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Synthesis of ^{11}C-amides using [^{11}C]carbon monoxide and *in situ* activated amines by palladium-mediated carboxaminations

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[^{11}C]Carbon monoxide at low concentrations, aryl halides and amines were used in the palladium-mediated synthesis of twenty ^{11}C-amides. In the study several approaches to improve the radiochemical yield were explored. Eight of the selected amides were prepared by *in situ* activation of the amines using lithium bis(trimethylsilyl)amide and the radiochemical yields of these reactions were improved compared to utilising a previous reported method. In the synthesis of 1-[*carbonyl*-^{11}C]benzoyl-3-methyl-1*H*-indole (**11**) from 3-methyl-1*H*-indole (**25**), the corresponding organotin–amine was prepared prior to the acylation reaction. In a typical experiment, *N*-(4-hydroxyphenyl)-[*carbonyl*-^{11}C]acetamide (**5**) was prepared in 15% radiochemical yield using 4-aminophenol (**20**) but the yield increased to 63% when the amine was activated by lithium bis(trimethylsilyl)amide.

Introduction

Short-lived positron-emitting radionuclides have been incorporated into compounds for applications in non-invasive *in vivo* studies using Positron Emission Tomography (PET).[1] Special synthetic strategies are required due to the short half-life of ^{11}C ($t_{½}$ = 20.3 min) and the use of sub-micromole quantities of reactants. [^{11}C]Carbon monoxide has been recognised as a potential precursor for ^{11}C-labelling, but so far it has found limited use in labelling chemistry[2] due to its low reactivity and the difficulty of trapping it in the reaction medium.[3] The trapping problem was overcome by the development of a micro-autoclave system.[4] By use of this technique, a wide range of compounds containing a carbonyl functionality[5] have been prepared in ^{11}C-synthesis.

In this paper, the method of synthesising ^{11}C-amides has been improved by the activation of amine nucleophiles, *e.g. in situ* activation of aniline, before reacting with the Pd–acyl complex.

Results and discussion

In the last few years palladium-mediated reactions using [^{11}C]carbon monoxide at low concentrations have been explored as an approach to isotopic labelling with a view to preparing compounds containing various functional groups.[6]

In order to further expand the use of the previously reported method for synthesis of ^{11}C-amides,[5a] a series of relatively reactive amines such as pyrrolidine (**19**) and dimethylamine was studied. When using less reactive amines, *e.g.* aniline, aniline derivatives and indole (**25**), the previous method gave products in low yields or even no product at all. One approach to solving this problem may be to perform the reaction in two steps. In the first step the corresponding organo-acyl-complex ($R^{11}COPd(PPh_3)_2X$) is generated and then the second step involves the reaction of the appropriate anion of the amine.[7]

The short half-life of ^{11}C frequently restricts the experimental procedure and so, if possible, it is advantageous to perform the labelling synthesis by a one-pot procedure. In the case of *in situ* amide synthesis, activation of the appropriate amines could be an approach to overcome this limitation (Scheme 1).

All the ^{11}C-amides were synthesised using a stainless steel micro-autoclave. The reaction mixtures containing tetrakis(triphenylphosphine)palladium(0), aryl halide and the appropriate amine were transferred to the micro-autoclave reactor vessel pre-charged with [^{11}C]carbon monoxide. The reaction was standardised and performed by heating the autoclave to the appropriate temperature for 5 min before releasing the crude mixture into an evacuated receiving flask. The target compounds and the corresponding halides and amines are presented in Figs. 1–3. The results are summarised Tables 1–3.

$$RX \xrightarrow{^{11}CO,\ Pd(PPh_3)_4} R^{11}COPd(PPh_3)_2X \xrightarrow{R_1R_2NM} R^{11}CONR_1R_2$$

Scheme 1

The ^{11}C-labelling of the target molecules **1a**–**1g**, **3** and **4** was performed according to the previous method (method A) using the amines *i.e.* pyrrolidine and dimethylamine. The isolated radiochemical yields of the compounds were in the range of 72–91% (Table 1).

Further investigation showed that this method[5a] was not effective in ^{11}C-labelling when using less reactive amines, aniline derivatives and indoles. Compounds **5**–**10** were therefore selected to explore how the synthesis of the ^{11}C-amides using lithium bis(trimethylsilyl)amide could improve the radiochemical yields (method B) compared to method A. The isolated radiochemical yields for compounds **5**–**10** were in the range of 19–85% (Table 1) when method B was used.

The aniline derivatives showed low reactivities in the palladium-promoted carboxamination when compounds **5**, **6a**, **8**, **9a** and **10b** were synthesized by method A. In these cases the analytical radiochemical yields were 31, 27, <0.1, 20 and 10% (Table 1). Using lithium bis(trimethylsilyl)amide (1 M in THF) to activate the amine by method B, the isolated radiochemical yields of **5**, **6a**, **8**, **9a** and **10b** were increased to 63, 72, 25, 80 and 65%, respectively (Table 1).

The isolated radiochemical yield of 7-pyridin-2-yl-7-aza-bicyclo[4.2.0]octa-1,3,5-trien-8-[*carbonyl*-^{11}C]one (**7**) was 19% when the synthesis was performed in the presence of lithium bis(trimethylsilyl)amide (method B). However, the isolated radiochemical yield of **7** was increased to 71% using method A. The explanation is that the higher reactivity of *N*-(2-bromophenyl)pyridin-2-amine (**17**) is favored by the ring closure reaction (Table 1).

The impact of the lithium bis(trimethylsilyl)amide concentration was investigated in the synthesis of 5-[*carbonyl*-^{11}C]-benzoyl-5*H*-dibenzo[*b*,*f*]azepine (**8**) and *N*-phenyl[*carbonyl*-^{11}C]benzamide (**9a**). For compound **8**, amide concentrations of

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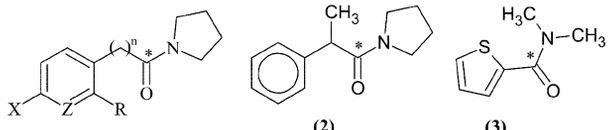
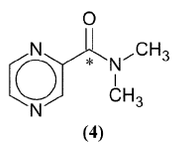


(1a) n = 0, Z = N, R = X = H
(1b) n = 0, Z = C, R = X = H
(1c) n = 0, Z = C, R = H, X = Cl
(1d) n = 0, Z = C, R = H, X = OCH_3
(1e) n = 0, Z = C, R = H, X = NO_2
(1f) n = 1, Z = C, R = H, X = F
(1g) n = 0, Z = C, R = COOEt, X = H

(2)

(3)



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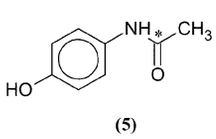

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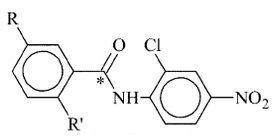
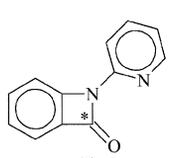


(6a) R = Cl, R' = OH
(6b) R = R' = H



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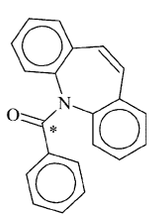

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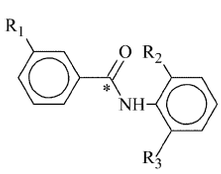
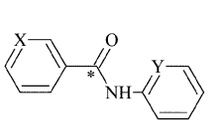
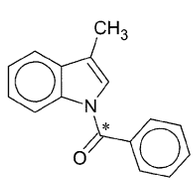


(9a) $R_1 = R_2 = R_3 = H$
(9b) R = OCH_3, $R_2 = R_3 = CH_3$

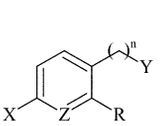


(10a) X = C, Y = N
(10b) X = N, Y = C

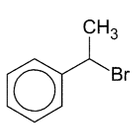


(11)

Fig. 1 Target compounds.



(12a) n = 0, Z = N, R = X = H, Y = I
(12b) n = 0, Z = C, R = X = H, Y = I
(12c) n = 0, Z = C, R = H, X = Cl, Y = I
(12d) n = 0, Z = C, R = H, X = OCH_3, Y = I
(12e) n = 0, Z = C, R = H, X = NO_2, Y = I
(12f) n = 1, Z = C, R = H, X = F, Y = Br
(12g) n = 0, Z = C, R = COOEt, X = H, Y = I



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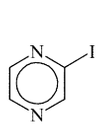

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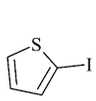

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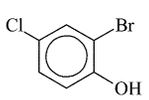

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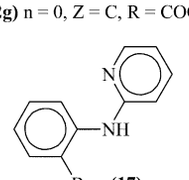

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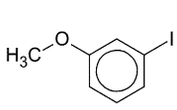
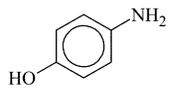


(18)

Fig. 2 Halides.

(19)



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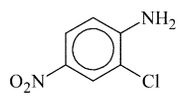

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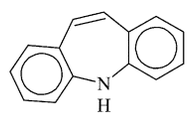

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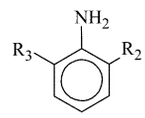
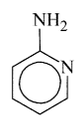


(23a) $R_1 = R_2 = R_3 = H$
(23b) R = OCH_3, $R_2 = R_3 = CH_3$



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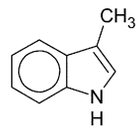


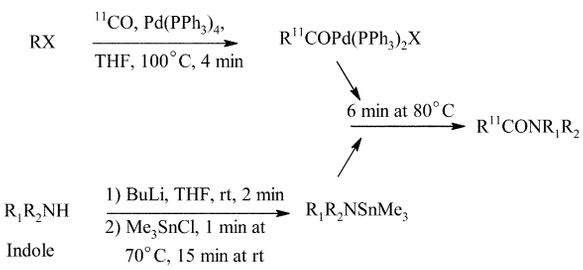
(25)

Fig. 3 Amines.

0.1, 0.2 and 0.3 M gave analytical radiochemical yields of 33, 18 and 2%, respectively. In the case of **9a**, the analytical radiochemical yields were 90 and 55% when the concentrations of the reagent were 0.1 and 0.2 M (Table 2).

Further investigation showed that lithium bis(trimethylsilyl)-amide gave higher radiochemical yields than potassium bis-(trimethylsilyl)amide (0.5 M in toluene). For compound **9a** the radiochemical yield decreased from 90% to 8% when 0.1 M of potassium bis(trimethylsilyl)amide was used instead of 0.1 M of lithium bis(trimethylsilyl)amide. Similarly the radiochemical yield of **10b** decreased form 76% to 19% under similar conditions (Table 2).

The labelling method was further studied in the synthesis of 1-benzoyl-3-methyl-1*H*-indole (**11**). When 3-methyl-1*H*-indole (**25**) was used in method A or activated by lithium bis(trimethylsilyl)amide (method B), the analytical radiochemical yield was in both cases less than 0.1%. However, the isolated radiochemical yield was improved to 32% by *in situ* generation of the corresponding organotin–amine by treating lithium amide with trimethyltin chloride at room temperature (Scheme 2, Table 1). In the attempts to perform the synthesis of (**11**) in a



Scheme 2

one-pot procedure, around 90% of radioactivity remained in the stainless steel micro-autoclave.

It is well-known that organohalides, *e.g.* (1-bromoethyl)-benzene (**13**), having β-protons bound to sp^3 carbons may give low yields due to competing elimination when utilized in palladium-catalysed reactions.[5a,8] It was therefore assumed that the competing reaction would limit its use in amide synthesis. However when trying to synthesize 1-(2-phenyl[*carbonyl*-^{11}C]-propanoyl)pyrrolidine (**2**) using (1-iodoethyl)benzene, the trapping efficiency was good (99%) although the radiochemical yield as expected was low (<1%) when performed at 150 °C. In another case compound **13** was used, and the trapping efficiency was 94% with a 28% radiochemical yield of **2** at 150 °C. When the synthesis was performed at 100 °C, the isolated radiochemical yield increased to 58%. The synthesis of **2** using

Table 1 Trapping efficiencies and radiochemical yields for the ^{11}C-labelled amides shown in Fig. 1

Comp.	Method	Trapping efficiency (%)[a,b,c]	Radiochemical yield (%)[a,d,e]	LC-MS (ESI$^+$)[f] m/z[M + H]$^+$
1a	A	99(3)	94(85%)	177
1b	A	99(2)	98(89%)	176
1c	A	99(2)	92(81%)	210
1d	A	99(3)	97(88%)	206
1e	A	99(2)	94(83%)	221
1f	A	99(4)	98(91%)	208
1g	A	97(2)	80(72%)	248
2	A[g]	99(2)	<0.1	204
	A[h]	94(2)	28	
	A[h,i]	95(3)	77(58%)	
3	A	99(3)	96(87%)	156
4	A	96(2)	88(79%)	152
5	A	84(2)	31(15%)	152
	B	99(2)	71(63%)	
6a	A	85(7)	27(17%)	328
	B	99(2)	82(72%)	
6b	B	99(2)	85(74%)	277
7	A	98(3)	79(71%)	197
	B	89(2)	28(19%)	
8	A	80(2)	<0.1	298
	B	87(2)	33(25%)	
9a	A	93(2)	20	198
	B	96(3)	90(80%)	
9b	B	98(2)	92(85%)	256
10a	B	99(2)	58(48%)	199
10b	A	83	10	199
	B	99(2)	76(65%)	
11	A	93(5)	<0.1	236
	B	85(2)	<0.1	
	C	97(3)	41(32%)	

[a] All results are presented as mean values with a maximum range of ±5%. [b] Decay-corrected mean values and the fraction of radioactivity left in the crude product after purging with nitrogen. [c] Values in parentheses show the number of runs. [d] Analytical yield determined by HPLC. [e] Values in parentheses show decay-corrected isolated radiochemical yields calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC purified product. [f] Using mobile phases C and D. [g] Using (1-iodoethyl)benzene. [h] Using (1-bromoethyl)-benzene. [i] The reaction was performed at 100 °C.

Table 2 Trapping efficiencies and radiochemical yields for compounds **8**, **9a** and **10b** varying the reagents

		Trapping efficiency (%)[c,d,e]		Radiochemical yield (%)[b,c,f]	
Comp.	R–X[a]/M–R′[b]	150 °C	190 °C	150 °C	190 °C
8	X = I/M = Li (0.1 M)	99(2)	—	33(25%)	—
8	X = I/M = Li (0.2 M)	99	—	18	—
8	X = I/M = Li (0.3 M)	98	—	2	—
9a[g]	X = I	93(2)	—	20	—
9a	X = I/M = Li (0.1 M)	96(3)	—	90(80%)	—
9a	X = I/M = Li (0.2 M)	99	—	55	—
9a	X = I/M = K (0.1 M)	99(2)	—	8	—
9a	X = I/M = K (0.05 M)	99(2)	—	48	—
9a	X = I/M = K (0.03 M)	99(2)	—	28	—
9a	X = OTf/M = Li (0.1 M)	98(2)	96(2)	6	32
9a[h]	X = OTf/M = Li (0.1 M)	—	94(2)	—	65(55%)
10b	X = I/M = Li (0.1 M)	99(2)	—	76(65%)	—
10b	X = I/M = K (0.1 M)	99	—	19	—
10b	X = I/M = K (0.05 M)	99	—	24	—

[a] R–X = the corresponding organoiodide or triflate. [b] M–R′ = lithium or potassium bis(trimethylsilyl)amide [c] All results are presented as mean values with a maximum range of ±5%. [d] Decay-corrected mean values and the fraction of radioactivity left in the crude product after purging with nitrogen. [e] Analytical yield determined by HPLC. Values in parentheses show number of runs. [f] Values in parentheses show decay-corrected isolated radiochemical yields calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC purified product. [g] The synthesis was performed as described in method B. [h] The synthesis was performed using tetrabutylammonium iodide.

(1-iodoethyl)benzene indicated that the possible competing β-hydride elimination may be suppressed under some specific conditions.

In this report, the use of organoiodides is usually preferred but sometimes they are not easy to prepare. Occasionally the triflate may be an alternative.[9]

In our previous report[5a] it was suggested that the bromide in R^{11}COPd(PPh$_3$)$_2$Br may be exchanged with iodide under certain conditions. In the ^{11}C-labelling of *N*-phenyl[*carbonyl*-^{11}C]benzamide (**9a**), the use of phenyl trifluoromethanesulfonate and aniline (**23a**) was studied. Compound **9a** was produced in 32% yield after pre-treating the aniline with lithium bis(trimethylsilyl)amide. We also investigated the impact of using tetrabutylammonium iodide with triflates in the carbonylation reaction. The radiochemical yield of **9a** increased to 65% when performing the reaction at 190 °C using phenyl trifluoromethanesulfonate treated with tetrabutylammonium iodide combined with activation of the amine as described in method B. As a comparison, the synthesis of **9a** using iodobenzene gave 80% isolated radiochemical yield at 150 °C

Table 3 Experimental data for the synthesis of compounds **1a**–**1f**, **2**, **8**, **11** and **17**

Comp.	Yield (%)	GC-MS	δ_H	δ_C
1a	93	177, 175, 106	—	—
1b	94	176, 174, 105	—	—
1c	97	210, 208, 139	7.41 (2H, d), 7.30 (2H, d), 3.56 (2H, t), 3.35 (2H, t), 1.85 (4H, m)	168.3, 135.6, 135.3, 128.5, 128.3, 49.4, 46.1, 26.2, 24.2
1d	86	206, 204, 135	—	—
1e	98	221, 178, 150	—	—
1f	96	208, 207, 98	7.23 (2H, t), 6.98 (2H, t), 3.59 (2H, s), 3.43 (4H, m), 1.85 (4H, m)	169.2, 163.3, 160.1, 130.5, 130.4, 115.4, 115.1, 46.8, 45.9, 41.1, 26.1, 24.3
2	94	204, 203, 98	—	—
8[a]	98	298, 297, 192	—	—
11[b]	94	236, 235, 105	—	—
17	—	250, 249, 169	—	154.8, 148.0, 137.6, 132.6, 127.9, 122.8, 119.9, 115.8, 109.8

[a] To a solution of 5*H*-dibenzo[*b*,*f*]azepine (1.04g, 5.4 mmol) in THF (5 ml) butyllithium (2.5 M in hexane, 2.4 ml) was added at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 15 min. The solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and benzoyl chloride (0.70 ml, 6.0 mmol) was added. The resulting mixture was stirred overnight at room temperature, treated with saturated $NaHCO_3$ (50 ml) and extracted with methylene chloride (3 × 50 ml). The pooled extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified to give **8** (1.57g). [b] A mixture of 3-methyl-1*H*-indole (**25**) (0.75 g, 5.72 mmol) in dry methylene chloride (3.0 ml) was treated with lithium bis(trimethylsilyl)amide (1 M in THF, 5.9 ml, 5.9 mmol) under nitrogen atmosphere at room temperature. To this was added benzoyl chloride (0.7 ml, 6.03 mmol) and the mixture stirred at room temperature for 24 h. The reaction mixture was diluted with $NaHCO_3$ (50 ml) and extracted with methylene chloride (3 × 50 ml). The combined organic phases were dried and concentrated under reduced pressure. The crude product was purified to give **11** (1.26, 94%).

(Table 2). This suggests that organoiodides are preferred compared to the corresponding triflate, which occasionally may be used.

Since a closed system is used for all the syntheses, washing of the system is an important factor to consider in order to secure a reasonable reproducibility of the experiments. Could there be a risk of contamination when performing a series of experiments? This so called "carry over effect" between experiments in the micro-autoclave was explored. When the micro-autoclave was washed and conditioned as described in the Experimental section, the reproducibility was better than 95%.

Conclusions

[^{11}C]Carbon monoxide at low concentrations with tetrakis-(triphenylphosphine) palladium(0) and the organohalide with *in situ* activated amine (as nucleophile) may be an efficient approach to the synthesis of ^{11}C-amides, when using an amine of low reactivity such as aniline. The method is rapid, mild and in many cases the reaction can be conducted in a one-pot procedure probably suitable for automation.

Experimental

General

[^{11}C]Carbon was produced by the ^{14}N(p,α)^{11}C nuclear reaction[10] using the Scanditronix cyclotron at Uppsala University PET Centre and a target containing a N_2 gas target. The produced [^{11}C]carbon dioxide was transferred from the target and trapped on a Porapak Q column at −196 °C. The trapped labelled gas was then released by heating in a slow stream of helium (g) (10 ml min^{-1}). The gas flow was passed through a small tube containing zinc powder at 400 °C.[11] The [^{11}C]carbon monoxide produced was trapped on a short silica column at −196 °C[12] and released by warming the silica column to 60 °C, and finally transferred into the high-pressure stainless steel micro-autoclave.[13,14] At the beginning of each experimental session, the micro-autoclave was washed and conditioned using 10 ml THF, then heated to 150 °C for 5 min, followed by repeating the washing with 10 ml THF. The reactor was washed with 2 ml THF between each experiment.

Liquid chromatographic analysis (LC) was performed with a Beckman 126 gradient pump and a Beckman 166 variable wavelength UV-detector (Fullerton, CA, USA) in series with a β^+-flow detector.[15] The following mobile phases were used: 0.05 M ammonium formate pH 3.5 (A), acetonitrile–water (50 : 7) (B), acetonitrile (C) and 0.01 M formic acid (D). For analytical LC, a Jones Chromatography Genesis C_{18}, 4 μm, 250 × 4.6 mm (id) column was used at a flow of 1.5 ml min^{-1}. For semi-preparative LC, a Jones Chromatography Genesis (UK) C_{18}, 4 μm, 250 × 10 mm (id), column was used at a flow of 4 ml min^{-1}. Synthia, an automated synthesis system,[16] was used for LC injection and fraction collection. Data collection and LC control were performed using a Beckman System Gold chromatography software package (USA).

Radioactivity measurements were performed using an ion chamber (Veenstra Instrumenten bv, VDC-202, Holland). For coarse estimations of radioactivity during synthesis, a portable dose-rate meter was used (Långenäs eltekniska AB, Sweden).

In the analysis of the ^{11}C-compounds, unlabelled reference substances were used for comparison in all LC runs. The identity of the synthesised compounds was determined using ^{1}H and ^{13}C NMR and LC-MS. NMR spectra were recorded on a Varian XL 300 (300 MHz) and chloroform-d_1 was used as internal standard. LC-MS was performed using a Micromass VG Quattro with electrospray ionisation using mobile phases C and D. A Beckman 126 pump, a CMA 240 autosampler and a XTerra™ MS C_{18} 3.5 μm, 100 × 4.6 mm (id) column were used.

THF was distilled under nitrogen from sodium–benzophenone.

The synthesis of compounds **1a**,[17] **1b**,[18] **1c**, **1d**,[19] **1e**,[20] **1f**, **2**,[21] **8**,[22] **11**[23] and **17**[24] (Table 3) were performed according to the literature. All chemicals were purchased from Aldrich, Fluka, Chemtronica (Sweden) or Research Biochemical International.

General procedure for synthesis of compounds 1a,[17] 1b,[18] 1c, 1d,[19] 1e,[20] 1f and 2[21] (presented in Table 3)

Thionyl chloride (2 ml, 27.4 mmol) was added dropwise to the appropriate carboxylic acid (2.28 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h. The volatile fraction was evaporated under reduced pressure. The mixture was dissolved in CH_2Cl_2 (2 ml). To this was added a solution of the corresponding amine (2.34 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was then poured into saturated $NaHCO_3$ (50 ml) and extracted with methylene chloride (3 × 50 ml). The pooled extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography.

Labelling experiments

Method A (^{11}C-compounds 1a–1g and 2–4). Tetrakis(triphenylphosphine)palladium(0) (≈ 2.6 μmol) and halide (≈ 9.0 μmol) were placed in a vial (1 ml). The vial was flushed with nitrogen gas and dry THF (250 μl) was added. The resulting mixture was heated at 70 °C for 1 min and kept at room temperature for 10–15 min. Amine (≈ 50 μmol) was added and the reaction mixture was shaken just before injection into the micro-autoclave pre-charged with [^{11}C]carbon monoxide. The mixture was heated at the selected temperature for 5 min. The crude product was transferred to a pre-evacuated vial (3 ml). The micro-autoclave was washed with THF (250 μl) and the wash collected in the same vial. The radioactivity of the reaction mixture was measured before and after purging with nitrogen. The solvent was reduced to 0.1 ml by heating at 80 °C and flushing with nitrogen. The crude mixture was dissolved in acetonitrile–water and injected onto a semi-preparative LC. The identity of the collected fraction was determined by analytical LC and LC-MS.

7-Pyridin-2-yl-7-azabicyclo[4.2.0]octa-1,3,5-trien-8-[*carbonyl*-^{11}C]one (7). *N*-(2-Bromophenyl)pyridin-2-amine (**17**) (4.4 mg, 18 μmol) and tetrakis(triphenylphosphine)palladium(0) (3.0 mg, 2.6 μmol) were used as described in method A.

Method B (^{11}C-compounds 5–6 and 8–10b). A capped vial (1 ml) containing a solution of tetrakis(triphenylphosphine)-palladium(0) (≈ 2.6 μmol) and halide (≈ 9.0 μmol) in dry THF (125 μl) was flushed with nitrogen. The reaction mixture was heated at 70 °C for 1 min and kept at room temperature for 10–15 min. Another capped vial (1 ml) was flushed with nitrogen and charged with amine (≈ 25.0 μmol) in anhydrous THF (100 μl) and lithium bis(trimethylsilyl)amide (1 M in THF, 25 μl, 25 μmol), then shaken and kept at room temperature for 10–15 min. The reaction mixture in the first vial was transferred to the vial containing the amine just before injection into the micro-autoclave pre-charged with [^{11}C]carbon monoxide. The micro-autoclave was heated at 150 °C for 5 minutes. The crude product was transferred to a vial (3 ml) under reduced pressure. The crude product was treated as described for method A.

7-Pyridin-2-yl-7-azabicyclo[4.2.0]octa-1,3,5-trien-8-[*carbonyl*-^{11}C]one (7). A vial (1 ml) was charged with tetrakis-(triphenylphosphine)palladium(0) (3.0 mg, 2.6 μmol), *N*-(2-bromophenyl)pyridin-2-amine (**17**) (4.2 mg, 17 μmol) and THF (225 μl). The solution was heated at 70 °C for 1 min and kept at room temperature for 10–15 min. Lithium bis(trimethylsilyl)-amide (1 M in THF, 25 μl, 25 μmol) was added just before injection into the micro-autoclave. The resulting mixture was treated as described for method B.

***N*-Phenyl[*carbonyl*-^{11}C]benzamide (9a) using the corresponding triflate.** Tetrakis(triphenylphosphine)palladium(0) (3.0 mg, 2.6 μmol) and phenyl trifluoromethanesulfonate (1.4 μl, 8.9 μmol) were put into a vial (1 ml). The vial was flushed with nitrogen gas and dry THF (100 μl) was added. The resulting mixture was heated at 70 °C for 1 min and kept at room temperature for 5 min. The resulting mixture was transferred into another vial (1 ml) containing a solution of tetrabutylammonium iodide (18 mg, 49 μmol) in DMSO (25 μl). The reaction mixture was flushed with nitrogen gas, heated at 70 °C for 1 min and kept at room temperature for 15 min. Another capped vial (1 ml) was flushed with nitrogen and charged with amine in anhydrous THF (100 μl) and lithium bis(trimethylsilyl)amide (1 M in THF, 25 μl, 25 μmol), then shaken and kept at room temperature for 10–15 min. The reaction mixture in the first vial was transferred to the vial containing the amine just before injection into the micro-autoclave pre-charged with [^{11}C]carbon monoxide. The reactor was heated at the setting temperature (190 °C) for 5 min. The crude product was treated as described in method B.

Method C

1-[*carbonyl*-^{11}C]Benzoyl-3-methyl-1*H*-indole (11). A capped vial (1 ml) containing a solution of tetrakis(triphenylphosphine)palladium(0) (3.0 mg, 2.6 μmol) and iodobenzene (**12b**) (1.0 μl, 8.9 μmol) in dry THF (125 μl) was flushed with nitrogen and shaken for 10 min. The reaction mixture was injected into the micro-autoclave pre-charged with [^{11}C]carbon monoxide. The micro-autoclave was heated at 100 °C for 4 minutes. The crude product was placed in a pre-evacuated vial (3 ml), which was charged with 3-methyl-1*H*-indole (**25**) (5.9 mg, 45 μmol) dissolved in THF (75 μl), treated with BuLi (1.6 M in hexane, 15 μl) followed with trimethyltin chloride (1 M in THF, 25 μl), heated at 70 °C for 1 min and kept at room temperature for 15 min. The resulting mixture was heated at 80 °C for an additional 6 min, and the remaining procedure was as described in method B.

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