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Gold Nanoclusters as a Catalyst for Intramolecular Addition of Primary Amines to Unactivated Alkenes under Aerobic Conditions

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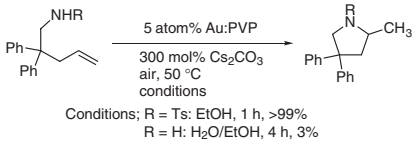
Gold nanoclusters stabilized by the poly(*N*-vinyl-2-pyrrolidone) hydrophilic polymer (Au:PVP) catalyzed the intramolecular cycloaddition of primary amines to unactivated alkenes in the presence of formic acid derivatives. The reaction proceeded under neutral to slightly acidic conditions in air.

We have previously demonstrated that gold nanoclusters (mean size: 1.3 nm) stabilized by poly(*N*-vinyl-2-pyrrolidone) (Au:PVP), promote the intramolecular hydroamination of toluenesulfonamide to unactivated alkenes[1] in aqueous or polar solvents under mild, basic, and aerobic conditions (eq 1). Among the reported catalysts for the hydroamination of primary amines such as organolanthanides,[2] group IV metals,[3] alkali metals,[4] and transition metals,[5] there are still few moisture- and air-stable catalyst systems.[6] In addition, the reactivity of the catalysts is highly dependent on the substituent located on nitrogen, and no versatile catalyst for various types of amine derivatives is known. We expected that Au:PVP would function as a moisture-/air-stable catalyst for the hydroamination of primary amines, but disappointingly, the cyclized product was obtained in only 3% yield under similar conditions to that used for the toluenesulfonamide reaction (eq 1). In this paper, we report that Au:PVP can also be a good catalyst for the hydroamination of primary amines in the presence of formic acid derivatives.



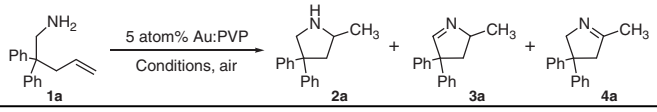
(1)

Conditions; R = Ts: EtOH, 1 h, >99%
R = H: H_2O/EtOH, 4 h, 3%

2,2-Diphenyl-4-pentenyl-1-amine (**1a**) was treated with 5 atom % of Au:PVP in a H_2O/EtOH mixed solvent in air (Table 1). As shown in eq 1 and Table 1, the cyclization with Cs_2CO_3 did not proceed efficiently (Entry 1). When Cs_2SO_4 was used, the rate of cyclization was sluggish at 50 °C, but increased at elevated temperature (80 °C), to yield **2a** with significant amounts of the imines **3a**/**4a** (Entry 2). Formate salts operate as a reductant in the presence of Au:PVP;[7] therefore, the imines **3a**/**4a** were expected to be converted to **2a** by reduction.[8] The yield of **2a** was significantly increased when formate salts such as HCO_2Cs (Entry 3) or HCO_2NH_4 (Entry 4: condition A) were added. The NH_4OAc ammonium salt was not an effective additive, therefore a formate source is indispensable to promote the cyclization (Entry 5). It was also found that the reaction was dependent on the acidity of the solvent. When **1a** was treated with 400 mol % HCO_2H in a pH 6.86 buffer/EtOH mixed solvent (condition B), the yield of imines was slightly decreased (Entry 6). Furthermore, when the reaction was carried out in 1000 mol % aqueous HCO_2H and 500 mol % NH_3 solution/pH 4.01 buffer/EtOH mixed solvent (condition C), **2a** was obtained in 94% yield (Entry 7). Thus, the yield of the amine **2a** can be maximized in weakly acidic to neutral conditions.

Representative results of the hydroamination of primary amines are summarized in Table 2. In the reaction with **1b** and **1d**, conditions B and A gave the best results, respectively, affording the corresponding pyrrolidines **2b** and **2c** in quantitative yields (Entries 4–9). The cis diastereomer was obtained as a major product in both cases. On the other hand, no reaction occurred with the nonsubstituted amine **1d** (Entry 10). The δ-methyl-substituted alkene **1e** underwent cyclization in good yield with the **3e** imine as a minor product (Entries 11–13). **2f** was also obtained in moderate yield from **1f** at 27 °C with the **4f** imine as a minor product (Entries 14–16).

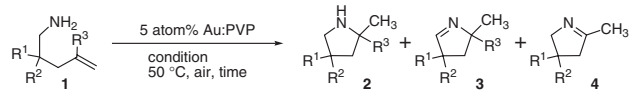
Table 1. Hydroamination of primary amines

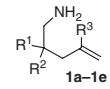
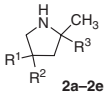
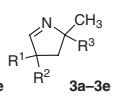
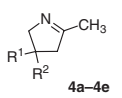
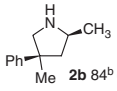
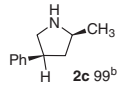
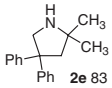
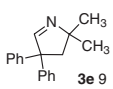
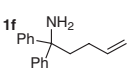
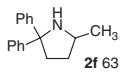
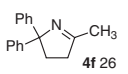


Entry	Additives	Solvent[a] (H_2O or buffer:EtOH = 2:1)		Temp/°C	Time/h	Yield/%[b]			
						2a	**3a**	**4a**	**1a**
1	300 mol % Cs_2CO_3	H_2O/EtOH		50	4	3	—	—	97
2	300 mol % Cs_2SO_4	H_2O/EtOH		50/80	4/6	25	2	28	45
3	300 mol % HCO_2Cs	H_2O/EtOH		50	4	64	5	3	28
4	1000 mol % HCO_2NH_4	H_2O/EtOH	(Condition A)	50	4	83	4	7	—
5	300 mol % NH_4OAc	H_2O/EtOH		50/80	4/6	18	trace	14	67
6	400 mol % HCO_2H	pH 6.86 buffer/EtOH	(Condition B)	50	4	80	3	3	—
7	1000 mol % HCO_2H 500 mol % NH_3 aq	pH 4.01 buffer/EtOH	(Condition C)	50	4	94	2	4	—

[a]H_2O or buffer/EtOH = 20 mL/10 mL, pH 9.18 buffer: 10 mM NaB_4O_7 solution, pH 6.18 buffer: 25 mM KH_2PO_4/24 mM Na_2HPO_4 solution, pH 4.01 buffer: 50 mM C_6H_4(COOH)(COOK) solution. [b]^{1}H NMR ratio (Entries 1–3 and 5) and isolated yield (Entries 4, 6, and 7).

Table 2. Au:PVP-catalyzed hydroamination[9,10]



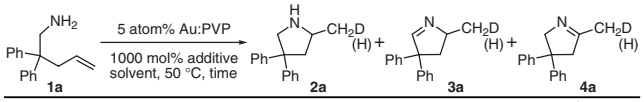
Entry	Alkene	Condition	Time/h	Yield/%[a]		
	 **1a–1e**			 **2a–2e**	 **3a–3e**	 **4a–4e**
1	**1a** R^1, R^2 = Ph, R^3 = H	A	4	**2a** 83	**3a** 4	**4a** 7
2		B	4	80	3	3
3		C	4	94	2	4
4	**1b** R^1 = Ph, R^2 = CH_3, R^3 = H	A	2	 **2b** 84[b] (1.2:1)[c]	—	—
5		B	3	>99[b] (1.2:1)[c]	—	—
6		C	2	72[b] (1.2:1)[c]	—	—
7	**1c** R^1 = Ph, R^2 = H, R^3 = H	A	2	 **2c** 99[b] (1.5:1)[c]	—	—
8		B	10	88[b] (1.2:1)[c]	—	—
9		C	4	11[b] (1.1:1)[c,e]	—	—
10	**1d** R^1, R^2, R^3 = H	A	—	no reaction		
11	**1e** R^1, R^2 = Ph, R^3 = CH_3	A	4	 **2e** 83	 **3e** 9	—
12		B	13	77	4	—
13		C	4	55[e]	—	—
14	**1f** 	A	24[d]	 **2f** 63	—	 **4f** 26
15		B	13[d]	56	—	38
16		C	24[d,e]	29	—	26

[a]Isolated yield. [b]GC yield. [c]Diastereomer ratio was determined as the corresponding tosyl amide. [d]27 °C. [e]**1** was recovered (Entry 10: 42%; Entry 13: 35%; Entry 16: 29%).

To elucidate the hydrogen source for the product and the role of the formic acid derivatives, **1a** was treated with 1000 mol % of HCO_2NH_4 or DCO_2NH_4 in D_2O and/or EtOH-d_6 (condition A), and the results are listed in Table 3. For the cyclization of alcohol[11] and toluenesulfonamide,[1] the hydrogen at the terminal methyl group of the products was introduced from the formyl group of DMF and the ethyl group of EtOH, both of which were used as a solvent, respectively. In contrast, EtOH was not a major hydrogen source in the case of the primary amines, as shown in Entries 1–3. **2a**-D was obtained effectively when DCO_2NH_4 was employed, which revealed that hydrogen was introduced from the formyl group of HCO_2NH_4 (Entry 4).

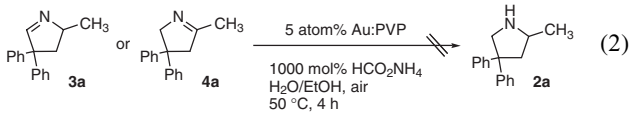
It should be noted that the D/H ratios in the imines **3a**/**4a** were slightly smaller than that in **2a** in every case, which indicates that a minor pathway without hydrogenation by a formate could occur. It is also noteworthy that D was selectively introduced at the terminal methyl position and no other positions, such as the methine position, as determined from ^{2}H NMR. This indicates that the formate does not act as a reductant of the imines. **3a** and **4a** were treated under condition A to afford a quantitative recovery of the imines (eq 2).

Table 3. Hydroamination labeling experiments



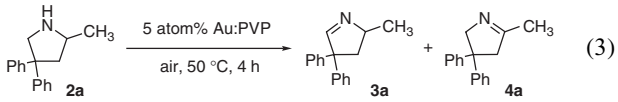
Entry	Solvent	Additive	Time /h	Yield/%[a] (%D[b])		
				2a	**3a**	**4a**
1	D_2O/EtOD	HCO_2NH_4	17	81 (0)	9 (0)	7 (0)
2	H_2O/EtOH-d_6	HCO_2NH_4	17	67 (9)	9 (5)	5 (2)
3	D_2O/EtOH-d_6	HCO_2NH_4	17	81 (11)	8 (4)	8 (1)
4	H_2O/EtOH	DCO_2NH_4	4	82 (89)	—	trace (82)

[a]Isolated yield. [b]Calcd by GCMS.



(2)

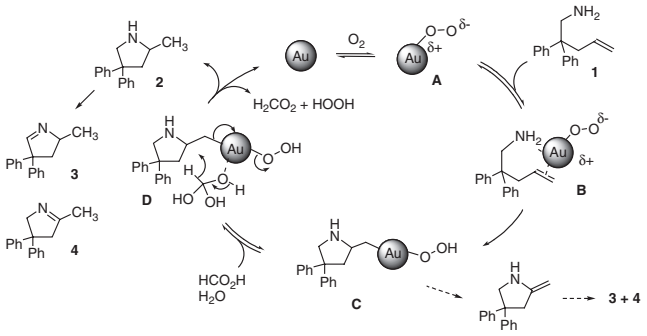
Due to the character of Au:PVP as an aerobic oxidation catalyst,[12] the imines **3a** and **4a** could be formed by the secondary oxidation of **2a**.[13] Since the aerobic oxidation is performed under basic conditions, it is expected that the pathway for the secondary oxidation of **2a** might be more efficient in a higher pH reaction mixture caused by the consumption of formic acid as a hydrogen source. Therefore, **2a** was treated with 5 atom % Au:PVP in various pH (pH 9.18, 6.86, and 4.01 buffer)/EtOH solutions at 50 °C. Although the oxidation to **3a** or **4a** did not proceed sufficiently in every case, the reaction rate was slightly higher under basic conditions (eq 3). The imines **3a** and **4a** were not detected by ^{1}H NMR from the pH 6.86 and 4.01 buffer/EtOH solutions after 4 h, which indicates that secondary oxidation is promoted under basic conditions.



(3)

1000 mol% HCO_2NH_4 H_2O/EtOH,	6%	7%
pH 9.18 Buffer/EtOH	5%	3%
pH 6.86 Buffer/EtOH	-	-
pH 4.01 Buffer/EtOH	-	-

As proposed in previous studies,[1,7,11,12] the reaction is initiated by the adsorption of O_2 onto the surface of the Au nanoclusters as a key intermediate (**A**) that possesses electron-deficient site (Scheme 1). The most important difference from the previous reactions, such as cyclization of alcohols and toluenesulfonamides, is that the reaction should be carried out under neutral to slightly acidic conditions. In the reaction with alcohols or toluenesulfonamides, basic conditions are necessary to assist the adsorption of less nucleophilic substrates. In contrast, primary amines can adsorb onto the gold surface, even under neutral/slightly acidic conditions (**B**).[14] Although the reason why the cyclization does not proceed under basic conditions is not yet clear, the formal Lewis acidic character of Au clusters might be more efficient under neutral/acidic conditions. After insertion of a N–H bond into the olefin followed by the formation of a Au–C intermediate (**C**), selective hydrogenation from HCO_2H might occur due to insufficient



Scheme 1. Proposed mechanism.

neutral/slightly acidic conditions (**D**), in contrast with the hydroamination of toluenesulfonamide under basic conditions. The formyl group hydrogen is abstracted, affording amine **2**. The formate should be transformed to carbon dioxide, which may act as a reductant of oxygen, yielding hydrogen peroxide. The formation of imines **3** and **4** might occur through both the secondary oxidation of amine **2** as a major pathway and through isomerization after β-hydrogen elimination from the Au–C intermediate **C** as a minor pathway. The latter is supported by the smaller D/H ratio in **3**/**4** than that in **2**. The former oxidation pathway can be reduced using the buffer as a co-solvent, because the pH of the reaction mixture gradually increases by the consumption of formic acid as a hydrogen source.

As described above, Au:PVP can be used to catalyze both cycloaddition from toluenesulfonamides and primary amines by changing the reaction conditions. The Au:PVP catalyst is expected to be a versatile and easy-to-handle catalyst for cycloamination reactions, due to its moisture-/air-stable characteristics.

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9 General procedure for the hydroamination reaction of primary amine is as follows: a test tube ($\varphi = 30$ mm) was placed with **1** (0.1 mmol), and dried Au:PVP (38.1 mg, 5 atom %). Water (20 mL), EtOH (10 mL), and HCO_2NH_4 (63.1 mg, 0.1 mol) were added. The reaction mixture was stirred vigorously (1300 rpm) at 50 °C for the time specified. The reaction mixture was quenched by saturated $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (3 × 20 mL), and then the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the product was carried out by PTLC.

10 **1f**: Pale yellow oil; IR (neat): 3374, 3314, 3060, 3023, 2931, 1639, 1492, 1445, 911 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66 (br, 2H), 1.90–1.96 (m, 2H), 2.25–2.29 (m, 2H), 4.90 (dd, $J = 10.3$, 1.7 Hz, 1H), 4.96 (dd, $J = 17.1$, 1.7 Hz, 1H), 5.79 (dddd, $J = 17.1$, 10.3, 6.6, 6.6 Hz, 1H), 7.15–7.19 (m, 2H), 7.23–7.38 (m, 8H); ^{13}C NMR: δ 148.56, 138.65, 128.05, 126.49, 126.26, 114.38, 60.92, 41.56, 28.61; Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90%. Found: C, 85.96; H, 8.18; N, 5.85%. HRFAB m/z Calcd for $C_{17}H_{20}N$ $[M + H]^+$: 238.1596. Found: 238.1595. **2f**: Pale yellow solid; mp 77–78 °C; IR (KBr): 3434, 2963, 1486, 1448 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (d, $J = 6.4$ Hz, 3H), 1.46 (dddd, $J = 12.4$, 8.8, 6.6, 5.5 Hz, 1H), 1.91 (dddd, $J = 12.4$, 7.6, 7.5, 7.1 Hz, 1H), 2.37 (ddd, $J = 12.5$, 8.8, 7.6 Hz, 1H), 2.61 (ddd, $J = 12.5$, 7.5, 5.5 Hz, 1H), 3.34 (ddq, $J = 7.1$, 6.6, 6.4 Hz, 1H), 7.14–7.18 (m, 2H), 7.24–7.29 (m, 4H), 7.43–7.48 (m, 4H); ^{13}C NMR: δ 148.83, 147.98, 128.12, 128.08, 126.40, 126.33, 126.23, 125.98, 71.89, 53.26, 39.16, 33.33, 22.24; Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90%. Found: C, 85.86; H, 8.02; N, 5.86%. HRMS m/z Calcd for $C_{17}H_{19}N$: 237.1517. Found: 237.1522. **3a**: Colorless oil; IR (neat): 3058, 2968, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (d, $J = 7.2$ Hz, 3H), 2.01 (dd, $J = 13.1$, 9.2 Hz, 1H), 2.84 (dd, $J = 13.1$, 6.7 Hz, 1H), 4.16 (ddq, $J = 9.2$, 7.2, 6.7 Hz, 1H), 7.15–7.35 (m, 10H), 7.84 (s, 1H); ^{13}C NMR: δ 168.72, 145.65, 143.38, 128.59, 128.59, 127.28, 127.04, 126.76, 126.59, 67.72, 66.83, 46.32, 21.61; HRMS m/z Calcd for $C_{17}H_{17}N$: 235.1361. Found: 235.1353. **3e**: Yellow oil; IR (neat): 3380, 2967, 2926, 1631, 1493, 1446 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (s, 6H), 2.51 (s, 2H), 7.16–7.18 (m, 4H), 7.20–7.24 (m, 2H), 7.29–7.33 (m, 4H), 7.74 (s, 1H); ^{13}C NMR: δ 166.01, 145.50, 128.58, 127.24, 126.54, 74.06, 67.23, 50.57, 29.46; HRMS m/z Calcd for $C_{18}H_{19}N$: 249.1517. Found: 249.1512. **4f**: White solid; mp 80–81 °C; IR (KBr): 3432, 3020, 2948, 1644, 1488, 1446 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H), 2.59 (br, 4H), 7.14–7.37 (m, 10H); ^{13}C NMR: δ 173.98, 147.67, 128.07, 126.55, 126.28, 83.86, 40.57, 37.71, 19.99; Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95%. Found: C, 86.65; H, 7.46; N, 5.91%. HRMS m/z Calcd for $C_{17}H_{17}N$: 235.1361. Found: 235.1365.

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