Rapid methylation on carbon frameworks useful for the synthesis of $^{11}CH_3$-incorporated PET tracers: Pd(0)-mediated rapid coupling of methyl iodide with an alkenyltributylstannane leading to a 1-methylalkene†‡

Takamitsu Hosoya,[a,b] Kengo Sumi,[a] Hisashi Doi,[a] Masahiro Wakao[a] and Masaaki Suzuki*[a,b]

Received 26th October 2005, Accepted 8th December 2005
First published as an Advance Article on the web 3rd January 2006
DOI: 10.1039/b515215a

The Pd(0)-mediated rapid coupling of methyl iodide with an excess of alkenyltributylstannane was examined with the aim of incorporating a short-lived ^{11}C-labeled methyl group into a biologically significant organic compound with a 1-methylalkene unit for the synthesis of a PET tracer. Four sets of reaction conditions (A–D) were used, all performed in DMF at 60 °C for 5 min. Condition B, using CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 4–6 : 2 : 5), works well in almost all cases. Condition D, using CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuX (X = Br, Cl, or I)/CsF (1 : 40 : 0.5–5 : 2–20 : 2–20 : 5–50), shows the best results with regard to general applicability to tin substrates, affording the corresponding methylated product in >90% yield based on consumption of methyl iodide. P(*t*-Bu)$_2$Me was less effective than P(*o*-tolyl)$_3$, particularly for α,β-unsaturated carbonyl substrates. No regio- or stereoisomerization occurred under these reaction conditions. The efficiency of the protocol was demonstrated by synthesis of an ^{11}C-methylated compound.

Positron emission tomography (PET) is a non-invasive *in vivo* imaging method that enables distribution analysis of a radiotracer in living systems, such as the brain, heart, and other active tissues and organs.[2] PET tracers with a short-lived positron-emitting radionuclide as a detectable indicator are utilized to monitor the biochemical processes and localization of target molecules involved in important biofunctions and related phenomena, and are useful tools for the diagnosis of disease and drug development.[2–4] Due to the high level of radioactivity and strong permeability of γ-ray photons produced through annihilation events of such short-lived radionuclides, to be safe enough for PET in humans, the dosage of the radiotracer must be extremely low (femto–attomolar level), far below its critical concentration at which pharmacological effects can arise – a concept referred to as microdosing.[3]

Among the positron-emitting radionuclides currently available, ^{11}C is one of the most practical in terms of radioactivity,[4] (half-life, $t_{1/2}$ = 20.3 min), and, most importantly, it can potentially replace carbon atoms in all organic compounds. In addition, various synthetically well-established precursors, such as $^{11}CH_3I$, ^{11}CO, and $^{11}CO_2$, are readily available.[5] In contrast to these advantages, there is a temporal restriction in the preparation of PET tracers incorporating ^{11}C,[5c] as the total time allowed for synthesis of a PET tracer should generally be set within two to three radionuclide half-lives. This means that the complete preparation of a ^{11}C-labeled tracer must be accomplished within 40 to 60 min. Considering the time for reaction, purification, and injection, the time allowed for the reaction in tracer synthesis is only about 5 to 10 min, and thus the development of a rapid reaction is crucial. To meet this necessity, we have already established the rapid Stille-type cross-coupling[6] of methyl iodide with excess amounts of aryl- or alkynyltributylstannanes.[1a–f] These Pd(0)-mediated reactions, between sp^3 and sp^2 or sp-hybridized carbons, respectively, at the reaction centers, proceed efficiently within 5 min (60 °C in DMF) to give the corresponding methylated compounds in high yields.[1g–k] The use of an organostannane[7] as a precursor is favorable because of (1) its high tolerance to various chemical reaction and chromatographic purification conditions, which enables the incorporation of a radioisotope in the final step, and (2) its extremely low polarity, which enables easy separation of the desired product from the large amount of unreacted stannane. Indeed, the sp^3–sp^2(aryl) coupling reaction was applied successfully to the synthesis of 15*R*-[^{11}C]TIC methyl ester,[1b,c,f,8] an efficient prostaglandin probe, and we achieved imaging of a novel prostacyclin receptor (IP$_2$)[8b,d] expressed in the central nervous system in living monkey and human brains by intravenous injection.[1b,f,8e]

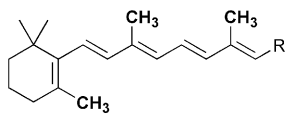
Some notable benefits of PET tracer synthesis using such simple ^{11}C-methylation on carbon frameworks are as follows: (1) the methyl group, being nonpolar and the least bulky group, has little effect on the biological activity of the parent compound; (2) its half-life (20.3 min) is short, making many basic research experiments or clinical trials possible per day without any special precautions, including treatment of radiolabeled byproducts after the synthesis reaction; and (3) the tolerance of C–CH_3 derivatives to metabolic processes is high compared with O–CH_3 and N–CH_3 derivatives. Taking these advantages into consideration, we focused on expanding the utility of the rapid methylation to a wider range of substrates. Here, we have investigated the rapid sp^3–sp^2(alkenyl) coupling for the synthesis of new PET tracers with a 1-methylalkene structure, which is observed frequently in various biologically significant compounds, exemplified by the retinoids

[a]*Division of Regeneration and Advanced Medical Science, Gifu University Graduate School of Medicine, Yanagido 1-1, Gifu, 501-1194, Japan. E-mail: suzukims@biomol.gifu-u.ac.jp*
[b]*Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu, 501-1193, Japan*

† Electronic supplementary information (ESI) available: General experimental remarks and synthetic methods, and characterization of alkenyltributylstannanes and the corresponding 1-methylalkenes. See DOI: 10.1039/b515215a

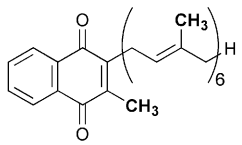
‡ Rapid methylation on carbon frameworks for PET tracer synthesis: Part 7. For Parts 1–6, see ref. 1*a–f*.

(**1a–c**), vitamin K_2 (**2**), squalene (**3**), and other isoprenoids, and have succeeded in developing a novel general protocol applicable to a wide variety of alkenyltributylstannanes.

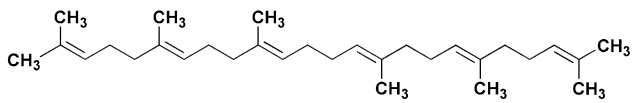


retinoids

R = CH_2OH: all-*trans*-retinol (**1a**, vitamin A)
R = CHO: all-*trans*-retinal (**1b**)
R = COOH: all-*trans*-retinoic acid (**1c**)



vitamin K_2 (**2**)



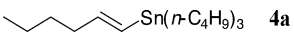
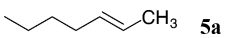
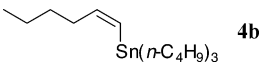
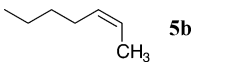
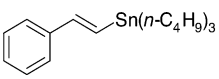
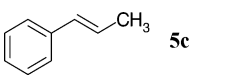
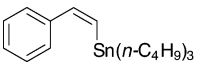
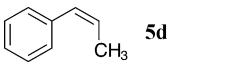
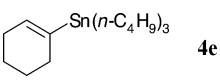
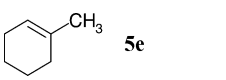
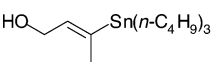
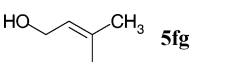
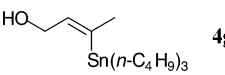
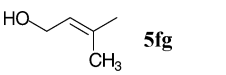
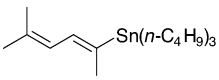
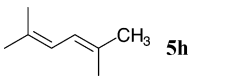
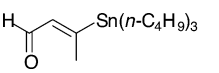
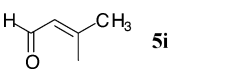
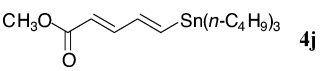
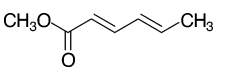
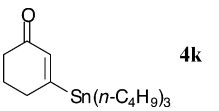
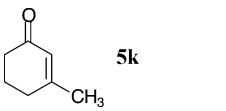
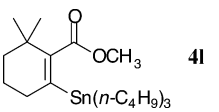
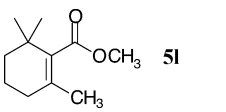
squalene (**3**)

We chose 12 non-functional and functional 1-alkenyltributylstannanes, **4a–l**. With a practical PET tracer synthesis in mind, we used a 1 : 40 ratio[9] of methyl iodide to tin substrate for rapid methylation (Table 1). First, we examined the conditions reported previously by Fu and co-workers for sp^3–sp^2(vinyl) coupling.[10a,b] However, the methylation of **4a** and **4e** based on CH_3I/**4a** or **4e**/[(π-allyl)PdCl]$_2$/P(*t*-Bu)$_2$Me/Me_4NF (molar ratio 1 : 40 : 0.5 : 3 : 1.9) system in the presence of 3 Å molecular sieves in THF for 5 min at 60 °C gave the desired products **5a** and **5e** in yields of only 5 and 2% (GLC), respectively, based on the consumption of CH_3I. The reaction using $Pd_2(dba)_3$/P(*t*-Bu)$_2$Me as the Pd(0) source with CH_3I/**4a** or **4e**/$Pd_2(dba)_3$/P(*t*-Bu)$_2$Me/Me_4NF (1 : 40 : 0.5 : 3 : 1.9) in THF for 5 min at 60 °C also gave the desired products **5a** and **5e**, in only 23 and 7%, respectively. Changing the solvent to DMF slightly improved the yields, but the extent of improvement was unsatisfactory (51 and 12%, respectively). Therefore, we applied our conditions established previously for sp^3–sp^2(aryl) coupling to the vinyl system.[1a] Thus, the mixture CH_3I/**4a**/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 2 : 2 : 2) in DMF was heated at 60 °C for 5 min (Table 1, entry 1, condition **A**), giving the methylated product (*E*)-2-heptene (**5a**) as a single product in 95% yield. Likewise, the reaction of *Z*-isomer **4b** gave (*Z*)-2-heptene (**5b**) in 96% yield (entry 2). Thus, methylation proceeded with complete stereocontrol. Further, we checked the reactions for 10 additional 1-alkenyltributylstannanes, **4c–l**, to confirm the generality of condition **A**. The reaction of the tin substrate with a β-styryl structure or a substituent at the α-position tended to lower the reaction yield to 70% (entries 3–6, 8, and 12). The use of Cs_2CO_3 instead of K_2CO_3 in condition **A** was effective in improving the yields of some of these substrates with conjugated alkenes, such as **4h**, **4k**, and **4l**, giving the products in yields of >95% (entries 8, 11, and 12). However, methylation of β-tributylstannylstyrenes and α-substituted non-conjugated alkenylstannanes **4c–g** was still unsatisfactory, affording the products in yields of 71–82% (entries 3–7). In these cases, increasing the quantity of added P(*o*-tolyl)$_3$ up to 4–6 equiv. under condition **A** markedly improved the yield of the reaction product of **4e** in the presence of CuCl or CuBr but not CuI, giving **5e** in a yield of 96–98% (Table 2).[11] The results using CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 4–6 : 2 : 5) (condition **B**) are summarized in Table 1. These conditions were found to improve the reactions of **4c–h** (entries 3–8) markedly, with the exception of **4l** (entry 12). Therefore, the nature and quantity of the sterically congested triaryl phosphine are important for facilitating the cross-coupling reaction.

We reviewed the reaction conditions that have been used for standard sp^2–sp^2 coupling, and our observations indicated that combined use of a Cu(I)X salt, CsF, and phosphines works very efficiently, as shown in Table 3. The Cu(I)/F^- system was first reported by Baldwin *et al.* to enhance the Stille cross-coupling of the sp^2–sp^2 substrate combination.[12] However, their original conditions, ($Pd(PPh_3)_4$/CuI/CsF, or $PdCl_2$/P(*t*-Bu)$_3$/CuI/CsF, were insufficient for our purposes – the methylation of **4e** using CH_3I/stannane/$Pd(PPh_3)_4$/CuI/CsF (1 : 40 : 1 : 2 : 2) and CH_3I/stannane/$PdCl_2$/P(*t*-Bu)$_3$/CuI/CsF (1 : 40 : 1 : 2 : 2 : 2) in DMF for 5 min at 60 °C gave **5e** in yields of only 24 and 2%, respectively. Likewise, reaction using CH_3I/stannane/$Pd_2(dba)_3$/PPh_3/CuI/CsF (1 : 40 : 0.5 : 4 : 2 : 5) and CH_3I/stannane/$Pd_2(dba)_3$/P(*t*-Bu)$_3$/CuI/CsF (1 : 40 : 0.5 : 2 : 2 : 5) in DMF for 5 min at 60 °C also gave **5e** in yields of only 31 and 27%, respectively. However, during the course of the study, we found that use of the bulky phosphines P(*t*-Bu)$_2$Me or P(*o*-tolyl)$_3$, instead of P(*t*-Bu)$_3$, strongly promoted the reaction. The details are summarized in Table 3. The conditions consisting of P(*t*-Bu)$_2$Me, CuBr, and CsF in 2 equiv. each with respect to methyl iodide (Table 3, entry 1, 5th column; condition **C** of Table 1) seemed the best in terms of the minimum use of the phosphine and fluoride ions, affording the desired product **5e** in 99% yield, but the reaction was very sensitive to the quantity of the phosphine; using 2 to 4 equiv. gave the coupling product in only 36% yield. This limitation was overcome by changing the copper(I) salt from CuBr to CuCl or CuI in addition to increasing the quantity of fluoride ions. Thus, the reaction using P(*t*-Bu)$_2$Me/CuCl or CuI/CsF (2 or 4 : 2 : 5) gave the coupling product in 99% yield (Table 3, entries 1 and 2, 3rd and 9th columns; modified condition **C** of Table 1). The use of P(*o*-tolyl)$_3$ proved to be another good choice to promote the coupling reaction efficiently. Thus, the process using P(*o*-tolyl)$_3$ (2 equiv.), CuBr (2 equiv.), and CsF (5 equiv.) afforded **5e** in 99% yield (Table 3, entry 3, 6th column; condition **D** in Table 1).[13] Further, the increase in the quantity of this bulky phosphine (4 equiv.) promoted the reaction almost perfectly (Table 3, entry 4, 3rd, 6th and 9th columns; modified condition **D** in Table 1).

Considering these results in Table 3, conditions **C** and **D** including their slight modifications, namely CH_3I/stannane/$Pd_2(dba)_3$/P(*t*-Bu)Me/CuX/CsF (1 : 40 : 0.5 : 2–4 : 2 : 2–5) and CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuX/CsF (1 : 40 : 0.5 : 2–4 : 2 : 5), respectively, were applied to the other tin compounds, **4a–d,f–l** (Table 1). Condition **D** and its modification based on the quantity of P(*o*-tolyl)$_3$ worked well for all entries, giving the coupling products in >90% yields, but condition **C** was poorer than **D** for entries 9 and 12. This difference is presumably due to the higher nucleophilic character of trialkylphosphines compared with triarylphosphines,[14] which tends to undergo 1,4-conjugate addition to α,β-unsaturated carbonyl groups.[15] This unfavorable side effect was enhanced with the increase in quantity of the phosphine ligand (Table 1, modification of condition **C**, entries 9 and 12), the effects of which are in marked contrast to the reactions using P(*o*-tolyl)$_3$, which favor larger amounts of the phosphine ligand (Table 1, modification of condition **D**, entries 9 and 12). From a practical viewpoint, the use of P(*o*-tolyl)$_3$ is also more convenient than P(*t*-Bu)$_2$Me, because the former is a crystalline

Table 1 Rapid trapping of methyl iodide with 1-alkenyltributylstannanes

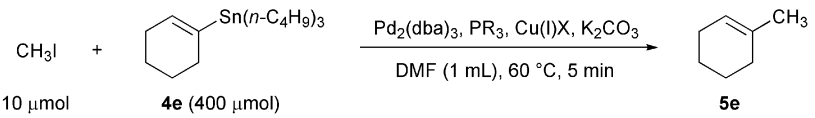
Entry	1-Alkenyltributylstannane[a]	Methylated product	Yield of **5** (%)[b] Conditions[c] **A**	**B**	**C**	**D**
1	 **4a**	 **5a**	95	98	99	98
2	 **4b**	 **5b**	96	99	99	99
3	 **4c**	 **5c**	70	89 (88[e])	90	83 (87,[g] 88,[h] 91[i])
4	 **4d**	 **5d**	77	89 (89[e])	87(90[f])	84 (90,[g] 89,[h] 95[i])
5	 **4e**	 **5e**	71	96	99	99 (99,[j] 99[k])
6	 **4f**	 **5fg**	71	91	98	99
7	 **4g**	 **5fg**	84	99	99	99
8	 **4h**	 **5h**	77 (95[d])	88 (93[e])	95	89 (91[h])
9	 **4i**	 **5i**	96	99	83 (80[f])	85 (96[h])
10	 **4j**	 **5j**	94	95	99	86 (93[h])
11	 **4k**	 **5k**	91 (96[d])	90	86 (90[f])	95
12	 **4l**	 **5l**	71 (98[d])	71 (72[e])	54 (41[f])	84 (91[h])

[a] Stereoisomerically pure (>99 : 1) as judged from ^{1}H-NMR spectra. [b] The products were detected by GLC analysis (as single products) by comparison with authentic samples. Yields were determined by GLC analysis based on CH_3I consumption using *n*-nonane, *n*-heptane, or *n*-decane as an internal standard, and are an average of 2 or 3 runs. [c] All reactions performed in DMF at 60 °C for 5 min. *Reaction conditions* (molar ratio): **A**: CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 2 : 2 : 2); **B**: CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 4 : 2 : 5); **C**: CH_3I/stannane/$Pd_2(dba)_3$/P(*t*-Bu)$_2$Me/CuBr/CsF (1 : 40 : 0.5 : 2 : 2 : 2); **D**: CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuBr/CsF (1 : 40 : 0.5 : 2 : 2 : 5). [d] Cs_2CO_3 was used instead of K_2CO_3. [e] CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 6 : 2 : 5). [f] CH_3I/stannane/$Pd_2(dba)_3$/P(*t*-Bu)$_2$Me/CuCl/CsF (1 : 40 : 0.5 : 4 : 2 : 5). [g] CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/CsF (1 : 40 : 0.5 : 4 : 2 : 5). [h] CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuBr/CsF (1 : 40 : 0.5 : 4 : 2 : 5). [i] CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuI/CsF (1 : 40 : 0.5 : 4 : 2 : 5). [j] CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuBr/CsF (1 : 40 : 2.5 : 10 : 10 : 25). [k] CH_3I/stannane/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuBr/CsF (1 : 40 : 5 : 20 : 20 : 50).

compound that is stable in air, while the latter is an air-sensitive oily material, which necessitates handling in a glove-box under an inert gas. Thus, considering the wide range of applicable tin substrates and the ease of use of triarylphosphines, condition **D** should be better than **C** for actual PET tracer synthesis.

The use of a coordinatively unsaturated Pd(0) complex, such as Pd[P(*o*-tolyl)$_3$]$_2$,[16] and therefore the use of sterically bulky phosphines (*e.g.*, cone angle 194° (P(*o*-tolyl)$_3$) *vs.* 145° (PPh_3)),[17] seems to be important to enhance the sp^3–sp^2(alkenyl) coupling efficiency under any of the conditions, similar to the case of sp^3–sp^2(phenyl) coupling.[1a,c] The trialkylphosphines P(*t*-Bu)$_2$Me and P(*t*-Bu)$_3$ have markedly higher σ-electron-donating ability than aryl-substituted phosphines (*e.g.*, pK_a 11.4 (P(*t*-Bu)$_3$) *vs.* 3.1 (P(*o*-tolyl)$_3$, 2.7 (PPh_3)).[14] In these trialkylphosphines, the

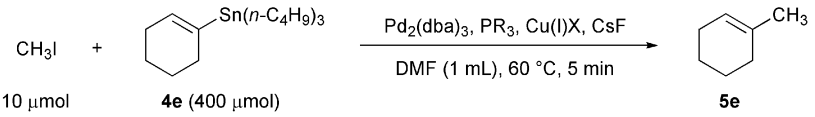
Table 2 Rapid trapping of methyl iodide with tributyl(cyclohexen-1-yl)stannane (**4e**) to give **5e**, using K_2CO_3 [a]



		Additives (equiv.)								
		CuCl (2) + K_2CO_3 (y)			CuBr (2) + K_2CO_3 (y)			CuI (2) + K_2CO_3 (y)		
Entry	Phosphine (x equiv.)	$y = 0$	$y = 2$	$y = 5$	$y = 0$	$y = 2$	$y = 5$	$y = 0$	$y = 2$	$y = 5$
1	P(*o*-tolyl)$_3$ ($x = 2$)	—	71	84	—	56	82	—	21	51
2	P(*o*-tolyl)$_3$ ($x = 4$)	—	76	96	—	59	96	—	23	50
3	P(*o*-tolyl)$_3$ ($x = 6$)	—	79	98	—	61	98	—	27	63

[a] Yields (%) of **5e** determined by GLC analysis based on CH_3I consumption using *n*-nonane as an internal standard. Data are the averages of two runs. *Reaction conditions*: CH_3I/**4e**/$Pd_2(dba)_3$/PR_3/CuX/K_2CO_3 (molar ratio, 1 : 40 : 0.5 : x : 2 : y) in DMF, 60 °C, 5 min.

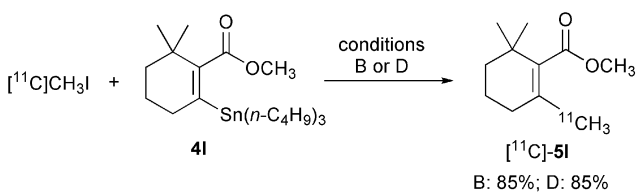
Table 3 Rapid trapping of methyl iodide with tributyl(cyclohexen-1-yl)stannane (**4e**) to give **5e**, using CsF [a]



		Additives (equiv.)								
		CuCl (2) + CsF (y)			CuBr (2) + CsF (y)			CuI (2) + CsF (y)		
Entry	Phosphine (x equiv.)	$y = 0$	$y = 2$	$y = 5$	$y = 0$	$y = 2$	$y = 5$	$y = 0$	$y = 2$	$y = 5$
1	P(*t*-Bu)$_2$Me ($x = 2$)	—	43[b]	99	40[b]	99	99	—	27[b]	99
2	P(*t*-Bu)$_2$Me ($x = 4$)	—	—	99	—	36	33	—	—	99
3	P(*o*-tolyl)$_3$ ($x = 2$)	—	—	96	31[b]	66[b]	99	—	—	38[b]
4	P(*o*-tolyl)$_3$ ($x = 4$)	47[b]	86[b]	99	—	—	99	18[b]	59[b]	99

[a] Yields (%) of **5e** determined by GLC analysis based on CH_3I consumption using *n*-nonane as an internal standard. Data are the averages of two runs unless otherwise noted. *Reaction conditions*: CH_3I/**4e**/$Pd_2(dba)_3$/PR_3/CuX/CsF (molar ratio, 1 : 40 : 0.5 : x : 2 : y) in DMF, 60 °C, 5 min. [b] Data from a single run.

property of an alkyl ligand on the phosphine atom influences the coupling efficiency to a great extent, as indicated by the large difference between the rapid methylation of alkynylstannanes (sp^3–sp coupling)[1e] and the rapid sp^3–sp^2(alkenyl) coupling in this study. However, the role of an alkyl substituent for such marked discrimination remains unclear. The high efficiency of the combined use of Cu(I)X and CsF is considered to be due to the synergic effect of the generation of a more reactive organocopper species through Sn/Cu transmetallation[18,19] and the removal of (n-Bu)$_3$SnX (X = Cl, Br, or I) by the formation of insoluble (n-Bu)$_3$SnF to shift the equilibrium to the alkenylcopper.[12] In a similar manner, the efficiency of the combination of Cu(I)X and K_2CO_3, as employed in conditions **A** or **B** in Table 1, could be explained by another synergic effect of Sn/Cu transmetallation and formation of the stable bis(tributylstannyl)carbonate, [(n-Bu)$_3$SnO]$_2$C=O.[20] Thus, the synergic effect concept[12] and the introduction of a bulky triarylphosphine allowed realization of an efficient general protocol for rapid sp^3–sp^2(alkenyl) Stille coupling reaction potentially useful for PET tracer synthesis. We also investigated the reactions using excess Pd/Cu/F additives for methyl iodide (5- and 10-fold), CH_3I/**4e**/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuBr/CsF (1 : 40 : 2.5 : 10 : 10 : 25 and 1 : 40 : 5 : 20 : 20 : 50), giving **5e** in the same 99% yield (Table 1, modified condition **D**, entry 5). Thus, the reaction is not influenced by the increase in Pd/Cu/F additives with respect to methyl iodide, promising that the combined Pd/Cu/F system would be applicable to actual PET studies.[9] From our experience of PET studies, heating the mixture of methyl iodide/stannane/Pd(0)/CuX/F^- under continuous operations with (1) prior mixing of [^{11}C]methyl iodide and Pd(0), and then (2) mixing the resulting solution with a stannane, copper(I) salt, and fluoride salt, was expected to be better in terms of high reproducibility.[1c,f] Using this method, the reaction of **4e** using CH_3I/$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1 : 2.5 : 10) and **4e**/CuBr/CsF (40 : 10 : 25), gave **5e** in 99% yield. Accordingly, the actual synthesis of the PET tracer was conducted under conditions **B** and **D** with continuous stepwise mixing using [^{11}C]CH_3I and the stannane **4l** to give [^{11}C]-**5l** in a high radiochemical yield of 85% (HPLC analytical yield) for both conditions (Scheme 1).[21]



Scheme 1 Synthesis of [^{11}C]-**5l**.

In summary, we have developed an efficient protocol for the rapid trapping of methyl iodide with an excess of an alkenyltributylstannane, by rapid sp^3–sp^2(alkenyl) coupling.[22] This method provides a firm chemical basis for the synthesis of short-lived $^{11}CH_3$-labeled PET tracers with a 1-methylalkene unit. Retinoids (**1**) and their artificial derivatives are involved in important biological signal pathways as agonists targeting nuclear RAR/RXR receptors[23] and the prototypical G protein-coupled receptor, rhodopsin.[24] Squalene (**3**), a triterpenoid containing six isoprene units, is a major metabolite derived from mevalonic acid and is a key intermediate in the production of important bioactive steroids. PET studies using the corresponding ^{11}C-labeled tracers would contribute to the possibility of *in vivo* biomolecular studies. The synthesis of the above-mentioned PET tracers and their use in molecular imaging will be reported in due course.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Creative Scientific Research (No. 13NP0401) of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan. M.W. thanks JSPS. Incorporation of ^{11}C was performed in a PET laboratory at Hamamatsu photonics K.K.

Notes and references

1 (*a*) M. Suzuki, H. Doi, M. Björkman, Y. Andersson, B. Långström, Y. Watanabe and R. Noyori, *Chem.–Eur. J.*, 1997, **3**, 2039–2042; (*b*) M. Suzuki, R. Noyori, B. Långström and Y. Watanabe, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 1053–1070; (*c*) M. Suzuki, H. Doi, K. Kato, M. Björkman, B. Långström, Y. Watanabe and R. Noyori, *Tetrahedron*, 2000, **56**, 8263–8273; (*d*) M. Björkman, H. Doi, B. Resul, M. Suzuki, R. Noyori, Y. Watanabe and B. Långström, *J. Labelled Compd. Radiopharm.*, 2000, **43**, 1327–1334; (*e*) T. Hosoya, M. Wakao, Y. Kondo, H. Doi and M. Suzuki, *Org. Biomol. Chem.*, 2004, **2**, 24–27; (*f*) M. Suzuki, H. Doi, T. Hosoya, B. Långström and Y. Watanabe, *Trends Anal. Chem.*, 2004, **23**, 595–607. See also the applications by other groups based on our method: [*p*-^{11}C-methyl]MADAM: (*g*) J. Tarkiainen, J. Vercouillie, P. Emond, J. Sandell, J. Hiltunen, Y. Frangin, D. Guilloteau and C. Halldin, *J. Labelled Compd. Radiopharm.*, 2001, **44**, 1013–1023; [^{11}C]toluene: (*h*) M. Gerasimov, J. Logan, R. A. Ferrieri, R. D. Muller, D. Alexoff and S. L. Dewey, *Nucl. Med. Biol.*, 2002, **29**, 607–612, and references therein; 5-[^{11}C]methyl-6-nitroquipazine: (*i*) J. Sandell, M. Yu, P. Emond, L. Garreau, S. Chalon, K. Någren, D. Guilloteau and C. Halldin, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3611–3613, and references therein (*j*) J. Madsen, P. Merachtsaki, P. Davoodpour, M. Bergström, B. Långström, K. Andersen, C. Thomsen, L. Martiny and G. M. Knudsen, *Bioorg. Med. Chem.*, 2003, **11**, 3447–3456; 5-^{11}C-methyl-A-85380: (*k*) Y. Iida, M. Ogawa, M. Ueda, A. Tominaga, H. Kawashima, Y. Magata, S. Nishiyama, H. Tsukada, T. Mukai and H. Saji, *J. Nucl. Med.*, 2004, **45**, 878–884; (3-ethyl-2-[^{11}C]methyl-6-quinolinyl)(*cis*-4-methoxycyclohexyl)methanone: (*l*) Y. Huang, R. Narendran, F. Bischoff, N. Guo, Z. Zhu, S.-A. Bae, A. S. Lesage and M. Laruelle, *J. Med. Chem.*, 2005, **48**, 5096–5099.

2 (*a*) J. S. Fowler, A. P. Wolf, J. R. Barrio, J. C. Mazziotta and M. E. Phelps, in: *Positron Emission Tomography and Autoradiography*, ed. M. E. Phelps, J. C. Mazziotta and H. R. Schelbert, Raven Press, New York, 1986, ch. 9–11; (*b*) B. Långström and R. F. Dannals, in: *Principles of Nuclear Medicine* (2nd edn), ed. H. N. Wagner, Z. Szabo and J. W. Buchanan, W. B. Saunders Publishing, Philadelphia, 1995, sect. 1, ch. 11; (*c*) J. S. Fowler and A. P. Wolf, *Acc. Chem. Res.*, 1997, **30**, 181–188.

3 (*a*) M. Bergström, A. Grahnén and B. Långström, *Eur. J. Clin. Pharmacol.*, 2003, **59**, 357–366; (*b*) G. Lappin and R. C. Garner, *Nat. Rev. Drug Discovery*, 2003, **2**, 233–240.

4 C. M. L. West, T. Jones and P. Price, *Nat. Rev. Cancer*, 2004, **4**, 457–469.

5 (*a*) R. A. Ferrieri and A. P. Wolf, *Radiochim. Acta*, 1983, **34**, 69–83; (*b*) B. Långström, G. Antoni, P. Gullberg, C. Halldin, P. Malmborg, K. Någren, A. Rimland and H. Svärd, *J. Nucl. Med.*, 1987, **28**, 1037–1040; (*c*) G. Antoni, T. Kihlberg and B. Långström, in: *Handbook of Radiopharmaceuticals*, ed. M. J. Welch and C. S. Redvanly, Wiley, West Sussex, 2003, pp. 141–194.

6 (*a*) J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508–524; (*b*) V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React.*, 1997, **50**, 1–657; (*c*) P. Espinet and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 4704–4734.

7 For reviews on organostannanes, see: A. G. Davies, *Organotin Chemistry* (2nd edn), Wiley-VCH, Weinheim, 2004.

8 (*a*) M. Suzuki, K. Kato, R. Noyori, Yu. Watanabe, H. Takechi, K. Matsumura, B. Långström and Y. Watanabe, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 334–336; (*b*) H. Takechi, K. Matsumura, Yu. Watanabe, K. Kato, R. Noyori, M. Suzuki and Y. Watanabe, *J. Biol. Chem.*, 1996, **271**, 5901–5906; (*c*) M. Björkman, Y. Andersson, H. Doi, K. Kato, M. Suzuki, R. Noyori, Y. Watanabe and B. Långström, *Acta Chem. Scand.*, 1998, **52**, 635–640; (*d*) Yu. Watanabe, K. Matsumura, H. Takechi, K. Kato, H. Morii, M. Björkman, B. Långström, R. Noyori, M. Suzuki and Y. Watanabe, *J. Neurochem.*, 1999, **72**, 2583–2592; (*e*) R. Noyori, *Angew. Chem., Int. Ed.*, 2002, **41**, 2008–2022.

9 The synthesis of PET tracers is rather different from standard organic syntheses. The reaction involves the trapping of an extremely small amount of $^{11}CH_3I$ (approximately 100 nmol level containing $^{12}CH_3I$) with a large amount (mg) of reacting substrate. Therefore, we set up the reaction using an excess of alkenylstannane, with respect to methyl iodide.

10 (*a*) K. Menzel and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 3718–3719; (*b*) H. Tang, K. Menzel and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 5079–5082.

11 The increased amount of P(*o*-tolyl)$_3$ was not effective when Cs_2CO_3 was used instead of K_2CO_3, as confirmed using **4e**.

12 S. P. H. Mee, V. Lee and J. E. Baldwin, *Angew. Chem., Int. Ed.*, 2004, **43**, 1132–1136.

13 Typical procedure (Table 1, entry 5, condition **D**): In a dry Schlenk tube (10 mL), $Pd_2(dba)_3$ (4.6 mg, 5.0 μmol), P(*o*-tolyl)$_3$ (6.1 mg, 20 μmol), CuBr (2.9 mg, 20 μmol), and CsF (7.6 mg, 50 μmol) were placed under Ar. After addition of DMF (500 μL), the mixture was stirred for 5 min at room temperature followed by successive additions of solutions of stannane **4e** (148 mg, 400 μmol) in DMF (500 μL) and methyl iodide (12.5 μL, 0.80 M DMF solution, 10 μmol). After stirring at 60 °C for 5 min, the mixture was cooled rapidly in an ice bath. After addition of diethyl ether (1 mL), the mixture was loaded onto a short column of silica gel (0.5 g) and then eluted with diethyl ether (*ca.* 1 mL), followed by addition of *n*-nonane (50 μL, 0.10 M DMF solution, 5.0 μmol) as an internal standard. The resulting solution was analyzed by GLC (Shimadzu GC-2010 instrument equipped with a flame ionization detector; capillary column: GL Science TC-1701, 60 m × 0.25 mm i.d., film thickness of stationary phase = df = 0.25 μm; carrier gas: He; flow rate: 0.4 mL min^{-1}; injector temperature: 280 °C; detector temperature: 280 °C; column temperature: initial 80 °C, final 100 °C; temperature gradient: +5 °C min^{-1}, from 10 to 14 min); yield of 1-methylcyclohexene (**5e**): 99% based on starting CH_3I; retention time: 12.2 min (*cf. n*-nonane: 16.1 min).

14 T. Allman and R. G. Goel, *Can. J. Chem.*, 1982, **60**, 716–722.

15 (*a*) D. A. White and M. M. Baizer, *Tetrahedron Lett.*, 1973, 3597–3600; (*b*) E. Gómez-Bengoa, J. M. Cuerva, C. Mateo and A. M. Echavarren, *J. Am. Chem. Soc.*, 1996, **118**, 8553–8565; (*c*) D. H. Valentine, Jr. and J. H. Hillhouse, *Synthesis*, 2003, 317–334; (*d*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811–891.

16 (*a*) S. Enomoto, H. Wada, S. Nishida, Y. Mukaida, M. Yanaka, H. Takita, *Jpn. Kokai Tokkyo Koho*, JP 53144552, 1978; (*b*) F. Paul, J. Patt and J. F. Hartwig, *J. Am. Chem. Soc.*, 1994, **116**, 5969–5970; (*c*) F. Paul, J. Patt and J. F. Hartwig, *Organometallics*, 1995, **14**, 3030–3039.

17 C. A. Tolman, *Chem. Rev.*, 1977, **77**, 313–348.

18 (*a*) V. Farina, S. Kapadia, B. Krishnan, C. Wang and L. S. Liebeskind, *J. Org. Chem.*, 1994, **59**, 5905–5911; (*b*) X. Han, B. M. Stoltz and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 7600–7605; (*c*) A. L. Casado and P. Espinet, *Organometallics*, 2003, **22**, 1305–1309.

19 A. García Martínez, J. Osío Barcina, M. R. Colorado Heras and Á. De Frensno Cerezo, *Organometallics*, 2001, **20**, 1020–1023.

20 (*a*) R. E. Maleczka, Jr., W. P. Gallagher and I. Terstiege, *J. Am. Chem. Soc.*, 2000, **122**, 384–385; (*b*) W. P. Gallagher, I. Terstiege and R. E. Maleczka, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 3194–3204.

21 PET tracer synthesis (Table 1, entry 12, condition **D**): [^{11}C]Methyl iodide was prepared from [^{11}C]CO_2 by reduction with $LiAlH_4$, followed

by HI treatment according to the established method. [^{11}C]Methyl iodide was trapped in a solution of $Pd_2(dba)_3$ (1.8 mg, 1.9 μmol) and P(*o*-tolyl)$_3$ (2.4 mg, 7.9 μmol) in DMF (270 μL) at room temperature. The solution was transferred to a vial containing stannane **4l** (2.1 mg, 4.5 μmol), CuBr (2.9 mg, 20 μmol), and CsF (7.6 mg, 50 μmol) in DMF (60 μL), washed with DMF (40 μL), and the resulting mixture was heated at 65 °C for 5 min. Salts and palladium residues in the reaction mixture were removed by solid-phase extraction, and washed with DMF–H_2O (1 : 5, 0.3 mL). The combined eluates were analyzed by HPLC. Radiochemical yield of [^{11}C]-**5l**: 85%; retention time: 9.9 min. (GL Science inertsil ODS3, 5 μm, 150 × 4.6 mm i.d.; mobile phase: CH_3CN–H_2O 57 : 43; flow rate: 1.5 mL min^{-1}; detection: 230 nm).

22 The reaction of CH_3I with an equimolar amount of **4a** (30 μmol each) using a catalytic amount of Pd(0), $Pd_2(dba)_3$/P(*o*-tolyl)$_3$/CuCl/CsF (0.05 : 0.8 : 2 : 5), in DMF (3 mL) at 80 °C for 5 min afforded **5a** in 72% yield. Thus, methylation is also useful for introduction of $^{13}CH_3$, CD_3, and long-lived $^{14}CH_3$ into organic frameworks to synthesize molecular probes for metabolic studies. In particular, the synthesis of a ^{14}C-enriched methylated probe has attracted a great deal of attention in view of drug microdosing in humans and the subsequent long-term analysis of metabolites by accelerator mass spectrometry (AMS) – see ref. 3*b*.

23 H. Kagechika, *Curr. Med. Chem.*, 2002, **9**, 591–608.

24 Y. Fujimoto, N. Fishkin, G. Pescitelli, J. Decatur, N. Berova and K. Nakanishi, *J. Am. Chem. Soc.*, 2002, **124**, 7294–7303.