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INTRODUCTION OF HETEROARENE FUNCTIONALITY ON THE BIPEDAL-THIOL-CAPPED GOLD NANOPARTICLE BY DEPROTONATIVE C-H COUPLING WITH PALLADIUM COMPLEX

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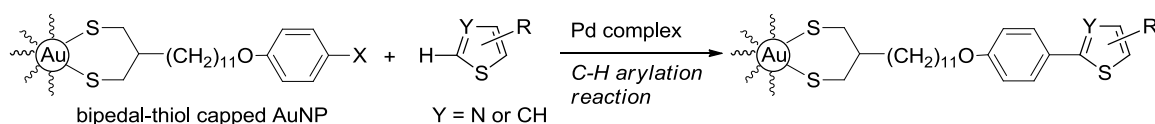
‡This paper is dedicated to Professor Victor Snieckus on celebration of his 77th birthday.

Abstract – Gold nanoparticle stabilized by adsorption of bipedal thiol whose end is modified with bromoarene is prepared to undergo palladium-mediated deprotonative C-H arylation reaction. Heteroarenes are introduced onto the organic moiety of the nanoparticle.

INTRODUCTION

Gold nanoparticle (AuNP) stabilized by adsorption of thiols has attracted considerable attention as a wide range of advanced materials.^{1,2} As the demand of AuNP increases as materials, precise modification by organic transformation on AuNP becomes a significant issue to introduce the functionality. Transition-metal-catalyzed cross-coupling reaction³ on AuNP can thus be a promising tool, which enables diversity-oriented construction of the functionalized AuNP.⁴ We have recently shown that Suzuki-Miyaura and Sonogashira coupling, which are cross-coupling employing a palladium complex, indeed, take place on the surface of AuNP, in which the aryl halide moiety is located at the end of alkanethiol. The reactions proceeded efficiently without fatal aggregation when 1,3-dithiol is employed for the ligand to improve stable adsorption to the gold atom that is tolerable to the reaction conditions of cross coupling, whereas the reaction with monodentate thiol has resulted in unsuccessful.⁵

On the other hand, we have been engaged in transition-metal-catalyzed deprotonative C-H arylation reactions at the C-H bond of thiophenes and thiazoles with aryl halides. We have revealed that lithium alkoxide⁶ and magnesium amide⁷ effectively deprotonate heteroarenes and couples with variety of organic halides catalyzed by transition metal showing advantages in step efficiency and operational simplicity compared with conventional cross-coupling reactions employing main-group organometallics such as boron, silicon, and tin. Accordingly, we considered that C-H arylation can also be employed for the modification protocol on AuNP as shown in Scheme 1. Herein, we describe that the C-H arylation reaction occurs at the bipedal-thiol capped AuNP and introduction of thiophene and thiazole moieties are performed on the AuNP surface.

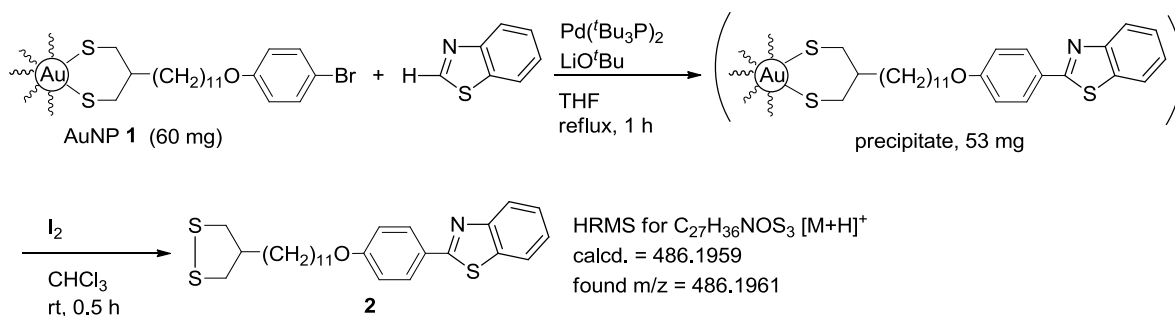


Scheme 1. Surface modification of AuNP by C-H coupling reaction

RESULTS AND DISCUSSION

We first prepared the bipedal-thiol-capped AuNP. Bipedal thiol, whose terminal was modified by 4-bromophenoxy group, was chosen as a capping agent of AuNP.⁸ Synthesis of bipedal-thiol-capped AuNP **1** was carried out by treatment of a THF solution of $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ and the corresponding 1,3-dithiol with $t\text{BuNH}_2 \cdot \text{BH}_3$ as a reducing agent.⁹ TEM observation of the obtained AuNP **1** exhibited spherical nanoparticle with a diameter of 7.6 ± 2.0 nm.

Palladium-catalyzed C-H arylation reaction with LiO^tBu as a base was first employed to introduce a thiazole group as shown in Scheme 2. A THF solution of AuNP **1**, benzothiazole, LiO^tBu , and $\text{Pd}(t\text{Bu}_3\text{P})_2$ was stirred under reflux for 1 h. Unfortunately, it was found to disappear characteristic purple color of the solution derived from surface plasmon resonance¹ suggesting unexpected aggregation of AuNP. However, the collected particle by the addition of ethanol to the solution was found to partially disperse to organic solvents such as THF and CHCl_3 . Nevertheless, the coupling reaction was found to take place on AuNP. Cleavage of the organic moiety from gold surface was carried out by treatment of the precipitated suspension with iodine¹⁰ in chloroform to afford 1,2-dithiolane **2** bearing a benzothiazole moiety. Analyses by ^1H NMR and HRMS (ESI+) suggested conversion of the bromide into thiazole.



Scheme 2. C-H arylation reaction of benzothiazole with AuNP **1**

Table 1. C-H arylation reaction of heteroarenes with AuNP **1** in the presence of LiO^tBu^a

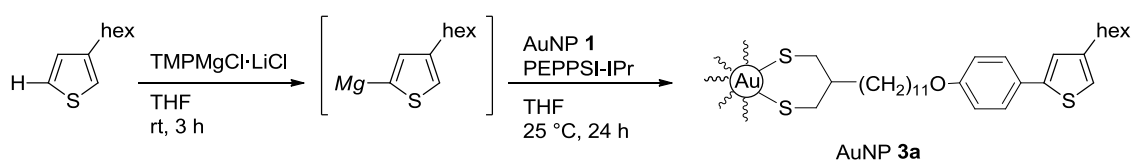
Entry	Heteroarenes	Solvent	Yield/mg ^b
1 ^c		THF	53 (60)
2		CPME ^d	18 (20)
3 ^e		THF/DMF (3:1)	18 (20)

^a Unless otherwise specified, the reaction was carried out with AuNP **1**, 0.1 mmol of heteroarenes, 0.01 mmol of Pd(^tBu₃P)₂ and 0.1 mmol of LiO^tBu in solvent (2 mL). ^b In parenthesis, amount of starting AuNP **1** (mg) was shown. ^c Benzothiazole (0.3 mmol), Pd(^tBu₃P)₂ (0.03 mmol), and LiO^tBu (0.3 mmol) was employed in 6 mL of THF. ^d Cyclopentyl methyl ether. ^e LiO^tBu (0.3 mmol) was used.

The similar reaction was carried out with several heteroarenes (Table 1). HRMS (ESI⁺) analysis of the organic moiety of the obtained precipitates suggested undergoing coupling of two thiazole derivatives and 2-methylthiophene with aryl bromide on AuNP albeit aggregation was also observed.

We then examined application of deprotonative C-H arylation reaction using magnesium amide as a base. We have been reported the reaction of thiophene with Knochel-Hauser base TMPMgCl·LiCl¹¹ (TMP = 2,2,6,6-tetramethylpiperidine) induces the metalation at the C-H bond adjacent to the sulfur atom and following arylation of the metalated thiophene proceeded smoothly by transition-metal catalyzed cross coupling.⁷ With such reaction conditions, the reaction of thiophene with aryl bromide on AuNP was examined. The reaction procedure follows: A THF solution of TMPMgCl·LiCl was stirred with thiophene derivative at room temperature for 3 h to complete metalation. To the resulting solution were added AuNP **1**, palladium complex with NHC ligand (PEPPSI-IPr), and additional THF. After stirring for 24 h at room temperature, the reaction was quenched by addition of aqueous NH₄Cl. Ethanol was then added to the separated organic layer to form precipitates which were purified by iterative centrifugation and

precipitation to give AuNP **3a**. When the reaction was carried out by 3-hexylthiophene, which is known to be metalated at the 5-position regioselectively by treatment of $\text{TMPMgCl} \cdot \text{LiCl}$,⁷ purple color of the mixture was observed throughout the reaction. The isolated nanoparticle obtained by the addition of ethanol was found to be redispersible to CHCl_3 and THF. The result suggests that the bipedal-thiol-capped AuNP is tolerable to the reaction conditions of the coupling reaction despite the presence of highly reactive carbanion. Formation of the carbon-carbon bond was confirmed by comparison of ^1H NMR spectra of AuNP **1** (A) and **3a** (B) shown in Figure 1.¹² The signal of bromophenoxy group of AuNP **1** at 6.75 ppm in the spectrum (A) disappeared in (B), suggesting that the reaction proceeded in high conversion. New signals at 7.46, 7.02, 6.86, 6.78 ppm, which are assigned as arylthiophene moiety, were observed in (B). Additional signals corresponding to the hexyl group were also observed at 2.59 and 0.86 ppm (See supporting information). Since TEM image of AuNP **3a** showed spherical nanoparticles with an average diameter of 7.6 ± 2.0 nm, no problematic morphological change of the nanoparticle was suggested to occur during the reaction.



Scheme 3. Deprotonative C-H arylation reaction of 3-hexylthiophene with AuNP **1**

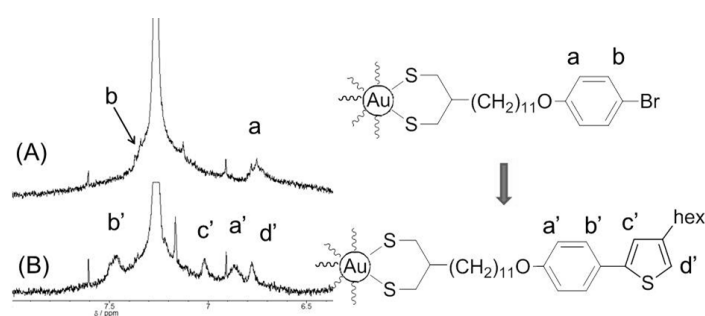
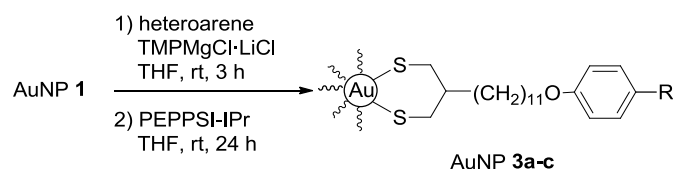


Figure 1. ^1H NMR spectra of AuNP **1** (A) and **3a** (B) (300 MHz, CDCl_3)

The similar reaction was carried out with thiophene dendrimers **3T** and **7T**¹³ as shown in Table 2. The reactions proceeded smoothly to afford the corresponding AuNP **3b** and **3c** in high conversions, respectively. Conversion of the reaction to **3b** and **3c** was confirmed by ^1H NMR comparing chemical shifts of the methylene group adjacent to the phenoxy group (See supporting information). TEM observation exhibited that the size of AuNP **3b** and **3c** were 7.3 ± 1.2 and 7.9 ± 1.4 nm, which were comparable with that of AuNP **1** (Table 3). It should be pointed out that introduction of bulky dendrons onto AuNP induced

increase in mean interparticle distance compared to that of AuNP **1** in TEM observation. Although Advincula and co-workers recently reported synthesis of thiophene dendrimer-capped AuNPs, the thiophene-dendrimer moiety had been introduced into the capping thiol prior to the modification of AuNP.¹⁴ Notably, the present introduction protocol of thiophene dendron is coupling at the C-H bond of thiophene on the nanoparticle, the reaction of which is a complimentary pathway for the functionalization of gold nanoparticles. In contrast with the conventional top-down method to prepare functionalized AuNPs, bottom-up-type fabrication by the reaction at the bipedal-thiol-capped organic moiety would suit to the diversity-oriented AuNPs synthesis.

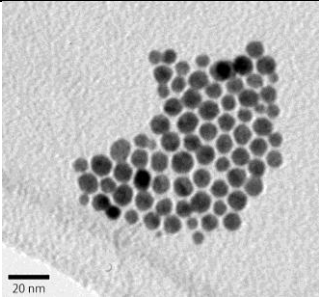
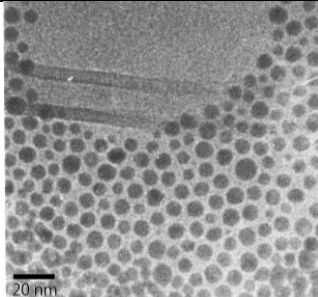
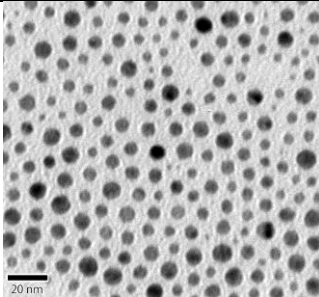
Table 2. C-H coupling reaction of aryl bromide on AuNP with thiophenes^a



Product (-R)	Yield/mg	(C ₆ H ₄ thienyl/C ₆ H ₄ Br)/% ^b
 3a	12.4	>95
 3b	13.9	>95
 3c	9.2	>95

^a The reaction was carried out with heteroarene (0.1 mmol), AuNP **1** (20 mg), TMPMgCl·LiCl (0.12 mmol), PEPPSI-IPr (0.012 mmol) in THF (2 mL). ^b The ratio of C₆H₄thienyl/C₆H₄Br moiety on AuNP estimated by measurement of ¹H NMR.

Table 3. TEM image of AuNPs

	Gold nanoparticles		
	1	3b	3c
TEM image			
Particle Size/nm	7.6±2.0	7.3±1.2	7.9±1.4
Interparticle Distance/nm	1.6±0.66	2.0±0.90	4.5±0.97

In summary, we have shown that introduction of thiophene moiety onto bipedal-thiol-capped gold nanoparticle was accomplished by C-H coupling reaction employing $\text{TMPMgCl}\cdot\text{LiCl}$ as deprotonating agent in the presence of a palladium complex. Although highly reactive carbanion was involved in the reaction system, the nanoparticle was tolerant toward aggregation. Thus, the established protocol would be a choice for the synthesis of thiophene-functionalized gold nanoparticles.

EXPERIMENTAL

General. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Varian Gemini 300 as a CDCl_3 solution unless noted. The chemical shifts were expressed in ppm with CHCl_3 (7.26 ppm for ^1H) or CDCl_3 (77.0 ppm for ^{13}C) as internal standards. IR spectra were recorded on PERKIN ELMER FT-IR Spectrometer SPECTRUM 1000. High resolution mass spectra (HRMS) were measured by JEOL JMS-700 MStation (EI) at the Graduate School of Material Science, Nara Institute of Science and Technology and JEOL JMS-T100LP AccuTOF LC-Plus (ESI). Transmission electron microscopic (TEM) observations were performed by using JEOL JEM-1230 BU and JEOL JEM-1200EX II with an acceleration voltage of 100 and 120 kV, respectively. TEM samples were prepared by dropping of the THF or toluene/hexane solution of gold nanoparticle (AuNP) on 150 mesh carbon coated copper grids, which were purchased from Okensyoji Co. Ltd. $\text{HAuCl}_4\cdot 4\text{H}_2\text{O}$ was purchased from Tanaka Kikinzoku Kogyo Co. Ltd. $\text{Pd}(\text{tBu}_3\text{P})_2$ and PEPPSI-IPr were purchased from Sigma-Aldrich Co. Ltd. $\text{TMPMgCl}\cdot\text{LiCl}$ was prepared by following the literature procedure^{11h} and stored in the freezer as 1.0 M THF solution. THF was purchased from Kanto Chemical Co. Inc. as an anhydrous grade and stored in a Schlenk tube under nitrogen atmosphere. Other chemicals were purchased and used as such. Preparation of thiophene dendrimer **3T** and **7T** was performed

by the method shown in the literature.¹³

Synthesis of dithiol-capped AuNP 1: To a screw-capped test tube equipped with a magnetic stirring bar were added H₂AuCl₄·4H₂O (41.2 mg, 0.1 mmol), the bipedal thiol (43.4 mg, 0.1 mmol) and 5 mL of THF and the resulting solution was stirred at 40 °C for 3 h. THF (5 mL) solution of ^tBuNH₂·BH₃ (8.7 mg, 0.1 mmol) was then added to the reaction mixture at 55 °C. After stirring for 0.5 h at 55 °C, EtOH was added to the solution to precipitate gold nanoparticle, which was centrifuged to isolate the dithiol-capped gold nanoparticle **1** (22.6 mg) as a dark brown powder.

C-H coupling reaction of benzothiazole with AuNP 1 in the presence of LiO^tBu:

To a Schlenk tube equipped with a magnetic stirring bar were added AuNP **1** (60.0 mg) and 6 mL of THF at rt. The mixture was sonicated to form a homogeneous purple solution. To the resulting mixture were added benzothiazole (33 μL, 0.3 mmol), Pd(^tBu₃P)₂ (15.3 mg, 0.03 mmol), and THF solution of LiO^tBu (2.2 M, 135 μL). After stirring for 1 h under reflux, EtOH was added to the mixture to obtain precipitate (53.0 mg) as dark brown powder which did not disperse in organic solvents such as CHCl₃ and THF.

The precipitate was then subjected to the reaction with iodine to remove the organic moiety from the gold surface.¹⁰ The precipitate (53.0 mg) was added to 5 mL of THF to form suspension. To the resulting suspension was added I₂ (53.0 mg). After stirring 30 minutes at rt, the mixture was centrifuged and the supernatant was collected. Concentration of the solution under reduced pressure left a crude mixture, which was passed through a silica gel column to leave the organic moiety of the precipitate as 1,2-dithiolane **2**. The compound **2** was subjected to ¹H NMR measurement as a CDCl₃ solution suggesting that aryl bromide was coupled with benzothiazole to form the corresponding product (See below). Result of HRMS (ESI+) measurement of **2** also suggested formation of the corresponding product (Calcd for C₂₇H₃₆NOS₃ [M+H]⁺: 486.1959; found: *m/z* 486.1961).

C-H coupling reaction of 5-{4-(trifluoromethyl)phenyl}thiazole with AuNP 1 in the presence of LiO^tBu: The reaction was carried out in a similar manner as above using AuNP **1** (20 mg), 5-{4-(trifluoromethyl)phenyl}thiazole (22.9 mg, 0.1 mmol), THF solution of LiO^tBu (2.2 M, 45 μL), Pd(^tBu₃P)₂ (5.1 mg, 0.01 mmol) in 2 mL of cyclopentyl methyl ether. Treatment of the obtained nanoparticle with iodine was also carried out in the similar manner. Result of HRMS (ESI+) measurement of the obtained organic compound suggested formation of the corresponding dithiorane (Calcd for C₃₀H₃₇NOS₃ [M+H]⁺: 580.1989; found: *m/z* 580.1989).

C-H coupling reaction of 2-methylthiophene with AuNP 1 in the presence of LiO^tBu: The reaction was carried out in a similar manner as above using AuNP 1 (20 mg), 2-methylthiophene (9.7 μ L, 0.1 mmol), THF solution of LiO^tBu (2.2 M, 45 μ L), Pd(^tBu₃P)₂ (5.1 mg, 0.01 mmol) in 2 mL of cyclopentyl methyl ether. Treatment of the obtained nanoparticle with iodine was also carried out in the similar manner. Result of HRMS (ESI⁺) measurement of the obtained organic compound suggested formation of the corresponding dithiorane (Calcd for C₂₅H₃₆NaOS₃ [M+Na]⁺: 471.1826; found: *m/z* 471.1823).

General procedure for C-H coupling of thiophenes with AuNP 1 in the presence of TMPMgCl·LiCl:

To a Schlenk tube equipped with a magnetic stirring bar were added THF solution of TMPMgCl·LiCl (1 M, 0.12 mL, 0.12 mmol) and thiophene derivative (0.1 mmol). After stirring for 3 h at rt, AuNP 1 (20 mg), PEPPSI-IPr (8.2 mg, 0.012 mmol), and THF (2 mL) were added to the mixture. After stirring for 24 h at rt, aqueous NH₄Cl was added to quench the reaction. EtOH was then added to the separated organic layer to precipitate AuNP 3a-c as dark brown powder. Measurement of the ¹H NMR spectrum was carried out as a CDCl₃ solution to estimate the conversion of aryl bromide to the corresponding thienylaryl group. In case that the resolution of the spectrum was insufficient, AuNP was subjected to the treatment of iodine in a similar manner to the case of the reaction of AuNP 1 with benzothiazole.

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