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Rapid methylation of terminal acetylenes by the Stille coupling of methyl iodide with alkynyltributylstannanes: a general protocol potentially useful for the synthesis of short-lived $^{11}CH_3$-labeled PET tracers with a 1-propynyl group †

Takamitsu Hosoya,[a,b] Masahiro Wakao,[a] Yurie Kondo,[b] Hisashi Doi[a] and Masaaki Suzuki*[a,b]

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

[b] *Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan*

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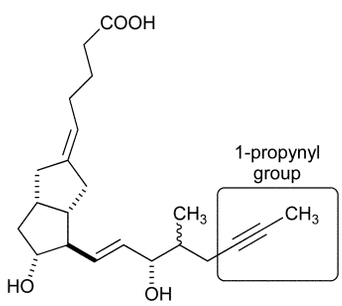
The Pd(0)-mediated rapid coupling (trapping) reaction of methyl iodide with an excess amount of alkynyltributylstannane has been developed with the aim to incorporate a short-lived ^{11}C-labeled methyl group into biologically active organic compounds with a 1-propynyl structural unit.

Positron emission tomography (PET) is a particularly powerful, noninvasive method for the molecular imaging of living systems such as the brain, heart, and other active organs.[1] In the PET study, a specific organic PET tracer is efficiently used as a molecular probe to monitor the biochemical processes and localization of a target molecule involved in important biofunctions and related phenomena. The need for the development of new PET tracers has grown with the increase in the use of this technique in in vivo biochemistry and medicine.[1] In light of this need, we have recently developed the rapid Stille cross-coupling (5 min, 60 °C in DMF) of methyl iodide with aryltributylstannanes possessing sp^3 and sp^2 carbons, respectively, at the reaction centers[2] and applied it successfully to the synthesis of a short-lived, ^{11}C-incorporated PET tracer ($t_{1/2}$ = 20.3 min), 15*R*-[^{11}C]TIC methyl ester,[3] an efficient prostaglandin probe, using $^{11}CH_3I$,[4] a synthetically established precursor, to image a novel prostacyclin (PGI_2) receptor (IP_2) present in the central nervous system in living monkey and human brains.[3,5]

Our next interest has been directed at the rapid introduction of a $^{11}CH_3$ group to an alkyne terminal to develop new PET tracers of biologically significant molecules with a 1-propynyl structure. Examples of molecules with this structure include iloprost (**1**) (a stable PGI_2 analogue specific for the PGI_2 receptor, IP_1,[3] in peripheral systems used as potential therapeutic agent),[6,7] beraprost (a PGI_2 analogue possessing the same ω side-chain as **1**),[8] 2-(1-propnyl)estradiol (a tubulin polymerization inhibitor),[9] RU 28362 (a glucocorticoid receptor agonist),[10] E3620 (a 5-HT_3 receptor antagonist/5-HT_4 receptor agonist),[11] 2′-deoxy-5-(1-propynyl)uridine (an antiviral agent),[12] and several others. Among the numerous methylation methods available,[13] the Stille coupling[14] using an alkynyltributylstannane as a trapping substrate of methyl iodide is ideal because: (1) the usual reaction conditions are compatible with a broad range of functional groups,[13] (2) alkynylstannanes are tolerant enough of various reaction, workup, and chromatographic conditions to be transformed intact to the actual stage of the coupling reaction,[15,16] and (3) the extremely low polarity of tributyl-substituted alkynylstannanes makes for easy chromatographic isolation of the desired ^{11}C-incorporated coupling product from the remaining excess amount of tin substrate after the reaction.[13,16] Although innumerable reports have described,[14,17] the reports of Stille reactions between sp^3/sp carbons are quite limited,[18,19] and, to our surprise, Stille reactions including methyl iodide remain unexplored. Described herein is a general protocol which provides a firm chemical basis for the synthesis of a $^{11}CH_3$-incorporated PET tracer with a 1-propynyl moiety in the structure.



iloprost (**1**)

Non-functional tributyl-1-hexynylstannane (**2**) was used as a trapping agent to establish the standard reaction conditions. The reaction conditions were fixed at 60 °C in DMF[2a] for 5 min with the use of a large excess (40-fold) of the stannyl substrate, keeping the actual PET tracer synthesis in mind.[13] Initially, some Pd(0)-complexes often utilized in the Stille reaction[14] (Table 1, entries 1–4), and our conditions previously established in the rapid methylation of aryl substrates[2] (entry 6) were investigated, resulting in the desired 2-heptyne (**3**) in yields between 11 and 61%. In the course of further studies, we noted that the steric and electronic properties of phosphine ligands influenced the yield of the coupling product. Among the ligands examined, tri-*tert*-butylphosphine ($PtBu_3$)[20] facilitated the reaction the most, resulting in a 72% yield (entry 9). The reaction was further improved to give an 81% yield (entry 10) by the direct use of bis(tri-*tert*-butylphosphine)palladium(0) ($Pd(PtBu_3)_2$), a commercially available complex,[21] instead of generating it *in situ* by mixing $Pd_2(dba)_3$ and $PtBu_3$. Further, the addition of CsF or KF facilitated an even higher reaction yield (entries 14 and 15, respectively), while the addition of LiCl or TBAF retarded the reaction (entries 12 and 13, respectively).[22] Thus, as can be seen in Table 1, the highest yield (95%) was generated by the reaction in the presence of KF (entry 15). ‡

† Electronic supplementary information (ESI) available: general experimental remarks and synthetic methods and characterization of tributylalkynylstannanes and the corresponding methylacetylenes. See http://www.rsc.org/suppdata/ob/b3/b311532a/

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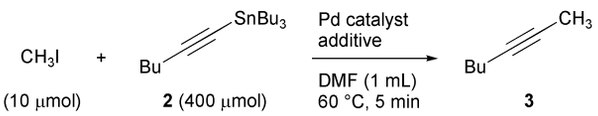
Table 1 Rapid coupling of methyl iodide with tributyl-1-hexynylstannane (**2**)



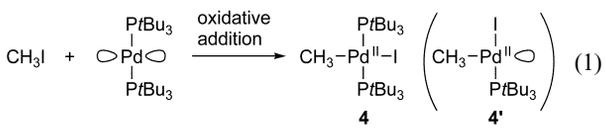
Entry	Pd catalyst (μmol)	Additive(s) (μmol)	Yield of **3**[a] (%)
1	$Pd(PPh_3)_4$ (10)	—	27
2	$Pd_2(dba)_3$ (5)	PPh_3 (20)	11
3	$Pd_2(dba)_3$ (5)	P(2-furyl)$_3$ (20)	30
4	$Pd_2(dba)_3$ (5)	$AsPh_3$ (20)	61
5	$Pd_2(dba)_3$ (5)	P(*o*-tolyl)$_3$ (20)	20
6	$Pd_2(dba)_3$ (5)	P(*o*-tolyl)$_3$ (20), K_2CO_3 (20), CuCl (20)	43
7	$Pd_2(dba)_3$ (5)	P(cyclohexyl)$_3$ (20)	49
8	$Pd_2(dba)_3$ (5)	PMe(*t*Bu)$_2$ (20)	67
9	$Pd_2(dba)_3$ (5)	P*t*Bu$_3$ (20)	72
10	Pd(P*t*Bu$_3$)$_2$ (10)	—	81
11	Pd(P*t*Bu$_3$)$_2$ (10)	K_2CO_3 (20), CuCl (20)	45
12	Pd(P*t*Bu$_3$)$_2$ (10)	LiCl (20)	27
13	Pd(P*t*Bu$_3$)$_2$ (10)	TBAF (20)	15
14	Pd(P*t*Bu$_3$)$_2$ (10)	CsF (20)	92
15	Pd(P*t*Bu$_3$)$_2$ (10)	KF (20)	95
16	$Pd_2(dba)_3$ (5)	PMe(*t*Bu)$_2$ (20), CsF (20)	10

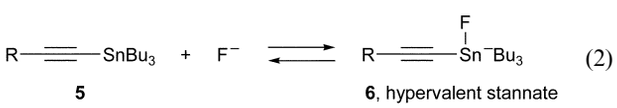
[a] Determined by GLC analysis based on CH_3I consumption.

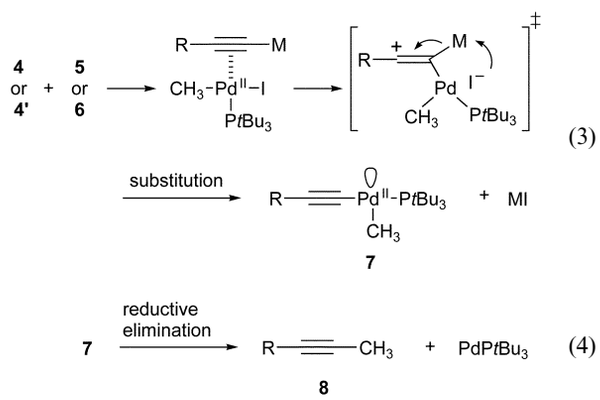
Interestingly, the addition of CsF to the $Pd_2(dba)_3$/PMe(*t*Bu)$_2$ system[19,20] led to an unexpectedly poor result (entry 16).

The reaction of methyl iodide and a stoichiometric amount of **2** at 60 °C for 5 min also proceeded under catalytic conditions (CH_3I/**2**/Pd(P*t*Bu$_3$)$_2$/KF = 1/1/0.1/1 and 1/1/0.02/1) to give 96 and 91% of **3**, respectively, strengthening the utility of the coupling reaction from the synthetic point of view.[23]

The reaction most likely proceeds by the mechanism proposed in eqns. (1)–(4), where M = Bu_3Sn or Bu_3SnF^-. First, methyl iodide undergoes oxidative addition with Pd(P*t*Bu$_3$)$_2$ to generate methyl–Pd(II) iodide **4** or **4′** (eqn. (1)).[24,25] These Pd(II) complexes may then react directly with alkynylstannane **5** or more favorably with the hypervalent stannate **6**, formed in situ by the addition of a fluoride ion source (eqn. (2)), to afford the (alkynyl)(methyl)Pd(II) complex **7** (eqn. (3)). Finally, the desired methylalkyne **8** is formed by reductive elimination of the Pd(II) complex **7** (eqn. (4)).[13f] Here, we assume that the bulkiness (cone angle 182°)[26] and the strong σ-electron-donating ability (pK_a = 11.4)[27] of P*t*Bu$_3$ would contribute to the generation of highly reactive, coordinatively unsaturated Pd(0) and Pd(II) intermediates, and also to the stabilization of the palladium complexes to avoid metal precipitation at high temperatures throughout the reaction cycle. We further assume that the extraordinarily high basicity of P*t*Bu$_3$ would also serve not only to increase the nucleophilicity for the oxidative addition step (eqn. (1)), but also to facilitate the dissociation of iodide to stabilize the transition state structure for the substitution step (eqn. (3)). In addition, the effect of fluoride ion can be explained by its facilitation of the formation of the hypervalent stannyl complex **6**, whose nucleophilic C–Sn bond is more polar than that in **5** (eqn. (2)).[20,28] The choice of a proper counter cation in the formation of the stannate complex **6** is also important to promote the reaction effectively, although the role of the cationic species remains unclear.







The best protocol (entry 15 in Table 1)‡ allows for the controlled methylation of a variety of alkynyltributylstannanes consisting of oxygen-based functional groups such as ethers, hydroxy groups, and ester groups. Compounds **9**–**14** are examples in our studies that were generated in 80, 89, 91, 88, 96 and 82% yields, respectively.[29] The reaction was also applicable to the stannyl precursors **15** and **16**, which are the substrates with steroid and deoxyribonucleoside frameworks, giving methylated compounds **17** and **18**[12] in 87 and 74%[29] yields, respectively.

Finally, we demonstrated the trapping protocol of methyl iodide with a five-fold amount of stannyl precursor **19** leading to iloprost methyl ester (**20**) in 81% yield (based on the consumption of CH_3I) (Scheme 1).§ This ester **20** undergoes rapid enzymatic hydrolysis in the vital system to generate the free acid **1** as the bioactive form,[3] and, therefore, the corresponding [^{11}C]iloprost methyl ester can be used as a PET tracer.[30]

Thus, we have succeeded in elaborating the rapid methylation of terminal acetylenes under mild conditions, which is potentially useful for the synthesis of short-lived $^{11}CH_3$-labeled PET tracers to promote *in vivo* molecular science for medical purposes. The synthesis of actual PET tracers and their use for molecular imaging will be reported in due course.

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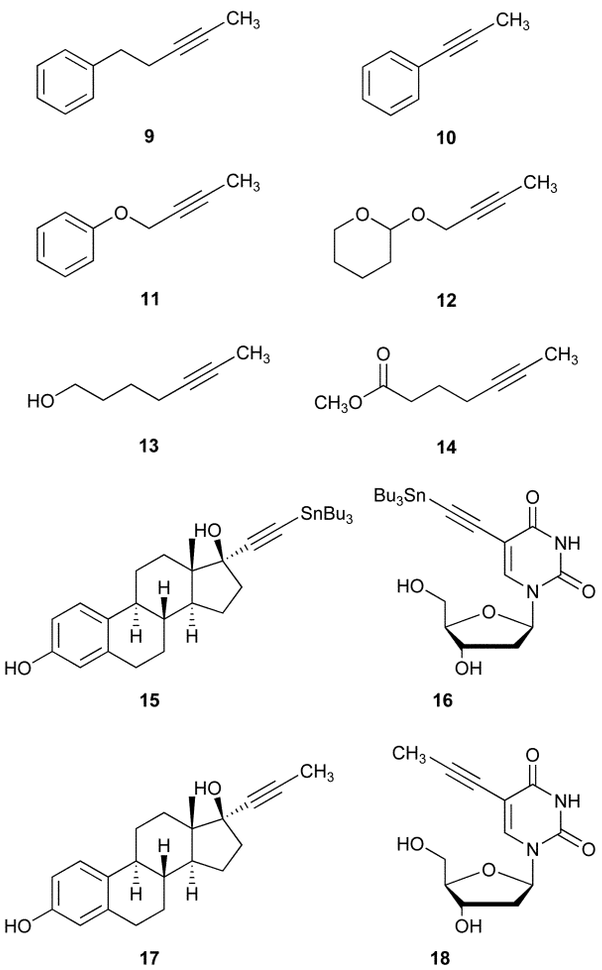

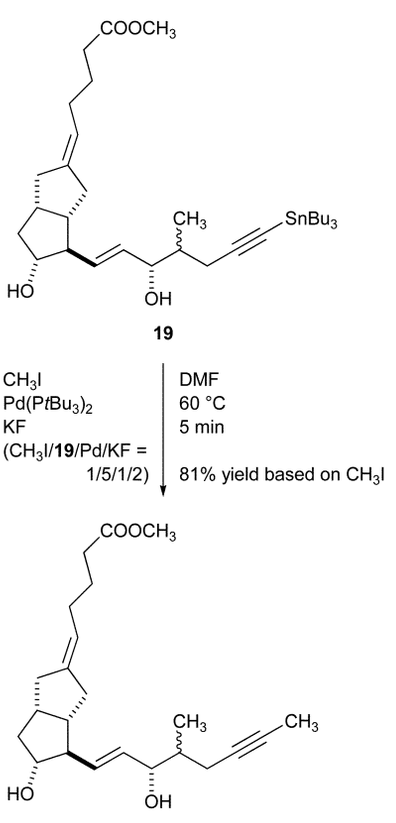

Scheme 1

Notes and references

‡ *Trapping reaction of methyl iodide with an excess amount of tributyl-1-hexynylstannane* (**2**) *leading to 2-heptyne* (**3**): In a dry Schlenk tube (10 mL), bis(tri-*tert*-butylphosphine)palladium(0) (5.1 mg, 10 μmol) and potassium fluoride (1.2 mg, 20 μmol) were placed under Ar. After the addition of DMF (950 μL), the mixture was stirred for 5 min at room temperature followed by successive additions of a methyl iodide solution (50 μL, 0.20 M, 10 μmol) in DMF and a stannane **2** (148 mg, 400 μmol). After stirring at 60 °C for 5 min, the mixture was rapidly cooled in an ice bath, followed by the addition of *n*-nonane (50 μL, 0.10 M diethyl ether solution, 5.0 μmol) as an internal standard, and diethyl ether (1 mL). The mixture was loaded onto a short column of silica-gel (1.0 g) and then eluted with diethyl ether (*ca*. 1 mL). The combined eluates were analyzed by GLC (Shimadzu GC-14B instrument equipped with a flame ionization detector; capillary column: GL Science TC-5, 60 m × 0.25 mm i.d., d_f = 0.25 μm; carrier gas: He; flow rate: 0.5 mL min^{-1}; injector temperature: 280 °C; detector temperature: 280 °C; column temperature: initial 70 °C, final 100 °C; temperature rising rate: 5 °C min^{-1}, from 10 to 16 min): yield of 2-heptyne (**3**): 95% based on starting CH_3I; retention time: 12.6 min (*cf*. *n*-nonane: 17.9 min).

§ *Application to the synthesis of iloprost methyl ester* (**20**): In a dry Schlenk tube (10 mL), bis(tri-*tert*-butylphosphine)palladium(0) (0.8 mg, 1.6 μmol) and potassium fluoride (0.2 mg, 3.2 μmol) were placed under Ar. After the addition of DMF (400 μL), the mixture was stirred for 5 min at room temperature followed by successive additions of a methyl iodide solution (32 μL, 50 mM, 1.6 μmol) in DMF and a solution of stannane **19** (5.1 mg, 8.0 μmol) in DMF (400 μL). After stirring at 60 °C for 5 min, the mixture was rapidly cooled in an ice bath, followed by the removal of insoluble materials by filtration through a plug of cotton. The filtrate was azeotropically concentrated with toluene under reduced pressure, and the residual material was filtered through a short column of silica-gel (1.0 g, eluted with *n*-hexane–ethyl acetate = 1 : 1). Anisole (10 μL, 0.20 M CH_3CN solution, 2.0 μmol) was added to the combined eluates as an internal standard, and the mixture was then analyzed by reversed-phase HPLC (Mightysil RP-18 GP column: Kanto Chemical, 150 × 4.6 mm i.d.; eluted by CH_3CN/H_2O = 45/55; flow rate 1.0 mL min^{-1}; column oven temperature 40 °C; detected by UV at 203 nm); yield of iloprost methyl ester (**20**): 81% based on starting CH_3I; retention time: 21.1 and 22.6 min (16*R*- and 16*S*-epimers, respectively) (*cf*. anisole: 7.4 min).

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30 Successful synthesis of [^{11}C]iloprost methyl ester will be reported independently.