Carbon-11 carboxylation of trialkoxysilane and trimethylsilane derivatives using [^{11}C]CO_2

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Abstract

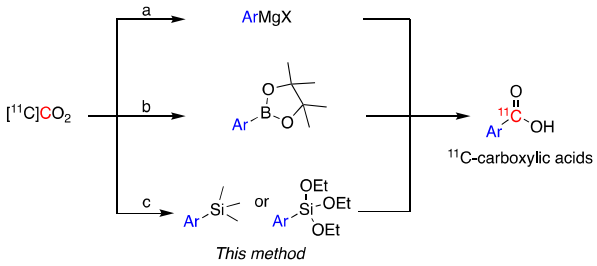
A novel carboxylation radiosynthesis methodology is described starting from cyclotron-produced [^{11}C]CO_2 and fluoride-activated silane derivatives. Six [^{11}C]carboxylic acids were obtained from their corresponding trimethylsilyl and trialkoxysilyl precursors in a one-pot labelling methodology. Radiochemical purity ranged from 18% to 93% within 12 minutes post [^{11}C]CO_2 delivery with yields of 5-82%.

Carbon-11 (^{11}C) is a short-lived radionuclide ($t_{1/2}$ = 20.4 min) commonly applied in positron emission tomography (PET) imaging.[1] The isotopic substitution of carbon-12 for a carbon-11 atoms in bioactive molecules maintains the chemical and biological properties of the non-radioactive authologue, allowing the study of the pharmacokinetics and biodistribution of a wide range of biologically active molecules in living subjects.[1]

^{11}C is cyclotron-produced in the form of carbon dioxide ([^{11}C]CO_2) which can be directly incorporated into a variety of biologically relevant molecules, such as [*carbonyl*-^{11}C]carboxylic acids.[2] Traditionally, aromatic [^{11}C]carboxylic acids have been labelled directly from [^{11}C]CO_2 using either *i)* Grignard reagents[3] or *ii)* aromatic boronic esters as supporting reagents.[4]

However, these methodologies present some challenges which limit their wider application. For instance, the high reactivity of Grignard reagents is not well tolerated by many functional groups, limiting their utility to labelling functionally simple substrates.[3] In addition, Grignard reagents are very sensitive to moisture or reaction with atmospheric CO_2, even if great care is used in the storage and use of these reagents, leading to isotopic dilution of [^{11}C]CO_2 and concomitant low molar activity (A_m) of ^{11}C-labelled products.

Compared to Grignard reagents, boronic esters have greater stability to atmospheric CO_2 and moisture which broadens their use for radiolabelling aromatic and heteroaromatic compounds.[4] However, the radiolabelling of the latter class of compounds (e.g. pyridyl, pyrazyl and thienyl boronic ester derivatives) is inconsistent and gives low- moderate radiochemical yields (RCY's 3% - 69%).[4a]

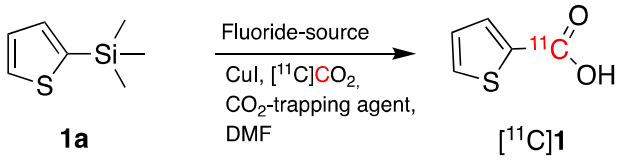


Scheme 1 Current methods for the preparation of aromatic [^{11}C]carboxylic acids from [^{11}C]CO_2 using: (a) Grignard reagents, (b) boronic esters and (c) trialkoxysilane and trimethylsilane derivatives - the latter used in *this work*.

Based on a search of the traditional synthetic chemistry literature, improved methods for the ^{11}C-carboxylation of aryl and heteroaryl groups might be achieved by the use of trialkoxysilyl and trimethylsilyl derivatives *via* a so-called copper-catalysed desilylative carboxylation reaction.[5] Arylsilanes reacted readily with a fluoride anion source, such as cesium fluoride (CsF), potassium fluoride (KF), tetramethylammonium fluoride (Me_4NF) to form a pentavalent silicate.[5-6] The pentavalent silicate was then converted in the presence of a copper catalyst to an arylcopper intermediate which reacted with non-radioactive CO_2 in moderate to excellent yields (27-99%).[5-6] Varying the substitution patterns of the aromatic ring with electron-withdrawing or electron donating groups did not alter the efficiency of substrate carboxylation.[5a-c] Excellent results were also reported for the carboxylation of heteroaromatic compounds, such as thiophenyl, pyridyl and furanyl silane derivatives and their derivatization to ester products (89%-93%).[5b, c]

Compared to the traditional ^{11}C-carboxylation methodologies, the use of silyl derivatives would provide greater air and moisture stability and therefore easier handling and storage. Moreover, trimethylsilyl and trialkoxysilyl precursors are readily obtained *via* a plethora of synthetic reagents: Grignard or organolitium reagents[7] or functionalization of arylamides,[8] arylacyl fluorides,[9] aryl esters,[10] aryl cyanides[11] via transition-metals (Nickel, Copper, Ruthenium).

With the aim developing more robust and versatile ^{11}C-carboxylation methodologies, we herein present the development of a novel ^{11}C-carboxylation protocol involving the use of arylsilyl derivatives. The [^{11}C]carboxylic acids were obtained in short synthesis times, with high molar activities and with broad applicability to range of trimethylsilane and trialkoxysilane derivatives.



Scheme 2 Radiosynthetic approach to radiolabelled [^{11}C]carboxylic acids from cyclotron-produced [^{11}C]CO_2.

2-(Thienyl)trimethylsilane (**1a, Scheme 2**) was initially chosen as model substrate for cyclotron-produced [^{11}C]CO_2 carboxylation reactions. Liu *et al.* reported that the combination of CsF and 18-crown-6 in the presence of CO_2 (1 atm) allowed the carboxylation of trimethylsilane derivatives in high yields.[12] As a starting point, we applied the same approach of using CsF and 18-crown-6 (CsF-crown) in the presence of [^{11}C]CO_2 to carboxylate **1a**. However, when **1a** (100 µmol, 1 equiv.) was reacted with [^{11}C]CO_2 for 5 minutes at 100 °C in dimethylformamide (DMF), no [^{11}C]**1** was formed and the resulting [^{11}C]CO_2 trapping efficiency (TE) was poor (entry 1, **Table 1**).

This might be due to the poor reactivity of the pentavalent silicate intermediate and/or the absence of any [^{11}C]CO_2 trapping agent. The transmetallation of hypervalent silicates with copper catalysts (10%) however have been shown to form arylcopper intermediates that readily react with non-radioactive CO_2.[5a] Despite this finding, in our hands, the addition of 10% CuI to the reaction mixture did not promote the formation [^{11}C]**1** (entry 2, **Table 1**). Moreover, the addition of a [^{11}C]CO_2 trapping agent (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU, 0.6 equiv.) did not favour the formation of [^{11}C]**1** either, although the TE increased from 6% to 77% (entry 1 versus 3).

We subsequently focused on selecting alternative fluoride sources, as CsF is highly hygroscopic and poorly soluble in organic solvents - even in the presence of 18-crown-6, which might have hampered the formation of [^{11}C]**1**. KF was investigated as a fluoride source as it has previously been used for the carboxylation of aryltrimethylsilanes, however, due its low reactivity KF in organic solvents the corresponding carboxylic acid derivative was only obtained with a low to moderate yield (17-74%).[5c, 13] To increase the reactivity of KF in organic solvents, we opted to explore the use of the polyether kryptofix (K2.2.2), to form a K^+ - cryptand complex.

Interestingly, replacing CsF-crown with KF-K2.2.2 improved the formation of [^{11}C]**1** (100 °C, 5 minutes) giving radiochemical yields (RCY)[14] of 20% and high TE (96%, entry 4).

In order to further increase the RCY of [^{11}C]**1**, an optimization process was subsequently performed by modifying: *i)* the amount of fluoride source, *ii)* the reaction temperature, *iii)* the amount of trapping reagent, *iv)* the amount of copper catalyst and *v)* the solvent.

The effect of the equivalents of fluoride source was initially investigated.

Lowering the equivalents of the KF-K2.2.2 complex from 3 to 0.5 and 0.25 equivalents, and keeping the temperature at 100 °C, enhanced the RCY of [^{11}C]**1** (20% with 3 equiv., 25% with 0.5 equiv., and 28% with 0.25 equiv., entries 4-6). A similar trend was obtained at 140 °C (31% with 0.5 equiv., 37% with 0.25 equiv., entries 7-8).

Additionally, we observed that higher temperatures favoured the formation of [^{11}C]**1** - either when 0.5 equivalents (25% at 100 °C *versus* 31% at 140 °C, entries 5 and 7) or 0.25 equivalents (28% at 100 °C *versus* 37% at 140 °C, entries 6 and 8) of KF-K2.2.2 complex was used. Conversely, lowering the temperature to 70 °C had a detrimental effect, decreasing the TE and yield of [^{11}C]**1** (entry 9).

Increasing the amount of the trapping agent (DBU) from 0.6 to 0.9 equivalents did not alter the RCY of [^{11}C]**1** significantly (28% *versus* 24%, entries 6 and 10, respectively). Similarly, increasing the content of CuI from 10% to 20% did not markedly affect the RCY of [^{11}C]**1** (24%, entry 11).

The use of a different solvent was investigated. Using tetrahydrofuran (THF) instead of DMF, had a negative effect on reactivity, with the RCY of [^{11}C]**1** dropping to 1% (entry 12).

Optimal conditions were obtained when **1a** (100 μmol, 1 equiv.) was reacted with the cyclotron-produced [^{11}C]CO_2 at 140 °C in the presence of 0.25 equiv. of KF-K2.2.2, 10% of CuI and DMF (entry 8, **Table 1**).

Table 1 Reaction conditions and optimisation for the synthesis of [^{11}C]**1** using DBU as trapping agent.[14]

Entry[a]	Fluoride source (equiv.)	Additive (equiv.)	DBU (equiv.)	CuI (%)	Temp (°C)	TE (%)	RCP of [^{11}C]**1** (%)	RCY of [^{11}C]**1** (%)
1[b]	CsF (3)	18-crown-6 (3)	-	-	100	6	0	0
2[b]	CsF (3)	18-crown-6 (3)	-	10	100	99	0	0
3[b]	CsF (3)	18-crown-6 (3)	0.6	10	100	77	0	0
4[b]	KF (3)	K2.2.2 (3)	0.6	10	100	96	21	20
5	KF (0.5)	K2.2.2 (0.5)	0.6	10	100	63±14	41±9	25±7
6	KF (0.25)	K2.2.2 (0.25)	0.6	10	100	52±5	53±23	28±12
7[a]	KF (0.5)	K2.2.2 (0.5)	0.6	10	140	77	40	31
8	KF (0.25)	K2.2.2 (0.25)	0.6	10	140	67±13	55±7	37±9
9[b]	KF (0.25)	K2.2.2 (0.25)	0.6	10	70	37	0	0
10	KF (0.25)	K2.2.2 (0.25)	0.9	10	100	86±5	28±11	24±10
11	KF (0.25)	K2.2.2 (0.25)	0.6	20	100	61±31	44±26	24±3
12[b/c]	KF (0.25)	K2.2.2 (0.25)	0.6	10	140	7	15	1

Reaction conditions: [^{11}C]CO_2 was bubbled in a solution of 1a (100 μmol, 1 equiv.), DBU (0.6–0.9 equiv.), fluoride source CsF or KF (3-0.25 equiv.) and additive 18-crown-6 or K2.2.2 (3-0.25 equiv.) in DMF (500 μL) at 0 °C. Then, the reaction mixture was heated (70–140 °C) for 5 minutes and after the system flushed with helium (60 ml/min) for 20 seconds. Subsequently, the temperature was reduced to 0 °C and the reaction quenched with a solution of 0.5% trifluoroacetic acid (TFA) in water and acetonitrile (H_2O:MeCN, 1:1, 1 mL) *[a]n=3. [b]n=1;[c]THF.*

Aiming to further increase the RCY of [^{11}C]**1**, DBU was substituted with BEMP as CO_2 trapping agent. Although no significant difference was observed at 100 °C (27% with BEMP, entry 1, **Table 2** *versus* 28% with DBU, entry 8, **Table 1**), high yields of [^{11}C]**1** were obtained when the temperature was increased to 140 °C (82% with BEMP, entry 2, **Table 2** *versus* 37% with DBU, entry 8, **Table 1**). Encouraged by these results, BEMP was used as trapping agent for the following experiments which initially focused on the effect of a shorter reaction times. Halving the reaction time from 5 to 2.5 minutes resulted in halving the RCY of [^{11}C]**1** (44% at 2.5 min. *versus* 82% at 5 min., entries 2-3, **Table 2**).

To understand the role of each reagent on the reaction mechanism, experiments were conducted with the omission of key reagents (KF, K2.2.2, BEMP, or CuI) from the reaction mixture. Removing BEMP or CuI, yielded [^{11}C]**1** but with a significantly lower RCY (5% without BEMP and 15% without CuI, entries 4-5). Notably, [^{11}C]**1** was not formed at all when KF or K2.2.2 were eliminated from the reaction mixture (entries 6 and 7, respectively). Similarly, when the amount of KF-K2.2.2 was halved, the RCY of [^{11}C]**1** was reduced three-fold (27%, entry 8). These results highlight the primary role of the fluoride source as a desilylative reagent to promote the formation of a highly nucleophilic intermediate, which is stabilized by copper catalyst.

The effect of the solvent was also investigated during the optimisation of reaction conditions. The use of THF and acetonitrile (MeCN) gave low or zero yields of [^{11}C]**1** (2% in THF and 0% in MeCN, entries 9-10, **Table 2**).

Table 2 Reaction conditions and optimisation for the synthesis of [^{11}C]**1** using BEMP as trapping agent.[14]

Entry[a]	KF (equiv.)	K2.2.2 (equiv.)	BEMP (equiv.)	CuI (%)	Solvent	Temp (°C)	TE (%)	RCP of [^{11}C]1 (%)	RCY of [^{11}C]1 (%)
1	0.25	0.25	0.6	10	DMF	100	84±3	33±15	27±11
2	0.25	0.25	0.6	10	DMF	140	89±8	93±6	82±3
3[b]	0.25	0.25	0.6	10	DMF	140	76±12	58±9	44±10
4	0.25	0.25	-	10	DMF	140	6±2	95±0	5±1
5	0.25	0.25	0.6	-	DMF	140	76±22	24±18	15±6
6[c]	-	0.25	0.6	10	DMF	140	40, 30	0	0
7[d]	0.25	-	0.6	10	DMF	140	48	0	0
8	0.125	0.125	0.6	10	DMF	140	55±15	47±9	27±11
9	0.25	0.25	0.6	10	THF	140	12±5	20±7	2±1
10[d]	0.25	0.25	0.6	10	MeCN	140	50	0	0

Reaction conditions: [^{11}C]CO_2 was bubbled in a solution of 1a (100 μmol, 1 equiv.), BEMP (0.6 equiv.), KF (0.125-0.25 equiv.), and K2.2.2 (0.125-0.25 equiv.) in DMF (500 μL) at 0 °C. Then, the reaction mixture was heated (100–140 °C) for 2.5-5 minutes and then the system flushed with helium (60 ml/min) for 20 seconds. Subsequently, the temperature was reduced to 0 °C and the reaction quenched a solution of 0.5% TFA in H_2O:MeCN (1:1, 1 mL). *[a]n=3; [b]2.5 minutes; [c]n=2; [d]n=1;*

The results presented in **Table 1** and **Table 2** show that the RCY of [^{11}C]**1** is maximized when 100 μmol of **1a** is reacted with 0.6 equiv. of BEMP, 0.25 equiv. of KF-K2.2.2 and 0.1 equiv. of CuI in DMF for 5 minutes at 140 °C (entry 2, **Table 2**). Following this protocol, A_m of 3.1±0.4 Gbq/μmol for [^{11}C]**1** was obtained at end of bombardment (EOB) - starting from 2.30 ± 0.3 GBq of [^{11}C]CO_2.

Reaction conditions were subsequently kept constant whilst studying the substrate scope of additional trialkoxysilyl and trimethylsilyl compounds.

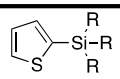
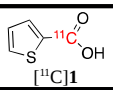
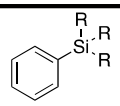
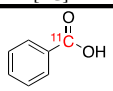
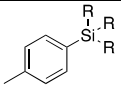
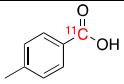
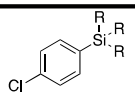
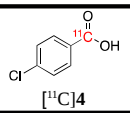
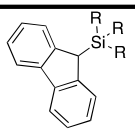
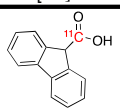
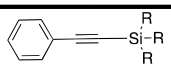
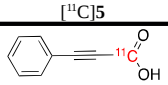
Initially, the effect of silyl substituents other than the trimethyl silyl moiety on the thienyl ring was explored using a triethoxysilyl substituent (triethoxy-2-thienylsilane, **1b**, **Table 3**). Both precursors **1a** and **1b**, yielded the corresponding [^{11}C]**1.** However, the use of **1b** resulted in lower RCY (51%, entry 1, **Table 3**) compared with **1a** (RCY = 82%, entry 2, **Table 2**).

Next, we directed our attention on radiolabelling other ^{11}C-labelled aromatic carboxylic acids such as [^{11}C]benzoic acid ([^{11}C]**2**, entries 2-3) and [^{11}C]p-toluic acid ([^{11}C]**3**, entries 4-5) using trimethyl silyl (**2a** and **3a**) and the triethoxysilyl (**2b** and **3b**) precursors. In contrast to that observed with [^{11}C]**1**, the trimethyl silyl derivatives showed a different reactivity to triethoxysilyl analogues. Indeed, **2b** and **3b** produced the corresponding [^{11}C]carboxylic acids in good yields (RCY of [^{11}C]**2** = 64%, entry 3; RCY of [^{11}C]**3** = 63%, entry 5), whereas the trimethylsilyl derivatives, **2a** and **3a,** did not form the desired products (RCY = 0% for [^{11}C]**2** and [^{11}C]**3**, entries 2 and 4, respectively). As expected, the low reactivity of benzyl-trimethylsilyl substrates was also observed using 1-chloro-4-(trimethylsilyl)benzene (**4a**), yielding only small amounts of [^{11}C]**4** (5%, entry 6).

Further studies focused on non-aromatic silane precursors such as fluorene and alkyne derivatives (entries 7-10). The radiolabelling of a fluorene moiety (**5a**) was effective, producing [^{11}C]fluorene-9-carboxylic acid ([^{11}C]**5**) in moderate RCY (35%, entry 7). The radiolabelling of prop-1-yn-1-ylbenzene (**6a**) to [^{11}C]3-phenylpropiolic acid ([^{11}C]**6**), instead, was ineffective at 140 °C (entry 8) and 100 °C (entry 9). However, lowering the temperature to 30 °C yielded [^{11}C]**6**, although with low RCY (3%, entry 10).

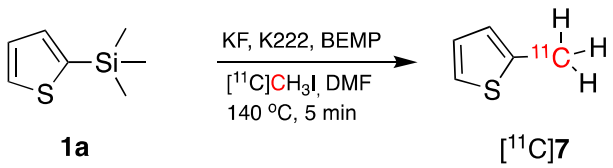
Table 3 Radiolabelling aromatic ^{11}C-carboxylic acids ([^{11}C]**1-6**) with [^{11}C]CO_2 and silyl derivatives.[14]

Entry[a]	Reagent	R	Product	Temp (°C)	TE (%)	RCP (%)	RCY (%)

1		**1b**	OEt	 [^{11}C]**1**	140	57±18	90±4	51±16
2		**2a**	Me	 [^{11}C]**2**	140	13±8	0	0
3		**2b**	OEt		140	76±8	84±2	64±6
4		**3a**	Me	 [^{11}C]**3**	140	15±8	0	0
5		**3b**	OEt		140	81±2	78±2	63±1
6		**4a**	Me	 [^{11}C]**4**	140	23±15	18±7	5±4
7		**5a**	Me	 [^{11}C]**5**	140	40±1	87±6	35±2
8		**6a**	Me	 [^{11}C]**6**	140	5±4	0	0
9					100	3±2	9±8	0
10					30	21±12	19±15	3±2

Reaction conditions: [^{11}C]CO_2 was bubbled in a solution of **1b**, **2a-b, 3a-b**, **4a-6a** (0.1 mmol, 1 equiv.), BEMP (0.6 equiv.), KF (0.25 equiv.), and K2.2.2 (0.25 equiv.) in DMF (500 µL) at 0 °C. Then, the reaction mixture was heated (30-140 °C) for 5 minutes and then the system flushed with helium (60 ml/min) for 20 seconds. Subsequently, the temperature was reduced to 0 °C and the reaction quenched a solution of 0.5% TFA in H_2O:MeCN (1:1, 1 mL).[a] *n=3;*

To demonstrate that the arylcopper intermediates were obtained by the KF-K2.2.2 mediated desilylation of trimethylsilyl derivatives, we replaced [^{11}C]CO_2 by [^{11}C]CH_3I. [^{11}C]**7** was obtained by direct aromatic ^{11}C-methylation of **1a**, with a RCP of of 16 ± 4% % (n=3). Although this method has not been optimised here, we note a potential application of this strategy as an alternative route to produce a plethora of ^{11}C-methylaromatic radiopharmaceuticals such as (15R)-[^{11}C]TIC, [^{11}C]MNQP, [^{11}C]M-MTEB, [^{11}C]celecoxib, [^{11}C]cibbi-772, and [^{11}C]UCB-J by direct aromatic ^{11}C-methylation.[2]



1a [^{11}C]**7**

Scheme 3 Aromatic ^{11}C-methylation of **1a** using [^{11}C]CH_3I to obtain [^{11}C]**7**.

In summary, we have developed a novel carbon-11 reaction using cyclotron-produced [^{11}C]CO_2 and aryltrimethylsilane and aryltrialkoxysilanes to obtain ^{11}C-carboxylic acid derivatives. Aryltrimethylsilanes and aryltrialkoxysilanes are activated by a fluoride source (KF-K2.2.2) and copper catalyst which readily react with cyclotron-produced [^{11}C]CO_2. We have also expanded the use

of activated aryltrimethylsilanes as nucleophilic compounds for aromatic ^{11}C-methylation using [^{11}C]CH_3I. The application of silane-mediated ^{11}C-carboxylation and ^{11}C-methylation reactions using to relevant radiopharmaceuticals will be reported in due course.

Acknowledgments

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14 , Radiochemical yield was calculated by multiplying TE and RCP. Radiochemical purity (RCP) of the crude product has been determined by analytical radio-HPLC. The trapping efficiency (TE) has been calculated as a ratio of the decay corrected radioactivity in the vial and the total radioactivity produced by the cyclotron.

Carbon-11 carboxylation of trialkoxysilane and trimethylsilane derivatives using [^{11}C]CO_2

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Supplementary Information

General Method and Materials

2-Thiophencarboxylic acid **(1,** 99%), benzoic acid (**2**, 99%), toluic acid (**3,** 99%), fluorene-9-carboxylic acid (**4**, 96%), phenylpropiolic acid (**5**, 99%), 4-chlorobenzoic acid(**6**, 99%), 2-methyltiophene (**7,** 99%), trimethyl-2-thienylsilane (**1a,** 97%), triethoxy-2-thienylsilane (**1b,** 97%), trimethyl(phenyl)silane (**2a,** 99%), triethoxy(phenyl)silane (**2b,** 98%), trimethyl-p-tolylsilane (**3a,** 97%), triethoxy-p-tolylsilane (**3b,** 97%), 9-trimethylsilylfluorene (**4a,** 98%), 1-phenyl-2-trimethylsilylacetilene (**5a,** 99%), 1-chloro-4(trimethylsilyl)benzene (**6a,** 98%), potassium fluoride (KF, 99%), 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (K2.2.2, 99%), 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, 98%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 98%) copper(I) iodide (99%), N,N-dimethylformamide (DMF, 99%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 98%), Acetonitrile (ACN, 99%) Tetrahydrofuran (THF, 99%), Trifluoroacetic acid (TFA, 99%), Acetonitrile (ACN, for HPLC ≥99%), Water (H_2O, for HPLC). All chemicals and dry solvents were purchased from Sigma-Aldrich, Alfa Aesar, Merck, Fisher Scientific and Acros Organics. TE, RCP, RCY and molar activity values are reported as mean ± standard deviation.

Carbon-11 Radiochemistry

Preparation of the Vial

An oven-dried vial (KX Microwave Vials, 5 mL) and a crimp cap (Fisherbrand, centre hole with 3.0 mm PTFE seal aluminium silver 20 mm, part # 10132712) were used. The vials were prepared in a glovebox

(Plas-Labs, Inc. 815 PGB Series) under nitrogen atmosphere and controlled CO_2 levels (lower than 30 ppm).

$[^{11}C]CO_2$ Production

$[^{11}C]CO_2$ was produced using a Siemens RD112 cyclotron by the 11 MeV proton bombardment of nitrogen (+0.5% O_2) gas via the $^{14}N(p,\alpha)^{11}C$ reaction. The cyclotron-produced $[^{11}C]CO_2$ was bubbled in a stream of helium gas with a flow rate of 60 mL/min post target depressurisation directly into a reaction v-vial (time from end of bombardment (EOB) to end of delivery (EOD) = 1 minute and 50 seconds).

Description of the system

The set up was implemented on an Eckert & Ziegler system (Modular-Lab Standard) and included two switching valves and a heating block. All gas transfer lines were fabricated from PTFE tubing (length: 10–30 cm, O.D.: 0.79 x 0.4 in., I.D.: 1/32 x 0.16 in.). A P_2O_5 trap and one-way valve (BRAUN, normally closed backcheck valve, part # 415062) were placed before the vial. The outlet gas line of the vial was connected to a cartridge (Biosys Solutions Ltd, Fritted Empty MiniSpeed Cartridges, part # 2447) filled with ascarite® (Sigma-Aldrich, 1310-73-2) to trap unreacted $[^{11}C]CO_2$. A tedlar® gas waste bag was placed at the outlet of the ascarite's cartridge to prevent any gaseous emission.

Description of the carbon-11 carboxylation

A cyclotron beam current of 5 μA was maintained for a bombardment time of 1 minute for all reaction optimization experiments producing ~ 300 MBq of carbon-11 at EOD.

$[^{11}C]CO_2$ (carried by helium gas) was bubbled directly from the target into a reaction vial containing aryltrimethylsilane or aryltrialkoxysilanes and reagents described in **Tables 1-3** at 0 °C. The outlet gas line of the vial was connected to an Ascarite® cartridge. After the delivery of $[^{11}C]CO_2$ (1.75 minutes from end of bombardment) the temperature was increased to 30, 70, 100, 140 °C for 2.5-5 minutes. At five minutes, the system was flushed with helium (60 ml/min) for 20 seconds. Thereafter, the reaction was cooled at 0 °C and quenched with a solution of 0.5% trifluoroacetic acid TFA (CF_3COOH) in MeCN/H_2O (1:1, 1 mL). The amount of radioactivity in the Ascarite® and vial were measured (to determine the trapping efficiency, TE), and an aliquot of the crude mixture analysed by radio-HPLC to determine the radiochemical purity, RCP.

Molar Activity calculation of $[^{11}C]$1

Eleven samples of **1** at different concentrations (1.15-0.011 μmol/mL) were analysed by HPLC to obtain a calibration curve of the peak area (mAU*s) versus μmol/mL. The peak areas of **1** were averaged and plotted in function of the corresponding μmol/mL (**Figure S2**).

[^{11}C]**1** was produced following the procedure of entry 2 (**Table 2**) by starting from 2.30 ± 0.3 GBq of [^{11}C]CO_2. After quenching the reaction, [^{11}C]**1** was purified by semipreparative HPLC and the peak corresponding to [^{11}C]**1** collected.

The radioactivity in 1.00 mL of solution containing the purified [^{11}C]**1** was determined. An aliquot of purified [^{11}C]**1** (20 μL) was analysed by analytical radio-HPLC (**Figure S3**) and the UV peak corresponding to **1** was integrated. The area of the UV peak was used to determine the μmol/mL of the associated ^{12}C-carrier content for [^{11}C]**1** from the equation of the calibration curve. The molar activity (A_m) of [^{11}C]**1** was calculated to be 3.1 ± 0.4 GBq/μmol (n = 3).

Description of the carbon-11 methylation to obtain [^{11}C]7

The [^{11}C]CO_2 was transferred in a stream of helium at 70 mL/min to a GE TRCAERLab® FX MeI module ($t_{delivery}$ = 1 minute and 50 seconds). [^{11}C]CH_3I was produced by gas phase conversion from [^{11}C]CO_2 and transferred in a vial containing 1 mL of DMSO.

A DMSO solution of [^{11}C]CH_3I (2-4 MBq) was transferred into a reaction vial containing **1a** (0.1 mmol, 1 equiv.), KF (0.25 equiv.), K2.2.2, (0.25 equiv.), BEMP (0.6 equiv.) and CuI (10%) in 500 μL of DMF at 0 °C. The temperature was then increased to 140 °C for 5 minutes. Thereafter, the reaction was cooled at 0 °C and quenched with a solution of 0.5% TFA in MeCN/H_2O 1:1. An aliquot of the crude mixture analysed by radio-HPLC to determine the radiochemical purity, RCP.

Quality control of compounds [^{11}C]1-[^{11}C]7

HPLC analysis was performed on an Agilent 1200 system equipped with a UV detector (λ=254 nm) and a β+-flow detector coupled in series. A reverse-phase column (Phenomenex Luna-C18, 4.6 x 150 mm, 5 μm) was used with a flow rate of 1 mL/min.

Identification of all radioactive products was confirmed by co-elution of ([^{11}C]**1**-[^{11}C]**7**) with the corresponding non-radioactive compounds (**1**-**7**).

Compounds [^{11}C]**1** and [^{11}C]**7**

The HPLC method was isocratic between 0-5.5 minutes (CH_3CN + 0.5% TFA: H_2O + 0.5% TFA, 25:75), gradient between 5.5-6 minutes (25:75 to 0:100), isocratic between 6-9 minutes (0:100), gradient between 9-10 minutes (0:100 to 25:75), isocratic between 10-13 minutes (25:75).

[^{11}C]**1** t_R= 5 minutes and 20 seconds (**Figure S1**).

[^{11}C]**7** t_R= 8 minutes and 40 seconds.

Compound [^{11}C]**2**

The HPLC method was isocratic between 0-9 minutes (CH_3CN + 0.5% TFA: H_2O + 0.5% TFA, 25:75), gradient between 9-10 minutes (25:75 to 0:100), isocratic between 10-13 minutes (0:100), gradient between 13-14 minutes (0:100 to 25:75) and isocratic between 14-17 minutes (25:75).

t_R= 7 minutes and 30 seconds.

Compounds [^{11}C]**3** and [^{11}C]**5**

The HPLC method was isocratic between 0-5.5 minutes (CH_3CN + 0.5% TFA: H_2O + 0.5% TFA, 35:65), gradient between 5.5-9 minutes (35:65 to 0:100), isocratic between 9-12 minutes (0:100), gradient between 12-13 minutes (0:100 to 35:65), isocratic between 13-16 minutes (35:65).

[^{11}C]**3**: t_R= 6 minutes and 20 seconds.

[^{11}C]**5**: t_R= 7 minutes and 7 seconds.

Compound [^{11}C]**4**

The HPLC method was isocratic between 0-5.5 minutes (CH_3CN + 0.5% TFA: H_2O + 0.5% TFA, 50:50), gradient between 5.5-9 minutes (50:50 to 0:100), isocratic between 9-12 minutes (0:100), gradient between 12-13 minutes (0:100 to 50:50), isocratic between 13-16 minutes (50:50).

t_R= 5 minutes and 46 seconds.

Compound [^{11}C]**6**

The HPLC method was isocratic between 0-5.5 minutes (CH_3CN + 0.5% TFA: H_2O + 0.5% TFA, 45:55), gradient between 5.5-9 minutes (45:55 to 0:100), isocratic between 9-12 minutes isocratic (0:100), gradient between 12-13 minutes (0:100 to 45:55), isocratic between 13-16 minutes (45:55).

t_R= 5 minutes and 30 seconds.

Semipreparative HPLC method for the purification of [^{11}C]1.

HPLC analysis was performed on an Agilent 1200 system equipped with a UV detector (λ=254 nm) and a β+-flow detector coupled in series. A reverse-phase column (Phenomenex Luna-C18, 10 x 250 mm, 5 μm) was used with a flow rate of 4 mL/min.

The HPLC method was isocratic between 0-10.4 minutes (CH_3CN + 0.5% TFA: H_2O + 0.5% TFA, 25:75), gradient between 10.4-11.8 minutes (25:75 to 0:100), isocratic between 11.8-17.7 minutes (0:100), gradient between 17.7-19.69 minutes (0:100 to 25:75), isocratic between 19.69-26 minutes (25:75). t_R= 11 minutes and 48 seconds.

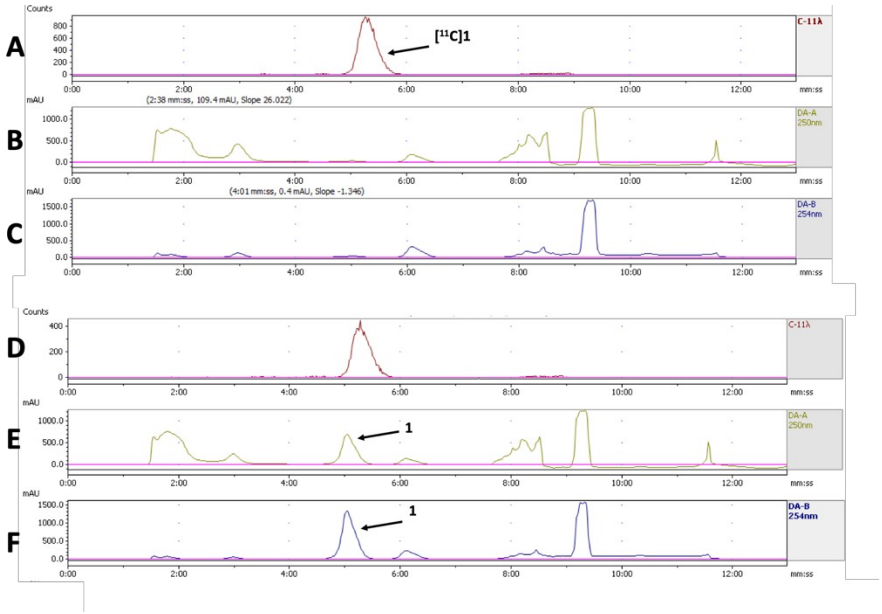

Fig. S1 A) Radio-HPLC chromatogram of crude [^{11}C]**1**. **B** and **C)** UV chromatograms of crude [^{11}C]**1** at 250 and 254 nm, respectively. **D)** Radio-HPLC chromatogram of crude [^{11}C]**1** co-injected with **1**. **E** and **F)** UV chromatograms of crude [^{11}C]**1** co-injected with **1** at 250 and 254 nm, respectively. The difference between UV peaks (retention time (t_R) = 5 minutes and 7 seconds) and radioactivity peaks (t_R = 5 minutes and 20 seconds) is 13 seconds, consistent with the expected delay time between detectors (13 seconds).

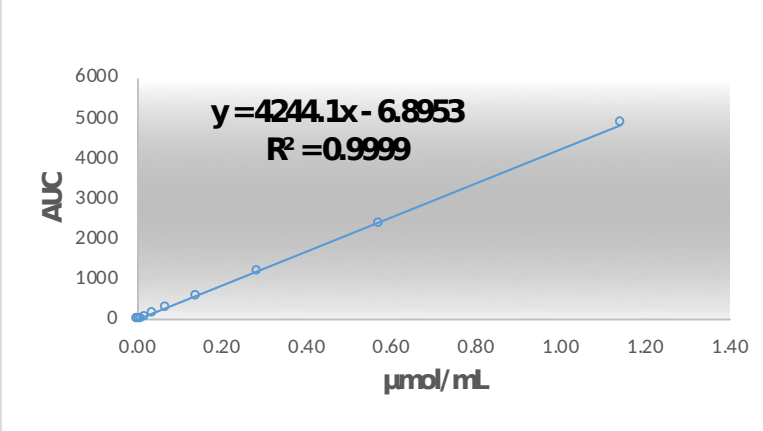

Fig. S2 Calibration Curve for **1**.

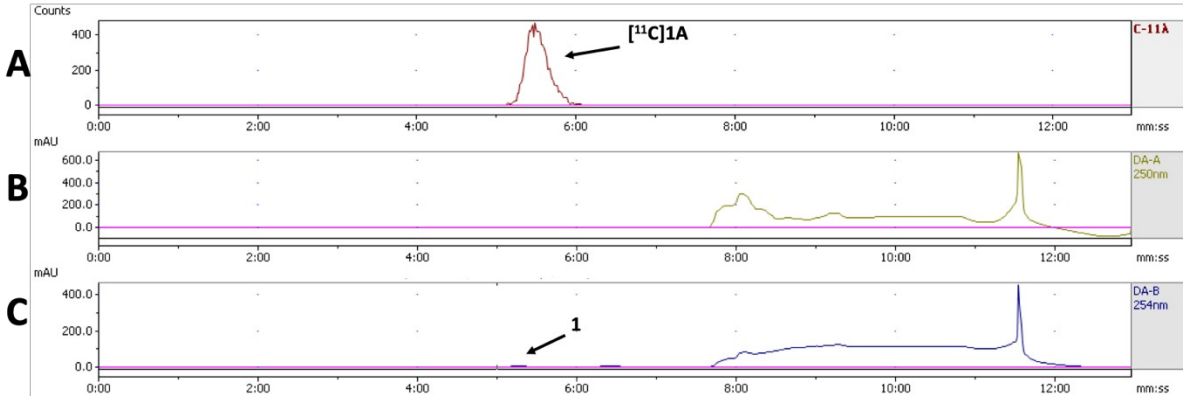

Fig. S3 A) Radio-HPLC chromatogram of HPLC-purified [^{11}C]**1**. **B** and **C)** UV chromatograms of HPLC-purified [^{11}C]**1** at 250 and 254 nm, respectively. The difference between UV peaks (retention time (t_R) = 5 minutes and 15 seconds) and radioactivity peaks (t_R = 5 minutes and 28 seconds) is 13 seconds consistent with the expected delay time between detectors (13 seconds).