Supplementary Material (ESI)

$[^{11}C]CO_2$ to $[^{11}C]CO$ Conversion Mediated by $[^{11}C]$Silanes: A Novel Route for $[^{11}C]$Carbonylation Reactions

Supporting Information

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General Method and Materials

All chemicals and dry solvents were purchased from Sigma-Aldrich and Alfa Aesar and used as received. 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 (Agilent Eclipse XDB-C18, 4.6 x 150 mm, 5 μm) was used with a flow rate of 1 mL/min. The gradient for **7** was linear between 10–90% over 5 min (CH_3CN:0.1 M NH_4HCO_2, 10:90), isocratic in between 5–9 min (CH_3CN:0.1 M NH_4HCO_2, 90:10) and linear in between 9–13 min (CH_3CN:0.1 M NH_4HCO_2, 90:10). The gradient for **CX546** was linear between 10–90% over 4 min (CH_3CN:0.1 M NH_4HCO_2, 10:90), isocratic in between 4–8 min (CH_3CN:0.1 M NH_4HCO_2, 90:10) and linear in between 8–13 min (CH_3CN:0.1 M NH_4HCO_2, 90:10). Identification of all radioactive products was confirmed by co-elution with the corresponding non-radioactive compounds. ^1H and ^{13}C-NMR spectra were obtained using a BRUKER AVANCE DRX 400 MHz spectrometer. Mass spectroscopy was performed using on an Agilent 6520 Accurate-Mass Q-TOF LC/MS connected to an Agilent 1200 HPLC system with UV detector and autosampler.

Representative Procedure for the Preparation of Silane Lithium Chloride Derivatives (2a–2c)

2a–**2c** were synthesised using modified literature procedure.[1] Small pieces of lithium (0.864 mmol, 2.7 eq.) were added to dry THF (0.9 mL) under argon in an oven-dried reaction v-vial. **1a–1c** (0.322 mmol, 1.0 eq.) was added *via* syringe under argon atmosphere (Glovebox). The reaction vial was sealed and stirred for 3 h at 20 °C under argon. The resulting brownish THF solution of the silane lithium chloride **2a**–**2c** was used without further processing in carboxylation studies with $[^{11}C]CO_2$.

Carboxylation Procedure of 2b with CO_2

A sealed vial containing **2b** in dry THF under argon atmosphere was purged with CO_2. Then, CO_2 was bubbled in the reaction solution *via* a balloon for 1 min at 20 °C. An aliquot of the resulting greyish turbid reaction mixture was diluted with CH_3CN and analysed by HPLC (method described in **General Method and Materials**). The UV chromatogram showed the presence of **3b** at retention time (RT) of 6.9 min (**Fig. SI6**).

Representative Carboxylation Procedure of 2a–2c with $[^{11}C]CO_2$

$[^{11}C]CO_2$ was produced using a Siemens RDS112 cyclotron by the 11 MeV proton bombardment of nitrogen (+ 2% 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 1.4 mL/min post target depressurisation directly into a reaction v-vial containing **2a–2c** (0.322 mmol) in dry THF (0.9 mL) for one minute at 20 °C. $[^{11}C]CO_2$ trapping efficiency (98%) was determined by comparison of the radioactivity measured in the reaction vial after helium purge and the total radioactivity delivered from the cyclotron (bombardment: 1 min, beam current: 5 μA). An aliquot of the reaction mixture from Vial A was analysed by radio-HPLC after dilution with CH_3CN. As 98% of all radioactivity delivered by the cyclotron was present in Vial A, the radiochemical yield (RCY) was estimated as percentage of the product peak area compared to the sum of all radioactive peak areas. $[^{11}C]$**3b** was obtained with a RCY of 85% (**Fig. SI1A**). For **2a** and **2c** almost no $[^{11}C]CO_2$ trapping was observed. Moreover, the radio-HPLC analysis did not reveal the formation of the corresponding $[^{11}C]$silane carboxylates.

Two-vial Setup for the Synthesis of $[^{11}C]$7 and $[^{11}C]$CX546

Crimp caps (centre hole with 3.0 mm PTFE seal aluminium silver 20 mm, Fisherbrand, 10132712) and two oven dried v-vials (KX Microwave Vials, 0.5–2mL) were used. All the lines used to allow the passage of gases were PTFE tubing (length: 10–20 cm, O.D.: 0.79 x 0.4 in., I.D.: 1/32 x 0.16 in.). The two vials, Vial A and B, were placed in two heating blocks of a Eckert and Ziegler Modular-Lab equipped with magnetic stirring (**Fig. SI2A**).

To Vial A was added **1b** (67.5 µL, 0.322 mmol, 1 eq.), Li (6 mg, 0.864 mmol, 2.7 eq.), dry THF (0.9 mL) and prepared according the procedure described before (**Representative Procedure for the Preparation of Silane Lithium Chloride Derivatives (2a–2c)**). The resulting brownish dry THF solution of **2b** was used in carboxylation studies with $[^{11}C]CO_2$. Vial B was charged with the relative carbonylation precursors for the synthesis of $[^{11}C]$**7** or $[^{11}C]$**CX546** (**Fig. SI2A**).

Synthesis of $[^{11}C]$7 *via* released $[^{11}C]$CO from Vial A

Vial B was charged with **5** (1.12 µL, 0.01 mmol, 1 eq.), **6** (50.24 µL, 0.46 mmol, 46 eq.), $[(Cynnamil)PdCl]_2$ (3.6 mg, 0.007 mmol, 0.07 eq.), Xantphos (4.0 mg, 0.007 mmol, 0.07 eq.) in dry THF (0.5 mL) under argon atmosphere.

$[^{11}C]CO_2$ was bubbled directly into Vial A containing **2b** in dry THF for 1 min at 20 °C. The trapping efficiency in Vial A was measured after helium purge (1.4 mL/min). Vial A was heated to 60 °C and Vial B to 40 °C under magnetic stirring (**Fig. SI2B**). Subsequently TBAF (5 M in dry dioxane) was added (with or without acidification of $[^{11}C]$**3b** using HCl 4 M in dry dioxane) and a helium stream (0.5 min at 1.4 mL/min) was introduced at 1.5, 4, 10 and 15 min from TBAF addition (**Fig. SI2B and SI3**). After 21 min from end of bombardment (EOB), the conversion of $[^{11}C]CO_2$ to $[^{11}C]$CO was measured by comparison of the trapping efficiency in Vial B with the total radioactivity delivered from the cyclotron (Vial A, Vial B and Ascarite). Aliquots of the reaction mixture of Vial B were diluted with CH_3CN and the carbonylation product $[^{11}C]$*N*-benzylbenzamide, $[^{11}C]$**7** was monitored by radio-HPLC (RT = 6.1 min, **Fig. SI2B**). $[^{11}C]$**7** was obtained with RCY ≥ 87% in all the experiments (**Table 1** and **Fig. SI4**).

$[^{11}C]$CO Release Study with $[^{11}C]$4b (Route 1)

After measuring the trapping efficiency in Vial A, HCl 4 M in dry dioxane (150 µL) was added to the reaction mixture containing $[^{11}C]$**3b**. Addition of acid in Vial A favoured the formation of $[^{11}C]$**4b**. Different amounts of TBAF (2–10 mmol) were added to optimise the release of $[^{11}C]$CO from $[^{11}C]$**4b** (**Table 1**, **entries 1–4**).

$[^{11}C]$CO Release Study with $[^{11}C]$3b (Route 2)

To study the protonation effect of $[^{11}C]$**3b** on the release of $[^{11}C]$CO, different amounts of TBAF were tested without acidification of the Vial A reaction mixture (**Table 1**, **entries 5–15**).

Conversion of $[^{11}C]CO_2$ to $[^{11}C]$CO *via* $[^{11}C]$3b

Radio-HPLC analysis of the reaction mixture in Vial A after EOB showed $[^{11}C]$**3b** (RT = 7.4 min) (**Fig. SI1A**). After 1 min from TBAF addition, $[^{11}C]$**3b** was no longer detected, indicating a complete conversion of the trapped $[^{11}C]CO_2$ to $[^{11}C]$CO *via* $[^{11}C]$**3b** (**Fig. SI1B**). A small radioactive peak at RT = 2 min corresponds to unreacted $[^{11}C]CO_2$.

Time Course Study of $[^{11}C]$CO Trapping in Vial B

The time course of $[^{11}C]$CO trapping in Vial B was monitored over 21 min from EOB (t_0 in **Fig. SI3**) by a calibrated pin diode radioactivity detector (Eckert and Ziegler Modular-Lab). After heating to 60 °C and TBAF addition in Vial A, no radioactivity increase was detected in Vial B (**b** in **Fig. SI3**). Subsequent introduction of a helium stream (0.5 min at 1.4 mL/min) caused the almost complete transfer of the produced $[^{11}C]$CO from Vial A to Vial B (**c** in **Fig. SI3**). At 4 min after TBAF addition a second helium stream (0.5 min at 1.4 mL/min) was applied and the transfer of $[^{11}C]$CO completed (**c** in **Fig. SI3**). Further helium flushing (0.5 min at 1.4 mL/min) at 10 and 15 min from TBAF addition showed only radioisotope decay and no further transfer of $[^{11}C]$CO from Vial A to Vial B (**d–f** in **Fig. SI3**).

Production of [^{11}C]CX546 *via* [^{11}C]3b

Precursor **2b** was prepared in Vial A according the procedure described before (**Representative Procedure for the Preparation of Silane Lithium Chloride Derivatives (2a–2c)**). Vial B was charged with **8** (1.6 µL, 0.01 mmol, 1 eq.), **9** (45.4 µL, 0.46 mmol, 46 eq.), $[(Cynnamil)PdCl]_2$ (3.6 mg, 0.007 mmol, 0.07 eq.), Xantphos (4.0 mg, 0.007 mmol, 0.07 eq.) and THF (0.5 mL) under argon atmosphere. [^{11}C]CO_2 was bubbled into Vial A for 1 min at 20 °C. The trapping efficiency in Vial A was measured after helium purge (1.4 mL/min). Vial A was heated to 60 °C and Vial B to 40 °C under magnetic stirring (**Fig. SI2B**). Subsequently 5 M TBAF in dry dioxane (0.750 mL, 15 mmol) was added and a helium stream (0.5 min at 1.4 mL/min) was introduced at 1.5 and 4 min from TBAF addition (**Fig. SI2B**). After 6 min from EOB, the conversion of [^{11}C]CO_2 to [^{11}C]CO was measured by comparison of the trapping efficiency in Vial B with the total radioactivity delivered from the cyclotron (Vial A, Vial B and Ascarite). Aliquots of the reaction mixture of Vial B were diluted with CH_3CN and the carbonylation product [^{11}C]**CX546** was monitored by radio-HPLC (RT = 5.1 min, **Fig. SI5A**). [^{11}C]**CX546** was obtained with RCY ≥ 90% (**Table 1**, **entry 17**).

Automated System

A Modular-Lab synthesis system consisting of three valves and two reactor vessels was used to implement the automated setup shown in **Fig. 3**. Precursors in Vial A and Vial B were prepared according the procedures described previously (**Synthesis of [^{11}C]7 *via* released [^{11}C]CO from Vial A** and **Production of [^{11}C]CX546 *via* [^{11}C]3b**). [^{11}C]CO_2 was bubbled into Vial A for 1 min at 20 °C through valve $\mathbf{v_1}$ with valve $\mathbf{v_2}$ closed and valve $\mathbf{v_3}$ opened to Ascarite 1. Vial A and Vial B were heated to 60 °C and 40 °C, respectively, under magnetic stirring (**Fig. 3**). Subsequently, $\mathbf{v_1}$ and $\mathbf{v_2}$ were opened to deliver helium (0.5 min at 1.4 mL/min) to the vial containing 5 M TBAF in dry dioxane (0.750 mL, 15 mmol) effecting the transfer to Vial A. Similtaneously, $\mathbf{v_3}$ was opened to release [^{11}C]CO from Vial A to Vial B. At 4 min post TBAF addition, a second helium flush was employed (for 0.5 min at 1.4 mL/min) to complete the transfer of [^{11}C]CO to the reagents in Vial B. The conversion of [^{11}C]CO_2 to [^{11}C]CO was measured as the radioactivity in Vial B as a percentage of the total radioactivity delivered from the cyclotron (Vial A, Vial B, Ascarite 1 and Ascarite 2).

Analysis of Reference Compounds

N-benzylbenzamide (7)

The reference compound **7** elutes at RT = 5.6 min (**Fig. SI4B**).

^{1}H NMR ($CDCl_3$, ppm): δ = 7.91 – 7.78 (m, 2H), 7.45 (t, *J* = 11.7 Hz, 3H), 7.37 – 7.17 (m, 5H), 6.64 (s, 1H), 4.56 (d, *J* = 28.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, ppm): δ = 169.39 (s, 1C), 139.85 (s, 1C), 135.85 (s, 1C), 131.22 (s, 1C), 128.43 (s, 2C), 128.27 (s, 2C), 128.00 (s, 2C), 127.58 (s, 1C), 126.92 (s, 1C), 44.75 (s, 1C).

CX546

The reference compound **CX546** elutes at RT = 4.6 min (**Fig. SI5B**).

Figure and Schemes

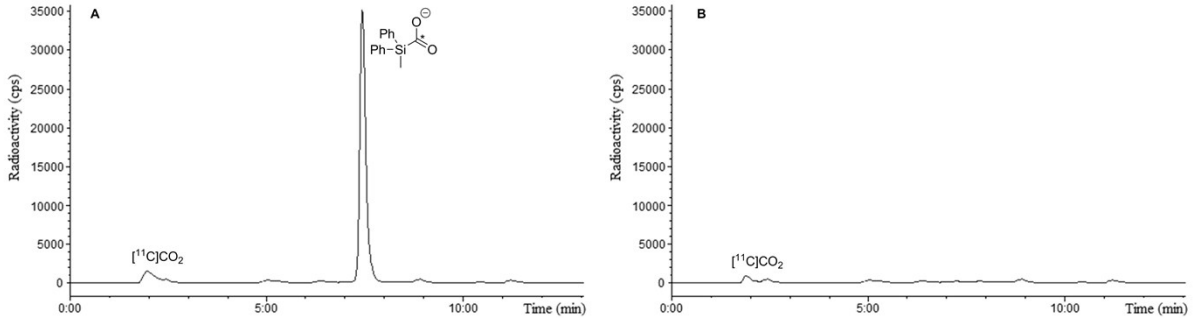


Fig. SI1 A) HPLC radiochromatogram of Vial A before TBAF addition. B) HPLC radiochromatogram of Vial A after TBAF addition.

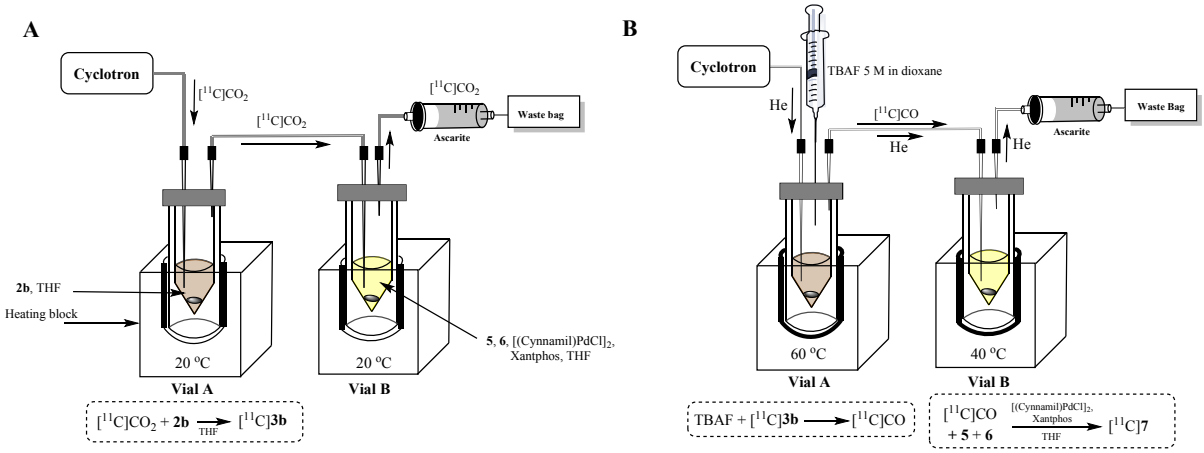


Fig. SI2 Two-vial setup for [^{11}C]CO release and [^{11}C]carbonylation reactions. A) Formation of [^{11}C]3b in Vial A. B) TBAF addition in Vial A and formation of [^{11}C]7 in Vial B.

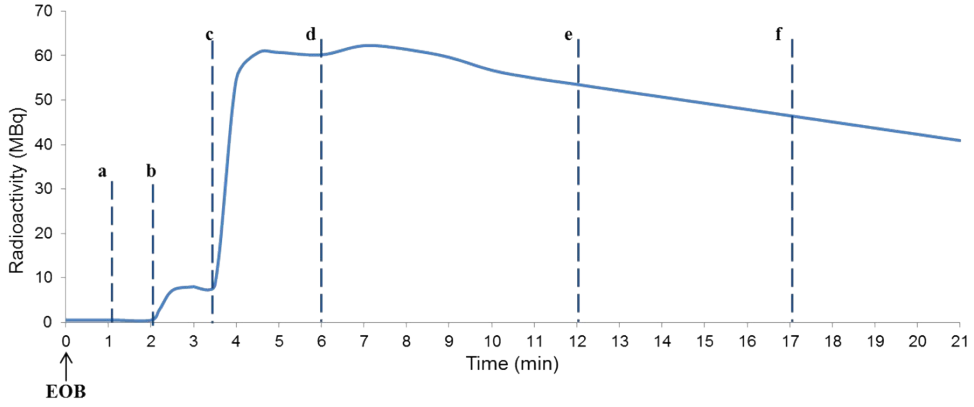


Fig. SI3 Time scale monitoring of [^{11}C]CO trapping in Vial B. (a): End of [^{11}C]CO_2 delivery (b): TBAF addition in Vial A; (c, d, e, and f): helium flushing (0.5 min at 1.4 mL/min).

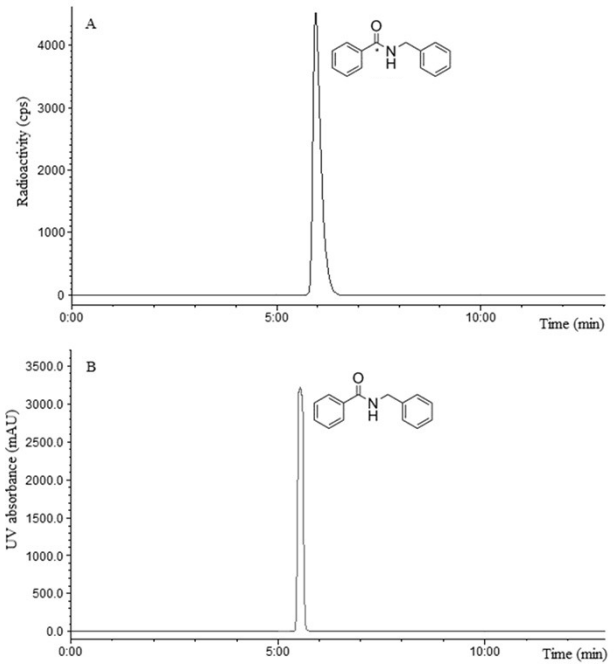


Fig. SI4 A) HPLC radiochromatogram of crude [^{11}C]7. B) HPLC chromatogram of the reference compound 7.[2]

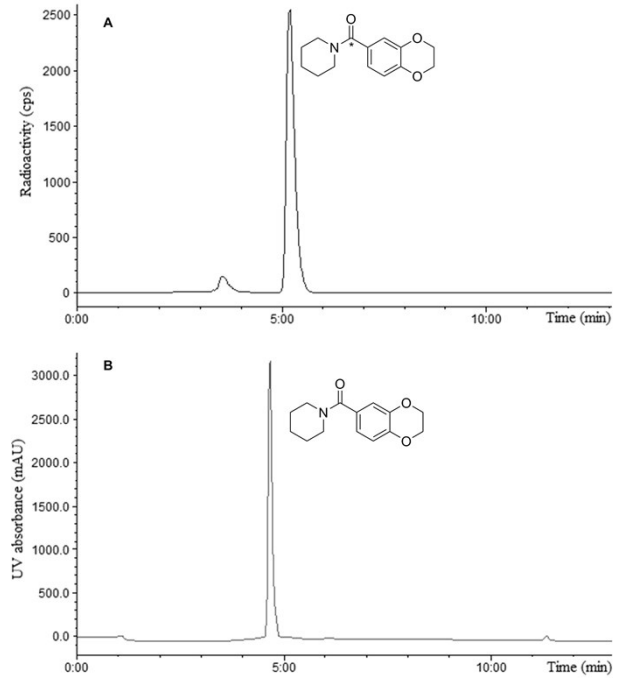


Fig. SI5 A) HPLC radiochromatogram of crude [^{11}C]CX546. B) HPLC chromatogram of the reference compound CX546.[2]

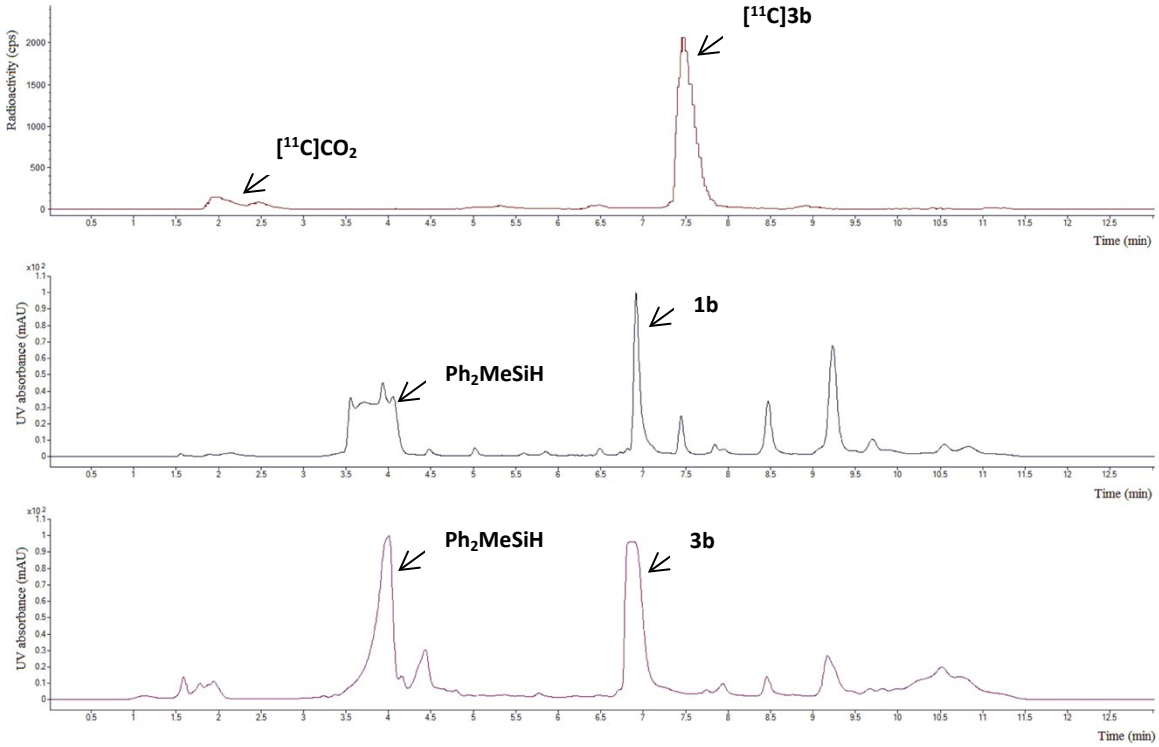
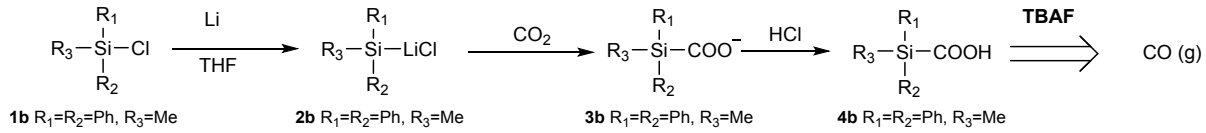


Fig. SI6 Radio-HPLC (A) and UV chromatogram (B) of crude [^{11}C]3b;[2] C) UV chromatogram of co-injected 3b and Ph_2MeSiH.



Scheme SI1

Notes and references

1 S. D. Friis, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 18114.

2 The delay between UV detector and radio-detector at flow rate on 1 mL/min is 0.5 min.