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Evaluation of TlOH Effect for Pd^0-Mediated Cross-Coupling of Methyl Iodide and Excess Boronic Acid Ester toward Fabrication of [^{11}C]CH_3-Incorporated PET Tracer

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ABSTRACT

The use of thallium(I) hydroxide (TlOH) as a base is known to extremely accelerate the Suzuki-Miyaura cross-coupling reaction using organoboronic acid or organoboronic acid ester as a substrate. Here, we investigated the effects of TlOH by comparing with other conventional bases such as KOH, K_2CO_3, and CsF for Pd^0-mediated rapid cross-coupling reactions between CH_3I and organoborane reagents, such as phenyl-, (*Z*)-4-benzyloxy-2-butenyl-, and benzylboronic acid pinacol esters under the conditions CH_3I/borane/Pd^0/base (1:40:1:3) in THF/H_2O or DMF/H_2O for 5 min with an aim to fabricate a PET tracer efficiently. Consequently, however, the use of TlOH was much less efficient than the other bases for the acceleration of cross-coupling reactions. Thus, it was reconfirmed that the milder and non-toxic conditions using K_2CO_3 or CsF so far developed by our group were most appropriate for the rapid *C*-methylations.

Keywords: Synthesis of Short-Lived Positron Emission Tomography Probes; Suzuki-Miyaura-Type Rapid Cross-Coupling; Rapid *C*-Methylation; TlOH

1. Introduction

Cross-coupling reactions are among the most powerful synthetic tools for the formation of carbon-carbon bonds. The Suzuki-Miyaura reaction (SMR) is the most prominent cross-coupling reaction, and involves the Pd^0-catalyzed coupling of an alkyl halide with an organoboronic acid or ester [1]. For example, the reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides in the presence of [Pd{$P(C_6H_5)_3$}$_4$] and a base such as $NaOC_2H_5$ or NaOH produced the corresponding coupled products in high yields [2]. During the synthesis of the complex marine natural product, palytoxin, the SMR was employed for the formation of C(75)-C(76) bond [3]. The rate of the coupling reaction significantly decreased when the reaction was carried out on complex substrates with high molecular weight. As a result, none of the desired intermediates was observed when the reaction was carried out in the presence of KOH even at elevated temperatures (70˚C) and for extended duration (18 h). This problem was solved by replacing the KOH with thallium hydroxide (TlOH). TlOH was found to significantly accelerate the coupling reaction (1000 times), resulting in the desired product in good yield (63%) after only 25 min at room temperature [3].

Positron emission tomography (PET) provides a highly sensitive and accurate quantification method for elucidating pharmacokinetics of molecules in the whole-bodies of animals and humans through the use of a specific molecular probe labeled with a positron-emitting radionuclide [4]. This technique could also be applied to the efficient screening of drug candidates. When human trial is introduced at an early stage in the drug development process, it could suppress the number of drop-out candidates in clinical trials, significantly reducing the

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investment and time for drug development. In view of the high stability of the resulting C-C bond and the safety concerns associated with radiation exposure, we focused our studies on the short-lived ^{11}C radionuclide (half-life: 20.4 min). Four types of rapid cross-coupling reactions (rapid *C*-[^{11}C]methylations) were developed for arene, alkene, alkyne, and alkane frameworks using [^{11}C]methyl iodide and excess amounts of organostannyl and organoborane substrates [5]. Pd^0-mediated Suzuki-Miyaura-type rapid *C*-methylations were conducted using methyl iodide and a phenyl- [6], an alkenyl- [7] a benzyl- [8], or a cinnamylboronic acid ester [8] in the presence of either [Pd{P(*o*-$CH_3C_6H_4)_3$}$_2$] or [Pd{P(*tert*-$C_4H_9)_3$}$_2$] and a conventional base such as K_2CO_3 and CsF. These conditions are superior to the method using [Pd(dppf)Cl_2] (dppf = 1,1'-bis(diphenylphosphino)ferrocene) and K_3PO_4 under microwave heating [9]. Though the effect of TlOH as a base for the abovementioned methylation is an attractive alternative, its scope and limitations largely remain unexplored.

Described herein is the evaluation of TlOH for the acceleration of Pd^0-mediated *C*-methylations using methyl iodide and a series of organoborane reagents, as well as its comparison with other commonly used bases.

2. Results and Discussion

For the actual PET tracer synthesis, we set up a model reaction using excess boronic acid pinacol ester for methyl iodide (40 equiv) [6-8]. The reaction time was fixed at 5 min, which is similar to our previous studies using organoborane compounds [7,8]. First, we attempted Kishi's conditions that involve the reaction of phenylboronic acid pinacol ester (**1a**) under CH_3I/**1a**/[Pd{P($C_6H_5)_3$}$_4$]/ TlOH (1:40:1:3) in 90:10 THF/H_2O at RT for 5 min [3]. However, the reaction did not afford any of the desired product (toluene, **2a**). The use of the corresponding phenylboronic acid (3) as a substrate also gave toluene (2a) in low yield (9%) under CH3I/3/[Pd{P(C6H5)3}4]/ TlOH/THF/H2O/RT. The use of such an acid as a substrate is also unfavorable, because in the actual PET probe synthesis, the separation of an extremely small amount of the product (~100 ng) from the large excess of the substrate (>1000-fold equiv) would not be easy by reverse-phase HPLC because of high polarity of the acid substrate. Therefore, further study using the boronic acid as substrate has not been continued. Moreover, increasing the temperature to 60˚C did not result in any appreciable improvement either, providing only 39% of the desired product **2a** (**Table 1**, entry 1). In contrast, the use of a bulky monodentate phosphine (P(*o*-$CH_3C_6H_4)_3$) accelerated the reaction to a considerable extent [5], affording the desired product in yields of 60% and 65% in THF; 43% and 73% in DMF at 25˚C and 60˚C, respectively (**Table 1**, entries 2 and 3) [11]. However, these yields were much lower than those obtained under conditions using conventional bases such as KOH, K_2CO_3, and CsF (>93%, **Table 1**, entries 4-7).

The rate of the *C*-methylation reaction using TlOH as a base in THF/H_2O was not enhanced in the presence of the bulky monodentate ligand such as 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) or the bidentate ligands such as dppf and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, providing **2a** in only 7%, 21%, and 0% yields, respectively.

The effects of TlOH on the *C*-methylation of an alkenylboronic acid ester were similar to those of the phenylboronic acid ester (**Table 1**, entries 8-10). For example, none of the desired product was obtained upon the reaction of (*Z*)-4-benzyloxy-2-butenylboronic acid pinacol ester (**1b**) [10] with CH_3I/**1b**/[Pd{P($C_6H_5)_3$}$_4$]/ TlOH (1:40:1:3) in 90:10 THF/H_2O (*v*/*v*) for 5 min at RT. Even elevated temperature and the use of the bulky P(*o*-$CH_3C_6H_4)_3$ provided lower yields for the TlOH system, compared to the condition when K_2CO_3 and CsF were used (entries 8-10 vs. 12 and 13), as was observed for the methylation of **1a**.

When the *C*-methylation reaction was applied to the benzylboronic acid pinacol ester (**1c**), none of the desired ethylbenzene (**2c**) was obtained. Increasing the reaction temperature to 80˚C resulted in the formation of **2c**, albeit in only 14% yield (**Table 1**, entry 14) [11]. Use of the bulky phosphines P(*o*-$CH_3C_6H_4)_3$ or P(*tert*-$C_4H_9)_3$ in conjunction with TlOH tended to raise the yield to some extent, but they were still much less effective than the conventional bases (entries 14-17 vs. 18 and 19). Activation of an organoborane nucleophile by the coordination of a base is important to promote the cross-coupling reaction [2]. It is considered [3] that TlOH might be involved in the halogen/OH exchange to generate R1PdIIOH-L2, namely, by the reaction of TlOH and R1PdIIX-L2 which is formed by the oxidative addition of an organic halide (R1X) with Pd0Ln complex, accelerating the cross-coupling reaction extremely. However, such a particular effect of TlOH did not reflect on the present C-methylations

In conclusion, TlOH did not provide any benefit as compared with other conventional bases for the acceleration of the cross-coupling reactions of methyl iodide and various types of organoborane reagents. Particularly, the use of highly toxic TlOH as a base would be unfavorable in the actual synthesis of short-lived PET probe because rapid purification of the radioactive product from a mixture containing TlOH is quite difficult. Such a strong base may also be detrimental for base-sensitive substrates. The results presented herein serve as a confirmation that the conditions described in our previous Pd^0-mediated rapid *C*-methylation studies [5-8] are currently the most efficient [3,9]. The four novel types of rapid *C*-methylations discussed above are potential groundbreaking

methods for fabricating short-lived ^{11}C-incorporated PET probes for *in vivo* molecular imaging studies in both animals and humans. Acutually, Pd0-mediated rapid C-methylations using soft bases have already been applied for clinical investigation under approval of ethical committee. Thus, PET probes can be synthesized in high yield with high radiochemical and chemical purities adequately applicable to human studies [12,13]

3. Experimental

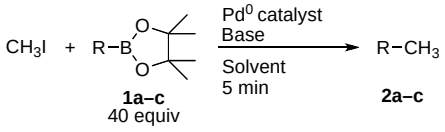
3.1. General

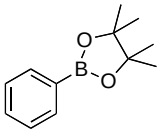
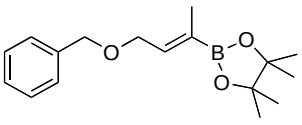
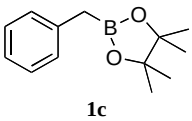
All manipulations were carried out under an Ar atmosphere using Schlenk techniques. The reaction yields were determined by gas chromatographic (GC) analysis per formed on a Shimadzu GC-2010 instrument equipped with a flame ionization detector; capillary column, TC-1701, 60 m × 0.25 mm i.d., df = 0.25 mm, GL Science Inc. (Tokyo, Japan).

3.2. Reagents

THF was continuously refluxed and then freshly distilled from sodium benzophenone ketyl under Ar. DMF was refluxed and freshly distilled over CaH_2 under Ar. Phenyl- and benzyl-boronic acid pinacol esters were purchased from Wako Pure Chemical Industries (Osaka, Japan) and Sigma-Aldrich (Tokyo, Japan), respectively, and used without further purification. $[Pd\{P(C_6H_5)_3\}_4]$, $[Pd_2(dba)_3]$, and $P(o\text{-}CH_3C_6H_4)_3$ were purchased from Sigma-Aldrich. $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$ (Strem Chemicals, Inc., Massachusetts, US) was recrystallized from de-

Table 1. Comparison of TlOH with other conventional bases on the coupling of methyl iodide with excess boronic acid pinacol ester (1) [a].



Entry	Boron	Pd[0] [b]	Base	Solvent [c]	Yield (%) [d]		
					25˚C	60˚C	80˚C
1 [e]		A	TlOH	THF/H_2O	0	39	–
2		B	TlOH	THF/H_2O	60	65	–
3		B	TlOH	DMF/H_2O	43	73	–
4		B	KOH	THF/H_2O	–	93	–
5	**1a**	B	KOH	DMF/H_2O	–	97	–
6		B	K_2CO_3	DMF/H_2O	–	94 [f]	–
7		B	CsF	DMF/H_2O	–	100	–
8 [e]		A	TlOH	THF/H_2O	0	38	–
9		B	TlOH	THF/H_2O	26	64	–
10		B	TlOH	DMF/H_2O	–	76	–
11		B	KOH	DMF/H_2O	–	80	–
12	**1b**	B	K_2CO_3	DMF/H_2O	–	95	–
13		B	CsF	DMF/H_2O	–	100	–
14 [e]		A	TlOH	THF/H_2O	0	–	14
15		B	TlOH	THF/H_2O	0	–	24
16		B	TlOH	DMF/H_2O	1	–	51
17		C	TlOH	DMF/H_2O	–	48	41
18	**1c**	C	KOH	DMF/H_2O	–	64	78
19		C	CsF	DMF/H_2O	–	–	88 [g]

[a] Reaction was carried out under the conditions using CH_3I/**1**/Pd^0/base (1:40:1:3 molar ratio). [b] Pd^0: A, $[Pd\{P(C_6H_5)_3\}_4]$; B, $[Pd_2(dba)_3]/P(o\text{-}CH_3C_6H_4)_3$ (1:4 molar ratio); C, $[Pd\{P(tert\text{-}C_4H_9)_3\}_2]$. [c] 90:10 (*v*/*v*). [d] 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. [e] Ref. [3]. [f] Ref. [7]. [g] Ref. [8].

gassed THF at –30˚C, dried under high vacuum, and stored in a Schlenk tube under Ar at 4˚C. Methyl iodide was purified via distillation over P_2O_5 under Ar. Aqueous TlOH solutions were prepared from Tl_2SO_4 and $Ba(OH)_2$ just before using them.

3.3. Typical Procedure of Rapid *C*-Methylation Using Methyl Iodide and Large Excess of Phenylboronic Acid Pinacol Ester (1a, Table 1, Entry 2)

$[Pd_2(dba)_3]$ (0.9 mg, 1 μmol) and P(*o*-$CH_3C_6H_4)_3$ (1.2 mg, 4.0 μmol) were placed under Ar in a 1-mL Schlenk tube. Then, the solution of boronic acid ester **1a** (16.3 mg, 80.0 μmol), DMF (180 μL), TlOH (0.30 M aqueous solution, 20 μL, 6.0 μmol), and methyl iodide (0.20 M DMF solution, 10 μL, 2.0 μmol) were added sequentially. The resulting mixture was then stirred at 60˚C for 5 min. Next, the solution 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 (0.10 M DMF solution, 10 μL, 5.0 μmol) as an internal standard. The fractions were analyzed by GC and the product was compared to an authentic reference.

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