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Gold(I)-Catalyzed Intra- and Intermolecular Hydroamination of Unactivated Olefins

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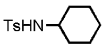
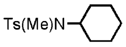
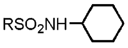
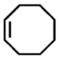
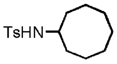
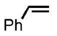
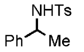
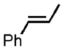
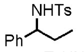
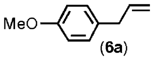
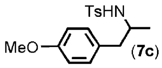
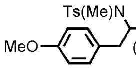
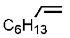
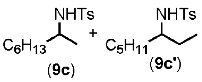
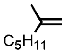
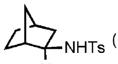
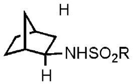
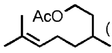
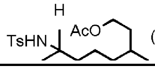
Metal-catalyzed hydroamination of simple olefins is one of the important strategies to prepare nitrogen-containing molecules.[1,2] Despite significant efforts that have been devoted into this idea,[2−4] only a few examples of intermolecular hydroamination of unactivated olefins are known. On the basis of some recent studies,[5] we envisioned that hydroamination of unactivated olefins might be catalyzed by gold complexes, as well. We report here the gold(I)-mediated hydroamination of inert olefins to afford acyclic or cyclic nitrogen-containing molecules. This discovery adds another new methodology into the growing list of reactions that can be catalyzed by gold ions.[6]

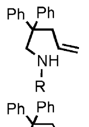
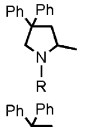
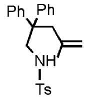
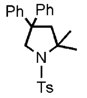
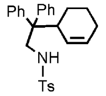
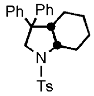
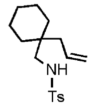
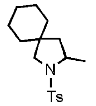
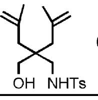
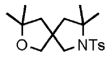
In preliminary experiments, we tested reactions between cyclohexene and various nitrogen nucleophiles. *p*-Toluenesulfonamide ($TsNH_2$) stands out as an excellent candidate for this reaction. *N*-cyclohexyl-*p*-toluenesulfonamide could be prepared in 90% isolated yield by reacting $TsNH_2$ with 4 equiv of cyclohexene in toluene with a catalytic amount (5 mol %) of $Ph_3PAuOTf$ (generated by mixing equal equivalents of Ph_3PAuCl and AgOTf) at 85 °C for 15 h (eq 1). With the use of other nitrogen-based molecules, such as amines, anilines, carboxyamides, carbamates, alkylsulfonamides, or sulfamates, the reactions gave none or very low yields of the desired products. Other Lewis acids, such as $Zn(OTf)_2$ and $Cu(OTf)_2$, could not catalyze the same reaction, and $Sc(OTf)_3$ gave less than 20% of the addition product under the same conditions.

Table 1. Intermolecular Hydroamination of Olefins[a]

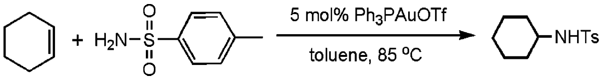
Entry	Olefin	Nucleophile	Time(h)	Product	Yield(%)[b]
1	 (**1a**)	$TsNH_2$ (**1b**)	15	 (**1c**)	90(91)[c]
2[d]	**1a**	$TsNHCH_3$ (**2b**)	44	 (**2c**)	56
3[e]	**1a**	RSO_2NH_2 (**3b**)	15	 (**3c**)	89
4	 (**3a**)	**1b**	20	 (**4c**)	83
5	 (**4a**)	**1b**	14	 (**5c**)	51
6	 (**5a**)	**1b**	16	 (**6c**)	56
7	 (**6a**)	**1b**	14	 (**7c**)	95(93)[c]
8	**6a**	**2b**	48	 (**8c**)	55
9	 (**8a**)	**1b**	14	 (**9c**) (**9c'**)	85[f]
10	 (**9a**)	**1b**	38	 (**10c**)	51
11[g]	 (**10a**)	**1b**	15	 (**11c**)	89
12[g]	**10a**	**3b**	15	 (**12c**)[e]	80
13	 (**11a**)	**1b**	48	 (**13c**)	44

[a] Reactions were conducted with 1 mmol of nucleophiles, 4 mmol of olefins (2.0−2.8 mmol could be recovered after the reaction in most cases), and 5 mol % of Ph_3PAuCl/AgOTf in 2 mL of toluene at 85 °C. [b] Isolated yield. [c] The yield in parentheses refers to a reaction performed without solvent. [d] At 95 °C. [e] R = $MeOC_6H_4$. [f] **9c**:**9c'** = 2:1. [g] A 1:1 ratio of $TsNH_2$ and norbornene was used.

Table 2. Gold(I)-Catalyzed Intramolecular Hydroamination of Tosylated Amino Olefins[a]

Entry	Substrate	Time(h)	Product	Yield(%)[b]
1	 R = Ts, **1d**	17	 R = Ts, **1e**	96
2[c]	R = Ns, **2d**	48	R = Ns, **2e**	99
3	R = Ac, **3d**	48	R = Ac, **3e**	0
4	 (**4d**)	15	 (**4e**)	91
5	 (**5d**)	15	 (**5e**)	95
6	 (**6d**)	15	 (**6e**)	99
7	 (**7d**)	10	 (**7e**)	97

[a] Reactions were conducted with 0.5 mmol of substrate and 5 mol % of Ph_3PAuCl/AgOTf in 2 mL of toluene at 85 °C. [b] Isolated yield. [c] Ns= 2-nitrobenzenesulfonate.

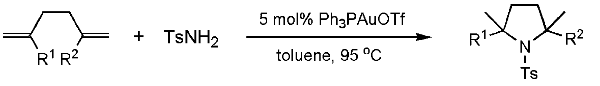


(1)

This reaction works for a range of different olefins, as shown in Table 1. Terminal olefins can serve as good substrates to afford the Markovnikov addition products (Table 1, entries 6−9). *N*-methyl-*p*-toluenesulfonamide (**2b**) as well as *p*-methoxyphenylsulfonamide could be used as the nucleophiles (Table 1, entries 2, 3, 8, and 12). The β-hydride elimination step that typically leads to the unsaturated addition products with palladium-mediated reactions[3,7] does not occur with the use of gold(I) catalyst. Intramolecular alkene hydroamination was also examined, and several N-tosylated γ-amino olefins were efficiently cyclized to afford pyrrolidines with gold(I) (Table 2). 2-Nitrobenzene sulfonamide could also be employed as an efficient nucleophile (Table 2, entry 2). Amides did not work as nucleophiles for this reaction (one example is shown in Table 2, entry 3). Preliminary studies indicate that carbamates also work as nucleophiles in intramolecular additions.

10.1021/ja053864z CCC: $33.50

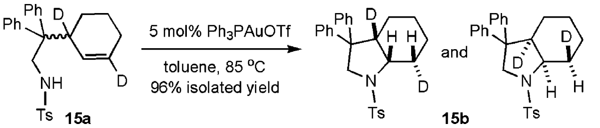
Scheme 1



12a, R^1 = H, R^2 = H — **12b**, 64% (*cis*/*trans*:37/63)
13a, R^1 = H, R^2 = Me — **13b**, 90%
14a, R^1 = Me, R^2 = Me — **14b**, 80%

We further tested hydroamination of 1,5-dienes with $TsNH_2$. The first intermolecular hydroamination of a 1,5-diene by $TsNH_2$ could be followed by a second intramolecular hydroamination to produce pyrrolidines in an "one-pot" operation (Scheme 1).[3h] A mixture of *cis* and *trans* products was isolated in 64% yield with the use of **12a**. Introduction of substitutions at the internal olefinic carbon led to the higher product yields, as shown in Scheme 1 with **13a** and **14a**.

A d_2-labeled substrate **15a** was synthesized to probe the reaction (eq 2). Product **15b** was isolated in 96% yield under the same reaction conditions. The stereochemistry of the two protons in **15b** was assigned conclusively based on the measured coupling constant and comparison to analogous compounds. This result suggests that the sulfonamide attacks from the opposite face of a gold(I)-bound olefin to give the *trans*-addition product after protonolysis of the resulting gold(I)−C bond (a *cis*-addition mechanism would give the product with the two protons *trans* to each other). A previous calculation has suggested that gold(I)-mediated addition of water/alcohol to alkynes may proceed through a *cis*-addition mechanism.[6e] The sulfonamide used here is a weak ligand that appears to add *trans* to the gold(I)−olefin complex. A similar anti-oxyauration has also been shown recently.[6n]



15a **15b** (2)

The interaction between the catalyst and substrates was studied by ^{31}P NMR at 85 °C.[8] $Ph_3PAuCl/AgOTf$ gave a peak at 25.8 ppm; addition of 20 equiv of $TsNH_2$ shifted the peak to 26.1 ppm (perhaps there is a weak interaction between $TsNH_2$ and gold). Addition of 20 equiv of norbornene to this solution further shifted the signal to 29.6 ppm (the same peak was observed if mixing just norbornene with $Ph_3PAuOTf$). This peak is assigned to a $(Ph_3PAu{-}olefin)^+$ complex, which shifted to 27.3 ppm if cyclohexene was used instead of norbornene. In control experiments with an excess of $TsNH_2$, these peaks shifted back to 26.1 ppm after all olefins were consumed, suggesting that these might be the active species during the reaction. A small peak at 42.6 ppm was also observed and assigned to $(Ph_3P)_2Au^+$,[9] which did not catalyze this reaction in control experiments with an extra equivalent of Ph_3P. An unlikely mechanism involving formation of $Ph_3PAuNHTs$ and triflic acid from reacting $Ph_3PAuOTf$ with $TsNH_2$ can be ruled out.[10] $Ph_3PAuNHTs$ was synthesized,[10] which gives a ^{31}P NMR signal at 30.9 ppm. This is very different from the ^{31}P NMR signal observed in the mixture of $Ph_3PAuOTf$ with $TsNH_2$. In fact, we have never observed this signal from our reactions.

Interestingly, addition of alkylamines or aniline (same equivalent as $TSNH_2$) completely inhibits the reaction. No product was observed even when 30% of the catalyst was employed. These more nucleophilic/basic molecules do not appear to inhibit the reaction by simply shutting down the proton transfer pathway (work as bases to interfere with protonolysis of the gold−C bond); otherwise, stoichiometric addition of these molecules or $TsNH_2$ to olefin should be observed. These molecules may compete with olefin to bind gold(I) and thus inhibit the addition step.

In summary, we demonstrate that gold(I) catalyzes intra- and intermolecular hydroamination of unactivated olefins under relatively mild conditions. Saturated products with tosyl-protected amines were obtained with a range of olefins.

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Supporting Information Available: Experimental details and Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See Supporting Information.

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(10) Suggested by a reviewer, for a synthetic procedure to make $Ph_3PAuNHTs$, see: Perevalova, E. G.; Struchkov, Yu. T.; Kravtsov, D. N.; Kuz'mina, L. G.; Smyslova, E. I.; Kalinina, O. N.; Dyadchenko, V. P.; Voevodskaya, T. I. *Zh. Obshch. Khim.* **1988**, *58*, 62−71.

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