# Tetra- and Monoorganotin Reagents in Palladium-Mediated Cross-Coupling Reactions for the Labeling with Carbon-11 of PET Tracers

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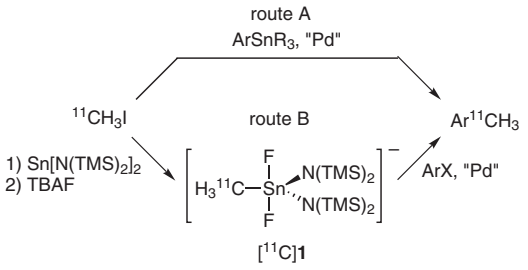
**Abstract:** The palladium-catalyzed cross-coupling reactions between a (trimethylstannyl)arene and [$^{11}$C]methyl iodide (Stille reaction) or between an aryl halide and a [$^{11}$C]monomethyltin reagent issued from Lappert's stannylene, were developed for the synthesis of polyfunctional [$^{11}$C]methyl quinolines and quinolinimides as potential tracers for positron emission tomography (PET).

**Key words:** positron emission tomography, carbon-11, Stille, monoorganotin, [$^{11}$C]methyl iodide

Positron emission tomography (PET) is a powerful imaging technique for clinical, medical, and biological investigations in various areas such as oncology, cardiology, and neuroscience, and also for drug development. This technique requires a specific radiotracer used as a probe to monitor the biochemical processes and localization of a target molecule involved in important biofunctions and related phenomena. Due to the increasing need of this technique in *in vivo* biochemistry and medicine, the development of new PET tracers and radiolabeling strategies is always demanding.[1–3] PET uses short half-life radioisotopes, e.g. carbon-11 ($t_{1/2}$ = 20.4 min) and fluorine-18 ($t_{1/2}$ = 109.6 min). Thus, rapid synthetic processes including organic transformations and purifications are required. Moreover, the radioisotopes are available in forms of a limited number of labeled precursors in submicromolar quantities (e.g., for carbon-11: $^{11}CO_2$ and $^{11}CH_4$ produced by the cyclotron then giving access to H$^{11}$CN, $^{11}CO$, $^{11}COCl_2$ or $^{11}CH_3I$). Reactions are carried out using a large excess of substrate and reagents compared to the labeled reactant, and have to be efficient, selective, and preferably without any intermediate purification. Finally, the overall radiosyntheses have to be suitable for automation to avoid radiation exposure.

The majority of $^{11}$C-labeled PET tracer preparations involve the synthetically well-established [$^{11}$C]methyl iodide[4] either in nucleophilic alkylation reactions on nitrogen, oxygen, and sulfur or in carbon–carbon bond-forming reactions where organometallic compounds are widely applied.[5–20] The Stille reaction remains the only reliable method for the radiosynthesis of PET tracers by introducing a methyl group labeled with carbon-11 onto an aryl moiety.[9–20] It proceeds by a palladium-mediated cross-coupling reaction between an aryltriorganostannane precursor and [$^{11}$C]methyl iodide as the electrophilic partner leading to the formation of a $Csp^2$–$^{11}Csp^3$ bond (Scheme 1, route A). It is compatible with a broad range of functional groups and can be run under neutral conditions. However, several drawbacks can be pointed out such as the recovery of tetraorganotin byproducts of high toxicity in the crude final mixture and, in case of a functionalized organostannane, the occurrence of the $^{11}$C-methylation of nucleophilic groups as an unwanted side reaction.[15,18] Thus, difficulties for tracer purification may be encountered and additional protection/deprotection steps could be envisaged.

Recently, we described a new methodology based on the transfer reaction of the [$^{11}$C]methyl group from the $^{11}$C-labeled hypervalent methylstannate [$^{11}$C]**1** onto an aryl halide (Scheme 1, route B).[21] The monoorganotin reagent [$^{11}$C]**1** was obtained by oxidative addition of [$^{11}$C]methyl iodide to Lappert's stannylene[22,23] {Sn[N(TMS)$_2$]$_2$} followed by in situ activation with tetrabutylammonium fluoride as fluoride source. Both steps were immediate and quantitative. The further palladium-mediated [$^{11}$C]methyl transfer between [$^{11}$C]**1** and various bromoquinolines and naphthalenes as model substrates, was found very efficient for the synthesis of the corresponding [$^{11}$C]methylarenes. Although less straightforward compared to the Stille reaction, this new approach holds several advantages such as the ligand-free conditions, the formation of a nontoxic and easily removable inorganic tin byproduct, the ease for purification, as well as the availability of the aryl halide as the substrate. Due to the




**Scheme 1** Palladium-mediated coupling reactions using [$^{11}$C]methyl iodide and tetraorganotin (route A) or monoorganotin (route B) reagents

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total conversion of [$^{11}$C]methyl iodide into [$^{11}$C]methylstannate [$^{11}$C]**1**, no $^{11}$C-methylation of nucleophilic group bearing the starting aryl halide could be expected.

Our next interest was directed to the rapid introduction of a [$^{11}$C]methyl group onto a polyfunctional arene for the synthesis of new PET tracers. In the course of our program with the aim of developing radioligands for the non-invasive study of the functions and diseases involving cerebral neurokinin and opiate receptors, such as anxiety, depression, psychosis, schizophrenia, and Parkinson's disease, we identified SB 222200 **2**[24–28] and analogues **3** and **4**[29] (NK-3 receptor antagonists) and quinolinimide **5**[30,31] (ligand of delta opioid receptors) as candidates for radiolabeling (Figure 1). These compounds bear a methyl group at different positions on the heterocyclic ring (quinoline or pyridine), we undertook to study their radiosynthesis according to both methods A and B. We report herein our comparative results in terms of efficiency, mildness of conditions, reliability, and automation.

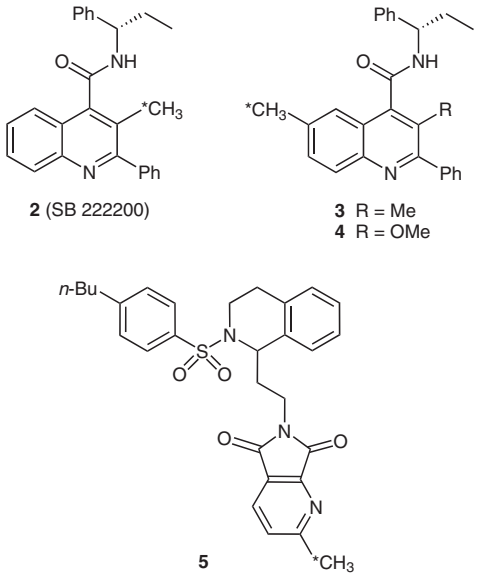
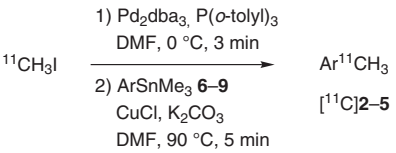


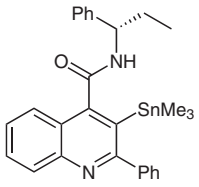
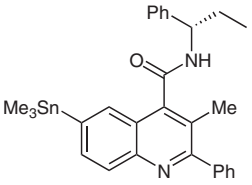
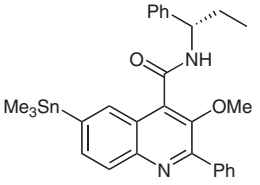
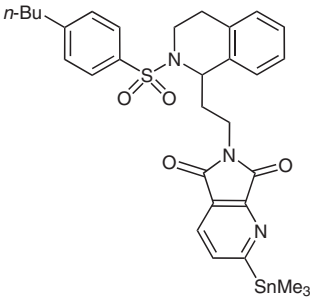

**Figure 1** Target molecules **2–5** for labeling with carbon-11 (*C = $^{12}$C or $^{11}$C)

The Stille reaction using [$^{11}$C]methyl iodide has been previously carefully examined both on model compounds and for tracer development.[9–20] From these studies, the use of tris(dibenzylideneacetone)dipalladium(0) and tri-2-tolylphosphine in *N*,*N*-dimethylformamide in the presence of potassium carbonate and copper(I) chloride, has been established as the optimized reaction conditions. We applied those conditions to the radiosynthesis of tracers [$^{11}$C]**2–5** from the corresponding aryltrimethylstannanes **6–9** (see experimental part for preparation). A five-minute cross-coupling reaction time was chosen (Scheme 2). Briefly, the procedure was as follows. [$^{11}$C]Methyl iodide, obtained by reduction of [$^{11}$C]carbon dioxide followed by reaction with hydroiodic acid, was trapped in *N*,*N*-dimethylformamide containing tris(dibenzylideneacetone)dipalladium (0) and tri-2-tolylphosphine. Then, a freshly prepared mixture of potassium carbonate, copper(I) chloride, and tin precursor in *N*,*N*-dimethylformamide was added. The reaction vial was heated at 90 °C for five minutes. Analysis of the crude products was assessed by HPLC and radioTLC by comparison with authentic stable samples as references. The [$^{11}$C]methyl incorporation rate was calculated by combining both radioTLC and HPLC. RadioTLC displayed the ratio between the tracer [$^{11}$C]**2–5** and radioactive polar species[7] due to the complexation of [$^{11}$C]methyl iodide with palladium. HPLC was used to calculate the ratio between the tracer [$^{11}$C]**2–5** and unreacted [$^{11}$C]methyl iodide.




**Scheme 2** Synthesis of radiotracers [$^{11}$C]**2–5** by Stille reaction (route A)

**Table 1** Radiochemical Yields in [$^{11}$C]**2–5** Obtained by Stille Coupling (Route A)[a]

| Entry | $ArSnMe_3$ | | $Ar^{11}CH_3$ | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **6** |  | [$^{11}$C]**2** | 53 ± 5 |
| 2 | **7** |  | [$^{11}$C]**3** | 30 ± 3 |
| 3 | **8** |  | [$^{11}$C]**4** | 60 ± 4 |
| 4 | **9** |  | [$^{11}$C]**5** | 65 ± 6 |

[a] $ArSnMe_3$ (3.75 μmol), $Pd_2dba_3$ (1.5 μmol), P(*o*-Tol)$_3$ (6 μmol), CuCl (6 μmol), $K_2CO_3$ (6 μmol).
[b] [$^{11}$C]Methyl incorporation rate decay corrected and calculated from trapped $^{11}CH_3I$ (n = 5–10).

[$^{11}$C]Methyl incorporation rates for compounds [$^{11}$C]**2**, [$^{11}$C]**4**, and [$^{11}$C]**5** ranged from 50 to 70% (Table 1, entries 1, 3, 4). The percentages of recovered [$^{11}$C]methyl iodide and labeled polar species were each ca. 15–20%. [$^{11}$C]Methylquinoline [$^{11}$C]**3** was formed in radiochemical yield that did not exceed 33% (entry 2). In this latter case, most of radioactivity was recovered as polar compounds. Due to the minor structural modifications between (trimethylstannyl)quinolines **7** and **8**, we have no explanation for this falling yield. No attempts to increase the radiochemical yield by increasing the Stille reaction temperature were undertaken.

The radiosynthesis of tracers [$^{11}$C]**2** and [$^{11}$C]**5** was carried out in production mode using an automated system including HPLC purification. Both radiotracers [$^{11}$C]**2** and [$^{11}$C]**5** were isolated within 35 minutes total synthesis time EOB (End Of Bombardment). Decay corrected radiochemical yields calculated from the amount of trapped [$^{11}$C]methyl iodide were close to the [$^{11}$C]methyl incorporation rates reported above. The radiochemical purity was greater than 95% determined by analytical HPLC.

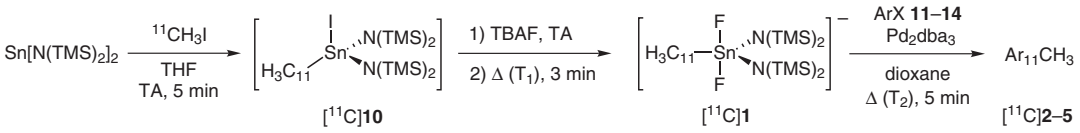
We performed the radiosynthesis of radiotracers [$^{11}$C]**2–5** via the stannate [$^{11}$C]**1** according to Scheme 3. [$^{11}$C]Methyl iodide obtained from cyclotron produced [$^{11}$C]$CO_2$, was trapped into tetrahydrofuran containing Lappert's stannylene leading immediately and quantitatively to [$^{11}$C]methyltin [$^{11}$C]**10**. Tetrabutylammonium fluoride was added at room temperature to obtain the stannate [$^{11}$C]**1**, and tetrahydrofuran was removed by heating under nitrogen. After addition of the catalyst and the electrophile **11–14** in dioxane, the mixture was heated for five minutes and the transfer reaction was quenched with water. Analysis of the crude products was assessed as above by HPLC and radioTLC. Only two radioactive products corresponding to the expected radiotracer [$^{11}$C]**2–5** and to polar tin byproduct derived from hydrolysis of unreacted stannate [$^{11}$C]**1**, were detected.

Several parameters such as a Lappert's stannylene/tetrabutylammonium fluoride ratio of 1:3, the removal of tetrahydrofuran after the formation of the [$^{11}$C]methylstannate [$^{11}$C]**1**, the use of tris(dibenzylideneacetone)dipalladium(0) under ligand-free conditions as the catalytic system, and the need for dioxane as coupling solvent, were previously identified as crucial for the radiosynthesis.[21] In a first set of experiments, the heating temperatures for tetrahydrofuran elimination ($T_1$) and [$^{11}$C]methyltransfer reaction ($T_2$) were both fixed at 120 °C as described for the synthesis of model $^{11}$C-compounds.[21] Under these conditions, the radiochemical yields of [$^{11}$C]**2–5** did not exceed 11% (Table 2, entries 1, 3, 6, 8). The [$^{11}$C]methyl incorporation rate for 6-[$^{11}$C]methylquinoline [$^{11}$C]**3** was increased to 30% by elevating temperatures $T_1$ and $T_2$ to 150 °C (entry 5). This former reached 65% by using two different temperatures, respectively 120 and 150 °C for $T_1$ and $T_2$ (entry 4). Under the same conditions, the analogue [$^{11}$C]**4** was formed in similar radiochemical yield (entry 7). These results showed that more drastic conditions were required to obtain 6-[$^{11}$C]methylquinolinecarboxamides compared to the unsubstituted 6-[$^{11}$C]methylquinoline[21] and that degradation of [$^{11}$C]methylstannate [$^{11}$C]**1** probably occurred during tetrahydrofuran evaporation at 150 °C. None of the tested conditions allowed the formation of 3-[$^{11}$C]methylquinolinecarboxamide [$^{11}$C]**2** and 2-[$^{11}$C]methylquinolinimide [$^{11}$C]**5** (entries 2, 9). Reactions being successful starting from bromoquinolines as model substrates,[18] the fact that the electrophiles were bromo compounds instead of iodo derivatives as for the radiosynthesis of quinolines [$^{11}$C]**3** and [$^{11}$C]**4**, did not seem to us relevant. We found that the bromoquinolinimide precursor **14** was not stable at temperatures higher than 100 °C. However, this was not the case for 3-bromoquinoline **11**.

The automated radiosynthesis of tracers [$^{11}$C]**3** and [$^{11}$C]**4** via the stannate [$^{11}$C]**1** was achieved within 50 minutes total synthesis time including HPLC purification. In all assays, the radiochemical yields ranged from 18 to 56% (n >10) and the radiochemical purity was greater than 99% determined by analytical HPLC.

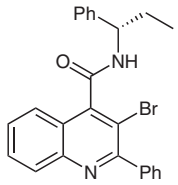
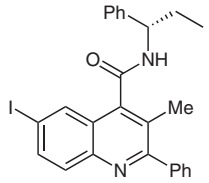
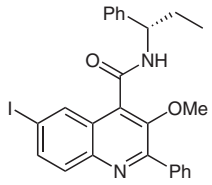
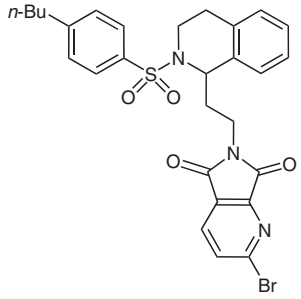
In order to investigate why the route B has failed for the radiosynthesis of 3-[$^{11}$C]methylquinolinecarboxamide [$^{11}$C]**2**, we studied the cross-coupling reaction in nonradioactive chemistry[32] using stable stannate **1** prepared from methyl iodide (Scheme 3). The formation of 3-methylquinolinecarboxamide **2** was not observed. The starting 3-bromoquinoline **11** was not recovered and the corresponding reduced quinolinecarboxamide **15** was isolated as the only identified product (50% yield). It is noteworthy that quinoline **15** was also formed in Stille reaction from 3-bromoquinoline **6** leading to SB 222200 **2**, but to a lesser extent.[28] We presumed that the oxidative addition of 3-bromoquinoline **11** to palladium occurred and that an intramolecular hydrogen transfer leading to quinoline **15** took place instead of the transmetalation step (Scheme 4). Under the same conditions, 6-iodoquinolines **12** and **13** were converted into 6-methylquinolines **3** and **4** in 65 and 60% yields respectively.

In conclusion, we explored the use of the monoorganotin derivative [$^{11}$C]**1** in the radiosynthesis of polyfunctional and heteroaromatic tracers [$^{11}$C]**2–5** as an alternative route to the classical Stille reaction. Although not applicable in all cases, this novel approach was as or more efficient as the Stille method for the radiosynthesis of the

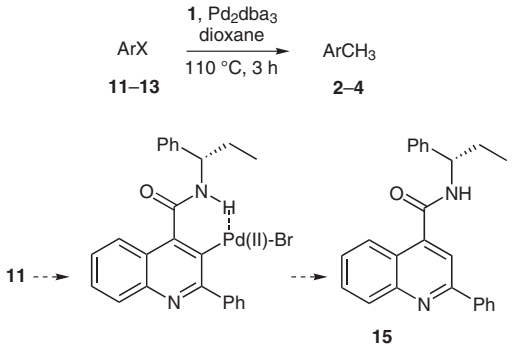



**Scheme 3** Synthesis of radiotracers [$^{11}$C]**1–4** through [$^{11}$C]monomethyltin reagent (route B)

**Table 2** Radiochemical Yields in Radiotracers [$^{11}$C]**2**–**5** (Route B)[a]

| Entry | ArX | $Ar^{11}CH_3$ | $T_1$ (°C) | $T_2$ (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **11**  | [$^{11}$C]**2** | 120 | 120 | – |
| 2 | | | 120 | 150 | – |
| 3 | **12**  | [$^{11}$C]**3** | 120 | 120 | 8 ± 4 |
| 4 | | | 120 | 150 | 59 ± 6 |
| 5 | | | 150 | 150 | 37 ± 3 |
| 6 | **13**  | [$^{11}$C]**4** | 120 | 120 | 11 ± 3 |
| 7 | | | 120 | 150 | 60 ± 5 |
| 8 | **14**  | [$^{11}$C]**5** | 120 | 120 | <3 |
| 9 | | | 120 | 150 | 10 ± 3 |

[a] ArX (15 μmol), $Sn[N(TMS)_2]_2$ (15 μmol), TBAF (45 μmol), $Pd_2dba_3$ (5 μmol).
[b] Radiochemical yield decay corrected and calculated from $^{11}CH_3I$ (n = 5–10).




**Scheme 4** Nonradioactive methyl-transfer reaction from stannate **1** to quinolines **11**–**13**

tracers [$^{11}$C]**3**,**4**. It was also advantageous from purification point of view as tracers [$^{11}$C]**3**,**4** were obtained with a higher purity than that found with the Stille reaction. All these results confirmed the potential of this method for the radiosynthesis of PET tracers.

$^1$H, $^{13}$C, and $^{119}$Sn NMR spectra were recorded on a Bruker DPX 250 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. $^{13}$C and $^{119}$Sn NMR spectra were recorded at 62.9 and 93.2 MHz, respectively, with broadband $^1$H decoupling. MS analyses and HRMS were recorded using a QTOF Micro spectrometer (Waters). IR spectra were recorded on a Perkin-Elmer spectrophotometer 16 PC-FT-IR. The melting points were obtained from a Electrothermal digital apparatus. TLC was performed on silica gel $60F_{254}$ plates and visualized by UV irradiation. Optical rotation are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. THF was dried and distilled from Na/benzophenone ketyl under $N_2$ prior to use. MeCN was dried over $CaH_2$ and distilled. DMF was dried over $CaH_2$ and distilled under vacuum prior to use (0.02 bar). All the reagents commercially available were used without further purification. Compounds **2**,[24,25] **5**,[31] **6**,[28] **11**,[28] **13**,[33] and **14**[31] were prepared according to previously described procedures.

### 6-Iodo-3-methyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]quinoline-4-carboxamide (12)

A mixture of 5-iodoisatin (1 equiv), propiophenone (1.2 equiv), and KOH pellets (85%, 3 equiv) in EtOH (5–50 mL) was refluxed for 72 h. After concentration under vacuum, the residue was dissolved in $H_2O$ and washed with $Et_2O$ (2 ×). The ice-cold aqueous layer was acidified to pH 1 with 37% HCl. The precipitate formed was filtered, washed with $H_2O$, and dried at 65 °C in an oven to give the crude 6-iodo-3-methyl-2-phenylquinoline-4-carboxylic acid hydrochloride (10 g, 85%) as a beige solid; mp 198 °C.

$^1$H NMR (DMSO-$d_6$): δ = 8.12 (d, *J* = 1.8 Hz, 1 H), 8.02 (dd, *J* = 8.8 Hz, *J* = 1.8 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.65–7.57 (m, 2 H), 7.53–7.42 (m, 3 H), 2.38 (s, 3 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 168.3, 160.8, 144.4, 139.7, 139.4, 137.8, 132.5, 131.1, 128.9, 128.5, 128.1, 125.2, 124.1, 94.0, 17.7.

EDCI (2 equiv) was added slowly at –5 °C to a mixture of $Et_3N$ (2 equiv), (*S*)-phenylpropylamine (1.1 equiv), HOBt (2 equiv), and 6-iodo-3-methyl-2-phenylquinoline-4-carboxylic acid hydrochloride (1 equiv) in THF–MeCN (7:3, 20–40 mL). The mixture was stirred at –5 °C for 1 h, then at r.t. for 18 h. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in $Et_2O$ (80 mL), and the organic phase was washed with sat. NaCl, dried ($MgSO_4$), and filtered. Purification by column chromatography (pentane–EtOAc, 85:15 containing 0.1% $Et_3N$) afforded the title quinoline **12** as a yellow solid; yield: 1.7 g (87%); mp 212–215 °C.

$[\alpha]_D$ –58.4 (*c* 0.5, MeOH).

IR (KBr): 3238, 1709, 1489, 1459, 1425, 1371, 1335, 1205, 1133, 887, 822, 759, 696 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.96–7.85 (m, 1 H), 7.79 (dd, *J* = 8.8 Hz, *J* = 1.8 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.40–7.29 (m, 10 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 5.15–5.02 (m, 1 H), 2.19 (s, 3 H), 1.87–1.79 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR ($CDCl_3$): δ = 166.6, 161.1, 145.0, 141.7, 141.5, 139.9, 137.9, 133.2, 131.0, 129.0, 128.7, 128.4, 127.7, 126.7, 125.8, 125.3, 93.2, 55.7, 28.8, 17.5, 11.2.

MS (EI$^+$): *m*/*z* (%) = 506 (M$^+$, 8), 380 (43), 246 (86), 91 (100).

**3-Methyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]-6-(trimethylstannyl)quinoline-4-carboxamide (7); Typical Procedure**

To a mixture of **12** (0.9 g, 1.77 mmol) and $(Me_3Sn)_2$ (0.83 g, 2.5 mmol) in anhyd dioxane (10 mL) was added, under $N_2$, $Pd(PPh_3)_4$ (0.150 g, 0.13 mmol). After stirring at reflux for 2 h, the mixture was cooled to r.t. and filtered through Celite. The filtrate was concentrated under reduced pressure. The oily residue was purified by chromatography (silica gel, heptane–EtOAc, 8:2) to give **7** as a white solid; yield: 0.616 g (64%); mp 159–160 °C.

$[\alpha]_D$ –18.8 (*c* 0.5, MeOH).

IR (KBr): 3230, 1630, 1537, 1494, 1444, 1344, 823, 758, 696 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 6.99–7.30 (m, 13 H), 6.07–6.16 (m, 1 H), 5.21–5.27 (m, 1 H), 2.26 (s, 3 H), 1.91–2.10 (m, 2 H), 1.02 (t, *J* = 7.3 Hz, 3 H), 0.25 (s, 9 H).

$^{13}$C NMR ($CDCl_3$): δ = 169.7, 156.8, 152.5, 147.5, 144.6, 141.8, 139.3, 134.4, 128.8, 128.2, 127.6, 126.1, 125.6, 123.5, 122.5, 121.8, 49.8, 28.1, 16.1, 11.2, –9.5.

$^{119}$Sn NMR ($CDCl_3$): δ = –23.58.

Anal. Calcd for $C_{29}H_{32}N_2OSn$: C, 64.11; H, 5.94; N, 5.16. Found: C, 64.19; H, 6.44; N, 5.25.

**3-Methoxy-2-phenyl-*N*-[(*S*)-1-phenylpropyl]-6-(trimethylstannyl)quinoline-4-carboxamide (8)**

Following the typical procedure for **7** using **13** (1.11 g, 2.12 mmol), $(Me_3Sn)_2$ (0.89 g, 2.7 mmol), anhyd dioxane (10 mL), and $Pd(PPh_3)_4$ (0.150 g, 0.13 mmol); chromatography (silica gel, heptane–EtOAc, 8:2) gave **8** as a white solid; yield: 1.0 g (84%); mp 148–150 °C.

$[\alpha]_D$ –19.4 (*c* 0.5, MeOH).

IR (KBr): 3238, 1630, 1538, 1445, 1381, 1343, 1301, 1024, 825, 759, 694 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.26–7.54 (m, 13 H), 6.26–6.34 (m, 1 H), 5.29–5.38 (q, 1 H), 3.53 (s, 3 H), 1.95–2.07 (m, 2 H), 1.09 (t, *J* = 7.4 Hz, 3 H), 0.31 (s, 9 H).

$^{13}$C NMR ($CDCl_3$): δ = 166.9, 158.2, 155.4, 147.2, 145.6, 141.7, 131.4, 130.3, 129.3, 129.2, 129.0, 128.9, 128.4, 127.8, 125.6, 123.5, 119.7, 57.2, 49.9, 28.1, 10.8, –9.6.

$^{119}$Sn NMR ($CDCl_3$): δ = –23.29.

Anal. Calc for $C_{29}H_{32}N_2O_2Sn$: C, 62.28; H, 5.77; N, 5.72. Found: C, 62.31; H, 5.46; N, 5.37.

**6-{2-[2-(4-Butylphenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl}-2-(trimethylstannyl)-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione (9)**

Following the typical procedure for **7** using chloroquinolinimide analogue precursor[31] (0.718 g, 1.33 mmol), $(Me_3Sn)_2$ (0.662 g, 2 mmol), anhyd dioxane (11 mL), and $Pd(PPh_3)_4$ (0.078 g, 0.067 mmol); chromatography (silica gel, heptane–EtOAc, 8:2) gave **9** as a white solid; yield: 0.544 g (61%); mp 86–88 °C.

IR (KBr): 1779, 1728, 1336, 1162 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.92 (d, *J* = 7.4 Hz, 1 H), 7.74 (d, *J* = 7.4 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 7.15–6.95 (m, 5 H), 6.81 (d, *J* = 7.3 Hz, 1 H), 5.10 (dd, *J* = 9.7 Hz, *J* = 5.1 Hz, 1 H), 4.05–3.85 (m, 3 H), 3.70–3.50 (m, 1 H), 2.60–2.45 (m, 4 H), 2.30–2.00 (m, 2 H), 1.48 (qt, *J* = 7.3 Hz, 2 H), 1.21 (sextet, *J* = 7.3 Hz, 2 H), 0.86 (t, *J* = 7.3 Hz, 3 H), 0.40 (s, 9 H).

$^{13}$C NMR ($CDCl_3$): δ = 182.8, 167.1, 166.8, 151.4, 148.1, 137.4, 135.5, 134.4, 132.5, 128.9, 128.7, 127.4, 127.0, 126.8, 126.7, 126.2, 125.8, 54.6, 38.8, 35.8, 35.3, 33.0, 25.8, 22.9, 13.8, –9.0.

$^{119}$Sn NMR ($CDCl_3$): δ = –35.4.

Anal. Calcd for $C_{31}H_{37}N_3O_4SSn$: C, 55.87; H, 5.60; N, 6.31. Found: C, 55.86; H, 6.04; N, 6.28.

**3,6-Dimethyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]quinoline-4-carboxamide (3); Typical Procedure**

To a mixture of iodo-bis(*N*,*N*-bistrimethylsilylamino)methyltin **10**[32] (2.22 mmol) and 1 M TBAF in THF (6.65 mL, 6.65 mmol) in dioxane (10 mL) was added, under $N_2$, a mixture of **12** (0.69 g, 1.33 mmol) and $Pd_2(dba)_3$ (101 mg, 0.11 mmol) in dioxane (5 mL). After stirring at 120 °C for 10 min, the mixture was cooled to r.t. and filtered through Celite. The filtrate was concentrated under reduced pressure. The oily residue was purified by chromatography (silica gel, pentane–EtOAc, 85:15 containing 0.1% $Et_3N$) to give **3** as a white solid; yield: 0.35 g (65%); mp 100–101 °C.

$[\alpha]_D$ –37.4 (*c* 0.5, MeOH).

IR (KBr): 3232, 1642, 1547, 1345, 1301, 762, 698 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 8.27 (d, *J* = 8.8 Hz, 1 H), 7.83–7.72 (m, 11 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 5.58–5.50 (m, 1 H), 2.74 (s, 3 H), 2.62 (s, 3 H), 2.31–2.25 (m, 2 H), 1.36 (t, *J* = 7.4 Hz, 3 H).

$^{13}$C NMR ($CDCl_3$): δ = 167.4, 159.5, 144.7, 143.3, 141.8, 137.0, 131.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.5, 126.7, 126.6, 123.1, 55.4, 28.8, 21.6, 17.3, 11.0.

MS (EI$^+$): *m*/*z* (%) = 394 (M$^+$, 47), 260 (100), 217 (41).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{27}H_{26}N_2O$: 394.2047; found: 394.2045.

**3-Methoxy-6-methyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]quinoline-4-carboxamide (4)**

Following the typical procedure for **3** using **13** (0.70 g, 1.34 mmol) and a heating time of 25 min; chromatography (silica gel, pentane–EtOAc, 85:15 containing 0.1% $Et_3N$) gave **4** as a white solid; yield: 0.33 g (60%); mp 94–95 °C.

$[\alpha]_D$ –42.6 (*c* 0.5, MeOH).

IR (KBr): 3230, 1645, 1544, 1347, 1305, 763, 697 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 8.02–7.91 (m, 1 H), 7.55–7.31 (m, 11 H), 6.89 (d, *J* = 8.6 Hz, 1 H), 5.22–5.13 (m, 1 H), 3.60 (s, 3 H), 2.38 (s, 3 H), 1.99–1.85 (m, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR ($CDCl_3$): δ = 164.9, 153.2, 147.7, 143.5, 141.8, 137.4, 137.3, 133.4, 130.7, 129.1, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1, 127.2, 126.7, 126.6, 125.1, 123.1, 61.7, 55.4, 28.8, 21.5, 10.7.

MS (EI$^+$): *m*/*z* (%) = 410 ($M^+$, 31), 276 (100).

HRMS (EI$^+$): *m*/*z* [$M^+$] calcd for $C_{27}H_{26}N_2O_2$: 410.1994; found: 410.1993.

### Radiosyntheses

[$^{11}$C]$CO_2$ production was performed using a Cyclone 18/9 IBA cyclotron at the Cyceron PET Centre. The nuclear reaction $^{14}$N (p, a) $^{11}$C was performed in a $N_2$ target gas containing 0.5% $O_2$ which was bombarded with 18 MeV protons. $^{11}CH_3I$ was produced by reduction of [$^{11}$C]$CO_2$ with 0.1 M $LiAlH_4$ in THF (200 μL) at r.t., and subsequent reaction with 57% HI in $H_2O$ (1.5 mL) at 140 °C.[4] Radioactive products [$^{11}$C]**2**–**5** were identified by comparison with nonradioactive authentic samples **2**–**5**. HPLC analyses were carried out with a Merck L-6200 pump and a Merck L-4250 variable wavelength UV-detector in series with a Novelec b$^+$-flow detector. RadioTLC analyses were performed on Merck $60F_{254}$ silica gel plates using a Packard Instant Imager. The radiochemical yields were determined from the radioTLC and HPLC chromatograms representing the percentage of radioactivity area of cross-coupling product [$^{11}$C]**2**–**5** related to the total radioactivity area.

### $^{11}$C-Stille Reaction; General Procedure

$^{11}CH_3I$ was distilled into a vial (1 mL) previously purged with $N_2$ and containing $Pd_2dba_3$ (1.38 mg, 1.51 μmol), (*o*-Tol)$_3$P (1.84 mg, 6.01 μmol), and DMF (100 μL). After stirring for 3 min, the radioactivity was counted. A freshly prepared mixture containing 3-trimethylstannyl precursor **6**–**9** (3.78 μmol), CuCl (0.60 mg, 6.06 μmol), $K_2CO_3$ (0.84 mg, 6.08 μmol), and DMF (100 μL) was added to the radioactive reaction medium. The resulting mixture was heated under stirring at 90 °C for 5 min then filtered (Rotilabo Spritzenfilter 13 mm). The radioactivity of the filtrate was measured. The filtrate was analyzed by radioTLC and HPLC.

### $^{11}$C-Methyl Transfer Reaction through Monomethyltin Reagent [$^{11}$C]1; General Procedure

$^{11}CH_3I$ was distilled under $N_2$ into a soln of Lappert's stannylene (6 mg, 15 μmol) in anhyd THF (300 μL). After addition of 1 M TBAF in THF (41 μL, 41 μmol), THF was removed by heating at 120 °C under $N_2$. A mixture of $Pd_2dba_3$ (3–5 mg, 3–5 μmol) and electrophile **11**–**14** (15–25 μmol) in dioxane (250 μL) was added onto the radioactive residue and the resulting mixture was heated at 150 °C for 5 min under vigorous stirring. The reaction was quenched with $H_2O$ (100 μL), and analyzed by radioTLC and HPLC.

### 3-[$^{11}$C]Methyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]quinoline-4-carboxamide ([$^{11}$C]2)

TLC: $R_f$ = 0.22 (EtOAc–heptanes, 30:70).

HPLC (Nucleosil 100-5 C18 column, 4 × 250 mm, 10 mm; MeOH–$H_2O$ (75:25); flow rate: 1 mL/min; detection: l = 254 nm): $t_R$ = 11.2 min.

### 3-Methyl-6-[$^{11}$C]methyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]quinoline-4-carboxamide ([$^{11}$C]3)

TLC: $R_f$ = 0.23 (EtOAc–heptanes, 30:70).

HPLC (Nucleosil 100–5 C18 column, 4 × 250 mm, 10 mm; MeOH–$H_2O$ (75:25); flow rate: 1 mL/min; detection: l = 254 nm): $t_R$ = 11.0 min.

### 3-Methoxy-6-[$^{11}$C]methyl-2-phenyl-*N*-[(*S*)-1-phenylpropyl]quinoline-4-carboxamide ([$^{11}$C]4)

TLC: $R_f$ = 0.28 (EtOAc–heptanes, 30:70).

HPLC (Nucleosil 100-5 C18 column, 4 × 250 mm, 10 mm; MeOH–$H_2O$ (75:25); flow rate: 1 mL/min; detection: l = 254 nm): $t_R$ = 10.4 min.

### 6-{2-[2-(4-Butylphenylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl}-2-[$^{11}$C]methyl-5*H*-pyrrolo[3,4-*b*]pyridine-5,7(6*H*)-dione ([$^{11}$C]5)

TLC: $R_f$ = 0.45 (EtOAc–heptanes, 50:50).

HPLC (Zorbax RX-SIL column, 2.1 × 150 mm, 5 μm; EtOAc–heptanes (30:70); flow rate: 0.5 mL/min; detection: λ = 254 nm): $t_R$ = 7.8 min.

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