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Synthesis of [*carbonyl*-^{11}C]acetophenone via the Stille cross-coupling reaction of [1-^{11}C]acetyl chloride with tributylphenylstannane mediated by $Pd_2(dba)_3$/$P(MeNCH_2CH_2)_3N$·HCl

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ABSTRACT

The Stille cross-coupling reaction of [1-^{11}C]acetyl chloride with tributylphenylstannane leading to [*carbonyl*-^{11}C]acetophenone was studied with the goal of developing a new ^{11}C-labeling method for positron emission tomography tracer synthesis. The coupled product [*carbonyl*-^{11}C]acetophenone was synthesized using the $Pd_2(dba)_3$/$P(MeNCH_2CH_2)_3N$·HCl system with a 60–61% radiochemical conversion from [1-^{11}C]acetyl chloride (decay-corrected, $n = 3$).

Positron emission tomography (PET) is a powerful technique for in vivo molecular imaging[1] and drug research and development[2] that uses positron-emitting radionuclides coupled to specific compounds. A number of positron-emitting radionuclides, such as ^{11}C, ^{13}N, ^{15}O, ^{18}F, and ^{76}Br, are applied in PET studies, but ^{11}C is particularly valuable because of the ubiquitous presence of the carbon atom in biologically active organic molecules. However, PET chemistry with ^{11}C differs significantly from conventional organic chemistry, and several specific features have posed severe synthetic limitations: the short half-life of ^{11}C ($t_{1/2} = 20.3$ min), the use of submicromolar amounts of the starting materials, and a need for an automated remote-controlled system for radiation protection.[3] The synthesis time is a crucial parameter, and the synthesis of ^{11}C-labeled tracers requires extremely rapid and efficient reactions. In addition, ^{11}C is available from a cyclotron only in the form of [^{11}C]O_2 or [^{11}C]H_4, from which ^{11}C-labeling reagents must be synthesized.

So far, a typical method for labeling a target compound with ^{11}C is through methylation of amines, alcohols, and thiol groups using [^{11}C]H_3I.[4] By using ^{11}C methylation, a large number of ^{11}C-labeled tracers have been successfully developed. However, with increasing utilization of PET in biomedical research, there is a growing need for new PET tracers, and consequently for the development of new ^{11}C-labeling strategies.

Over the past decade, palladium-mediated cross-coupling reactions, especially the Stille cross-coupling reaction,[5] have proven to be a useful route for the incorporation of ^{11}C into target compounds.[6] Stille cross-coupling, which is a versatile carbon–carbon bond forming reaction, is an ideal and practical method for PET tracer synthesis, in part, due to the ready availability of organostannanes, their air- and moisture-stability compared to most organometallic reagents, and their extremely low polarity, which can facilitate chromatographic separation of the desired product from an excess amount of unreacted stannane.

Ketones constitute an important class of biologically and pharmacologically active molecules,[7] and are thus an attractive target for ^{11}C-labeling. In view of the importance of ketones, a number of approaches for the efficient synthesis of this functional group have been introduced in recent years. Among them, transition-metal-catalyzed cross-coupling reactions of acyl halides with organometallic reagents provide a quick and direct procedure for ketone synthesis,[7a] although few examples of cross-couplings with acyl halides can be found in the literature.[8] As part of our studies aimed at developing new ^{11}C-labeling methods, we were interested in the synthesis of [^{11}C]ketones via the Stille cross-coupling reaction with [^{11}C]acyl halides. Herein, we report the palladium-mediated cross-coupling of [1-^{11}C]acetyl chloride ([^{11}C]**1**) with tributylphenylstannane (**2**) leading to [*carbonyl*-^{11}C]acetophenone ([^{11}C]**3**) as a simple model reaction.

Our initial studies were conducted with nonradioactive reagents. Unlike standard organic syntheses, ^{11}C-labeled tracer synthesis requires specific conditions that depend on the use of

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short-lived ^{11}C and an extremely small amount of ^{11}C-labeling reagents. With this in mind, the coupling reaction between acetyl chloride (**1**) and (**2**) was conducted in dioxane at room temperature for 5 min in the presence of $Pd_2(dba)_3$ and a supporting ligand, and a 20-fold excess of **2** was used relative to **1** and $Pd_2(dba)_3$ (1:1) (Eq. 1).[9]

1 (20 μmol) **2** (400 μmol) **3**

(1)

We performed experiments to examine the effect of supporting ligands on the coupling of **1** with **2** leading to acetophenone (**3**) (Table 1). When the reaction between **1** and **2** was conducted only with $Pd_2(dba)_3$, the conversion to **3** was only 11% (entry 1). Disappointingly, almost no coupling of **1** with **2** occurred in the presence of any ligand surveyed, including trialkylphosphanes (entries 2 and 3), triarylphosphanes (entries 4 and 5), and bicyclic triaminophosphanes[10] (entries 6 and 7). We next investigated the influence of the ratio of Pd to ligand on this reaction in the $Pd_2(dba)_3/PCy_3$ system[11] (entries 8–10). It was discovered that the coupling of **1** with **2** under these specific conditions was very sensitive to the Pd/ligand ratio. Interestingly, a significant improvement in conversion was attained when a 1:0.25 ratio of Pd to ligand was used (31%). From these results, we decided to resurvey other ligands using a Pd/ligand ratio of 1:0.25 (entries 11–15). Among the best phosphane ligands surveyed was P(*i*-$BuNCH_2CH_2)_3N$, whereas P(*t*-Bu)$_3$, PPh_3, and P(*o*-tolyl)$_3$ were not effective for this reaction; bicyclic triaminophosphanes $P(MeNCH_2CH_2)_3N$ and P(*i*-$BuNCH_2CH_2)_3N$ produced a major improvement in conversion (61% and 67%, respectively).

The beneficial effect of LiCl on the Stille cross-coupling has been reported by several research groups.[12] We thus explored the utility of LiCl for the coupling of **1** with **2** using $Pd_2(dba)_3$/$P(MeNCH_2CH_2)_3N$ and P(*i*-$BuNCH_2CH_2)_3N$ (1:0.5) (Table 2). The addition of 1 equiv of LiCl relative to $Pd_2(dba)_3$ to the reaction mixture had a positive effect on the coupling with $Pd_2(dba)_3$/$P(MeNCH_2CH_2)_3N$, providing **3** in a 67% conversion (entry 1 vs entry 2). Increasing the quantity of LiCl to 2 and 5 equiv produced a further improvement in conversion (72% and 76%, respectively; entries 3 and 4). In contrast, the presence of LiCl was detrimental to the coupling with $Pd_2(dba)_3$/P(*i*-$BuNCH_2CH_2)_3N$ (52%, entry 5 vs entry 6). Surprisingly, when conducted with $Pd_2(dba)_3$ and LiCl (0.5–5 equiv) in the absence of $P(MeNCH_2CH_2)_3N$ and P(*i*-$BuNCH_2CH_2)_3N$, the same reaction proceeded with a higher conversion of 78–82% (entries 7–9). The addition of 0.25 and 0.0625 equiv of LiCl was also effective, but a decrease in conversion was observed (65% and 46%, respectively; entries 10 and 11). Furthermore, a similar enhancement of the cross-coupling process was observed when 1 equiv of Bu_4NCl was used in place of LiCl (80%; entry 12). It was found that chloride sources, such as LiCl and Bu_4NCl, exerted a beneficial effect that promoted this reaction.

Given that bicyclic triaminophosphanes as the supporting ligands and a chloride source as an additive were effective in the coupling of **1** with **2**, we explored the possibility that using the HCl salt of $P(MeNCH_2CH_2)_3N$, which is commercially available, might lead to a more efficient cross-coupling reaction (Table 3). As expected, $Pd_2(dba)_3/P(MeNCH_2CH_2)_3N{\cdot}HCl$ (1:0.5) provided **3** in an excellent conversion of 84%, which was comparable to that obtained with the $Pd_2(dba)_3$/LiCl system (entry 1). Interestingly, the ratio of Pd to ligand had little influence on the coupling of **1** with **2**, and the reaction occurred similarly with excellent conversion even when a 1:0.0625 ratio of Pd to ligand was used (entries 2 and 3). These results suggest that $P(MeNCH_2CH_2)_3N{\cdot}HCl$ serves as an effective chloride additive rather than as a supporting ligand. Although the detailed mechanism of the $Pd_2(dba)_3/P(MeNCH_2CH_2)_3N{\cdot}HCl$-mediated cross-coupling remains unclear, the results obtained in this study are very interesting because there are no reported examples of the Stille cross-coupling of an acyl chloride with an aryl stannane using this system.

From a practical standpoint, it should be noted that the use of air- and moisture-sensitive reagents can be deterrent to the

Table 1
Effect of ligand on the coupling of **1** with **2**[a]

Entry	Ligand	Pd/ligand	Conversion[b] (%)
1[c]	None	–	11
2	PCy_3	1:2	<4
3	P(*t*-Bu)$_3$	1:2	<4
4	PPh_3	1:2	<4
5	P(*o*-tolyl)$_3$	1:2	<4
6	$P(MeNCH_2CH_2)_3N$	1:2	<4
7	P(*i*-$BuNCH_2CH_2)_3N$	1:2	<4
8	PCy_3	1:1	14
9	PCy_3	1:0.25	31
10	PCy_3	1:0.0625	17
11	P(*t*-Bu)$_3$	1:0.25	4
12	PPh_3	1:0.25	9
13	P(*o*-tolyl)$_3$	1:0.25	6
14	$P(MeNCH_2CH_2)_3N$	1:0.25	61
15	P(*i*-$BuNCH_2CH_2)_3N$	1:0.25	67

[a] Reactions of **1** (20 μmol) with **2** (400 μmol) were conducted in the presence of $Pd_2(dba)_3$ (20 μmol) and the indicated ligand in dioxane at room temperature under Ar for 5 min, unless otherwise stated.
[b] Conversions to **3** were determined by HPLC with anisole as an internal standard (average of two runs).
[c] Reaction was conducted only with $Pd_2(dba)_3$.

Table 2
Effect of LiCl on the coupling of **1** with **2**[a]

Entry	Ligand	LiCl (μmol)	Conversion[b] (%)
1	$P(MeNCH_2CH_2)_3N$	None	61
2	$P(MeNCH_2CH_2)_3N$	20	67
3	$P(MeNCH_2CH_2)_3N$	40	72
4	$P(MeNCH_2CH_2)_3N$	100	76
5	P(*i*-$BuNCH_2CH_2)_3N$	None	67
6	P(*i*-$BuNCH_2CH_2)_3N$	20	52
7	None	10	78
8	None	20	82
9	None	100	80
10	None	5	65
11	None	1.25	46
12[c]	None	(Bu_4NCl, 20)	80

[a] Reactions of **1** (20 μmol) with **2** (400 μmol) were conducted in the presence of $Pd_2(dba)_3$ (20 μmol), the indicated ligand (10 μmol), and LiCl in dioxane at room temperature under Ar for 5 min, unless otherwise stated.
[b] Conversions to **3** were determined by HPLC with anisole as an internal standard (average of two runs).
[c] Bu_4NCl (20 μmol) was used in place of LiCl.

Table 3
The coupling of **1** with **2** using $Pd_2(dba)_3/P(MeNCH_2CH_2)_3N{\cdot}HCl$ system[a]

Entry	Pd/ligand	Conversion[b] (%)
1	1:0.25	84
2	1:1	82
3	1:0.0625	85

[a] Reactions of **1** (20 μmol) with **2** (400 μmol) were conducted in the presence of $Pd_2(dba)_3$ (20 μmol) and $P(MeNCH_2CH_2)_3N{\cdot}HCl$ in dioxane at room temperature under Ar for 5 min.
[b] Conversions to **3** were determined by HPLC with anisole as an internal standard (average of two runs).

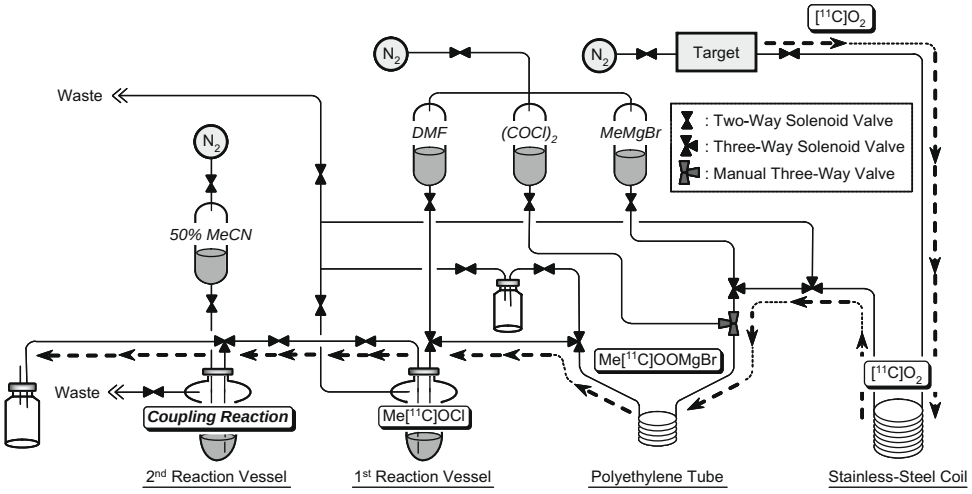
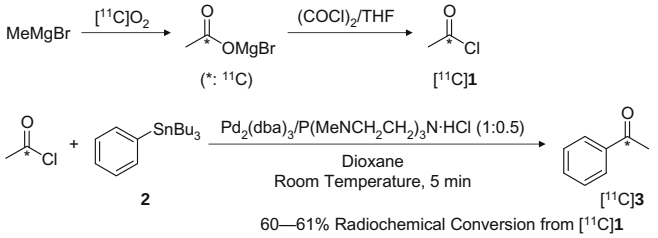


Figure 1. Automated system for the synthesis of [^{11}C]**3** from [^{11}C]**1**.

reproducible synthesis of PET tracers on a submicromolar scale. Unlike most phosphane ligands, P(MeNCH$_2$CH$_2$)$_3$N·HCl is very stable in air and moisture, and does not require special handling.[13] Considering the overall results, Pd$_2$(dba)$_3$/P(MeNCH$_2$CH$_2$)$_3$N·HCl was the most effective of the systems investigated in this study.

Finally, we demonstrated that the Pd$_2$(dba)$_3$/P(MeNCH$_2$CH$_2$)$_3$N·HCl (1:0.5) system could be applied for the coupling of [^{11}C]**1**[14,15] with **2** (Eq. 2).[16] The synthesis of [^{11}C]**1** and the subsequent coupling reaction were performed with the automated synthesis system as shown in Figure 1. The coupled product [^{11}C]**3** was reproducibly synthesized with a 60–61% radiochemical conversion from [^{11}C]**1** (decay-corrected, determined by HPLC, $n = 3$), which was sufficient for application to an actual PET tracer synthesis. To the best of our knowledge, this is the first example of the palladium-mediated cross-coupling of a [^{11}C]acyl halide with organostannane.



(2)

In summary, we demonstrated that the Pd$_2$(dba)$_3$/P(MeNCH$_2$CH$_2$)$_3$N·HCl system was highly effective for coupling [^{11}C]**1** with **2**. With this system, we could synthesize the coupled product [^{11}C]**3** with a high radiochemical conversion as a model of [^{11}C]ketone synthesis. Additional studies are underway to expand the scope and utility of this procedure to a wide variety of [^{11}C]acyl chlorides, which will be reported in due course.

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14. *The synthesis of [*^{11}*C]****1***: The synthesis of [^{11}C]**1** and the subsequent cross-coupling reaction were performed with an automated synthesis system. [^{11}C]Carbon dioxide was produced by ^{14}N(p,α)^{11}C nuclear reaction using a dry N_2 target containing 0.01% O_2 bombarded with a beam of 18 MeV protons (14.2 MeV on target). During the production of [^{11}C]O_2, MeMgBr solution (1 M

in THF, 1 mL) was passed through the polyethylene tube (i.d.: 0.75 mm; length: 40 cm), and then N_2 was passed through the tube to flush out the solvent and to leave a thin film of MeMgBr on the inner surface. After irradiation, [^{11}C]O_2 was trapped in the stainless-steel coil cooled between −170 and −165 °C, and then transferred with a flow of N_2 into the tube coated with MeMgBr. A solution of $(COCl)_2$ (5 μL) in THF (500 μL) was passed through the tube to give [^{11}C]**1**, and the radioactive mixture was transferred into the reaction vessel containing 2,6-di-*t*-butylpyridine (15 μL). After adding DMF (200 μL), [^{11}C]**1** was distilled under a flow of N_2 at 110 °C into the next reaction vessel for subsequent cross-coupling reaction, see: Arai, T.; Zhang, M.-R.; Ogawa, M.; Fukumura, T.; Kato, K.; Suzuki, K. *Appl. Radiat. Isot.* **2009**, *67*, 296–300.

15. The specific radioactivity for [^{11}C]**1** was approximately 5 GBq/μmol.
16. *Typical procedure for the conversion of [^{11}C]**1** to [^{11}C]**3***: Under N_2, a solution of $Pd_2(dba)_3$ (0.92 mg, 1.0 μmol) and $P(MeNCH_2CH_2)_3N{\cdot}HCl$ (0.13 mg, 0.5 μmol) in dioxane (300 μL) was stirred at room temperature for 3 min, and then a solution of **2** (2.6 μL, 8.0 μmol) in dioxane (200 μL) was added. The synthesized [^{11}C]**1** was transferred with a flow of N_2 into the mixture at 15 °C. The reaction mixture was heated at 30 °C for 5 min, diluted with 50% MeCN (1 mL), filtered through a 0.45-μm polypropylene filter, and then analyzed by HPLC with the nonradioactive reference compound for the identification of [^{11}C]**3**. The effluent was monitored for absorbance at 254 nm and radioactivity with NaI (Tl) scintillation detector system.