Synthesis of ^{11}C-/^{13}C-Ketones by Suzuki Coupling

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Aryl triflates, methyl- or arylboronic acids, and a low concentration of [^{11}C]carbon monoxide were employed on small scale in the syntheses of fifteen ^{11}C-labelled ketones using palladium-mediated Suzuki coupling reactions. The reagents were confined in a micro-autoclave and heated at 150 °C for 5 min. The reaction required the presence of LiBr, but no additional base. The ^{11}C-labelled products were obtained with decay-corrected radiochemical yields in the range 10–70% and with high specific radioactivity (150–640 GBq/μmol). The radiochemical purity of the final products exceeded 98%. One ^{13}C-substituted ketone ([^{13}C]-2′-benzonaphthone) was prepared and analysed by NMR spectroscopy for confirmation of the labelling position. The reference compound 2′-benzonaphthone was prepared by a palladium-catalysed reaction between sodium tetraphenylborate and 2-naphthoyl chloride. 2-Thienyl *p*-tolyl ketone, 4-nitrophenyl 2-thienyl ketone and 2-naphthyl 2-thienyl ketone were prepared by reactions between thiophene-2-boronic acid and the corresponding acid chlorides. The presented approach is novel and seems to be an efficient method for the synthesis of a wide range of ^{11}C- as well as ^{13}C-labelled ketones.

Introduction

In tracer labelling, isotopes of carbon have a pivotal role since most biologically active compounds are organic molecules. Of the two radioactive isotopes of carbon (^{11}C and ^{14}C), ^{11}C is being applied increasingly because of its decay properties and its short half-life ($T_{1/2}$ = 20.3 min). One important consequence of the short half-life and the method for production of ^{11}C, is that high levels of specific radioactivity can be obtained. So far, the most frequently used methods for introducing a ^{11}C unit into organic compounds are *S*-, *O*- and *N*-methylations using [^{11}C]methyl iodide or [^{11}C]methyl triflate,[1] while ^{11}C−C bond forming reactions, such as the Grignard reaction using [^{11}C]carbon dioxide,[2] are less useful. Recently, however, ^{11}C−C bond forming reactions using [^{11}C]carbon monoxide have become an increasingly employed ^{11}C-labelling strategy and a wide range of ^{11}C-labelled carbonyl compounds, such as ketones,[3] amides,[4] imides,[5] hydrazides,[6] carbamates,[7] and carboxylic acids[8], have been synthesised using this method.[9]

Transition metal-catalysed carbonylations using electrophiles, carbon monoxide and organostannanes[10] (Stille coupling) or organoboron compounds[11] (Suzuki coupling[12]) are approaches that are used frequently for the synthesis of ketones. In ^{11}C labelling chemistry, the Stille carbonylation has been subjected to a number of studies,[13] but the Suzuki carbonylation has been used rarely. This report describes the synthesis of ^{11}C-/^{13}C-labelled ketones by Suzuki coupling of aryl triflates, aryl or methylboronic acids, and [^{11}C]/[^{13}C]carbon monoxide. A similar approach was reported previously, but it used different reaction conditions and substrates.[14]

Results and Discussion

The ^{11}C-labelled ketones were synthesized in a micro-autoclave (200 μL volume) using tetrakis(triphenylphosphane)palladium(0), aryl triflates, aryl or methylboronic acids, lithium bromide and a low concentration of [^{11}C]carbon monoxide (Scheme 1). The concentrations of aryl triflate, aryl- or methylboronic acid, LiBr and tetrakis(triphenylphosphane)palladium(0) were 123, 196, 18 and 17 mM, respectively, while the concentration of [^{11}C]carbon monoxide was ca. 10^{-5} M. The conversions of [^{11}C]carbon monoxide to products (trapping efficiencies) were 60- 90% and the decay-corrected radiochemical yields of LC-purified ketones, calculated from [^{11}C]carbon monoxide, were in the range 10−68% (Table 1). The radiochemical purity exceeded 98%. Five aryl triflates (Figure 1) and three boronic acids (Figure 2) were selected in this investigation and each triflate was reacted with each boronic acid. Both the trapping efficiency (fraction of radioactivity left in the crude product after purging with nitrogen) and radiochemical yields for phenylboronic acid were higher than the corresponding methyl-and thiopheneboronic acid. In most cases, the radiochemical yields for the biaryl ketones were higher

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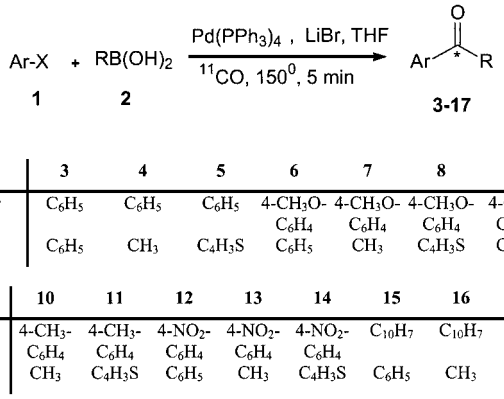


	3	4	5	6	7	8	9
Ar	C_6H_5	C_6H_5	C_6H_5	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	4-CH_3-C_6H_4
R	C_6H_5	CH_3	C_4H_3S	C_6H_5	CH_3	C_4H_3S	C_6H_5

	10	11	12	13	14	15	16	17
Ar	4-CH_3-C_6H_4	4-CH_3-C_6H_4	4-NO_2-C_6H_4	4-NO_2-C_6H_4	4-NO_2-C_6H_4	$C_{10}H_7$	$C_{10}H_7$	$C_{10}H_7$
R	CH_3	C_4H_3S	C_6H_5	CH_3	C_4H_3S	C_6H_5	CH_3	C_4H_3S

Scheme 1. Ar = phenyl, 4-methoxyphenyl, 4-methylphenyl, 4-nitrophenyl and 2-naphthyl; X = OTf and I; R = phenyl, methyl and thienyl. * = ^{11}C/^{13}C

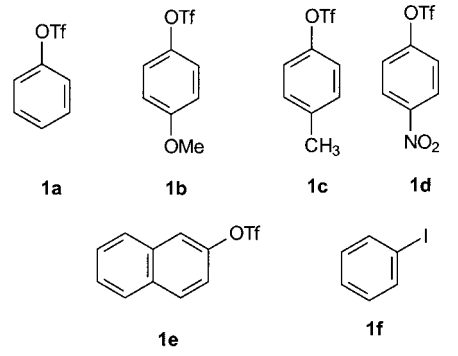


Figure 1. Substrates used in the synthesis

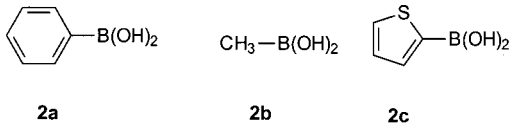


Figure 2. Boronic acids used in the synthesis

than those for the aryl methyl ketones. This observation indicates that phenylboronic acid is much more reactive than methylboronic acid and slightly more reactive than thiopheneboronic acid. For example, the radiochemical yield for compound **3** was twice as high as that for compound **4** and somewhat higher than that for compound **5**, even though they were prepared from the same triflate, i.e., phenyl triflate. Similar results were also observed for the other triflates. Only one triflate, 4-nitrophenyl triflate, gave almost the same radiochemical yield in the reactions with both phenyl and methylboronic acids and a somewhat lower radiochemical yield with thiopheneboronic acid.

An important feature of ^{11}C labelling using [^{11}C]carbon monoxide is the possibility of preparing compounds with high specific radioactivities. The specific radioactivities of some of the ^{11}C-labelled ketones were investigated using irradiation of 10 μAh. The obtained values of specific radioactivities, 40 min after the end of bombardment, were in the range 150−640 GBq/μmol (Table 1). The specific radioactivity of [^{11}C]benzophenone was much higher (150 GBq/μmol) than the value published previously (33.3 GBq/μmol)[14] for the same compound. The identities of products were assessed by LC-MS. The aryl methyl ketones could not be analysed by LC-MS or GC-MS because of their low concentrations and the difficulties encountered during their ionisation. These compounds were characterised by radio HPLC upon co-injection of non-radioactive reference compounds and comparing the retention times of the UV- and radio-active peaks. The preliminary identification and radiochemical purity of all of the products were also determined by radio HPLC. The labelling position of 2′-benzonaphthone was confirmed by comparison of the ^{13}C NMR

Table 1. Radiochemical yields and specific radioactivities for the ^{11}C-labelled ketones

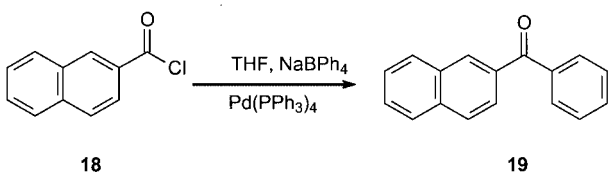
Entry	Substrate	Boronic acid	Product	Trapping efficiency (%)[a]	Isolated RCY[b], %, (*n*)[c]	Specific Radioactivity GBq/μmol
1	**1a**	**2a**	**3**	89 ± 1	64 ± 4 (3)	150
2	**1a**	**2b**	**4**	70 ± 5	30 ± 1 (3)	−
3	**1a**	**2c**	**5**	60 ± 5	39 ± 1 (3)	194
4	**1b**	**2a**	**6**	86 ± 3	63 ± 3 (3)	642
5	**1b**	**2b**	**7**	66 ± 4	14 ± 1 (2)	−
6	**1b**	**2c**	**8**	61 ±2	42 ± 3 (2)	−
7	**1c**	**2a**	**9**	90 ± 2	45 ± 3 (3)	−
8	**1c**	**2b**	**10**	70 ± 2	16 ± 1 (2)	−
9	**1c**	**2c**	**11**	74 ± 6	26 ± 2 (2)	−
10	**1d**	**2a**	**12**	68 ± 4	30 ± 2 (3)	−
11	**1d**	**2b**	**13**	88 ± 4	26 ± 2 (2)	−
12	**1d**	**2c**	**14**	60 ± 3	22 ± 1 (2)	−
13	**1e**	**2a**	**15**	80 ± 5	25 ± 2 (3)	−
14	**1e**	**2b**	**16**	64 ± 5	10 ± 2 (2)	−
15	**1e**	**2c**	**17**	56 ± 3	36 ± 1(2)	166
16	**1f**	**2a**	**3**	94 ± 3	68 ± 1 (3)	−
17	**1f**	**2b**	**4**	97 ± 1	56 ± 2 (3)	−

[a] Decay-corrected trapping efficiency, the fraction of radioactivity remaining in the crude product after purging with nitrogen. [b] RCY = radiochemical yield; decay-corrected, calculated from the amount of radioactivity present in the crude product before purging with nitrogen, and the radioactivity of the LC-purified product. [c] Values in parenthesis indicate the number of runs.

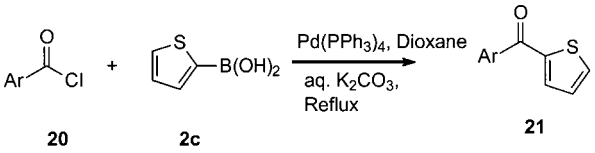
spectrum of the ^{13}C-substituted product with that of the non-radioactive compound. The ^{13}C-labelled compound was prepared using [^{13}C]carbon monoxide, 2-naphthyl triflate and phenylboronic acid under similar condition used for the ^{11}C-labelled compounds. The ^{13}C NMR spectrum of the product displayed a peak at $\delta = 196.9$ ppm matching the carbonyl peak in the ^{13}C spectrum of the reference compound.

Previously reported Suzuki coupling reactions have been performed in the presence of bases such as K_2CO_3, Cs_2CO_3, and KF. The boron-bound organic groups are only weakly nucleophilic and bases are usually needed to activate these groups.[15] We studied the effects of bases on the syntheses of the reference compounds. Addition of a base gave higher yields of the ketones prepared by the Suzuki coupling between acid chlorides and thiopheneboronic acid. In our initial ^{11}C-labelling experiment, KF was used as the base with good results. The low solubility, however, of KF in THF caused technical problems resulting from clogging of KF in the capillaries used in the synthesis system. Thus, we performed the reaction without any additional base and found that it worked equally well. Initially, we assumed that the lithium bromide used to assist the oxidative addition of aryl triflates might activate the organic boronic acid. To investigate whether this hypothesis was correct, we performed the reaction in the absence of LiBr using iodobenzene in place of phenyl triflate, since the presence of LiBr is essential to facilitate the oxidative addition of phenyl triflate. The reaction worked well and gave an isolated radiochemical yield of 68%. This result indicated that LiBr does not activate the boronic acid. For comparison, [^{11}C]benzophenone and [^{11}C]acetophenone were prepared from both iodobenzene and phenyl triflate. The radiochemical yield for [^{11}C]benzophenone was almost the same for both substrates, while iodobenzene gave a much higher radiochemical yield (56%) for [^{11}C]acetophenone.

The reference compound 2′-benzonaphthone (**19**) was prepared by the reaction of 2-naphthoyl chloride with sodium tetraphenylborate in the presence of tetrakis(triphenylphosphane)palladium(0) as a catalyst (Scheme 2).[16] The compounds 2-thienyl *p*-tolyl ketone (**21a**), 4-nitrophenyl 2-thienyl ketone (**21b**) and 2-naphthyl 2-thienyl ketone (**21c**) were prepared by the palladium-catalysed cross-coupling reactions between thiophen-2-boronic acid and the respective acid chlorides (Scheme 3).[17] The chemical yields for these compounds were 45−75% (Table 2). The NMR spectroscopic data for 2′-benzonaphthone (**19**),[18] 2-thienyl *p*-tolyl ketone (**21a**)[19] and 4-nitrophenyl 2-thienyl ketone (**21b**),[20] as well as MS data for **21b**,[20] were identified by comparison with literature values. The NMR and MS data for **21c** and MS data for **19** and **21a** were not available in literature previously and, thus, we present them here.



Scheme 2



Scheme 3. Ar = *p*-tolyl (**21a**), 4-nitrophenyl (**21b**) and 2-naphthyl (**21c**)

Table 2. Chemical yields and melting points of the reference compounds

Entry	Products	Yields, g (%)	Melting points (°C)
1	**19**	0.95 (75)	72−73 (ref.[18] 76−77)
2	**21b**	0.42 (45)	174−175 (ref.[23] 176−177)
3	**21a**	0.42 (52)	73 (ref.[24] 68−72)
4	**21c**	0.58 (60)	86−87 (ref.[25] 87)

Experimental Section

General: [^{11}C]Carbon dioxide was produced by the Scanditronix MC-17 cyclotron at the Uppsala Research Imaging Solution AB using the $^{14}N(p,\alpha)^{11}C$ reaction with 17 MeV protons in a gas target containing nitrogen (AGA, Nitrogen 6.0) and 0.1% oxygen (AGA, Oxygen 4.8). [^{11}C]Carbon monoxide was produced by reducing [^{11}C]carbon dioxide in a zinc furnace at 400 °C using a remote-controlled work station.[21]

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable-wavelength UV detector in series with a β^+-flow detector. The following mobile phases were used: 0.05 M ammonium formate, pH 3.5 (A1), acetonitrile (B1), acetonitrile/H_2O, 50:7 (B2), methanol (B3) and 0.01 M formic acid in H_2O (A2). For analytical LC, a Jones Chromatography Genesis C_{18}, 4 μm, 250 × 4.6 mm (i.d.) column was used at a flow rate of 1.5 mL/min. For semi-preparative LC, a Jones Chromatography Genesis C_{18}, 4 μm, 250 × 10 mm (i.d.), column was used at a flow rate of 4 mL/min. Synthia, an automated synthesis system, was used for LC injection and fraction collection.[22] Data collection and LC control were performed using a Beckman System Gold chromatography software package.

Radioactivity was measured in a Veenstra Instrumenten bv VDC-202 ion chamber. For coarse estimations of radioactivity during production, we used a Långenäs Eltekniska AB portable dose-rate meter.

The non-radioactive compounds were characterised by ^1H and ^{13}C NMR spectroscopy and by GC-MS. NMR spectra were recorded on Varian Unity-400 NMR instrument. [D_1]Chloroform was used as the internal standard. LC-MS was performed using a Micromass VG Quattro with atmospheric pressure chemical ionisation (APCI+). A Beckman 126 pump, a CMA 240 autosampler and a Beckman Ultrasphere ODS C_{18} (5 μm, 100 × 4.6 mm id) column

were used. Mobile phases were B3 and A2. GC-MS was performed using a Finnigan GCQ mass spectrometer coupled to a Finnigan Q-GC. Melting points were determined on a Büchi melting point apparatus.

All of the reference compounds were commercially available (Aldrich), except for 2′-benzonaphthone (**19**), 2-thienyl *p*-tolyl ketone (**21a**), 4-nitrophenyl 2-thienyl ketone (**21b**) and 2-naphthalyl 2-thienyl ketone (**21c**). The triflates and boronic acids used in the syntheses were also commercially available and used without further purification. Freshly distilled THF (from sodium/benzophenone under nitrogen) was used in all syntheses.

Synthesis of [Carbonyl-^{11}C]ketones (3−17). General Procedure: Tetrakis(triphenylphosphane)palladium(0) (5.0 mg, 4.3 μmol) was placed in a vial (1 mL). The vial was flushed with nitrogen and the contents were dissolved in THF (200 μL). The aryl triflate (30.8 μmol) and LiBr (10 μL of 0.46 M solution in THF, 4.6 μmol) were added. The mixture was shaken until the solution was homogeneous. The aryl- or alkylboronic acid (49.2 μmol) was dissolved in THF (100 μL) and added to the solution of the palladium complex, triflate and lithium bromide immediately prior to use. The resulting mixture was injected into the injection loop of the apparatus from where the appropriate volume (200 μL) was transferred under pressure (35 Mpa) to the micro-autoclave that was precharged with [^{11}C]carbon monoxide in helium. The micro-autoclave was heated at 150 °C for 5 min. The crude product was transferred to a pre-evacuated, septum-fitted vial (5 mL). The micro-autoclave was filled with THF (200 μL) and emptied into the collection vial. The radioactivity was measured before and after the vial was purged with nitrogen. The solvent volume was reduced to < 0.2 mL by heating at 75 °C and purging with nitrogen. An acetonitrile/water mixture (1:1, 2 mL) was added and the resulting solution was injected on the semi-preparative LC. Solvent A1/B1 (50:50), at a linear gradient to 0:100 within 10 min at a flow rate of 4 mL/min: t_R = 10.5, 7.4, 9.7, 10.2, 7.3, 9.6, 11.4, 8.4, 9.8, 10.6, 7.6, 9.6, 12.3, 9.8 and 11.6 min for products **3**, **4**, **5**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16** and **17**, respectively. The identity and radiochemical purity of the collected fractions were assessed by analytical LC. Solvent A1/B2 (70:30) at a linear gradient to 0:100 within 8 min, at a flow rate of 1.5 mL/min, wavelength 254 nm: t_R = 9.1, 6.5, 8.4, 8.1, 5.8, 7.5, 8.9, 6.5, 7.7, 8.8, 6.9, 7.8, 10.2, 7.6 and 9.0 min for products **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16** and **17**, respectively. LC-MS (APCI+): *m*/*z* = 183, 189, 213, 219, 197, 203, 228, 234, 233 and 239 [M + 1] for products **3**, **5**, **6**, **8**, **9**, **11**, **12**, **14**, **15** and **17**, respectively.

Synthesis of [Carbonyl-^{13}C]-2′-benzonaphthone: Tetrakis(triphenylphosphane)palladium(0) (7.8 mg, 13.8 μmol) and 2-naphthyl trifluoromethanesulfonate (13.0 mg, 47.0μmol) were placed in a vial (1 mL), flushed with nitrogen and then dissolved in THF (200 μL). LiBr (10 μL of 0.46 M solution in THF, 4.6 μmol) was added and shaken until the mixture was homogeneous. Phenylboronic acid (8.4 mg, 68.9 μmol) was dissolved in THF (100 μL) and added to the palladium solution and the resulting mixture was loaded into the injection loop. The resulting mixture and [^{13}C]carbon monoxide were transferred with pressure (35 Mpa) to the micro-autoclave (200 μL). The micro-autoclave was heated at 150 °C for 10 min. The crude product was transferred to a pre-evacuated, septum-fitted vial (5 mL). The solvent was evaporated by heating at 75 °C and purging with nitrogen. A sufficient amount of the corresponding, previously synthesised ^{11}C-labelled compound was added. The product was purified by semipreparative LC using the same chromatographic method as described for the ^{11}C-labelled compound. The radioactive fraction was collected and the solvents were evaporated under reduced pressure to yield the title compound (4.6 mg, 42% from the triflate). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.3, 119.6, 127.6, 128.0, 128.1, 130.7, 196.9 (main peak, carbonyl carbon) ppm.

Preparation of 2′-Benzonaphthone (19): Sodium tetraphenylborate (1.8 g, 5.2 mmol), naphthoyl chloride (1.0 g, 5.2 mmol) and tetrakis(triphenylphosphane)palladium(0) (60 mg, 0.05 mmol) were dissolved in dry THF (40 mL). The reaction mixture was stirred at ambient temperature for 20 h under nitrogen. The solvent was evaporated under reduced pressure and the product was then extracted from water using diethyl ether. The ethereal extract was washed with brine and water, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/diethyl ether, 9:1; R_f = 0.48) to give the title compound as a white solid. GC-MS (EI): *m*/*z* (%) = 232 (100) [$M^{\cdot+}$], 202 (7), 155 (93), 127 (30), 105 (5), 77 (6).

Preparation of 2-Thienyl *p*-Tolyl Ketone (21a), 4-Nitrophenyl 2-Thienyl Ketone (21b) and 2-Naphthyl 2-Thienyl Ketone (21c). General Procedure: The acid chloride (4.03 mmol), thiophene-2-boronic acid (3.91 mmol) and tetrakis(triphenylphosphane)palladium (0.04 mmol) were dissolved in dry dioxane (50 mL) and stirred at ambient temperature for 15 min. Aqueous potassium carbonate (4 mL of 1.2 M solution) was added and the resulting mixture was heated under reflux for 2 h. The cooled mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and washed successively with water (2 × 100 mL), saturated aqueous sodium hydrogen carbonate (2 × 100 mL) and brine (2 × 100 mL). The ethyl acetate extract was dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/diethyl ether, 8:2).

2-Thienyl *p*-Tolyl Ketone (21a): GC-MS(EI): *m*/*z* (%) = 202 (96) [$M^{\cdot+}$], 187 (58), 119 (100), 91 (71).

2-Naphthyl 2-Thienyl Ketone (21c): GC-MS(EI): *m*/*z* (%) = 238 (77) [$M^{\cdot+}$], 210 (9), 165 (16), 155 (100), 127 (83), 111 (41), 77 (11). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.1 (m, 1 H), 7.5−7.6 (m, 2 H), 7.7 (m, 2 H), 7.8−7.9 (m, 4 H), 8.3 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.3, 126.9, 127.8, 128.0, 128.2, 128.4, 129.3, 130.5, 132.3, 134.1, 134.8, 135.2, 135.4, 143.8, 188.1 ppm.

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[1] B. Långström, T. Kihlberg, M. Bergström, G. Antoni, M. Björkman, B. H. Forngren, T. Forngren, P. Hartvig, K. Markides, U. Yngve, M. Ögren, *Acta Chem. Scand.* **1999**, *53*, 651−669.
[2] [2a] R. J. Davenport, J. A. McCarron, K. Dowsett, D. R. Turton, K. G. Poole, V. W. Pike, *J. Labelled Compd. Radiopharm.* **1997**, *40*, S309−S311. [2b] C. Perrio-Huard, C. Aubert, M.-C. Lasne, *J. Chem. Soc., Perkin Trans. 1* **2000**, 311−316.
[3] [3a] Y. Andersson, B. Långström, *J. Chem. Soc., Perkin Trans. 1* **1995**, 287−289. [3b] P. Lidström, T. Kihlberg, B. Långström, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2701−2706.
[4] [4a] T. Kihlberg, B. Långström, *J. Org. Chem.* **1999**, *64*, 9201−9205. [4b] O. Rahman, T. Kihlberg, B. Långström, *J.*

Chem. Soc., Perkin Trans. 1 **2002**, 2699−2703. [4c] O. Rahman, T. Kihlberg, B. Långström, *J. Org. Chem.* **2003**, *68*, 3558−3562. [4d] F. Karimi, B. Långström, *Org. Biomol. Chem.* **2003**, *1*, 541−546.

[5] F. Karimi, T. Kihlberg, B. Långström, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1528−1531.

[6] F. Karimi, B. Långström, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2111−2115.

[7] T. Kihlberg, F. Karimi, B. Långström, *J. Org. Chem.* **2002**, *67*, 3687−3692.

[8] F. Karimi, B. Långström, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2256−2259.

[9] T. Kihlberg, G. Antoni, M. Björkman, F. Karimi, O. Rahman, M. Ögren, B. Långström, in *Synthesis and Application of Isotopically Labelled Compounds* (Eds.: U. Plesis, R. Voges), Vol. 7, John Wiley & Sons, New York, **2001**, pp. 322−325.

[10] [10a] F. Garrido, S. Raeppel, A. Mann, M. Lautens, *Tetrahedron Lett.* **2001**, *42*, 265−266. [10b] A. C. Gyorkos, J. K. Stille, L. S. Hegedus, *J. Am. Chem. Soc.* **1990**, *112*, 8465−8472.

[11] [11a] T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726−4731. [11b] T. Ishiyama, H. Kizaki, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1993**, *34*, 7595−7598. [11c] T. Ishiyama, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6923−6926.

[12] A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147−168.

[13] [13a] J. Barletta, M. Björkman, M. Ögren, B. Långström, *J. Labelled Compd. Radipharm.* **2001**, *44*, S979. [13b] M. H. Al-Qahtani, V. W. Pike, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1033−1036. See also refs.[3a,3b].

[14] [14a] S. K. Zeisler, M. Nader, A. Theobald, F. Oberdorfer, *Appl. Radiat. Isot.* **1997**, *48*, 1091−1095. [14b] M. W. Nader, F. Oberdorfer, *Appl. Radiat. Isot.* **2002**, *57*, 681−685.

[15] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457−2483.

[16] C. S. Cho, K. Itotani, S. Uemura, *J. Organomet. Chem.* **1993**, *443*, 253−259.

[17] M. Haddach, J. R. McCarthy, *Tetrahedron Lett.* **1999**, *40*, 3109−3112.

[18] S.-H. Kim, R. D. Rieke, *Synth. Commun.* **1998**, *28*, 1065−1072.

[19] R. Noto, M. Gruttadauria, S. Chimichi, G. Petrillo, D. Spinelli, *J. Phys. Org. Chem.* **1999**, *12*, 408−415.

[20] K. Wojciechowski, *Synth. Commun.* **1997**, *27*, 135−144.

[21] T. Kihlberg, B. Långström, Method and apparatus for production and use of [^{11}C]carbon monoxide in labelling synthesis. Swedish Pending Patent Application No. 0102174−0.

[22] P. Bjurling, R. Reineck, G. Westerberg, A. D. Gee, J. Sutcliffe, B. Långström, *Proceedings of the VIth workshop on targetry and target chemistry*; TRIUMF, Vancouver, Canada, **1995**, pp. 282−284.

[23] M. Fiorenza, A. Ricci, G. Sbrana, G. Pirazzini, C. Eaborn, J. G. Stamper, *J. Chem. Soc., Perkin Trans. 2* **1978**, 1232−1239.

[24] H. H. Moussa, S. Abdel-Meguid, *J. Heterocycl. Chem.* **1981**, *18*, 1519−1522.

[25] C. L. Cheng, I. G. John, G. L. D. Ritchie, P. H. Gore, L. Farnell, *J. Chem. Soc., Perkin Trans. 2* **1975**, 744−749.

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