Intramolecular Addition of Toluenesulfonamide to Unactivated Alkenes Catalyzed by Gold Nanoclusters under Aerobic Conditions

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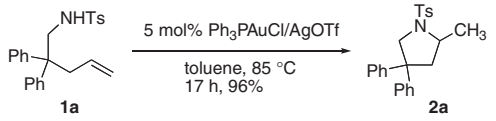
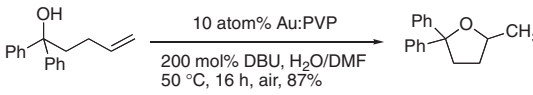
Gold nanoclusters stabilized by a hydrophilic polymer, poly(*N*-vinyl-2-pyrrolidone) (Au:PVP), catalyzed the intramolecular addition of toluenesulfonamide to unactivated alkenes in EtOH under aerobic conditions.

Hydroamination of the carbon–carbon multiple bond offers an efficient atom-economical route to nitrogen-containing molecules and is one of the most extensively studied transformations.[1] In particular, intramolecular reaction provides a useful method for the construction of heterocycles. Various types of activating reagents have been reported for the hydroamination of unactivated alkenes, including transition metals,[2] and acids.[3] However, many of the reported catalysts have a limited scope of substrates, sensitivity towards moisture and oxygen, and sluggish rates for reactions involving unactivated substrates. In the reaction with toluenesulfonamides,[2] He and coworkers reported that cationic Au^I complexes act as catalysts for intramolecular addition to unactivated alkenes. When **1a** was treated with 5 mol % of cationic Au catalyst generated by the addition of PPh_3AuCl and AgOTf in toluene at 85 °C for 17 h, the corresponding cyclized product **2a** was obtained in 96% yield (eq 1).[2a] It is proposed that the cationic Au catalyst behaves as a π-Lewis acid to activate the alkene, assisting the nucleophilic attack of toluenesulfonamide.



1a **2a** (1)

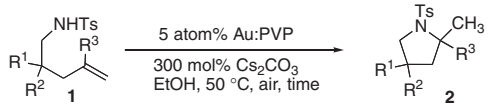
On the other hand, we have previously demonstrated that gold nanoclusters (average size: 1.3 nm) stabilized by a hydrophilic polymer, poly(*N*-vinyl-2-pyrrolidone) (Au:PVP),[4] behave as a formal Lewis acid catalyst, promoting the intramolecular hydroalkoxylation of unactivated alkenes at 50 °C (eq 2).[5] The characteristic features of the reaction are the basic aqueous and aerobic conditions, in contrast to the standard Lewis acidic conditions used for the cationic Au catalyst. It is proposed that the O_2 adsorbed on the gold cluster surface might play a key role as the catalytic center.[6] Therefore, oxygen is essential to promote the reaction and basic conditions are necessary to assist adsorption of the alcohols by increasing the nucleophilicity. According to an analogous reactivity, it is expected that intramolecular addition of toluenesulfonamides to unactivated alkenes could proceed using the Au:PVP catalyst under milder, basic, and aerobic conditions.

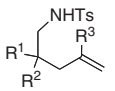
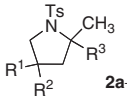
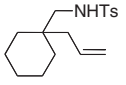
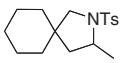
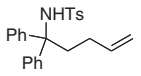
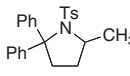


(2)

Representative results of the hydroamination of toluenesulfonamides are summarized in Table 1. Pyrrolidine derivative **2a** was obtained in quantitative yield when toluenesulfonamide (**1a**) was treated with 5 atom % of Au:PVP and 300 mol % of Cs_2CO_3 at 50 °C for 1 h in EtOH as solvent under aerobic conditions (Entry 1).[9] Cyclization did not occur under carefully degassed conditions (Entry 2), or with the use of the larger size of Au:PVP (average size: 9.5 nm) catalyst (Entry 3).[4–6] These results indicate that molecular oxygen plays an essential role in the hydroamination reaction, as for the hydroalkoxylation reaction.[5] The geminal effect at the β-position was then investigated. The cyclization proceeded smoothly in the reaction with methyl-, phenyl- (**1b**), phenyl- (**1c**), and dimethyl- (**1d**) substitutes, to afford the corresponding pyrrolidine derivatives **2b**, **2c**, and **2d** in excellent yields, respectively (Entries 4–6). Cyclization even took place using **1e** without the geminal effect, resulting in a moderate yield (Entry 7). These results are in contrast to those for the reaction with alcohols, which displayed an unusual substituent effect on the β-position.[5] The bicyclic product **2f** was also obtained in good yield (Entry 8). The diphenyl substitute at the α-position **1g** also underwent quantitative cyclization after 1 h (Entry 9).

Table 1. Au:PVP-catalyzed hydroamination of toluenesulfonamides[7,8]



Entry	Alkene	Time/h	Yield/%[a]
	 **1a–1f**		 **2a–2f**
1	**1a** R^1, R^2 = Ph, R^3 = H	1	**2a** >99
2	**1a**		**2a** 0[b]
3	**1a**		**2a** 0[c]
4	**1b** R^1 = Ph, R^2 = CH_3, R^3 = H	4	**2b** 93 (1.9:1)[d]
5	**1c** R^1 = Ph, R^2, R^3 = H	4	**2c** 89 (1.2:1)[d]
6	**1d** R^1, R^2 = CH_3, R^3 = H	16	**2d** 81
7	**1e** R^1, R^2 , R^3 = H	16	**2e** 41
8	 **1f**	1	 **2f** 87
9	 **1g**	1	 **2g** >99

[a]Isolated yield. [b]Under Ar. [c]9.5 nm Au:PVP. [d] ^{1}H NMR ratio.

There are some differences in the reactivity between alcohols and toluenesulfonamides, not only due to the β-substituent effect. For example, in the reaction of δ-methyl-substituted alkene **1h** or **3i**, **1h** quantitatively afforded **2h**, while the reactivity was significantly decreased by introducing a methyl group in the case of alcohol addition[5] (eqs 3 and 4). As for the benzylic substrates, aerobic oxidation of alcohol occurred predominantly from **3j**, providing

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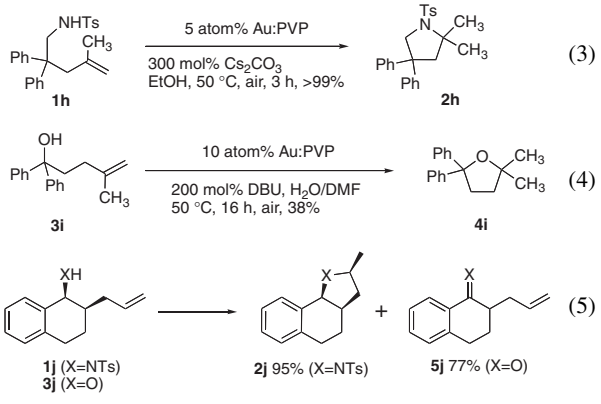
the ketone **5j**.[5] In contrast, no benzylic oxidation occurred, but cyclization from **1j** to **2j** (eq 5) did proceed.



1j : 5 atom% Au:PVP, 300 mol% Cs_2CO_3, H_2O/EtOH, 50 °C, air, 4 h.
3j :10 atom% Au:PVP, 200 mol% DBU, H_2O/DMF, 50 °C, air, 24 h.

To elucidate the source of hydrogen at the methyl group of the product, **1a** was treated with 300 mol % Cs_2CO_3 at 50 °C in EtOD or EtOH-d_6. Hydroamination proceeded quantitatively in EtOD after 6 h; however, **2a**-D was not obtained. **2a**-D was obtained in 96% yield (69.5%D) after 20 h when EtOH-d_6 was employed, which reveals that the hydrogen is introduced from the ethyl group of EtOH.[10] From these results, the reaction mechanism is likely to be similar to that of hydroalkoxylation. Firstly, the toluenesulfonamide anion is generated under the basic conditions and then adsorbed to the gold surface activated by molecular oxygen. From the adsorbed intermediate, nucleophilic attack of amide to the alkene proceeds. Ethoxide is also adsorbed on the gold surface, and then the hydrogen of the ethyl group is abstracted to yield the corresponding cyclized compound.

As described above, Au:PVP is a good catalyst for the intramolecular addition of toluenesulfonamides to unactivated alkenes. The Au:PVP catalyst system is expected to be applied to various types of formal Lewis acidic reactions in addition to oxidation reactions, due to its activity under basic, mild, and atmospheric reaction conditions.

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References and Notes

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4 PVP K-30 having average molecular weight of 40 kDa was used. For the details of the preparation of Au:PVP, see: H. Tsunoyama, H. Sakurai, N. Ichikuni, Y. Negishi, T. Tsukuda, *Langmuir* **2004**, *20*, 11293.

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7 Although many inorganic/organic bases can be used in the reaction, $CsCO_3$ gave the best result among them.

8 General procedure for the hydroamination reaction of tosyl amide is as follows: into a test tube ($\phi = 30$ mm) was placed **1** (0.1 mmol), Cs_2CO_3 (97.7 mg, 0.30 mmol), and dried Au:PVP (38.1 mg = 5 atom %). EtOH (30 mL) was added and the reaction mixture was stirred vigorously (1300 rpm) at 50 °C for the time specified. The reaction mixture was 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.

9 **1b**: Pale yellow solid; mp 67–68 °C; IR (KBr): 3441, 3278, 2977, 2920, 1425, 1328, 1161, 1093 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H), 2.29 (dd, $J = 13.7$, 7.4 Hz, 1H), 2.43 (s, 3H), 2.45–2.49 (m, 1H), 3.04 (dd, $J = 12.2$, 7.9 Hz, 1H), 3.12 (dd, $J = 12.2$, 5.1 Hz, 1H), 3.97–3.99 (br, 1H), 4.99 (dd, $J = 17.7$, 2.3 Hz, 1H), 5.00 (dd, $J = 10.4$, 2.3 Hz, 1H), 5.48 (dddd, $J = 17.7$, 10.4, 7.4, 6.7 Hz, 1H), 7.18 (d, $J = 8.3$ Hz, 2H), 7.21–7.32 (m, 5H), 7.63 (d, $J = 8.3$, 2H); ^{13}C NMR: δ 143.55, 143.33, 136.62, 133.52, 129.65, 128.69, 127.02, 126.65, 126.28, 118.23, 53.19, 44.40, 41.28, 22.48, 21.51; Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25; S, 9.73%. Found: C, 69.38; H, 7.16; N, 4.28; S, 9.75%; HRMS m/z: Calcd for $C_{19}H_{23}NO_2S$: 329.1449; found: 329.1443. **1g**: Pale yellow solid; mp 137–138 °C; IR (KBr): 3285, 3249, 3061, 2931, 1326, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.86–1.92 (m, 2H), 2.32 (s, 3H), 2.60–2.64 (m, 2H), 4.95 (dd, $J = 17.9$, 1.5 Hz, 1H), 4.96 (dd, $J = 9.9$, 1.5 Hz, 1H), 5.77 (dddd, $J = 17.9$, 9.9, 6.6, 6.6 Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 2H), 7.10–7.13 (m, 10H), 7.22 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR: δ 143.57, 142.23, 138.59, 138.01, 128.92, 127.84, 127.47, 126.97, 126.87, 114.94, 66.96, 38.18, 28.56, 21.36; Anal. Calcd for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44; N, 3.58; S, 8.19%. Found: C, 73.40; H, 6.72; N, 3.62; S, 8.01%. HRFAB m/z: Calcd for $C_{24}H_{26}NO_2S$ $[M + H]^+$: 392.1684; found: 392.1674. **1j**: Colorless solid; mp 147–149 °C; IR (KBr): 3422, 3247, 2932, 1334, 1162 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.51–1.61 (m, 1H), 1.79–1.83 (m, 2H), 1.95 (ddd, $J = 14.7$, 7.7, 7.4 Hz, 1H), 2.36 (ddd, $J = 14.7$, 5.7, 5.4 Hz, 1H), 2.40 (s, 3H), 2.69 (ddd, $J = 17.3$, 9.4, 7.1 Hz, 1H), 2.82 (ddd, $J = 17.3$, 5.4, 5.4 Hz, 1H), 4.48 (dd, $J = 9.2$, 3.9 Hz, 1H), 4.70 (d, $J = 9.2$ Hz, 1H), 4.99 (dd, $J = 9.7$, 1.3 Hz, 1H), 5.00 (dd, $J = 18.1$, 1.3 Hz, 1H), 5.77 (dddd, $J = 18.1$, 9.7, 7.4, 5.7 Hz, 1H), 6.69 (d, $J = 7.5$ Hz, 1H), 6.92 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 7.11 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR: δ 143.25, 138.72, 136.38, 136.01, 129.60, 129.08, 128.65, 127.57, 127.13, 125.95, 116.29, 55.62, 38.14, 34.91, 27.29, 23.08, 21.50; HRMS m/z: Calcd for $C_{20}H_{23}NO_2S$: 341.1449; found: 341.1443. **2b**: Yellow oil; IR (neat): 2966, 2872, 1345, 1159, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, diastereomer ratio = 1.9:1, major diastereomer): δ 0.84 (s, 3H), 1.40 (d, $J = 6.2$ Hz, 3H), 1.92 (dd, $J = 12.4$, 9.4 Hz, 1H), 2.21 (dd, $J = 12.4$, 6.4 Hz, 1H), 2.43 (s, 3H), 3.64 (pseud s, 2H), 3.87 (ddq, $J = 9.4$, 6.4, 6.2 Hz, 1H), 7.05–7.22 (m, 5H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.79 (d, $J = 8.1$ Hz, 2H); (minor diastereomer): δ 1.45 (s, 3H), 1.54 (d, $J = 6.3$ Hz, 3H), 1.80 (dd, $J = 12.0$, 6.0 Hz, 1H), 2.35–2.40 (m, 1H), 2.37 (s, 3H), 3.41 (d, $J = 9.5$ Hz, 1H), 3.59 (ddq, $J = 8.7$, 6.3, 6.0 Hz, 1H), 3.68 (d, $J = 9.5$ Hz, 1H), 6.05–7.22 (m, 5H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.60 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (diastereomer mixture): δ 146.66, 146.56, 143.19, 143.05, 135.80, 133.72, 129.52, 129.38, 128.43, 128.39, 127.44, 127.27, 126.34, 126.05, 125.45, 125.31, 60.90, 59.64, 55.52, 47.10, 46.26, 44.55, 29.70, 27.54, 23.38, 22.32, 21.45, 21.38; HRMS m/z: Calcd for $C_{19}H_{23}NO_2S$: 329.1449; found: 329.1458. **2g**: Colorless solid; mp 131–133 °C; IR (KBr): 2979, 1339, 1162, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.51 (d, $J = 6.4$ Hz, 3H), 1.64–1.69 (m, 1H), 2.10–2.23 (m, 1H), 2.36 (s, 3H), 2.72 (m, 2H), 4.45–4.53 (m, 1H), 6.82 (d, $J = 8.1$ Hz, 2H), 6.97 (d, $J = 8.1$ Hz, 2H), 7.20–7.40 (m, 6H), 7.36 (d, $J = 7.2$ Hz, 2H), 7.55 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR: δ 141.77, 130.16, 128.61, 128.49, 127.56, 127.15, 126.98, 126.68, 76.40, 58.78, 44.76, 32.05, 22.47, 21.33; Anal. Calcd for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44; N, 3.58; S, 8.19%. Found: C, 73.54; H, 6.68; N, 3.57; S, 8.30%. HRMS m/z: Calcd for $C_{24}H_{25}NO_2S$: 391.1606; found: 391.1608. **2j**: Pale yellow solid; mp 162–164 °C; IR (KBr): 2934, 1338, 1159 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.24 (d, $J = 5.6$ Hz, 3H), 1.31–1.40 (m, 1H), 1.49–1.57 (m, 1H), 1.73 (m, 1H), 1.86–1.96 (m, 2H), 2.45 (s, 3H), 2.55–2.62 (m, 1H), 2.69–2.77 (m, 1H), 3.68–3.76 (m, 1H), 4.74 (d, $J = 6.8$ Hz, 1H), 7.03 (d, $J = 7.6$ Hz, 1H), 7.17 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.27 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.80 (d, $J = 8.3$ Hz, 2H), 7.92 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR: δ 143.34, 136.38, 135.72, 135.37, 129.73, 129.45, 127.71, 127.59, 126.75, 126.59, 61.48, 57.43, 37.32, 36.37, 25.07, 23.94, 23.26, 21.54; HRMS m/z: Calcd for $C_{20}H_{23}NO_2S$: 341.1449; found: 341.1457.

10 In the case of hydroalkoxylation, it was found that the hydrogen source was the formyl hydrogen[11] of the co-solvent DMF.[5]

11 Unpublished result.

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