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Synthesis of PS-supported NHC-Pd Catalyst Derived from Theobromine and its Applications in Suzuki-Miyaura Reaction

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The synthesis of the PS-supported bis-NHC-palladium catalyst simply prepared from theobromine in four steps was reported. The air-stable PS-supported bis-NHC-Pd catalyst can be used as a good catalyst in running Suzuki-Miyaura cross-coupling reaction.

Keywords: Suzuki reaction; PS-supported bis-NHC-Pd complex; Theobromine; NHC.

INTRODUCTION

Recently, we have reported the synthesis of a new type of soluble polystyrene-supported palladium complex as an excellent and recyclable palladacycle catalyst and its applications for carbon-carbon bond formation in Heck-Mizoroki, Suzuki-Miyaura, and Sonogashira reactions.^{1,2} In view of the NHC-metal complexes have been proved to be more effective in many catalytic reactions than phosphine-metal complexes,³⁻⁵ we developed a simple and highly efficient synthesis of bis-NHC-Pd catalyst derived from caffeine and its applications in Suzuki-Miyaura, Heck-Mizoroki, and Sonogashira cross-coupling reactions in aqueous solution with or without adding additives.⁶ In order to support the development of sustainable chemistry and to apply the high recyclability and the development of polystyrene in organic synthesis,⁷⁻¹³ herein, we report another simple synthesis of PS-supported bis-NHC-Pd catalyst derived from theobromine, one appropriate natural methylated xanthine, in four steps and its applications in Suzuki-Miyaura reaction in water without adding other additives.

RESULTS AND DISCUSSION

Initially, we did the allylation of theobromine at N^{1} position via deprotonation by using sodium *t*-butoxide in DMF and followed by the allylation with allyl bromide to give 1-allyl-3,7-dimethylxanthine in 95% yield. 1-Allyl-3,7-dimethylxanthine was methylated at N^{9} -position by the reaction with excess of methyl iodide in dry DMF at 100 °C for 20 h. An excess amount of dry ethyl acetate was added to the clear solution to obtain a precipitate in yellow color. After filtration, concentration, and recrystallization from ethyl acetate we could obtain 1-allyl-3,7,9-trimethylxanthinium iodide as a yellowish white solid in 66% yield.^{14,15} MS of both FAB+ and ES+ showed one peak at m/z 597 which is corresponding to the cation $[2M - I^-]^+$, another peak at m/z 235 is the corresponding cation of $[M - I^-]^+$. MS of ES- showed one peak at m/z 489 which is the corresponding anion of $[M + I^{-}]$. The corresponding proton and carbon peaks appeared in ¹H- and ¹³C-NMR spectra were assigned in its chemical structure with the help of the spectral data shown in their 2D-NOESY and HSQC spectra. The following reaction of 1-allyl-3,7,9-trimethylxanthinium iodide with sodium t-butoxide in the presence of palladium acetate in THF at reflux could give bis(1-allyl-3,7,9-trimethylxanthine-8-ylidene)palladium diiodide 1 as a yellowish white powder in 51% yield after recrystallization from benzene and hexane as shown in Scheme I. The bis-NHC ligands in the Pd complex obtained via the similar reaction conditions was observed and reported in our previous studies.⁶ MS of EI+ of 1 showed its molecular ion at m/z 828, the radical cation of $[M - I]^+$ showed at m/z 701, and another radical cation $[M-2I]^+$ showed at m/z 574. Attempts to do the copolymerization of 1 with six equivalents of styrene with or without a catalytic amount of free radical initiator such as azobisisobutyronitrile (AIBN) or benzoyl peroxide in benzene, toluene, THF or DMF at 70 °C to 150 °C were all failed.

We then turned our attention to the use of *p*-styrylmethylene group at the N¹-position in theobromine. Thus, the benzylation of theobromine was done by deprotonation with sodium *t*-butoxide in DMF and followed by the addition of excess *p*-vinylbenzyl chloride to form 1-*p*-vinylbenzyltheobromine in 73% yield. 1-*p*-Vinylbenzyltheo-

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Scheme I Synthesis of 1 from theobromine



bromine was methylated at N⁹-position by the reaction with excess of methyl iodide in dry DMF at 100 °C for 20 h to give 1-p-vinylbenzyl-3,7,9-trimethylxanthinium iodide in 40% yield. MS EI+ showed a peak at m/z 749 which is corresponding to the cation $[2 \text{ M} - \Gamma]^+$, another peak at m/z 311 is corresponding to the cation $[M - I^-]^+$. The reaction of 1-p-vinylbenzyl-3,7,9-trimethylxanthinium iodide with sodium *t*-butoxide in the presence of palladium acetate in THF at reflux could give bis(1-p-vinylbenzyl-3,7,9-trimethylxanthine-8-ylidene)palladium diiodide 2 as a yellowish white crystal powder in 45% yield after recrystallization from benzene and hexane. Considering the proper space around the palladium in the catalyst, the complex 2 was successfully copolymerized with six equivalents of styrene in the presence of a catalytic amount of AIBN at 150 °C in DMF for 48 h to form the air-stable polystyrene-supported bis-NHC-Pd complex 3 after repeatedly washed by the solvent of THF/*n*-hexane (v/v =1/50) in a Soxhlet extraction apparatus as shown in Scheme II. Gel permeation chromatography analysis (mobile phase: THF, polystyrene standards) indicated that M_w of PS-supported bis-NHC-Pd complex 3 was 1.378×10^4 g/mol. Atomic absorption spectrophotometer analysis showed that palladium was containing as 59.83 mg per gram of the polymer 3.

Scheme II Synthesis of palladium complexes 2 and 3 from theobromine



To test the applicabilities of palladium complexes 1-3 in the carbon-carbon bond formation reactions, we examined the Suzuki-Miyaura cross-coupling reaction of phenylboronic acid with p- or m-bromotoluene and sodium *t*-butoxide or potassium carbonate¹ as the base in the absence or presence of a catalytic amount of complex 3 in water as shown in Table 1. It was noted that in the absence of the palladium complexes 1-3, there was no detectable amount of the desired coupling product as judged by the GC-MS spectral analysis (entry 1). The reaction was preferred to run at higher temperature, probably due to the higher solubility of the catalyst 3 at higher temperature (entries 4-5). When sodium t-butoxide was used as the base, the cross-coupling reaction using complex 3 as the catalyst could give a little bit higher yields than that of using potassium carbonate as the base (entries 4, 6-8). Although palladium complexes 1 and 2 could give similar results as that from complex 3 (entries 2-4), however, in view of the good solubilities of the PS-supported palladium complex 3 in tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, toluene, chloroform, dichloromethane and not very soluble in methanol, acetonitrile, hexane, and diethyl ether, we preferred to use complex 3 as a recyclable catalyst

 Table 1. Palladium complexes 1-3 catalyzed Suzuki-Miyaura cross-coupling reaction

Br	PhB(OH) ₂	
Me	0.5 mol % Pd cat. 1.5 equiv of base water, 6 h	Me

Entry	Bromotoluene	Pd catalyst	Base	Temp (°C)	Iso. Yield (%) of the Product ^a
1	р-		K ₂ CO ₃	80	
2	<i>p</i> -	1	K_2CO_3	80	75
3	<i>p</i> -	2	K_2CO_3	80	71
4	<i>p</i> -	3	K_2CO_3	80	73
5	<i>p</i> -	3	K_2CO_3	25	18
6	<i>m</i> -	3	K_2CO_3	80	66
7	<i>p</i> -	3	NaO-t-Bu	80	75
8	<i>m</i> -	3	NaO-t-Bu	80	71
9	р-	1 st recycled 3	K ₂ CO ₃	80	67
10	р-	2 nd recycled 3	K_2CO_3	80	65
11	р-	3 rd recycled 3	K ₂ CO ₃	80	61

^a The products were identified by comparison their ¹H-NMR and MS with that of authentic samples.

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for our further studies. The recyclability test of complex **3** showed that the yields of the Suzuki-Miyaura cross-coupling products could be isolated more than 60% after recycling one to three times of the complex **3** with diethyl ether as the solvent to precipitate **3** (entries 9-11).

EXPERIMENTAL

Preparation of 1-allyltheobromine¹⁶

Theobromine (9.0 g, 50 mmol) and sodium t-butoxide (5.28 g, 55 mmol) were dissolved in dry DMF (250 mL). The solution was added allyl bromide (4.32 mL, 50 mmol) at 150 °C and stirred for another 1 h. The solution was added another allyl bromide (4.32 mL, 50 mmol) and stirred for another 12 h at 100 °C. The reaction was then cooled to room temperature. Volatiles were removed by rotary evaporator and the crude material was extracted three times by water (50 mL \times 3) and ethyl acetate (200 mL \times 3) to give the crude title compound as pale yellow crystals. Recrystallization from methanol could give 10.5 g (47.5 mmol) of the title compound as white crystal in 95% yield. mp. 142-143 °C. ¹H-NMR (500 MHz, CDCl₃): δ 3.56 (s, 3H, CH₃ at N³), 3.96 (s, 3H, CH₃ at N⁷), 4.61 (d, J = 6 Hz, 2H), 5.17 (d, J = 11 Hz, 1H), 5.25 (d, J = 17 Hz, 1H), 5.85-5.94 (m, 1H), 7.49 (s, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): 8 29.92, 33.79, 43.53, 107.86, 117.78, 132.51, 141.70, 149.13, 151.54, 155.23 ppm. FAB+: *m*/*z* 221 (M⁺+ 1), 205, 193, 181. HRMS FAB+ calcd for C₁₀H₁₃N₄O₂ ([M $(+1)^{+}$ 221.1039, found 221.1034.

Preparation of 1-allyl-3,7,9-trimethylxanthinium iodide

1-Allyltheobromine (2.2 g, 10 mmol) was dissolved in 20 mL of dry DMF at 100 °C for 1 h until the solution appeared clear, then the solution was added iodomethane (3.1 mL, 50 mmol) dropwise and stirred for another 20 h at 100 °C. The solution was poured slowly into 100 mL of ethyl acetate to obtain precipitate with cream yellow color. The crude product was washed with ethyl acetate (60 mL \times 3). After drying in the air, the title compound was obtained as yellowish powder (2.4 g, 6.6 mmol) in 66% yield. mp. 152-154 °C. ¹H-NMR (500 MHz, CDCl₃): δ 3.83 (s, 3H), 4.23 (t, 3H), 4.40 (s, 3H), 4.58 (d, J=6 Hz, 2H), 5.24 (d, J= 11 Hz, 1H), 5.31 (d, *J* = 17 Hz, 1H), 5.78-5.88 (m, 1H), 10.45 (s, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): δ 32.44, 36.59, 38.91, 44.65, 108.58, 119.41, 130.68, 139.68, 139.88, 149.94, 153.16 ppm. FAB+: *m/z* 597 (2 M - I⁻), 235 (M - I⁻). ES+: *m*/*z* 597 (2 M - I⁻), 235 (M - I⁻). ES-: 489 (M + I⁻). HRMS FAB+ calcd for C₂₂H₃₀N₈O₄I (2 M - I⁻)

597.1435, found, 597.1431.

Preparation of bis(1-allyl-3,7,9-trimethylxanthine-8ylidene)palladium diiodide 1

In one 100 mL round-bottom flask was added 1-allyl-3,7,9-trimethylxanthinium iodide (1.3 g, 3.6 mmol), palladium acetate (0.4 g, 1.8 mmol), and sodium t-butoxide (0.35 g, 3.6 mmol). The air in the flask was removed under vacuum and the flask was flushed with nitrogen. The flask was added 20 mL of dry THF and the reaction mixture was stirred at room temperature for 1.5 h. Then the reaction mixture was heated and refluxed for another 3 h. After cooling, 60 mL of hexane was added slowly into the flask to obtain precipitate as the crude product with yellowish white color. The crude product was recrystallized three times with benzene (10 mL) and hexane (30 mL) to give the title compound (0.77 g, 0.92 mmol) as powder crystal with yellowish white color in 51% yield. mp. 175-176 °C. ¹H-NMR (400 MHz, CDCl₃): δ 3.79 (s, 3H), 4.24 (s, 3H), 4.35 (s, 3H), 4.57 (d, *J* = 6 Hz, 2H), 5.21 (d, *J* = 11 Hz, 1H), 5.28 $(d, J = 17 \text{ Hz}, 1\text{H}), 5.80-5.89 \text{ (m, 1H) ppm.}^{13}\text{C-NMR} (125 \text{ m})$ MHz, CDCl₃): δ 32.14, 37.70, 39.42, 44.26, 110.87, 118.92, 131.48, 140.54, 150.40, 152.87, 175.94 ppm. EI+: 828 (M⁺), 701, 574, 466, 360, 339, 234. HRMS EI+ calcd for C₂₂H₂₈N₈O₄I₂Pd (M⁺) 827.9358, found, 827.9368. HRMS EI+ calcd for $C_{22}H_{28}N_8O_4IPd$ (M⁺ - I) 701.0313, found, 701.0310; calcd for $C_{22}H_{28}N_8O_4Pd$ (M⁺ - 2 I) 574.1268, found, 574.1262.

Preparation of 1-p-vinylbenzyltheobromine

Theobromine (3.3 g, 18 mmol) and sodium t-butoxide (1.8 g, 19 mmol) was added into one 250 mL roundbottom flask. The air in the flask was removed under vacuum and then the flask was flushed with nitrogen. Dry DMF (90 mL) was added into the flask and the reaction mixture was heated to 80 °C, p-vinylbenzyl chloride (2.8 mL, 54 mmol) was added slowly into the mixture and reacted for another 1 h, then another portion of *p*-vinylbenzyl chloride (2.8 mL, 54 mmol) was added into the mixture and reacted for another 24 h. After cooling, DMF was removed under vacuum and the reaction mixture was added 100 mL of deionized water and the desired product was extracted with chloroform (300 mL \times 2). After the organic layer was concentrated to about 50 mL, 300 mL of hexane was slowly added into the organic layer to obtain the title compound (3.9 g, 13.2 mmol) with white color in 73% yield. mp. 141-143 °C. ¹H-NMR (400 MHz, CDCl₃): δ 3.57 (s, 3H, CH_3 at N³), 3.99 (s, 3H, CH_3 at N⁷), 5.18 (s, 2H), 5.20 (d, J = 11 Hz, 1H), 5.69 (d, J = 17 Hz, 1H), 6.68 (dd, J = 11, 17

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Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 7.49 (s, 1H) ppm. ¹³C-NMR (125 MHz, CDCl₃): δ 29.99, 33.82, 44.44, 107.92, 114.01, 126.46, 129.31, 136.76, 137.13, 137.16, 141.76, 149.13, 151.84, 155.48 ppm. MS EI+ m/z 296 (M⁺), 117. HRMS EI+: calcd. for C₁₆H₁₆O₂N₄ 296.1273, found: 296.1267.

Preparation of 1-*p*-vinylbenzyl-3,7,9-trimethylxanthinium iodide

1-p-Vinylbenzyltheobromine (2.96 g, 10 mmol) was dissolved in 20 mL of dry DMF within 1 h at 100 °C under nitrogen atmosphere. Methyl iodide (3.1 mL, 50 mmol) was added to the above solution to react for 20 h at 100 °C. After cooling, DMF was removed under vacuum and the desired product was recrystallized from ethyl acetate to give yellowish crystal (1.75 g, 4 mmol) in 40% yield. mp. 162-164 °C. ¹H-NMR (400 MHz, CDCl₃): δ 3.82 (s, 3H, CH₃ at N³), 4.23 (s, 3H, CH₃ at N⁷), 4.37 (s, 3H, CH₃ at N⁹), 5.14 (s, 2H), 5.22 (d, *J* = 11 Hz, 1H), 5.71 (d, *J* = 17 Hz, 1H), 6.65 (dd, *J* = 17, 11 Hz, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 10.40 (s, 1H) ppm. ¹³C-NMR (125 MHz, DMSO-D₆): δ 31.41, 35.62, 36.81, 44.32, 107.77, 114.37, 126.04, 128.02, 135.86, 136.11, 136.41, 139.61, 139.78, 150.01, 153.12 ppm. TOF-MS-ES+: 749 (2 M - I⁻), 639, 343, 311 (M - I). HRMS ES+: calcd. for $C_{34}H_{38}O_4N_8I$ (2 M - I⁻) 749.2061, found: 749.2064; calcd. for C₁₇H₁₉O₂N₄ (M - I⁻) 311.1508, found: 311.1510.

Preparation of bis(1-*p*-vinylbenzyl-3,7,9-trimethylxanthine-8-ylidene)palladium diiodide 2

1-p-Vinylbenzyl-3,7,9-trimethylxanthinium iodide (0.79 g, 1.8 mmol), palladium acetate (0.1 g, 0.9 mmol), and sodium t-butoxide (0.173 g, 1.8 mmol) were added into one 100 mL round-bottom flask. The air in the flask was removed by vacuum and the flask was then flushed with nitrogen. Dry THF (10 mL) was added into the above mixture and the reaction mixture was stirred at room temperature for 1.5 h and at reflux temperature for another 3 h. After cooling, hexane (60 mL) was slowly added into the flask to obtain yellowish white precipitate as the crude product. Recrystallization with benzene (10 mL) and hexane (30 mL) could give the title compound (0.4 g, 0.4 mmol) as yellowish white crystal powder in 45% yield. mp. 280-282 °C. ¹H-NMR (500 MHz, DMSO-D₆): δ 3.74 (s, 3H, CH₃ at N³), 4.12 (s, 3H, CH₃ at N⁷), 4.31 (s, 3H, CH₃ at N⁹), 5.03 (s, 2H), 5.22 (d, J = 11 Hz, 1H), 5.78 (d, J = 17 Hz, 1H), 6.70 (dd, J=11, 17 Hz, 1H), 7.29 (d, J=7 Hz, 2H), 7.40 (d, J=7 Hz, 2H) ppm. ¹³C-NMR (125 MHz, DMSO-D₆): δ 31.20, 36.43, 43.71, 108.90, 113.76, 125.64 (2 C's), 127.50, 135.78, 135.87, 136.21, 140.42, 149.77, 152.18, 174.11 ppm. FAB+: m/z 980 (M⁺), 853, 726. HRMS FAB+: calcd. for $C_{34}H_{36}O_4N_8I_2Pd$ (M⁺) 979.9984, found: 979.9993; calcd. for $C_{34}H_{36}O_4N_8IPd$ (M⁺ - I) 853.0939, found: 853.0936; calcd. for $C_{34}H_{36}O_4N_8Pd$ (M⁺ - 2I) 726.1894, found: 726.1885.

Synthesis of polystyrene-supported bis-NHC-Pd catalyst 3

Bis(1-p-vinylbenzyl-3,7,9-trimethylxanthine-8-ylidene)palladium diiodide 2 (980 mg, 1 mmol) was added into a test tube and flushed with nitrogen. A mixture of styrene (620 mg, 6 mmol) and dry DMF (5 mL) was injected into the test tube. Then, a mixture of AIBN (50 mg, 0.3 mmol) and DMF (2 mL) was injected into the stirring test tube. The reaction mixture was then heated at 150 °C for 48 h. After cooling, the mixture was concentrated to dryness. The dry solid was repeatedly washed by the solvent (THF/ hexane = 1:50) in Soxhlet extractor. The isolated polymer was 0.90 g (56% yield). ¹H NMR (500 MHz, CDCl₃) δ 1.3-2.2 (m, Ar-CHCH₂), 3.7-3.8 (m, CH₃ at N³), 4.2-4.4 (m, CH₃ at N⁷), 4.4-4.6 (m, CH₃ at N⁹), 5.0-5.1 (m, ArCH₂N), 6.3-6.8 (m, Ar-H), 6.8-7.4 (m, Ar-H) ppm; Gel permeation chromatography analysis (mobile phase: THF, polystyrene standards) indicated that M_w of catalyst **3** was 1.378×10^4 g/mol. Atomic absorption spectrophotometer analysis showed that palladium was containing at 59.83 mg of Pd per gram of polymer 3.

General Procedure for Suzuki-Miyaura Cross Coupling Reaction

A mixture of *p*-bromotoluene (1 mmol), phenylboronic acid (1.2 mmol), potassium carbonate (1.5 mmol) and 0.5 mol % of PS-supported bis-NHC-PdI₂ catalyst **3** in 1 mL of water was stirred at 80 °C for 6 h under nitrogen. The organic layer was extracted with diethyl ether, dried over magnesium sulfate, and the solvent was removed completely under high vacuum to give a crude product. The product was further purified by column chromatography on silica gel (neutral, 70-230 mesh, *n*-hexane). The products were identified by comparison their ¹H-NMR and MS spectral data as reported in the literature.

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