of ^{18}F tracers, although higher specific activities may be possible by using larger amounts of $^{18}F^-$.

The unique properties of ionic liquids provide an interesting and potentially very useful alternative reaction medium for enhancing radiolabeling reactions. In this regard, ^{18}F fluorinations of mesyloxyalkanes in the ionic liquid 1-butyl-3-methylimidazolium triflate ([bmim][OTf]) were investigated by Chi and co-workers (Scheme 65).[261] This method is particularly interesting since it tolerates relatively high amounts of water in the reaction solution. [^{18}F]Fluoride can be added directly to the precursor material without the normal rigorous



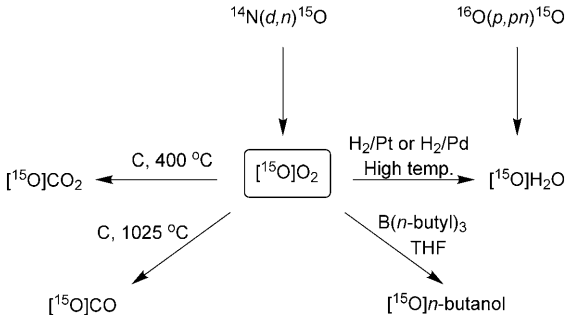
Scheme 65. Model reaction of 2-(3-methanesulfonyloxypropoxy)naphthalene (**117**) with aqueous [^{18}F]fluoride in the ionic liquid [bmim][OTf] to form the ^{18}F-labeled propoxynapthalene **118**.

drying methods typically required for nucleophilic ^{18}F fluorinations. Model reactions were carried out and RCYs of greater than 90% were obtained in 5–10 minutes at 100 °C.

Ionic liquids have also been used in a similar way to synthesize 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT)[262] and [^{18}F]FDG.[263] The radiosynthesis of the potential Alzheimer's disease imaging compound [^{18}F]FESB was found to be significantly enhanced when the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]) was used during the ^{18}F-fluorination step.[264]

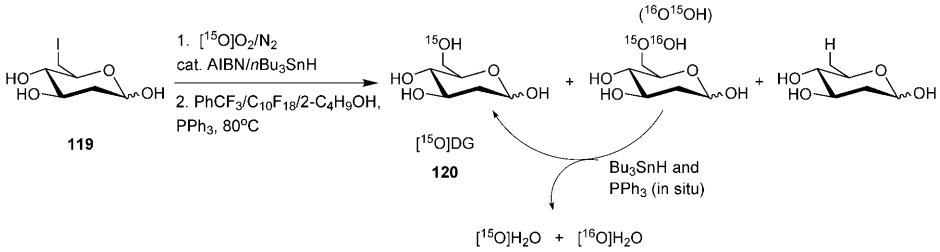
4. Radiolabeling with Oxygen-15 and Nitrogen-13

Besides carbon-11 and fluorine-18, the radionuclides oxygen-15 and nitrogen-13 are attractive choices for labeling since their stable isotopes (^{16}O and ^{14}N) are ubiquitous in biologically active organic molecules. The extremely short half-lives of ^{13}N ($t_{1/2} = 10$ min) and particularly ^{15}O ($t_{1/2} = 2$ min) has imposed limitations with regards to radiosynthetic methods for these two isotopes. In reality, their half-lives are too short to perform radiochemical syntheses of more than one reaction step, and they are rarely used in the synthesis of complex molecules which generally require time-consuming purification methods. Simple chemical products such as $[^{15}O]CO_2$, $[^{15}O]H_2O$, and $[^{13}N]NH_3$ can be obtained directly from the cyclotron target and used as is or rapidly converted into other simple products (for example $[^{15}O]CO_2 \rightarrow [^{15}O]CO$). The short half-lives of these isotopes can be a disadvantage in terms of the synthesis of tracers and their clinical applications; however, advantageously, repeat PET procedures may carried out on the same subject in a short time (an entire measurement is accomplished in 5–10 min). The potential application of ^{15}O- and ^{13}N-labeled compounds has remained largely untapped because of difficulties in synthesizing molecules with such short half-lives.



Scheme 66. Syntheses of common ^{15}O compounds for PET.

A recent report illustrated a single-step synthesis of 6-$[^{15}O]$-2-deoxy-D-glucose ($[^{15}O]$DG, **120**) from the corresponding iodide (Scheme 67) by a new ^{15}O-labeling methodology.[283] The authors claim that the use of mild and neutral radical-reaction conditions negates the need for protecting any free hydroxy groups. This method also features labeling as the last step in the synthesis, which is clearly important when using any short-lived radionuclide. The authors also redeveloped the ^{17}O and ^{18}O labeling of protected sugars (with air, alkyl halide, Bu_3SnH, and AIBN).[284] By forgoing the use of a protected sugar they reduced the reaction time from 10 hours to just a few minutes. A specially adapted hot-air jacket reaction vessel equipped with a sintered glass bottom introduced the ^{15}O-oxygen gas to the liquid reagents as fine bubbles. This improves the trapping efficiency of $[^{15}O]O_2$ in solution. After about 7 minutes, the RCY of $[^{15}O]$DG was calculated to be about 80% before purification, with a decay-corrected radiochemical purity of about 70% (the remainder was ^{15}O-labeled water). Sequential $[^{15}O]$DG-$[^{15}O]H_2O$-$[^{18}F]$FDG measurements were performed at five minute intervals to obtain PET images, which showed accumulation in the expected organs for glucose metabolism (the heart, kidneys, and bladder) in animal models. The reasonable quantity and yields of ^{15}O-labeled product, the simplicity of the oxygenation reaction, and the one-step synthetic operation make this an interesting ^{15}O-labeling method for obtaining high RCYs of $[^{15}O]$DG.



Scheme 67. Rapid synthesis of 6-$[^{15}O]$-2-deoxy-D-glucose ($[^{15}O]$DG, **120**) from iodinated sugar **119**.

4.1. Synthetic Procedures with ^{15}O

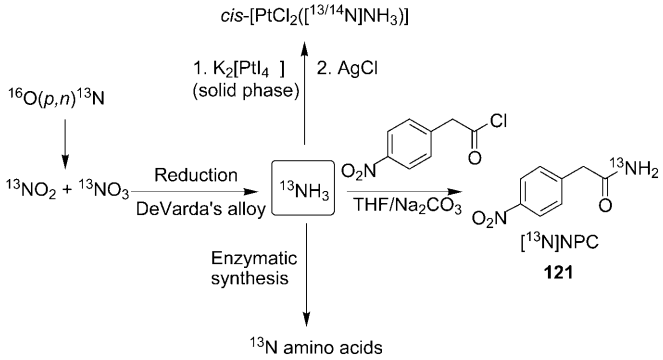
The earliest PET imaging was based on the use of ^{15}O-labeled O_2, CO, and CO_2, as one of the first cyclotrons was a deuteron machine and primarily used to produce ^{15}O. Not until the mid-1970s did a full range of isotopes become available to biomedical facilities. Oxygen-15 is commonly produced by the reaction $^{14}N(d,n)^{15}O$, whereby irradiation of nitrogen gas with an oxygen content of less than 5% gives the common precurser $[^{15}O]O_2$. A common application of oxygen-15 is the study of regional cerebral blood flow (rCBF) by using ^{15}O-labeled water.[265–268] There are generally three ways to form ^{15}O-labeled water: 1) by the conversion of $[^{15}O]O_2$ into $[^{15}O]CO_2$ (Scheme 66), which after inhalation is instantaneously converted into $[^{15}O]H_2O$ in the lungs by the carbonic anhydrase enzyme;[269] 2) conversion of $[^{15}O]O_2$ into $[^{15}O]H_2O$ by reduction over a platinum[270] or palladium[271–273] catalyst at high temperature (Scheme 66); or 3) by bombardment of $[^{16}O]H_2O$ with protons (Scheme 66).[274,275] This yields $[^{15}O]H_2O$ which can be administered intravenously. Early investigations used $[^{15}O]O_2$ or $[^{15}O]H_2O$ for blood-flow studies in the brain and other organs.[276–278] $[^{15}O]$CO, produced by the reaction of $[^{15}O]O_2$ over carbon beads at high temperature,[270,272] can be used to measure regional blood volume.[270,279] ^{15}O-Labeled butanol[280,281] has proven to be superior to $[^{15}O]H_2O$ in the measurement of cerebral blood flows and for neuroactivation studies.[282]

4.2. Synthetic Procedures with ^{13}N

Nitrogen-13 is produced in the cyclotron by the nuclear reaction $^{16}O(p,\alpha)^{13}N$. ^{13}N is available as nitrate or nitrite in

water ([^{13}N]NO_x), and subsequent reduction with the DeVarda alloy (Al/Cu/Zn alloy) yields the most commonly used ^{13}N source, [^{13}N]ammonia.[285–288] By addition of ethanol to the target water,[289] or the use of methane gas,[290] in-target production of [^{13}N]NH_3 is also possible.

The ten-minute half-life of nitrogen-13 precludes extensive synthetic reactions, and its routine application in PET is limited to simple procedures, such as using [^{13}N]ammonia to measure myocardial blood flow[291–294] and the labeling of nitrogen in amino acids using enzymatic synthesis.[295–300] [^{13}N]Ammonia has been used to prepare [^{13}N]*cis*-platin,[301] one of the most extensively studied anticancer drugs. Several, low-yielding multistep syntheses of [^{13}N]*cis*-platin have been reported, but in 1997 a convenient and fast on-column method was developed in which a strong anion exchange resin was used as the solid-state support (Scheme 68).[301] The



Scheme 68. Synthesis of ^{13}N compounds for PET.

method involved a combined two-step reaction/purification process: the first step consisted of a reaction of gaseous [^{13}N]ammonia with a tetraiodoplatinum salt attached to a strong anion exchange resin (LiChrolut SAX). In the second step, the intermediate diiododiamino species was transformed into [^{13}N]*cis*-platin by a ligand-exchange reaction using solid silver(I) chloride. The complete synthesis, including sterile formulation of the product, can be accomplished within 15 minutes. With optimization of the reaction parameters, carrier-added [^{13}N]*cis*-platin can be obtained ready for injection in a decay-corrected RCY of 80%, a specific activity of 30 MBq μmol^{-1}, and a radiochemical purity of greater than 98%.

An automated system has also been developed to synthesize ^{13}N-labeled compounds with high specific activity by using [^{13}N]NH_3 as a synthetic precursor.[288,302] The system enabled the production of an aqueous solution of [^{13}N]NH_3, concentration and desiccation of the [^{13}N]NH_3 solution, reaction of anhydrous [^{13}N]NH_3 with substrate, and purification and formulation. As an example, [^{13}N]*p*-nitrophenyl carbamate ([^{13}N]NPC, **121**) could be obtained ready for intravenous injection in approximately 5 minutes with a specific activity of 460 GBq μmol^{-1} and a radiochemical purity of greater than 99%. Under modified conditions, [^{13}N]NPC can be obtained at an extremely high specific activity of 1800 GBq μmol^{-1}.

5. Conclusions and Outlook

Positron emission tomography imaging is a multidisciplinary area that requires cooperation between physicists, chemists, engineers, pharmacologists, medical doctors, veterinary doctors, mathematicians, and computer scientists to efficiently produce and interpret PET scans. As PET becomes more widely available for clinical use and for research, there will be a greater demand to develop new radiotracers and to improve the synthetic methods for existing compounds. Chemists have a pivotal role in meeting this demand. Radiosynthesis with short-lived positron-emitting isotopes is a challenging area of chemistry. Difficulties of dealing with radioactivity and the necessity of rapid reactions and purification processes are apparent. A major concern in this area is that of the limited number of available building blocks for subsequent labeling reactions to prepare PET markers. Mainstream chemistry research at such elementary levels, beginning with basic elemental forms of carbon, nitrogen, oxygen, and fluorine, to form simple synthetic building blocks, is almost unheard of nowadays but could have important implications in radiolabeling studies. A wider range of basic synthetic building blocks for labeling reactions would, most certainly, lead to more diverse labeling strategies and hence greater possibilities for molecules that are currently difficult or impossible to label by existing methods.

It is a considerable achievement, on the part of the chemists involved in this area, that such a wide array of reactions has been developed and adapted for the synthesis of, in many cases, complex molecules for use in PET scans. Developments from the mainstream chemical literature invariably play a key role and can have a profound knock-on effect in the advancement of radiosynthetic methods. The use of palladium-mediated coupling reactions, the exploitation of the fluorinase enzyme for ^{18}F–C bond formation, the use of supported reagents, and the application of microfluidic technology are just some recent examples. Collaboration between mainstream chemists and radiochemists is vital for future advancements in this area. This review will hopefully go some way in highlighting the field to mainstream chemists and stressing some of the issues and challenges facing radiosynthesis with short-lived isotopes for application in PET.

Abbreviations

AIBN	azobisisobutyronitrile
BBB	blood brain barrier
Bn	benzyl
COX	cyclooxygenase enzyme
c(RGD)	cyclic RGD peptide
dba	dibenzylideneacetone
DIPEA	*N*,*N*′-diisopropylethylamine
DMA	dimethylacetamide
DME	dimethyl ether
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene

dppp	1,3-bis(diphenylphosphino)propane
EOB	end of bombardment
[^{18}F]ANBF	3-azido-5-nitrobenzyl [^{18}F]fluoride
[^{18}F]FBA	4-[^{18}F]fluorobenzaldehyde
[^{18}F]FBABM	*N*-{4-[(4-[^{18}F]fluorobenzylidene)aminooxy]butyl}-maleimide
[^{18}F]FBAM	*N*-{6-[(4-[^{18}F]fluorobenzylidene)aminooxy]hexyl}-maleimide
[^{18}F]FBzA	4-[^{18}F]fluorobenzoic acid
[^{18}F]-5′-FDA	5′-[^{18}F]fluoro-5′-deoxyadenine
[^{18}F]FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose
[^{18}F]FES	16α-[^{18}F]fluoroestradiol
[^{18}F]FESB	1-(2′-[^{18}F]-fluoroethoxy)-2,5-bis(4′-methoxystyryl)benzene
[^{18}F]FLT	3′-deoxy-3′-[^{18}F]fluorothymidine
[^{18}F]FMISO	[^{18}F]fluoromisonidazole
4F-M[^{18}F]FES	11β-methoxy-4,16α-[16α-^{18}F]difluoroestradiol
Fmoc	9-fluorenylmethylcarbonyl
[^{18}F]FPA	2-[^{18}F]fluoropropionic acid
[^{18}F]FPB	4-[^{18}F]fluorophenacyl bromide
[^{18}F]FP-CIT	*N*-(3-[^{18}F]fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane
[^{18}F]FPT	3-[^{18}F]fluoropropane-1-thiol
[^{18}F]FpyBrA	2-bromo-*N*-[3-(2-[^{18}F]fluoropyridin-3-yl-oxy)propyl]acetamide
[^{18}F]FpyME	1-[3-(2-[^{18}F]fluoropyridin-3-yloxy)propyl]-pyrrole-2,5-dione
[^{18}F]SFB	*N*-succinimidyl-4-[^{18}F]fluorobenzoate
GABA	γ-aminobutyric acid
HMPT	hexamethylphosphoramide
HSA	human serum albumen
5-HTT	serotonin transporter protein
HYNIC	hydrazinonicotinic acid
K_{222}	krytopfix{222} (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane)
Ms	mesylate
[^{13}N]NPC	[^{13}N]*p*-nitrophenyl carbamate
*n*Pr	*n*-propyl
PBS	phosphate-buffer saline solution
[^{15}O]DG	6-[^{15}O]-2-deoxy-D-glucose
P(*o*-tolyl)$_3$	tri-*o*-tolylphosphine
rCBF	regional cerebral blood flow
RCY	radiochemical yield
RGD	arginine-glycine-aspartic acid (peptide)
SA	specific activity
SFS	supercritical fluid synthesis
SPE	solid-phase extraction
TBACN	tetrabutylammonium cyanide
TBAF	tetrabutylammoniumfluoride
Tf	triflate
TFA	trifluoroacetic acid
TFP	tri-2-furylphosphine
TIS	triisopropylsilane
TMS	trimethylsilyl
Tr	trityl(triphenylmethyl)

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