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

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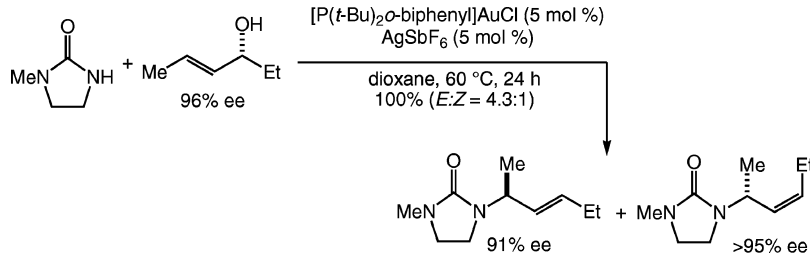
ABSTRACT



A 1:1 mixture of [P(*t*-Bu)$_2$-*o*-biphenyl]AuCl and AgSbF$_6$ 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

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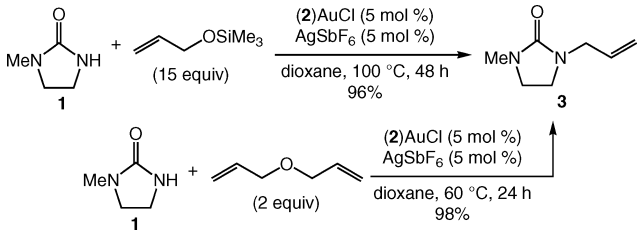
assistance of a Lewis acidic cocatalyst.[9] Although a number of these transformations display high regio- and/or stereoselectivity, regiospecific amination of allylic alcohols remains problematic, presumably due to the intermediacy of π-allyl complexes or allylic carbocations. Here we describe a gold(I)-catalyzed 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 $AgSbF_6$ gave none of the anticipated hydroamination products but instead led to allylic amination with isolation of 1-allyl-3-methylimidazolidin-2-one (**3**) in >95% yield (Scheme 1).

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/$AgSbF_6$ 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 allylic alcohol (Table 1, entries 2 and 4−7). Pyrrolidin-2-one and benzyl carbamate also underwent gold(I)-catalyzed allylation with allylic alcohol, albeit with diminished efficiency (Table 1, entries 3 and 8).

Table 1. Amination of Allyl Alcohol (2 equiv) as a Function of Nucleophile Catalyzed by a Mixture of (**2**)AuCl (5 mol %) and $AgSbF_6$ (5 mol %) in Dioxane

entry	nucleophile	product	temp (°C)	time (h)	yield (%)[a]
1	X = NMe (**1**)		60	2	99[b]
2	X = O		100	48	98
3	X = CH_2		80	48	42
4			60	24	100
5	TsNMeH	TsMeN	100	24	99
	RNH_2	RNH			
6	R = Ts		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.

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-d_2) (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**-*1*-d_1) formed allylic urea **11**-γ-d_1 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 **5**, whereas gold(I)-catalyzed amination of 3-methyl-2-buten-1-ol with **1** led to formation of a 12:1 mixture 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

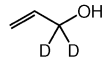
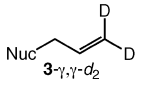
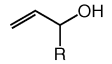
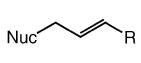
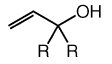
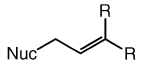
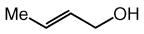
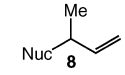
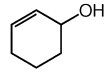
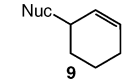
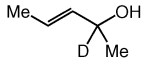
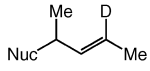
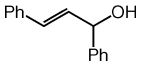
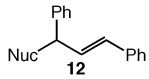
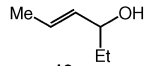
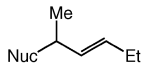
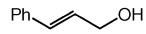
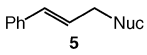
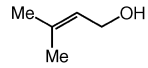
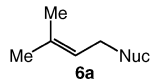
(9) See also: Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.

(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.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.

(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) $AgSbF_6$, (3) a 1:1 mixture of $AgSbF_6$ 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 $AgSbF_6$ (5 mol %) in Dioxane (Nuc = *N*-Methylimidazolidin-2-one)

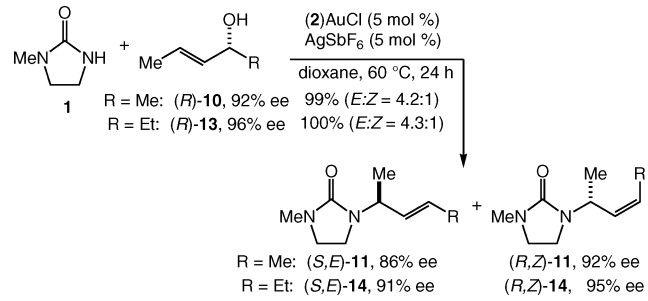
entry	alcohol	major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
1		 **3**-γ,γ-d_2	**A**	99	>25:1	—
2	 R = Me	 **4**	**B**	91	>25:1	2.4:1
3	R = Ph	**5**	**B**	94	>25:1	6.7:1
4	 R = Me	 **6a**	**A**	100	>25:1	—
5	R = –$(CH_2)_5$–	**7**	**A**	100	>25:1	—
6		 **8**	**C**	85	>25:1	—
7		 **9**	**D**	97	—	—
8	 **10**-1-d_1	 **11**-γ-d_1	**A**	100	>25:1	3.7:1
9		 **12**	**A**	100	—	>25:1
10	 **13**	 **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 ^{1}H 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 ≥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



σ-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**.

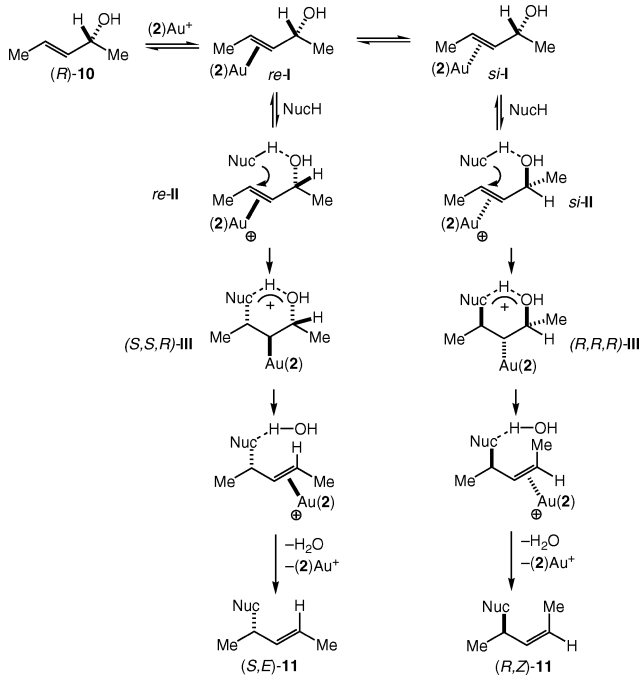
The π-activation mechanism for allylic amination outlined in Scheme 3 does not, however, account for the formation of α-substitution products, as was observed for the amination of cinnamyl alcohol and 3-methyl-2-buten-1-ol (Table 2, entries 11 and 12). These α-substitution products may result from the 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.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 6350. (b) Brown, T. J.; Dickens, M. G.; Widenhoefer, 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.

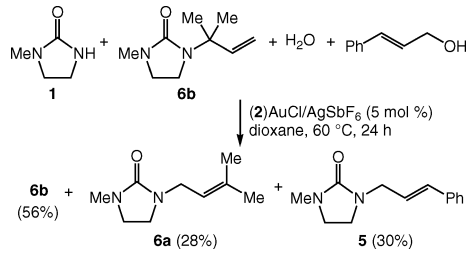
(15) Paton, R. S.; Maseras, F. *Org. Lett.* **2009**, *11*, 2237.

Scheme 3



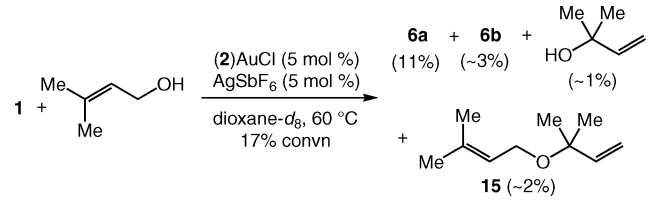
conditions and the allylic transposition of 3-methyl-2-buten-1-ol followed by γ-addition of **1**. In support of the former pathway, an equimolar mixture of **1**, **6b**, cinnamyl alcohol, and water that contained a catalytic amount of (**2**)AuCl and $AbSbF_6$ was heated at 60 °C in dioxane for 24 h.[16] ^{1}H 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).

Scheme 4



A pathway for formation of **6a** in the gold(I)-catalyzed amination of 3-methyl-2-buten-1-ol initiated by allylic 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 $AbSbF_6$ was heated at 60 °C in dioxane-d_8, ^{1}H 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]

Scheme 5



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.

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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.

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

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