Palladium-promoted Coupling Reactions of $^{11}$C-Methyl Iodide with Organotin and Organoboron Compounds

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Methods for the rapid incorporation of $^{11}$C ($\beta^+$, $t_1 = 20.3$ min) into a number of compounds have been developed. By the use of palladium-promoted cross-coupling of $^{11}$C-methyl iodide with organostannanes, the model compounds $[\alpha$-$^{11}$C]toluene, methyl 4-$^{11}$C]methylbenzoate and $[1$-$^{11}$C]propene were obtained in 4 min reaction time. Synthesis of $[1$-$^{11}$C]heptane was achieved by reaction of $^{11}$C-methyl iodide with 9-hexyl-9-borabicyclo[3.3.1]nonane in the presence of Pd(0). The radiochemical yields were between 40 and 85%, before purification and the decay-corrected radiochemical yields of isolated products were 30–54%, based on $^{11}$C-methyl iodide.

The advancement of positron emission tomography (PET) as a powerful technique for the in vivo investigation of biochemical and physiological processes has resulted in an increased demand for tracers labelled with short-lived radionuclides such as $^{11}$C and $^{18}$F (half-lives of 20.3 and 110 min, respectively). Production of the labelled compounds often requires modification of traditional synthetic procedures on account of the short half-life of the radionuclide and the high specific radioactivity of the $^{11}$C-labelled precursor. Development of new methods, suitable for rapid incorporation of positron-emitting nuclides into various target molecules, is therefore an important objective in increasing the number of accessible radionuclides. In addition, an extended arsenal of synthetic strategies provides further possibilities to label a specific tracer in different positions, thereby enabling more detailed investigation of various physiological processes.

In production of $^{11}$C-labelled PET-tracers, one of the most frequently used precursors is $^{11}$C-methyl iodide. So far the major part of labelling syntheses using $^{11}$C-methyl iodide has been alklylation reactions on nitrogen, oxygen or sulfur nucleophiles; a relatively small number of direct carbon–carbon bond forming reactions have been described. As a consequence of the sometimes rather harsh conditions that are used to generate the carbon nucleophile, these methods are limited to the synthesis of radiochemicals in which sensitive structures can be protected, and most importantly due to the time constraint, rapidly deprotected after the labelling reaction. Methods where $^{11}$C-methyl iodide could be used in carbon–carbon bond forming reactions with complex and highly functionalised substrates would therefore be generally useful in the production of $^{11}$C-labelled compounds.

The palladium-catalysed cross-coupling of organic electrophiles such as halides or triflates with various organometallic species has, over recent decades, been extensively used for the formation of new carbon–carbon bonds. Among the most versatile coupling reactions are those involving organostannanes and organoboranes, usually referred to as the Stille and Suzuki reactions, respectively. The cross-coupling of organotin or organoboron compounds with halides or triflates can be performed under mild conditions. Furthermore, since a wide range of functional groups may be present on either coupling partner, the protection/deprotection sequences that are necessary in many organometallic reactions can often be excluded.

The versatility of palladium-assisted reactions in rapid labelling synthesis has been demonstrated in the production of $^{11}$C-labelled nitriles and benzamides, employing $^{11}$C-cyanide as the labelled precursor. A recent study on the use of $^{11}$C-carbon monoxide in palladium-mediated carboxylations has also been presented. In this paper, the first application of palladium(0)-promoted cross-coupling reactions with $^{11}$C-methyl iodide is reported. The coupling of $^{11}$C-methyl iodide with organotin and organoboron reagents was investigated by synthesising some model compounds, as illustrated in Scheme 1.

The labelled products $[\alpha$-$^{11}$C]toluene (1), methyl 4-$^{11}$C]methylbenzoate (2) and $[3$-$^{11}$C]propene (3) were obtained in palladium-mediated reactions of $^{11}$C-methyl
iodide with aromatic and alkenylic trialkyltin reagents, and synthesis of [11C]heptane (4) was achieved by reaction of [11C]methyl iodide with a trialkylborane in the presence of Pd(0).

Results and discussion

The cyclotron-produced [11C]carbon dioxide was converted into [11C]methyl iodide via reaction with lithium aluminium hydride and subsequent reaction with hydriodic acid. By use of an automated production system [11C]methyl iodide was obtained within 6 min from [11C]carbon dioxide. The [11C]methyl iodide was transferred directly to the reaction vessel, using nitrogen gas as the carrier, and trapped in a solution of tetraakis(triphenylophosphine)palladium [Pd(PPh₃)₄] in the appropriate solvent. After addition of an organostannane or organoborane the reaction vessel was heated at 90 °C for a few min. In the case of compounds 1, 3 and 4, the product was purified by semi-preparative HPLC. The decay-corrected radiochemical yields were between 30 and 54%, based on [11C]methyl iodide, Table 1, and the products were obtained within 35 min from the end of bombardment.

Reactions of [11C]methyl iodide with organostannane and organoborane reagents. Generally, the procedure described above was used, i.e., introduction of the methyl iodide into a mixture of Pd(PPh₃)₄ and solvent and subsequent addition of the substrate. A more convenient method, in which all reagents were placed in the reaction vessel before the trapping of [11C]methyl iodide, was also employed in the syntheses of 1 and 2. No improvement in the radiochemical yield was observed, but the prospect of reducing synthesis times and manipulation of the radioactivity are important in the production of [11C]tracers.

As illustrated in Table 1 a variety of solvents could be used. In the synthesis of I, the highest radiochemical yield was obtained in dimethyl sulfoxide (DMSO), whereas dimethyl formamide (DMF) and N-methylpyrrolidinone (NMP) were found to be most suitable for the synthesis of 2. A substantial decrease in the radiochemical yield was observed when the aryltrimethyl substrate was replaced by the corresponding aryltributylstannane (entries 7 and 9).

Synthesis of [11C]heptane (4) was achieved by reaction of the labelled methyl iodide with 9-hexyl-9-borabicyclo[3.3.1]nonane (9-hexyl-9-BBN). The organoborane, obtained by hydroboration of 1-hexene, was generally used directly in the [11C]-synthesis. A number of solvents were employed, and high radiochemical yields of 4 (60–70%) were obtained in benzene, 1,4-dioxane or tetrahydrofuran (THF), whereas reactions in DMF resulted in low yields of the [11C]-labelled product, Table 1. Since the borane reagent and the base were added as THF and water solutions, respectively, the reaction medium when conducting the [11C]-reaction was a mixture of approximately 15% THF and 5–40% water in solvent. The role of the base in these coupling reactions has been postulated to involve activation of the Pd(II)-complex, initially formed through oxidative addition of Pd(0) to the alkyl halide, towards transmetallation with the borane re-

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**Table 1. Cross-coupling reactions of [11C]methyl iodide with tin and boron reagents.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhSnMe₃</td>
<td>DMSO</td>
<td>[α-11C]Toluene 1</td>
<td>75–85 (54)</td>
</tr>
<tr>
<td>2</td>
<td>PhSnBu₃</td>
<td>DMF or THF</td>
<td>65–75</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PhSnBu₃</td>
<td>MeCN or Toluene</td>
<td>50–60</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PhSnBu₃</td>
<td>NMP</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PhSnBu₃</td>
<td>NMP a</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PhSnBu₃</td>
<td>Dioxane</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PhSnBu₃</td>
<td>DMSO</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Methyl 4-(SnMe₃)benzoate</td>
<td>DMF or NMP</td>
<td>Methyl 4-[11C]methylbenzoate 2</td>
<td>30–40</td>
</tr>
<tr>
<td>9</td>
<td>Methyl 4-(SnBu₃)benzoate</td>
<td>DMF or NMP</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Vinyl-SnBu₃</td>
<td>DMSO</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Hexyl-9-BBN</td>
<td>DMSO</td>
<td>3-[11C]Propene 3</td>
<td>75–85 (30)</td>
</tr>
<tr>
<td>12</td>
<td>Hexyl-9-BBN</td>
<td>Benzene or dioxane or THF</td>
<td>1-[11C]Heptane 4</td>
<td>60–70 (35)</td>
</tr>
<tr>
<td>13</td>
<td>Hexyl-9-BBN</td>
<td>DMF</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

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* Reactions were performed with 10–15 μmol substrate and 0.5 μmol Pd(PPh₃)₄ in 300 μl solvent, reaction time 4 min and reaction temperature 90 °C. a MeCN = acetonitrile. b Radiochemical yield of crude product, i.e., the conversion of [11C]methyl iodide into labelled product, determined by analytical HPLC as the percentage of the total amount of radioactivity in samples withdrawn from the reaction mixture, n≥2. Values given within parentheses are decay-corrected isolated yields based on [11C]methyl iodide, with a radiochemical purity > 95%. c 1.5 μmol CuI added. d A mixture of THF–NaOH(aq)–solvent was used.
agent. Bases such as cesium carbonate, potassium carbonate, potassium phosphate and sodium hydroxide have been used, some of them under anhydrous conditions when base-sensitive structures were present in the reactants. In the $^{11}$C labelling of 9-hexyl-9-BBN, good results were achieved when aqueous NaOH was used, whereas in reactions employing $\text{K}_2\text{PO}_4$, a lower radiochemical yield was obtained. The amount of water appeared to have no effect on the outcome of the reaction, and similar results were obtained using 5–40% water in the solvent mixture.

In the $^{11}$C-synthesis discussed herein, satisfactory yields of the labelled products were obtained when Pd-$\text{(PPh}_3)_4$ was employed. The coupling of $[^{11}\text{C}]$methyl iodide with phenyltrimethylin and methyl 4-(tributylstannyl)benzoate was also investigated in a few experiments using triphenylarsine as ligand. The catalyst (0.5 μmol PdL$_4$) was generated in situ from tris(dibenzo-zylenecarboxyl)di-palladium and triphenylarsine according to the description by Farina et al. and the reactions were carried out in THF or NMP for 4 min at temperatures between 50 and 90°C. However, no improvement on the radiochemical yield was achieved, compared with the results with Pd-$\text{(PPh}_3)_4$, and at higher temperatures, rapid decomposition of the palladium compound was observed. An increase in the radiochemical yield was obtained when the synthesis of I was performed using Pd-$\text{(PPh}_3)_4$ in the presence of copper iodide (3 equiv.), $[^{11}\text{C}]$Toluene was then synthesised in 65% yield, while reactions without copper iodide under otherwise similar conditions afforded a 50% radiochemical yield (Table 1, entries 4 and 5).

Small amounts of $^{11}$C-labelled side products could be detected in the crude products (analytical HPLC). No effort was made to isolate and identify these compounds. However, the formation of $^{11}$C-methanol by reaction of $[^{11}\text{C}]$methyl iodide with trace amounts of water may take place. Other possible side products could be $^{11}$C-methane, formed in the coupling reaction if small amounts of proton-donating impurities are present in the reaction mixture, and $^{11}$C-ethane or $^{11}$C-pentane which may be obtained through transfer of a methyl or butyl group from the aryltrialkyltin reagents. In synthesis using tributyltin stannanes, large amounts of a $^{11}$C-labelled side product were obtained, and after a combined $^{11}$C/$^{13}$C-synthesis of 2, this compound was isolated and analysed by LC–MS.

The spectral data indicated that the side product was $[^{11}\text{C}]$methyli triphenylphosphonium iodide, which might be formed in a competing reaction of $[^{11}\text{C}]$methyl iodide with the phosphine ligands of the catalyst. In order to verify the identity of the side product, a reaction of $[^{11}\text{C}]$ $[^{11}\text{C}]$methyl iodide with triphenylphosphine was conducted. The chromatographic and spectral data thus obtained confirmed the proposed formation of $[^{11}\text{C}]$methyli triphenylphosphonium iodide in the coupling reaction.

Purification and characterisation of $^{11}$C-labelled products. Since some organometallic compounds are highly toxic, incomplete removal of these substances may prevent their use in synthesis of pharmaceutical and biological products. The use of polymer-supported organoati reagents as a convenient method to circumvent this problem has recently been reported. In order to investigate whether the rapid purification procedures employed in this work would be satisfactory, reactions of $[^{11}\text{C}]$methyl iodide with phenyltrimethylin were conducted and the product (1) was purified by solid-phase extraction (SPE), and by a combined SPE–HPLC procedure. The amount of tin and palladium in the purified products was determined by inductively coupled plasma atomic emission spectroscopy (ICP–AES).

After purification by SPE, the quantity of tin in the product was approximately 5% of the total tin employed in the reaction, and after the combined SPE–HPLC purification no residual tin could be detected within the detection limit of 1 μg. The volume of the fraction collected in the SPE–HPLC procedure was 10 ml, and the concentration of tin thus <0.1 ppm. In the synthesis with polymer-supported organoati reagents, the reported concentration of residual tin components varied between a few ppm and 45 ppm in crude product. The analysis of palladium following solid-phase extraction showed that >90% of the amount used in the reaction was eliminated by this measure, and after the combined SPE–HPLC purification no palladium could be detected within the detection limit of 1.5 μg, the concentration thus being <0.15 ppm. These values indicate that the reactions presented may be applied in synthesis of $^{11}$C-tracers for use in positron emission tomography studies in vivo.

The identity of the $^{11}$C-labelled compounds 1 and 2 was assessed by reversed-phase analytical HPLC of products by addition of unlabelled reference substances, using two different analytical HPLC systems. To ensure that all of the radioactive substances injected into the columns were eluted, a comparison of the radioactivity of the injected volume and of the collected fractions was made. No discrepancy was found. For $^{11}$C-labelled compounds 3 and 4 the identity was determined by GLC analyses before and after addition of unlabelled reference substances. Further verification of product identity was obtained by GLC analyses of 1, and by LC–MS analyses of compound 2 labelled simultaneously with $^{11}$C and $^{13}$C. In conclusion, it has been shown that the readily available precursor $[^{11}\text{C}]$methyl iodide can be used in the synthesis of $^{11}$C-labelled compounds via palladium-promoted cross-coupling reactions. The reaction of $[^{11}\text{C}]$methyl iodide with organotin or organoboror reagents enable incorporation of the labelled methyl group into aryl, alkynic and alkynic positions through direct carbon–carbon bond-formation. Considering the short synthesis times and the good radiochemical yields, these reactions provide versatile methods for synthesis of $^{11}$C-labelled tracers, as well as for preparation of new $^{11}$C-labelling precursors. Since the coupling reaction of
organic electrophiles with organostannanes and organoboranes is usually compatible with a wide range of functional groups, the $^{13}$C-synthesis presented herein may be of general interest in production of more complex radio pharmaceuticals.

**Experimental**

*General.* $[^{13}]$C Carbon dioxide was prepared by the $^{14}$N(p,$\gamma$)$^{13}$C nuclear reaction using a nitrogen (AGA Nitrogen 6.0) gas target (containing 0.1% oxygen, AGA Oxygen 4.8) and 17 MeV protons produced by the Scanditronix MC-17 Cyclotron at the Uppsala University PET Centre. The $[^{13}]$C carbon dioxide was converted into $[^{13}]$C methyl iodide by reaction with lithium aluminium hydride and subsequent reaction with hydroiodic acid, using the automated system Synthia, Uppsala University PET Centre. GLC analyses were performed on a Shimadzu GC-14 A chromatograph equipped with a flame ionization detector and a Raytest Raga 93 radiodetector. Columns used were DB-WAX (30 m x 0.25 mm i.d.) (A) or Alumina (50 m x 0.53 mm i.d.) (B) from J&W Scientific. The LC–MS equipment consisted of a Beckman 126 solvent delivery module, a CMA 240 autosampler (CMA Microdialysis, Sweden) and a Fisons VG Quattro mass spectrometer. The column was a Kromasil C-18 (100 x 4.6 mm), and a post-column 1:100 split was used, with 1% of the total flow of 1 ml min$^{-1}$ delivered to the spectrometer and 99% delivered to a Beckman 166 variable UV detector in series with a Bioscan Flow-Count beta$^+$-detector. Mobile phases were 5 mM trifluoroacetic acid in water and 5 mM trifluoroacetic acid in acetonitrile, and a linear gradient from 5% to 100% acetonitrile over 6 min was used. Ionization modes were electrospay (ES) or atmospheric-pressure chemical ionization (APCI). Analyses by inductively coupled plasma atomic emission spectroscopy (ICP-AES) were performed at the Department of Analytical Chemistry, Institute of Chemistry, Uppsala University.

HPLC was performed using a Beckman 126 Pump and a Beckman 166 UV detector in series with a beta$^+$-flow detector. A modified Gilson 231 Autosampler was used for injection and fraction collection, and data collection and decay correction were performed using a personal computer and the Beckman System Gold Chromatography Software Package. Analytical columns (C-18, 250 x 4.6 mm) were Beckman Ultrasphere 5 mm (C), Hamilton PRP-1 (D) and Spherisorb ODS1 5 mm (E). A C-18 Beckman Ultrasphere 5 mm (250 x 10 mm), equipped with a C-18 guard column, was used for semi-preparative HPLC. Mobile phases were 0.05 M ammonium formate pH 3.5 (F), 0.01 M potassium dihydrogen phosphate pH 4.7 (G), methanol (H) and acetonitrile–water (500/70 v/v) (I). HPLC was performed at room temperature and detection wavelengths were 220 or 254 nm.

9-Borabicyclo[3.3.1]nonane (0.5 M in THF), hexabutylditin, hexamethylditin, phenyltrimethyltin, phenyltrimethyltin, tetrakis(triphenylphosphine)palladium, triphenylarsine, tris(dibenzyldenediacetone)palladium and vinyltributyltin were purchased from Aldrich. Methyl 4-bromobenzoate and methyl 4-methylenbenzoate were obtained from the corresponding carboxylic acids. Methyl 4-(tributylstannyl)benzoate and methyl 4-(trimethylstannyl)benzoate were synthesised by palladium-catalysed stannylation of methyl 4-bromobenzoate with the corresponding hexaalkylditinidin as described in the literature. Products were characterised by $^1$H and $^{13}$C NMR spectroscopy (300 MHz and 75.4 MHz respectively, Varian XL-300 spectrometer). 1,4-Dioxane and THF were distilled from sodium benzenophenone ketyl. All other chemicals and solvents were of analytical or gradient grade purity and used as received.

**Synthesis of 9-hexyl-9-borabicyclo[3.3.1]nonane.** Hydroboration of 1-hexene with 9-BBN in THF was performed according to the literature. The organoborane solution obtained was used directly in the $^{13}$C-labelling reaction, as described below, or stored under argon for 1–7 days before use.

**General procedure for reaction of $[^{13}]$C methyl iodide with organostannanes.** $\text{Pd}(\text{PPh}_3)_4$ (0.4–1.2 mg, 0.3–1.0 $\mu$mol) and solvent (0.3 ml) were placed in a 1.3 ml vessel equipped with a septum and the vessel was purged with nitrogen gas for 1–5 min. The $[^{13}]$C methyl iodide was transferred to the vessel using nitrogen as the carrier gas. The trapping efficiency, i.e., the relative amount of radioactivity remaining in the vessel after transfer of the radioactivity through the reaction mixture, was higher than 90%. After addition of an organotin compound (10–15 $\mu$mol) the vessel was heated at 90°C for 4 min. The radiochemical yield was determined by HPLC analysis of samples withdrawn from the reaction mixture. In the purification of compounds 1–3 the reaction mixture was diluted with 0.5 ml mobile phase and injected onto the semi-preparative HPLC column. After isocratic elution at a flow rate of 5 ml min$^{-1}$, solvent F–I at 40:60 (I), 45:55 (2, 3), followed by a linear gradient 5–10 min to 5:95, the products 1, 2 and 3 were collected at approximately 10, 9 and 8 min, respectively. The identity and radiochemical purity of the isolated products were determined by analytical HPLC using column C and D or C and E. Elution with various compositions of solvent F–I or G–H were performed, and the retention times were between 4 and 10 min for the different products. Compound 1 was analysed by GLC using column A at a flow rate of 1 ml min$^{-1}$ ($\text{H}_2$), temperature 70–250°C from 2 to 14 min. The retention time was 3.0 min. The fraction containing 3 was extracted with pentane and the product identity was determined by GLC analysis using column B at a flow rate of 11 ml min$^{-1}$ ($\text{H}_2$), temperature 50–200°C from 5 to 20 min. The retention time was 4.2 min. Purification of 3 was also performed by distillation from the
reaction vessel held at 90°C, using nitrogen gas as the carrier. The labelled product was collected in 0.3 ml pentane at –72°C, and then analysed by GLC. (No change in the isolated yield of 3 was observed in this alternative purification method.)

Reaction of [11C]methyl iodide with 9-hexyl-9-borabicyclo[3.3.1]nonane. The reaction was performed according to the procedure above, with the following modifications. After trapping of the [11C]methyl iodide, a solution of 9-hexyl-9-BBN in THF (15 μmol) and 3 equivalents of aqueous sodium hydroxide (0.3–5 M) was added. In semi-preparative HPLC, isocratic elution at 25:75 of solvent F–H was employed, and the retention time was 12 min. The radiochemical purity was determined by analytical HPLC as above, and for identification of the product the fraction containing 4 was extracted with octane and analysed by GLC, using conditions as for 3 with an initial temperature at 100°C. The retention time was 7.5 min.

Synthesis of methyl 4-[[11C]C]methylbenzoate. The [11C]methyl iodide was transferred to a vessel containing Pd(PPh3)4 (3 mg, 2.6 μmol) and NMP (0.3 ml) using the general procedure described above. After trapping of the [11C]methyl iodide, [11C]methyl iodide (40 μmol in 12.5 μl heptane) and methyl 4-(tributylstanny)benzoate (30 μmol) were added and the vessel heated at 90°C for 30 min. The reaction mixture was diluted with 0.5 ml mobile phase and injected onto the semi-preparative HPLC column, using conditions as for compound 2. The retention time was 9 min, and the retention time for an 11C-labelled side product was 5 min. The radiochemical purity of the products was higher than 98% as determined by analytical HPLC. LC–MS analyses were performed of the radioactive products and after decay of 11C, using ApCI for methyl 4-[11C]C]methylbenzoate and ES for the side product. Methyl 4-[11C]C]methylbenzoate: retention time 6.2 min, m/z 151 [M+], 120, 92. Methyl 4-methylbenzoate: retention time 6.2 min, m/z 150 [M+], 119, 91. Isolated side product: retention time 4.1 min, m/z 277 [M + H]+, 278, 279, 280. [11C]C]methytrithiophosphonium iodide was obtained by heating a mixture of [11C]methyl iodide, [11C]methyl iodide (15 μmol) and triphenylphosphine (5 mg, 20 μmol) in 300 μl DMF at 90°C for 10 min. The product was purified by semi-preparative HPLC as above, retention time 4.1 min, m/z 277 [M + H]+, 278, 279, 280.

Determination of palladium and tin residues in 11C-labelled products. Synthesis of I was performed according to the general procedure, using Pd(PPh3)4 (0.8 mg, 0.7 μmol), phenylthiomythlin (4 μl, 22 μmol) and DMSO (0.5 ml). The vessel was heated at 90°C for 5 min, after which the reaction mixture was diluted with 9 ml of water and passed through a C-18 column (3 ml SPE, Supelco) which had been pre-conditioned with ethanol and water. The column was washed with 3 ml of water and the product eluted with 2 ml of ethanol. Combined solid-phase extraction and HPLC-purification was performed employing conditions as described above for compound 1. Blank experiments were conducted in order to provide samples with accurate solvent compositions for background correction. The content of palladium and tin in the product fractions was determined by ICP-EAS. Quantity of palladium used in the reaction: 74 μg. Found after SPE: 5.5 ± 1.5 μg (n = 3, detection limit 1 μg). Found after SPE–HPLC: no Pd detected (n = 2, detection limit 1.5 μg). Quantity of tin used in the reaction: 2.6 mg. Found after SPE: 128 ± 25 μg (n = 3, detection limit 0.4 μg). Found after SPE–HPLC: no Sn detected (n = 2, detection limit 1 μg).

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References
12. Andersson, Y. and Långström, B. Preliminary results presented at the 5th International Symposium on the Synthesis
and Applications of Isotopes and Isotopically Labelled Compounds, Strasbourg, France 1994.
18. If all of the tin were to originate from the highly toxic trialkyltin halides, the amounts of these compounds in the product would be less than 3 µg. According to Ref. 16(a), the LD₅₀ (rat i.v.) for trimethyltin chloride and tributyltin chloride are 2 and 5 mg kg⁻¹, respectively.

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