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Pd^0-mediated rapid coupling of methyl iodide with excess amounts of benzyl- and cinnamylboronic acid esters: efficient method for incorporation of positron-emitting ^{11}C radionuclide into organic frameworks by coupling between two sp^3-hybridized carbons†‡

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Pd^0-mediated rapid cross coupling between sp^3-hybridized carbons of CH_3I and benzyl- or cinnamylboronic acid esters using [Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF in DMF/H_2O gave the corresponding methylated compounds in high yield. The utility was well demonstrated for the synthesis of short-lived PET tracer, *N*-(4-[^{11}C]ethylphenyl)propionamide, in 90 ± 1% radio-HPLC analytical yield and 49 ± 3% radiochemical yield.

Introduction

Positron emission tomography (PET)[3] is a non-invasive method for monitoring drug behavior and its localization on target molecules in living systems including a human body with a short-lived positron-emitting radionuclide. Therefore, this technique is a useful tool for the diagnosis of diseases and the exploration of promising drug candidates by introducing microdosing studies in early stages of drug development. Among the positron-emitting radionuclides, ^{11}C is one of the most attractive nuclide, because it is possible to convert a wide range of organic compounds into PET probes by replacing a stable carbon atom with a ^{11}C radionuclide. In addition, ^{11}C labeling realizes multiple trials of a PET experiment during a day owing to a short half-life ($t_{1/2}$ = 20.4 min). Methylation for ^{11}C labeling has been accomplished mainly by the formation of O–, N–, and S–[^{11}C]methyl bonds. However, such heteroatom–carbon bonds eventually tend to undergo metabolic cleavage *in vivo* leading to the deficiency of the credibility of an image obtained in a PET study. To overcome these problems, we have investigated rapid C–[^{11}C]methylations with the aim to incorporate the [^{11}C]methyl group into carbon frameworks through carbon–carbon bond formation (Fig. 1). As a result, we have so far elaborated the Pd^0-mediated rapid cross couplings (referred to as rapid C–methylations) of methyl iodide with excess amounts of arenyl-, alkenyl-, and alkynyl(tributyl)-stannanes, and arenyl- and alkenylboronic acid pinacol esters (the connections of sp^2(arenyl)–sp^3-, sp^2(alkenyl)–sp^3-, and sp–sp^3-hybridized carbons) as well matched with the synthesis of a short-lived PET tracer.[1,2]

The rapid cross-coupling reactions between sp^3- and sp^3-hybridized carbons still remain to be explored. Described herein is a method for Pd^0-mediated rapid alkyl–alkyl cross couplings of methyl iodide (and [^{11}C]methyl iodide) with benzyl- and cinnamylboronic acid pinacol esters and trimethylboroxine (TMB) for the site-specific incorporation of the ^{11}C-labeled methyl group into organic frameworks.

Results and discussion

With an actual PET tracer synthesis in mind,[3] we used a 1 : 40 ratio of methyl iodide to a tin or boron substrate for rapid

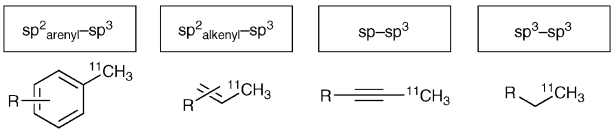

Fig. 1 Types of rapid C–[^{11}C]methylations.

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† Electronic supplementary information (ESI) available: Procedures for the rapid C-methylation under several conditions, synthesis of benzylboronic acid pinacol ester derivatives and corresponding methylated derivatives, and radio-HPLC charts for the analyses of the radioactive compounds. See DOI: 10.1039/c3ra40815a

‡ Rapid methylations on carbon frameworks for PET tracer synthesis, Part 14; for Parts 1–13, see refs cited in ref. 1 and 2.

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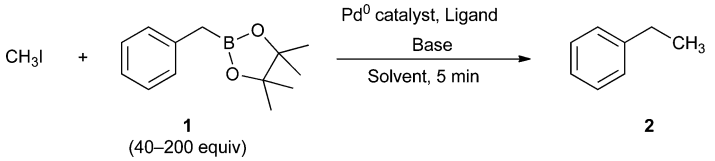
methylation. First, the cross-coupling reaction of methyl iodide with benzyl(tributyl)stannane was conducted under the following conditions according to our previous studies: CH_3I/stannane/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/CuCl/K_2CO_3 (1 : 40 : 0.5 : 2–12 : 2 : 2)[1a] in DMF, giving ethylbenzene in 5–30% yield at 60–100 °C for 5 min, accompanied to a considerable extent with the production of pentane by undesired cross coupling between methyl iodide and a butyl group on the stannane.[4] The side reaction was problematic from the viewpoints of radiation safety and reaction efficiency in consideration of the actual PET tracer synthesis, prompting us to investigate another rapid coupling, namely, the rapid reaction using a boronic acid ester substrate.[1l–m] It is well known that transition-metal-mediated coupling reactions using alkylboronic acid esters are accompanied with the production of an alkene as a major side product, which is induced by β-elimination. In fact, we reconfirmed that the Pd^0-mediated rapid reaction of methyl iodide with an excess amount of an alkylboronic acid ester under the optimized conditions was unavoidably accompanied by β-elimination to produce the undesired alkene.[5,6] In an actual radiosynthesis, the reaction of such a substrate containing a β-hydrogen would suffer from the co-production of undesired volatile [^{11}C]methane upon β-hydride elimination *via* [^{11}C]$H_3Pd(H)L_n$ complex, causing safety and environmental problems. Therefore, our study here was focused on the realization of the rapid reaction of methyl iodide with excess amounts of benzyl- and cinnamylboronic acid pinacol esters lacking hydrogens on the neighboring sp^3 carbons. Thus, benzylboronic acid ester **1** was selected as a standard substrate for the reaction with CH_3I.[7] Here, we manipulated the conditions, particularly focusing on the use of the combination of bulky triarenyl- or trialkylphosphine ligands and carbonate or fluoride as a base in DMF. The results are summarized in Table 1. The methylation of **1** using CH_3I/**1**/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/K_2CO_3 (1 : 40 : 0.5 : 2 : 2 molar ratio) in DMF for 5 min at 60 °C (the previous standard conditions we developed for sp^2(arenyl)–sp^3 coupling)[1a] gave the desired product, ethylbenzene (**2**), in only 6% yield (by gas chromatography (GC) analysis based on the consumption of CH_3I) (Table 1, entry 1). The yield was increased to 18% at a higher temperature (100 °C). Addition of H_2O to DMF (10%, v/v) improved the yield slightly (entry 2), and the yield increased to 39% by increasing the temperature to 100 °C (entry 2). Increasing the amount of K_2CO_3 (10 equiv. for methyl iodide) and increasing the temperature to 100 °C improved the yield to 46% (entry 3). The yield increased slightly when Cs_2CO_3 or CsF were used instead of K_2CO_3 at 80 °C (55 and 47%, entries 5 and 6, respectively) and did not improve at an increased temperature (120 °C). The profile of the reaction conducted using bis(tri-*tert*-butylphosphine)palladium(0) ($[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$)[8] was found to be quite different. The reaction of the CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/$K_2CO_3$ (1 : 40 : 1 : 2 molar ratio) combina-

Table 1 Synthesis of ethylbenzene (**2**) by rapid coupling of methyl iodide with excess amounts of benzylboronic acid pinacol ester (**1**)



1 (40–200 equiv) **2**

		Base		Yield[c] (%)						
Entry[a]	Pd^{0b}	(Equiv)	Solvent	60 °C	70 °C	80 °C	90 °C	100 °C	110 °C	120 °C
1	A	K_2CO_3 (2)	DMF	6	—	—	—	18	—	—
2	A	K_2CO_3 (2)	DMF/H_2O[d]	20	24	32 (27)[f]	34 (28)[f]	39 (45)[f]	44 (43)[f]	43 (37)[f]
3	A	K_2CO_3 (10)	DMF/H_2O[d]	23	—	41	—	46	—	—
4	A	K_2CO_3 (10)	DMF/H_2O[d]	—	—	(34)[e]	—	—	—	—
5	A	Cs_2CO_3 (10)	DMF/H_2O[d]	10	—	55	—	37	—	48
6	A	CsF (10)	DMF/H_2O[d]	34	—	47 (36)[f]	—	36		40
7	B	K_2CO_3 (2)	DMF	—	—	35	—	26	—	—
8	B	K_2CO_3 (10)	DMF/H_2O[d]	—	—	40 (70)[f]	—	32	—	25
9	B	CsF (2)	DMF	35	—	38	—	—	—	—
10	B	CsF (10)	DMF	42	—	58	—	—	—	—
11	B	KF (10)	DMF/H_2O[d]	—	—	62	—	61	—	—
12	B	KF (10), K 2.2.2 (10)	DMF/H_2O[d]	50	—	55	—	74 (71)[f]	—	—
13	B	CsF (10)	DMF/H_2O[d]	54	56	**88** (**100**)[f]	—	62	49–73	6–59
14	B	CsF (10)	DMF/H_2O[d]	—	—	(78)[e]	—		—	—

[a] Reaction was carried out under the condition using CH_3I/**1**/Pd^0/ligand/Base (1 : 40 : 1 : 2 : 2–10 molar ratio). [b] Pd^0/ligand: A, $[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$; B, $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$. [c] The product was identified by GC analysis by comparison with authentic samples. The yield of **2** was determined by GC based on methyl iodide consumption using n-nonane as the internal standard, and the average of more than two runs. [d] 90 : 10 (v/v). [e] Reaction was carried out under the conditions of CH_3I/**1**/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/K_2CO_3 (1 : 200 : 0.5 : 2 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) or CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF (1 : 200 : 1 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v). [f] Reaction was carried out using a five fold excess of boronic acid ester substrate (200 equiv.) at the corresponding temperature under the conditions of CH_3I/**1**/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/K_2CO_3 (1 : 200 : 2.5 : 10 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) or CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF (1 : 200 : 5 : 50 molar ratio) in 90 : 10 DMF/H_2O (v/v). dba: dibenzylideneacetone; DMF: *N*,*N*-dimethylformamide; K 2.2.2: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane.

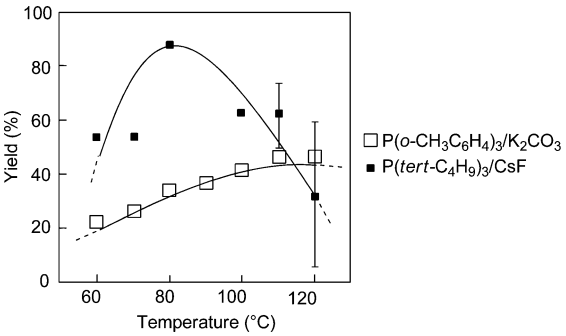
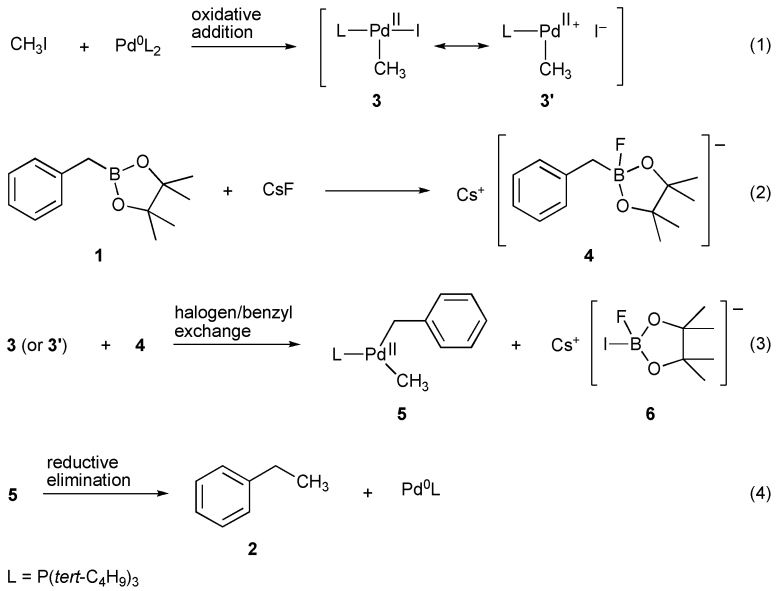


Fig. 2 The change in the yield of ethylbenzene (**2**) in reactions at various temperatures using CH_3I/**1**/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/K_2CO_3 (1 : 40 : 0.5 : 2 : 2) (white squares) and CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF (1 : 40 : 1 : 10) (black squares) in 90 : 10 DMF/H_2O (v/v) for 5 min. The yield of **2** was the average of more than two runs. The reactions at 110 and 120 °C lacked reproducibility, giving **2** in the yields from 49 to 73 and 6 to 59%, respectively.

tion in DMF at 80 °C for 5 min gave the methylated product in 35% yield, and heating at 100 °C rather decreased the yield to 26% (entry 7). Further, it was found that the addition of H_2O to $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/$K_2CO_3$ tended to improve the yield to 40% (entries 8 *vs.* 7). The use of fluoride anion instead of carbonate seemed more effective for the reaction;[9] the reaction using CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF (1 : 40 : 1 : 2 molar ratio) in DMF at 60 and 80 °C for 5 min gave the desired product in yields of 35 and 38%, respectively (entry 9). Higher concentrations of fluoride ion seemed more beneficial (entry 10). The addition of H_2O to the reactions under the conditions using KF as a base improved the yield slightly (61–62% at 80–100 °C, entry 11). The naked fluoride ion generated by the addition of 4,7,13,16,21,24-hexaoxa-1,10-diazabiyclo[8.8.8]hexacosane (K 2.2.2) gave no improvement over the use of CsF alone (50–74% at 60–100 °C, entry 12).[10] Finally, the conditions using CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF (1 : 40 : 1 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) at 80 °C markedly raised the yield, giving desired product **2** in 88% yield (entry 13). The yield decreased when the reaction temperature was elevated to 100 °C (entry 13). The reaction under microwave heating[11] of the reaction for $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF in 90 : 10 DMF/$H_2O$ (v/v) for 5 min at 80 °C rather retarded the reaction to some extent, giving **2** in 58% yield. As shown in Fig. 2, the yields obtained upon changing the temperature were counter-productive for the conditions of CH_3I/**1**/$[Pd_2(dba)_3]$/$P(o\text{-}CH_3C_6H_4)_3$/K_2CO_3 (1 : 40 : 0.5 : 2 : 2 molar ratio) and CH_3I/**1**/$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$/CsF (1 : 40 : 1 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) shown in entries 2 and 13 (Table 1), respectively. The yields under the latter reaction conditions were dependent on the temperature, giving a bell-shaped curve, whereas the yields under the former conditions showed a steady increase when the temperature was increased from 60 to 120 °C,[12] although the reaction efficiency was still unsatisfactory. Therefore, it should be noted that the reaction using $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$ and CsF should be conducted with particular care in selecting the reaction temperature. Thus, we found the optimized conditions for efficiently promoting the rapid C–methylation for the synthesis of **2** (entry 13).[13]

The rapid C–methylation did not proceed at all under the conditions of CH_3I/**1**/$[Pd\{P(C_6H_5)_3\}_4]$/TlOH (1 : 40 : 1 : 3) in THF/H_2O[14] at 25 °C for 5 min, which are considered to accelerate the Suzuki–Miyaura cross-coupling reactions to a great extent.[14] The use of monodentate phosphine ligands such as $P(C_6H_{11})_3$,[7b,c] $P(tert\text{-}C_4H_9)_2(CH_3)$,[15] $P(i\text{PrNCH}_2\text{CH}_2)_3\text{N}$ (Verkade's proazaphosphatrane),[16] and P(biphenyl)($tert$-$C_4H_9)_2$[17] did not show any appreciable effect in enhancing the reactivity.[18] The use of 2-(di-*tert*-butylphosphino)-2′,4′,6′-triisopropyl-3,6-dimethoxy-1,1′-biphenyl (*t*BuBrettPhos)[19] under the conditions of CH_3I/**1**/$[Pd_2(dba)_3]$/*t*BuBrettPhos/K_3PO_4 (1 : 40 : 0.5 : 2 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) at 80 °C was also ineffective, giving **2** in only 8% yield. The use of *N*-heterocyclic carbene (NHC) ligand 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene[20] only gave **2** in 15% yield. A ferrocenyl bidentate phosphine ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf) has been used as an effective ligand for the Pd-mediated cross coupling of sp^2(arenyl)–sp^3-hybridized carbons,[21] in which it is believed that a bidentate phosphine with a proper bite angle[22] can fix the two organo groups on the intermediate palladium(II) complex in the *cis*-orientation to efficiently facilitate the reductive elimination. However, the reaction of methyl iodide with **1** (40 equiv.) based on the reported conditions, $[PdCl_2(dppf)]$/K_3PO_4 in THF at 60 °C or reflux (bp 65–67 °C), for 5 min, did not give **2** at all. The desired product **2** was given in a poor yield of only 5% by running the reaction at a higher temperature (80 °C) in DMF in the presence of 10% (v/v) H_2O. The use of bidentate ligands such as 1,2-bis(diphenylphosphino)ethane, 1,2-bis(dicyclohexylphosphino)ethane, and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene[23] instead of dppf also did not give **2** under the conditions with $[Pd_2(dba)_3]$/ligand/CsF (0.5 : 1 : 10 molar ratio) at 80 °C in 90 : 10 DMF/H_2O (v/v) for 5 min. As such, we found that the selection of the bulky trialkylphosphine (cone angle = 182° for $P(tert\text{-}C_4H_9)_3$),[24] which could serve to form the unsaturated Pd^0 complex, together with its much higher basicity (pK_a = 11.4 for $P(tert\text{-}C_4H_9)_3$)[25] relative to an arenylphosphine (pK_a = 3.8 for $P(o\text{-}CH_3C_6H_4)_3$)[25] is important in the promotion of the present rapid C–methylation.

Yamamoto and Stille provided kinetic evidence for the reductive elimination from a tricoordinate intermediate, where it was considered that a T- and/or Y-shaped transition state structure would be directly responsible for the reductive elimination process.[26] In this context, it was reported that an arenylphosphine was superior to an alkylphosphine as judged by the homocoupling reactions of organolithium compounds such as C_6H_5Li, (*E*)-*tert*-C_4H_9CH = CHLi, CH_3Li, *etc.* catalyzed by $PdCl_2L_2$ (L = $P(C_6H_5)_3$, $P(C_2H_5)_3$, and *etc.*).[27] Both phosphines used in the reaction are relatively small; therefore, such superiority could be explained by considering that the dissociation of the less basic arenylphosphine from a R_2PdL_2-type (L = phosphine ligand) tetracoordinated saturated complex is easier than that of a more basic alkylphosphine to form, *via* equilibration, a tricoordinated complex activated



Scheme 1 Assumed mechanism for the rapid reaction of methyl iodide and benzylboronic acid ester **1** using [Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF in 90 : 10 DMF/H_2O (v/v).

for the coupling reaction.[26] The use of the *tert*-butyl-substituted bidentate phosphine 1,2-bis(di-*tert*-butylphosphinomethyl)benzene gave **2** in 32% yield under [$Pd_2(dba)_3$]/ligand/CsF (0.5 : 1 : 10 molar ratio) at 80 °C in 90 : 10 DMF/H_2O (v/v) for 5 min, and it is supposed that one of the phosphines could dissociate, owing to the steric bulkiness of their *tert*-butyl groups to form the coordinatively unsaturated tricoordinated Pd complex in order to facilitate the reaction to some extent. With above-mentioned valuable information in hand, we considered that the present rapid *C*–methylation could be realized, particularly by acceleration of the processes of oxidative addition and halogen/benzyl group substitution as a result of a great deal of strong electron donation of P(*tert*-C_4H_9)$_3$ in comparison with that of the arenylphosphine P(*o*-$CH_3C_6H_4$)$_3$. Thus, as shown in Scheme 1, the bulky ligand P(*tert*-C_4H_9)$_3$ with strong σ-electron-donating ability would serve to generate coordinatively unsaturated tricoordinated Pd^{II} complex [$CH_3Pd^{II}I(L)$] **3** by oxidative addition (eq. 1), which could be resonated with highly polarized (or ionized) palladium(II) complex [$CH_3Pd^{II}(L)$]$^+I^-$ **3′** owing to strong electron donation from an alkylphosphine ligand.[1f] The resulting complex **3** (or **3′**) readily undergoes the iodide/benzyl group exchange upon the reaction with fluoro benzylboronate **4** formed by the coordination of fluoride with boron (eqs. 2 and 3),[10,11] giving tricoordinated complex **5** followed by the reductive elimination to give **2** as the final cross-coupling product. The unsaturated tricoordinated Pd^{II} complex **5**, which was generated directly owing to the high bulkiness of the phosphine ligand, could also be responsible for the smooth reductive elimination.[26] Thus, overall, the Pd^0-mediated cross coupling was tremendously accelerated by the use of P(*tert*-C_4H_9)$_3$ (>200 fold) in comparison with conventional Suzuki–Miyaura cross-coupling reactions.[28]

The established optimized conditions (Table 1, entry 13) were applied to various kinds of benzyl- and cinnamylboronic acid pinacol esters, in which electron-donating or electron-withdrawing groups are substituted on the phenyl rings (Table 2), by carefully taking the bell-shaped curve of the yields into consideration. Here, the conditions of CH_3I/**7a–n**/[Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF (1 : 40 : 1 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) at several temperatures ranging from 60 to 120 °C for 5 min were used for the reaction. Accordingly, it was found that the reaction efficiency is sensitive to the substituent on the aromatic ring. Electron-donating methoxy and amide substituents at *para* positions (**7a** and **7c**, respectively) accelerated the methylation to a great extent, giving the corresponding methyl compounds in high yields even at a mild temperature (60 °C, 98 and 91%, entries 1 and 3, respectively). The six-membered cyclic boronic acid ester **7e** was also applicable to the reaction (75% at 70 °C, entry 6). Halogen (Cl and F)-substituted substrates were also tolerant of the present Pd-mediated reaction. Thus, *p*-chloro, and *p*-fluoro substituted substrates (**7f** and **7g**, respectively) gave the corresponding methylated products in quantitative (100 °C) and 82% (80 °C) yields (entries 7 and 8), respectively. Surprisingly, 2-fluorobenzylboronic acid pinacol ester (**7h**) was much less reactive. The deceleration effect of the fluorine substituent is presumably due to the intramolecular interaction between the fluorine orbital and vacant boron orbital which prohibits the coordination of an anionic base with the boron atom.[29] While substrate **7k**, with a strong electron-withdrawing trifluoromethyl group substituted at *para* position gave quite low yield (19–21%, entry 12), the boronic acid esters **7i** and **7j** with electron-withdrawing ethyl ester and trifluoromethyl groups, respectively, at *meta* positions were good substrates for the reaction (80 °C) to give the desired

Table 2 Rapid coupling of methyl iodide with excess amounts of benzyl- (**1** and **7a–d, f–k**) and cinnamylboronic acid pinacol ester (**7l** and **7m**), benzylboronic acid neopentyl glycol ester (**7e**), and trimethylboroxine (**7n**)

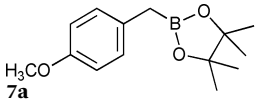
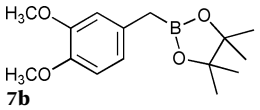
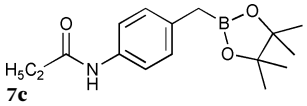
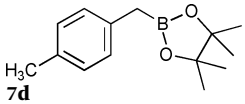
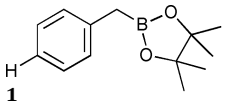
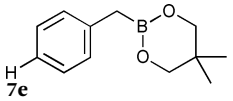
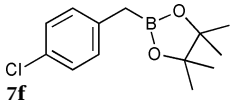
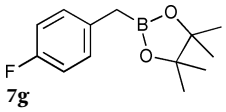
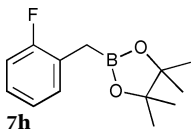
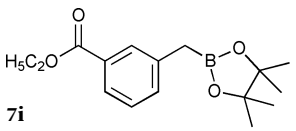
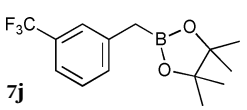
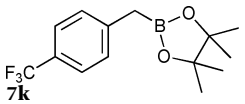
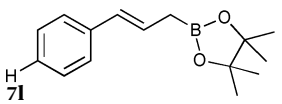
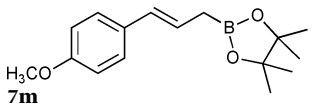
		Yield[b] (%)				
Entry[a]	Boronic acid ester	60 °C	70 °C	80 °C	100 °C	120 °C
1	 **7a**	98	—	100	—	—
2	 **7b**	77	—	80	—	81
3	 **7c**	91[c]	—	100[c]	—	—
4	 **7d**	65	—	91	—	—
5[d]	 **1**	54	56	88 (100)[e]	62	6–59
6	 **7e**	—	75	72 (89)[e]	—	—
7	 **7f**	80	—	84	—	100
8	 **7g**	—	—	82	—	68
9	 **7h**	6	—	39 (60)[e]	34	35
10	 **7i**	69	—	96	—	—
11	 **7j**	87	—	91	—	—
12	 **7k**	—	—	19 (29)[e]	—	21
13	 **7l**	—	—	43	100	33

Table 2 (*Continued*)

		Yield[b] (%)				
14	 **7m**	30	37	87	59	58
15	$(CH_3BO)_3$**7n**	—	—	100[f]	—	—

[a] Reaction was carried out using CH_3I (2 μmol), **7** (80 μmol), and Pd^0 (2 μmol) under the conditions of CH_3I/**7**/[Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF (1 : 40 : 1 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) for 5 min. [b] The product was identified by GC analysis by comparison with an authentic sample. The yields of the corresponding ethylbenzene or 1-phenyl-1-butene derivatives were determined by GC based on CH_3I consumption using n-nonane or *n*-tridecane as the internal standard, and the average of more than two runs. [c] The yield was determined by HPLC analysis based on CH_3I consumption using naphthalene as the internal standard. [d] See Table 1, entry 13. [e] Reaction was carried out under the conditions using CH_3I/**7**/[Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF (1 : 200 : 5 : 50 molar ratio) in 90 : 10 DMF/H_2O (v/v) for 5 min. [f] The yield was determined by ^{1}H NMR based on the consumption of methyl iodide (2.13 ppm) using dibromomethane (1.81–1.84 ppm) as the internal standard.

products in 96 and 91% yields (entries 10 and 11, respectively). Similar bell-shaped curves of the yields were also observed in the reactions of nonsubstituted and 4-methoxy-cinnamylboronic acid esters **7l** and **7m** (entries 13 and 14), giving methylated products in quantitative and 87% yields at 100 and 80 °C, respectively. Further, the reaction of methyl iodide with excess amounts (40 equiv.) of TMB (**7n**) conducted at 80 °C for 5 min gave the ethane product in quantitative yield as judged by ^{1}H NMR.[30]

It is of interest to note that the use of excess amounts of boron substrate (40 to 200 equiv.) and Pd^0/Phosphine/base relative to methyl iodide (fivefold excess) for both systems, CH_3I/**1**/[$Pd_2(dba)_3$]/P(*o*-$CH_3C_6H_4$)$_3$/K_2CO_3 (1 : 200 : 2.5 : 10 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) and CH_3I/**1**/[Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF (1 : 200 : 5 : 50 molar ratio) in 90 : 10 DMF/H_2O (v/v) provided different results.[30] The change in the yield under the former conditions was not appreciable (Table 1, entries 2 and 4), while the reaction under the latter conditions was accelerated considerably to give **2** in quantitatively yield (Table 1, entry 13),[31] matching well with an actual PET probe synthesis ([[^{11}C]methyl iodide]/[substrate] is typically 1 : >1000).[32]

The yields increased upon the use of larger amounts of various boronic acid ester substrates (200 equiv. for CH_3I, Table 2, entries 5, 6, 9, and 12) as matched with a forthcoming radiosynthesis. The optimized conditions, [Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF (1 : 10 molar ratio) in 90 : 10 DMF/H_2O (v/v) (Table 1, entry 13, and Table 2, entry 3), were easily adapted to the actual synthesis of a PET tracer, *N*-(4-[^{11}C]ethylphenyl)propionamide ([^{11}C]**8c**) using [^{11}C]methyl iodide and boronic acid esters **7c**. The reactions conducted at 90 °C for 5 min gave [^{11}C]**8c** in radio-HPLC analytical yield of 90 ± 1% (n = 3) (Fig. 3).[33] Purification by preparative HPLC gave product [^{11}C]**8c** with radioactivity 5.9 ± 0.4 GBq (n = 3) and specific radioactivity in the range of 98–150 GBq μmol^{-1} and high radiochemical purity (>99%) together with chemical purity 95 ± 1% (n = 3). The isolated radiochemical yield of [^{11}C]**8c** was 49 ± 3% (n = 3) (decay-corrected based on the radioactivity of [^{11}C]methyl iodide trapped in a Pd solution).[34] Total synthesis time of [^{11}C]**8c**, including HPLC purification time, was 32 min.

Conclusions

In conclusion, we developed an efficient Pd^0-mediated sp^3–sp^3-type rapid C–methylation using methyl iodide with excess amounts (40 equiv.) of various benzyl- and cinnamylboronic acid pinacol esters with [Pd{P(*tert*-C_4H_9)$_3$}$_2$] and CsF in 90 : 10 DMF/H_2O (v/v) at 60–120 °C for 5 min with the aim of incorporating a short-lived ^{11}C into organic frameworks. The method is useful for various benzyl- and cinnamylboronic acid pinacol ester derivatives, giving the yields in >80%, except *o*-fluoro-, and *p*-trifluoromethyl-substituted benzyl pinacol

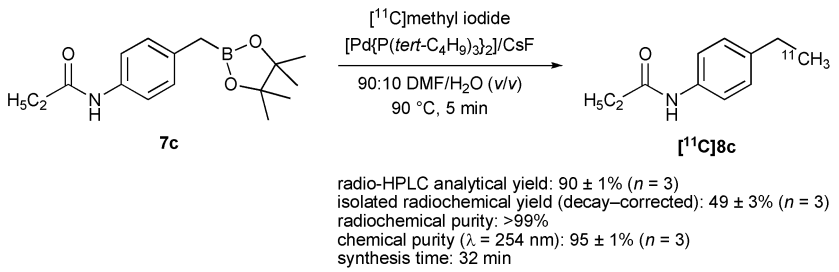


Fig. 3 Rapid synthesis of *N*-(4-[^{11}C]ethylphenyl)propionamide ([^{11}C]**8c**) using [Pd{P(*tert*-C_4H_9)$_3$}$_2$]/CsF (1 : 10 molar ratio) at 90 °C, 5 min.

esters. The optimized yields tended to increase further by increasing the amount of the substrate (200 equiv.) and matched well with an actual radiosynthesis. The utility of the method was demonstrated by the synthesis of *N*-(4-[^{11}C]ethylphenyl)propionamide ([^{11}C]**8c**) with high radio-HPLC analytical yield. The product, [^{11}C]**8c**, was isolated in high radiochemical yield with high radiochemical and chemical purities. Thus, the novel rapid C–[^{11}C]methylation methodology possesses a high potential to incorporate the ^{11}C radionuclide into biologically significant molecules comprised of ethylphenyl- and 1-butenylphenyl unit structures, such as (*RS*)-5-(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl)thiazolidine-2,4-dione (pioglitazone; antihyperglycemic drug),[35] and *trans*-1-(4-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene (tamoxifen; anti-estrogenic[36] and activating agent of the expression of a reporter gene in stem cell progenies),[37] and so on.

By realizing novel, rapid cross coupling between two sp^3-hybridized carbons in the present work, the four possible types of rapid C–[^{11}C]methylations, namely, the rapid [^{11}C]methylations on arene, alkene, alkyne, and alkane frameworks, have been established based on the reactions of [^{11}C]methyl iodide (a readily available precursor for PET probe synthesis) with stable soft metalloid substrates, allowing the rapid ^{11}C labeling of almost any organic compound with high purity. The advantage of the ^{11}C-labeling methods through C–C bond formation is quite obvious in terms of the high credibility of a PET image caused by high *in vivo* stability of ^{11}C-labeled probe molecules, thus providing a useful bible for synthetic chemists working in interdisciplinary scientific areas. Obviously, the C–methylation can also be useful to introduce [^{13}C]H_3, CD_3, and long-lived [^{14}C]H_3 units into biologically important compounds to synthesize molecular probes for various purposes including metabolic studies needing long time.[13]

Experimental

General remarks

All apparatuses used in the cross-coupling reaction were dried in an oven (100 °C) and then with a heat gun under reduced pressure to remove air and moisture. They were then filled with Ar after cooling to room temperature (RT). The air and moisture sensitive materials were treated under Ar using a glove box, vacuum line, and syringe techniques.

The ^{1}H and ^{13}C NMR spectra were recorded on JEOL ECS 400 and Bruker Avance 500 spectrometers (Center for Emerging Infectious Diseases, Gifu University). The chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (δ 0.00 and 0.00) or in ppm relative to $CHCl_3$ (δ 7.26 and 77.0 in ^{1}H and ^{13}C NMR, respectively). The abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. High-resolution mass spectrometry (HRMS) studies were conducted on a PE Biosystems Mariner system or a JEOL JMS-700/GI. Microwave experiment was performed in a Personal Chemistry Emrys Optimizer Automated Microwave Synthesizer (Biotage). Reaction was carried out in heavy-walled Pyrex tubes sealed with screw cap fitted Teflon septa. The [^{11}C]methylation reactions were conducted in a lead-shielded hot cell with remote control of all operations. A CYPRIS HM-12S Cyclotron (Sumitomo Heavy Industry, Tokyo, Japan) was used to produce [^{11}C]carbon dioxide by the ^{14}N(p,α)^{11}C nuclear reaction. An original automated radiolabeling system consisting of the heating of the reaction mixture, dilution, HPLC injection, fractional collection, and evaporation was used for the production of [^{11}C]methyl iodide and the ^{11}C-labeled compounds. Radioactivity was quantified with an ATOMLAB^{TM}300 dose calibrator (Biodex Medical Systems, Inc.). The analytical HPLC system used for the [^{11}C]methylated products consisted of an Aloka radioanalyzer (RLC-700) and a Shimadzu HPLC system with a system controller (CBM-20A), an online degasser (DGU-20A3), a solvent delivery unit (LC-20AD), a column oven (CTO-20AC), a photodiode array detector (SPD-20A), and software (LC-solution). The columns used for analytical and semipreparative HPLC were COSMOSIL C_{18} MS-II 4.6 × 150 mm and C_{18} AR-II 20 × 250 mm (Nacalai Tesque, Inc.).

Materials

Dried DMF was refluxed and freshly distilled over CaH_2 under Ar. Dried THF was continuously refluxed and then freshly distilled from sodium benzophenone ketyl under Ar. All chemicals and solvents were purchased from Sigma-Aldrich (Tokyo, Japan), Wako Pure Chemical Industries (Osaka, Japan), Tokyo Kasei Kogyo (Tokyo, Japan), Kanto Chemical (Tokyo, Japan), and Nacalai Tesque (Kyoto, Japan) and used without further purification. Benzylboronic acid pinacol ester (**1**) and TMB (**7n**) were purchased from Sigma-Aldrich, Japan. Starting benzylboronic acid pinacol ester derivatives were prepared according to literature procedures. Authentic samples of methylated products **2**, **8a**, and **8d**, were purchased from Nacalai Tesque, Japan, and Tokyo Kasei Kogyo, Japan. The other methylated products were prepared according to literature procedures. The [Pd{P(*tert*-C_4H_9)$_3$}$_2$] (Strem Chemicals, Inc.) was recrystallized from degassed THF at −30 °C,[38] dried under high vacuum, and stored in a Schlenk tube under Ar at 4 °C.

Product analysis

The yield of the reactions were determined by GC analysis performed on a Shimadzu GC-2010 instrument equipped with a flame ionization detector; capillary column, TC-1701, 60 m × 0.25 mm i.d., df = 0.25 mm, GL Science Inc., carrier gas: He, flow rate: 0.57 mL min^{-1}, injector temperature: 280 °C, detector temperature: 280 °C, initial column temperature: 70 °C for 5 min, final column temperature: 230 °C, progress rate: 15 °C min^{-1} and 20 °C min^{-1}. The retention times (t_Rs) of the products under these conditions were as follows: ethylbenzene (**2**), 15.4 min; butylbenzene, 20.0 min; 3-phenyl-1-propene, 17.3 min; 1-ethyl-4-methoxybenzene (**8a**), 23.1 min; 1-ethyl-4-methylbenzene (**8d**), 18.4 min; 1-chloro1-4-ethylbenzene (**8f**), 21.6 min; 1-ethyl-3-(trifluoromethyl)benzene (**8j**), 16.0 min; 1-ethyl-4-(trifluoromethyl)benzene (**8k**), 16.2 min; (*E*)-but-1-enylbenzene (**8l**), 23.0 min; 1-[(*E*)-but-1-enyl]-4-methoxybenzene (**8m**), 29.2 min; and n-nonane, 14.5 min. Under conditions of flow rate: 0.57 mL min^{-1}, injector temperature:

280 °C, detector temperature: 280 °C, initial column temperature: 70 °C for 5 min, final column temperature: 270 °C, and progress rate: 20 °C min^{-1}, values of t_R were as follows: 1,2-dimethoxy-4-ethylbenzene (**8b**), 23.8 min; 3-ethyl-benzoic acid ethyl ester (**8j**), 24.6 min; *n*-tridecane, 22.5 min. HPLC was also performed on a Shimadzu HPLC system with a system controller (SCL-10AVP), a degasser (DGU-12A), a liquid chromatograph pump (LC-10AT and LC-10ATVP), a column oven (CTO-10AVP), a UV-vis detector (SPD-10A), and software (CLASS-VP), column: Mightsil RP-18 (4.6 mm i.d. × 150 mm, Kanto Corporation), mobile phase: CH_3CN : H_2O (30 : 70 and 70 : 30, v/v), flow rate: 1.0 mL min^{-1}, detection: UV 254 nm, column temperature: 40 °C, values of t_R were as follows: *N*-(4-ethylphenyl)propionamide (**8c**), 14.5 min; naphthalene, 17.6 min; mobile phase: CH_3CN : H_2O (50 : 50 and 70 : 30, v/v), t_R were as follows: 1-ethyl-4-fluorobenzene (**8g**), 14.6 min; 1-ethyl-2-fluorobenzene (**8h**), 14.8 min; naphthalene, 13.0 min.

Synthesis of ethylbenzene (2) by rapid C–methylation using methyl iodide and large excess amounts of benzylboronic acid pinacol ester (1) (Table 1, entry 13)

[Pd{P(*tert*-C_4H_9)$_3$}$_2$] (5.1 mg, 10 μmol) was placed under Ar in a 10 mL Schlenk tube. Then, the solution of boronic acid ester **1** (87.2 mg, 400 μmol) and CsF (15.2 mg, 100 μmol) in 90 : 10 DMF/H_2O (v/v) (500 μL), made before use, were added. The mixture was stirred at 80 °C for 1 min and methyl iodide (0.8 M DMF solution, 12.5 μL, 10 μmol) was added. After stirring at 80 °C for 5 min, the resulting mixture was rapidly cooled in an ice bath, filtered through a short column of silica gel (0.5 g), and eluted with ethyl ether (*ca.* 2 mL), followed by the addition of n-nonane (0.1 M DMF solution, 50 μL, 5 μmol) as an internal standard. The resulting solution was analyzed by GC. The yield of **2** was 88% based on the starting methyl iodide. The product was identified by GC with an added authentic reference. The methylation reactions under other conditions in Table 1 were conducted using the same procedure as those in entry 13.

The rapid C–methylation of 1 using twofold excess amount of [Pd{P(*tert*-C_4H_9)$_3$}$_2$]

[Pd{P(*tert*-C_4H_9)$_3$}$_2$] (6.1 mg, 12 μmol) was placed under Ar in a 20-mL Schlenk tube. Then, the solution of boronic acid ester **1** (10.9 mg, 60 μmol) and CsF (18.2 mg, 120 μmol) in 90 : 10 DMF/H_2O (v/v) (4.0 mL) were added. The mixture was stirred at 80 °C for 1 min and methyl iodide (0.4 M DMF solution, 15 μL, 6 μmol) was added. After stirring at 80 °C for 5 min, the resulting mixture was rapidly cooled in an ice bath, diluted with diethyl ether (1.0 mL). The organic layer was separated, and the aqueous layer is extracted with diethyl ether (1.0 mL). The combined organic phase was filtered through a short column of silica gel (0.5 g), and eluted with ethyl ether (*ca.* 2 mL), followed by the addition of n-nonane (0.1 M DMF solution, 50 μL, 5 μmol) as an internal standard. The resulting solution was analyzed by GC. The yield of **2** was 91% based on the starting methyl iodide.

Synthesis of 2-(3,4-dimethoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7b)

7b was synthesized according to the reported procedure.[39] 3,4-Dimethoxybenzyl chloride (1.96 g, 10.5 mmol) gave the colorless solid product **7b** (1.40 g, 5.04 mmol, 48.0%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70–6.77 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.23 (s, 2H), 1.24 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 148.7, 131.1, 120.8, 112.5, 111.4, 109.2, 83.5 (2C), 56.0, 55.8, 25.1, 24.8 (4C) ppm; HRMS (EI$^+$): *m*/*z*: calcd for $C_{15}H_{23}BO_4$: 278.1689; found: 278.1676.

Synthesis of *N*-(4-(bromomethyl)phenyl)propionamide

To a solution of 4-aminobenzyl alcohol (1.2 g, 10 mmol) in dried tetrahydrofuran (10 mL) was added $NaHCO_3$ (840 mg, 10 mmol). After the mixture was cooled to 0 °C, propionyl chloride (0.92 mL, 930 mg, 10 mmol) was added, and the mixture was stirred for overnight at RT. The reaction mixture was poured into water (*ca.* 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtrated, and concentrated. The crude product was subjected to silica gel column chromatography {silica gel (50 g), hexane/ethyl acetate = 3 : 2} to afford the colorless solid product *N*-(4-(hydroxymethyl)phenyl)propionamide (570 mg, 3.2 mmol, 32%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J*(H,H) = 4.4 Hz, 2H), 7.32 (d, *J*(H,H) = 4.4 Hz, 2H), 5.05 (s, 2H), 2.32–2.41 (m, 4H), 1.24 (t, *J*(H,H) = 7.6 Hz, 3H), 1.14 (t, *J*(H,H) = 7.6 Hz, 3H) ppm.

To a solution of *N*-(4-(hydroxymethyl)phenyl)propionamide (51 mg, 0.28 mmol) in dried dichloromethane (2.0 mL) was added triphenylphosphine (79 mg, 0.30 mmol) and tetrabromomethane (99 mg, 0.30 mmol) successively, and the mixture was stirred for overnight at RT. The resulting reaction mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography {silica gel (15 g), hexane/ethyl acetate = 3 : 2} to afford the colorless solid product *N*-(4-(bromomethyl)phenyl)propionamide (22 mg, 90 mmol, 32%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J*(H,H) = 8.4 Hz, 2H), 7.33 (d, *J*(H,H) = 8.5 Hz, 2H), 7.13 (s, 1H), 4.47 (s, 1H), 2.38 (q, *J*(H,H) = 7.6 Hz, 2H), 1.24 (t, *J*(H,H) = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): 172.0, 138.1, 133.5, 129.9 (2C), 119.9 (2C), 33.4, 30.9, 9.7 ppm; HRMS (EI$^+$): *m*/*z*: calcd for $C_{10}H_{12}NO^+$: 162.0913; found 162.0901.

Synthesis of *N*-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenyl)propionamide (7c)

7c was synthesized according to the reported procedure.[39] *N*-(4-(Bromomethyl)phenyl)propionamide (43 mg, 0.18 mmol) gave the colorless solid product **8c** (33 mg, 0.12 mmol, 64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J*(H,H) = 8.5 Hz, 2H), 7.10 (d, *J*(H,H) = 8.2 Hz, 2H), 5.05 (s, 1H), 2.34 (q, *J*(H,H) = 7.6 Hz, 2H), 2.23 (s, 2H), 1.22 (q, *J*(H,H) = 7.6 Hz, 3H), 1.21 (s, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.8, 135.1, 134.6, 129.5 (2C), 112.0 (2C), 83.5 (2C), 30.8, 24.9, 24.8 (4C), 9.8 ppm; HRMS (EI$^+$): *m*/*z*: calcd for $C_{16}H_{24}BNO_3$ 289.1849; found 289.1862.

Synthesis of ethyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzoate (7i)

7i was synthesized according to the reported procedure.[39] Ethyl 3-(bromomethyl)benzoate (2.8 g, 12 mmol) gave the colorless solid product (2.0 g, 6.8 mmol, 59%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.89 (m, 4H), 4.35 (q, ^{3}*J*(H,H) = 7.1 Hz,

2H), 2.33 (s, 2H), 1.37 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.22 (s, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 141.6, 139.1, 133.6, 133.1, 130.1, 128.3, 126.3, 83.6 (2C), 60.9, 37.6, 24.8 (4C), 14.4 ppm; HRMS (EI^+): *m*/*z*: calcd for $C_{16}H_{23}BO_4$ 290.1689; found 290.1686.

Synthesis of (*E*)-2-(3-(4-methoxyphenyl)allyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7m)

7m was synthesized according to the reported procedure[40] using 4-methoxybenzyl allylic alcohol (78 mg, 0.48 mmol), affording the colorless solid product **7i** (31 mg, 0.13 mmol, 26%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.26 (m, 2H), 6.79–6.82 (m, 2H), 6.30 (d, ^3J(H,H) = 15.6 Hz, 1H), 6.08–6.16 (m, 2H), 3.78 (s, 3H), 1.83 (d, ^3J(H,H) = 7.6 Hz, 2H), 1.26 (s, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 158.5, 131.2, 129.7, 126.9 (2C), 124.1, 113.9 (2C), 83.4 (2C), 55.4, 24.9 (4C), 24.7 ppm; HRMS (EI^+): *m*/*z*: calcd for $C_{16}H_{23}BO_4$: 274.1740; found 274.1720.

The attempted rapid C–methylation of 1 using various mono- and bidentate ligands

$[Pd_2(dba)_3]$ (1.0 mg, 1.0 μmol), *t*BuBrettPhos (1.9 mg, 4 μmol), and K_3PO_4 (4.2 mg, 20 μmol) were placed under Ar in a 2-mL Schlenk tube. Then, the solution of boronic acid ester **1** (17.4 mg, 80 μmol) in 90 : 10 DMF/H_2O (v/v) (200 μL) was added, and methyl iodide (0.2 M DMF solution, 10 μL, 2 μmol) was added. After stirring at 80 °C for 5 min, the resulting mixture was rapidly cooled in an ice bath, filtered through a short column of silica gel (0.5 g), and eluted with ethyl ether (*ca.* 2 mL), followed by the addition of n-nonane (0.1 M DMF solution, 10 μL, 1 μmol) as an internal standard. The resulting solution was analyzed by GC. The yield of **2** was 8% based on the starting CH_3I. The methylation reactions under other conditions: CH_3I/**1**/$[Pd_2(dba)_3]$/P(*tert*-$C_4H_9)_2(CH_3)$/CsF (1 : 40 : 0.5 : 2 : 10 molar ratio, the yield of **2**: 6%), CH_3I/**1**/$[Pd_2(dba)_3]$/P(biphenyl)(*tert*-$C_4H_9)_2$/CsF (1 : 40 : 0.5 : 2 : 10 molar ratio, the yield of **2**: 3%), and CH_3I/**1**/$[Pd_2(dba)_3]$/P(*i*PrNCH$_2$CH$_2)_3$N/CsF (1 : 40 : 0.5 : 2 : 10 molar ratio, the yield of **2**: 37%) in 90 : 10 DMF/H_2O (v/v) at 80 °C, and CH_3I/**1**/$[Pd(OAc)_2]$/P($C_6H_{11})_3$/K_3PO_4 (1 : 40 : 1 : 2 : 2 molar ratio, the yield of **2**: 2%) in THF at reflux, CH_3I/**1**/[Pd–PEPPS–iPr]/K_3PO_4 (1 : 40 : 1 : 2 : 2 molar ratio, the yield of **2**: 15%), CH_3I/**1**/$[PdCl_2(dppf)]$/K_3PO_4 (1 : 40 : 1 : 10 molar ratio, the yield of **2**: 5%), CH_3I/**1**/$[Pd_2(dba)_3]$/1,2-bis(diphenylphosphino)ethane/CsF (1 : 40 : 0.5 : 1 : 10 molar ratio, the yield of **2**: 0%), CH_3I/**1**/$[Pd_2(dba)_3]$/1,2-bis(dicyclohexylphosphino)ethane/CsF (1 : 40 : 0.5 : 1 : 10 molar ratio, the yield of **2**: 0%), and CH_3I/**1**/$[Pd_2(dba)_3]$/4,5-bis(diphenylphosphine)-9,9-dimethylxanthene/CsF (1 : 40 : 0.5 : 1 : 10 molar ratio, the yield of **2**: 0%) in 90 : 10 DMF/H_2O (v/v) at 80 °C were conducted using the same procedure.

Synthesis of ethane (8n) by rapid methylation using methyl iodide and an excess amount of TMB (7n) (Table 2, entry 15)

$[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$ (1.0 mg, 2 μmol) was placed under Ar in an 1 mL Schlenk tube. The solution of TMB (50 wt% THF solution, 12.6 mg, 8.4 μL, 80 μmol) and CsF (3.0 mg, 20 μmol) in DMF (200 μL) were added, and methyl iodide (0.2 M DMF solution, 10 μL, 2 μmol) was added. After stirring at 80 °C for 5 min, the resulting mixture was rapidly cooled in an ice bath, followed by the addition of dibromomethane (5.0 mg, 2 μL, 29 μmol) as an internal standard. The resulting solution (50 μL) and chloroform-d were added at 0 °C to give a total volume of 750 μL. Yield was 100% determined by ^{1}H NMR integrals based on the consumption of methyl iodide (2.13 ppm) using dibromomethane (1.81–1.84 ppm) as the internal standard.

Synthesis of *N*-(4-[^{11}C]ethylphenyl)propionamide ([^{11}C]8c) by rapid [^{11}C]methylation using [^{11}C]methyl iodide and *N*-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenyl)propionamide (7c)

[^{11}C]Methyl iodide[41] was trapped in the mixture containing $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$ (3.4 mg, 6.6 μmol), boronic acid ester **7c** (5.0 mg, 17 μmol), CsF (10.0 mg, 66 μmol), and DMF (400 μL)/H_2O (50 μL) co-solvent at RT. The radioactivity of [^{11}C]methyl iodide trapped in the Pd solution was measured as 24.8 ± 0.6 GBq (n = 3). The resulting reaction mixture was heated at 90 °C for 5 min. Salts and palladium residue in the resulting reaction mixture was removed by a solid phase extraction, washed with 50 : 50 CH_3CN/H_2O (v/v, 1.3 mL). The mixture was injected onto a semipreparative HPLC column with a mobile phase consisting of 50 : 50 CH_3CN/H_2O (v/v) under the flow rate of 9.9 mL min^{-1} with equipped UV detection at 254 nm. The retention time of [^{11}C]**8c** was 12.8 min. The HPLC analytical yield of [^{11}C]**8c** was 90 ± 1% (n = 3), calculated from peak area ratio of the [^{11}C]product distributions. The desired fraction was collected in a flask containing 25% ascorbic acid solution (0.25 mL) to give product with radioactivity 5.9 ± 0.4 GBq (n = 3) and specific radioactivity in the range of 98–150 GBq μmol^{-1}. The isolated yield was decay corrected as 49 ± 3% (n = 3), based on the radioactivity of [^{11}C]methyl iodide trapped in the Pd solution. Total synthesis time was 32 min. A sample solution (20 μL) of product was analyzed by HPLC with a UV absorbance detector and a radiation detector (column, COSMOSIL 5C_{18}-MS-II, 4.6 mm i.d. × 150 mm; mobile phase, 50 : 50 CH_3CN/H_2O (v/v); flow rate, 1.0 mL min^{-1}; detection, UV 254 nm). The retention time of [^{11}C]**8c** was 4.5 min. Radiochemical and chemical purities were >99% (n = 3) and 95 ± 1% (n = 3), respectively.

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