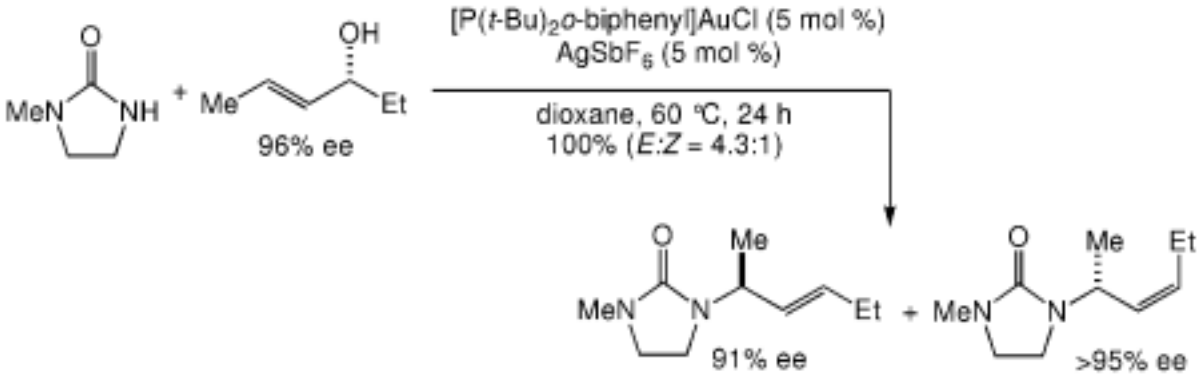
Published in final edited form as:
Org Lett. 2010 March 19; 12(6): 1184–1187. doi:10.1021/ol902923e.

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, NC 27708–0346

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-methyl-imidazolidin-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 co-catalysts.[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 Lewis acidic co-catalysts.[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 assistance of a Lewis acidic co-catalyst.[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-methyl-imidazolidin-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*-biphenyl phosphine complexes.[11] As part of our ongoing efforts

rwidenho@chem.duke.edu .

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

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-methyl-imidazolidin-2-one (**3**) in >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/$AgSbF_6$ 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).

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-methyl-imidazolidin-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-butenyl urea **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 reaction 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 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** are characteristic of a concerted S_N2' substitution.[13] However, a mechanism for the gold(I)-catalyzed γ-amination of allylic alcohols involving σ-activation of the hydroxyl group appears 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 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). Outer-sphere 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 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 AgOTf 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).

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 AgOTf 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]

In summary, we have developed a gold(I)-catalyzed method for the amination of allyl alcohols with 1-methyl-imidazolidin-2-one (**1**) and related nucleophiles that proceedes 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-butene-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

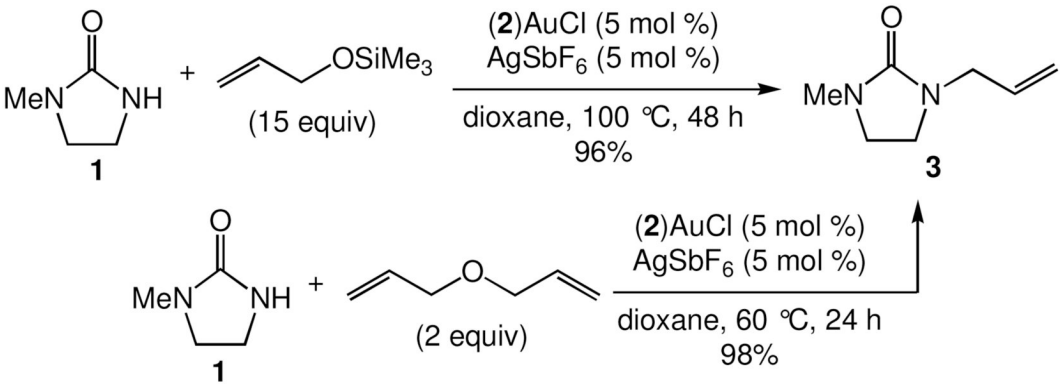
Acknowledgment is made to the NIH (GM-080422) for support of this research.

References

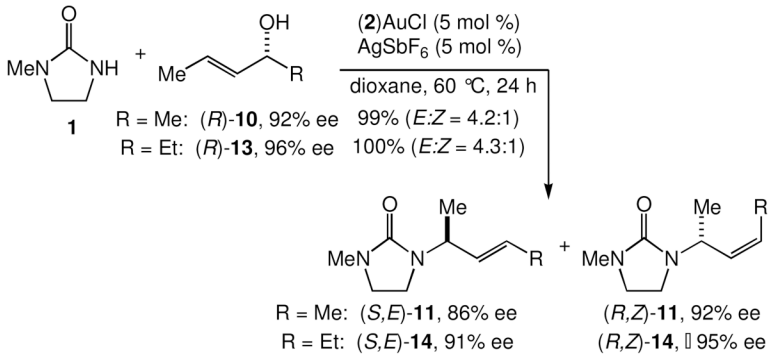
1. Johannsen M, Jørgensen KA. Chem Rev 1998;98:1689. [PubMed: 11848944]
2. (a) Lu X, Lu L, Sun J. J Mol Catal 1987;41:245. (b) Lu X, Jiang X, Tao X. J Organomet Chem 1988;344:109. (c) Masuyama Y, Takahara JP, Kurusu Y. J Am Chem Soc 1988;110:4473. (d) Masuyama Y, Kagawa M, Kurusu Y. Chem Lett 1995:1121. (e) Itoh K, Hamaguchi N, Miura M, Nomura M. J Chem Soc, Perkin Trans 1992;1:2833. (f) Satoh T, Ikeda M, Miura M, Nomura M. J Org Chem 1997;62:4877. (g) Yang SC, Hung CW. J Org Chem 1999;64:5000. (h) Yang SC, Tsai YC, Shue YJ. Organometallics 2001;20:5326. (i) Shue YJ, Yang SC, Lai HC. Tetrahedron Lett 2003;44:1481. (j) Stary I, Star IG, Kocovsky P. Tetrahedron Lett 1993;34:179. (k) Tsay S, Lin LC, Furth PA, Shum CC, King DB, Yu SF, Chen B, Hwu JR. 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. [PubMed: 11603997] (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. [PubMed: 12224930]
4. (a) Muzart J. Eur J Org Chem 2007:3077. (b) Kinoshita H, Shinokubo H, Oshima K. Org Lett 2004;6:4085. [PubMed: 15496105] (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. [PubMed: 15049667] (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. [PubMed: 17076503] (h) Mora G, Deschamps B, van Zutphen S, Le Goff XF, Ricard L, le Floch P. Organometallics 2007;26:1846. (i) Usui I, Schmidt S, Keller M, Breit B. Org Lett 2008;10:1207. [PubMed: 18302396]
5. (a) Ohshima T, Miyamoto Y, Ipposhi J, Nakahara Y, Utsunomiya M, Mashima K. J Am Chem Soc 2009;131:14317. [PubMed: 19761183] (b) Utsunomiya M, Miyamoto Y, Ipposhi J, Ohshima T, Mashima K. Org Lett 2007;9:3371. [PubMed: 17658842] (c) Mora G, Piechaczyk O, Houdard R, Mezailles N, Le Goff XF, 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 HB, Yamagiwa N, Matsunaga S, Shibasaki M. Angew Chem Int Ed 2007;46:409.
8. Guo S, Song F, Liu Y. Synlett 2007:964.
9. See also: Defieber C, Ariger MA, Moriel P, Carreira EM. 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 CY, Biannic B. Org Lett 2008;10:669. [PubMed: 18217767] (c) Aponick A, Li CY, Palmes JA. Org Lett 2009;11:121. [PubMed: 19049406] (d) Aponick A, Li CY, Malinge J, Marques EF. Org Lett 2009;11:4624. [PubMed: 19772313] (e) Lu Y, Fu X, Chen H, Du X, Jia X, Liu Y. Adv Synth Catal 2009;351:129. (f) Shu XZ, Liu XY, Xiao HQ, Ji KQ, Guo LN, Liang YM. Adv Synth Catal 2008;350:243. (g) Terrasson V, Marque S, Georgy M, Campagne JM, Prim D. Adv Synth Catal 2006;348:2063. (h) Georgy M, Boucard V, Debleds O, Dal Zotto C, Campagne JM. Tetrahedron 2009;65:1758. (i) Kothandaraman P, Foo SJ, Chan PWH. J Org Chem 2009;74:5947. [PubMed: 19603765]
11. Zhang Z, Lee SD, Widenhoefer RA. J Am Chem Soc 2009;131:5372. [PubMed: 19326908]
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 allylic 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**.
13. (a) Magid RM. Tetrahedron 1980;36:1901. (b) Paquette LA, Stirling CJM. Tetrahedron 1992;48:7383.
14. For examples of cationic, two-coordinate gold(I) π-complexes see: (a) Brown TJ, Dickens MG, Widenhoefer RA. J Am Chem Soc 2009;131:6350. [PubMed: 19368391] (b) Brown TJ, Dickens MG, Widenhoefer RA. Chem Commun 2009:6451. (c) Hooper TN, Green M, Mcgrady JE, Patel JR,

Russell CA. Chem Commun 2009:3877. (d) Zuccaccia D, Belpassi L, Tarantelli F, Macchioni A. J Am Chem Soc 2009;131:3170. [PubMed: 19219980] (e) de Frémont P, Marion N, Nolan SP. J Organomet Chem 2009;694:551.

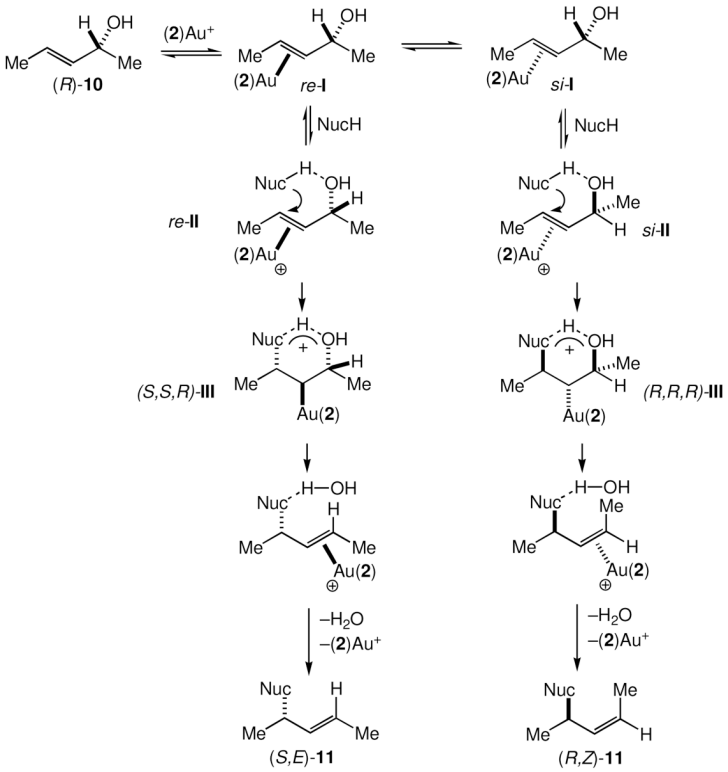
15. Paton RS, Maseras F. Org Lett 2009;11:2237. [PubMed: 19400580]
16. These conditions mimic the reaction mixture at ~50% conversion.
17. See Supporting Information for details regarding these experiments.



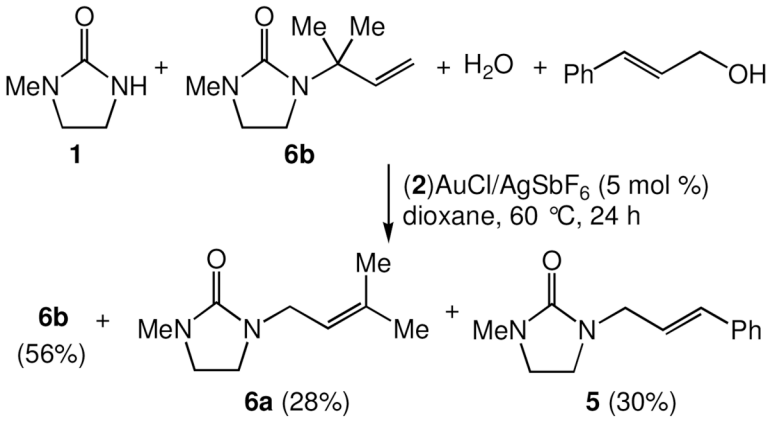
Scheme 1.



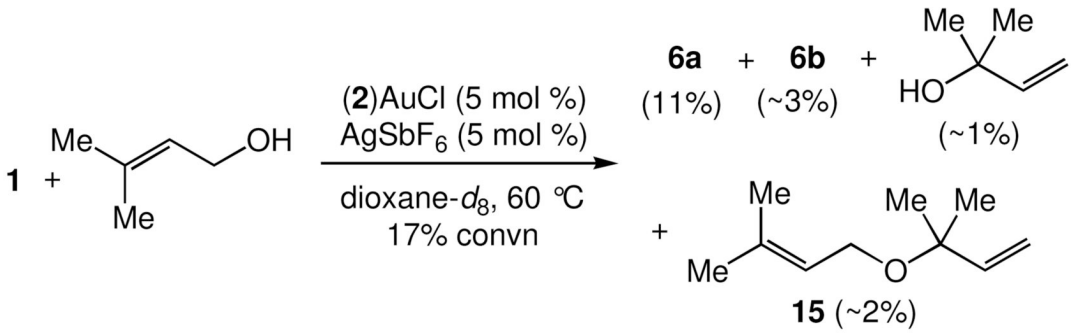
Scheme 2.



Scheme 3.



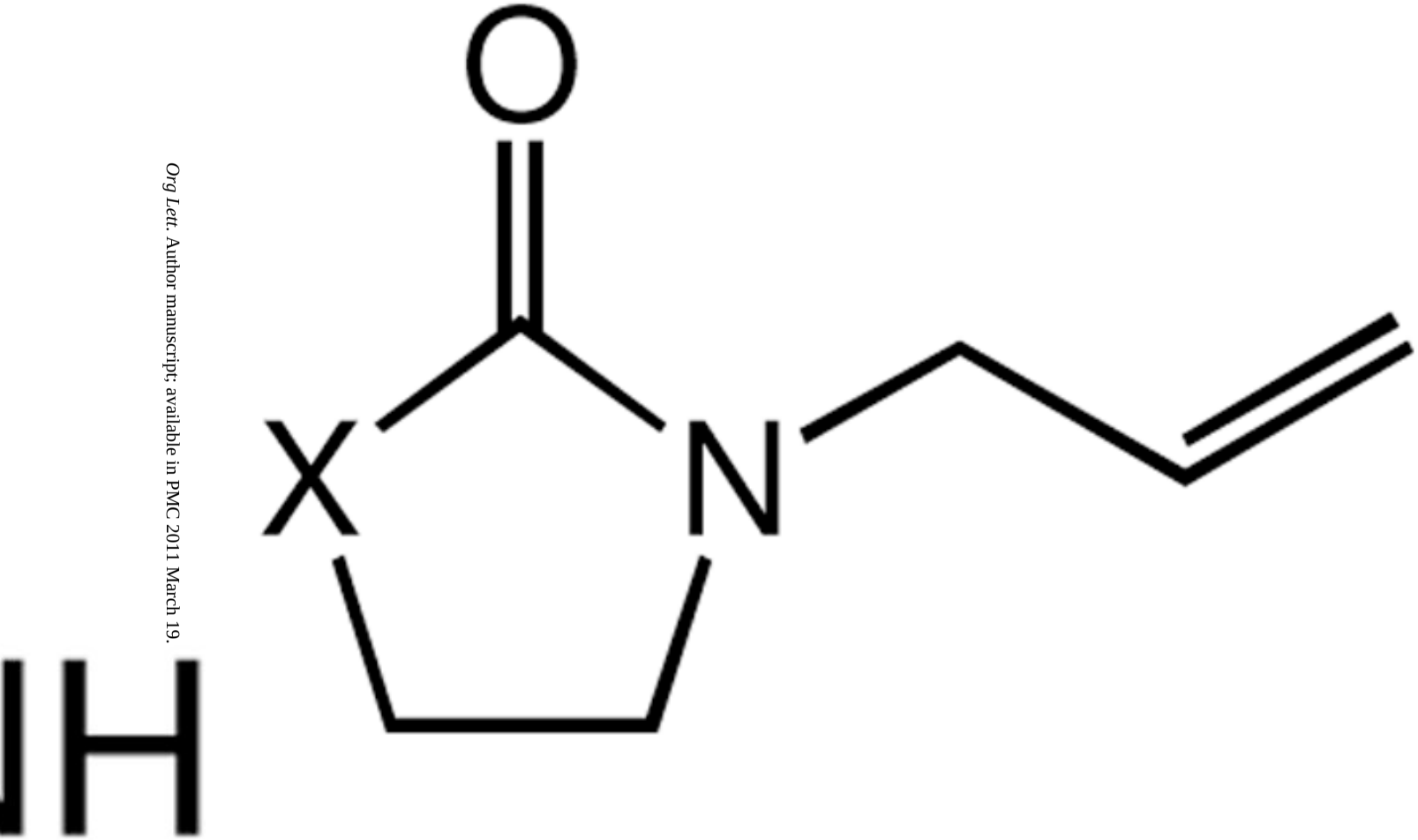
Scheme 4.



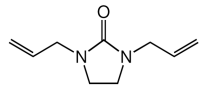
Scheme 5.

Table 1

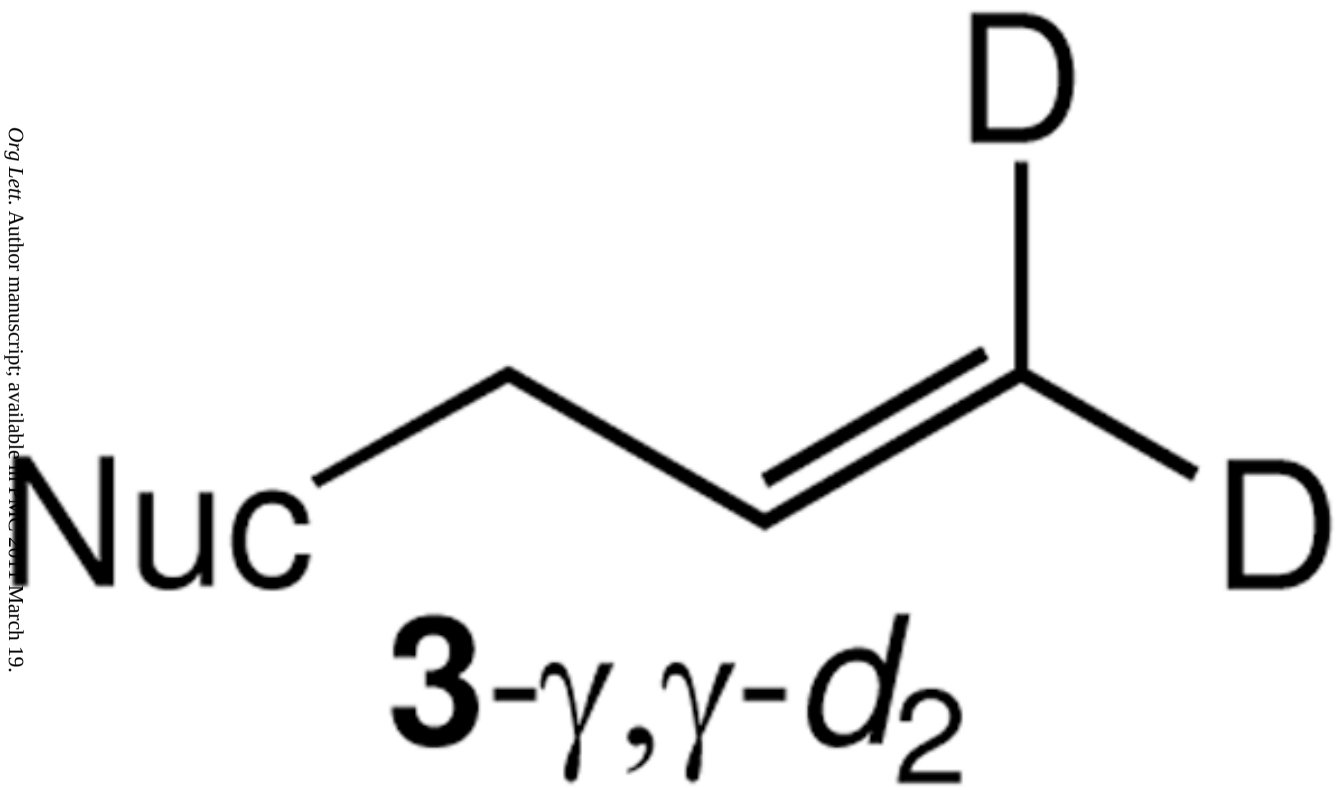
2)AuCl (5 mol %) and $AgSbF_6$ (5 mol %) in dioxane.

product	temp (°C)	time (h)	yield (%)[a]
			

Org Lett. Author manuscript; available in PMC 2011 March 19.

product	temp (°C)	time (h)	yield (%)[a]
	60	2	99[b]
	100	48	98
	80	48	42
	60	24	100
	100	24	99
	100	48	78
	100	24	80[c]
	100	72	23

) and $AgSbF_6$ (5 mol %) in dioxane

major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
 **3**-γ,γ-d_2	**A**	99	>25:1	—

	major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
4		**B**	91	>25:1	2.4:1
5		**B**	94	>25:1	6.7:1

major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
6a	**A**	100	>25:1	—
7	**A**	100	>25:1	—

major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
	C	85	>25:1	—

cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]	major product
D	97	—	—	

major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
11-γ-d_1	**A**	100	>25:1	3.7:1

major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
12	A	100	—	>25:1

	major product	cond[a]	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
OH		A	100	>25:1	4.3:1

cond[a]	major product	yield (%)[b]	γ/α ratio[c]	E/Z ratio[c]
D	6a	85	<1:25	>25:1
B	6a	100	1:12	—