Rapid Coupling of Methyl Iodide with Aryltributylstannanes Mediated by Palladium(0) Complexes: A General Protocol for the Synthesis of $^{11}CH_3$-Labeled PET Tracers

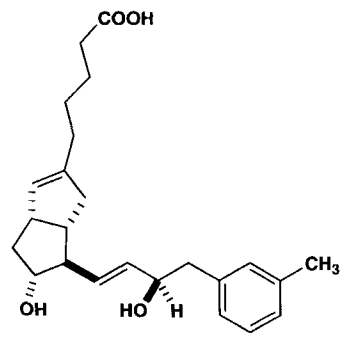
Masaaki Suzuki,* Hisashi Doi, Margareta Björkman, Yvonne Andersson, Bengt Långström, Yasuyoshi Watanabe, and Ryoji Noyori*

Abstract: The reaction of methyl iodide and (excess) aryltributylstannane to give a methylarene has been studied with the focus on the realization of rapid coupling for incorporation of short-lived radionuclides into bioactive organic compounds. The coupling of methyl iodide with tributylphenylstannane (40 equiv) is accomplished in >90% yield within 5 min at 60 °C with a tri-*o*-tolylphosphine-bound, coordinatively unsaturated Pd^0 complex together with a Cu^I salt and K_2CO_3 in DMF. This protocol is applicable to a variety of homo- and heteroaromatic tin compounds, to give the corresponding methylated derivatives. The effects of the tri-*o*-tolylphosphine ligand, a Cu(I) salt, and DMF are discussed. This new protocol provides a firm chemical basis for the synthesis of $^{11}CH_3$-incorporated PET tracers.

Keywords
arylphosphanes · C–C coupling · isotopic labeling · palladium · tin

Introduction

Efficient chemical reactions for isotope labeling are extremely important in the study of the behavior and metabolism of biologically significant substances. Positron emission tomography (PET) is a particularly powerful noninvasive method for the investigation of in vivo biochemistry, especially in the human brain. The need for the development of new PET tracers has grown with the increase in the use of this technique in medicine.[1] In the light of this need, we recently developed (15*R*)-TIC (**1**), a prostaglandin (PG) ligand, which is selectively responsive to a prostacyclin receptor in the central nervous system.[2] The tolyl group in **1** was intended as a trigger component to create a radioligand incorporating ^{11}C. It was assumed that the $^{11}CH_3$ group would be readily introduced by the Stille reaction[3] with $^{11}CH_3I$, a frequently used precursor for $^{11}CH_3$-labeled tracers. In fact, the Stille reaction would be ideal, because a) the incorporation of the short-lived ^{11}C nuclide ($t_{1/2}$ = 20.3 min) is accomplished at the final stage of the synthesis, b) organotin reagents are tolerant of most functional groups present in biomolecules, and c) it has broad applicability. However, to our surprise, there is little information on the Stille reaction with methyl iodide,[4] although many sp^2 or allylic organic halides have successfully been utilized.[3] Methylation with this method has remained difficult. Screening of various existing Pd catalysts in the Uppsala laboratories to trap $^{11}CH_3I$, with tributylphenylstannane as a model, revealed that trapping was very sluggish,[5] hampering the incorporation of ^{11}C into **1**. The reaction must be accomplished within several minutes to leave enough time for work-up and chromatographic purification. If trimethylphenylstannane is used, both phenyl and methyl moieties participate in the reaction, producing undesired $^{11}CH_3$-containing ethane as a by-product.[5, 6] The problems with this potentially attractive method led us to develop a rapid coupling reaction of methyl iodide with a variety of aryltributylstannanes. We now report on a general protocol which provides a firm chemical basis for the synthesis of $^{11}CH_3$-incorporated PET tracers, including ^{11}C-labeled (15*R*)-TIC (**1**).



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[*] Prof. Dr. M. Suzuki
Department of Biomolecular Science, Faculty of Engineering
Gifu University, Gifu 501-11 (Japan)
Fax: Int. code + (58)293-2635
e-mail: suzukims@apchem.gifu-u.ac.jp
Prof. Dr. R. Noyori, H. Doi
Department of Chemistry and Molecular Chirality Research Unit
Nagoya University, Nagoya 464-01 (Japan)
Fax: Int. code + (52)783-4177
e-mail: noyori@chem3.chem.nagoya-u.ac.jp
M. Björkman, Dr. Y. Andersson, Prof. Dr. B. Långström
Department of Chemistry and PET Centre, Uppsala University
Uppsala (Sweden)
Dr. Y. Watanabe
Subfemtomole Biorecognition Project, Japan Science and Technology Cooperation (JST)
Osaka Bioscience Institute, Osaka 565 (Japan)

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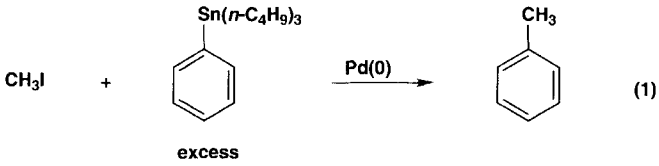
Results and Discussion

Conditions for the synthesis of PET tracers are very different from those found in ordinary organic syntheses. In particular, the reaction is conducted with an extremely small amount of $^{11}CH_3I$. Therefore, the coupling reaction was set up with a large excess (40:1) of tributylphenylstannane relative to methyl iodide [Eq. (1)]. The results are summarized in Table 1. The Stille



(1)

reaction usually uses tetrakis(triphenylphosphine)palladium(0) ($[Pd(PPh_3)_4]$) or a Pd^0 complex formed in situ from $[Pd_2(dba)_3(CHCl_3)]$ (dba = dibenzylideneacetone) and PPh_3 (1:4) or $[Pd_2(dba)_3]$ and PPh_3 (1:4), as the standard catalyst.[3] Sometimes, the use of dissociative ligands such as tri(2-furyl)-phosphine and triphenylarsine or the Pd^0/Cu^I co-catalytic system results in largely improved rates and yields.[7] However, the application of these standard conditions to the methylation did not give satisfactory results (entries 1–5 in Table 1). Initially, we found that the use of a coordinatively unsaturated Pd^0 complex, formed in situ by mixing $[Pd_2(dba)_3CHCl_3]$ and four equivalents of tri-*o*-tolylphosphine,[8, 9] instead of triphenylphosphine, greatly increased the coupling efficiency (up to 76% yield after 30 min in ethereal solvents; entries 6 and 7). If the amount of the tin substrate was increased to 200 equiv, then the yield was further enhanced to 86% (entry 8). We then concentrated on the acceleration of the coupling reaction in order to match the reaction with the time-limited ^{11}C-tracer synthesis. After extensive experimentation with a fixed reaction time of 5 min, the ultimate solution to the Stille methylation for this purpose was provided by the stoichiometric use of a combined $[Pd\{P(o\text{-}CH_3C_6H_4)_3\}_2]$/$CuCl/K_2CO_3$ system[9, 10] (entry 11). The reaction of tributylphenylstannane and methyl iodide (40:1) with this promoter system in DMF at 60 °C gave toluene in 81% yield. Both CuCl or CuBr and K_2CO_3 were necessary. Interestingly, CuI was totally ineffective (entry 12). The Pd^0 complex generated in situ from $[Pd_2(dba)_3]$ and $P(o\text{-}CH_3C_6H_4)_3$ (1:4) was more effective than the preformed complex and gave the desired product in 91% yield (entry 14). The reaction in the absence of the Cu(I) salt and K_2CO_3 gave lower yields. For example, the reaction at 80 °C in DME gave only a 41% yield (entry 9), while the yield improved to 63% in DMF (entry 10).[11] Biphenyl derivatives, which form as by-products under standard conditions,[4] were not detected.

The reaction with trimethylphenylstannane furnished toluene in >100% yield (122–129%) together with ethane, indicating that an unexpected cross-coupling reaction between phenyl and methyl on the tin atom was contaminating the product to a considerable extent by scrambling the methyl group of the desired toluene product, and that the participation of the methyl group on the tin atom in the reaction with methyl iodide cannot be avoided.[6, 12] Thus, aryltributylstannanes appear to be more succesful as trapping agents than aryltrimethylstannanes.

The conditions of this reaction are significantly different from those of the original Stille reaction. The coupling of methyl iodide and tributylphenylstannane probably proceeds by the mechanism proposed in Equations (2)–(5), where X = Cl or Br, M = $(n\text{-}C_4H_9)_3Sn$ or $Cu\{P(o\text{-tolyl})_3\}$. In the first step,

$$CH_3I + [Pd\{P(o\text{-tolyl})_3\}_2] \longrightarrow \underset{\mathbf{2}}{[CH_3PdI\{P(o\text{-tolyl})_3\}]} + P(o\text{-tolyl})_3 \quad (2)$$

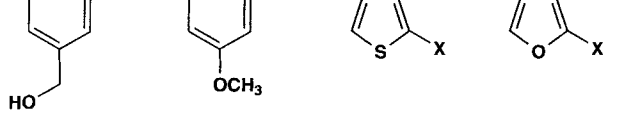
$$\underset{\mathbf{3}}{[C_6H_5Sn(n\text{-}C_4H_9)_3]} + CuX + P(o\text{-tolyl})_3 \longrightarrow \underset{\mathbf{4}}{[C_6H_5Cu\{P(o\text{-tolyl})_3\}]} + [(n\text{-}C_4H_9)_3SnX] \quad (3)$$

$$\underset{\mathbf{2}}{[CH_3PdI\{P(o\text{-tolyl})_3\}]} + C_6H_5M \longrightarrow \underset{\mathbf{5}}{[CH_3Pd(C_6H_5)\{P(o\text{-tolyl})_3\}]} + MI \quad (4)$$

$$\underset{\mathbf{5}}{[CH_3Pd(C_6H_5)\{P(o\text{-tolyl})_3\}]} \longrightarrow CH_3\text{–}C_6H_5 + [Pd\{P(o\text{-tolyl})_3\}] \quad (5)$$

methyl iodide undergoes oxidative addition with a Pd^0 species to generate the methyl–Pd^{II} iodide **2** [Eq. (2)]. The Pd^{II} complex **2** may react directly with the phenyltin compound **3** to afford the (methyl)(phenyl)Pd^{II} complex **5** [Eq. (4)]; however, the formation of the latter would be facilitated by the phenylcopper compound **4** formed by prior Sn/Cu transmetalation[7, 10] [Eq. (3)]. Finally, toluene is formed by reductive elimination from the Pd^{II} complex **5** [Eq. (5)]. The marked ligand effect of tri-*o*-tolylphosphine is attributed to its great bulkiness [cone angle = 194°, which is greater than that in tri-*tert*-butylphosphine (182°)],[13] which facilitates the generation of the coordinatively unsaturated Pd^0 and Pd^{II} intermediates.[8, 14] Transmetalation to give **5** and/or reductive elimination of toluene requires the formation of the tricoordinate Pd^{II} complex.[4, 8] DMF may stabilize such Pd intermediates at high temperatures. The effect of K_2CO_3 remains unclear.

This protocol allows controlled methylation of a variety of aromatic tin compounds such as **6**–**9** to produce the methylated derivatives of benzyl alcohol, anisole, thiophene, and furan (**10**–**13**), in 100, 92, 73, and 40% yield, respectively.



6, X = Sn(*n*-C4H9)3 **7**, X = Sn(*n*-C4H9)3 **8**, X = Sn(*n*-C4H9)3 **9**, X = Sn(*n*-C4H9)3

10, X = CH3 **11**, X = CH3 **12**, X = CH3 **13**, X = CH3

Abstract in Japanese:

短寿命放射性核種を生物活性有機化合物へ導入するために、その基本反応となるヨウ化メチルとアリールトリブチルスタンナン(過剰量使用)の高速カップリング反応の実現にむけて研究を行なった。その結果、ヨウ化メチルとトリブチルフェニルスタンナン(40当量)の反応は、DMF中、銅(I)塩と炭酸カリウム存在下、配位不飽和なトリ-*o*-トリルホスフィンパラジウム(0)錯体を用いて、60 °C、5分以内に90%以上の収率で達成された。この方法は種々のホモまたはヘテロ芳香族スズ化合物にも適用され、相当するメチル化体を与える。この反応におけるトリ-*o*-トリルホスフィン配位子、銅塩、および DMFの効果についても言及した。本新手法は陽電子放射断層画像撮影法に用いる$^{11}CH_3$基含有トレーサー合成のための確固たる化学的基盤を提供するものである。

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Table 1. Pd(0)-mediated coupling of methyl iodide with excess tributylphenylstannane.

Entry [a]	Pd(0) complex	Ligand	Pd:L [mol ratio]	Additive [b]	Solvent	t (min)	T (°C)	Toluene yield (%) [c]
1	$[Pd(PPh_3)_4]$	–	–	–	DMSO	30	40	0
2	$[Pd(PPh_3)_4]$	–	–	–	DMSO	30	90	10
3	$[Pd(PPh_3)_4]$	–	–	$CuCl/K_2CO_3$	THF	5	40	20
4	$[Pd(PPh_3)_4]$	–	–	$CuCl/K_2CO_3$	THF	5	60	23
5	$[Pd_2(dba)_3]$	$AsPh_3$	1:2	CuI	DMF	5	60	0
6	$[Pd_2(dba)_3CHCl_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	–	1,4-dioxane	30	40	75
7	$[Pd_2(dba)_3CHCl_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	–	DME	30	40	76
8 [d]	$[Pd_2(dba)_3CHCl_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	–	DME	30	40	86
9	$[Pd_2(dba)_3CHCl_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	–	DME	5	80	41
10	$[Pd_2(dba)_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	–	DMF	5	80	63
11	$[Pd[P(o\text{-}CH_3C_6H_4)_3]_2]$	–	–	$CuCl/K_2CO_3$	DMF	5	60	81
12	$[Pd_2(dba)_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	CuI	DMF	5	60	3
13	–	–	–	$CuCl/K_2CO_3$	DMF	5	60	0
14	$[Pd_2(dba)_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	$CuCl/K_2CO_3$	DMF	5	60	91
15	$[Pd_2(dba)_3]$	$P(o\text{-}CH_3C_6H_4)_3$	1:2	$CuBr/K_2CO_3$	DMF	5	60	90

[a] Reaction was carried out with 40 mol tributylphenylstannane and 1 mol Pd(0) relative to methyl iodide. [b] Two mol of the additive were used relative to Pd(0). [c] Yield was determined by GLC analysis; product yield (%) based on methyl iodide. [d] Reaction was carried out with 200 mol of tributylphenylstannane relative to methyl iodide.

Thus, we have developed a general method for the rapid methylation of homo- and heteroaromatic organotin compounds with methyl iodide. This procedure only requires the use of stoichiometric amounts of transition metal promoters. We are currently trying to find conditions for the catalytic reaction in order to make the coupling more useful.

Conclusion

We have succeeded in developing a rapid coupling reaction of methyl iodide with a series of aryltributylstannanes (excess) in the presence of the tri-*o*-tolylphosphine-bound coordinatively unsaturated Pd^0 complex, a Cu^I salt, and K_2CO_3.[15] This new protocol is useful not only for the synthesis of $^{11}CH_3$-incorporated PET tracers but also for the incorporation of other carbon isotopes such as ^{13}C and ^{14}C into a variety of aromatic compounds, and awakes interest in the wide area of the isotope labeling. The applications of this method to the synthesis of ^{11}C-labeled (15*R*)-TIC and its biological use for brain imaging will be reported separately.[11, 16]

Experimental Section

General: GLC analysis was performed on a Shimadzu GC-14B instrument equipped with a flame ionization detector; capillary column, TC-5, 60 m × 0.25 mm i.d., GL Science Inc.; carrier gas: N_2, flow rate: 0.9 mL min^{-1}; injection temp: 280 °C; detection temp: 280 °C. All reactions were performed under Ar with Schlenk techniques. Solvents and solutions were transferred by syringe–septum and cannula techniques. Tetrahydrofuran (THF), dimethoxyethane (DME), and 1,4-dioxane were used after distillation over sodium-benzophenone ketyl under Ar. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were used after distillation over CaH_2 under Ar. Tributylphenylstannane, trimethylphenylstannane, 2-(tributylstannyl)thiophene, 2-(tributylstannyl)furan, tetrakis(triphenylphosphine)palladium(0) (all from Aldrich), tris(dibenzylideneacetone)dipalladium(0)–chloroform adduct (Kanto Chemicals), tris(dibenzylideneacetone)dipalladium(0) (Aldrich), tri(2-furyl)phosphine (Lancaster), triphenylarsine (Aldrich), tri-*o*-tolylphosphine (Aldrich), copper(I) chloride, copper(I) bromide, copper(I) iodide, potassium carbonate, and nonane (all from Wako) were commercial grade. Toluene, 4-methylbenzyl alcohol, 4-methylanisole, 2-methylthiophene, 2-methylfuran, and 2-phenyltoluene were used as authentic samples. Methyl iodide was distilled over P_4O_{10} prior to use. Stannane **6** was prepared by the palladium-catalyzed cross-coupling reaction of 4-bromobenzyl alcohol with bis(tributyltin). A literature procedure was used to prepare (*p*-anisyl)tributyltin **7**.[17]

Product analysis: Toluene (Table 1): initial column temperature 80 °C, final 100 °C, flow rate 5 °C min^{-1} from 10 to 14 min, retention time 10.3 min; 4-methylbenzyl alcohol: initial column temperature 100 °C, final 200 °C, flow rate 10 °C min^{-1} from 10 to 20 min, retention time 19.3 min; 4-methylanisole: initial column temperature 100 °C, final 200 °C, flow rate 10 °C min^{-1} from 10 to 20 min, retention time 15.8 min; 2-methylthiophene: initial column temperature 60 °C, final 100 °C, flow rate 10 °C min^{-1} from 10 to 14 min, retention time 12.7 min; 2-methylfuran: initial column temperature 30 °C, final 150 °C, flow rate 10 °C min^{-1} from 8 to 20 min, retention time 9.9 min.

Rapid coupling of methyl iodide with tributylphenylstannane (40 equiv) to afford toluene (Table 1, entry 14): In a dry Schlenk tube (10 mL), tris(dibenzylideneacetone)dipalladium(0) (4.6 mg, 5.0 μmol), tri-*o*-tolylphosphine (6.1 mg, 20 μmol), CuCl (2.0 mg, 20 μmol), and K_2CO_3 (2.8 mg, 20 μmol) were placed under Ar. After addition of DMF (0.5 mL), the mixture was stirred for 5 min at RT, followed by successive addition of solutions of tributylphenylstannane (147 mg, 400 μmol) in DMF (0.5 mL) and methyl iodide in DMF (0.8 M, 12.5 μL, 10 μmol). The resulting mixture was stirred under Ar at 60 °C for 5 min, rapidly cooled (ice bath), filtered through a short column of SiO_2 (0.5 g) and then eluted with ether. The combined eluates were analyzed by GLC with nonane (0.1 M, 50 μL, 5 μmol) as the internal standard. Yield of toluene: 91%. The concentration of methyl iodide used in this experiment is the minimum concentration required for exact direct analysis of toluene produced in the reaction.

Rapid coupling of methyl iodide with stannane 6 (40 equiv) to afford 10: In a dry Schlenk tube (10 mL), tris(dibenzylideneacetone)dipalladium(0) (5.0 mg, 5.5 μmol), tri-*o*-tolylphosphine (6.7 mg, 22 μmol), CuCl (2.2 mg, 22 μmol), and K_2CO_3 (3.0 mg, 22 μmol) were placed under Ar. After addition of DMF (0.5 mL), the mixture was stirred for 5 min at RT followed by successive additions of solutions of **6** (159 mg, 400 μmol) in DMF (0.5 mL) and methyl iodide in DMF (0.8 M, 12.5 μL, 10 μmol). The resulting mixture was stirred under Ar at 60 °C for 5 min, rapidly cooled (ice bath), filtered through a short column of SiO_2 (0.5 g), and then eluted with ether. GLC analysis of the combined eluates was performed with nonane (0.1 M, 50 μL, 5 μmol) as the internal standard. Yield of methylation product **10**: 100%. Synthesis of compounds **7**–**9** was conducted by the same procedure.

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