

Gold(I)-Catalyzed Amination of Allylic Alcohols with Cyclic Ureas and Related Nucleophiles

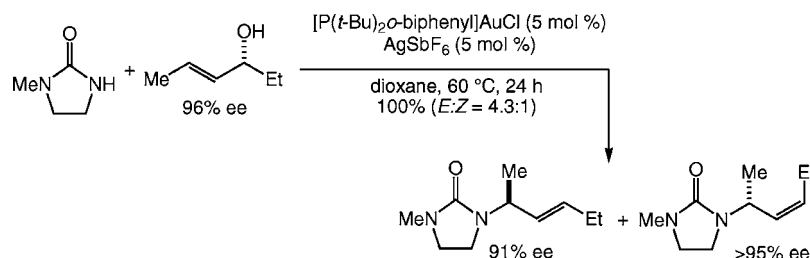
Paramita Mukherjee and Ross A. Widenhoefer*

Duke University, Department of Chemistry, French Family Science Center,
Durham, North Carolina 27708-0346

rwidenho@chem.duke.edu

Received December 19, 2009

ABSTRACT



A 1:1 mixture of [P(*t*-Bu)₂-o-biphenyl]AuCl and AgSbF₆ catalyzes the intermolecular amination of allylic alcohols with 1-methylimidazolidin-2-one and related nucleophiles that, in the case of γ -unsubstituted or γ -methyl-substituted allylic alcohols, occurs with high γ -regioselectivity and *syn*-stereoselectivity.

There has been an ongoing interest in the direct catalytic amination of underivatized allylic alcohols as a route to allylic amines and related derivatives.¹ Initial headway in this area was realized through the in situ activation of the hydroxyl functionality with Lewis acid cocatalysts.² In 2002, Ozawa reported the amination of allylic alcohols with anilines catalyzed by a cationic Pd(II) π -allyl complex in the absence

of a Lewis acidic cocatalyst.³ Since this time, a number of metals including Pd(0),⁴ Pt(II),⁵ Mo(VI),⁶ Bi(III),⁷ Au(I), and Au(III)⁸ have been shown to catalyze the intermolecular amination of underivatized allylic alcohols without the

(1) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.
(2) (a) Lu, X.; Lu, L.; Sun, J. *J. Mol. Catal.* **1987**, *41*, 245. (b) Lu, X.; Jiang, X.; Tao, X. *J. Organomet. Chem.* **1988**, *344*, 109. (c) Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4473. (d) Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett.* **1995**, 1121. (e) Itoh, K.; Hamaguchi, N.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2833. (f) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4877. (g) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000. (h) Yang, S.-C.; Tsai, Y.-C.; Shue, Y.-J. *Organometallics* **2001**, *20*, 5326. (i) Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett.* **2003**, *44*, 1481. (j) Stary, I.; Star, I. G.; Kocovsky, P. *Tetrahedron Lett.* **1993**, *34*, 179. (k) Tsay, S.; Lin, L. C.; Furth, P. A.; Shum, C. C.; King, D. B.; Yu, S. F.; Chen, B.; Hwu, J. R. *Synthesis* **1993**, 329. (l) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627. (m) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401. (n) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234.

(3) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968.

(4) (a) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077. (b) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085. (c) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, *23*, 1698. (d) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595. (e) Piechaczyk, O.; Doux, M.; Ricard, L.; le Floch, P. *Organometallics* **2005**, *24*, 1204. (f) Thoumazet, C.; Grützmacher, H.; Deschamps, B.; Ricard, L.; le Floch, P. *Eur. J. Inorg. Chem.* **2006**, 3911. (g) Piechaczyk, O.; Thoumazet, C.; Jean, Y.; le Floch, P. *J. Am. Chem. Soc.* **2006**, *128*, 14306. (h) Mora, G.; Deschamps, B.; van Zutphen, S.; Le Goff, X. F.; Ricard, L.; le Floch, P. *Organometallics* **2007**, *26*, 1846. (i) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207.

(5) (a) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 14317. (b) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* **2007**, *9*, 3371. (c) Mora, G.; Piechaczyk, O.; Houdard, R.; Mezailles, N.; Le Goff, X. F.; le Floch, P. *Chem.—Eur. J.* **2008**, *14*, 10047.

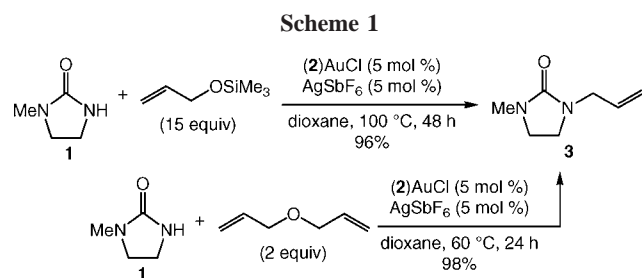
(6) Yang, H.; Fang, L.; Zhang, M.; Zhu, C. *Eur. J. Org. Chem.* **2009**, 666.

(7) Qin, H. B.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

(8) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964.

assistance of a Lewis acidic cocatalyst.⁹ Although a number of these transformations display high regio- and/or stereoselectivity, regiospecific amination of allylic alcohols remains problematic, presumably due to the intermediacy of π -allyl complexes or allylic carbocations. Here we describe a gold(I)-catalyzed protocol for the intermolecular amination of allyl alcohols with 1-methylimidazolidin-2-one (**1**) and related nucleophiles that, in the case of γ -unsubstituted or γ -methyl-substituted allylic alcohols, occurs with high γ -regioselectivity and *syn*-stereoselectivity.¹⁰

We recently reported the intermolecular hydroamination of unactivated 1-alkenes with cyclic ureas catalyzed by gold(I) *o*-biphenylphosphine complexes.¹¹ As part of our ongoing efforts to expand the scope of intermolecular alkene hydroamination, we investigated the gold(I)-catalyzed reaction of cyclic ureas with allylic ethers. However, reaction of **1** with either allyloxytrimethylsilane or diallyl ether catalyzed by a 1:1 mixture of (2)AuCl [**2** = P(*t*-Bu)₂-*o*-biphenyl] and AgSbF₆ gave none of the anticipated hydroamination products but instead led to allylic amination with isolation of 1-allyl-3-methylimidazolidin-2-one (**3**) with >95% yield (Scheme 1).



The efficient amination of both allyloxytrimethylsilane and diallyl ether suggested that unprotected allylic alcohols might also undergo gold(I)-catalyzed allylic amination. Indeed, reaction of **1** with allyl alcohol (1 equiv) catalyzed by (2)AuCl/AgSbF₆ at 60 °C for 2 h led to isolation of **3** in 99% yield (Table 1, entry 1).¹² In addition to **1**, oxazolidin-2-one, imidazolidin-2-one, and primary and secondary sulfonamides underwent efficient gold(I)-catalyzed allylation with allyl alcohol (Table 1, entries 2 and 4–7). Pyrrolidin-2-one and benzyl carbamate also underwent gold(I)-catalyzed

(9) See also: Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.

(10) For relevant examples of the gold-catalyzed addition of nucleophiles to allylic alcohols and related substrates see: (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9533. (b) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (c) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121. (d) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624. (e) Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 129. (f) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-Q.; Guo, L.-N.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 243. (g) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063. (h) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J.-M. *Tetrahedron* **2009**, *65*, 1758. (i) Kothandaraman, P.; Foo, S. J.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 5947.

(11) Zhang, Z.; Lee, S. D.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.

Table 1. Amination of Allyl Alcohol (2 equiv) as a Function of Nucleophile Catalyzed by a Mixture of (2)AuCl (5 mol %) and AgSbF₆ (5 mol %) in Dioxane

entry	nucleophile	product	temp (°C)	time (h)	yield (%) ^a
1			60	2	99 ^b
2	X = O		100	48	98
3	X = CH ₂		80	48	42
4			60	24	100
5	TsNMeH		100	24	99
6	RNH ₂		100	48	78
7	R = 4-MeOC ₆ H ₄ SO ₂		100	24	80 ^c
8	R = Cbz		100	72	23

^a Isolated material of >95% purity. ^b One equivalent of allyl alcohol employed. ^c *N,N*-Diallyl-4-methoxybenzenesulfonamide was also isolated in 20% yield.

allylation with allylic alcohol, albeit with diminished efficiency (Table 1, entries 3 and 8).

We evaluated the scope and stereospecificity of the gold(I)-catalyzed allylation of **1** as a function of allylic alcohol (Table 2). In the cases of γ -unsubstituted or γ -methyl-substituted allylic alcohols, amination occurred selectively at the γ -carbon atom of the allylic alcohol. For example, gold(I)-catalyzed reaction of **1** with 1,1-dideuterio-2-propenol led to exclusive formation of 1-(3,3-dideuterio-2-propenyl)-3-methylimidazolidin-2-one (**3- γ,γ -d₂**) (Table 2, entry 1). Likewise, gold(I)-catalyzed amination of 3-buten-2-ol with **1** led to exclusive formation of the *N*-2-butenylurea **4**, while amination of 2-buten-1-ol with **1** formed exclusively the *N*-(1-methyl-2-propenyl)urea **8** (Table 2, entries 2 and 6). Gold(I)-catalyzed reaction of **1** with 2-deuterio-3-penten-2-ol (**10-*l*-d₁**) formed allylic urea **11- γ -d₁** as the exclusive product (Table 2, entry 8), while gold(I)-catalyzed reaction of **1** with 4-hexen-3-ol (**13**) led to exclusive formation of urea **14** (Table 2, entry 10). Conversely, gold(I)-catalyzed amination of cinnamyl alcohol with **1** led to exclusive formation of α -substitution product **6a** and γ -substitution product **6b** in quantitative yield (Table 2, entries 11 and 12).

The presence of a γ -selective pathway in the gold(I)-catalyzed amination of γ -methyl-substituted allylic alcohols

(12) Mixtures of (2)AuCl and AgOTf also catalyzed the conversion of **1** and allyl alcohol to **3** at 60 °C. Conversely, control experiments ruled out the contribution of acid- or silver-catalyzed pathways to the amination of allyl alcohol. Heating a mixture of **1** and allyl alcohol with a catalytic amount of (1) (2)AuCl, (2) AgSbF₆, (3) a 1:1 mixture of AgSbF₆ and **2**, (4) HOTf, or (5) a 1:1 mixture of HOTf and **2** in 1,4-dioxane (0.5 mL) at 100 °C for 24 h led to no detectable consumption of **1** or formation of **3**.

Table 2. Allylation of 1-Methylimidazolidin-2-one (**1**) as a Function of Allylic Alcohol Catalyzed by a Mixture of (**2**)AuCl (5 mol %) and AgSbF₆ (5 mol %) in Dioxane (Nuc = *N*-Methylimidazolidin-2-one)

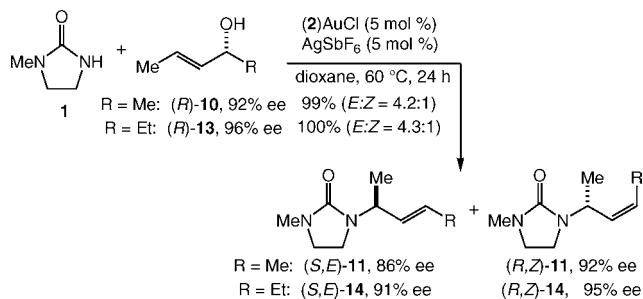
entry	alcohol	major product	cond ^a	yield (%) ^b	γ/α ratio ^c	E/Z ratio ^c
1			A	99	>25:1	—
2		4	B	91	>25:1	2.4:1
3		5	B	94	>25:1	6.7:1
4		6a	A	100	>25:1	—
5		7	A	100	>25:1	—
6		8	C	85	>25:1	—
7		9	D	97	—	—
8		11-γ-d₁	A	100	>25:1	3.7:1
9		12	A	100	—	>25:1
10		14	A	100	>25:1	4.3:1
11		5	D	85	<1:25	25:1
12		6a	B	100	1:12	—

^a Conditions: **A** = 2 equiv of alcohol, 60 °C, 24 h; **B** = 1 equiv of alcohol, 60 °C, 24 h; **C** = 2 equiv of alcohol, 25 °C, 36 h; **D** = 2 equiv of alcohol, 100 °C, 48 h. ^b Isolated material of >95% purity. ^c Determined by ¹H NMR analysis of the purified reaction mixture.

pointed to the potential for 1,3-chirality transfer in these transformations. Indeed, two experiments employing enantiomerically enriched allylic alcohols established the preferential addition of urea to the alkene π -face *syn* to the departing hydroxyl group. In one experiment, gold(I)-catalyzed reaction of (*R*)-**10** (92% ee) with **1** at 60 °C gave a 4.2:1 mixture of (*S,E*)-**11** with 86% ee and (*R,Z*)-**11** with 92% ee in 99% combined yield (Scheme 2). In a second experiment, gold(I)-catalyzed reaction of **1** with (*R*)-**13** (96% ee) at 60 °C for 24 h led to isolation of a 4.3:1 mixture of (*S,E*)-**14** with 91% ee and (*R,Z*)-**14** with \geq 95% ee in quantitative yield (Scheme 2).

The stereochemical outcome of the gold(I)-catalyzed amination of (*R*)-**10** and (*R*)-**13** with **1** is characteristic of a concerted S_N2' substitution.¹³ However, a mechanism for the gold(I)-catalyzed γ -amination of allylic alcohols involving

Scheme 2



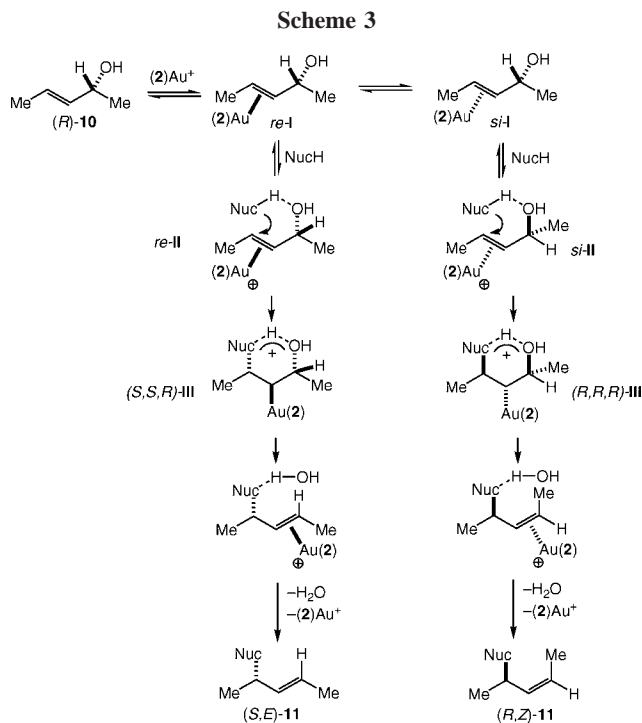
α -activation of the hydroxyl group appears to be at odds with the low oxophilicity of gold(I), particularly considering the modest nucleophilicity of **1**. Rather, a mechanism involving π -activation of the allylic C=C bond also accounts for the stereochemistry of gold(I)-catalyzed allylic amination and appears to be more in line with the pronounced π -acidity of cationic gold(I) complexes.¹⁴ Notably, Maseras has proposed a π -activation pathway for the gold(I)-catalyzed isomerization of allylic ethers with alcohols on the basis of DFT calculations.¹⁵ Guided by these results, we propose a mechanism for gold(I)-catalyzed allylic amination of (*R*)-**10** initiated by formation of the gold(I) π -alkene complexes *si*-**I** and *re*-**I** (Scheme 3). Outersphere addition of **1** to *si*-**I** and *re*-**I**, facilitated by an N–H...O hydrogen bond (*si*-**II** and *re*-**II**),¹⁵ would form the cyclic, hydrogen-bonded gold alkyl intermediates (*S,S,R*)-**III** and (*R,R,R*)-**III**, respectively (Scheme 3). *Anti*-elimination of a hydrogen-bonded water molecule followed by displacement of gold would then release allylic ureas (*S,E*)-**11** and (*R,Z*)-**11** (Scheme 3). Preferential formation of (*S,E*)-**11** relative to (*R,Z*)-**11** presumably results from the unfavorable *cis* relationship of the gold moiety and the C1 methyl group in the transition state for formation of (*R,R,R*)-**III** that is absent in the transition state for formation of (*S,S,R*)-**III**.

The π -activation mechanism for allylic amination outlined in Scheme 3 does not, however, account for the formation of α -substitution products, as was observed for the amination of cinnamyl alcohol and 3-methyl-2-buten-1-ol (Table 2, entries 11 and 12). These α -substitution products may result from the presence of a Lewis acid-catalyzed reaction pathway involving carbocationic intermediates. Alternatively, we have obtained evidence for the formation of α -substitution product **6a** in the gold(I)-catalyzed amination of 3-methyl-2-buten-1-ol with **1** through indirect pathways, in particular, the isomerization of γ -addition product **6b** under reaction

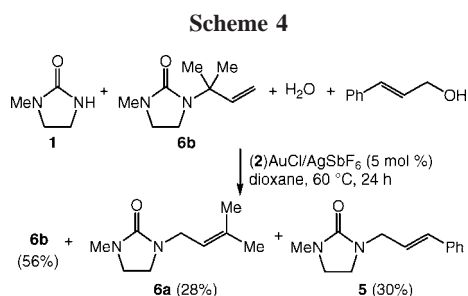
(13) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

(14) For examples of cationic, two-coordinate gold(I) π -alkene complexes see: (a) Brown, T. J.; Dickens, M. G.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 6350. (b) Brown, T. J.; Dickens, M. G.; Widenhofer, R. A. *Chem. Commun.* **2009**, 6451. (c) Hooper, T. N.; Green, M.; Mcgrady, J. E.; Patel, J. R.; Russell, C. A. *Chem. Commun.* **2009**, 3877. (d) Zuccaccia, D.; Belpassi, L.; Tarantelli, F.; Macchioni, A. *J. Am. Chem. Soc.* **2009**, *131*, 3170. (e) de Frémont, P.; Marion, N.; Nolan, S. P. *J. Organomet. Chem.* **2009**, *694*, 551. (f) Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2779.

(15) Paton, R. S.; Maseras, F. *Org. Lett.* **2009**, *11*, 2237.



conditions and the allylic transposition of 3-methyl-2-buten-1-ol followed by γ -addition of **1**. In support of the former pathway, an equimolar mixture of **1**, **6b**, cinnamyl alcohol, and water that contained a catalytic amount of (2)AuCl and AbSbF₆ was heated at 60 °C in dioxane for 24 h.¹⁶ ¹H NMR analysis of the purified reaction mixture revealed a ~2:1:1 mixture of unreacted **6b**, cinnamyl urea **5**, and isomerized urea **6a** (Scheme 4).

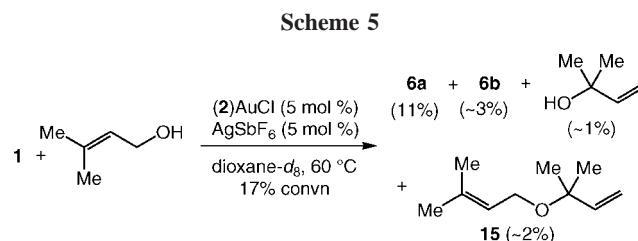


A pathway for formation of **6a** in the gold(I)-catalyzed amination of 3-methyl-2-buten-1-ol initiated by allylic

(16) These conditions mimic the reaction mixture at ~50% conversion.

(17) See the Supporting Information for details regarding these experiments.

transposition of 3-methyl-2-buten-1-ol was validated through a second set of experiments. When an equimolar mixture of 3-methyl-2-buten-1-ol and **1** that contained a catalytic amount of (2)AuCl and AbSbF₆ was heated at 60 °C in dioxane-*d*₈, ¹H NMR analysis at low conversion (~17%) revealed the presence of 2-methyl-3-buten-2-ol and γ -alkoxylation product **15** that together accounted for ~3% of the reaction mixture (Scheme 5). These compounds persisted throughout the conversion of 3-methyl-2-buten-1-ol to **6a** and **6b** and were consumed at high conversion (~95%). Importantly, gold(I)-catalyzed reaction of **1** with either 2-methyl-3-buten-2-ol or **15** formed **6a** as the exclusive product at rates that were ≥ 6 times greater than the rate of reaction of **1** with 3-methyl-2-buten-1-ol under comparable conditions.¹⁷



In summary, we have developed a gold(I)-catalyzed method for the amination of allyl alcohols with 1-methylimidazolidin-2-one (**1**) and related nucleophiles that proceeds in high yields under mild conditions. In the case of γ -unsubstituted or γ -methyl-substituted allylic alcohols, amination occurs with high γ -regioselectivity and *syn*-stereoselectivity. In the case of 3-methyl-2-buten-1-ol or cinnamyl alcohol, gold(I)-catalyzed amination led to predominant formation of α -amination products via secondary π -activation reaction pathways or through a Lewis acid catalysis involving carbocationic intermediates. We are currently working toward expanding the scope of gold(I)-catalyzed allylic amination with respect to nucleophile and toward the development of more general and more selective catalyst systems for the γ -amination of underivatized allylic alcohols.

Acknowledgment is made to the NIH (GM-080422) for support of this research.

Supporting Information Available: Experimental procedures, analytical and spectroscopic data, and copies of HPLC traces and NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL902923E