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Gold-catalyzed intramolecular hydroamination of allenes: a case of chirality transfer

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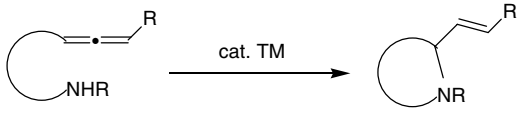
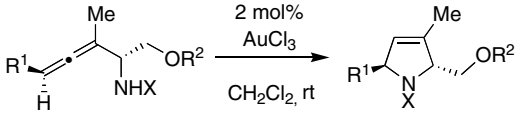
Abstract—The hydroamination of allenes proceeded smoothly in the presence of gold catalysts to give the corresponding 2-vinyl pyrrolidines and piperidines in high yields. The reaction is very efficient and can be carried out with only 1–5 mol % catalyst at room temperature and under extremely mild conditions. As an example of chirality transfer, it is shown that aminoallene **1a** (96% ee), synthesized from (*S*)-(−)-1-octyn-3-ol, was converted into the corresponding pyrrolidine **2a** (94% ee) in 99% yield.

The synthesis of heterocycles via the metal-catalyzed addition of nucleophiles to activated and non-activated C–C bonds is one of the most important processes in organic synthesis.[1] Intramolecular cyclization of allenes with tethered amines, formerly known as hydroamination,[2] in the presence of a transition metal catalyst represents the most common route for generating nitrogen-containing heterocycles (Eq. 1). Silver and mercury salts have been used for this purpose.[3] However, the Lewis acidity of the former catalyst and toxicity of the latter catalyst restrict their use in the hydroamination. An alternative strategy involves the use of organolanthanides[4] and titanium[5] as well as group four bis(sulfonamido) complexes.[6] Our own interest on the palladium catalyzed reactions of allenes[7] encouraged us to examine the possibility of the use of a palladium catalyst. In this regard, we previously reported the cyclization of aminoallenes in the presence of catalytic amounts of a palladium complex under acidic conditions (0.15–1.0 equiv of acetic acid) (Eq. 1, TM = Pd).[8] The use of a carboxylic acid as an additive and high reaction temperature (70 °C) were the drawbacks of the palladium catalyzed hydroamination.



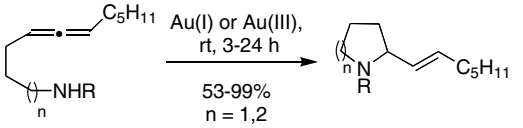
(1)

The use of gold catalysts in organic synthesis has received much attention in recent years because of their ability to co-ordinate with C–C bonds, thereby allowing the attack of various nucleophiles.[9] Taking into consideration the recent reports on allene activation by gold catalysis,[10] and more particularly a recent report by Morita and Krause on the cyclization of α-amino allenes (Eq. 2),[10a] it occurred to us that it would be possible to synthesize N-heterocycles in the presence of gold salts. Herein, we report our preliminary results concerning Au(I) and Au(III) catalyzed room temperature intramolecular hydroamination of allenes leading to pyrrolidines and piperidines (Eq. 3).[11]



(2)

single diastereomer — high diastereoselectivity



(3)

single enantiomer — high enantioselectivity

Initial experiments were performed using aminoallene **1a** as a model substrate, which was easily prepared by the literature procedure.[12] The cyclization was attempted in the presence of 5 mol % of commercially available $AuBr_3$ in various solvents, and was found to occur very smoothly in THF at room temperature in just 3 h. After an easy work-up that consisted of filtration of

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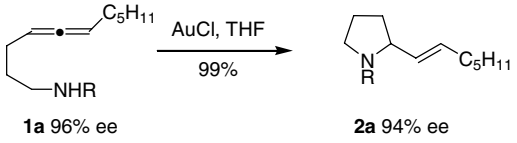
the reaction mixture on a short column of silica gel, the corresponding pyrrolidine **2a** was isolated in high purity and in 99% yield as a single *E*-isomer. Further optimization studies revealed that only 1 mol % of the catalyst was required in order to obtain the product in quantitative yield (Table 1, entry 1). Bearing in mind that the gold catalyst coordinates the allene moiety through its Lewis acidic character, we then examined the activity of a variety of gold(I) and gold(III) salts. As shown in entry 2, $AuCl_3$ also gave an almost complete conversion giving the product **2a** in 98% yield. The use of gold(I) chloride as a catalyst resulted in the formation of **2a** in 99% yield (entry 3). Although gold(I) or gold (III) salts gave similar results, we preferred AuCl *because of its air stability* compared to $AuCl_3$ and $AuBr_3$. Further investigations on the protecting groups on the amine were then pursued. The substrate **1b** containing an ethoxycarbonyl group on the amine reacted smoothly in the presence of 1 mol % AuCl, giving the pyrrolidine **2b** in 97% yield (entry 4). The use of a benzyloxycarbonyl group, which is used more frequently in organic synthesis, also proved excellent for this hydroamination reaction (entry 5). However, in the case of the benzyl protected amine **1d**, 5 mol % of AuCl was necessary in order to obtain **2d** in 76% yield after stirring for 24 h (entry 6). As shown in entry 7, the substrate **1e**, wherein the amine was not protected by any protecting group, did not give any desired product; a complex mixture was obtained. The failure of this reaction can be explained on the basis of the Lewis acidity of the gold catalyst. Presumably, the coordination of the gold catalyst with the basic amine takes place which in turn deactivates the catalyst. The use of a very strong electron withdrawing group did not lead to a reaction. When substrate **1f** containing an –Nf protected amine was subjected to gold catalysis under the standard conditions, no desired product was obtained at all; the starting material was recovered (entry 8). Thus, it became clear that the use of –Ts, –COOEt, –Cbz or –Bn as amine protecting groups was required for the present reaction. An unprotected amine and an amine bearing a strong electron withdrawing group did not undergo reaction. To further examine the scope of this process for the synthesis of piperidines, we synthesized the substrates **1g** and **1h** and tested their reactivity. The piperidines **2g** and **2h** were obtained in 53% and 80% yields, respectively.

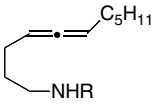
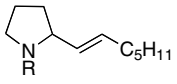
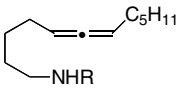
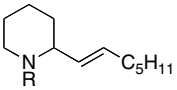
It is clear that the scope and synthetic utility of this process would be enhanced dramatically if the chirality was transferred from the starting aminoallenes to the products. To check this possibility, we synthesized amino allene **1a** (96% ee) from (S)-(−)-1-octyn-3-ol, following the literature procedure.[13] Treatment of enantiomerically pure aminoallene **1a**with 1 mol % AuCl in THF at rt gave pyrrolidine**2a** in excellent yield with 94% ee $\{[\alpha]_D^{25}$ −39 (*c* 1.0, $CHCl_3)\}$ (Eq. 4).



(4)

In conclusion, we have found that Au(I) or Au(III) catalysts promote a highly efficient intramolecular hydroamination of allenes under very mild conditions. The method allowed the synthesis of five and six-membered nitrogen heterocycles in high yields and in an atom economical manner. The high catalyst activity of gold catalysts associated with very mild conditions would allow further applications towards the synthesis of natural products.

Table 1. Au catalyzed cyclization of aminoallenes[a]

Entry	Aminoallene **1**		Product **2**	Time (h)	Yield (%)[b]
					
1	**1a** R = Ts	$AuBr_3$	**2a** R = Ts	3	99
2	**1a** R = Ts	$AuCl_3$	**2a** R = Ts	3	98
3	**1a** R = Ts	AuCl	**2a** R = Ts	3	99
4	**1b** R = COOEt	AuCl	**2b** R = COOEt	3	97
5	**1c** R = Cbz	AuCl	**2c** R = Cbz	3	99
6	**1d** R = Bn	AuCl	**2d** R = Bn	24	76[c]
7	**1e** R = NH_2	AuCl	**2e** R = NH_2	24	0[c,d]
8	**1f** R = Nf	AuCl	**2f** R = Nf	24	0[c,e]
					
9	**1g** R = Ts	AuCl	**2g** R = Ts	24	53[c]
10	**1h** R = Cbz	AuCl	**2h** R = Cbz	24	80[c]

[a] The reaction of **1** in the presence of 1 mol % of gold salts were carried out at rt in THF unless otherwise noted.
[b] Isolated yields.
[c] 5 mol % of catalyst was used.
[d] A complex mixture of products was obtained.
[e] The starting material was recovered.

General procedure: The preparation of **2a** is representative. **1a** (100 mg, 0.3112 mmol) and AuCl (3.6 mg, 0.0156 mmol in THF (2 mL) were stirred at rt in a screw capped vial for 3 h. The reaction mixture was directly loaded on a silica gel column and eluted with 1:1 hexane–ethyl acetate to afford pure **2a** (99 mg, 99%).

References and notes

1. (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159; (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309; (e) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007; (f) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198.
2. For a review, see: (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703; (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114.
3. (a) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997–4000; (b) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243–244; (c) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1991**, *32*, 6359–6362; For the use of this method in natural product synthesis, see: (d) Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550–4551; (e) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012–10020.
4. (a) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871–4872; (b) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *Organometallics* **1998**, *18*, 1949–1960; (c) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633–3639; (d) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686.
5. (a) Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614–4620; (b) Ackermann, L.; Bergmann, R. G. *Org. Lett.* **2002**, *4*, 1475–1478.
6. Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956–11963.
7. Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199–207; For recent examples, see: (a) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Synthesis* **2004**, *12*, 2186–2190; (b) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Can. J. Chem.* **2005**, *83*, 569–573.
8. Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421–5424; For the intramolecular hydroamination of allenes, in situ generated from alkynes, see: (a) Kadota, I.; Shibuya, A.; Lutete, M. L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570–4571; (b) Lutete, M. L.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347–357; (c) Lutete, M. L.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623.
9. Reviews: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237–4239; (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3–9; (c) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51–65; (d) Arcadi, A.; Giuseppe, S. D. *Curr. Org. Chem.* **2004**, *8*, 795–812; (e) Hoffmann-Roder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391; (f) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990–6993; (g) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203; For some recent examples on the activation of C–C bond by gold catalysts, see: (h) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798–1799; (i) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113; (j) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747–1749; (k) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409–5412; (l) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966–6967; (m) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261; (n) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977; (o) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805.
10. (a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121–4123; (b) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501; (c) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; (d) Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1897–1899; (e) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387–1389; (f) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925–3927; (g) Hoffmann-Roder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537–2538; (h) Zhou, C.-Y.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 325–328; (i) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; (j) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288; (k) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443.
11. We have recently reported the gold catalyzed intermolecular reaction between allenes and amines, see: Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314–3317.
12. The method for the preparation of racemic **1a** is known, see: Jonasson, C.; Horvath, A.; Backvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600–9609.
13. The chiral allene **1a** was prepared from (*S*)-(−)-1-octyn-3-ol, following the same procedure[12] {$[\alpha]_D^{25}$ −60 (*c* 1.0, $CHCl_3$), 94% ee}. For the preparation of chiral allenes from chiral propynyl methanesulfonates, see: Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726–3730, The enantioselectivity of the compounds shown in Eq. 4 was determined by chiral HPLC [Shimadzu LC9A and SPD-10A using a Daicel CHIRALCEL OD column (4.6 mm × 250 mm)]. The absolute configuration of **2a** was not determined.