Synthesis of ^{11}C-Labelled Amides by Palladium-Mediated Carboxamination Using [^{11}C]Carbon Monoxide, in situ Activated Amines and 1,2,2,6,6-Pentamethylpiperidine

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Twenty-seven ^{11}C-labelled amides were synthesised using [^{11}C]carbon monoxide in low concentrations, palladium(0), organohalides and amines in a small micro-autoclave (200 μL). The focus of the study was to improve the radiochemical yields in this palladium-mediated amide synthesis when employing less-reactive amines, such as methylamine, [(2*R*)-1-ethylpyrrolidin-2-yl]methylamine (**40**) and 2-(pyridin-2-yl)ethanamine (**41**). The radiochemical yields were improved when utilizing 1,2,2,6,6-pentamethylpiperidine (pempidine) in combination with the amine substrates. The ^{11}C-labelled amides were obtained mostly in high radiochemical yields (in the range 16–94%) and the specific radioactivity varied between 650 and 1250 GBq/μmol. 1-(1,3-Benzodioxol-5-yl[^{13}C]carbonyl)piperidine **(6a)** was synthesised to verify the labelling position (δ = 169.8 ppm) using ^{13}C NMR spectroscopy. The radiochemical purity of the target compounds was determined by analytical HPLC and exceeded 95%.

Introduction

[^{11}C]Carbon monoxide (^{11}C, $t_{1/2}$ = 20.3 min) is a versatile precursor for the synthesis of ^{11}C-carbonyl compounds despite limitations that result from its low reactivity and solubility.[1] These limitations may result in a low trapping efficiency. Utilizing a recently developed stainless steel reaction chamber, i.e., in the micro-autoclave technique,[2] this problem has been overcome to some extent and the compound has been used for ^{11}C labelling of various carbonyl compounds.[3]

A recently reported synthesis of ^{11}C-labelled amides employed [^{11}C]carbon monoxide and amines with high reactivity, such as pyrrolidine.[3a] The versatility of this method was further explored and applied to the ^{11}C labelling of amides using lithium bis(trimethylsilyl)amide to activate the amine nucleophile.[3e] Even this approach has restrictions, however, such as when it is applied to aniline derivatives.

The ^{11}C-labelled-amide synthesis has been developed further and interesting results have been obtained for their preparation in a series of experiments using relatively less-reactive amines — e.g., methylamine, [(2*R*)-1-ethylpyrrolidin-2-yl]methylamine (**40**) and 2-(pyridin-2-yl)ethanamine (**41**) — in the presence of 1,2,2,6,6-pentamethylpiperidine (pempidine), a sterically hindered tertiary amine.

Some of the compounds prepared in this series, such as **1**,[4] **2**,[5] **3**,[6] **4**,[7] **5**,[8] **6a**,[9] **6b**,[10] **9**[11] and **20**[12], are also of interest because of their various biological activities.

Results and Discussion

Twenty-seven labelled amides were prepared using [^{11}C]carbon monoxide in low concentration (0.1 mm) together with tetrakis(triphenylphosphane)palladium(0) (12 mm), the appropriate organohalide (36 mm) and the corresponding amines (200 mm) in a 200-μL micro-autoclave. The target compounds and corresponding substrates are presented in Figure 1−3 and the results are presented in Table 1−4. The trapping efficiencies (the degree of incorporation of [^{11}C]carbon monoxide into the crude products) and the isolated radiochemical yields for these compounds were in the ranges 75−99% and 26−94%, respectively.

The effect of solvents on the radiochemical yields was investigated for compounds **2**, **4**, **5** and **7** and the highest radiochemical yield was observed using THF; i.e., the radiochemical yield was slightly increased (by 10%) when using THF instead of dioxane. Dioxane was preferred to THF, however, when DMSO was used as a co-solvent under some special conditions exemplified later.

The effect of temperature was also studied for compounds **1**−**5**, **6a** and **6b** at 130, 150 and 180 °C. The trapping efficiency at these temperatures was 94 ± 5%. The radiochemical yields decreased, however, by up to 35 and 50% (relative to the yield at 150 °C) when the setting temperatures were 130 and 180 °C, respectively.

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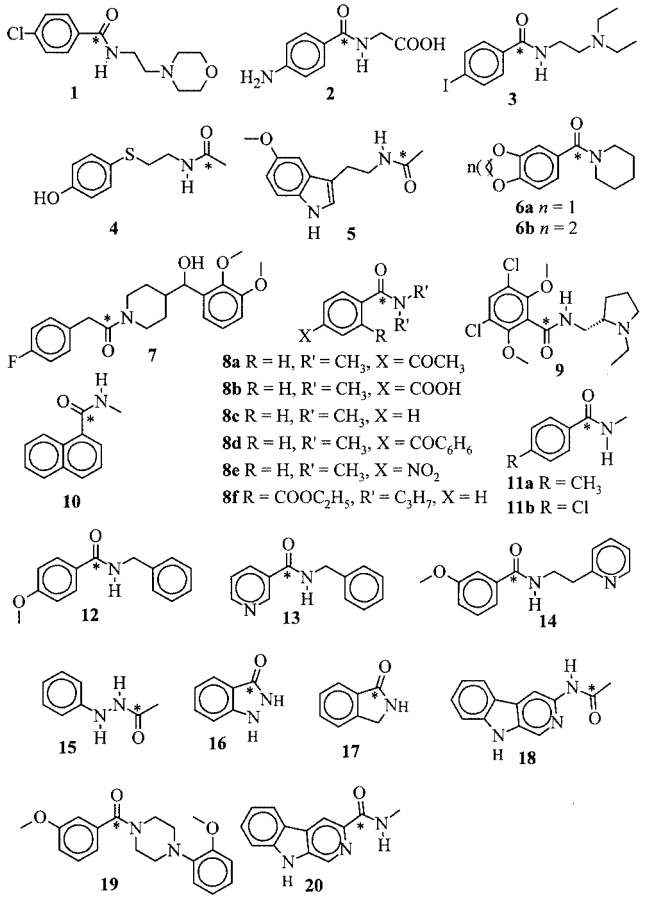


Figure 1. Target compounds (* = ^{11}C)

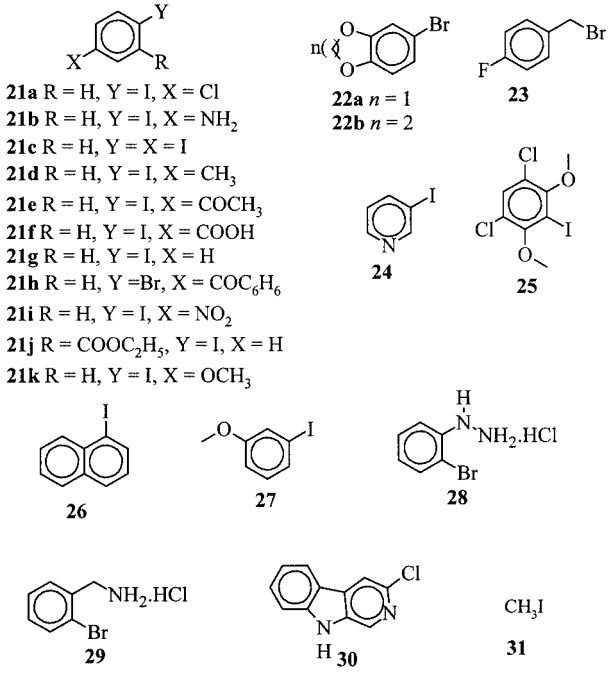


Figure 2. Halides

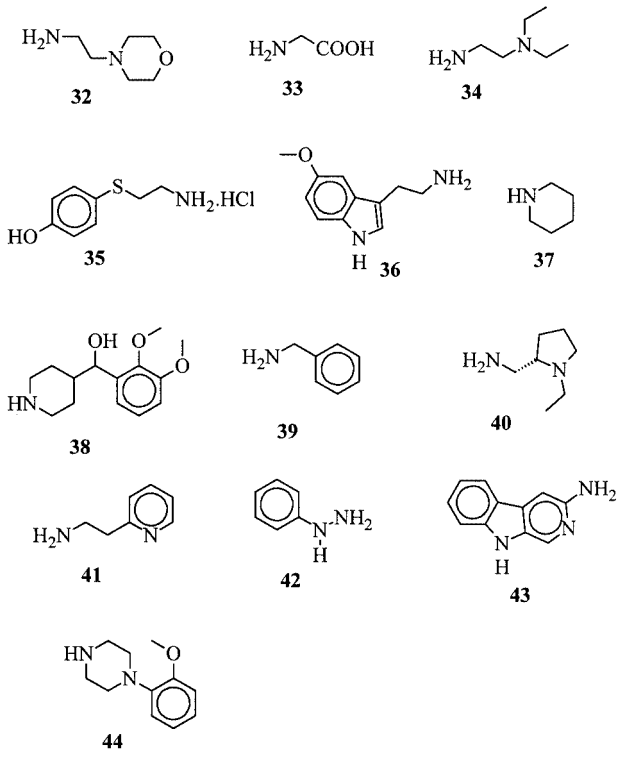


Figure 3. Amines

The highest radiochemical yields were obtained at 150 °C in all cases (**1**−**6b**) when aryl halides were used (Table 1).

Some specific features have also been explored; for example, with compound **2**, which is an amide of glycine. Glycine itself has low solubility in organic solvents, but its tetrabutylammonium salt is partially soluble in DMSO. The reaction was performed at 130−180 °C and a good radiochemical yield (26%) was obtained at 150 °C [tetrabutylammonium hydroxide (QOH), 40 μmol]. The analytical radiochemical yields were 12 and 8% when the reaction temperatures were set at 130 and 180 °C, respectively. Increasing the concentration of QOH resulted in lower yields (Table 2).

To test competitive reactions using diiodoaryl compounds, *N*-(2-diethylaminoethyl)-4-iodobenzamide (**3**) was chosen to confirm whether diiodoaryl compound **21c** could result in formation of side products under the labelling conditions. Based on the previous report,[3a] a low radiochemical yield was expected to result because of side reactions. To our surprise, the isolated radiochemical yield was 75%. This yield might be because THF was used instead of dioxane.

Substituted organoiodides and the appropriate amines were used for the synthesis of compounds **8a**−**c** and **8e**−**f**. The labelling of compound **8d** was performed using 4-(bromophenyl)(phenyl)methanone. The lower decay-corrected radiochemical yield of **8d** (45%) could be a result of the lower reactivity of the organobromide compared to the organoiodide.

Compounds **9**−**19** (Figure 1) were selected to explore the influence of pempidine on the radiochemical yields in the synthesis of these ^{11}C-labelled amides.

Table 1. Radiochemical yields and trapping efficiencies for ^{11}C-labelled amides shown in Figure 1 (*: all results are presented as mean values with a maximum range of ± 5%)

Comp.	Method	Trapping efficiency [%]*[a]	Radiochemical yield [%]*[b]	LC-MS [ESI$^+$][c] m/z [M + H]$^+$
1	B	96 % (3)[d]	85 (71 %)[e]	269
2	B	93 % (2)	34 (26 %)	195
3	B	99 % (3)	82 (75 %)	347
4[f]	B	94 % (2)	59 (44 %)	212
5	B	99 % (3)	95 (83 %)	233
6a	A	97 % (2)	74 (59 %)	234
6b	A	94 % (2)	82 (70 %)	248
7	A	99 % (4)	98 (90 %)	388
8a	A	99 % (2)	90 (78 %)	192
8b	A	99 % (2)	87 (71 %)	194
8c	A	98 % (2)	99 (94 %)	150
8d	A	94 % (2)	55 (45 %)	254
8e	A	99 % (2)	90 (79 %)	195
8f	A	79 % (2)	75 (61 %)	278
9	C	86 % (3)	44 (32 %)	361
10	C	99 % (2)	48 (38 %)	186
11a	C	99 % (2)	91 (80 %)	150
11b	C	99 % (2)	66 (56 %)	170
12	C	99 % (2)	71 (61 %)	242
13	C	95 % (2)	63 (52 %)	213
14	C	99 % (2)	94 (85 %)	257
15	C	75 % (2)	28 (16 %)	176
16	D	80 % (2)	88 (75 %)	135
17	D	98 % (2)	78 (65 %)	134
18	C	99 % (2)	69 (54 %)	226
19	C	99 % (2)	82 (73 %)	327
20	–	98 % (2)	91 (78 %)	226

[a] Decay-corrected mean values; the fraction of radioactivity remaining in the crude product after purging with nitrogen. [b] Radiochemical yield determined by HPLC. Analytical yields are presented outside the parentheses. [c] Mobile phases C and D were used. [d] Values in parentheses represent the number of runs. [e] Values in parentheses show the decay-corrected isolated radiochemical yield, calculated from the amount of radioactivity in the crude product before the nitrogen purge, and the radioactivity of the LC-purified product. [f] 2,2,6,6-Tetramethylpiperidine (TMP, 2 μL) was also added to the solution of the corresponding amine in DMSO.

When using Method A, the isolated radiochemical yield of 3,5-dichloro-*N*-{[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-2,6-dimethoxy[carbonyl-^{11}C]benzamide (**9**) was less than 10%. The yield of **9** was improved slightly when the concentration of **40** was increased from 25 to 90 μmol. The radiochemical yield of compound **9** was increased fourfold, however, when 90 μmol of **40** and pempidine were used (Table 2). Moreover, increasing the reaction temperature to 180 °C resulted in a slightly decreased radiochemical yield of **9**.

Using Method B, *N*-methyl-1-naphth[carbonyl-^{11}C]amide **(10)** was prepared in 10% analytical radiochemical yield, but it was increased to 38% by using pempidine.

We made a comparison of this labeling method with the previously described methods.[3e] A series of experiments were carried out to synthesize compound **10** using various concentrations of lithium bis(trimethylsilyl)amide and pempidine (Table 3). The highest radiochemical yield was obtained using 12.5 μmol of lithium bis(trimethylsilyl)amide.

Table 2. Influence of the reagent and substrate concentrations on the trapping efficiency and radiochemical yield of compounds **2** and **9** (*: all results are presented as mean values with a maximum range of ± 5%).

Comp.	Substrate	Conc. [μmol]	Trapping efficiency [%]*[a] 150 °C	Radiochemical yield [%]*[b] 150 °C
2	Q−Gly[c]	–	93 % (7)[d]	34 (26 %)[e]
2	Q−Gly[f]	–	94 % (2)	24 (12 %)
9[g]	40	25	96 % (2)	19 (8 %)
9[g]	40	90	97 % (2)	22 %
9[h]	40	25	99 % (2)	28 (19 %)
9[h]	40	50	75 % (2)	35 %
9[h]	40	90	86 % (3)	45 (33 %)

[a] Decay-corrected mean values; the fraction of radioactivity remaining in the crude product after purging with nitrogen. [b] Analytical yields determined by HPLC are presented outside the parentheses. [c] QOH (40 μmol) + glycine (Gly, 121 μmol). [d] Values in parentheses represent the number of runs. [e] Values in parentheses represent the decay-corrected isolated radiochemical yields, which are calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC-purified product. [f] QOH (60 μmol) + glycine (Gly, 121 μmol). [g] The reaction was performed as described in Method A. [h] The reaction was performed as described in Method C.

Table 3. The impact of pempidine or lithium bis(trimethylsilyl)amide on the radiochemical yield and trapping efficiency of compounds **10**, **11a**, **12** and **13** (*: all results are presented as mean values with a maximum range of ± 5%)

Comp.	Reagent	Conc. [μmol]	Trapping efficiency [%]*[a] 150 °C	Radiochemical yield [%]*[b] 150 °C
10[c]	–	–	96 % (2)[d]	10 %
10[e]	R′−Li[f]	12.5	99 % (2)	42 %
10	R′−Li	25	99 %	24 %
10	R′−Li	7.5	99 %	12 %
10[g]	PMP[h]	138	99 % (2)	48 (38 %)[i]
11a[e]	R′−Li	12.5	99 %	31 %
11a[g]	PMP	138	99 % (2)	91 (80 %)
12[e]	R′−Li	12.5	99 %	30 %
12[g]	PMP	138	99 % (2)	70 (61 %)
13[c]	–	–	98 % (3)	15 %
13[g]	PMP	138	95 % (2)	63 (52 %)

[a] Decay-corrected mean values; the fraction of radioactivity left in the crude product after purging with nitrogen. [b] Analytical yields determined by HPLC are presented outside the parentheses. [c] The reaction was performed as described in Method A. [d] Values in parentheses represent the number of runs. [e] The reaction was performed as described in Method C, but using lithium bis(trimethylsilyl)amide (1 M in THF, 50 μL, 50 μmol) instead of pempidine. [f] R′−Li = lithium bis(trimethylsilyl)amide. [g] The reaction was performed as described in Method C. [h] PMP = pempidine. [i] Values in parentheses show the decay-corrected isolated radiochemical yields, which were calculated from the amount of radioactivity in the crude product before nitrogen purge, and the radioactivity of the LC purified product.

The trend of the results, however, indicated that pempidine was better than lithium bis(trimethylsilyl)amide.

With the intention of exploring this observation in more depth, the study was extended to the synthesis of *N*-4-di-

methyl[carbonyl-^{11}C]benzamide (**11a**) and *N*-benzyl-4-methoxy[carbonyl-^{11}C]benzamide (**12**) using either pempidine or lithium bis(trimethylsilyl)amide. Using the latter base, the analytical radiochemical yields of **11a** and **12** were around 30%. The isolated radiochemical yields, however, for compounds **11a** and **12** were increased to 80 and 61%, respectively, when pempidine was used (Table 3).

Furthermore, compounds **13**−**19** were synthesised using pempidine with isolated radiochemical yields in the range 16−85% (Table 1). When the synthesis of **13** was performed in the absence of pempidine, the analytical radiochemical yield decreased to 15% (Table 3). The lower yield of *N*′-phenyl[carbonyl-^{11}C]acetohydrazide (**15**, 16%) compared to 1,2-dihydro-3*H*-indazol-3-[carbonyl-^{11}C]one (**16**, 75%) is probably a result of a favourable ring-closure reaction.

In previous reports,[3c,3e] it has been shown that triflates and heteroaryl bromides may undergo iodide exchange using tetrabutylammonium iodide (QI). We studied this process further in the synthesis of *N*-methyl-9*H*-β-carboline-3-[carbonyl-^{11}C]carboxamide (**20**). A good radiochemical yield of **20** (78%) was obtained when combining QI with pempidine.

The identity of **6a** was further investigated by ^{13}C NMR spectroscopic analysis of 1-(1,3-benzodioxol-5-yl[carbonyl-^{13}C])piperidine to confirm the position of the label. The ^{13}C NMR spectroscopic signal at δ = 169.8 ppm was in agreement with that of authentic **6a**.

The specific radioactivity of compounds **5** and **6b** was determined by LC-MS, 26 min after 5- and 10-μAh bombardment, respectively, to be 650 ± 10 and 1250 ± 8 GBq/μmol, respectively.

Conclusions

Using pempidine provides a way to improve the radiochemical yields of ^{11}C-labelled amides derived from amines that are less reactive than pyrrolidine.

Experimental Section

General: The target-produced [^{11}C]carbon dioxide was passed through a quartz tube filled with zinc, in which the [^{11}C]carbon dioxide was reduced to [^{11}C]carbon monoxide.[13] Each ^{11}C-labelled amide was synthesised using [^{11}C]carbon monoxide, [tetrakis(triphenylphosphane)palladium(0)], an organohalide and an amine. The substrates were transferred using anhydrous THF at high pressure (35 Mpa) into the micro-autoclave that was pre-charged with [^{11}C]carbon monoxide at room temperature. The micro-autoclave was then heated for 5 min before releasing the crude mixture into an evacuated flask. At the beginning of each session, the stainless-steel micro-autoclave was washed with THF (10 mL), a blank experiment was performed by heating at 150 °C for 5 min, and then it was washed with additional of THF (10 mL). The reactor was cleaned with THF (2 mL) after each experiment.

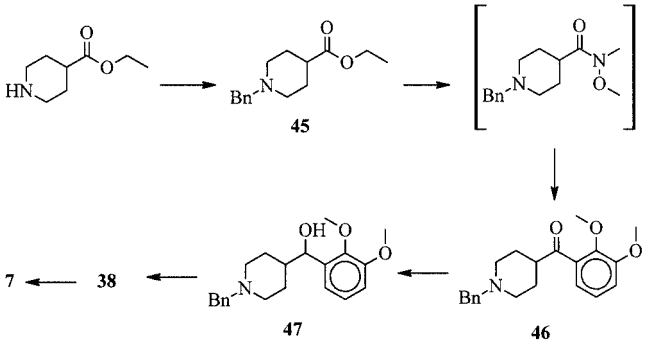
Liquid chromatographic (LC) analyses were performed with a Beckman 126 gradient pump and a Beckman 166 variable-wavelength UV-detector in series with a β^+-flow detector.[14] The following mobile phases were used: (A) 0.05 M ammonium formate, pH 3.5; (B) acetonitrile/water (50:7); (C) acetonitrile; (D) 0.01 M formic acid. For analytical LC, a Jones Chromatography Genesis C_{18} column (4 μm, 250 × 4.6 mm ID) was used at a flow rate of 1.5 mL/min. For semi-preparative LC, a Jones Chromatography Genesis C_{18} column (4 μm, 250 × 10 mm ID) was used at a flow rate of 4 mL/min. Synthia, an automated synthesis system,[15] was used for LC injection and fraction collection. Data collection and LC control were performed using a Beckman System Gold chromatography software package.

Radioactivity was measured in an ion chamber (Veenstra Instrumenten bv, VDC-202). A portable dose-rate meter was used to trace the radioactivity during experiments.

In the analysis of the ^{11}C-labelled compounds, unlabelled reference substances were used for comparison in all the LC runs. Identities of the synthesised compounds were established using ^{1}H and ^{13}C NMR spectroscopy and LC-MS. NMR spectra were recorded on a Varian XL 300 spectrometer (300 MHz) using $CDCl_3$ as the internal standard. LC-MS was performed with a Micromass VG Quattro spectrometer by electrospray-ionisation of mobile phases C and D, using a Beckman 126 pump, a CMA 240 autosampler and an XTerra MS C_{18} column (3.5 μm, 4.6 × 100 mm).

THF was distilled under nitrogen from sodium/benzophenone.

The compounds **7** and **38** are synthesised as presented in Scheme 1. Reference compounds **1**,[16] **3**,[17] **4**,[18] **17**,[19] and **18**[20] were synthesised according to literature procedures. The reference compounds **2**, **5**, **6a**, **6b**, **8c**, **15**, **16**, and **20**, and all other chemicals, were purchased from Aldrich, Fluka, Chemtronica (Sweden) or Research Biochemical International.



Scheme 1

General Procedure for the Synthesis of Compounds 8e,[21] **9**−**11b**,[22] **and 13**[23] **(Table 4):** Thionyl chloride (2.00 mL, 27.4 mmol) was added dropwise to the appropriate carboxylic acid (2.28 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 2 h. The volatile fraction was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), a solution of the corresponding amine (2.34 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was then poured into saturated $NaHCO_3$ (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography.

Compounds **45**−**47** (Table 4, Scheme 1) were synthesised based on literature procedures with some minor modifications.[24]

Table 4. Data for the synthesis of amides **8e**,[20] **9**, **10**−**11b**,[21] **13**,[22] **38**, **45**−**47**[23] and **7**

	Yield [%]	GC-MS	^{1}H NMR, δ [ppm]	^{13}C NMR, δ [ppm]
8e	88	194, 164	−	−
9	97	361, 98	7.39 (s, 1 H), 6.50 (br, 1 H), 3.73−3.90 (m, 7 H), 3.10−3.33 (m, 2 H), 2.60−2.90 (m, 2 H), 2.22 (m, 2 H), 1.90 (m, 1 H), 1.70 (m, 3 H), 1.08 (t, 3 H)	163.9, 152.2, 131.2, 129.3, 123.8, 62.5, 62.3, 53.4, 48.0, 40.6, 27.9, 22.6, 13.5
10	89	185, 155	8.20 (m, 1 H), 7.81 (m, 2 H), 7.82−7.31 (m, 4 H), 6.37 (br, 1 H), 2.93 (s, 3 H)	170.2, 134.3, 133.4, 130.2, 129.9, 128.1, 126.8, 126.2, 125.3, 124.7, 125.5, 26.6
11a	95	149, 119	−	−
11b	97	169, 139	−	−
13	85	213, 106	−	−
45	98	247, 156	7.32 (m, 5 H), 4.13 (q, 2 H), 3.48 (s, 2 H), 2.85 (td, 2 H), 2.28 (tt, 1 H), 2.08 (dt, 2 H), 1.85 (m, 4 H), 1.25 (t, 3 H)	175.2, 138.3, 129.0, 128.1, 126.9, 63.2, 60.2, 52.8, 41.1, 26.2, 14.1
46	78	339, 248	7.29 (m, 5 H), 6.99 (m, 3 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.49 (s, 2 H), 3.07 (tt, 1 H), 2.87 (dt, 2 H), 2.05 (m, 2 H), 1.80 (m, 4 H)	206.6, 152.6, 146.8, 138.3, 134.4, 128.9, 128.0, 126.8, 124.2, 120.1, 114.6, 63.1, 61.6, 55.8, 53.1, 48.1, 28.0
47	97	341, 326	7.28 (m, 5 H), 7.02 (t, 1 H), 6.82 (d, 1 H), 6.80 (d, 1 H), 4.61 (d, 1 H), 3.86 (s, 6 H), 3.46 (s, 2 H), 2.70−3.0 (m, 2 H), 2.15 (s, 1 H), 1.80−1.94 (m, 3 H), 1.64 (m, 1 H), 1.13−1.55 (m, 2 H)	152.3, 146.3, 138.2, 136.5, 129.1, 128.0, 126.8, 123.8, 119.6, 111.2, 74.1, 63.2, 60.7, 55.5, 53.5, 42.8, 28.6
38[a]	76	252, 220	7.00 (t, 1 H), 6.88 (d, 1 H), 6.82 (d, 1 H), 4.61 (d, 1 H), 3.84 (s, 6 H), 3.15 (m, 4 H), 2.52 (m, 2 H), 2.01 (m, 1 H), 1.75 (m, 1 H), 1.15−2.45 (m, 3 H)	152.4, 146.3, 136.3, 123.9, 119.6, 111.3, 74.1, 60.8, 55.6, 42.8
7[b]	79	−	7.1−6.8 (m, 7 H), 4.60 (m, 2 H), 3.89−3.72 (m, 7 H), 3.62 (d, 2 H), 2.90−2.40 (m, 3 H), 2.10−1.00 (m, 5 H)	169.0, 152.3, 135.8, 130.9, 130.1, 124.0, 119.2, 115.3, 111.3, 73.5, 73.1, 60.7, 55.6, 46.1, 42.1, 41.9, 39.9, 28.7, 27.9

[a] Racemic alcohol **47** (0.50 g, 1.48 mmol), ammonium formate (1.13 g, 17.92 mmol) and palladium on activated carbon (10%, 0.59 g) were dissolved in methanol (18 mL) under argon. The reaction mixture was heated under reflux for 45 min, cooled to room temperature and filtered through Celite. The filtrate was concentrated in vacuo. The residue was treated with NaOH solution (1 M, 300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. Column chromatography (CH_2Cl_2/MeOH, 2:1) yielded **38** as a white solid (0.28 g, 76%). LC-MS (ESI^+, solvent A/B): m/z = 252 $[M + H]^+$. [b] Under argon, 4-fluorophenylacetyl chloride (0.29 mL, 2.1 mmol) was added to a solution of **38** (0.50 g, 2.0 mmol) in anhydrous THF (10 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h then at 40 °C for 2 h. The volatile compounds were removed in vacuo and the residue was partitioned between saturated sodium bicarbonate and dichloromethane. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel. Elution with ether yielded **7** (0.52 g, 79%) as a colourless oil that solidified. LC-MS (ESI^+, solvent A/B): m/z = 387 $[M + H]^+$.

Labelling Experiments

Method A: [Tetrakis(triphenylphosphane)palladium] (ca. 3 μmol) and halide (ca. 9 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 to 70 °C for 1 min and kept at room temperature for 10−15 min. Amine (ca. 50 μmol) was added and the reaction mixture was shaken just before injection into the micro-autoclave that was pre-charged with [^{11}C]carbon monoxide. The mixture was heated at the desired temperature for 5 min. The crude product was transferred to a vial (3 mL) under reduced pressure. The micro-autoclave was washed with THF (250 μL) and the solvents were combined in the vial. The radioactivity was measured before and after purging with nitrogen. The solvent volume 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 and radiochemical purity of the collected fraction was analysed by LC and LC-MS.

Method B: Halide (ca. 9 μmol) and [tetrakis(triphenylphosphane)-palladium] (ca. 3 μmol) were dissolved in anhydrous 1,4 dioxane (50 μL). Another vial (1 mL) was charged with the amine (ca. 50 μmol) dissolved in DMSO (50 μL) and anhydrous dioxane (150 μL). The reaction mixture was treated as described in Method A.

Method C: A capped vial (1 mL) containing a solution of [tetrakis-(triphenylphosphane)palladium] (ca. 3 μmol) and halide (ca. 7 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 the amine (ca. 50 μmol) in anhydrous THF (100 μL) and pempidine (25 μL, 138 μmol), and then it was 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 that was pre-charged with [^{11}C]carbon monoxide. The micro-autoclave was heated at 150 °C for 5 minutes. The crude product was treated as for Method A.

Method D: A vial (1 mL) was charged with [tetrakis(triphenylphosphane)palladium] (ca. 3 μmol), substrate (ca. 17 μmol) and THF (225 μL). The solution was heated to 70 °C for 1 min and kept at room temperature for 10−15 min. Pempidine (25 μL, 138 μmol)

was added just before injection into the micro-autoclave. The resulting mixture was treated as described for Method A.

1-(1,3-Benzodioxol-5-yl[^{13}C]carbonyl)piperidine (6a): A vial (1 mL) containing [tetrakis(triphenylphosphane)palladium(0)] (8 mg, 6.9 μmol) and halide **22a** (4.3 μL, 35.8 μmol) that were dissolved in anhydrous THF (200 μL) and amine **36** (20 μL, 202.2 μmol) was treated as described previously in Method B. The resulting reaction mixture and [^{13}C]carbon monoxide (1 mL) was transferred to the micro-autoclave, which was pre-charged with [^{11}C]carbon monoxide. The micro-autoclave was heated at 150 °C for 20 minutes. The crude product was transferred to a pre-evacuated vial, heated at 60 °C and purged with nitrogen to remove the volatile fraction. The crude product was dissolved in acetonitrile/water (1:1) and injected onto the semi-preparative LC (t_R = 8.4 min). Analytical LC: solvent A/C (80:20), linear gradient to 0:100 during 7 min then 100% B for 3 min, flow 1.5 mL/min, wavelength 254 nm (t_R = 6.3 min). LC-MS (ESI$^+$, solvent C/D): m/z = 234 $[M + H]^+$.

The solvent of the collected fraction was evaporated under reduced pressure to obtain the desired product (68%). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 169.8 ppm.

***N*-Methyl-9*H*-β-carboline-3-[carbonyl-^{11}C]carboxamide (20):** [Tetrakis(triphenylphosphane)palladium(0)] (3.0 mg, 2.6 μmol) and 3-chloro-9*H*-β-carboline (**48**) (1.9 mg, 9.0 μmol) were placed in 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 to 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 then kept at room temperature for 15 min. Another capped vial (1 mL) was flushed with nitrogen, charged with methylamine (2 M in THF, 25 μL, 50 mmol) in anhydrous THF (100 μL) and pempidine (25 μL, 138 μmol), shaken and then 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 that was pre-charged with [^{11}C]carbon monoxide. The crude product was treated as described for **6a**. Semi-preparative LC: t_R = 1.9 min. Analytical LC: t_R = 3.9 min. LC-MS (ESI$^+$, solvent C/D): m/z = 226 $[M + H]^+$.

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