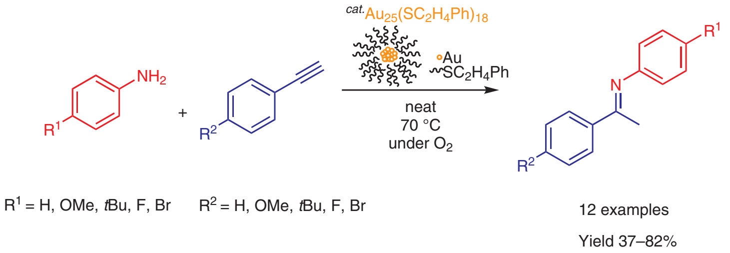
Thiolate-Protected $Au_{25}(SC_2H_4Ph)_{18}$ Nanoclusters as a Catalyst for Intermolecular Hydroamination of Terminal Alkynes

Tatsuki Nagata
Yurina Adachi
Yasushi Obora*

Department of Chemistry and Material Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan
obora@kansai-u.ac.jp



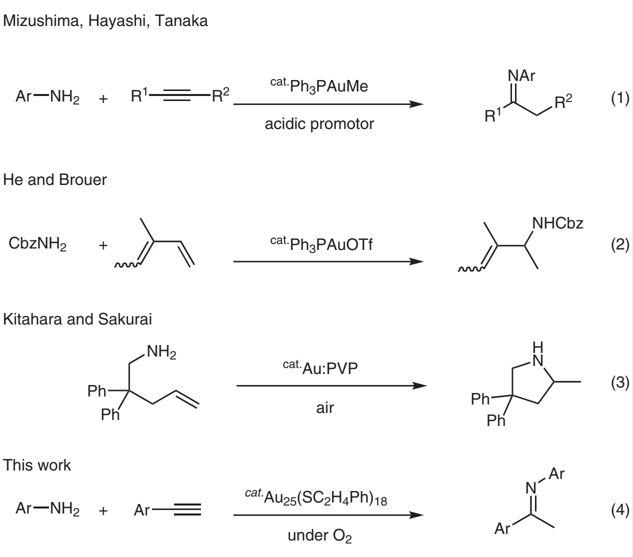
Received: 12.09.2018
Accepted after revision: 15.10.2018
Published online: 16.11.2018
DOI: 10.1055/s-0037-1610671; Art ID: st-2018-u0587-l

Abstract $Au_{25}(SC_2H_4Ph)_{18}$ nanoclusters have high catalytic activity for hydroamination of terminal alkynes. This reaction proceeds under O_2 or air. The presence of molecular oxygen has a profound effect on the $Au_{25}(SC_2H_4Ph)_{18}$ reactivity. The catalysts can be separated from the mixture after the reaction and reused.

Key words hydroamination, gold nanocluster, imines, gold catalyst, reusing catalyst

Imines are attractive building blocks for a variety of organic reactions. They have high reactivity toward various nucleophiles, such as in asymmetric hydrogenation, aza-Henry or Mannich-type reactions, cycloaddition, and nucleophilic addition.[1] Nitrogen-containing products are widely used as the scaffolds of synthetic drugs or natural products. Traditional imine synthesis is an equilibrium reaction, and hydroamination is one of the most atom economical and sustainable imine formation methods.[2]

In late-transition-metal-catalyzed (Pd, Ru, Ir, Rh, Pt, and Au) hydroamination of alkynes, C–C triple bond activation is generally the key step.[2,3] Au(I) catalysts have π-acidic properties, and various gold-activated reactions have been investigated for hydroamination.[4] Tanaka and Mizushima reported intermolecular hydroamination of alkynes with acidic promoters (Scheme 1, eq 1).[5a] He and Brouwer reported hydroamination of 1,3-dienes. The noncoordinating anion effect was observed (Scheme 1, eq 2).[5b] Generation of more electrophilic gold active species is necessary. Co-acidic and stable counteranions are required for application of the catalysts. Additives that can be easily removed from the desired products are desirable.



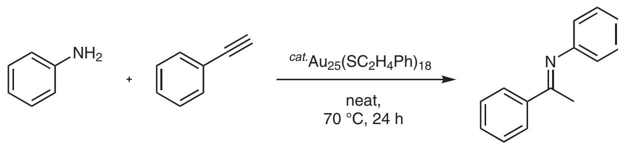
Scheme 1 Hydroamination of multiple bonds activated by gold catalysts

Among the attempts to activate gold, considerable attention has been focused on gold nanoparticles owing to their unique properties.[6] Haruta found significant differences in the catalytic activities of bulk metals and small particles.[7] Ligand-protected nanoclusters, such as thiolate-, phosphine-, and dendrimer-protected clusters, have been studied in detail, and they are suitable as models for catalytic reaction investigation because it is easy to produce nanoparticles of a specific size.[8] Atomically precise gold nanoclusters with very small particle sizes (1–2 nm) are known to have high catalytic activity[9] for CO oxidation, C–C bond formation, hydrogenation, styrene or alcohol oxidation, and hydroamination reactions. In 2010, Sakurai and Kitahara reported gold nanoclusters (NCs) stabilized by poly(*N*-vinyl-2-pyrrolidone) (Au:PVP NCs, mean size = 1.3 nm) as versatile catalysts for intramolecular cycloaddition of primary amines to unactivated alkenes (Scheme 1, eq 3).[10] They proposed that O_2 is initially adsorbed on the gold surface to form electron-deficient reactive sites. From the results of density functional theory calculations, absorption of O_2 provides superoxo-like species and Lewis acidic sites for Au NCs. Substrate alkene activation is favorable, whereas a high activation barrier prevents amine activation. Corma reported that nanogold supported on chitosan is an efficient catalyst for hydroamination of terminal alkynes in the absence of an acid promoter. Nanocatalysts possess the potential to replace conventional reaction promoters.[11] Thiolate-protected Au NCs catalyze the C–N bond formation reaction. Jin et al. reported that the thiolate-protected Au NCs $Au_{38}(SC_2H_4Ph)_{24}$ catalyzes three-component (amine, aldehyde, and alkyne, A_3) coupling reactions.[12] Recently, our research group reported that $Au_{25}(SC_2H_4Ph)_{18}$ gives the corresponding propargylamines in good to excellent yields under O_2.[12b] However, the A_3-coupling reaction mechanism has not been well-explored.

In this study, we propose $Au_{25}(SC_2H_4Ph)_{18}$ as an efficient catalyst for hydroamination of alkynes. Notably, the hydroamination yield is different under oxygen and argon atmospheres. $Au_{25}(SC_2H_4Ph)_{18}$ NCs are activated under an oxygen atmosphere and catalyze intermolecular hydroamination.

The reaction of aniline (**1a**, 0.5 mmol) with phenylacetylene (**2a**, 1.5 mmol) was performed in the presence of $Au_{25}(SC_2H_4Ph)_{18}$ (0.1 mol %) under an oxygen balloon at 70 °C for 24 h, giving **3a** in 80% NMR yield and 63% isolated yield (Table 1, entry 1). Side reactions were not observed and remaining starting material was recovered. The highest catalytic activity and yield of **3a** were achieved when the reaction was performed in the absence of a solvent. The use of representative nonpolar and polar solvents was ineffective under these conditions. (Table 1, entries 1–3). Reaction of **1a** with **2a** at a **1a**/**2a** molar ratio of 3:1 gave **3a** in high yield (54%, Table 1, entry 5). However, reaction with equimolar amounts of **1a** and **2a** gave in the higher yield (62%, Table 1, entry 4). The use of excess amine resulted in a decrease in the catalytic activity (Table 1, entry 5). The reaction proceeded under open air and argon atmospheres (Table 1, entries 6 and 7). However, the catalytic reaction performed better with O_2 rather than with air or inert gas. An amount of O_2 in the system gave a good yield (Figure 1).

Table 1 $Au_{25}(SC_2H_4Ph)_{18}$-Catalyzed Hydroamination of Terminal Alkynes



1a **2a** **3a**

Entry	Conditions[a]	Yield (%)[b]
1	standard	80 (63)
2	toluene solvent	trace
3	acetonitrile solvent	42
4	ratio of **1a**/**2a** = 1:1	62
5	ratio of **1a**/**2a** = 3:1	54
6	under air (balloon)	58
7	under Ar (balloon)	52

[a] Standard conditions: **1a** (0.5 mmol) was allowed to react with **2a** (1.5 mmol) in the presence of the $Au_{25}(SC_2H_4Ph)_{18}$ catalyst (0.1 mol % based on the amount of **1a**) at 70 °C for 24 h.
[b] NMR yields based on **1a**. The isolated yield is given in parenthesis.

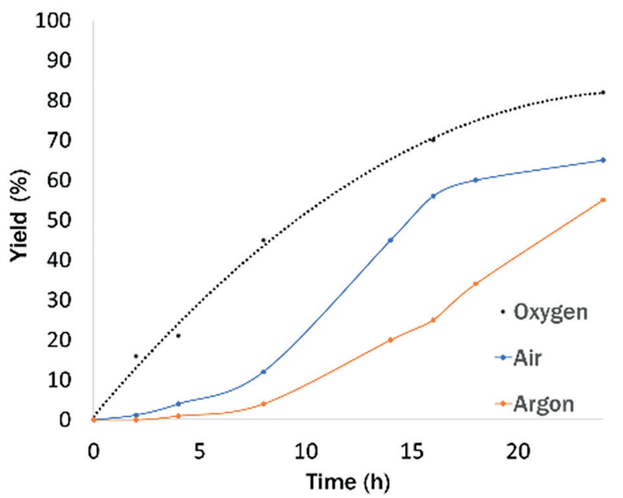
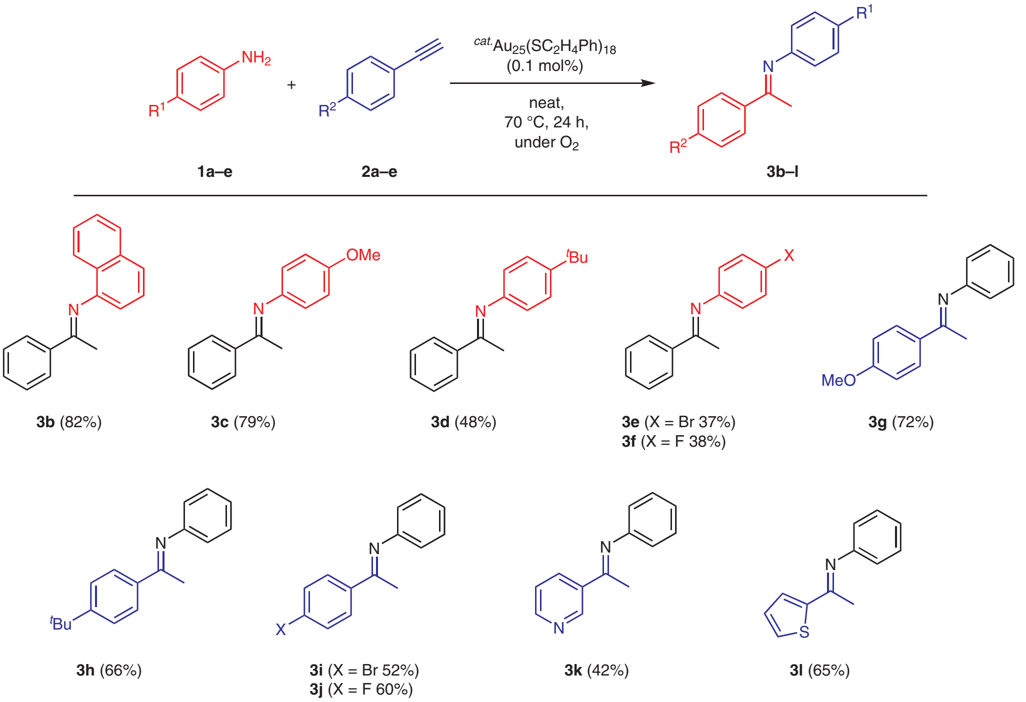


Figure 1 Plots of the reaction yields under (a) O_2 (black curve), (b) air (blue curve), and (c) argon (orange curve) atmospheres

The results of hydroamination of terminal alkynes under the standard conditions using various substituted anilines and phenylacetylenes are given in Scheme 2. Using anilines bearing electron-rich substituents gave the corresponding ketimines **3b**–**d** in good to moderate yields. Anilines bearing fluoro/chloro substituents were found to be less effective. Anilines bearing methoxy and *tert*-butyl groups gave the corresponding imines **3g** and **3h** in good yields. Heteroaromatic terminal alkynes were also tolerated in this reaction (**3k** and **3l**). The use of 3-aminopridine with phenylacetylene was not suitable for this reaction, and the desired product was obtained only in low yield (<10%) under these conditions. The reaction of **1a** with terminal aliphatic alkyne such as 1-octyne was sluggish. Unfortunately, aliphatic amines (e.g., hexylamine, cyclohexylamine) and internal alkynes (diphenylacetyrene, 4-octyne) did not give the desired products, and starting materials were recovered.



Scheme 2 Reaction of various anilines and phenylacetylenes.[a] [a]Reaction conditions: **1a–e** (0.5 mmol), **2a–e** (1.5 mmol), and $Au_{25}(SC_2H_4Ph)_{18}$ catalyst (0.1 mol % based on **1**) at 70 °C for 24 h. The values in parentheses are the isolated yields.

A plausible reaction mechanism based on the most general pathway is shown in Scheme S1.[2] Initially, $Au_{25}(SC_2H_4Ph)_{18}$ NCs generate Lewis acidic sites. Terminal alkynes are activated by electron-deficient (Lewis acidic) sites. An oxygen atmosphere results in nanoclusters oxidation.[13] $Au_{25}(SC_2H_4Ph)_{18}$ has an electron-rich Au_{13} core and delocalized valence electrons. The Au_{12} shell is positively charged owing to electron transfer from gold to sulfur. In the presence of molecular oxygen, it has been proposed that electron transfer from the Au_{13} core to absorbed oxygen occurs.[14] This coordination of dioxygen has been well investigated by research of CO oxidation and the olefin epoxidation mechanism.[15] Overall, cationic activated $Au_{25}(SC_2H_4Ph)_{18}$ promotes activation of the alkyne triple bond. After attack of the aniline, the hydroamination product is released from the enamine intermediate.

The catalyst recyclability is important for its use in industrial and chemical research. Metal nanoparticles are possible recoverable and recyclable catalysts.[16] We investigated the reusability of the catalyst. The reaction was performed under the standard conditions. Catalyst separation and recovery were performed by filtration and extraction (Figure S1). For five reusing experiments, the desired product **3a** was obtained in 38–78% yield (Figure 2). The catalyst tolerated multiple cycles. To understand the significant loss in the catalytic activity, the particle size was measured by dynamic light scattering (DLS). After the 1st run, the particles retained their size (1–2 nm). Aggregated clusters (210 nm) were found after the fifth run (Figure 3). The decrease in the yield can be attributed to gradual decomposition of $Au_{25}(SC_2H_4Ph)_{18}$. A study of the stability of $Au_{25}(SR)_{18}$ agrees with our results.[17]

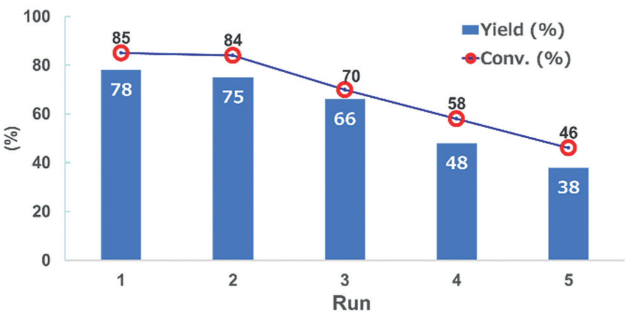


Figure 2 Reusing of the $Au_{25}(SC_2H_4Ph)_{18}$ catalyst five times

In conclusion, we have demonstrated that the $Au_{25}(SC_2H_4Ph)_{18}$ catalyst has high catalytic activity for hydroamination of terminal alkynes.[18,19] Abundant molecular oxygen plays an important role in gold activation. This catalytic system can be easily separated from the product and provides access to imines. The $Au_{25}(SC_2H_4Ph)_{18}$ catalyst can be reused. Further investigation of $Au_{25}(SC_2H_4Ph)_{18}$ and metal nanoparticles as catalysts is in progress.

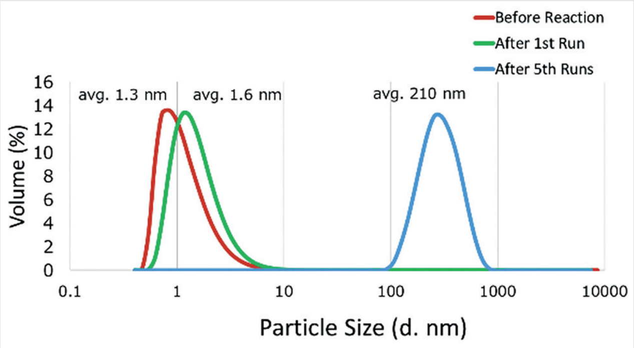


Figure 3 DLS average Au NCs sizes before the reaction (red curve), after first run (green curve), and after five runs (blue curve)

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610671.

Reference and Notes

(1) (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (b) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (c) Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. (d) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489. (e) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

(2) (a) Gooßen, L. J.; Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H. *Chem. Rev.* **2015**, *115*, 2596. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (c) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407. (d) Patil, R. D.; Adimurthy, S. *Asian J. Org. Chem.* **2013**, *2*, 726.

(3) (a) Chen, Q.; Lv, L.; Yu, M.; Shi, Y.; Li, Y.; Pang, G.; Cao, C. *RSC Adv.* **2013**, *3*, 18359. (b) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 3222. (c) Iali, W.; La Paglia, F.; Le Goff, X. F.; Sredojević, D.; Pfeffer, M.; Djukic, J. P. *Chem. Commun.* **2012**, *48*, 10310. (d) Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339. (e) Brunet, J. J.; Chu, N. C.; Diallo, O.; Vincendeau, S. *J. Mol. Catal. A: Chem.* **2005**, *240*, 245.

(4) (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (c) Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638. (d) Ranieri, B.; Escofet, I.; Echavarren, A. M. *Org. Biomol. Chem.* **2015**, *13*, 7103. (e) Joost, M.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 15022.

(5) (a) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (b) Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1744.

(6) (a) Mathew, A.; Pradeep, T. *Part. Part. Syst. Charact.* **2014**, *31*, 1017. (b) Chakraborty, I.; Pradeep, T. *Chem. Rev.* **2017**, *117*, 8208.

(7) (a) Haruta, M.; Kobayashi, T.; Sano, H.; Yamada, N. *Chem. Lett.* **1987**, *16*, 405. (b) Taketoshi, A.; Haruta, M. *Chem. Lett.* **2014**, *43*, 380.

(8) (a) Tsukuda, T. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 151. (b) Fang, J.; Zhang, B.; Yao, Q.; Yang, Y.; Xie, J.; Yan, N. *Coord. Chem. Rev.* **2016**, *322*, 1. (c) Fang, J.; Zhang, B.; Yao, Q.; Yang, Y.; Xie, J.; Yan, N. *Coord. Chem. Rev.* **2016**, *322*, 1.

(9) (a) Li, G.; Jin, R. *Acc. Chem. Res.* **2013**, *46*, 1749. (b) Nie, X.; Qian, H.; Ge, Q.; Xu, H.; Jin, R. *ACS Nano* **2012**, *6*, 6014. (c) Li, G.; Jiang, D. E.; Liu, C.; Yu, C.; Jin, R. *J. Catal.* **2013**, *306*, 177. (d) Li, G.; Jin, R. *J. Am. Chem. Soc.* **2014**, *136*, 11347. (e) Liu, Y.; Tsunoyama, H.; Akita, T.; Tsukuda, T. *Chem. Commun.* **2010**, *46*, 550. (f) Xie, S.; Tsunoyama, H.; Kurashige, W.; Negishi, Y.; Tsukuda, T. *ACS Catal.* **2012**, *2*, 1519.

(10) (a) Kitahara, H.; Sakurai, H. *Chem. Lett.* **2010**, *39*, 46. (b) Bobuatong, K.; Sakurai, H.; Ehara, M. *ChemCatChem* **2017**, *9*, 4490.

(11) (a) Corma, A.; Concepción, P.; Domínguez, I.; Forné, V.; Sabater, M. J. *J. Catal.* **2007**, *251*, 39. (b) Lee, L. C.; Zhao, Y. *ACS Catal.* **2014**, *4*, 688. (c) Liang, S.; Hammond, L.; Xu, B.; Hammond, G. B. *Adv. Synth. Catal.* **2016**, *358*, 3313.

(12) (a) Li, Q.; Das, A.; Wang, S.; Chen, Y.; Jin, R. *Chem. Commun.* **2016**, *52*, 14298. (b) Adachi, Y.; Kawasaki, H.; Nagata, T.; Obora, Y. *Chem. Lett.* **2016**, *45*, 1457.

(13) (a) Zhu, M.; Eckenhoff, W. T.; Pintauer, T.; Jin, R. *J. Phys. Chem.* **2008**, *112*, 14221. (b) Zhu, M.; Aikens, C. M.; Hendrich, M. P.; Gupta, R.; Qian, H.; Schatz, G. C.; Jin, R. *J. Am. Chem. Soc.* **2009**, *131*, 2490.

(14) (a) Okumura, M.; Kitagawa, Y.; Haruta, M.; Yamaguchi, K. *Appl. Catal., A* **2005**, *291*, 34. (b) Roldán, A.; Ricart, J. M.; Illas, F.; Pacchioni, G. *Phys. Chem. Chem. Phys.* **2010**, *12*, 10723. (c) Pal, R.; Wang, L. M.; Pei, Y.; Wang, L. S.; Zeng, X. C. *J. Am. Chem. Soc.* **2012**, *134*, 9438.

(15) (a) Zhu, Y.; Qian, H.; Jin, R. *Chem. - A Eur. J.* **2010**, *16*, 11455. (b) Zhu, Y.; Qian, H.; Zhu, M.; Jin, R. *Adv. Mater.* **2010**, *22*, 1915.

(16) (a) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 7852. (b) Li, M. B.; Tian, S. K.; Wu, Z. *Nanoscale* **2014**, *6*, 5714. (c) Fujita, K. I.; Fujii, A.; Sato, J.; Yasuda, H. *Synlett* **2016**, *27*, 1941.

(17) (a) Collins, C. B.; Tofanelli, M. A.; Crook, M. F.; Phillips, B. D.; Ackerson, C. J. *RSC Adv.* **2017**, *7*, 45061. (b) Dreier, T. A.; Ackerson, C. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 9249. (c) Tofanelli, M. A.; Ackerson, C. J. *J. Am. Chem. Soc.* **2012**, *134*, 16937.

(18) **Preparation of the $Au_{25}(SC_2H_4Ph)_{18}$ Catalyst**
The $Au_{25}(SC_2H_4Ph)_{18}$ nanoclusters were synthesized according to a previously reported method.[20] $HAuCl_4{\cdot}4H_2O$ (2 mmol, 0.8 g) was dissolved in 150 ml tetrahydrofuran (THF) solution containing tetraoctylammonium bromide (2.4 mmol, 1.3 g) at room temperature. After stirring for 15 min, 2-phenylethanethiol (10 mmol, 1.4 g) was added, and the solution was stirred for 15 min 2 h. A cold aqueous solution (25 ml) containing $NaBH_4$ (20 mmol, 0.8 g) was then rapidly added to the solution, and the solution was then stirred at room temperature. After 15 h, the THF solvent was evaporated, and the remaining red brown powder was washed with methanol to remove excess thiol and other byproducts. The $Au_{25}(SC_2H_4Ph)_{18}$ clusters were extracted from the dried sample using acetonitrile.

(19) **General Procedure and the Analytical Data of some Typical Compounds**
The reaction of aniline (**1a**) with phenylacetylene (**2a**) was performed as follows. The prepared 1 mM $Au_{25}(SC_2H_4Ph)_{18}$nanocluster solution in toluene (0.5 mL) was added to a Schlenk flask and the solvent was evaporated. Then, **1a** (0.5 mmol, 47 mg) and **2a** (1.5 mmol, 153 mg) were added, and the solution was stirred for 24 h at 70 °C under O_2 (balloon). The chemical yield of imine **3a** was determined by integrating the ^1H NMR spectrum with respect to an internal standard (1,3,5-trimethoxybenzene). Compound **3a** was isolated by column chromatography (25 µm silica gel, *n*-hexane/ethyl acetate = 99:1). The yield was 63% (61 mg).

3a *N*-(1-Phenylethylidene)benzenamine
Yellow solid; mp 40–41 °C. ^{1}H NMR (400 MHz CDCl$_3$): δ = 7.98–7.96 (2 H, m), 7.45–7.44 (3 H, m), 7.34 (2 H, t, *J* = 7.7 Hz), 7.08 (1 H, t, *J* = 7.2 Hz), 6.79 (2 H, d, *J* = 7.9 Hz), 2.22 (3 H, s); ^{13}C NMR (100 MHz CDCl$_3$): δ = 165.48 (C), 151.65 (C), 139.42 (C), 130.46 (CH), 128.94 (CH), 128.36 (CH), 127.14 (CH), 123.20 (CH), 119.36 (CH), 17.38 (CH$_3$). GC-MS (EI): *m/z* (relative intensity) = 195 (53) [M]$^+$, 180 (100), 118 (12).
3b *N*-(1-Phenylethylidene)-1-naphthalenamine
Yellow solid; mp 85–86 °C. ^{1}H NMR (400 MHz CDCl$_3$) δ = 8.12–8.10 (2 H, m), 7.84–7.77 (2 H, m), 7.60–7.40 (7 H, m), 6.78 (1 H, d, *J* = 7.2 Hz), 2.19 (3 H, s). ^{13}C NMR (400 MHz CDCl$_3$): δ = 166.42 (C), 147.93 (C), 139.20 (C), 134.15 (C), 130.64 (CH), 128.43 (CH), 127.94 (CH), 127.28 (CH), 126.08 (CH), 125.90 (C), 125.88 (CH), 125.37 (CH), 123.55 (CH), 123.21 (CH), 113.44 (CH), 17.66 (CH$_3$); GC-MS (EI) *m/z* (relative intensity) = 246 (12), 245 (62) [M]$^+$, 231 (20), 230 (100), 128 (6), 127 (53).

(20) (a) Dharmaratne, A. C.; Krick, T.; Dass, A. *J. Am. Chem. Soc.* **2009**, *131*, 13604. (b) Yamazoe, S.; Takano, S.; Kurashige, W.; Yokoyama, T.; Nitta, K.; Negishi, Y.; Tsukuda, T. *Nat. Commun.* **2016**, *7*, 10414.