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Review Article

# [$^{11}$C]Carbon monoxide, a versatile and useful precursor in labelling chemistry for PET-ligand development†

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**Abstract:** In this review the recent progress in the development of suitable precursors for $^{11}$C-labelling is discussed. Especially the last few years' advancement of the use of [$^{11}$C] carbon monoxide as a versatile and useful precursor in labelling chemistry is presented. The development is set in perspective of its potential in applying molecular imaging tools in drug and tracer development.The possibility of exploring small tracer libraries utilizing the microdosing concept is explored. Copyright © 2007 John Wiley & Sons, Ltd.

**Keywords:** $^{11}$C-precursors; $^{11}$C-carbon monoxide; metal-mediated carbonylations; radical carbonylations; tracer library

## Introduction

In the past 30 years, there has been an increasing interest in the development of tracer technologies in many areas of life science.[1,2] Of particular interest has been the use of short-lived positron emitters such as $^{15}$O, $^{13}$N and $^{11}$C (with half-lives, $T_{1/2}$, of 2, 10 and 20 min, respectively), because they are all radionuclides of key elements of life. Other interesting positron emitters are halogens like $^{18}$F, $^{76}$Br and $^{124}$I, which have longer half-lives ($T_{1/2}$ of 110 min, 16 h and 4.3 days, respectively) and different chemistry synthetic potentials. A number of interesting positron-emitting copper isotopes like $^{61}$Cu, $^{62}$Cu and $^{64}$Cu, which are produced by charged-particle nuclear reactions, and even a few generator-produced radionuclides (especially $^{68}$Ga; $T_{1/2} = 68$ min) are gaining interest.[3]

Each of these radionuclides is interesting for a different reason. The metals can be employed in chelation or complexation strategies, which are useful for labelling peptides proteins and other macromolecules.[3] The halogens have advantages, like longer half-life, which improves logistics in the clinical environment. Radionuclides ($^{15}$O, $^{13}$N, $^{11}$C) of endogenous elements are of special interest because they open up fascinating tracer applications utilizing combinations of tracers,[4–12] and the use in studies for *in vivo* biochemistry. In this context, $^{11}$C has unique labelling potential. The chemical diversity of $^{11}$C can be visualized by presenting the transformations that have been described in the majority of publications (Figure 1).

This review focuses on the recent development of [$^{11}$C]carbon monoxide chemistry, and aims to demonstrate the potential of this chemistry to facilitate future PET-tracer development. The synthetic versatility of [$^{11}$C]carbon monoxide is illustrated in Figure 2. Various labelling protocols can be used, and it is essential to consider the issue of specific radioactivity in tracer production, as this is a key requisite for studies of biological targets at low concentrations. The use of $^{11}$C-carbon monoxide might be favourable because lower atmospheric concentration of stable carbon monoxide compared with carbon dioxide may result in lower isotopic dilution from the environmental sources.

When using radionuclides that are produced at high specific radioactivity and incorporated in labelled compounds, the amount of the tracer is small, and this has opened up avenues for utilizing positron-emitting labelled compounds in a number of new applications. The concept of microdosing[13] is becoming accepted by regulatory bodies,[14–16] and is permitting

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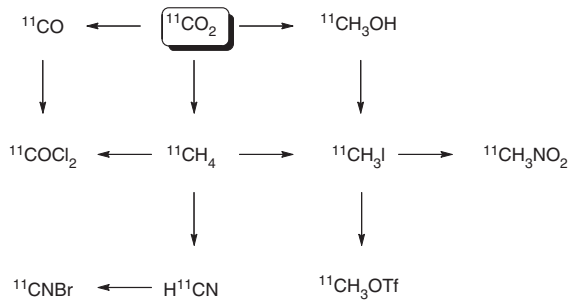



**Figure 1** Some $^{11}$C-labelled one-carbon precursors developed from [$^{11}$C]carbon dioxide.

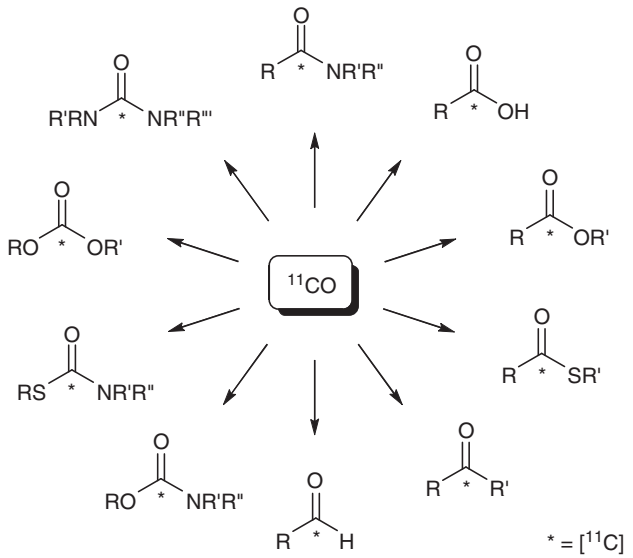



**Figure 2** A number of labelled functional groups have been prepared starting from [$^{11}$C]carbon monoxide of high specific radioactivity.

the use of molecular imaging in basic research applications such as the study of reaction mechanisms[17–22] or performance of analytical systems,[23,24] clinical research[25] and drug development.[26] It seems that the PET technique is slowly moving into clinical applications.

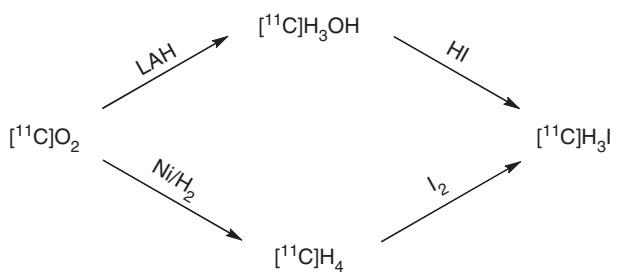
Time is a key parameter[27,28] when dealing with short-lived radionuclides, and is therefore a major limiting factor to be considered when developing synthetic methods employing [$^{11}$C]carbon monoxide. The small scale of operations, coupled with the high vapour pressure and low solubility of carbon monoxide in most solvents, further complicates the problem. Therefore, in work with $^{11}$C, the synthetic strategy is to prepare reactive $^{11}$C precursors and incorporate them as late as possible in a reaction sequence. It is also necessary to consider the work-up and purification methods. In this review we will present strategies for both the direct use of $^{11}$CO as a precursor and its use in preparing other labelled synthons.

## [$^{11}$C]Precursors used in labelling

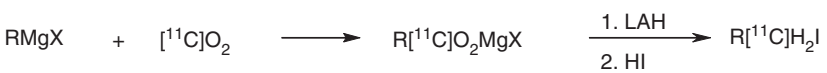
The precursor [$^{11}$C]methyl iodide is so far the most frequently utilized precursor in the preparation of $^{11}$C-labelled PET tracers.[29] Methylation of nitrogen, oxygen or sulphur nucleophiles is employed to attach $^{11}$C late in the synthetic sequence.[30] Alkylation reactions using higher alkyl halides like [$^{11}$C]ethyl, [$^{11}$C]propyl or [$^{11}$C]butyl iodides have also been explored to some extent. [$^{11}$C]Methyl iodide is prepared from [$^{11}$C]carbon dioxide either by reduction with lithium aluminium hydride to [$^{11}$C]methanol followed by iodination[31,32] or by reduction with $Ni/H_2$ to [$^{11}$C]methane followed by free radical iodination (Scheme 1).[33]

Ethyl and higher alkyl halides labelled with $^{11}$C have been prepared by carboxylation of Grignard reagents with [$^{11}$C]carbon dioxide, then reduction with lithium aluminium hydride and iodination with hydroiodic acid (Scheme 2).[34–38]

Carboxylation approaches have also been employed in the syntheses of [$^{11}$C]acyl chloride,[39] [$^{11}$C]ethanol,[40] [1-$^{11}$C]acetate,[41] carboxylic acids,[42,43] etc. In all cases the $^{11}$C-labelled Grignard salt was prepared by reacting [$^{11}$C]carbon dioxide with the appropriate Grignard reagent, then further converted to the expected




**Scheme 1**




**Scheme 2**

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products. As an example, the synthesis of [$^{11}$C]cyclohexanoic acid chloride is shown in Scheme 3.

Aryl nitriles are potentially useful for the functionalization of aromatic rings because the nitrile group can be converted to other functional groups, including carboxylic acids and amides. $^{11}$C-labelled hydrogen cyanide has been used to introduce a $^{11}$C-labelled cyano group into aromatic rings. This group has been introduced by metal-mediated reactions of aryl halides with [$^{11}$C]N$^-$[44,45] or H[$^{11}$C]N.[46] A few examples are shown in Scheme 4.[46]

$^{11}$C-labelled carboxylic acids have been prepared via Grignard reagents using [$^{11}$C]carbon dioxide,[42,43] or by the hydrolysis of the corresponding [$^{11}$C]nitrile obtained from [$^{11}$C]hydrogen cyanide.[47–49]

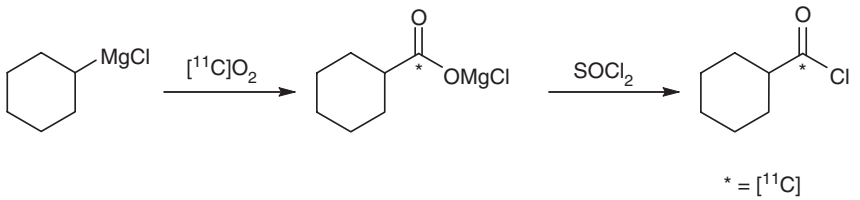
## Incorporation [$^{11}$C]carbon monoxide: a different labelling strategy

Carbonylation—direct synthesis from labelled carbon monoxide—is an attractive strategy because carbonylation reactions are multicomponent and, consequently, efficient. [$^{11}$C]Carbon monoxide may be obtained directly in a particle accelerator target, or in two steps via the reduction of target-produced [$^{11}$C]carbon dioxide (Figure 1).[3] Although methods for its production are well known, [$^{11}$C]carbon monoxide was recognized as a valuable labelling precursor relatively recently, as suitable synthesis instrumentation has been developed.

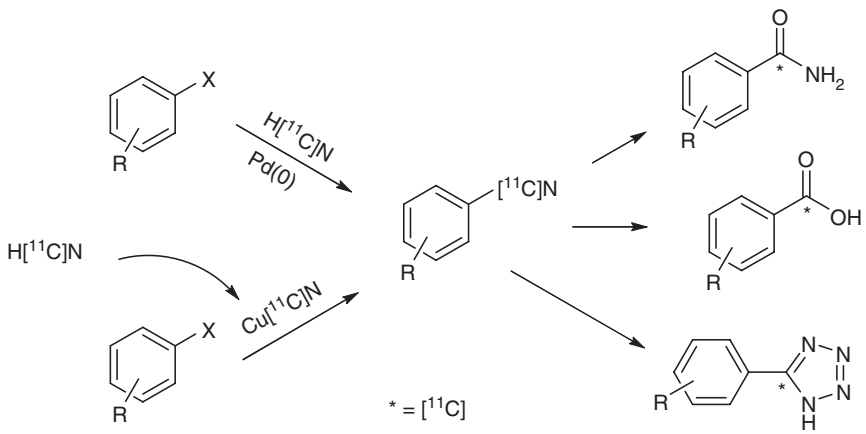
## Carbon monoxide technology

Technological developments have played a major role in overcoming problems in the handling of [$^{11}$C]carbon monoxide on a picomolar scale while achieving high conversion to a required product. This last aspect is a considerable issue, as [$^{11}$C]carbon monoxide is sparingly soluble in organic solvents.[50]

The first publications on $^{11}$C-carbonylation describe syntheses carried out at or near atmospheric pressure.[51–53] The reactions were generally selective, but the conversion of [$^{11}$C]carbon monoxide was low and 90% or more of the [$^{11}$C]carbon monoxide remained unreacted.[52–55] Thus, overall decay-corrected radiochemical yields calculated from [$^{11}$C]carbon monoxide were at most 10%, and lower with less reactive substrates. The proposed approaches to increase the conversion of [$^{11}$C]carbon monoxide include: (a) recirculation techniques, (b) high-pressure techniques and (c) increasing the atmospheric-pressure solubility of [$^{11}$C]carbon monoxide by chemical complexation. The first two approaches require sophisticated synthetic apparati. The third, in contrast, utilizes the higher solubility of the $BH_3 \cdot$[$^{11}$C]O complex in organic




**Scheme 3**




**Scheme 4**

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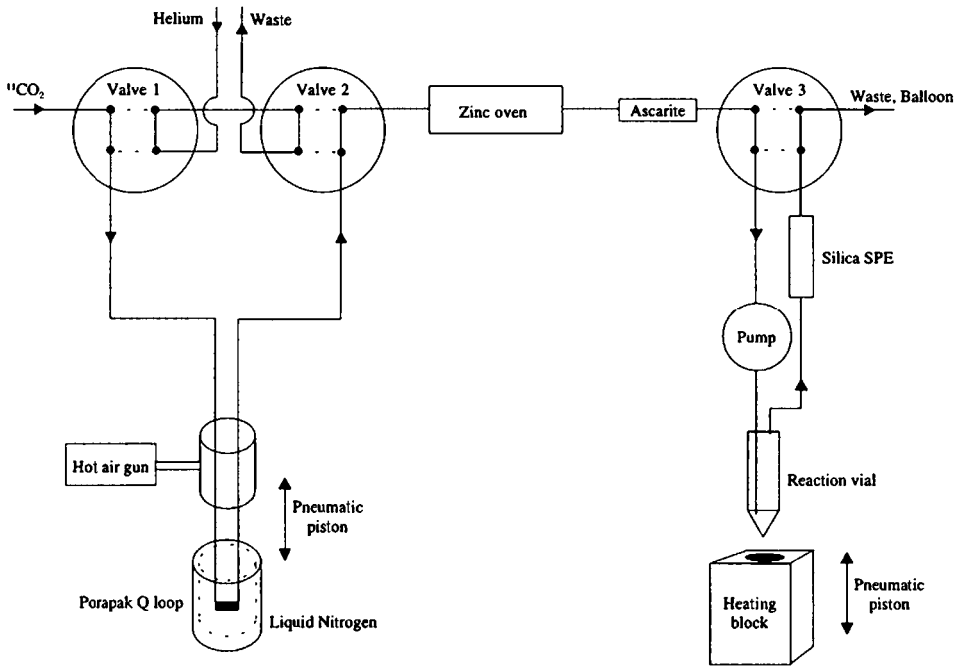


**Figure 3** Recirculation system for synthesis with [$^{11}$C]O.

solvents at atmospheric pressure.[56] Reported yields in carbonylation using $BH_3 \cdot [^{11}C]O$ average around 30–40%, but the efficiency of complexation and the amount of [$^{11}$C]carbon monoxide or $BH_3 \cdot [^{11}C]O$ that remained after reaction were not obviously stated.

The recirculation technique (Figure 3) allowed researchers to obtain high radiochemical yields in 5-min reactions, owing to enhanced transfer of [$^{11}$C]carbon monoxide from the gas phase into solution.[57] The same report highlights the importance of the concentration factor in ensuring minimal dilution of [$^{11}$C]carbon monoxide in a carrier gas. To assure a high concentration factor, [$^{11}$C]carbon dioxide was preconcentrated on a cold trap before being reduced to [$^{11}$C]carbon monoxide.

The next generation of the [$^{11}$C]carbon-monoxide-synthesis units was the high-pressure system[58] schematically presented in Figure 4. The ability to perform carbonylation reactions at over 350 atm[†] allowed researchers to demonstrate the versatility of [$^{11}$C]carbon monoxide as a precursor for the preparation of $^{11}$C-labelled compounds, including synthetically demanding targets. The system is divided into two main parts: one to reduce the accelerator-produced [$^{11}$C]carbon dioxide to [$^{11}$C]carbon monoxide, and another to deliver liquid reagents into the reactor and pressurize it. The operation of the system was described,[59] and detailed technical information is available in the patent literature.[58] Most of the published data on [$^{11}$C]carbon monoxide chemistry discussed below were obtained using this system.[60] In a number of cases, near-quantitative and product-selective incorporation of [$^{11}$C]carbon monoxide was reported.[61]

An alternative high-pressure apparatus has also been designed (Figure 5).[62] Although this apparatus contains fewer valves, the gas and liquid reagents are not handled separately. Thus, [$^{11}$C]carbon monoxide is taken up from the cold trap to the reactor by a stream of liquid rather than an inert carrier gas. This could result in sub-quantitative transfer of [$^{11}$C]carbon monoxide into the reaction loop.

Although the reactors described above are small scale (typically 0.2–1 cm$^3$), they are essentially miniaturized variants of conventional batch reactors, and therefore do not fall into the contemporary classification of micro-structured reactors (microreactors).[63] By now, several publications have demonstrated the use of microreactors in single-phase $^{11}$C and $^{18}$F PET radiochemistry.[64–68] The applications of this technology in multiphase gas–liquid reaction systems are more challenging. In a very recent report a microtube reactor was used for carbonylation.[69]

## Insertion reactions involving [$^{11}$C]phosgene

[$^{11}$C]Phosgene was used in $^{11}$C-labelling in the synthesis of carbonyl compounds as early as 1977.[70]

[†]This value represents the total pressure in the reactor. The *partial* pressure of [$^{11}$C]carbon monoxide is likely to be well below 1 atm.



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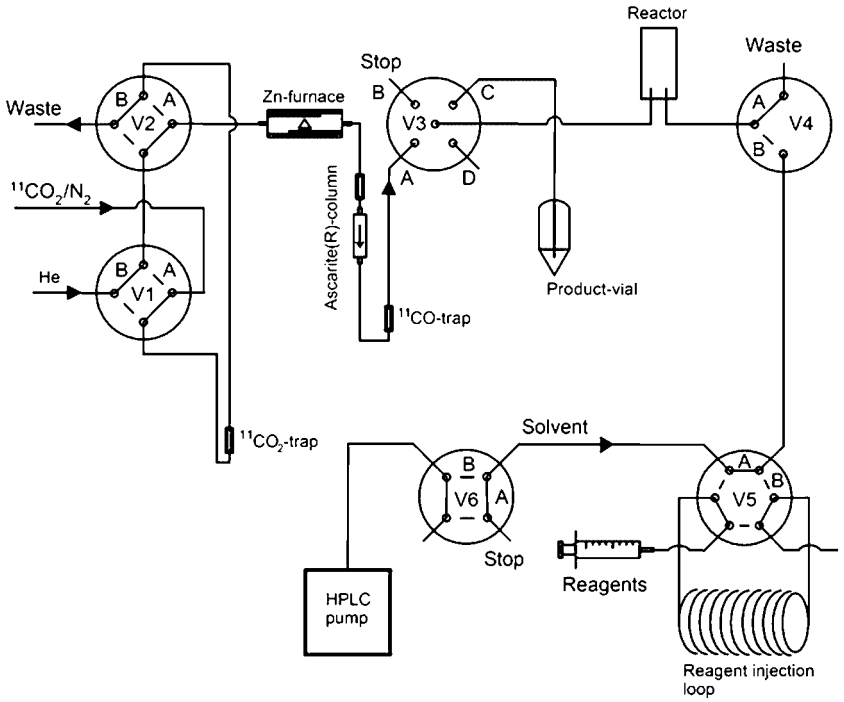



**Figure 4** Carbon monoxide synthia.

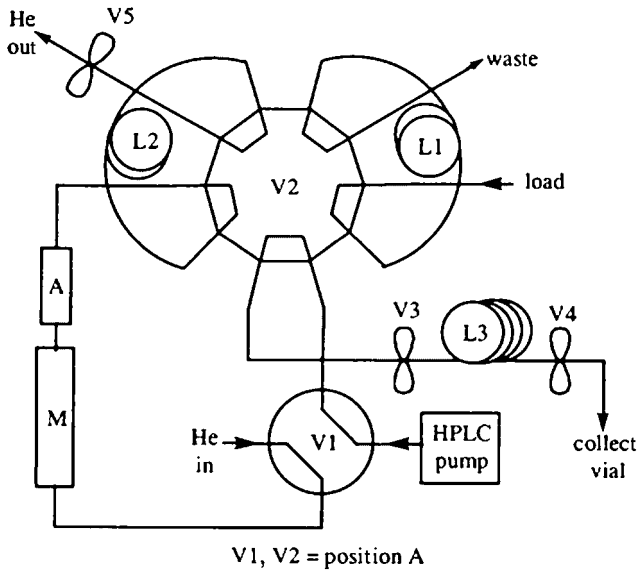
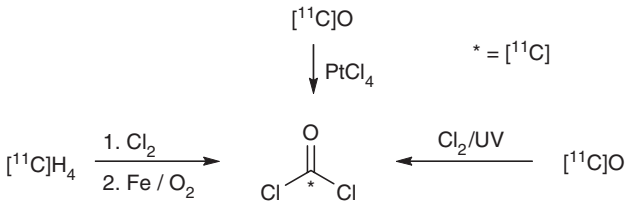



**Figure 5** Alternative high-pressure reactor.

$^{11}$C-Labelled phosgene can be produced from [$^{11}$C]methane by reaction with chlorine followed by oxidation,[71–73] or from [$^{11}$C]carbon monoxide by reaction with $PtCl_4$[74] or with chlorine in the presence of UV irradiation, as presented in Scheme 5.[75]

$^{11}$C-labelled phosgene reacts very quickly with most nucleophiles (amines, alcohols, aminoalcohols, etc.) to give an insertion of [$^{11}$C]carbonyl group. However, the




**Scheme 5**

low radiochemical yield and poor reproducibility of [$^{11}$C]phosgene production have limited its wider use. Additionally, the specific radioactivity of the labelled products obtained using [$^{11}$C]phosgene is usually low. Examples of the conversion of [$^{11}$C]phosgene to some [$^{11}$C]carbonyl functional groups are presented in Scheme 6.[75]

## Lithium amide salts with [$^{11}$C]carbon monoxide

The reaction of [$^{11}$C]carbon monoxide with lithium amides, followed by quenching with water or alkyl halides, was explored in the preparation of $^{11}$C-labelled amides.[76] The compounds *N*-[$^{11}$C]formylpiperidine, *N*-[$^{11}$C]acetylpiperidine and *N*-[$^{11}$C]propionylpiperidine were prepared (Scheme 7), but the trapping of [$^{11}$C]carbon monoxide was low (10–20%).



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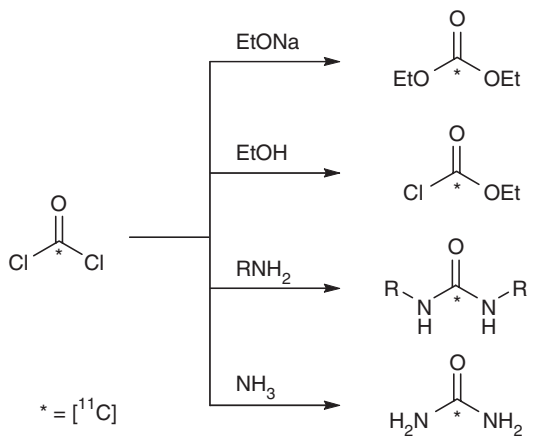
## Insertion of [$^{11}$C]carbon monoxide by metal-mediated reactions

Transition-metal-mediated reactions are useful in modern synthetic organic chemistry. Organometallic complexes, most frequently of palladium (Pd), rhodium (Rh) or platinum (Pt),[77,78] catalyse solution-phase reactions that yield versatile routes for the formation of C–C bonds. The application of transition-metal complexes in organic synthesis was pioneered by Heck.[79,80] Transition-metal-mediated reactions such as the Stille[81] and Suzuki[82] couplings have become methods of choice in many sophisticated organic syntheses. An insertion of carbon monoxide or carbonylative cross coupling occurs when such a coupling reaction takes place in the presence of carbon monoxide. In conventional organic synthesis, a wide range of carbonyl compounds such as ketones[83–85], amides[86,87], carboxylic acids[88] and esters[89–92] have been synthesized by transition-metal-catalysed carbonylative cross-coupling reactions. The catalytic cycle for metal-mediated cross-coupling reactions involving aryl or vinyl halides, carbon monoxide and nucleophiles is shown in Scheme 8.

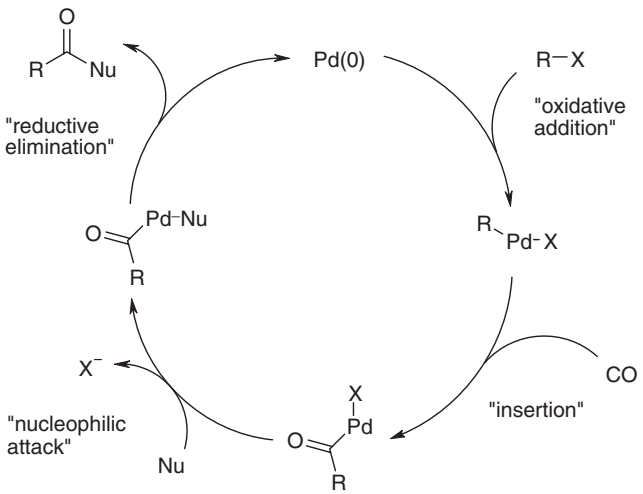
The concept for $^{11}$C-labelling synthesis using transition metals is similar, however, given that the concentration of metal complexes used is large compared with that of [$^{11}$C]carbon monoxide, the catalytic-cycle concept might not be relevant.

### Palladium-mediated reactions

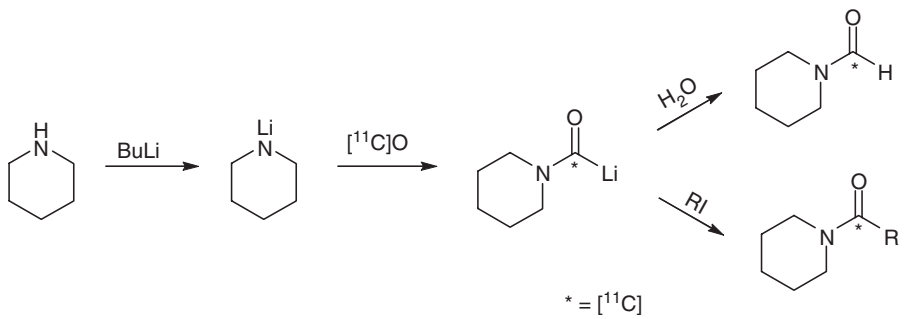
Although the application of Stille and Suzuki cross-coupling reactions in conventional organic synthesis is well established, their use in $^{11}$C-labelling chemistry has been limited. The first synthesis of $^{11}$C-labelled ketones was published only a decade ago.[51] In that report, a palladium-mediated carbonylation using [$^{11}$C]carbon monoxide and organostannanes was used to synthesize $^{11}$C-labelled acetophenone and benzophenone. In the past few years, a number of [*carbonyl*-$^{11}$C]ketones have been synthesized using Suzuki and Stille coupling reactions.[93–95] In case of Suzuki coupling reactions, aryl triflates and alkyl- or




**Scheme 6**




**Scheme 8**




**Scheme 7**

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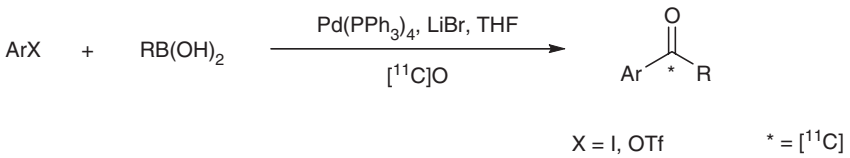
arylboronic acids were employed, and the catalyst was *tetrakis*(triphenylphosphine)-palladium (Scheme 9).[93] The trapping efficiency was 50–90% and the decay-corrected isolated radiochemical yield was 10–70%. The reaction worked with no added base when phenyl- or methylboronic acid was used as nucleophile. However, the radiochemical yields of corresponding ketones were low when alkylboronic acids having longer alkyl chains were employed. Adding organic bases like tetrabutylammonium fluoride (TBAF) or potassium *tert*-butoxide solved this problem.[94] Lithium bromide was employed to activate the aryl triflates towards coupling reactions. A series of unsymmetrical alkyl/aryl [*carbonyl*-$^{11}$C]ketones were prepared by carbonylative Stille coupling between alkyl/aryl iodides and organostannanes, with 37–98% radiochemical yields (Scheme 10).[95]

The use of [Pd{P(*o*-Tol)$_3$}$_2$], generated *in situ* from *tris*(dibenzylideneacetone)palladium(0) ([Pd$_2$(dba)$_3$]) and tri-*o*-tolylphosphine [P(o-Tol)$_3$], improved radiochemical yields. $^{11}$C-labelled ketones have also been prepared from [$^{11}$C]carbon monoxide that was produced by reducing [$^{11}$C]carbon dioxide on charcoal at 900°C,[52,53] or on molybdenum at 850°C.[54,55]

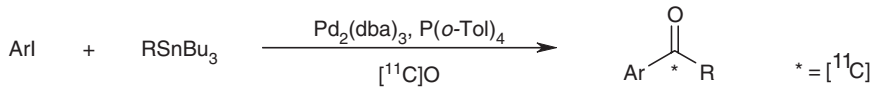
$^{11}$C-labelled ketones have recently been converted to $^{11}$C-labelled amines by reductive amination (Scheme 11).[96] Reductive amination was performed in the presence of $TiCl_4$ and $NaBH_3CN$, and decay-corrected radiochemical yields were in the range of 2–78%.

Amide functionality occurs frequently in bioactive organic molecules, and is therefore a potential labelling target. The $^{11}$C-labelling of amides using palladium chemistry has been explored and a number of biologically active [$^{11}$C]amides have been synthesized using palladium-mediated reactions with aryl halides and [$^{11}$C]carbon monoxide (Scheme 12).[97]

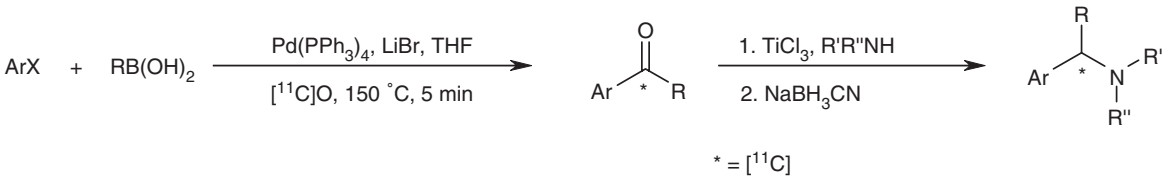
Although the synthesis of $^{11}$C-labelled amides was successful, radiochemical yields were reduced when less reactive amines like methylamine, aniline, indole, etc. were used as nucleophiles. The radiochemical yields for these cases were increased by 40 to 50% using *in situ* activation of the amines with 1,2,2,6,6-pentamethylpiperidine (PMP)[98] or lithium *bis*(trimethylsilyl)amide.[99] In few cases, the amines were activated by treating with butyllithium (BuLi) followed by trimethyltin chloride, making organotin-amine of the corresponding amines.[99] Aryl triflates and heteroaryl bromides usually give lower radiochemical yields



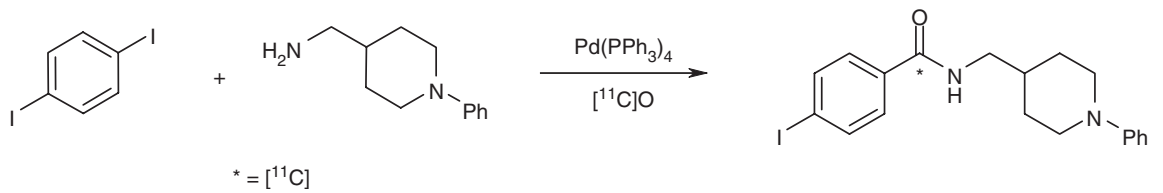

**Scheme 9**




**Scheme 10**




**Scheme 11**




**Scheme 12**



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in the synthesis of [$^{11}$C]amides, though an improvement of radiochemical yield was observed when these were treated with tetrabutylammonium iodide.[98] It was assumed that an iodide exchange took place, giving better radiochemical yields for carbonylation reaction. Imides[100] and hydrazides[101] were also successfully labelled with $^{11}$C utilizing palladium-mediated carbonylation (Scheme 13).

The most commonly used substrates for metal-mediated [$^{11}$C]carbonylations are aryl, vinyl, methyl or benzyl iodides or bromides. The potential of aryl triflates as substrates in the synthesis of $^{11}$C-labelled amides was explored[102]; when combined with LiBr, aryl triflates are a complement to aryl halides. A series of $^{11}$C-labelled amides were synthesized in useful radiochemical yields from aryl triflates and different amines (Scheme 14).

Several methods for using [$^{11}$C]carbon monoxide in the synthesis of compounds with different functional groups have been developed recently, with the aim of using these methods in the development of new PET tracers. So far, only a few examples using [$^{11}$C]carbon monoxide and metal-mediated reactions have been published. One of these is an alternative method for $^{11}$C-labelling of the peripheral benzodiazepine receptor (PBR) ligand PK11195 (Figure 6) via the palladium-mediated reaction of [$^{11}$C]carbon monoxide and 1-(2-chlorophenyl)isoquinolin-3-yl triflate (Scheme 15).[103]

In another example, an analogue of citalopram was labelled with $^{11}$C by palladium-mediated carbonylation of an aryl bromide and piperidine using $^{11}$CO (Scheme 16).[104]

A selective neuropeptide Y5 (NPY-5) PET ligand was recently used in a human study to explore the receptor occupancy of a selective NPY5-drug.[105] The lactone carbonyl group of this ligand, $^{11}$CMK-0233 (Figure 7), was labelled using [$^{11}$C]carbon monoxide.

Finally, a series of $^{11}$C-labelled acrylamides were recently synthesized in high radiochemical yields and with high specific radioactivity (Scheme 17).[106] This

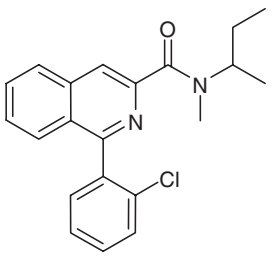
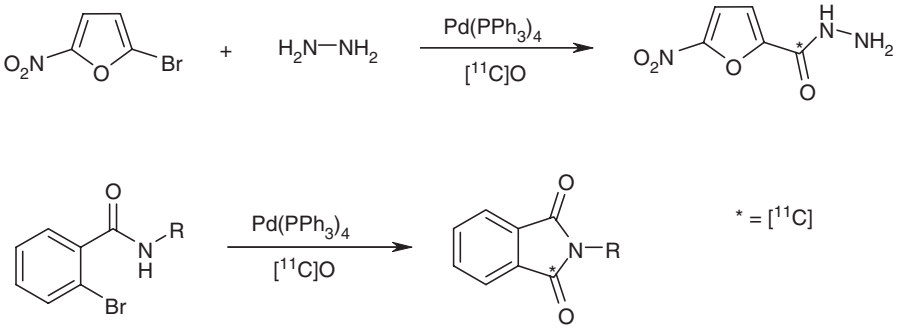
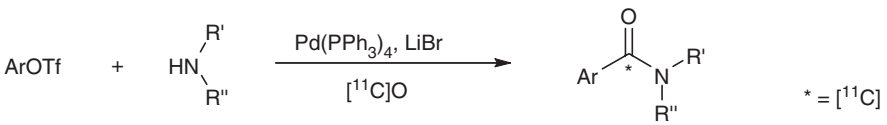


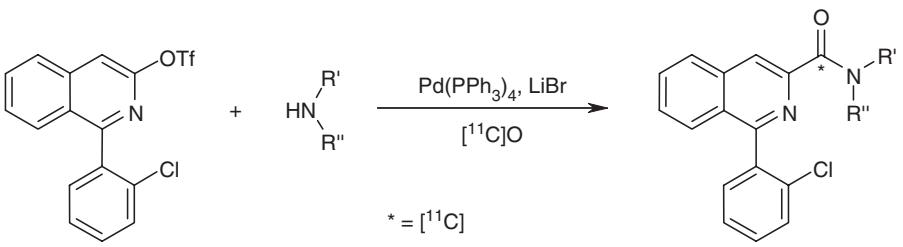
**Figure 6** Structure of PK11195.




**Scheme 13**




**Scheme 14**




**Scheme 15**

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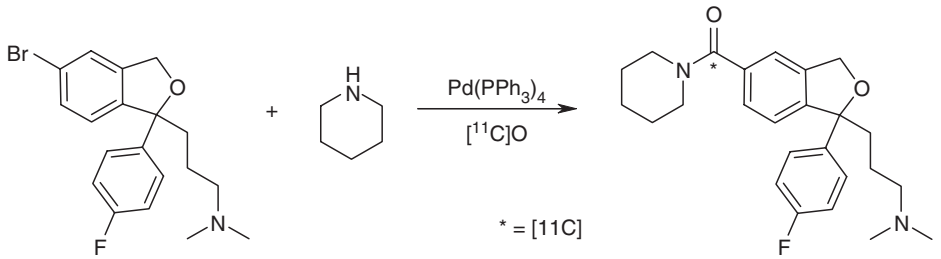
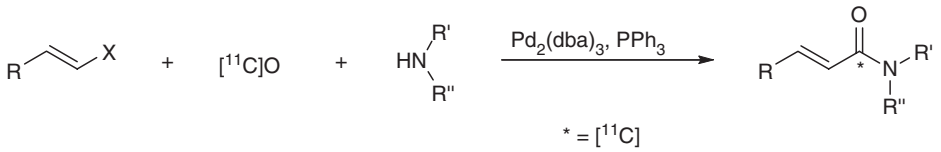



**Scheme 16**




**Scheme 17**

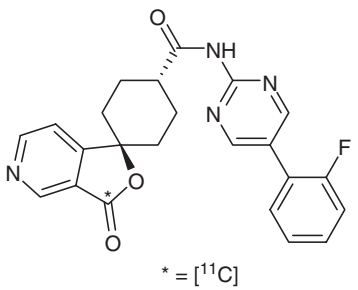



**Figure 7** Selective NPY-5 receptor ligand which was labelled with [$^{11}$C]O at the lactone carbonyl group.

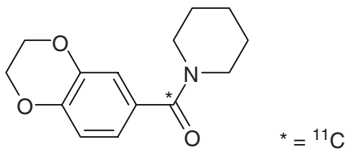



**Figure 8** [$^{11}$C]CX546, an AMPA receptor ligand.

approach could be implemented in developing PET tracers for tyrosine kinases.[107]

Palladium-mediated carbonylation with [$^{11}$C]carbon monoxide was also used to synthesize $^{11}$C-labelled amides and lactones including the AMPA receptor modulator CX546 (Figure 8).[62]

$^{11}$C-labelled carboxylic acids are important in the context of PET, as there are many bioactive molecules that contain this functional group. The palladium-mediated carboxylation of aryl halides or triflates using [$^{11}$C]carbon monoxide and tetrabutylammonium hydroxide was recently reported to produce [$^{11}$C]carboxylic acids.[108]

## Alkyl and alkenyl iodides from [$^{11}$C]carbon monoxide

Access to reliable methods of handling of [$^{11}$C]carbon monoxide has also enabled the preparation of $^{11}$C-labelled alkyl and alkenyl precursors, which were previously synthesized via Grignard reactions[34–38] with $^{11}$C-carbon dioxide, followed by reduction of the acids and conversion of the resulting alcohols to the corresponding iodides. The use of alkenes to produce mixtures of the labelled aldehydes and acids, which could then be converted after reduction to the corresponding halides (Scheme 18), provides an alternative pathway that could result in higher specific radioactivity.[109,110]

## Rhodium-mediated reactions

Rhodium is another transition metal that catalyses an impressive number of synthetically important organic transformations.[111–113] The application of Rh in $^{11}$C-labelling chemistry was explored when $^{11}$C-labelled *N,N*-diphenylurea and ethyl phenylcarbamate were formed using a rhodium-promoted carbonylation with [$^{11}$C]carbon monoxide (Scheme 19).[114]

The reaction is believed to proceed through the formation of $^{11}$C-labelled isocyanate, which could be a potential intermediate for the preparation of a number of $^{11}$C-labelled compounds.[115]

The syntheses of [*carbonyl*-$^{11}$C]hydroxyureas (Scheme 20)[116] and [*carbonyl*-$^{11}$C]malonate (Scheme 21)[117] using rhodium-mediated reactions have also been described.



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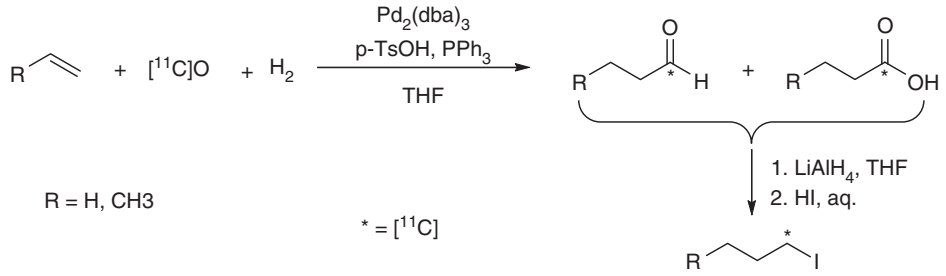
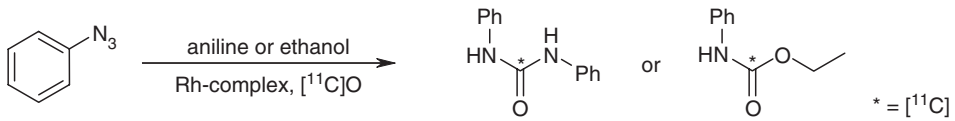



**Scheme 18**

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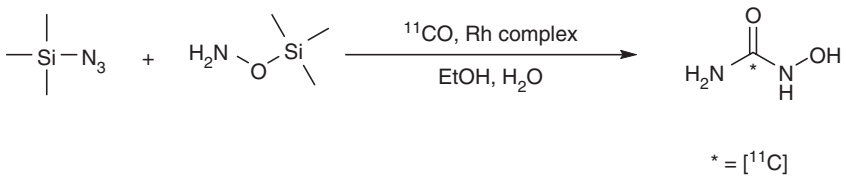
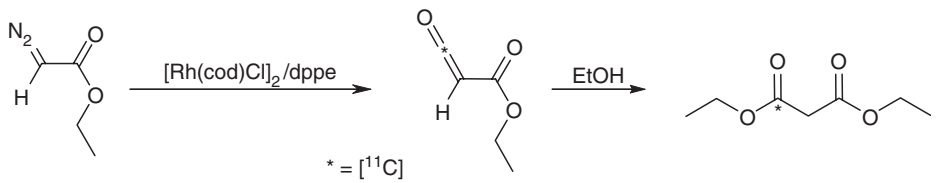



**Scheme 20**




**Scheme 21**

### Selenium-mediated reactions

Selenium-mediated carbonylation has been a useful method for the synthesis of ureas,[118,119] and the application of this in $^{11}$C-labelling syntheses was recently explored.[120] The use of metallic selenium, as is employed in conventional organic synthesis, did not give a suitable result in $^{11}$C-labelling; this was likely due to the insolubility of selenium in organic solvents. A modified method, in which a soluble complex of selenium with TBAF was used (Scheme 22), permitted some $^{11}$C-labelled ureas and carbamates to be synthesized with moderate to high radiochemical yields.

## Carbon monoxide–boron complexes in labeling synthesis

The trapping of [$^{11}$C]carbon monoxide in a reaction medium is difficult (see above), and several strategies have been developed to address this problem. The use of $BH_3 \cdot [^{11}C]O$ complex as a source of [$^{11}$C]carbon monoxide in the palladium-mediated carbonylation has been explored.[56] In this approach, [$^{11}$C]carbon monoxide is trapped by a $BH_3 \cdot THF$ complex, then reacted with an aryl halide and a nucleophile in the presence of Pd(0) and base (Scheme 23). Using this method, an amide and a lactone were labelled in radiochemical yield of 47%.

Complex formation between carbon monoxide and organoboranes was also utilized in transition-metal-free carbonylation, leading to aliphatic aldehydes[121] and alcohols[122] (Scheme 24).

## Free-radical carbonylation

A large number of pharmacologically active compounds contain carboxylic acid, amide or ester functionalities bound to an $sp^3$ carbon. These range from simple



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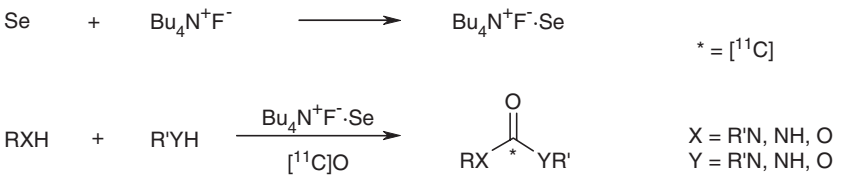
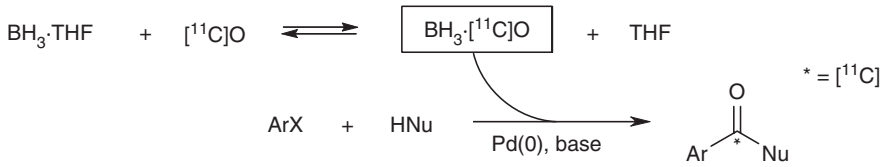
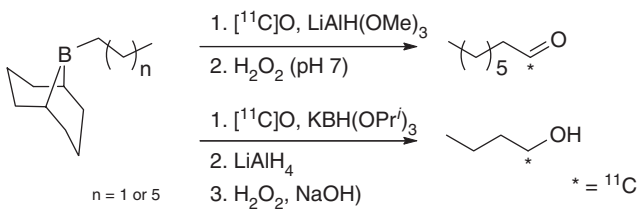



**Scheme 22**




**Scheme 23**




**Scheme 24**

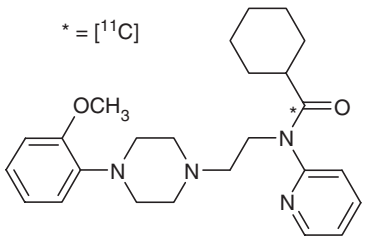


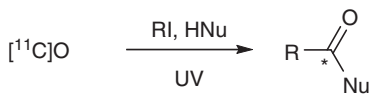

**Figure 9** [*Carbonyl*-$^{11}$C]WAY-100635.

saturated fatty acids to more complex compounds such as WAY-100635[123–125] (Figure 9). Due to competing $\beta$-elimination, transition-metal-mediated reactions could not be applied for synthesizing such compounds from alkyl halides.[126] Previously, labelling at aliphatic ester and amide functional groups was generally accomplished via [$^{11}$C]cyanides,[127] [*carbonyl*-$^{11}$C]acyl halides[128] or [1-$^{11}$C]ketenes,[129] which are prepared by the carboxylation of the alkyllithium or Grignard reagents with [$^{11}$C]carbon dioxide.[130] Except for the synthesis of carboxylic acids from Grignard reagents, these are multistep syntheses, and their practical application is often cumbersome.[131] For example, the preparation of [*carbonyl*-$^{11}$C]WAY-100635 was considered as 'very taxing'.[132]

The free-radical carbonylation of aliphatic iodides[133] offers a more robust and general route for introducing the [$^{11}$C]carboxy functional group.[134] $^{11}$C-labelled amides, esters and acids can be synthesized in a one-pot manner using different nucleophiles (Scheme 25).

This reaction has some analogy with palladium-catalysed carbonylation, but active acylating species are generated via a free-radical mechanism (Scheme 26).[134]

The reaction is initiated by the homolysis of an alkyl iodide. In the second step, the alkyl radical adds to




**Scheme 25**

carbon monoxide to form an acyl radical, which after iodine atom transfer from another molecule of alkyl iodide creates an acyl iodide. The reaction of the acyl iodide with a nucleophile to form a stable product serves as a driving force. A vast collection of data on the kinetics and mechanism of this reaction, helpful in designing and optimizing[134] $^{11}$C-labeling synthesis, is now available.[135–137]

The radical-mediated carbonylation reactions with [$^{11}$C]carbon monoxide were carried out using the high-pressure apparatus (Figure 4), which was equipped with a window reactor. Most of the reactions were initiated by ultraviolet light (UV).[134]

$^{11}$C-labelled alkyl amides were prepared using a solution of an alkyl iodide and an amine in the presence of triethylamine (Scheme 27).[138] The reagent mixture was pressurized into the reactor already containing



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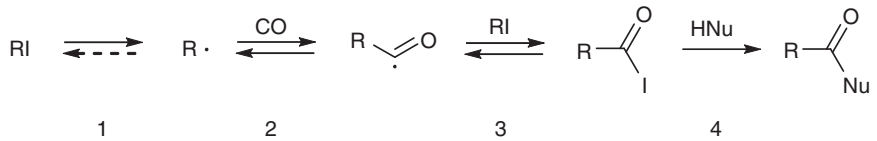
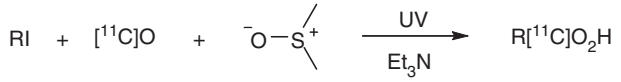



**Scheme 26**


**Scheme 27**




**Scheme 28**

[$^{11}$C]carbon monoxide, and then irradiated with UV light. These reactions were the favoured by polar solvents. The radiochemical yields were the highest with primary and secondary iodides; the carbonylation of *tert*-butyl iodide was more difficult. Radiochemical yields decreased with the reactivity of amines.

When employing alcohols as nucleophiles it was necessary to use strong bases such as BuLi and LiHDMS to obtain good radiochemical yield of [*carbonyl*-$^{11}$C]esters.[139] Alternatively, these reactions could be improved using photosensitizers in neutral media. Acetone solvent could be used for this purpose; several other sensitizers were also helpful, some in quantities as low as 5% with respect to the iodide. Photosensitizers most likely improve the initiation step of the reaction.[140]

Fatty [1-$^{11}$C]acids were synthesized using binary and ternary solvent mixtures to solubilize hydrophobic alkyl iodides in water, which acted as the nucleophile.[141] As was the case in the ester syntheses, the addition of base or photosensitizer was needed to promote the reaction.[140] Other [*carboxyl*-$^{11}$C]acids were also synthesized under mild conditions using sulphoxides as nucleophiles (Scheme 28).[142]

Some examples of compounds labelled via radical carbonylation are given in Figure 10.

The photolysis of alkyl iodides has proven to be a suitable method for the generation of alkyl radicals. When photoirradiation may cause side reactions, other methods for generating alkyl radicals may be applied. For example, AIBN–*tris*(trimethylsilyl)silane[143] combination gave satisfactory results in thermally induced carbonylations using [$^{11}$C]carbon monoxide.[134]

## Future perspectives in tracer development

An understanding of reaction mechanisms is valuable to the development of any new synthetic method. Regarding the chemistry discussed in this paper, there has been little exploration of reaction mechanisms, or of the eventual impact of the low precursor concentrations on the outcome of labelling synthesis. Early work on the use of $^{11}$C-methyl iodide in alkylations of N, O and S nucleophiles is an example of one mechanistic study.[30] It is fair to emphasize that $^{11}$C could be useful in studying the kinetics and mechanisms of organic reactions, and in selecting synthetic methods for $^{11}$C labelling. For example, $^{11}$C/$^{14}$C kinetic isotope effects have been used to elucidate details of $S_N$ reactions.[17–22]

In transition-metal-catalysed carbonylation with $^{11}$C, it could be anticipated that the reaction does not strictly follow the catalytic cycle that occurs in conventional organic synthesis, because of the low concentration of [$^{11}$C]carbon monoxide compared with the metal complex. The typical concentration of [$^{11}$C]carbon monoxide in these reactions is 10–100 μM, while the concentration of the transition metal complex is generally 17–18 mM. However, mechanistic studies have not yet been performed under such conditions.

Free-radical and photochemical reactions have been found suitable for the rapid synthesis of $^{11}$C-labelled aliphatic carboxylic acids and their derivatives. Some developments in $^{11}$C chemistry have been novel, and do not have analogues in bulk organic synthesis. Mechanistic details in such cases are often uncertain as, for example, in photosensitized carbonylation. The sensitizers were considered to facilitate the initiation step; however, an early hypothesis that they act through the energy-transfer mechanism[140] has not been supported by further investigations. Experimental data point to an atom-transfer mechanism, and this route is further supported by DFT calculations, which show that the radical-propagation steps are energetically favourable.[144]

Utilization of [$^{11}$C]carbon monoxide in the synthesis of $^{11}$C-labelled compounds has created a new strategy to develop potential PET tracers, because libraries of structurally related labelled compounds can be produced and studied *in vitro* and *in vivo*. This concept was applied in the preparation of five $^{11}$C-labelled analo-



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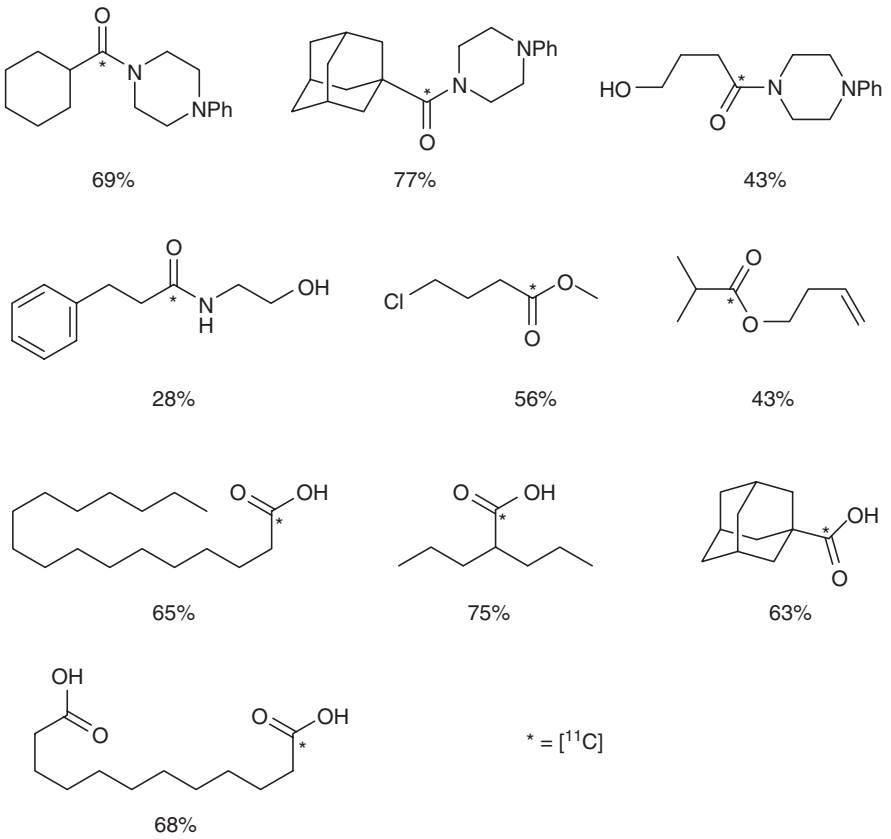


**Figure 10** Carboxylic acids, esters and amides labelled via radical carbonylation with isolated decay-corrected radiochemical yields.

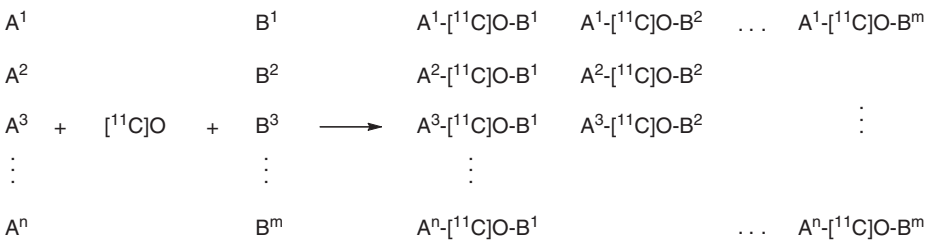


**Figure 11** Carbonylation as a multicomponent reaction allows the creation of a matrix library of labelled compounds.

gues of an interesting PBR ligand PK11195.[103] The library concept is useful when it is connected to preclinical imaging methods,[145] and these PBR ligands are good examples. Autoradiography is a useful technique for preliminary screening of binding properties, and may allow early selection of promising candidates from a group of analogues. This concept has recently been used to find useful, potent analogues of WAY[146] and DAA1106.[147] Twenty-six analogues of WAY and eight analogues of DAA1106 were prepared by keeping the major structure of the molecule unchanged, but using different amines.

As shown in Figure 11, the combination of **n** aryl or alkyl iodides **Ai** and **m** amines **Bj** permits the synthesis of a library of **n**×**m** labelled amides. Both free-radical and transition-metal-catalysed carbonylations with [$^{11}$C]carbon monoxide, which are complementary with respect to synthetic targets, may be utilized in creating such libraries.

In this paper, we have described a number of methods and techniques developed for $^{11}$C-labelling using simple one-carbon precursors starting from $^{11}$C-carbon dioxide. The improved synthetic methods using $^{11}$C-carbon monoxide have opened up an efficient way



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of developing these molecular tools for imaging existing and new biological targets.

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