

Methyl transfer reaction from monomethyltin reagent under palladium(0) catalysis: a versatile method for labelling with carbon-11†

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The ¹¹C-monomethylstannate prepared from [¹¹C]-methyl iodide and Lappert's stannylene, was subject to a palladium-mediated cross-coupling reaction with an aryl halide under ligand-free conditions, to afford easily purified ¹¹C-methyl-(hetero)arenes in high radiochemical yields.

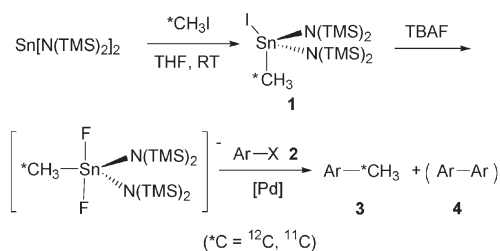
In recent years, the palladium mediated Stille reaction has proved to be an important route for the synthesis of radiotracers for Positron Emission Tomography.^{1–3} It usually involves the reaction of an aryltriorganostannane with easily synthesized [¹¹C]-methyl iodide as the electrophilic partner, leading to a ¹¹C-carbon-carbon coupled product. However, preparation of organostannane precursors is not always straightforward, and in the case of functionalized organostannanes, nucleophilic groups have to be protected in order to prevent methylation as a side-reaction.^{2,4} Moreover, the use of trimethylstannyl derivatives as substrates would result in low specific activities, due to the competitive transfer of an unlabelled methyl group.³ Finally, difficulties might be encountered in separating the tracer from triorganotin residues. For these reasons, the use of an original [¹¹C]-methyl labelled version of Vedejs' 1-aza-5-stannabicyclo[3,3,3]undecane was attempted,⁵ and the Suzuki reaction⁶ was also proposed as an alternative approach. However, no real improvement in terms of efficiency or in the scope of the reaction has been demonstrated so far.

Monoorganotins, activated by a fluoride source, have been shown to be very reactive in the Stille coupling reaction,⁷ allowing the transfer of vinyl, allyl, alkynyl, aryl, benzyl and even alkyl groups onto aryl or vinyl halides^{8,9} or triflates¹⁰ in good to excellent yields. They are far less toxic than di-, tri- and tetra-alkylstannanes¹¹ and inorganic tin by-products are easily removed.¹² Since such reagents are readily prepared from Lappert's stannylene¹³ (Sn[N(TMS)₂]₂) and an alkyl or aryl halide,^{8,9} we anticipated the possibility of synthesising the ¹¹C-monomethyltin reagent [¹¹C]-**1** from [¹¹C]-iodomethane, and

transferring the ¹¹C-methyl group onto an aromatic or heteroaromatic structure by reaction with an electrophile **2** (Scheme 1).

We first evaluated the feasibility of the cross-coupling reaction under rapid conditions⁴ using unlabelled methyl iodide. Formation of monoorganotin **1** from iodomethane and stannylene in THF according to the previously described procedure,⁹ was quantitative and immediate. After *in situ* activation with TBAF (tetrabutylammonium fluoride, 3 equiv.), the resulting hypervalent stannate reagent was engaged in a palladium-catalyzed cross-coupling reaction with an aryl halide **2** (0.6 equiv.) in refluxing dioxane. In order to minimize reaction times and optimize the reaction, the nature and the amount of the catalytic system were varied (Table 1). Results for reactions starting from 2-bromonaphthalene **2a** were found to be representative.

Initially, bis(triphenylphosphine)palladium(II) chloride (1 mol%), which was found to accelerate the transfer of *n*-alkyl groups more than tetrakis(triphenylphosphine)palladium,⁹ was used as precatalyst (entry 1). The anticipated 2-methylnaphthalene **3a** was obtained in 91% yield after 30 min. Only traces of substrate-substrate homocoupling product **4a** were detected as side-products. The catalyst was also generated *in situ* from Pd₂dba₃ (tris(dibenzilideneacetone)dipalladium, 1 mol%), used in conjunction with a ligand (4 mol%, 2 equiv. for each Pd atom). We observed that the steric and electronic properties of the ligand significantly influenced the course of the reaction. Using triphenylphosphine, the formation of the cross-coupling product **3a** was greatly reduced, whereas that of dinaphthalene **4a** was significantly enhanced (entry 2). Less donating trialkylphosphites, and especially less sterically hindered trimethylphosphite, facilitated the cross-coupling reaction, resulting in the recovery of product **3a** in high yields after a short time (entries 3 and 4). Finally, the reaction was performed under ligand-free conditions (entries 5–7). The cross-coupling reaction took place, and was strongly accelerated by increasing the amount of catalyst up to 5 mol%. Under the latter conditions, the yield of **3a** reached 90% after 5 min reaction time. The methyl transfer was found to be efficient either starting from 3-bromoquinoline **2b** (entry 10),



Scheme 1 Methyl transfer reaction from stannane **1**.

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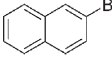
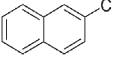
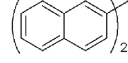
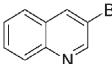
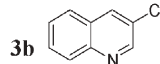
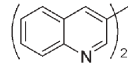
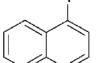
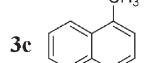
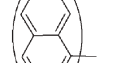
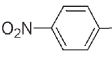
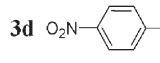
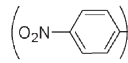
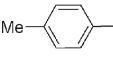
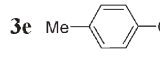
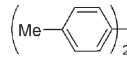
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Table 1 Palladium-mediated methyl transfer reaction between **1** and aryl halides **2**^a

Entry	Ar-X	Precatalyst/mol%	Ligand/mol%	Time/min	Ar-CH ₃	Yield ^b (%)	Ar-Ar	Yield ^c (%)
1		Pd(PPh ₃) ₂ Cl ₂ (1)	—	30		91		2
2		Pd ₂ dba ₃ (1)	PPh ₃ (4)	240		60		25
3		Pd ₂ dba ₃ (1)	P(OMe) ₃ (4)	30		91		2
4		Pd ₂ dba ₃ (1)	P(OiPr) ₃ (4)	20		54		1
5		Pd ₂ dba ₃ (1)	—	120		70		—
6		Pd ₂ dba ₃ (2)	—	90		60		30
7		Pd ₂ dba ₃ (5)	—	5		90		<1
8		Pd(PPh ₃) ₂ Cl ₂ (1)	—	15		82		<1
9		Pd ₂ dba ₃ (1)	P(OiPr) ₃ (4)	5		85		11
10		Pd ₂ dba ₃ (5)	—	2		90		<1
11		Pd ₂ dba ₃ (1)	—	120		60		—
12		Pd ₂ dba ₃ (2)	—	60		60		—
13		Pd ₂ dba ₃ (5)	—	2		100		—
14		Pd ₂ dba ₃ (1)	—	30		95		—
15		Pd ₂ dba ₃ (1)	—	5		86		—

^a **1** (1 mmol), **2** (0.6 mmol), TBAF (3 mmol). ^b Isolated yield. ^c Estimated by GC.

1-iodonaphthalene **2c** (entry 11–13), 4-bromonitrobenzene **2d** (entry 14) or 4-iodotoluene **2e** (entry 13).

Having in hand conditions allowing a few minutes' reaction time compatible with the half-life of carbon-11,⁴ studies using [¹¹C]-CH₃I were undertaken. To do so [¹¹C]-CH₃I obtained from cyclotron produced [¹¹C]-CO₂, was distilled into THF containing the stannylenes for the formation of [¹¹C]-I. TBAF was added at room temperature, and THF was removed by heating at 120 °C under nitrogen. After addition of the catalyst and the electrophile **2a,b,f-i** in dioxane, the mixture was heated at 120 °C for 5 min, then quenched with water. Analyses of the crude products were performed by radio TLC and HPLC, by comparison with authentic stable samples. Due to the small amount of [¹¹C]-CH₃I,⁴ and consequently of [¹¹C]-I, it has to be kept in mind that the coupling reactions were performed with an excess of palladium catalyst. Furthermore, the presence of remaining stannylenes associated with the large excess of the electrophile might favour the non-radioactive homocoupling reaction over the radioactive methyl transfer. Thus, the development of the cross-coupling reaction in radioactive chemistry required some adjustments and the influence of the amount of each reagent was carefully examined. The reaction using 3-bromoquinoline **2b** as substrate was taken as model (Table 2). In all cases, formation of the expected radioactive 3-methylquinoline [¹¹C]-**3b** was detected. Homocoupling product **4b** was obtained as a non-radioactive side-product which was easily separated from [¹¹C]-**3b** by preparative HPLC. Whatever the amount of stannylenes used (7–20 μmol), the trapping of [¹¹C]-CH₃I leading to [¹¹C]-**1**, was quantitative and immediate, and the radiochemical yield in

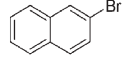
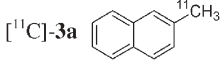
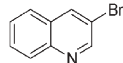
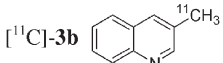
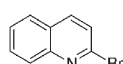
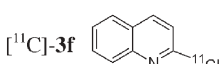
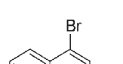
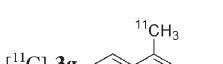


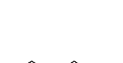

[¹¹C]-**3b** was not changed (entries 1–3). As anticipated, the amount of TBAF additive was shown to be crucial for an optimum ¹¹C-methyl transfer. The incorporation rate of carbon-11 increased from 4 to 75% by using 1 to 3 equiv. of TBAF compared to the stannylenes (entries 5, 9–10). The need for 3 equiv. of TBAF was explained as resulting from the side-reaction occurring between the stannylenes and the substrate **2b**, leading to the corresponding pentavalent tin species.⁹ The radiochemical yield of [¹¹C]-**3b** was not altered by decreasing the quantity of substrate **2b** from 110 to 37 μmol, since it was always used in excess with respect to the stannylenes (entry 2 *versus* entry 4, and entry 5 *versus* entry 11). On the other hand, the catalyst amount could not be lowered below 3 μmol, otherwise formation of [¹¹C]-**3b** was significantly reduced

Table 2 [¹¹C]-Methyl transfer from [¹¹C]-**1** onto 3-bromoquinoline **2b**

Entry	Sn[N(TMS) ₂] ₂ / μmol	TBAF/ μmol	2b /μmol	Pd ₂ dba ₃ / μmol	Time/ min	[¹¹ C]- 3b (%) ^a
1	20	60	110	5	5	74 ± 5
2	15	40	110	5	5	77 ± 7
3	7	21	110	5	5	70 ± 8
4	15	45	75	5	5	78 ± 2
5	15	45	75	3	5	75 ± 4
6	15	45	75	3	10	74 ± 6
7	15	45	75	3	15	72 ± 3
8	15	45	75	1.5	5	52 ± 23
9	15	30	75	3	5	38 ± 2
10	15	15	75	3	5	4 ± 2
11	15	45	37	3	5	75 ± 1

^a Radiochemical yield decay corrected, based on [¹¹C]-CH₃I (*n* = 2 or 3).

Table 3 Scope of the ^{11}C -methyl transfer

Entry	Ar-X	μmol	Ar- $^{11}\text{C}\text{H}_3$	RCY (%) ^a
1	2a 	50	[^{11}C]- 3a 	65 ± 12
2	2b 	75	[^{11}C]- 3b 	78 ± 2
3	2f 	50	[^{11}C]- 3f 	41 ± 3
4	2g 	50	[^{11}C]- 3g 	78 ± 5
5	2h 	75	[^{11}C]- 3h 	63 ± 14
6	2i 	75	[^{11}C]- 3i 	69 ± 2

^a Radiochemical yield decay corrected, based on [^{11}C]- CH_3I ($n = 3$).

(entries 4–5, 8). Taking into account all results we identified as optimum conditions, the use of 15 μmol of stannylene, 45 μmol of TBAF, 50–70 μmol of 3-bromoquinoline **2b**, and 5 μmol of Pd_2dba_3 . Under these conditions, a radiochemical yield of [^{11}C]-**3b** up to 78% was obtained. We noted that the cross-coupling reaction did not continue beyond 5 min (entries 5–7). In the course of further studies aiming to simplify the procedure, dioxane was found to be necessary for the coupling reaction. We observed that the yield of [^{11}C]-**3b** decreased significantly if evaporation of THF was not complete (data not presented).

The radiosynthesis was extended to 2-bromonaphthalene **2a** and quinolines **2f–i** bearing a bromine atom at different positions (Table 3). Radiochemical yields of corresponding [^{11}C]-**3** were reproducible, in the range of 63–78% except for 2-methylquinoline [^{11}C]-**3f** (around 40%, entry 3).

In summary, we have developed the palladium-catalyzed methyl transfer reaction from monomethylstannane **1** or [^{11}C]-**1** to various aryl halide **2**. The quantitative and immediate conversion of [^{11}C]-methyl iodide into methyltin reagent [^{11}C]-**1**, the efficiency of the rapid coupling reaction under ligand-free and rapid conditions, the

use of easily available electrophiles as substrates, and the ease of purification, make this methodology highly suitable for radiosynthesis of PET tracers. We are currently further investigating the scope of this methodology for the radiosynthesis of complex biologically active compounds.

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- Chemistry using carbon-11 is linked to the short half-life of the radioisotope ($t_{1/2} = 20.4$ min) and to the use of submicromolar quantities of labelled reactant. Radiosyntheses have to be carried out within a minimum of steps, and reactions have to be rapid, efficient, selective and preferably without purification in between reaction steps, while leading to high chemical and radiochemical purities, and high specific radioactivities. Radiosynthesis strategies avoiding deprotection steps are welcome. R. A. Ferrieri, G. Antoni, T. Khilberg and B. Långström, in *Handbook of Radiopharmaceuticals. Radiochemistry and Applications*, ed. M. J. Welch and C. S. Redvanly, Wiley, Chichester, 2003, pp. 229–282.
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