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Regio- and Stereoselective Synthesis of Alkyl Allylic Ethers via Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of Allenes with Alcohols

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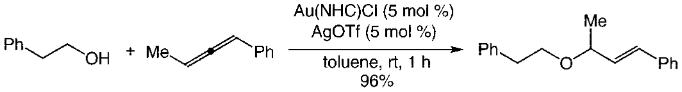
ABSTRACT



Reaction of 1-phenyl-1,2-butadiene with 2-phenyl-1-ethanol catalyzed by a 1:1 mixture of a gold(I) *N*-heterocyclic carbene complex and AgOTf at room temperature for 1 h led to isolation of (*E*)-(3-phenethoxy-1-butenyl)benzene in 96% yield as a single regio- and stereoisomer. Gold(I)-catalyzed intermolecular allene hydroalkoxylation was effective for monosubsituted, 1,1- and 1,3-disubstituted, trisubstituted, and tetrasubstituted allenes and for a range of primary and secondary alcohols, methanol, phenol, and propionic acid.

Alkyl allylic ethers are found in many naturally occurring and biologically active molecules and are versatile substrates and building blocks in organic synthesis. Nevertheless, effective methods for their synthesis are limited.[1] Alkylation or allylation of a secondary or tertiary alkoxide with an allyl or alkyl halide is generally impractical owing to the high basicity and modest nucleophilicity of the alkoxide.[1] Although transition-metal-catalyzed *O*-allylation of a copper[2] or zinc[3] alkoxide or an alkyl borate[4] with an allylic electrophile circumvents the problems associated with alkoxide basicity, issues regarding the scope and regioselectivity of these transformations have not been fully resolved. For these reasons, development of complementary approaches to the regio- and stereoselective synthesis of alkyl allylic ethers would constitute an important advance. The intermolecular hydroalkoxylation of allenes with alcohols represents a conceptually distinct and potentially expedient route to the synthesis of alkyl allylic ethers. A number of metals including Ag(I),[5] Au(I),[6–8] Au(III),[9] Pd(II),[10] Cu(I),[11] and Ln(III)[12] catalyze the intramolecular hydroalkoxylation of allenes. Conversely, the intermolecular hydroalkoxylation of allenes to form alkyl allylic ethers has been realized only in the case

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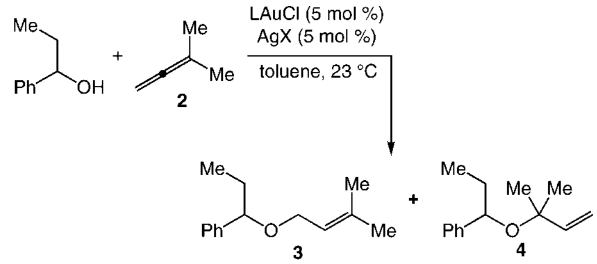
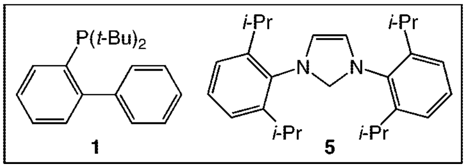
of monosubstituted aryl allenes at elevated temperatures.[13–15] Here, we report a general, regio- and stereoselective gold(I)-catalyzed protocol for the hydroalkoxylation of allenes to form alkyl allylic ethers.

Table 1. Effect of Ligand and Counterion on the Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of 3-Methyl-1,2-butadiene (**2**) with 1-Phenyl-1-propanol



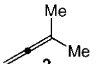
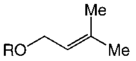
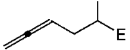
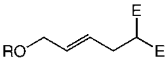
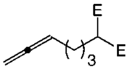
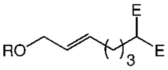
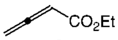
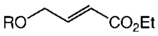
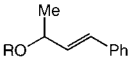
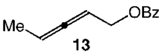
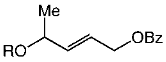
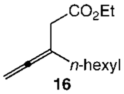
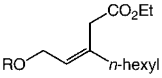
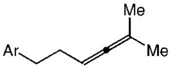
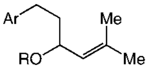
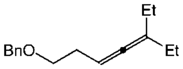
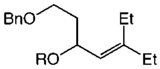
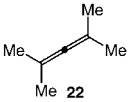
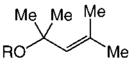
entry	L	X	time (h)	convn (%)[a]	3:4
1	**1**	OTs	27	19	67:33
2	**1**	BF_4	24	76	97:3
3	**1**	OTf	24	100	99:1
4	**5**	OTs	24	9	40:60
5	**5**	BF_4	5	62	97:3
6	**5**	OTf	4	100	99:1



[a] **3** and **4** were the only products detected by GC analysis.

We recently reported that mixtures of (**1**)AuCl [**1** = P(*t*-Bu)$_2$*o*-biphenyl] and AgOTs constituted a highly active catalyst system for the intramolecular hydroalkoxylation of γ- and δ-hydroxy allenes.[8a] Although the high activity of (**1**)AuCl/AgOTs suggested potential application to intermolecular allene hydroalkoxylation, reaction of 3-methyl-1,2-butadiene (**2**) with 1-phenyl-1-propanol (1.1 equiv) catalyzed by a 1:1 mixture of (**1**)AuCl and AgOTs at room temperature for 27 h led to only 19% conversion to form a 67:33 mixture of regioisomeric allylic ethers **3** and **4** (Table 1, entry 1). However, gold(I)-catalyzed allene hydroalkoxylation was sensitive to the nature of both the counterion and ligand, and subsequent optimization (Table 1) identified the gold(I) NHC complex (**5**)AuCl [**5** = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine] in combination with AgOTf as an effective catalyst for intermolecular allene hydroalkoxylation (Table 1, entry 6). In a preparative-scale experiment, reaction of **2** and 1-phenyl-1-propanol (1.1 equiv) catalyzed by a 1:1 mixture of (**5**)AuCl and AgOTf led to isolation of **3** in 88% yield (Table 2, entry 1).[16]

Table 2. Intermolecular Hydroalkoxylation of Allenes Catalyzed by a Mixture of (**5**)AuCl (5 mol %) and AgOTf (5 mol %) in Toluene at 23 °C

entry	R of ROH	allene	allyl ether	compd	yield (%)[a]
1	CH(Ph)Et	 **2**		**3**	88
2	CH_2CH_2Ph	 **6** (E = CO_2Me)		**9a**	81
3	CH(Ph)Et			**9b**	83
4	Cy			**9c**	84
5	CH_2CH_2Ph	 **7** (E = CO_2Me)		**10a**	68[b]
6	CH(Ph)Et			**10b**	85
7	Cy			**10c**	75
8	Ph			**10d**	55
9	CH_2CH_2Ph	 **8**		**11a**	73
10	CH(Ph)Et			**11b**	75[c]
11	CH_2CH_2Ph	 **12**		**14a**	96
12	CH(Ph)Et			**14b**	90[d]
13	CH_3			**14c**	90[e]
14	C(O)Et			**14d**	80
15	CH_2CH_2Ph	 **13**		**15a**	87
16	$CH_2CH=CH_2$			**15b**	81
17	Cy			**15c**	71
18	CH_2CH_2Ph	 **16**		**17**	62
19	CH_2CH_2Ph	 **18** (Ar = 2-C_6H_4OBn)		**20a**	80
20	Cy			**20b**	64
21	CH_2CH_2Ph	 **19**		**21**	41
22	CH_2CH_2Ph	 **22**		**23**	55

[a] Yield of isolated, regio- and stereochemically pure material of >95% chemical purity unless noted otherwise. [b] Dimethyl 2-(4-phenethoxy-5-hexenyl)malonate also isolated in 17% yield. [c] Employment of (*R*)-1-phenyl-1-propanol (99% ee) formed **11b** with 99% ee. [d] Formed as a 2.7:1 diastereomeric mixture. [e] Yield determined by ^1H NMR.

The intermolecular hydroalkoxylation of allenes with alcohols catalyzed by (**5**)AuCl/AgOTf was effective for monosubstituted, 1,1- and 1,3-disubstituted, trisubstituted, and tetrasubstituted allenes and for a range of primary and secondary alcohols, methanol, and phenol. The effective employment of propionic acid as a nucleophile for allene hydroalkoxylation suggests this approach may constitute a useful method for the preparation of allylic acetates (Table 2, entry 14). Intermolecular hydroalkoxylation of monosubstituted allenes **6**−**8** led to selective delivery of the alcohol

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(13) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Can. J. Chem.* **2005**, *83*, 569.

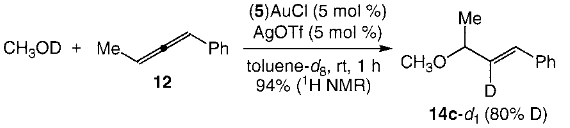
(14) A BASF patent reported the Au(I)-catalyzed sequential addition of two molecules of methanol to the central carbon atom of allene to form 2,2-dimethoxypropane: Schulz, M.; Teles, J. H. (BASF AG), WO-A1 9721648, 1997; *Chem. Abstr.* **1997**, *127*, 121499.

(15) For some related transformations, see: (a) Utsunomiya, M.; Kawatsura, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5865. (b) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (c) Nishina, N.; Yamamoto, Y. *Synlett* **2007**, 1767. (d) Kim, I. S.; Krische, M. J. *Org. Lett.* **2008**, *10*, 513.

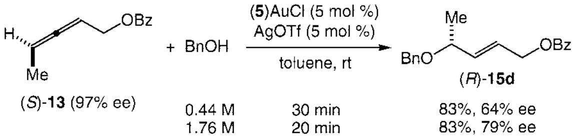
(16) Control experiments ruled out the presence of Ag(I) or acid-catalyzed hydroalkoxylation pathways (see the Supporting Information).

to the less hindered terminus of the allene with exclusive formation of (*E*)-allylic ethers **9**−**11**, respectively (Table 2, entries 2−10). Hydroalkoxylation of 1,3-disubstituted allenes such as **12** and **13** formed the chiral (*E*)-allylic ethers **14** and **15** via selective delivery of the alcohol to the more electron-rich methyl-substituted allene terminus (Table 2, entries 11−17). Hydroalkoxylation of the differentially 1,1-disubstituted allene **16** with 2-phenyl-1-ethanol formed (*Z*)-**17** without formation of detectable amounts of the (*E*)-stereoisomer (Table 1, entry 18). Hydroalkoxylation of trisubstituted allenes **18** and **19** formed chiral allylic ethers **20** and **21** via selective delivery of the alcohol to the less substituted allene terminus (Table 2, entries 19−21).

Several experiments were performed to further probe the mechanism of gold(I)-catalyzed allene hydroalkoxylation. In one experiment, reaction of **12** with CH_3OD led to formation of **14c**-d_1 (80% D) with exclusive incorporation of deuterium at the alkene carbon atom bearing the 1-methoxyethyl group (eq 1). In a second series of experiments, reaction of (*S*)-**13** (97% ee) with benzyl alcohol (0.44 M) led to isolation of (*R*)-**15d** in 83% yield with 64% ee (eq 2). The efficiency of chirality transfer increased with increasing alcohol concentration and gold(I)-catalyzed reaction of (*S*)-**13** (97% ee) with 1.76 M benzyl alcohol led to formation of (*R*)-**15d** with 79% ee (eq 2), which pointed to racemization in an alcohol-independent pathway. Indeed, treatment of (*S*)-**13** with (**5**)AuCl/AgOTf (5 mol %) in toluene at room temperature for 30 min led to complete racemization of (*S*)-**13**.[6,17]



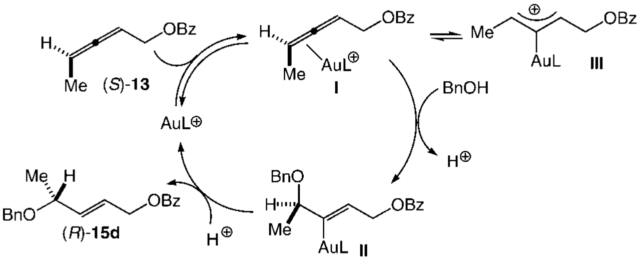
(1)



(2)

Stereospecific conversion of (*S*)-**13** to (*R*)-**15d** (eq 2) is in accord with a mechanism involving outer-sphere attack of the alcohol on the gold π-allene intermediate **I** to form the gold(I) σ-alkenyl complex **II** (Scheme 1).[18] Protonolysis of the Au−C bond of **II** with retention of configuration[19] would release (*R*)-**15d** with regeneration of a cationic gold (NHC) complex. The intermediacy of **II** is supported by the stereoselective conversion of **12** and CH_3OD to **14c**-d_1 (eq 1). We propose that racemization of (*S*)-**13** occurs via formation of a gold σ-allyl cation such as **III**, analogous to the intermediate proposed by Krause to account for the racemization of α-hydroxy allenes by AuCl.[6,20]

Scheme 1



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Supporting Information Available: Experimental procedures, spectroscopic data, and scans of NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (c) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (d) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

(19) Johnson, A.; Puddephatt, R. J. *J. Chem. Soc., Dalton Trans.* **1978**, 980.

(20) The intermediacy of **III** is further supported by the rapid ($\leq$ 10 min) racemization of (*R*)-**12** (78% ee) at room temperature in the presence of (**5**)AuCl/AgOTf, presumably due to enhanced stabilization of the allylic cation by the conjugated phenyl group (see the Supporting Information).