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Pd^0-Mediated Rapid Coupling between Methyl Iodide and Heteroarylstannanes: An Efficient and General Method for the Incorporation of a Positron-Emitting ^{11}C Radionuclide into Heteroaromatic Frameworks**

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Abstract: The Pd^0-mediated rapid trapping of methyl iodide with an excess amount of a heteroaryl-substituted tributylstannane has been investigated with the aim of incorporating a short-lived ^{11}C-labelled methyl group into the heteroaromatic carbon frameworks of important organic compounds, such as drugs with various heteroaromatic structures, in order to execute a positron emission tomography (PET) study of vital systems. The reaction was first performed by using our previously developed CH_3I/stannane/[$Pd_2(dba)_3$]/P(*o*-$CH_3C_6H_4)_3$/CuCl/K_2CO_3 (1:40:0.5:2:2:2) system in DMF at 60 °C for 5 min (conditions A), however, the reaction gave low yields for various heteroaromatic compounds. Increasing the amount of phosphine ligand (conditions B) led to a significant improvement in the yield, but the conditions were still not suitable for a range of basic heteroaromatic structures. Use of the CuBr/CsF system (conditions C) also provided a result similar to that obtained under conditions B with an increased amount of the phosphine. Thus, pyridine and related heteroaromatic compounds remained less reactive substrates. The problem was overcome by replacing the DMF solvent with *N*-methyl-2-pyrolidinone (NMP). The reaction in NMP at 60–100 °C for 5 min using a CH_3I/stannane/[Pd_2-(dba)$_3$]/P(*o*-$CH_3C_6H_4)_3$/CuBr/CsF (1:40:0.5:16:2:5) combination (conditions D) gave the methylated products in yields of more than 80 % (based on the reaction of CH_3I) for all of the heteroaromatic compounds listed in this study. Thus, the combined use of NMP and an increased amount of phosphine is important for promoting the reaction efficiently. The use of this general approach to rapid methylation has been well demonstrated by the synthesis of the PET tracers 2- and 3-[^{11}C]methylpyridines by using [Pd_2-(dba)$_3$]/P(*o*-$CH_3C_6H_4)_3$/CuBr/CsF (1:16:2:5) in NMP at 60 °C for 5 min, which gives the desired products in HPLC analytical yields of 88 and 91 %, respectively.

Keywords: C–C coupling · heterocycles · isotopic labeling · palladium · tin

Introduction

Positron emission tomography (PET) is a noninvasive, in vivo molecular imaging method that enables the analysis of the dynamic behavior of a radiotracer in living systems, such as the brain, the heart, and other active tissues and organs.[2] In this regard, a PET tracer is utilized to visualize the localization of a target molecule involved in biofunctions and also its biochemical processes (metabolic pathways), and therefore PET imaging is a useful tool for disease diagnosis.[2–4] Because PET requires only an extremely low dose of a radiotracer, much lower than its pharmacological dose, the introduction of a human microdose study using PET during the early stage of drug development (phase 0) has been proposed as an efficient means of avoiding the huge attrition (>90 %) of drug candidates during clinical trials, which causes the high cost per approved new molecular entity (NME).[3]

Among the available positron-emitting radionuclides, ^{11}C is one of the most expedient in terms of high radioactivity,[4]

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short radiation lifetime ($t_{1/2}$ = 20.4 min), and, most of all, all the carbon atoms present in organic compounds could potentially be replaced by ^{11}C. In addition, various synthetically well-established precursors, such as $^{11}CH_3I$, ^{11}CO, and $^{11}CO_2$, are readily available.[4] In particular, the introduction of a $^{11}CH_3$ group into an organic framework by carbon–carbon bond formation has the following significant benefits: 1) A flexible molecular design is possible because the methyl group is the least bulky and nonpolar organic functional group and thus produces only a slight change in the biological activities of the parent compound, 2) the short half-life of the ^{11}C-incorporated tracer allows many preclinical or clinical trials per day without any special care, such as the treatment of radiolabeled byproducts produced after the synthesis, thereby allowing fast and safe drug screening, and 3) a much higher tolerance of the *C*-CH_3 derivatives against metabolic processes in comparison with *O*-CH_3 and *N*-CH_3 derivatives, which ensures that the information obtained in a PET study is highly reliable. However, there exists a temporal restriction on the preparation of ^{11}C-incorporated PET tracers.[5] Because, in general, the total synthesis time should be set to within 2–3 half-lives of the radionuclide, the time allowed for ^{11}C incorporation is only about 5–10 min on the basis of the total reaction time, purification, and injection. In addition, an extremely small amount of the desired radiolabeled product should be cleanly separated from the reaction mixture, particularly from the large amount of the trapping substrate that remains after the reaction.[6] To meet such severe restrictions for the PET tracer synthesis, we have been developing a procedure for the rapid cross-coupling of methyl iodide with excess amounts of aryl-, alkenyl-, or alkynyltributylstannanes[1a–g] in addition to a reaction involving the use of boranes.[1h] These Pd^0-mediated cross-coupling reactions between sp^3- and sp^2-, and sp^3- and sp-hybridized carbon atoms at the reaction centers proceeded within 5 min under mild conditions (60 °C in DMF) to give the desired compounds in high yields.[1a–h] Among these methods, the sp^3–sp^2(aryl) coupling reaction has successfully been utilized for the synthesis of the (15*R*)-[^{11}C]TIC methyl ester ((15*R*)-TIC = (15*R*)-16-*m*-tolyl-17,18,19,20-tetranorisocarbacyclin),[1b,c,f,7] a novel ^{11}C-incorporated prostaglandin probe used in the molecular imaging of a novel prostacyclin receptor (IP_2, which is a target protein of prostacyclin (PGI_2))[7b,d] in living monkey and human brains administered by intravenous injections.[1b,f,7e] Our rapid coupling reactions are now increasingly being utilized in the ^{11}C-labeling of biologically significant molecules by other groups.[1i,k–n] However, as indicated by us[1a–h] and others,[1i–s] the reaction conditions for rapid *C*-methylation using stannanes seem not to have been optimized, particularly in the case of heteroaromatic frameworks such as thiophene and furan as well as pyridine-type structures with a basic nitrogen atom(s) in the core structure.[1m,q] The strong demand for high-yielding rapid methylation of such structures with a heteroaromatic core, which often appear in major drugs and their promising candidates, prompted us to conduct this study.

We disclose herein an efficient, general protocol for the rapid *C*-methylation of heteroaromatic frameworks for the synthesis of PET tracers in high yields.[1h]

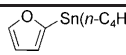
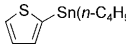
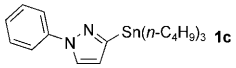
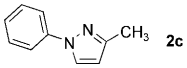
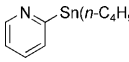
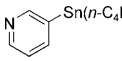
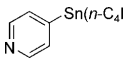
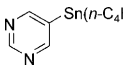
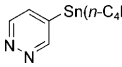
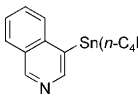
Abstract in Japanese:

本研究は、多くの医薬品の基本分子構造をなす重要なヘテロ芳香環構造を短寿命 ^{11}C 放射核種(半減期約 20 分)でラベル化するための高速 *C*-メチル化反応の実現を記載したものである。反応は、Pd^0 錯体存在下、ヨウ化メチルを 40 当量のヘテロ芳香環置換トリブチルスタナンで捕捉することにより行った。これまでにフェニル（トリブチル）スタナンに対して行ってきた DMF 中、CH_3I/スタナン/$Pd_2(dba)_3$/P(*o*-$CH_3C_6H_4)_3$/CuCl/K_2CO_3 の反応条件は、チオフェン、フランなどのヘテロ芳香環およびピリジンなどの塩基性芳香環置換トリブチルスタナンに対して、対応するメチル化体は低収率でしか得られなかった。上記条件あるいは K_2CO_3 を CsF に代えた条件下、*o*-トリルフォスフィンを増量すると、一部の中性ヘテロ芳香環置換スタナンに対して、メチル化の収率が 80%以上に向上したが、塩基性芳香環置換スタナンに対しては依然収率が低く、一般的性の高い条件には至らなかった。この残された問題は、使用溶媒を DMF から *N*-メチル-2-ピロリジノン（NMP）に代えることにより解決された。すなわち、NMP 中、CH_3I/スタナン/$Pd_2(dba)_3$/P(*o*-$CH_3C_6H_4)_3$/CuBr/CsF（モル比：1:40:0.5:16:2:5）条件下、60−100°C、5 分間の加熱で、今回、取り挙げたすべてのヘテロ芳香族置換スタナンに対していずれも 80%以上の高収率（ヨウ化メチルの消費量に基づく）でメチル化体が得られた。本高速 *C*-メチル化反応の有用性は、実際の ^{11}C 含有 PET トレーサーである 2-および 3-[^{11}C]メチルピリジンの高収率合成（HPLC 分析収率：順に 88 および 91%）により実証された。

Results and Discussion

We chose nine basic and nonbasic heteroaromatic aryltributylstananes, **1a–i**, for the rapid methylation reaction (Table 1) and a 1:40 ratio[8] of methyl iodide and tin substrate was set up for the PET tracer synthesis. To start with we evaluated the conditions previously reported by Saji and co-workers for the synthesis of 5-methyl-3-[2-(*S*)-azetidinylmethoxy]pyridine ([^{11}C]5MA) in a radiochemical yield of 30 %[1m] by using the tin substrate **1e** (entry 5 in Table 1) as a model compound. Thus, the reaction was conducted by using CH_3I/**1e**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuCl/K_2CO_3 (1:40:0.5:2:2:2 molar ratio) in DMF at 80 °C for 3 min to give the methylated product **2e** in a yield of 53 % (GLC) based on the reaction of CH_3I. Furthermore, the conditions reported by Laruelle and co-workers for the synthesis of the [^{11}C]-incorporated quinoline derivative (3-ethyl-2-[^{11}C]methyl-6-quinolinyl)(*cis*-4-methoxycyclohexyl)methanone (radiochemical yield 47 %)[1q] were also evaluated in the reaction of methyl iodide and **1d** as a model reaction (entry 4 in Table 1) using the combination CH_3I/**1d**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$ (1:40:0.5:2) in DMF in a stepwise procedure: $[Pd_2(dba)_3]$ and P(*o*-$CH_3C_6H_4)_3$ (1:4) were mixed

Table 1. Rapid trapping of methyl iodide with heteroaryl-substituted tributylstannanes.

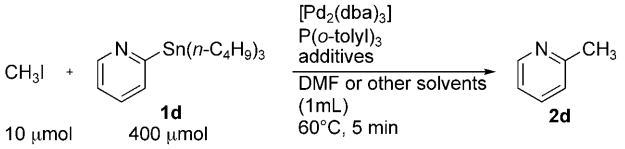
Entry	Heteroarylstannane	Methylated product	Yield [%][a] A[b]	B[b]	C[b]	D[b]
1	 **1a**	 **2a**	28	75	73	80
2	 **1b**	 **2b**	57	87	91	94
3	 **1c**	 **2c**	52	88	90	94
4	 **1d**	 **2d**	16 (14)[c]	67	63	81
5	 **1e**	 **2e**	25 (53)[d]	61	66	80
6	 **1f**	 **2f**	79	60	68	87
7	 **1g**	 **2g**	3	50	48	62 (87)[e]
8	 **1h**	 **2h**	25	72	70	90
9	 **1i**	 **2i**	12	83	75	83

[a] The products were identified by GLC analysis by comparison with authentic samples. The yields were determined by GLC based on CH_3I consumption using *n*-nonane and *n*-heptane as internal standards and are the average of 2 or 3 runs. [b] 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) in DMF at 60 °C for 5 min; B: CH_3I/stannane/$[Pd_2(dba)_3]$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1:40:0.5:16:2:5) in DMF at 60 °C for 5 min; C: CH_3I/stannane/$[Pd_2(dba)_3]$/P(*o*-tolyl)$_3$/CuBr/CsF (1:40:0.5:16:2:5) in DMF at 60 °C for 5 min; D: CH_3I/stannane/$[Pd_2(dba)_3]$/P(*o*-tolyl)$_3$/CuBr/CsF (1:40:0.5:16:2:5) in NMP at 60 °C for 5 min. [c] CH_3I/stannane/$[Pd_2(dba)_3]$/P(*o*-tolyl)$_3$ (1:40:0.5:2) in DMF at 120 °C for 5 min (stepwise procedure; see ref. [1m]). [d] CH_3I/stannane/$[Pd_2(dba)_3]$/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 (1:40:0.5:2:2:2) in DMF at 80 °C for 3 min (see ref. [1n]). [e] The reaction was conducted at 100 °C.

in DMF at room temperature and stirred for 1 min and then the resulting Pd^0 complex was transferred to a DMF solution of **1d** and heated at 120 °C for 5 min to give **2d** in a yield of only 14%. Based on these results, we concluded that the reaction conditions previously used for the methylation of heteroaromatic compounds are still insufficient and therefore a further basic study is needed to improve the yields, which prompted us to systematically reinvestigate the rapid methylation of the compounds listed in Table 1.

First, we conducted the reactions of stannanes **1a–i** under the conditions[1a] previously developed by us for sp^3–sp^2-(aryl) rapid coupling using a combination of CH_3I/**1a–i**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuCl/K_2CO_3 (1:40:0.5:2:2:2) at 60 °C for 5 min in DMF (see conditions A in Table 1), which gave far-from-ideal yields (3–57%), except for the conversion of **1f** to **2f** (79%, entry 6). Again, we recognized the difficulty of optimizing the conditions of these reactions. We then chose the conversion of **1d** to **2d** as a model reaction for optimizing the reaction conditions (Table 2). Interestingly, increasing the quantity of added phosphine for Pd^0 from 2 to 20 equiv significantly improved the yield from 16 to 71% (entry 4 in Table 1 and entry 4 in Table 2, respectively). Similar phenomena were observed in our previous studies involving rapid sp^3–sp^2(alkenyl) coupling with the CuCl/K_2CO_3 synergic system.[1g] The reagents comprised the CH_3I/**1d**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuBr/CsF combination, which gave yields of 35–67% with 6–20 equiv of phosphine. Thus, we found that the reaction efficiency was typically increased by increasing the quantity of the added phosphine up to 16 equiv for both the CuCl/K_2CO_3 and CuBr/CsF synergic systems. With such a phosphine effect, we conducted the reaction with the other stannanes listed in Table 1 using CH_3I/**1d**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuCl/K_2CO_3 (1:40:0.5:16:2:5) at 60 °C for 5 min in DMF (conditions B) and CH_3I/stannane/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuBr/CsF (1:40:0.5:16:2:5) at 60 °C for 5 min in DMF (conditions C), which gave yields of 87, 88, and 83% for **2b**, **2c**, and **2i**, respectively, under conditions B, 91 and 90% for **2b** and **2c**, respectively, under conditions C, and 48–75% for the other entries under both conditions. Thus, pyridine and related basic heteroaromatic compounds still remained less reactive substrates even under these conditions (entries 4–8). Therefore we continued to search for reaction conditions that generally give high yields for a wide range of substrates. The answer surprisingly involved simply changing the solvent from DMF to *N*-methyl-2-pyrrolidinone (NMP)! It is of interest that such a solvent effect was not observed for the CH_3I/**1d**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuCl/K_2CO_3 system, but was apparent for the CH_3I/**1d**/$[Pd_2(dba)_3]$/P(*o*-$CH_3C_6H_4)_3$/CuBr/CsF reaction system (entry 3 in Table 2), which gave **2d** in a yield of 81%. The effects of other solvents are also summarized in Table 2. HMPA, DMSO, 1,3-dimethylimidazolidin-2-one (DMI), THF, and toluene were not effective (Table 2, entry 3). Accordingly, NMP was the best of the amide-type solvents used, including *N*,*N*-dimethylacetamide (DMA), NMP gave the highest yield of 81%, whereas DMA gave a yield of 69%. Note that the reaction with the CH_3I/**1d**/$[Pd\{P(t\mathrm{Bu})_3\}_2]$/CsF (1:40:1:5) system in NMP, in which the bulky triarylphosphine, P(*o*-$CH_3C_6H_4)_3$, is replaced by the trialkylphosphine, P(*t*Bu)$_3$, gave an unexpectedly poor yield (21%, Table 2, entry 3).[9a,d] The addition of CuBr to this system improved the yield only to a small extent (39%). The addition of amines such as 2,6-lutidine, triethylamine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) to the reaction under conditions B or C prohibited the reaction to a significant extent.

Table 2. Rapid trapping of methyl iodide with tri-*n*-butyl(2-pyridyl)stannane (**1d**) to give **2d** and the effects of solvent and additives.[a]

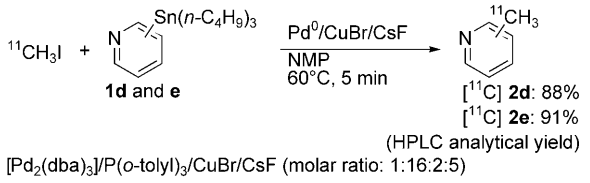


Entry	$P(o\text{-tolyl})_3$ (equiv of CH_3I)	Yield [%][b] $CuCl/K_2CO_3$ synergic system	$CuBr/CsF$ synergic system
1	6	43	35
2	8	55	49
3	16	67 (66)[c] (10)[d] (34)[e] (46)[f]	(**81**)[c] (21)[g] (39)[h] 65 (69)[i] (18)[j,k] (20)[l] (38)[m] (23)[d] (34)[e] (19)[f] (20)[n] (7)[o]
4	20	71	67

[a] Reaction conditions (molar ratio): CH_3I/**1d**/$[Pd_2(dba)_3]$/$P(o\text{-tolyl})_3$/$CuCl/K_2CO_3$ (1:40:0.5:6–20:2:2) or CH_3I/**1d**/$[Pd_2(dba)_3]$/$P(o\text{-tolyl})_3$/$CuBr/CsF$ (1:40:0.5:6–20:2:5) in DMF at 60°C for 5 min. [b] Yields of **2d** were determined by GLC analyses based on CH_3I consumption using *n*-heptane as the internal standard. [c] Reaction performed in NMP as the solvent. [d] Reaction performed in DMSO as the solvent. [e] Reaction performed in HMPA as the solvent. [f] Reaction performed in DMF in the presence of 2,6-lutidine (17 equiv). [g] Fu's original conditions[9a,d] (molar ratio): CH_3I/**1d**/$Pd[P(t\text{Bu})_3]_2$/CsF (1:40:1:2) in NMP. [h] Fu's original conditions + CuBr (molar ratio): CH_3I/**1d**/$Pd[P(t\text{Bu})_3]_2$/CuBr/CsF (1:40:1:2:5) in NMP. [i] Reaction performed in DMA as the solvent. [j] Reaction performed in DMI as the solvent. [k] The yields of **2d** were determined by HPLC analysis based on CH_3I consumption using isoquinoline as the internal standard. [l] Reaction performed in toluene as the solvent. [m] Reaction performed in THF as the solvent. [n] Reaction performed in DMF in the presence of triethylamine (14 equiv). [o] Reaction performed in DMF in the presence of DABCO (18 equiv).

With the best solvent in hand, the reaction with CH_3I/stannane/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/CuBr/CsF (1:40:0.5:16:2:5) in NMP at 60°C for 5 min (conditions D) was conducted for the other stannanes listed in Table 1 and gave yields in excess of 80% for all compounds except for the stannane **1g** in entry 7 of Table 1.[10] The yield of **2g** was improved to 87% by conducting the reaction at 100°C (improved conditions D). Thus, we established the conditions for rapid methylation that are generally applicable to a wide range of heteroaromatic frameworks including those with a basic nitrogen atom(s) in the structure. As described in our previous studies, the use of a coordinatively unsaturated Pd^0 complex, such as $[Pd\{P(o\text{-}CH_3C_6H_4)_3\}_2]$[1a–d,f–h] and $[Pd\{P(t\text{Bu})_3\}_2]$,[1e] is crucial for promoting rapid cross-coupling reactions. The bulky triaryl- and trialkylphosphines serve to generate the reactive coordinatively unsaturated Pd^0 and Pd^{II} complexes during the course of the reaction. An increase in the quantity of the reactive trapping substrate transmetalated by a combination of Cu^I/K_2CO_3[1a] or Cu^I/CsF[1g] through synergic effects is also important for promoting the reaction.[1g] Because the yields did not change by using a combination of Cu^I and CsF instead of Cu^I and K_2CO_3 (see Table 1, conditions B and C), the formation of a hypervalent tin intermediate is not important in the reaction.[1t,u,v] DMF weakly coordinates to the unstable Pd^0, Pd^{II}, and Cu^I intermediates transiently formed in the reaction to suppress metal deposition. We have found in this study that the use of an excess amount of the triarylphosphine, $P(o\text{-}CH_3C_6H_4)_3$, and NMP as the solvent for the combination CH_3I/stannane/Pd^0/phosphine/Cu^I/CsF is the best choice for the reaction. The basicity of the phosphine influences the reaction to a significant extent,[1e] as is evident by the fact that the use of $P(o\text{-}CH_3C_6H_4)_3$ gives results much superior to $P(t\text{Bu})_3$ in the rapid methylation reaction (81 vs. 21%, respectively, see Table 2, entry 3).[9a] We considered that a heteroatom with a lone-pair electron or a basic nitrogen atom included in the tin substrate structure could possibly coordinate to the metal species to decrease the nucleophilicity of the C–Sn bond, prohibiting the substitution reaction between Aryl–Sn (or Aryl–Cu) and CH_3–Pd^{II}–I to a considerable extent. Here, excess phosphine[11] and the NMP solvent serve to dissociate such a coordination to regenerate the nucleophilic tin(IV) or copper(I) to promote the reaction. The reason why the use of DMSO, HMPA, or a urea derivative is not efficient for the reaction, but not polar aprotic solvents like amide, remains unclear. The inhibitory effect of an amine additive is presumably due to its strong coordination with the active site of the metal complexes.

The utility of conditions D was demonstrated by the synthesis of 2-[^{11}C]methylpyridine (2-[^{11}C]picoline, [^{11}C]**2d**) and 3-[^{11}C]methylpyridine (3-[^{11}C]picoline, [^{11}C]**2e**). In our experience of PET studies, the continuous operations of 1) mixing [^{11}C]methyl iodide and Pd^0, and then 2) mixing the resulting methylpalladium(II) with a stannane, copper(I) salt, and fluoride anion gives a better result in terms of the reproducibility of the reaction.[1c,f] Thus, the PET tracers [^{11}C]**2d** and [^{11}C]**2e** were synthesized by such a protocol. The successive mixing of the Pd^0 complex with [^{11}C]CH_3I in NMP and then with the stannanes **1d** and **1e** in the presence of CuBr and CsF in NMP under conditions D ($[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/CuBr/CsF (1:16:2:5))[12] at 60°C for 5 min produced 2- and 3-[^{11}C]methylpyridine in yields of 88 and 91%, respectively (by HPLC analysis; Scheme 1).[13]



Scheme 1. Synthesis of 2- and 3-[^{11}C]methylpyridines ([^{11}C]**2d** and [^{11}C]**2e**).

These conditions are useful for methylation using an excess amount of an organostannane as the substrate, but also for the methylation with a nearly equal amount of the substrate. Thus, the reaction of CH_3I with 1.4 equiv of **1d** using $[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/CuBr/CsF (0.5:16:2:5) in NMP (1 mL) at 60°C for 60 min afforded **2d** in a yield of 84%. Accordingly, this methylation reaction can be used to

introduce $^{13}CH_3$, CD_3, and the long-lived $^{14}CH_3$ into heteroaromatic frameworks to synthesize molecular probes for metabolic studies. In particular, the synthesis of a ^{14}C-enriched methylated probe is attracting considerable attention for drug microdosing in humans as is the long-term analytical tool of metabolites by accelerator mass spectrometry (AMS).[2b,14]

Conclusion

We have developed an efficient protocol for Pd^0-mediated rapid *C*-methylation by the reaction of methyl iodide with an excess amount of a heteroaryl-substituted tributylstannane using NMP as the solvent in the presence of excess phosphine with the aim of synthesizing a short-lived ^{11}C-incorporated PET tracer. The rapid *C*-methylation strategy is quite general and applicable to a wide variety of basic and nonbasic heteroaromatic compounds. The method is well demonstrated by the reactions of [^{11}C]CH_3I with the tin precursors **1d** and **1e**, which give 2-[^{11}C]methylpyridine ([^{11}C]**2d**) and 3-[^{11}C]methylpyridine ([^{11}C]**2e**), respectively, both in high radiochemical yields. Two kinds of rapid *C*-methylation reactions are now available, the reaction of methyl iodide with a heteroaromatic stannane and also with a borane[1h] precursor. These methods could be used complementarily depending on the ease of synthesis of the tin or borane precursor and the efficiency of their reactions with methyl iodide. The combination of PET and AMS technologies allows the dynamic behavior of organic molecules (drugs and their candidates) in the human body to be analyzed by using the microdosing concept[3,15] at an early stage of drug development to significantly improve the attrition of drug candidates during clinical trials. The application of these methods to the synthesis of PET tracers of biological significance and their use in molecular imaging will be demonstrated in due course.

Experimental Section

General: GLC analysis was performed on Shimadzu GC-2010 and GC-17A instruments equipped with a flame ionization detector; capillary columns: TC-1701 (60 m × 0.25 mm i.d., df = 0.25 μm, GL Science) and CP-Volamine (60 m × 0.32 mm i.d., GL Science); carrier gases: N_2 or He. The organic chemical reactions, except for the radiolabeling reaction shown in Scheme 1, were performed by using Schlenk techniques under argon. Solvents and solutions were transferred by syringe-septum and cannula techniques. Dehydrated *N*,*N*-dimethylformamide (DMF; Kanto Kagaku), dehydrated *N*-methyl-2-pyrrolidinone (NMP; Kanto), dehydrated tetrahydrofuran (THF; Wako), and dehydrated toluene (Wako) were of commercial grade. Methyl iodide was distilled prior to use. Tris(dibenzylideneacetone)dipalladium(0) (Aldrich), tri-*o*-tolylphosphine (Aldrich), copper(I) chloride (Wako), copper(I) bromide (Wako), potassium carbonate (Wako), cesium fluoride (Aldrich), 1,3-dimethylimidazolidine-2-one (DMI; Nacalai Tesque, Inc.), *N*,*N*-dimethylacetamide (DMA; Kanto), dimethyl sulfoxide (Kanto), hexamethylphosphoramide (HMPA; Tokyo Kasei), 2,6-lutidine (Nacalai), triethylamine (Nacalai), and 1,4-diazabicyclo[2.2.2]octane (DABCO; Kanto) were of commercial grade. Tri-*n*-butyl(2-furyl)stannane (Aldrich), tri-*n*-butyl(2-thienyl)stannane (Tokyo Kasei), tri-*n*-butyl(2-pyridyl)stannane (Tokyo Kasei), and tri-*n*-butyl(3-pyridyl)stannane (Frontier) are commercially available. 2-Methylfuran, 2-methylthiophene, 3-methyl-1-phenylpyrazole, 2-methylpyridine, 3-methylpyridine, 4-methylpyridine, 5-methylpyrimidine, 4-methylpyridazine, and 4-methylisoquinoline were used as authentic samples. *n*-Nonane and *n*-heptane used as the internal standard for GC analyses were of commercial grade. 1-Phenyl-3-(tributylstannyl)pyrazole[16] and tri-*n*-butyl(4-pyridazinyl)stannane[17] were prepared according to literature procedures. Tri-*n*-butyl(4-pyridyl)stannane was prepared by the reaction of 4-pyridnyllithium with tributylstannyl chloride in diethyl ether. Tri-*n*-butyl(4-isoquinolyl)stannane was prepared by the same procedure. Tri-*n*-butyl(5-pyrimidinyl)stannane was prepared by the reaction between the corresponding bromide compounds and hexabutylditin in the presence of tetrakis(tiphenylphosphine)palladium(0). The [^{11}C]methylation reaction in Scheme 1 was conducted in a lead-shielded hot cell with remote control of all operations. [^{11}C]Carbon dioxide was produced by a $^{14}N(p,\alpha)^{11}C$ reaction using a Sumitomo CYPRIS HM-12S cyclotron (Sumitomo Heavy Industries) and then converted into [^{11}C]methyl iodide by treatment with lithium aluminum hydride followed by hydriodic acid using an original automated synthesis system for ^{11}C-labeling in RIKEN Center for Molecular Imaging Science. The [^{11}C]methyl iodide obtained was used for the palladium(0)-mediated rapid [^{11}C]methylation reaction shown in Scheme 1. The analytical HPLC system used for the [^{11}C]methylation products consisted of an Aloka radioanalyzer (RLC-700) and a Shimadzu HPLC system with a system controller (CBM-20A), an online degasser (DGU-20A_3), a solvent delivery unit (LC-20AB), a column oven (CTO-20AC), a photodiode array detector (SPD-M20A), and software (LC solution).

Product analysis

Conditions A: Instrument: Shimadzu GC-2010; carrier gas: He; capillary column: GL Science TC-1701; injection temperature: 280 °C; detection temperature: 280 °C; initial column temperature: 80 °C; final temperature: 100 °C; temperature ramp rate ; 5 °C min^{-1} from 10 to 14 min; flow rate: 0.50 mL min^{-1}; retention time: 2-methylfuran (**2a**) 9.2 min, 2-methylthiophene (**2b**) 13.4 min.

Conditions B: Instrument: Shimadzu GC-17A; carrier gas: N_2; capillary column: GL Science CP-Volamine; injection temperature: 260 °C; detection temperature: 260 °C; column temperature: 230 °C; flow rate: 2.1 mL min^{-1}; retention time: 3-methyl-1-phenylpyrazole (**2c**) 26.6 min, 4-methylpyridine (**2e**) 15.1 min, 4-methylisoquinoline (**2i**) 29.6 min.

Conditions C: Instrument: Shimadzu GC-17A; carrier gas: N_2; capillary column: GL Science CP-Volamine; injection temperature: 260 °C; detection temperature: 260 °C; initial column temperature: 100 °C; final temperature: 200 °C; temperature ramp rate; 10 °C min^{-1} from 10 to 20 min; flow rate: 0.50 mL min^{-1}; retention time: 2-methylpyridine (**2d**) 19.6 min.

Conditions D: Instrument: Shimadzu GC-17A; carrier gas: N_2; capillary column: GL Science CP-Volamine; injection temperature: 260 °C; detection temperature: 260 °C; initial column temperature: 150 °C; final temperature: 200 °C; temperature ramp rate; 10 °C min^{-1} from 10 to 15 min; flow rate: 0.40 mL min^{-1}; retention time: 3-methylpyridine (**2e**) 15.1 min, 5-methylpyrimidine (**2g**) 15.1 min, 4-methylpyridazine (**2h**) 22.3 min.

HPLC analysis of 2-[^{11}C]methylpyridine: Column: COSMOSIL, C18-MS-II (4.6 × 150 mm, Nacalai); eluent: CH_3CN/H_2O = 20:80 (v/v); flow rate: 1.0 mL min^{-1}; column temperature: 30 °C; UV wavelength: 254 nm; retention time: 4.9–5.0 min.

HPLC analysis of 3-[^{11}C]methylpyridine: Column: COSMOSIL, C18-MS-II (4.6 × 150 mm, Nacalai); eluent: CH_3CN/H_2O = 25:75 (v/v); flow rate: 1.0 mL min^{-1}; column temperature: 30 °C; UV wavelength: 254 nm; retention time: 4.6–4.8 min.

Rapid coupling of methyl iodide with tri-*n*-butyl(4-isoquinolyl)stannane (1i) to afford 4-methylisoquinoline (2i; Table 1, entry 9, conditions B): In a dry Schlenk tube (10 mL), [$Pd_2(dba)_3$] (4.6 mg, 5.0 μmol), P(*o*-$CH_3C_6H_4)_3$ (49 mg, 160 μmol), CuCl (2.0 mg, 20 μmol), and K_2CO_3 (6.9 mg, 50 μmol) were placed under argon. After the addition of DMF (500 μL), the mixture was stirred for 5 min at RT and then solutions of stannane **1i** (167 mg, 400 μmol, 40 equiv) in DMF (500 μL) and methyl iodide (12.5 μL, 0.800 M in DMF, 10.0 μmol) were successively added.

After stirring at 60 °C for 5 min, the mixture was rapidly cooled in an ice bath and diethyl ether (1 mL) was added. The resulting mixture was loaded onto a short column of silica gel (0.5 g) and eluted with diethyl ether (ca. 1 mL) followed by the addition of *n*-nonane (50 μL, 0.10 M DMF solution, 5.0 μmol) as the internal standard. The resulting solution was analyzed under conditions B; yield of **2i**: 83 % based on starting CH_3I. The methylation reactions reported in entries 1–8 of Table 1 and entries 1–4 of Table 2 using the synergic system of $CuCl/K_2CO_3$ were conducted by following the same procedure.

Rapid coupling of methyl iodide with tri-*n*-butyl(2-thienyl)stannane (1b) to afford 2-methylthiophene (2b; Table 1, entry 2, conditions C): In a dry Schlenk tube (10 mL), $[Pd_2(dba)_3]$ (4.6 mg, 5.0 μmol), $P(o\text{-}CH_3C_6H_4)_3$ (49 mg, 160 μmol), CuBr (2.9 mg, 20 μmol), and CsF (7.6 mg, 50 μmol) were placed under argon. After the addition of DMF (500 μL), the mixture was stirred for 5 min at RT and then solutions of stannane **1b** (149 mg, 400 μmol, 40.0 equiv) in DMF (500 μL) and methyl iodide (12.5 μL, 0.800 M in DMF, 10.0 μmol) were successively added. After stirring at 60 °C for 5 min, the mixture was rapidly cooled in an ice bath and diethyl ether (1 mL) was added. The resulting mixture was loaded onto a short column of silica gel (0.5 g) and eluted with diethyl ether (ca. 1 mL), followed by the addition of *n*-nonane (50 μL, 0.10 M DMF solution, 5.0 μmol) as the internal standard. The resulting solution was analyzed under conditions A; yield of **2b**: 91 % based on starting CH_3I. The methylation reactions reported in entries 1 and 3–9 of Table 1 and entries 1–4 of Table 2 using the synergic system of CuBr/CsF were conducted by following the same procedure.

Rapid coupling of methyl iodide with tri-*n*-butyl(2-pyridyl)stannane (1d) to afford 2-methylpyridine (2d; Table 1, entry 4, conditions D): In a dry Schlenk tube (10 mL), $[Pd_2(dba)_3]$ (4.6 mg, 5.0 μmol), $P(o\text{-}CH_3C_6H_4)_3$ (49 mg, 160 μmol), CuBr (2.9 mg, 20 μmol) and CsF (7.6 mg, 50 μmol) were placed under argon. After the addition of NMP (500 μL), the mixture was stirred for 5 min at RT and then solutions of stannane **1d** (147 mg, 400 μmol, 40.0 equiv) in NMP (500 μL) and methyl iodide (12.5 μL, 0.800 M in NMP, 10.0 μmol) were successively added. After stirring at 60 °C for 5 min, the mixture was rapidly cooled in an ice bath and diethyl ether (1 mL) was added. The resulting mixture was loaded onto a short column of silica gel (0.5 g) and eluted with diethyl ether (ca. 1 mL), followed by the addition of *n*-heptane (50 μL, 0.10 M DMF solution, 5.0 μmol) as the internal standard. The resulting solution was analyzed by GLC under conditions C; yield of **2d**: 81 % based on starting CH_3I. The methylation reactions reported in entries 1–3 and 5–9 of Table 1 were conducted by following the same procedure.

Rapid coupling of [^{11}C]methyl iodide with tri-*n*-butyl(2-pyridyl)stannane (1d) to afford 2-[^{11}C]methylpyridine ([^{11}C]2d; Scheme 1): [^{11}C]Methyl iodide (ca. 5–10 GBq) formed from $[^{11}C]CO_2$ according to the established method[2] was trapped in a solution of $[Pd_2(dba)_3]$ (2.5 mg, 2.7 μmol) and $P(o\text{-}CH_3C_6H_4)_3$ (13 mg, 44 μmol) in NMP (0.27 mL) at RT. The mixture was added to a solution of stannane **1d** (3.0 mg, 8.1 μmol), CuBr (0.78 mg, 5.4 μmol), and CsF (2.1 mg, 14 μmol) in NMP (0.06 mL). The resulting mixture was placed at RT for 1 min and then heated at 60 °C for 5 min. The reaction mixture was diluted with CH_3CN (2 mL) and filtered. A sample solution (5 μL) taken from the filtrate was analyzed by HPLC with a UV absorbance detector and a radiation detector. HPLC analytical yield of [^{11}C]**2d**: 88 %, calculated by peak area ratio of the [^{11}C]product distributions. The isolated yield was not determined because the isolation of volatile 2-[^{11}C]methylpyridine was dangerous. Rapid coupling using tri-*n*-butyl(3-pyridyl)stannane (**1e**) to afford 3-[^{11}C]methylpyridine ([^{11}C]**2e**) was conducted by the same procedure. The HPLC analytical yield of [^{11}C]**2e** was 91 %.

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[6] The palladium-catalyzed cross-coupling reaction of ^{11}C-labelled hypervalent methylstannane and a heteroaromatic halide has been reported. However, it would be difficult to separate the [^{11}C]methylated product from the large amount of remaining unreactive halide substrate, see ref. [1t–v].

[7] a) M. Suzuki, K. Kato, R. Noyori, Yu. Watanabe, H. Takechi, K. Matsumura, B. Långström, Y. Watanabe, *Angew. Chem.* **1996**, *108*, 366–369; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 334–336; b) H. Takechi, K. Matsumura, Yu. Watanabe, K. Kato, R. Noyori, M. Suzuki, Y. Watanabe, *J. Biol. Chem.* **1996**, *271*, 5901–5906; c) M. Björkman, Y. Andersson, H. Doi, K. Kato, M. Suzuki, R. Noyori, Y. Watanabe, 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, Y. Watanabe, *J. Neurochem.* **1999**, *72*, 2583–2592; e) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.

[8] The synthesis of PET tracers is rather different by usual organic synthetic methods. The reaction involves the trapping of an extremely small amount of $^{11}CH_3I$ (approximately 100 nmol of $^{12}CH_3I$) with a large amount (mg) of a reacting substrate. Therefore, we performed the reaction by using an excess amount of an alkenylstannane with the methyl iodide.

[9] For the effect of NMP on the [Pd{P(*t*Bu)$_3$}$_2$]-catalyzed Stille reaction in the presence of CsF, see: a) A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348; see also the iron-catalyzed alkenylation of organomagnesium compounds: b) G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199–1205; and the palladium-catalyzed arylation with aryl chlorides: c) H. A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449–1451; d) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564. The combination of [Pd{P(*t*Bu)$_3$}$_2$]/CsF in DMF is effective for the rapid methylation of 1-alkynylstannane with methyl iodide, which gives 1-methylalkyne.[1e]

[10] Pyridine formed by destannylation was not observed by GC analysis.

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[12] Phosphine was limited to 16 equiv in the small-scale synthesis of the PET tracers due to its limited solubility. Thus, the conditions defined by the use of NMP as solvent and an increased ratio of the phosphine ligand are highly tolerant and could be applied to some improved conditions in actual PET tracer synthesis, as long as such required two factors are not changed.

[13] Trimethylstannane derivatives have sometimes been used as trapping substrates because of their high reactivity.[1o–s] However, their use has serious disadvantages from a practical point of view: 1) Tin(IV) compounds of the trimethylstannyl group are extremely toxic; 2) their reactions suffer from scrambling due to the undesired cross-coupling reactions between $^{11}CH_3I$ and $(CH_3)_3SnR$, which produce highly volatile $^{11}CH_3CH_3$ which is quite dangerous for radiotracer synthesis. Such a side-reaction inevitably decreases the yield and specific radioactivity of the desired labeled compound to a significant extent. Based on this information, we emphasize again[1a] the fact that tributylstannane[1a–g,i–n] or bisalkoxyborane derivatives[1h] are much better precursors for PET tracer synthesis.

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