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^{11}C–C bond formation by palladium-mediated cross-coupling of alkenylzirconocenes with [^{11}C]methyl iodide

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Summary

A novel ^{11}C–C bond formation based on the palladium-mediated cross-coupling reaction of alkenylzirconocenes with [^{11}C]methyl iodide is described. The conversion of internal alkynes into the corresponding alkenylzirconocenes followed by transmetalation with $Pd(PPh_3)_4$ and subsequent cross-coupling with [^{11}C]methyl iodide gave several ^{11}C-labelled α,α'-dimethyl-substituted alkenes. The palladium complex $Pd(PPh_3)_4$ proved to be superior to $Pt(PPh_3)_4$ or $Ni(PPh_3)_4$ as transition metal complex.

The scope and limitations of the novel palladium-mediated cross-coupling reaction of alkenylzirconocenes with [^{11}C]methyl iodide were tested with various internal alkynes. After heating at 60°C for 6 min radiochemical yields of up to 75% (based upon [^{11}C]methyl iodide) could be achieved. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: ^{11}C–C bond formation; [^{11}C]methyl iodide; alkenylzirconcenes

Introduction

The 3,3-dimethylallyl moiety, also referred to as prenyl group, is known as an important structural building block in many natural and medicinal products. Prominent examples comprise the naturally occurring linear isoprenoids geranyl pyrophosphate and farnesyl pyrophosphate. Moreover, as key intermediates in the isoprenoid pathway they are involved in the biosynthesis of a broad range of compounds such as steroids, carotenoids and terpenes.[1]

The isotopic substitution of one of the two methyl groups with a [^{11}C]methyl group would provide an access to a large number of interesting ^{11}C-labelled

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compounds. A commonly employed strategy to form α,α′-dimethyl-substituted alkenes comprises, the formation of alkenylzirconocenes by the *syn*-insertion of a C–C triple bond into the Zr–H bond of Schwartz reagent [$Cp_2Zr(H)Cl$] followed by metal-mediated C–C bond formation with electrophiles under retention of the configuration of the C–C douple bond.[2,3] The insertion of the C–C triple bond into the Zr–H bond represents the key step for the preparation of synthetically useful alkenylzirconocenes. The process is closely related to the hydroboration reaction with alkynes. In principle, the formation of alkenylzirconocenes by *syn*-addition of one equivalent Schwartz reagent onto unsymmetrically-substituted internal alkynes may lead to a mixture of regioisomers enriched in the regioisomer where the zirconium–carbon bond is placed geminal to the sterically less demanding substituent. However, further treatment with Schwartz reagent readily isomerises the mixture of regioisomers presumably via a dimetalated intermediate to favour the formation of the thermodynamically stable isomer.

Alkenylzirconocenes generated *in situ* by hydrozirconation of alkynes readily undergo transmetalation reactions with several transition metal complexes $M(PPh_3)_4$ enabling subsequent cross-coupling reactions of the formed organometallic reagent with organic halides R^1-X. This also includes the use of [^{11}C]methyl iodide as electrophile in cross-coupling reactions to give the corresponding ^{11}C-labelled compounds (Figure 1).

In this paper, we describe a novel ^{11}C–C bond formation based upon the transition metal-mediated cross-coupling reaction between alkenylzirconocenes and [^{11}C]methyl iodide. Scope and limitations of the reaction were studied by screening several internal alkynes in terms of functional group compatibility.

Results and discussion

In a first set of reactions, the principle feasibility of the approach was elaborated by the synthesis of 2-[^{11}C]methylpropenyl benzene **[^{11}C]3** via

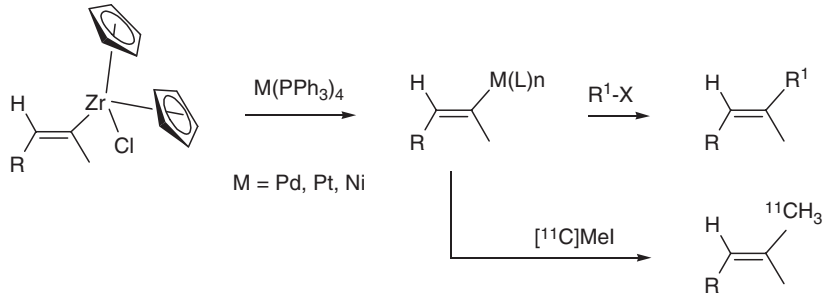


Figure 1. Transmetalation of alkenylzirconocenes and subsequent cross-coupling reaction with organic halides R^1-X, including [^{11}C]methyl iodide

transition metal complex-mediated hydrozirconation/^{11}C-methylation of prop-1-ynyl-benzene **1** with [^{11}C]methyl iodide as a model reaction (Figure 2).

The reaction conditions were optimized by the variation of different group 10 transition metal complexes. Prop-1-ynyl-benzene **1** was treated with 1.2 equiv. of Schwartz reagent in THF at room temperature. Due to the steric bulk of the phenyl group a slight 1.2 equivalent excess of Schwartz reagent is sufficient to give the thermodynamically stable alkenylzirconocene **2** exclusively. Formation of alkenylzirconocene **2** could be monitored by formation of a clear orange-coloured solution.

Alkenylzirconocene **2** was treated with 5 mol% $M(PPh_3)_4$ (M = Ni, Pd, Pt) prior to distillation of [^{11}C]methyl iodide into the solution. The reaction mixture was heated at 60°C for 6 min. Aliquots of the reaction mixture were taken for radio-HPLC analysis. The determined radiochemical yield represents the percentage of radioactivity area of the ^{11}C-labelled product **[^{11}C]3** related to the total radioactivity area. The results are summarized in Table 1.

Transition metal complexes $Ni(PPh_3)_4$ or $Pt(PPh_3)_4$ gave only 4 and 11% radiochemical yield, respectively, whereas sufficient radiochemical yields of up to 70% could be obtained when $Pd(PPh_3)_4$ was used. Besides the desired cross-coupled product **[^{11}C]3**, only unreacted [^{11}C]methyl iodide could be found in the reaction mixture as detected by radio-HPLC. The low radiochemical yield of 4% obtained with $Ni(PPh_3)_4$ is somewhat surprising since nickel-mediated cross-coupling reactions according to a Negishi reaction are known to proceed in high chemical yields.[4] However, the transmetalation of internal alkenyl units with $Ni(PPh_3)_4$ was shown to proceed very slowly in the cross-coupling process.[2,3] This fact along with the known air and moisture sensitivity of

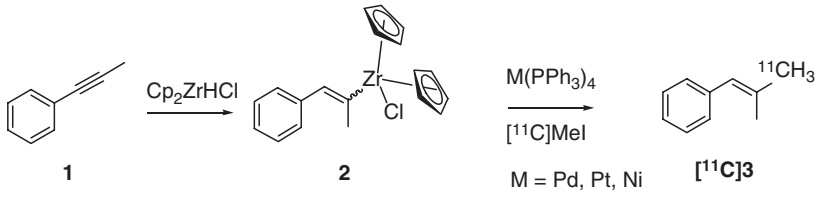


Figure 2. Hydrozirconation of prop-1-ynyl-benzene 1 followed by transition metal-mediated cross-coupling with [^{11}C]methyl iodide

Table 1. Radiochemical yields of transition metal-mediated cross-coupling reaction of alkenylzirconocene 2 with [^{11}C]methyl iodide

Transition metal complex	Radiochemical yield (%)
$Ni(PPh_3)_4$	4
$Pt(PPh_3)_4$	11
$Pd(PPh_3)_4$	70

$Ni(PPh_3)_4$, which makes the handling of this transition metal complex especially difficult during the radiosynthesis with [^{11}C]methyl iodide, may explain the observed low radiochemical yield. On the other hand, the more stable $Pd(PPh_3)_4$ complex was found to be a suitable metal complex for sufficient cross-couplings of alkenylzirconocene **2** with [^{11}C]methyl iodide. Reduction of the reaction time from 6 to 3 min led to lower radiochemical yields of 29%. A direct cross-coupling between alkenylzirconocene complex **2** and [^{11}C]methyl iodide was not possible as demonstrated in a control experiment without a transition metal complex. In this experiment, only [^{11}C]methyl iodide was found in the reaction mixture.

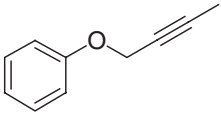
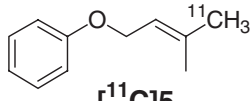
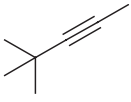
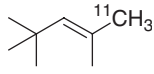
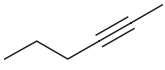
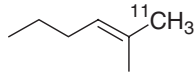
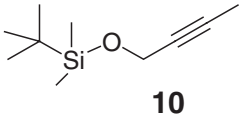
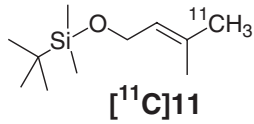
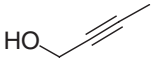
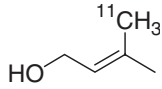
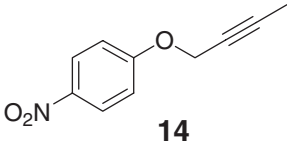
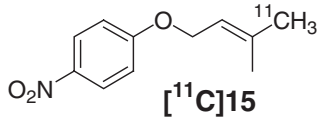
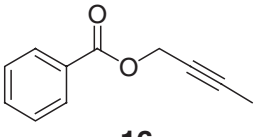
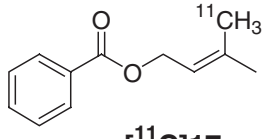
The scope and limitations of the elaborated novel radiolabelling method were tested using other methyl-substituted alkynes (**4**, **6**, **8**, **10**, **12**, **14**, **16**). Optimized reaction conditions were applied to the radiosynthesis of other ^{11}C-labelled alkenes bearing a prenyl group (**[^{11}C]5**, **[^{11}C]7**, **[^{11}C]9**, **[^{11}C]11**, **[^{11}C]13**, **[^{11}C]15**, **[^{11}C]17**).

The results are summarized in Table 2.

In contrast to the hydrozirconation reaction employing model compound **1**, a total amount of 2.5 equivalents of Schwartz reagent was used in the case of sterically less-hindered internal alkynes **4**, **6**, **8**, **10** and **14** to force the hydrozirconation reaction in favour to thermodynamically controlled regioselectivity. For this purpose, additional 1.5 equivalents of Schwartz reagent were added to the reaction mixture containing a mixture of alkenylzirconocene regioisomers as described in Figure 1. This procedure provided the formation of the preferred thermodynamically stable isomer. Subsequent transmetalation with $Pd(PPh_3)_4$ and treatment with [^{11}C]methyl iodide gave the desired cross-coupled products **[^{11}C]5**, **[^{11}C]7**, **[^{11}C]9** and **[^{11}C]11** in good radiochemical yields of up to 75% based upon [^{11}C]methyl iodide. The obtained low radiochemical yield (5%) of 4-nitrophenyl compound **[^{11}C]15** is an example for the incompatibility of Schwartz reagent towards nitro groups. In the case of butynol **12**, a larger excess of 5.0 equivalents of Schwartz reagent had to be used to compensate the reaction of Schwartz reagent with the free OH-group. The first equivalent of the hydrozirconation reagents is reacting with the free OH-group of **12** to form a zirconium–alkoxide intermediate. This intermediate can accommodate further Schwartz reagent according to the desired *syn*-addition to the triple bond. The resulting alkenylzirconocene compound undergoes transmetalation with $Pd(PPh_3)_4$ and cross-coupling with [^{11}C]methyl iodide to afford prenyl alcohol **[^{11}C]13** after hydrolysis in good radiochemical yield of 62% (Figure 3).

In order to avoid an expected competitive reduction reaction of the ester group in compound **16**, only 1.2 equivalents of Schwartz reagent were used for the radiosynthesis of ester **[^{11}C]17**. However, treatment of compound **16** with 1.2 equivalents of Schwartz reagent gave a pale yellow turbid solution instead

Table 2. Radiochemical yield (RCY) determined by analytical radio-HPLC referring to as the percentage of the total amount of radioactivity in the reaction mixture

Alkyne	Equiv. Cp_2ZrClH	RCY (%)	Unreacted [^{11}C]methyl iodide (%)	Product
 **4**	2.5	65	35	 **[^{11}C]5**
 **6**	2.5	75	25	 **[^{11}C]7**
 **8**	2.5	50	50	 **[^{11}C]9**
 **10**	2.5	70	30	 **[^{11}C]11**
 **12**	5	62	38	 **[^{11}C]13**
 **14**	2.5	5	95	 **[^{11}C]15**
 **16**	1.2	0	> 95	 **[^{11}C]17**

of a clear orange-coloured solution. This might be an indicator that the formation of the desired alkenylzirconocene has failed due to undesired side reactions of Schwartz reagent with the ester group. Consequently, no product

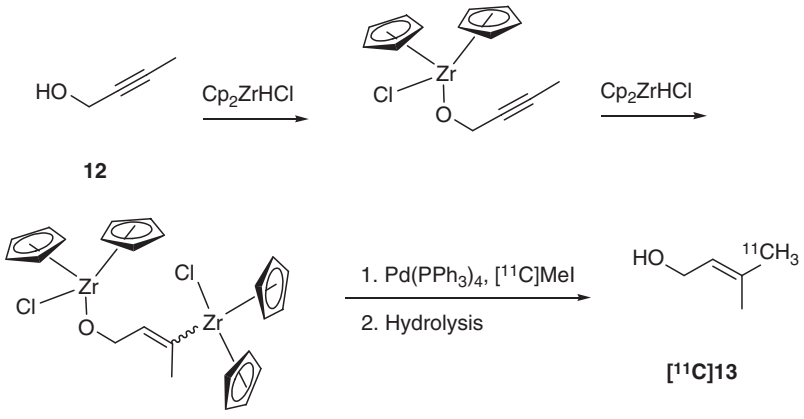


Figure 3. Radiosynthesis of prenyl alcohol [^{11}C]13

formation of **[^{11}C]17** was observed when the reaction mixture was treated with $Pd(PPh_3)_4$ and [^{11}C]methyl iodide. For all other compounds (**4**, **6**, **8**, **10**, **12** and to a lower extent for compound **14**) conversion of alkynes into the corresponding alkenylzirconocene complexes could be monitored by the formation of a clear orange-coloured solution.

In summary, we have elaborated a novel ^{11}C–C bond forming reaction based upon the palladium-mediated cross-coupling between alkenylzirconocenes with [^{11}C]methyl iodide. The excellent regioselectivity of the formed alkenyl–zirconocene complexes makes this approach a promising route for the convenient preparation of ^{11}C-labelled compounds containing a prenyl group. However, easily reducible functional groups such as nitro groups or esters are not compatible with the reaction conditions employing Schwartz reagent for the hydrozirconation reaction of internal alkynes.

Experimental

General

^{1}H-NMR spectra were recorded on a Varian Inova-400 at 400 MHz. Chemical shifts (δ) are determined relative to the solvent and converted to the TMS scale. Melting points were determined on a Galen III melting point apparatus (Cambridge Instruments). Elemental analysis were obtained on a LECO CHNS 932 elemental analyser. Flash chromatography was conducted according to Still *et al.*[5] Analytical HPLC was conducted using LaChrom systems from Merck-Hitachi.

Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plastic plates, with visualization under UV (254 nm). Compounds **1**, **3**, **6**, **7**, **8**, **9**, **12** and **13** were purchased from Aldrich. References to previous syntheses of known compounds for comparing analytical results have been listed.

Chemical syntheses

General procedure for the synthesis of arylethers **4**, **5**, **14** *and* **15**

Phenol or 4-nitrophenol (3.0 mmol), 2-butyne-1-ol or 3-methyl-2-butene-1-ol (4.5 mmol) and triphenylphosphine (3.6 mmol) were dissolved in 40 ml of THF and cooled to 0°C by means of an ice bath. DIAD (4.8 mmol) was slowly added via syringe. The resulting clear yellow–orange-coloured solution was stirred at room temperature for 2 h. The volume of the solution was reduced by evaporation of THF. The residue (2–3 ml) was purified by flash chromatography (10% EtOAc/hexane) to give the desired compounds **4**, **5**, **14** and **15**.

But-2-ynyloxy-benzene **4**. Pale yellow oil. Yield: 63%. ^{1}H-NMR ($CDCl_3$): δ 1.87 (t, $J = 2.4$ Hz, 3H; CH_3), 4.65 (q, $J = 2.4$ Hz, 2H; CH_2), 6.96–7.00 (m, 3H; Ar-H), 7.28–7.32 (m, 2H; Ar-H).[6]

(3-Methyl-but-2-enyloxy)-benzene **5**. Pale yellow oil. Yield: 86%. ^{1}H-NMR ($CDCl_3$): δ 1.77 (s, 3H; CH_3), 1.82 (s, 3H; CH_3), 4.53 (d, $J = 6.6$ Hz, 2H; CH_2), 5.53 (m, 1H), 6.93–6.98 (m, 3H; Ar-H), 7.28–7.32 (m, 2H; Ar-H).[7]

1-But-2-ynyloxy-4-nitrobenzene **14**. Yellow solid. Yield: 75%. Melting point 125–127°C. ^{1}H-NMR ($CDCl_3$): δ 1.87 (t, $J = 2.4$ Hz, 3H; CH_3), 4.75 (q, $J = 2.4$ Hz, 2H; CH_2), 7.03 and 8.21 (2d of AA′BB′ system, $J = 9.3$ Hz, 4H; Ar-H). Analytically calculated for $C_{10}H_9NO_3$: C, 62.82; H, 4.47; N, 7.33. Found C, 62.51; H, 4.05; N, 6.98.

(3-Methyl-but-2-enyloxy)-4-nitrobenzene **15**. Yellow oil. Yield: 71%. ^{1}H-NMR ($CDCl_3$): δ 1.77 (s, 3H; CH_3), 1.82 (s, 3H; CH_3), 4.61 (d, $J = 6.8$ Hz, 2H; CH_2), 5.47 (m, 1H), 6.95 and 8.19 (2d of AA′BB′ system, $J = 9.3$ Hz, 4H; Ar-H).[8]

General procedure for the synthesis of silyl ethers **10** *and* **11**. A mixture of 2-butyne-1-ol or 3-methyl-2-butene-1-ol (10 mmol), TBDMSCl (1.81 g, 12 mmol) and *i*-PrNEt (1.95 ml, 20 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 6 h. The mixture was washed with saturated solutions of NH_4Cl and $NaHCO_3$ and brine. The organic layer was dried and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (10% ETOAc/hexane) to give silyl ethers **10** and **11**.

tert.-Butyl-but-2-ynyloxy-dimethyl-silane **10**. Yield: 89%. ^{1}H-NMR ($CDCl_3$): δ 0.10 (s, 6H; $Si(CH_3)_2$), 0.89 (s, 9 H; $C(CH_3)_3$), 1.82 (t, $J = 2.4$ Hz, 3H; CH_3), 4.62 (q, $J = 2.4$ Hz, 2H; CH_2).[9]

tert.-Butyl-dimethyl-(3-methyl-but-2-enyloxy)-silane **11**. Yield: 94%. ^{1}H-NMR ($CDCl_3$): δ 0.08 (s, 6H; $Si(CH_3)_2$), 0.90 (s, 9 H; $C(CH_3)_3$), 1.61 (s, 3H; CH_3), 1.70 (s, 3H; CH_3), 4.15 (d, $J = 6.3$ Hz, 2H; CH_2), 5.29 (m, 1H).[10]

General procedure for the synthesis of benzoic esters **16** *and* **17**

2-Butyne-1-ol or 3-methyl-2-butene-1-ol (10 mmol) was dissolved in dry pyridine (2 ml). Benzoylchloride (12 mmol) was slowly added and the mixture was stirred for 30 min at room temperature. Then the mixture was poured into ice-water and 1 M HCl was added. Extraction with EtOAc, evaporation of the solvent under reduced pressure and subsequent flash chromatography (10% EtOAc/hexane) gave benzoic esters **16** and **17**.

Benzoic acid but-2-ynyl ester **16**. Pale yellow oil. Yield: 70%. ^{1}H-NMR ($CDCl_3$): δ 1.88 (t, $J = 1.9$ Hz, 3H; CH_3), 4.89 (q, $J = 1.9$ Hz, 2H; CH_2), 7.44 (m, 2H, Ar-H), 7.60 (m, 1H; Ar-H), 8.07 (m, 2H; Ar-H).[11]

Benzoic acid 3-methyl-but-2-enyl ester **17**. Pale yellow oil. Yield: 89%. ^{1}H-NMR ($CDCl_3$): δ 1.80 (s, 3H; CH_3), 1.85 (s, 3H; CH_3), 4.11 (d, $J = 6.6$ Hz, 2H; CH_2), 5.42 (m, 1H), 7.41 (m, 2H, Ar-H), 7.56 (m, 1H; Ar-H), 8.06 (m, 2H; Ar-H).[12]

Radiochemical syntheses

[^{11}C]CO_2 was produced by the $^{14}N(p,\alpha)^{11}C$ reaction on a IBA CYCLONE 18/9 cyclotron. The synthesis was carried out in a remotely controlled synthesis apparatus by Nuclear Interface (Münster). [^{11}C]Methyl iodide was prepared according to Crouzel *et al.*[13] [^{11}C]Methyl iodide was transferred in a stream of nitrogen into the reaction vessel at room temperature. After completion of the transfer, the reaction vessel was heated and aliquots were taken for radio-HPLC analysis after the indicated time. Radio-HPLC analyses were carried out with Phenomenex RP 18 column (LUNA C18(2) 4.6 × 250 mm, 5 μm) using an indicated isocratic eluent with a flow rate of 1.0 ml/min. The products were monitored by an UV detector L4500 (Merck, Hitachi) at 240 nm and by γ-detection with a scintillation detector GABI (X-RAYTEST).

Optimization of reaction conditions for the transition metal-mediated cross-coupling of alkenylzirconocenes with [^{11}C]methyl iodide

Prop-1-ynyl-benzene **1** (21.4 μl, 0.17 mmol) and Schwartz reagent (53 mg, 0.2 mmol) were dissolved in dry THF (1 ml) under argon atmosphere. After being stirred for 3 h at room temperature the clear orange-coloured solution was treated with the metal complex $M(PPh_3)_4$ (4.5 μmol). 400 μl of the solution was added to the synthesis module. After [^{11}C]methyl iodide transfer and

subsequent heating for 6 min at 60°C, aliquots were taken for radio-HPLC analysis.

2-[^{11}C]methylpropenyl benzene [**^{11}C]3**. HPLC analysis: CH_3CN/0.1 M ammonium formate (70/30), $t_R = 13.4$ min.

Radiosyntheses of compounds [**^{11}C]5**, [**^{11}C]7**, [**^{11}C]9**, [**^{11}C]11** *and* [**^{11}C]15**. Schwartz reagent (0.5 mmol) was dissolved in dry THF (1 ml). Alkyne **4**, **6**, **8**, **10** or **14** (0.2 mmol) was added. After 3 h, $Pd(PPh_3)_4$ (5.0 μmol) was added to the clear orange-coloured solution. Four hundred microlitres of the solution was added to the synthesis module. After [^{11}C]methyl iodide transfer and subsequent heating for 6 min at 60°C, aliquots were taken for radio-HPLC analysis.

3-([^{11}C]methyl-but-2-enyloxy)-benzene [**^{11}C]5**. Yield (based upon [^{11}C]methyl iodide: 65%. HPLC analysis: CH_3CN/0.1 M ammonium formate (70/30), $t_R = 9.3$ min.

2,4,4-[^{11}C]trimethyl-pent-2-ene [**^{11}C]7**. Yield (based upon [^{11}C]methyl iodide: 75%. HPLC analysis: CH_3CN/0.1 M ammonium formate (80/20), $t_R = 5.4$ min.

2-[^{11}C]methyl-hex-2-ene [**^{11}C]9**. HPLC analysis: CH_3CN/0.1 M ammonium formate (80/20), $t_R = 10.2$ min.

Tert.-butyl-dimethyl-(3-[^{11}C]methyl-but-2-enyloxy)-silane [**^{11}C]11**. Yield (based upon [^{11}C]methyl iodide: 70%. HPLC analysis: CH_3CN/0.1 M ammonium formate (80/20), $t_R = 9.0$ min.

3-([^{11}C]methyl-but-2-enyloxy)-4-nitrobenzene [**^{11}C]15**. Yield (based upon [^{11}C]methyl iodide: 5%. HPLC analysis: CH_3CN/0.1 M ammonium formate (70/30), $t_R = 10.2$ min.

Radiosyntheses of 3-[^{11}C]methyl-but-2-en-1-ol [**^{11}C]13**

Schwartz reagent (1.0 mmol) was dissolved in dry THF (1 ml). Butynol **12** (0.2 mmol) was added. After 3 h, $Pd(PPh_3)_4$ (5.0 μmol) was added. 400 μl of the solution was added to the synthesis module. After [^{11}C]methyl iodide transfer and subsequent heating for 6 min at 60°C, aliquots were taken for radio-HPLC analysis.

3-[^{11}C]methyl-but-2-en-1-ol [**^{11}C]13**. Yield (based upon [^{11}C]methyl iodide: 62%. HPLC analysis: CH_3CN/0.1 M ammonium formate (70/30), $t_R = 3.8$ min.

Radiosyntheses of benzoic acid 3-[^{11}C]methyl-but-2-enyl ester [**^{11}C**]**17**

Schwartz reagent (0.5 mmol) was dissolved in dry THF (1 ml). Ester **18** (0.4 mmol) was added. After 3 h, $Pd(PPh_3)_4$ (5.0 μmol) was added. Four hundred microlitres of the solution was added to the synthesis module. After [^{11}C]methyl iodide transfer and subsequent heating for 6 min at 60°C, aliquots were taken for radio-HPLC analysis.

3-[^{11}C]methyl-but-2-enyl ester [**^{11}C**]**17**. Yield (based upon [^{11}C]methyl iodide: 0%.

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