Recent progress in $^{11}$C carbon dioxide ($^{11}$C$\text{CO}_2$) and $^{11}$C carbon monoxide ($^{11}$C$\text{CO}$) chemistry

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$^{11}$C Carbon dioxide ($^{11}$C$\text{CO}_2$) and $^{11}$C carbon monoxide ($^{11}$C$\text{CO}$) are 2 attractive precursors for labelling the carbonyl position (C=O) in a vast range of functionalised molecules (e.g., ureas, amides, and carboxylic acids). The development of radiosynthetic methods to produce functionalised $^{11}$C-labelled compounds is required to enhance the radiotracers available for positron emission tomography, molecular, and medical imaging applications. Following a brief summary of secondary $^{11}$C-precursor production and uses, the review focuses on recent progress with direct $^{11}$C-carboxylation routes with $^{11}$C$\text{CO}_2$ and $^{11}$C$\text{CO}$-carboxylation with $^{11}$C$\text{CO}$. Novel approaches to generate $^{11}$C$\text{CO}$ using CO-releasing molecules (CO-RMs), such as silacarboxylic acids and disilanes, applied to radiochemistry are described and compared with standard $^{11}$C$\text{CO}$ production methods. These innovative $^{11}$C$\text{CO}$ synthesis strategies represent efficient and reliable $^{11}$C$\text{CO}$ production processes, enabling the widespread use of $^{11}$C$\text{CO}$ chemistry within the wider radiochemistry community.

KEYWORDS
$^{11}$C$\text{CO}$, $^{11}$C$\text{CO}_2$, $^{11}$C-carbonylation, $^{11}$C-carboxylation, $^{11}$C-labelling, carbon-11, CO-releasing molecules, PET

1 | INTRODUCTION

1.1 | Production and applications

Carbon-11 ($^{11}$C) is an unstable positron-emitting isotope of carbon with a half-life of 20.4 minutes. It is generally produced using a cyclotron by the proton bombardment of $^{14}$N according to the following nuclear reaction: $^{14}$N(p, α)$^{11}$C. The 2 major primary $^{11}$C-precursors used in radiosynthesis are $^{11}$C$\text{CO}_2$ and $^{11}$C$\text{CH}_4$. These are produced in the gas target when the proton bombardment of $^{14}$N occurs in the presence of traces of oxygen (0.5%–1%) or hydrogen (5%–10%), respectively.1 One of the main challenges in $^{11}$C-chemistry is the development of rapid, versatile, and reliable methods to integrate these primary $^{11}$C-precursors into functionalised molecules.2 Despite the low reactivity of $^{11}$C$\text{CO}_2$ and $^{11}$C$\text{CH}_4$, an extensive number of methods have been developed to label functionalised $^{11}$C-molecules from these $^{11}$C-precursors.3–5 $^{11}$C$\text{CO}_2$ and $^{11}$C$\text{CH}_4$ can be also transformed into more reactive secondary $^{11}$C-precursors, Scheme 1. These, however, often require significant processing times and vary in yields.

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1.2 | $[^{11}\text{C}]$methyl iodide, $[^{11}\text{C}]$methyl triflate, $[^{11}\text{C}]$hydrogen cyanide, $[^{11}\text{C}]$phosgene

1.2.1 | $[^{11}\text{C}]$methyl iodide and $[^{11}\text{C}]$methyl triflate

One of the most widespread $^{11}\text{C}$-incorporation methodology uses $[^{11}\text{C}]$methyl iodide ($[^{11}\text{C}]\text{CH}_3\text{I}$) as a $^{11}\text{C}$-methylation reagent. $[^{11}\text{C}]\text{CH}_3\text{I}$ can be generated via the “wet” method or the gas-phase method. The first approach involves the reduction of cyclotron-produced $[^{11}\text{C}]\text{CO}_2$ with LiAlH$_4$ followed by reaction with HI, Scheme 2 (A).$^6$ The second method is based on the gas-phase iodination of $[^{11}\text{C}]\text{CH}_4$, which can be formed directly from the cyclotron or by reduction of $[^{11}\text{C}]\text{CO}_2$ in the presence of hydrogen gas on a nickel support at high temperatures, Scheme 2 (B).$^7$ Due to its higher reactivity than $[^{11}\text{C}]\text{CH}_3\text{I}$, this labelling agent has recently found increased utilisation.

$[^{11}\text{C}]$Methyl triflate ($[^{11}\text{C}]\text{CH}_3\text{OTf}$), another $^{11}\text{C}$-methylation reagent, is generally prepared by passing gaseous $[^{11}\text{C}]\text{CH}_3\text{I}$ over silver triflate at 160°C to 200°C, Scheme 2 (C).$^9$ $^{11}\text{C}$-Methylation reactions generally involve nucleophilic substitution of $[^{11}\text{C}]\text{CH}_3\text{I}$ or $[^{11}\text{C}]\text{CH}_3\text{OTf}$ with a primary amine, alcohol, or thiol group to form the corresponding secondary amine, ether, or thioether, Scheme 3 (A). This approach requires the trapping of the $^{11}\text{C}$-methylation reagents in a solution of the precursor followed by heating for a short period of time. Due to its simplicity, $^{11}\text{C}$-methylation is widely used for research and clinical production of functionalised $^{11}\text{C}$-tracers as extensively reviewed in the literature.$^{2,4,5,10-18}$ The recent development of “loop” chemistry has enabled technical and yield improvements in $^{11}\text{C}$-methylation reactions.$^2$

“Loop” $^{11}\text{C}$-methylation involves depositing a solution of the reagents in a thin film on the inside of an HPLC loop. The passage of $[^{11}\text{C}]\text{CH}_3\text{I}$ or $[^{11}\text{C}]\text{CH}_3\text{OTf}$ through this loop produces the methylated $^{11}\text{C}$-product.$^{19}$ This approach allows a high reactive surface area, minimal technical handling, and simplified $^{11}\text{C}$-product purification leading to improved $^{11}\text{C}$-methylation reaction yields.

$^{11}\text{C}$-Methylation has also been applied in palladium-mediated cross-coupling reactions for $^{11}\text{C}$–C bond formation to radiolabel molecules of interest with $^{11}\text{C}$ in specific positions. Good functional group tolerance has been shown using organostannanes as precursors in Stille cross-coupling reactions, Scheme 3 (B).$^{20,21}$ $[^{11}\text{C}]\text{CH}_3\text{I}$ is typically trapped in a solution containing a Pd-complex and a co-ligand. This mixture is then transferred in a vial containing the organostannane and heated for a few minutes (2–5 minutes). Despite the broad functional group compatibility, toxic trace
amounts of stannanes are difficult to remove completely from the reaction mixture and may raise concerns about this methodology for in vivo applications.

The Suzuki cross-coupling reaction using boronic acids and boronic esters as precursors is an alternative route to $^{11}$C—C bond formation which avoids concerns about using organostannane reagents, Scheme 3 (C).20,22,23 In analogy to the Stille coupling, $[^{11}\text{C}]\text{CH}_3\text{I}$ is added to a solution containing a Pd-complex, the boronic acid (or boronic ester), and a potassium salt. This mixture is then heated (e.g., by microwave [MW] activation), and the reaction is quenched with water, Scheme 3 (C).

1.2.2 | $^{[11}\text{C}]$hydrogen cyanide

$[^{11}\text{C}]$Hydrogen cyanide ($[^{11}\text{C}]\text{HCN}$) is another useful secondary $^{11}$C-precursor for the synthesis of functionalised $^{11}$C-tracers.24-28 It is commonly produced by the conversion of $[^{11}\text{C}]\text{CH}_4$ in the presence of NH$_3$ over platinum at high temperatures, Scheme 4.29 $[^{11}\text{C}]\text{HCN}$ can be used for $^{11}$C-cyanation reactions, such as for the production of $[^{11}\text{C}]$-succinonitrile,29 or converted to other functional groups, such as $[^{11}\text{C}]$amides,2,23 Scheme 4.

1.2.3 | $[^{11}\text{C}]$phosgene

$[^{11}\text{C}]$Phosgene ($[^{11}\text{C}]\text{COCl}_2$) is usually produced by the chlorination of $[^{11}\text{C}]\text{CH}_4$ to $[^{11}\text{C}]\text{CCl}_4$ followed by oxidation to $[^{11}\text{C}]\text{COCl}_2$.30 Thanks to its high reactivity, $[^{11}\text{C}]\text{COCl}_2$ can be utilised for the synthesis of functionalised $[^{11}\text{C}]$ureas, $[^{11}\text{C}]$carbamates, and $[^{11}\text{C}]$amides via formation of the corresponding $[^{11}\text{C}]$carbamoyl chlorides, Scheme 5.33 However, the production of $[^{11}\text{C}]\text{COCl}_2$ has been found to lack reliability and reproducibility at some radiochemistry sites, limiting its widespread use in $^{11}$C-chemistry.34

1.3 | Direct $^{11}$C-carboxylation

Despite its low reactivity and solubility in organic solvents, the direct incorporation of cyclotron-produced $[^{11}\text{C}]\text{CO}_2$ is of great interest because, in principle, rapid synthesis times might be achieved with a reduced number of reaction steps and technical processing. Several methodologies have been developed to access a vast range of $^{11}$C-tracers, including $[^{11}\text{C}]$carboxylic acids, $[^{11}\text{C}]$esters, $[^{11}\text{C}]$amides, $[^{11}\text{C}]$amines, $[^{11}\text{C}]$ureas, $[^{11}\text{C}]$carbamates, and $[^{11}\text{C}]$acid chlorides.2,3,35-42 The direct carboxylation of Grignard reagents with $[^{11}\text{C}]\text{CO}_2$ enables the rapid synthesis of $[^{11}\text{C}]$carboxylic acids and $[^{11}\text{C}]$acid chlorides, Scheme 6 (A). These have been shown to be useful $^{11}$C-reagents for the synthesis of functionalised radiopharmaceuticals, such as $[^{11}\text{C}]{\text{WAY}}$ 100365.43 The produced
\[^{11}\text{C}\]-carboxylate intermediates can also be utilised to yield the corresponding \[^{11}\text{C}\]amides from the reaction with primary and secondary amines, Scheme 6 (B). Furthermore, the synthesised \[^{11}\text{C}\]amides can be subsequently reduced yielding the corresponding \[^{11}\text{C}\]amines, Scheme 6 (B).³

Using a similar approach, organolithium reagents readily react with \[^{11}\text{C}\]CO\(_2\) producing the corresponding \[^{11}\text{C}\]ketones. For example, \[^{11}\text{C}\]acetone is obtained from the coupling of \[^{11}\text{C}\]CO\(_2\) with methyllithium followed by hydrolysis, Scheme 6 (C).³ \[^{11}\text{C}\]Acetone has itself been utilised as a useful labelling intermediate in \[^{11}\text{C}\]-chemistry.⁴⁴⁻⁴⁶

Grignard and organolithium reagents are often used in \[^{11}\text{C}\]-chemistry due to their great reactivity as nucleophiles for \[^{11}\text{C}\]CO\(_2\). However, as a consequence of their reactivity, these reagents do not have wide functional group compatibility and readily react with atmospheric CO\(_2\) lowering the molar activity (Am) of the final \[^{11}\text{C}\]-tracer. This aspect restricts the functionalised \[^{11}\text{C}\]-molecules achievable using this methodology. In addition, the required careful handling under inert atmosphere limits the routine applicability of these reagents.³

Other carboxylation methods using \[^{11}\text{C}\]CO\(_2\) have been developed in order to overcome the limitations of Grignard and organolithium reagents. An example is the copper-catalysed incorporation of \[^{11}\text{C}\]CO\(_2\) into the more stable and less moisture sensitive boronic esters yielding functionalised \[^{11}\text{C}\]carboxylic acids, Scheme 7.³⁵,⁴⁷ These can be subsequently transformed to \[^{11}\text{C}\]-esters or \[^{11}\text{C}\]-amides, Scheme 7.³⁵ However, 1 drawback of this methodology relies on its restriction to benzyl and unsaturated aliphatic boronic esters.

As discussed earlier, 2 main challenges in the trapping of \[^{11}\text{C}\]CO\(_2\) are its solubility in the reaction media and its low reactivity towards nucleophiles. The advent of fixation agents, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), has overcome this issue and has enabled the further development of new synthesis methodologies for functionalised \[^{11}\text{C}\]-tracers, such as \[^{11}\text{C}\]carbamates and \[^{11}\text{C}\]ureas.³⁶⁻³⁹,⁴⁸ An example is the 1-pot synthesis of a wide range of \[^{11}\text{C}\]carbamate esters under mild reaction conditions utilising \[^{11}\text{C}\]CO\(_2\) and DBU as a trapping reagent, Scheme 8.³⁸,³⁹

It has been found that by stoichiometric control of the reagents, the \[^{11}\text{C}\]carbamate salts can be dehydrated to \[^{11}\text{C}\]isocyanates and transformed into \[^{11}\text{C}\]ureas or \[^{11}\text{C}\]carbamates, Scheme 9.⁴⁸ Despite the broad applicability of this methodology, low yields were obtained for the more unreactive aromatic amines.

Two novel methodologies based on \[^{11}\text{C}\]CO\(_2\) trapping in the presence of BEMP and subsequent addition of Mitsunobu reagents have been developed, Scheme 10 (A and B) to expand the range of functionalised \[^{11}\text{C}\]ureas.³⁶,³⁷ A similar approach has been also recently discovered for the synthesis of \[^{11}\text{C}\]amides via rapid addition of Grignard regents after Mitsunobu reaction, Scheme 10 (C).⁴⁹ These direct \[^{11}\text{C}\]CO\(_2\) fixation methodologies are attractive alternatives for the synthesis of functionalised \[^{11}\text{C}\]ureas and \[^{11}\text{C}\]amides compared with the \[^{11}\text{C}\]COCl\(_2\)-based methods.
Based on the potential of Mitsunobu reactions, a continuous-flow loop setup for $^{[11}C\text{CO}_2$ trapping and $^{[11}C\text{C}]$ ureas synthesis has been recently presented by Downey et al.$^{50,51}$ This work demonstrated the rapid and efficient $^{[11}C\text{CO}_2$ trapping in DBU/amine solutions (average of 78%) at a high delivery flow rate (70 mL/min) within a low volume polymer loop (150 μL). This $^{[11}C\text{CO}_2$ trapping system was integrated into a continuous $^{11}C$-labelling of a model symmetric urea, $N,N'[^{11}C]$dibenzylurea via Mitsunobu reaction, Scheme 11. $N,N'[^{11}C]$Dibenzylurea was obtained in high decay-corrected radiochemical yield (RCY) of up to 72% and crude radiochemical purity (RCP) of up to 83% under ambient temperature and pressure within short synthesis time (<3 minutes from end of delivery [EOD]).$^{51}$

A very similar approach has been recently reported by Dahl et al to produce a diverse range of compounds, including $[^{11}C]$carbamates, $[^{11}C]$oxazolidinones, and $^{[11}C]$ureas in good decay-corrected RCYs (18%–50%) and high isolated RCPs (>99%).$^{52}$ This work together with the results presented by Downey et al demonstrates the utility of a simple and efficient “in-loop” $^{[11}C\text{CO}_2$ trapping method allowing the reliable production of a diverse array of $^{11}C$-products with minimal loss in radioactivity. This approach might be useful in a routine environment for positron emission tomography (PET) tracer development.

2 | $[^{11}C]$CARBON MONOXIDE ($[^{11}C]$CO)

2.1 | Production: Oven-based method

$[^{11}C]$Carbon monoxide ($[^{11}C]$CO) was one of the first $^{11}C$-tracers used for blood volume measurements in humans.$^{53}$ $[^{11}C]$CO is generally produced by the gas-phase reduction of cyclotron-produced $[^{11}C]\text{CO}_2$ on a metal surface (zinc or molybdenum) placed in a heated quartz tube at high temperatures, Scheme 12.$^{54-57}$

One of the first developed $[^{11}C]$CO synthesis methodologies was the reduction of $[^{11}C]\text{CO}_2$ to $[^{11}C]$CO on a zinc heated column (400°C) followed by concentration of the produced $[^{11}C]$CO on a silica column. This method produced low $[^{11}C]$CO yields and low trapping efficiency (~10%) for 2 main reasons:

1. the high flow rate used (100–200 mL/min) to deliver $[^{11}C]$CO to the reaction vial,
2. the re-oxidation of $[^{11}C]$CO to $[^{11}C]\text{CO}_2$ upon heating of the silica column.$^{55}$

These factors triggered the development of improved $[^{11}C]$CO gas handling systems.

The pre-concentration of $[^{11}C]\text{CO}_2$ prior reduction and the introduction of a $[^{11}C]$CO recirculation unit allowed $[^{11}C]$CO yields of up to 70%.$^{55,57}$ Furthermore, reduced delivery flow rates (20–30 mL/min) improved the $[^{11}C]$CO trapping efficiency in organic solvents.$^{55}$

A further development in $[^{11}C]$CO chemistry was the introduction of high pressure micro-autoclaves and “loop” synthesis systems. These assured an efficient $[^{11}C]$CO trapping in the reaction mixture thanks to a very low gas-phase volume and a higher reaction efficiency due to the greater reactive surface area and elevated pressures.$^{58}$

Methods for the reduction of $[^{11}C]\text{CO}_2$ using zinc ovens often suffer from the degradation of the metal surface by formation of zinc oxides over a few $[^{11}C]$CO production cycles. Zinc columns require frequent changes, cleaning, and careful pre-purification of the $[^{11}C]\text{CO}_2$ in order to assure reproducible $[^{11}C]$CO yields.$^{54,56,59}$ In addition, the melting point of zinc (420°C) is close to the temperature required for the $[^{11}C]\text{CO}_2$ reduction to occur (400°C). Therefore, the inadvertent overheating of the zinc column during the process is a risk to the robustness of this method.$^{56}$

The use of molybdenum as a reducing metal in high-pressure systems has recently shown more reproducible $[^{11}C]$CO yields compared with the zinc method.$^{54}$ Molybdenum is known to readily react with $[^{11}C]\text{CO}_2$ to form

![Scheme 11](image-url)

**Scheme 11** $[^{11}C]\text{CO}_2$ trapping loop combined with a reaction loop for the Mitsunobu reaction yielding $N,N'-[^{11}C]$dibenzylurea presented by Downey et al
\[^{11}\text{C}]\text{CO}\) and molybdenum oxide with a maximum efficiency at 850°C.\(^{56}\) The latter has also shown reducing properties towards \(^{11}\text{C}]\text{CO}_2\) yielding \(^{11}\text{C}]\text{CO}\), which might improve the performance of the system and avoid repeated maintenance.\(^{56}\) This methodology enables the production of \(^{11}\text{C}]\text{CO}\) in yields of up to 70% over several production cycles.\(^{54}\) In addition, the high melting point of this metal (>>850°C) avoids the risk of catalyst melting during the conversion process.

Zinc and molybdenum ovens are used as the standard method for generating \(^{11}\text{C}]\text{CO}\) from \(^{11}\text{C}]\text{CO}_2\). However, the need of dedicated infrastructure for these oven-based methods often limits the use of \(^{11}\text{C}]\text{CO}\) chemistry within the wider radiochemistry community.

An innovative \(^{11}\text{C}]\text{CO}\) production methodology has been recently developed under mild reaction conditions via electrochemical conversion of \(^{11}\text{C}]\text{CO}_2\) to \(^{11}\text{C}]\text{CO}\) catalysed by nickel and zinc complexes.\(^{60}\) Despite the appealing features of this method, only low \(^{11}\text{C}]\text{CO}\) yields were achieved (~10%). Therefore, novel \(^{11}\text{C}]\text{CO}\) synthesis methodologies based on simple laboratory setups leading to comparable \(^{11}\text{C}]\text{CO}\) yields to the standard oven-based methods are required to enhance the availability of \(^{11}\text{C}]\text{CO}\) for \(^{11}\text{C}\)-tracer development.

### 2.2 \(^{11}\text{C}\)-Carbonylation reactions

Because of the ubiquity of the \(\text{C}═\text{O}\) functional group in many biologically active molecules, the chemical versatility of \(\text{CO}\) and the potential of palladium-promoted carbonylation cross-coupling reactions have made \(^{11}\text{C}]\text{CO}\) an attractive tool for the development of \(^{11}\text{C}\)-chemistry methodologies. To date, \(^{11}\text{C}]\text{CO}\) has been used for direct \(^{11}\text{C}\)-carbonylation reactions producing a vast range of \(^{11}\text{C}\)-compounds, such as \(^{11}\text{C}\)amides, \(^{11}\text{C}\)ureas, \(^{11}\text{C}\)carboxylic acids, and \(^{11}\text{C}\)esters, Scheme 13.\(^{34,55,57,59,61-72}\) Compared with traditional chemical methods, a major challenge in radiochemistry is the reaction stoichiometry, because in radiochemistry the amount of \(^{11}\text{C}\) produced is generally in the nano-picomolar range (10⁻⁹–10⁻¹⁲ mol). Even “low levels” of impurities in the reagents and solvents used may be present in excess compared with the radiolabelled starting material. As a result, reactions working on a traditional chemistry scale can fail when translated to tracer radiochemistry, affecting the outcome of the radiolabelling reactions employed.

### 2.3 Mechanism of \(^{11}\text{C}\)-carbonylation with \([^{11}\text{C}\text{CO}\)

In radiochemistry, \(^{11}\text{C}]\text{CO}\) is typically delivered in a stream of nitrogen, helium, or xenon gas into a vial or a micro reactor containing carbonylation reagents: a palladium ligand complex, an organic halide and an amine or an alcohol. The reaction mechanism starts with the oxidation of the palladium/ligand complex due to addition to the organic halide, Scheme 14. It proceeds with the \([^{11}\text{C}\text{CO}\) insertion into complex I yielding intermediate \([^{11}\text{C}\text{II}\). Subsequent nucleophilic attack of an amine or an alcohol to the palladium centre gives intermediate \([^{11}\text{C}\text{III}\) with elimination of the corresponding halogen acid. The subsequent reductive elimination of the palladium/ligand complex from intermediate \([^{11}\text{C}\text{III}\) produces a \([\text{carbonyl}^{11}\text{C}\)amide or a \([\text{carbonyl}^{11}\text{C}\)ester with regeneration of the reduced palladium/ligand complex, Scheme 14. Low pressure Pd-mediated and Rh-mediated \(^{11}\text{C}\)-aminocarbonylations have shown to be adaptable to a broad range of applications, such as the production of \(^{11}\text{C}\)amides and \(^{11}\text{C}\)ureas.\(^{59}\) Because of the high solubility of xenon in organic solvents, the use of this gas as a \(^{11}\text{C}]\text{CO}\) delivery vector enables the transfer of \(^{11}\text{C}]\text{CO}\) into small volumes without a build-up of pressure.\(^{59}\) This methodology is appealing as it does not require additional CO trapping reagents to efficiently trap \(^{11}\text{C}\)CO in the carbonylation reaction vessel. Other work has shown the application of a photoinduced radical-mediated \(^{11}\text{C}\)-alkoxycarbonylation reaction to generate \(^{11}\text{C}\)esters. This approach affords functionalised aliphatic \(^{11}\text{C}\)esters from primary, secondary, and tertiary alkyl iodides.\(^{73}\) However, it requires specialised equipment for the photoinduction of the \(^{11}\text{C}\)-carbonylation reaction.

**SCHEME 13** Potential \(^{11}\text{C}\)-labelled compounds using \([^{11}\text{C}\text{CO}\)

![Scheme 13](image)

**SCHEME 14** \(^{11}\text{C}\)-Carbonylation reaction mechanism leading \([^{11}\text{C}\)amides and \([^{11}\text{C}\)esters

![Scheme 14](image)
3 | CO-RELEASING MOLECULES (CO-RMs)

Carbon monoxide-releasing molecules (CO-RMs) are compounds able to release carbon monoxide under specific conditions. Past studies have shown the application of CO-RMs in medicine as therapeutic agents and in synthetic chemistry as CO trapping-releasing agents. The synthesis of metal carbonyl complexes, such as ruthenium-CO and copper-CO complexes, and their application as in situ CO-releasing molecules have rapidly increased. These complexes are able to release CO under physiological conditions or by addition of a competing ligand. The latter approach was successfully applied to 11C-chemistry using a copper(I) tris(pyrazolyl)borate ligand (so-called “scorpionate” ligand), Scheme 15. This complex efficiently trapped [11C]CO, and by addition of PPh3 as a competing ligand, [11C]CO was released and subsequently utilised for in situ 11C-carbonylation reactions yielding functionalised [11C] amides, Scheme 15.

Using a similar approach, recent non-radiochemical studies have focused on in situ CO production mediated by molecules able to release CO upon heating. For example, boranocarbonates have demonstrated the ability to release CO during thermolysis, Scheme 16. These compounds have been successfully applied in radiochemistry for the production of 99mTc-complexes used in radiopharmaceutical applications. In addition, THF–BH3 has been implemented in 11C-chemistry due to its ability to readily retain [11C]CO via the formation of solvent-soluble adducts, such as BH3[11C]CO (b.p. −64°C). [11C] CO was trapped in organic solvents at ambient temperature and pressure in high efficiency (>95%) and utilised in subsequent palladium-mediated 11C-carbonylation reactions.

Many other CO production methodologies utilising aldehydes, carbamoylsilane, carbamoylstannanes, formic acid, and its derivatives have been developed and applied to the synthesis of carbonyl functionalised molecules. A recent work demonstrated the ability of 9-methyl-9H-fluorene-9-carbonyl chloride (named “COgen” upon commercialisation) to release CO via a palladium-catalysed decarbonylation reaction performed at 80°C, Scheme 17. The combination of this CO-releasing process with a CO-consuming reaction in an isolated 2-chamber system enabled a high trapping of the produced CO. This methodology was also successfully applied to 13C-chemistry for the labelling of aryl amides with [carbonyl-13C]COgen.

4 | NOVEL [11C]CO PRODUCTION METHODOLOGIES

4.1 | Silacarboxylic acids as CO-RMs

Other examples of useful CO-RMs are silacarboxylic acids and disilanes. These have been recently used as in-situ CO sources for ex-situ transition-metal catalysed carbonylation reactions. Past works have shown that silacarboxylic acids degrade upon heating (150°C–200°C) with elimination of CO and formation of the corresponding silanol, disiloxane, and the isomeric silyl formate, Scheme 18 (A). Subsequent studies demonstrated that silacarboxylate esters undergo degradation in a similar manner, Scheme 18 (B). In addition, silacarboxylic acids have shown to lead the corresponding silanol derivative with production of CO in the presence of a base (eg, NaOH), Scheme 18 (C).

The degradation of these compounds was hypothesised to proceed through the attack of a lone pair of electrons of the oxygen atom of the OR′ group to the
The silicon atom accompanied by elimination of the carbonyl group as CO, Scheme 19. This internal rearrangement was called the 1,2-Brook rearrangement due to the intensive studies on these compounds performed by Brook and co-workers. Organosilicon compounds have since found an extensive use in synthetic chemistry, such as in tandem bond formation strategies. A similar chemical behaviour has been observed for the same group's elements of silicon, such as germanium.

The ability of silacarboxylic acids to release CO under certain conditions and the high fluorophilicity of silicon inspired the exploration of fluoride sources as activators to trigger the release of CO from this class of compounds. Friis and co-workers investigated different reaction conditions, such as temperature, reaction time, type of solvent, and activator on a number of silacarboxylic acids. Their results showed Ph₂MeSiCOOH as yielding the most rapid decarbonylation with production of CO using KF as an activator in dioxane. These reaction conditions were successfully applied in different Pd-catalysed carbonylation reactions in a 2-chamber system yielding the corresponding carbonylation product.

The relevance of this CO chemical methodology relies on:

1. the production of a controlled amount of CO using easy-to-handle reagents,
2. no need of special infrastructure in laboratories (eg, CO gas cylinder and CO gas detectors),
3. absence of a transition-metal catalyst,
4. release of CO at ambient temperature.

The 2 latter features distinguish silacarboxylic acids from the previous presented CO-production methodologies (eg, COgen and boranocarbanates) and made this class of compounds an attractive target for ¹¹C-chemistry application.

4.2 Disilanes as CO₂ to CO reducing agents

In parallel with the use of CO-RMs, others reported the in situ chemical reduction of CO₂ to CO via molecules able to react with CO₂, remove an oxygen atom from CO₂, and release CO. An example is the copper complex (IPr)Cu—OrBu. This is able to coordinate with diboron compounds and the structurally related boronsilane compounds to yield (IPr)Cu—OBpin and (IPr)Cu—OSiMe₂Ph, respectively. These complexes have shown the ability to coordinate CO₂ producing the corresponding intermediates (IPr)Cu—O₂CBpin and (IPr)Cu—O₂CSiMe₂Ph at a low temperatures (−80°C–0°C). Upon thermal decomposition (rt), (IPr)Cu—O₂CBpin and (IPr)Cu—O₂CSiMe₂Ph release CO with formation of (IPr)Cu—OBpin or (IPr)Cu—OSiMe₂Ph, Scheme 20.

In order to simplify the catalytic protocol of this CO₂ to CO reduction, Lescot et al reported that the presence of Cu(OAc)₂ and the bidentate ligand, DPPBz, with stoichiometric amounts of disilane, (MePh₂Si)₂, efficiently reduces CO₂ to CO with production of the corresponding disiloxane, Scheme 21 (A). By investigating the influence of different counterions of the copper salt used, they hypothesised that the CO₂ to CO reduction process could be catalysed in the absence of copper. This was confirmed by the complete conversion of disilane to the corresponding disiloxane with release of CO in the presence of neat KOAc at 150°C, Scheme 21 (B). Further reaction condition optimisation showed that fluoride sources (eg, KF) led to increased reactivity at lower temperatures (80°C). CsF was shown to be an excellent catalyst for the reduction of CO₂ to CO at ambient temperature with the disilane (MePh₂Si)₂. Investigations on other disilanes showed that disilanes bearing only methyl or phenyl groups were detrimental to the reaction.

Fluoride-activated disilanes have also been utilised to promote the carboxylation of organic halides under transition-metal free conditions. The key aspect of this method is the formation of a silyl anion triggered by fluoride through the Si—Si bond cleavage.

The formation of metal-free silyl anions in the presence of disilanes and a catalytic amount of tetrabutylammonium fluoride (TBAF) in aprotic solvents (eg, HMPA) has been reported by past studies. In addition, the generated silyl anions were reacted with

![Scheme 18](image-url)

**SCHEME 18** (A) and (B) Thermolysis of silacarboxylic acids and silacarboxylate esters; (C) base-catalysed CO elimination of silacarboxylic acids

![Scheme 19](image-url)

**SCHEME 19** 1,2-Brook rearrangement of silacarboxylate derivatives
aldehydes and 1,3-dienes to produce the corresponding coupled organosilane products in good yields under extremely mild reaction conditions.106-108

The ability of disilane species to be activated by hypercoordination has become an interesting property for the development of new methodologies in synthetic chemistry and within the $^{11}$C-chemistry field.

4.2.1 | Bond energies in silicon chemistry

From the presented applications of silacarboxylic acids and disilanes, it is evident that the fluoride anion can promote an intramolecular rearrangement of the Si—C bond or the cleavage of the Si—Si bond. Both routes mediate the formation of Si—O and Si—F bonds.

The formation of the strong Si—F bond can be used as a driving force in silicon chemistry, such as in the cleavage of the weak Si—Si bond (Si—F >> Si—O >> Si—C and Si—Si).109 In addition, Si—O bond-dissociation energy >> Si—Si bond-dissociation energy indicating that the Si—O bond-dissociation energy can also be utilised as a driving force in silicon chemistry, such as in the 1,2-Brook rearrangement catalysed by hydroxide and the effect of KOAc on the CO$_2$ to CO reduction via disilanes.76,78 The trend of the bond-dissociation energies of silicon with halogens is as follows: Si—F >> Si—Cl >> Si—Br >> Si—I.109 Therefore, the substantial fluorophilicity and oxophilicity of silicon in conjunction to its hyper-coordination properties$^{110,111}$ make organosilicon compounds extremely interesting targets for the development of synthetic and radiosynthetic strategies.

4.3 | Conversion of $^{11}$C$\text{CO}_2$ to $^{11}$C$\text{CO}$ via $^{11}$C-silacarboxylic acids

An innovative rapid and reliable chemical conversion of $^{11}$C$\text{CO}_2$ to $^{11}$C$\text{CO}$ mediated by $^{11}$C-silacarboxylates and $^{11}$C-silacarboxylic acids triggered by a stoichiometric excess of TBAF has been recently reported by our group and others, Scheme 22.112-114 This work was inspired by the previously presented non-radiochemical studies showing silacarboxylic acids as efficient CO-releasing molecules when in the presence of fluoride.76,77

In our laboratory, Ph$_2$MeSiLi (2), synthesised from the corresponding chlorosilane (1), was chosen for method development after an initial screening of different silyl lithium derivatives. The corresponding $^{11}$C$\text{CO}_2$ to $^{11}$C$\text{CO}$ conversion via $^{11}$C-silacarboxylates
silacarboxylate ([11C]3 and [11C]4) was obtained in good to high RCY (~40%–80%) by coupling crude 2 with cyclotron-produced [11C]CO2. [11C]CO production yields ≥50% based on total [11C]CO2 were obtained either with [11C]3 or [11C]4 within short synthesis time (3 minutes from EOD) and mild reaction conditions (ambient temperature), Scheme 23. Mechanistic investigations revealed that [11C]CO yields of 80% ± 20% from [11C]4 could be produced within 3 minutes from EOD at ambient temperature.114

The utility of this [11C]CO synthesis process was confirmed by radiolabelling functionalised amides and esters, N-[11C]benzylbenzamide, [11C]CX546 and [11C]tert-butyl acrylate,115 in good RCY (>30%) and high RCP (>70%) within 6 minutes from EOD, Scheme 23. The automated synthesis system based on a 2-vial setup using an Eckert and Ziegler Modular Lab apparatus has been successfully tested112 yielding N-[11C]benzylbenzamide and [11C]CX546 in Am of ~60 to 90 GBq/μmol.116

This novel [11C]CO production methodology is based on a simple labware setup and utilises mild reaction conditions enabling the production of [11C]CO in different laboratory configurations without the need for the traditional dedicated [11C]CO infrastructure (eg, oven-based methods). However, this method requires the prior preparation of the silyl lithium precursor and addition of TBAF post [11C]CO2 delivery, which may be a limiting aspect to its applicability in a routine setting.

4.4 Production of [11C]CO via fluoride-activated disilanes

Due to the remaining caveats implied in the [11C]CO synthesis via [11C]silacarboxylic acids, our group focused on fluoride-activated disilanes as [11C]CO2 reducing agents to develop an improved [11C]CO synthesis methodology. This work was inspired by the non-radiochemical studies showing disilanes as CO2 to CO reducing agents when in the presence of a fluoride source.78

(MePh2Si)2 (disilane a) was chosen as disilane for method development and reaction optimisation. Various fluoride sources were investigated showing TBAF as the most efficient activator for [13C]CO release compared with other fluoride salts. Different solvents were explored revealing THF as the most efficient reaction media for this process. It has been reported that polar aprotic solvents, such as THF, increase the solubility of disilanes and the reactivity of the fluoride anion.106,117 0.1 equiv. of TBAF showed to be optimum for the [11C]CO2 conversion. No [11C]CO production was observed in the absence of TBAF or disilane or the TBAF/disilane complex. No [11C]CO production was observed when other TBA salts (eg, TBAB and TABCl) were used instead of TBAF. This demonstrated the relevance of silicon’s high fluorophilicity (Si–F >> Si–Br > Si–Cl > Si–I)109 in the [11C]CO2 to [11C]CO reduction process. A [11C]CO yield of 59% from total cyclotron-produced [11C]CO2 was achieved by decreasing the [11C]CO2 delivery flow rate from 60 mL/min to 10 mL/min. Various disilanes were investigated demonstrating that by using (Me2PhSi)2 (disilane d), TBAF (0.1 equiv.), and THF, [11C]CO2 was converted to [11C]CO in RCYs of 74 ± 6% within 10 minutes from end of bombardment (EOB) under mild reaction conditions (ambient temperature) and at flow rate of 10 mL/min.118

The produced [11C]CO was used in a model 11C-carbonylation reaction to yield N-[11C]benzylbezamide in up to 74% RCY, RCP > 99%, and in an estimated Am of 79 to 135 GBq/μmol116 within 10 minutes from EOB, Scheme 24 (A). In addition, [11C]tert-butyl acrylate was obtained in acceptable RCY (≥10%) and high RCP...
(≥ 80%) within 10 minutes from EOB, Scheme 24 (B). This demonstrated the applicability of this [11C]CO synthesis process to produce different compound classes.

This [11C]CO2 to [11C]CO methodology utilises a simple 2-vial labware setup and readily available reagents eliminating the remaining caveats of [11C]CO production via the [11C]silacarboxylic acid methodology, such as the time-consuming pre-synthesis reagent preparation (silyl lithium precursor) and TBAF addition post [11C]CO2 delivery.118

5 | CONCLUSIONS

A broad variety of novel [11C]CO2 fixation methods are increasingly being utilised to incorporate cyclotron-produced [11C]CO2 directly into functionalised molecules leading to a vast range of 11C-compounds, such as [11C] amides, [11C]ureas, and [11C]carbamates. Improved synthesis loop setups have shown to enhance the rapid and efficient production of 11C-tracers with minimal purification requirements and radioactivity losses. This is an important feature in routine clinical productions of PET tracers. Other [11C]CO fixation approaches have been introduced over recent years, such as high-pressure apparatus, low-pressure xenon systems, and photoinduction of the 11C-carbonylation reaction. Furthermore, innovative [11C]CO production methodologies are emerging as alternative process to the standard oven-based methods (Mo/Zn). In particular, the [11C]silacarboxylic acids to [11C] CO methodology and the fluoride-activated disilanes to [11C]CO process may enable the low-cost, widespread use of [11C]CO in diverse laboratory environments for PET tracer development without the need for specialist platforms and infrastructure.

Ultimately, this continued development and expansion of 11C-chemistry will enhance the potential of PET tracer development in both clinical and research environments.

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CONFLICT OF INTEREST

None declared.

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REFERENCES

1. McQuade P, Rowland DJ, Lewis JS, Welch MJ. Positron-emitting isotopes produced on biomedical cyclotrons. Curr Med Chem. 2005;12(7):807-818.
2. Miller PW, Long NJ, Vilar R, Gee AD. Synthesis of $^{11}$C, $^{18}$F, $^{1}$O, and $^{13}$N radiolabels for positron emission tomography. Angew Chem Int Ed. 2008;47(47):8998-9033.

3. Rotstein BH, Liang SH, Holland JP, et al. $^{11}$CO$_2$ fixation: a renaissance in PET radiochemistry. Chem Commun. 2013;49(50):5621-5629.

4. Oleksiy I, Vanessa G-V, Jordi L, Jacek K. On $^{11}$C chemistry reviews—surveying and filling the gaps. Curr Org Chem. 2013;17(19):2067-2096.

5. Antoni G, Långström B. Progress in $^{11}$C radiochemistry. In: Reviews in Radiochemistry. Berlin: Springer-Verlag; 2007: 183-213.

6. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid protein aggregates. J Nucl Med. 1987;28(6):1037-1040.

7. Larsen P, Ulin J, Dahlstrom K, Jensen M. Synthesis of $^{11}$C iodomethane by iodination of $^{13}$C-methane. Appl Radiat Isot. 1997;48(2):153-157.

8. Link JM, Krohn KA, Clark JC. Production of $^{11}$C=CH$_2$ by single pass reaction of $^{11}$CCH$_4$ with I$_2$. Nucl Med Biol. 1997;24(1):93-97.

9. Jewett DM. A simple synthesis of $^{11}$C=methyl triflate. Int J Rad Appl Instrum A. Appl Radiat Isot. 1992;43(11):1383-1385.

10. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer’s disease with Pittsburgh compound-B. Ann Neurol. 2004;55(3):306-319.

11. Oi N, Terauchi T, Erich M, et al. Synthesis and evaluation of novel radioligands for positron emission tomography imaging of the Orexin-2 receptor. J Med Chem. 2013;56(16):6371-6385.

12. Bolton R. Isotopic methylation. J Label Compd Radiopharm. 2000;14(10):701-736.

13. Antoni G. Development of carbon-11 labelled PET tracers—radiochemical and technological challenges in a historic perspective. J Label Compd Radiopharm. 2015;58(3):65-72.

14. Liu L, Xu Y, Shee C, Fowler JS, Hooker JM, Tonge PJ. Radiosynthesis and bioimaging of the tuberculosis chemotherapeutics isoniazid, rifampicin and pyrazinamide in baboons. J Med Chem. 2010;53(7):2882-2891.

15. Cai H, Mangner TJ, Muzik O, Wang M, Chugani DC, Chugani HT. Radiosynthesis of $^{11}$C-Levetracetam: a potential marker for PET imaging of SV2A expression. ACS Med Chem Lett. 2014;5(10):1152-1155.

16. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer’s disease with Pittsburgh compound-B. Ann Neurol. 2004;55(3):306-319.

17. Link JM, Krohn KA, Clark JC. Production of $^{11}$C=CH$_2$ by single pass reaction of $^{11}$CCH$_4$ with I$_2$. Nucl Med Biol. 1997;24(1):93-97.

18. Jewett DM. A simple synthesis of $^{11}$C=methyl triflate. Int J Rad Appl Instrum A. Appl Radiat Isot. 1992;43(11):1383-1385.

19. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer’s disease with Pittsburgh compound-B. Ann Neurol. 2004;55(3):306-319.

20. Oi N, Terauchi T, Erich M, et al. Synthesis and evaluation of novel radioligands for positron emission tomography imaging of the Orexin-2 receptor. J Med Chem. 2013;56(16):6371-6385.

21. Hostetler ED, Terry GE, Donald BH. An improved synthesis of substituted $^{11}$Ctoluenes via Suzuki coupling with $^{11}$C methyl iodide. J Label Compd Radiopharm. 2005;48(9):629-634.

22. Andersson Y, Cheng AP, Langström B. Palladium-promoted coupling reactions of $^{11}$C=methyl-iodide with organotin and organoboron compounds. Acta Chem Scand. 1995;49:683-688.

23. Cai H, Mangner TJ, Muzik O, Wang M, Chugani DC, Chugani HT. Radiosynthesis of $^{11}$C-Levetracetam: a potential marker for PET imaging of SV2A expression. ACS Med Chem Lett. 2014;5(10):1152-1155.

24. Liu L, Xu Y, Shee C, Fowler JS, Hooker JM, Tonge PJ. Radiosynthesis and bioimaging of the tuberculosis chemotherapeutics isoniazid, rifampicin and pyrazinamide in baboons. J Med Chem. 2010;53(7):2882-2891.

25. Cai H, Mangner TJ, Muzik O, Wang M, Chugani DC, Chugani HT. Radiosynthesis and bioimaging of the tuberculosis chemotherapeutics isoniazid, rifampicin and pyrazinamide in baboons. J Med Chem. 2010;53(7):2882-2891.

26. Oi N, Tokunaga M, Suzuki M, et al. Development of novel PET probes for central 2-aminobenzamide receptors and PK (peripheral benzodiazepine) binding sites-current status*. Nucl Med Biol. 1993;20(4):503-525.

27. Nordeman P, Johansson LBG, Bäck M, et al. $^{11}$C and $^{18}$F radiolabeling of tetra- and pentathiophenes as PET-ligands for amyloid protein aggregates. ACS Med Chem Lett. 2016;7(4):368-373.

28. Cai H, Mangner TJ, Muzik O, Wang M, Chugani DC, Chugani HT. Radiosynthesis of $^{11}$C-Levetracetam: a potential marker for PET imaging of SV2A expression. ACS Med Chem Lett. 2014;5(10):1152-1155.

29. Oi N, Tokunaga M, Suzuki M, et al. Development of novel PET probes for central 2-aminobenzamide receptors and PK (peripheral benzodiazepine) binding sites-current status*. Nucl Med Biol. 1993;20(4):503-525.

30. Cai H, Mangner TJ, Muzik O, Wang M, Chugani DC, Chugani HT. Radiosynthesis of $^{11}$C-Levetracetam: a potential marker for PET imaging of SV2A expression. ACS Med Chem Lett. 2014;5(10):1152-1155.

31. Andersson Y, Bergström M, Langström B. Synthesis of $^{11}$C-labelled benzamide compounds as potential tracer for poly(ADP-ribose) synthetase. Appl Radiat Isot. 1994;45(6):707-714.

32. Cai H, Mangner TJ, Muzik O, Wang M, Chugani DC, Chugani HT. Radiosynthesis of $^{11}$C-Levetracetam: a potential marker for PET imaging of SV2A expression. ACS Med Chem Lett. 2014;5(10):1152-1155.

33. Landais P, Crouzel C. A new synthesis of carbon-11 labelled phosgene. Int J Rad Appl Instrum A. Appl Radiat Isot. 1987;38(2):97-102.

34. Lemoucheux L, Rouden J, Ibazizene M, Sobrio F, Lasne M-C. Debenzylation of tertiary amines using phosgene or triphosgene: an efficient and rapid procedure for the preparation of carbamoyl chlorides and unsymmetrical ureas. J Org Chem. 2004;69(19):7289-7297.

35. Rotstein BH, Liang SH, Placzek MS, et al. $^{11}$C=O bonds made force in molecular imaging. Berlin: Springer-Verlag; 2007: 183-213.

36. Hosoya T, Sumi K, Doi H, Wakao M, Suzuki M. Rapid methylation on carbon frameworks useful for the synthesis of $^{13}$CH$_3$-incorporated PET tracers: Pd(0)-mediated rapid coupling of methyl iodide with an alkynyltributylstannane leading to a 1-methylalkane. Org Biomol Chem. 2006;4(3):410-415.

37. Rotstein BH, Liang SH, Placzek MS, et al. $^{11}$C=O bonds made force in molecular imaging. Berlin: Springer-Verlag; 2007: 183-213.
35. Riss PJ, Lu S, Telu S, Aigbirhio FI, Fike VW. Cul-catalyzed $^{11}$C carboxylation of boronic acid esters: a rapid and convenient entry to $^{11}$C-labeled carboxylic acids, esters, and amides. Angew Chem Int Ed. 2012;51(11):2698-2702.

36. Haji Dheere AK, Yusuf N, Lee A. Rapid and efficient synthesis of $[^{11}\text{C}]$ureas via the incorporation of $[^{11}\text{C}]$CO$_2$ into aliphatic and aromatic amines. Chem Commun. 2013;49(74):8193-8195.

37. Haji Dheere AK, Bongarzone S, Taddei C, Van R, Lee A. Synthesis of $^{11}$C-labelled symmetrical ureas via the rapid incorporation of $[^{11}\text{C}]$CO$_2$ into aliphatic and aromatic amines. Synlett. 2015;26(16):2257-2260.

38. Wilson AA, Garcia A, Houle S, Vasdev N. Direct fixation of $[^{11}\text{C}]$CO$_2$ by amines: formation of $[^{11}\text{C}]$carbonyl- $[^{11}\text{C}]$methylcarbamates. Org Biomol Chem. 2010;8(2):428-432.

39. Hooker JM, Reibel AT, Hill SM, Schueller MJ, Fowler JS. One-pot, direct incorporation of $[^{11}\text{C}]$CO$_2$ into carbamates. Angew Chem Int Ed. 2009;48(19):3482-3485.

40. Mossine AV, Brooks AF, Jackson IM, et al. Synthesis of diverse $^{11}$C-labeled PET radiotracers via direct incorporation of $[^{11}\text{C}]$CO$_2$. Bioconjug Chem. 2016;27(5):1382-1389.

41. van Tilburg EW, Windhorst AD, van der Mey M, Herscheid JDM. One-pot synthesis of $[^{11}\text{C}]$ureas via triphenylphosphinimines. J Label Compd Radiopharm. 2006;49(4):321-330.

42. Elsinga PH, van Waarde A, Jaeggi KA, Schreiber G, Heldorn M, Vaalburg W. Synthesis and evaluation of (S)-4-(3-(2-$[^{11}\text{C}]$Isopropylamino)-2-hydroxypropoxy)-2-H-benzimidazol-2-one ((S)-$[^{11}\text{C}])$CGP 12388) and (S)-4-(3-((1-$[^{11}\text{F}]$Fluorosopropyl) amino)-2-hydroxypropoxy)-2-H-benzimidazol-2-one (S)-$[^{11}\text{F}])$ fluoro-CGP 12388) for visualization of $\beta$-adrenoceptors with positron emission tomography. J Med Chem. 1997;40(23):3829-3835.

43. Krasikova RN, Andersson J, Truong P, Nag S, Shchukin EV, Halldin C. A fully automated one-pot synthesis of [carbonyl-$[^{11}\text{C}]$]WAY-100635 for clinical PET applications. Appl Radiat Isot. 2009;67(1):73-78.

44. Prenant C, Sastre J, Crouzel C, Syrota A. Synthesis of $^{11}$C-pindolol. J Label Compd Radiopharm. 1987;24(2):227-232.

45. Matareese M, Soloviev D, Toda S, et al. Preparation of $[^{11}\text{C}]$radioligands with high specific radioactivity on a commercial PET tracer synthesizer. Nucl Med Biol. 2003;30(1):79-83.

46. van der Meij M, Carruthers NI, Herscheid JDM, Jablonowski JA, Leyse J, Windhorst AD. Reductive N-alkylation of secondary amines with [2-$[^{11}\text{C}]$]acetone. J Label Compd Radiopharm. 2003;46(11):1075-1085.

47. Rotstein BH, Hooker JM, Woo J, et al. Synthesis of $[^{11}\text{C}]$ Bexarotene by cu-mediated $[^{11}\text{C}]$carbon dioxide fixation and preliminary PET imaging. ACS Med Chem Lett. 2014;5(6):668-672.

48. Wilson AA, Garcia A, Houle S, Sadovski O, Vasdev N. Synthesis and application of isocyanates radiolabeled with carbon-11. Chem A Eur J. 2011;17(1):259-264.

49. Bongarzone S, Kunser A, Taddei C, Dheere AKH, Gee AD. From $[^{11}\text{C}]$CO$_2$ to $[^{11}\text{C}]$amides: a rapid one-pot synthesis via the Mitsunobu reaction. Chem Commun. 2017;53(38):5334-5337.

50. Downey J. Oral presentation—22nd international symposium on radiopharmaceutical sciences 2017. J Label Compd Radiopharm. 2017;60(S1):S88:87-110.

51. Downey J, Bongarzone S, Hader S, Lee A. In-loop flow $[^{11}\text{C}]$ CO$_2$ fixation and radiosynthesis of N,N-$[^{11}\text{C}]$dibenzyllurea. J Label Compd Radiopharm. 2017. https://doi.org/10.1002/jlcr.3568

52. Dahl K, Collier TL, Chang R, et al. “In-loop” $[^{11}\text{C}]$CO$_2$-fixation: prototype and proof-of-concept. J Label Compd Radiopharm. 2017. https://doi.org/10.1002/jlcr.3528

53. Glass HI, Brand A, Clark JC, de Garetta AC, Day LG. Measurement of blood volume using red cells labeled with radioactive carbon monoxide. J Nucl Med. 1968;9(11):571-575.

54. Dahl K, Itsko O, Rahman O, et al. An evaluation of a high-pressure $[^{11}\text{C}]$CO radiolabeling apparatus. J Label Compd Radiopharm. 2015;58(5):220-225.

55. Lidstrom P, Kihlberg T, Langstrom B. $[^{11}\text{C}]$carbon monoxide as a more versatile and useful precursor in labelling chemistry for PET. J Label Compd Radiopharm. 2004;52(1):15-20.

56. Zeisler SK, Nader M, Theobald A, Oberdorfer F. Conversion of no-carrier-added $[^{11}\text{C}]$carbon dioxide to $[^{11}\text{C}]$carbon monoxide on molybdenum for the synthesis of $[^{11}\text{C}]$labeled aromatic ketones. Appl Radiat Isot. 1997;48(8):1091-1095.

57. Andersson Y, Langstrom B. Synthesis of $[^{11}\text{C}]$-labeled ketones via carbonylative coupling reactions using $[^{11}\text{C}]$carbon monoxide. J Chem Soc, Perkin Trans 1. 1997(18):2701-2706.

58. Eriksson J, Antoni G, Långström B. Synthesis of $[^{11}\text{C}]$propyl and $[^{11}\text{C}]$butyl iodide from $[^{11}\text{C}]$carbon monoxide and their use in alkylation reactions. J Label Compd Radiopharm. 2006;49(12):1105-1116.

59. Eriksson J, van den Hoek J, Windhorst AD. Transition metal mediated synthesis using $[^{11}\text{C}]$CO at low pressure—a simplified method for $[^{11}\text{C}]$carbonylation. J Label Compd Radiopharm. 2012;55(6):223-228.

60. Anders DA, Bongarzone S, Fortt R, Lee A, Long NJ. Electrophilic $[^{11}\text{C}]$CO$_2$ to $[^{11}\text{C}]$CO conversion for PET imaging. Chem Commun. 2017;53(20):2982-2985.

61. Långström B, Itsko O, Rahman O. $[^{11}\text{C}]$carbon monoxide, a versatile and useful precursor in labelling chemistry for PET-ligand development. J Label Compd Radiopharm. 2007;50(9-10):794-810.

62. Rahman O. $[^{11}\text{C}]$carbon monoxide in labeling chemistry and positron emission tomography tracer development: scope and limitations. J Label Compd Radiopharm. 2015;58(3):86-98.

63. Kealey S, Plisson C, Collier TL, et al. Microfluidic reactions using $[^{11}\text{C}]$carbon dioxide solutions for the synthesis of a positron emission tomography radiotracer. Org Biomol Chem. 2011;9(9):3313-3319.

64. Itsko O, Långström B. Radical-mediated carbonylation of alkyl iodides with $[^{11}\text{C}]$carbon monoxide in solvent mixtures. J Org Chem. 2005;70(6):2244-2249.

65. Ishii H, Minegishi K, Nagatsu K, Zhang M-R. Pd(0)-mediated $[^{11}\text{C}]$carbonylation of aryl and heteroaryl boronic acid pinacol esters with $[^{11}\text{C}]$carbon monoxide under ambient conditions.
and a facile process for the conversion of [carboxyl-13C]esters to [carboxyl-15N]amides. Tetrahedron. 2015;71(10):1588-1596.

66. Itsenko O, Kihlberg T, Langstrom B. Labeling of aliphatic carboxylic acids using [11C]carbon monoxide. Nat Protoc. 2006;1(2):798-802.

67. Karimi F, Langström B. Synthesis of 11C-labelled amides by palladium-mediated carbamoximation using [11C]carbon monoxide, in situ activated amines and 1,2,2,6,6-pentamethylpiperidine. Eur J Org Chem. 2003;2003(11):2132-2137.

68. Hostetler ED, Burns HD. A remote-controlled high pressure reactor for radiotracer synthesis with [11C]carbon monoxide. Nucl Med Biol. 2002;29(8):845-848.

69. Kealey S, Miller PW, Long NJ, Plisson C, Martarelo L, Gee AD. Copper(i) scorpionate complexes and their application in palladium-mediated [11C]carbonylation reactions. Chem Commun. 2009;(25):3696-3698.

70. Kealey S, Gee A, Miller PW. Transition metal mediated [11C] carbonylation reactions: recent advances and applications. J Label Compd Radiopharm. 2014;57(4):195-201.

71. Dahl K, Schou M, Amini N, Halldin C. Palladium-mediated [11C]carbonylation at atmospheric pressure: a general method using Xanthophos as supporting ligand. Eur J Org Chem. 2013;2013(7):1228-1231.

72. Filip U, Pees AL, Taddei C, et al. Efficient synthesis of 11C-Acrylestes, 11C-acrylamides and their application in Michael addition reactions for PET tracer development. Eur J Org Chem. 2017;2017(34):5154-5162.

73. Itsenko O, Kihlberg T, Långström B. Synthesis of aliphatic [carboxyl-13C]esters using [11C]carbon monoxide. Eur J Org Chem. 2005;2005(17):3830-3834.

74. Motterlini R, Sawle P, Bains S, et al. CORM-A1: a new pharmacologically active carbon monoxide-releasing molecule. FASEB J. 2004;18(2):284-286.

75. Motterlini R. Carbon monoxide-releasing molecules (CO-RMs): vasodilatory, anti-ischaemic and anti-inflammatory activities. Biochem Soc Trans. 2007;35(5):1142-1146.

76. Friis SD, Taaning RH, Lindhardt AT, Skyrdstrup T. Silacarboxylic acids as efficient carbon monoxide releasing molecules: synthesis and application in palladium-catalyzed carbonylation reactions. J Am Chem Soc. 2011;133(45):18114-18117.

77. Friis SD, Andersen TL, Skyrdstrup T. Palladium-catalyzed synthesis of aromatic carboxylic acids with silacarboxylic acids. Org Lett. 2013;15(6):1378-1381.

78. Lescot C, Nielsen DU, Makarov IS, Lindhardt AT, Daasbjerg K, Skyrdstrup T. Efficient fluoride-catalyzed conversion of CO3 to CO at room temperature. J Am Chem Soc. 2014;136(16):6142-6147.

79. Gockel SN, Hull KL. Chloroform as a carbon monoxide precursor: in or ex situ generation of CO for Pd-catalyzed aminocarbonylations. Org Lett. 2015;17(13):3236-3239.

80. Veyser C, Van Mileghem S, Egle B, Gilles P, De Borggraewe WM. Low-cost instant CO generation at room temperature using formic acid, mesyl chloride and triethylamine. React Chem Eng. 2016;1(2):142-146.

81. Gu L, Zhang Y. Unexpected CO2 splitting reactions to form CO with N-heterocyclic carbenes as organocatalysts and aromatic aldehydes as oxygen acceptors. J Am Chem Soc. 2010;132(3):914-915.

82. Laitar DS, Müller P, Sadighi JP. Efficient homogeneous catalysis in the reduction of CO2 to CO. J Am Chem Soc. 2005;127(49):17196-17197.

83. Kleeberg C, Cheung MS, Lin Z, Marder TB. Copper-mediated reduction of CO2 with pinB-SiMe3ph via CO2 insertion into a copper–silicon bond. J Am Chem Soc. 2011;133(47):19060-19063.

84. Davidek KS, Sanguinetti G, Yee CH, et al. Carbon monoxide-releasing antibacterial molecules target respiration and global transcriptional regulators. J Biol Chem. 2009;284(7):4516-4524.

85. Roberts B, Liptrot D, Alcaraz L, Luker T, Stocks MJ. Molybdenum-mediated carbonylation of aryl halides with nucleophiles using microwave irradiation. Org Lett. 2010;12(19):4280-4283.

86. Wu X, Ekegren JK, Larhed M. Microwave-promoted aminocarbonylation of aryl iodides, aryl bromides, and aryl chlorides in water. Organometallics. 2006;25(6):1434-1439.

87. Odell LR, Sävmarker J, Larhed M. Microwave-promoted aminocarbonylation of aryl triflates using Mo(CO)6 as a solid CO source. Tetrahedron Lett. 2008;49(42):6115-6118.

88. Elmore CS, Dorff PN, Richard HJ. Syntheses of the tricyclic cores of clozapine, dibenzono[β][1,4]thiazepin-11(10H)-one, and dibenzo[β][1,4]oxazepin-11(10H)-one in C-14 labeled form by [14C]carbonylation. J Label Compd Radiopharm. 2010;53(13):787-792.

89. Alberto R, Ortner K, Wheatley N, Schibli R, Schubiger AP. Synthesis and properties of boroncarbonate: a convenient in situ CO source for the aqueous preparation of [(99mTc(OH2)3(CO)3]+. J Am Chem Soc. 2001;123(13):3135-3136.

90. Audrain H, Martarelo L, Gee A, Bender D. Utilisation of [11C]-labelled boron carbonyl complexes in palladium carboxylation reaction. Chem Commun. 2004;5:558-559.

91. Morimoto T, Kakiuchi K. Evolution of carbonylation catalysis: no need for carbon monoxide. Angew Chem Int Ed. 2004;43(42):5580-5588.

92. Reproduced by permission of Sigma-Aldrich Co. LLC.

93. Hermange P, Lindhardt AT, Taarning RH, Bjerklund K, Lupp D, Skyrdstrup T. Ex situ generation of stoichiometric and substoichiometric 13CO and its efficient incorporation in palladium catalyzed aminocarbonylations. J Am Chem Soc. 2011;133(15):6061-6071.

94. Gøgsig TM, Taaning RH, Lindhardt AT, Skyrdstrup T. Palladium-catalyzed carbonylative α-arylation for accessing 1,3-diketones. Angew Chem Int Ed. 2012;51(3):798-801.

95. Friis SD, Skyrdstrup T, Buchwald SL. Mild Pd-catalyzed aminocarbonylation of (hetero)aryl bromides with a palladacycle precatalyst. Org Lett. 2014;16(16):4296-4299.

96. Brook AG. Thermal rearrangements of organosilicon and organogermanium compounds. J Am Chem Soc. 1955;77(18):4827-4829.
97. Benkeser RA, Severson RG. The preparation and reactions of triphenylsilylpotassium. J Am Chem Soc. 1951;73(4):1424-1427.
98. Brook AG, Mauris RJ. Thermal rearrangement of silanecarboxylate esters. J Am Chem Soc. 1957;79(4):971-973.
99. Brook AG, Gilman H. Base-catalyzed elimination reactions of triphenylsilanecarboxylic acid and its derivatives. J Am Chem Soc. 1955;77(8):2322-2325.
100. Brook AG. Molecular rearrangements of organosilicon compounds. Acc Chem Res. 1974;7(3):77-84.
101. Jankowski P, Raubo P, Wicha J. Tandem transformations initiated by the migration of a silyl group. Some new synthetic applications of silyloxiranes. Synlett. 1994;1994(12):985-992.
102. Moser WH. The Brook rearrangement in tandem bond formation strategies. Tetrahedron. 2001;57(11):2065-2084.
103. Fleming I, Lawrence AJ, Richardson RD, Sury DS, West MC. 1,1-Disilyl alcohols as d1 synthons: harnessing the 1,2-brook rearrangement. Helv Chim Acta. 2002;85(10):3349-3365.
104. Brook AG, Gilman H. Analogs of hexaphenylethane. III. Triphenylmethyltriphenylgermane, triphenylgermanecarboxylic acid and some of its derivatives. J Am Chem Soc. 1954;76(1):77-80.
105. Mita T, Suga K, Sato K, Sato Y. A strained disilane-promoted carboxylation of organic halides with CO2 under transition-metal-free conditions. Org Lett. 2015;17(21):5276-5279.
106. Hiyama T, Obayashi M, Mori I, Nozaki H. Generation of metal-free silyl anions from disilanes and fluoride catalyst. Synthetic reactions with aldehydes and 1,3-dienes. J Org Chem. 1983;48(6):912-914.
107. Hiyama T, Obayashi M, Sawahata M. Preparation and carbonyl addition of 1,7-difluoroallylsilanes. Tetrahedron Lett. 1983;24(38):4113-4116.
108. Hiyama T, Obayashi M. Generation of alkanal carbonyl and 1,3-diene units between Si–Si bonds of trisilanes. Synthesis of novel silicon-containing materials. Tetrahedron Lett. 1983;24(38):4109-4112.
109. Walsh R. Bond dissociation energy values in silicon-containing compounds and some of their implications. Acc Chem Res. 1981;14(8):246-252.
110. Wagler J, Böhme U, Roewer G. Activation of a Si–Si bond by hypercoordination: cleavage of a disilane and formation of a Si–C bond. Organometallics. 2004;23(25):6066-6069.
111. Magnusson E. Hypercoordinate molecules of second-row elements: d functions or d orbitals? J Am Chem Soc. 1990;112(22):7940-7951.
112. Taddei C, Bongarzone S, Haji Dheere AK, Gee AD. [11C]CO2 to [11C]CO conversion mediated by [11C]silanes: a novel route for [11C]carbonylation reactions. Chem Commun. 2015;51(59):11795-11797.
113. Nordeman P, Friis SD, Andersen TL, et al. Rapid and efficient conversion of 13CO2 to 13CO through silanocarboxylic acids: applications in Pd-mediated carbonylations. Chem A Eur J. 2015;21(49):17601-17604.
114. Bongarzone S, Taddei C, Gee AD. Poster presentations—22nd international symposium on radiopharmaceutical sciences 2017. J Label Compd Radiopharm. 2017;60(S1):S575:111-640.
115. The synthesis of [11C]1-tert-butyl acrylate was performed in collaboration with U. Filip and A. Pekosak, VU University Medical Center, Department of Radiology and Nuclear Medicine, Amsterdam, Netherlands.
116. At end of synthesis. This is conform with Av values obtained at this production facility for 13C-tracers.
117. Kuwajima I, Nakamura E. Quaternary ammonium enolates as synthetic intermediates. Regiospecific alkylation reaction of ketones. J Am Chem Soc. 1975;97(11):3257-3258.
118. Taddei C, Bongarzone S, Gee AD. Instantaneous conversion of [11C]CO2 to [11C]CO via fluoride-activated disilane species. Chem A Eur J. 2017;23(32):7682-7685.

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