

Regioselective Synthesis of *tert*-Allylic Ethers via Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of Allenes

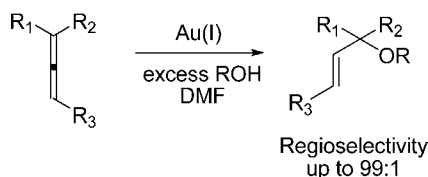
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ABSTRACT

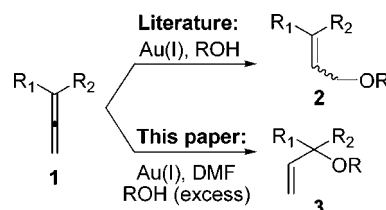


A highly regioselective method towards tertiary allylic ethers via gold(I)-catalyzed intermolecular hydroalkoxylation of allenes is disclosed. Preventing subsequent isomerization of the tertiary allylic ether products to primary allylic ethers appears to be the key to achieving high regioselectivities.

The preparation of ethers is one of the most fundamental reactions in organic synthesis. For example, alkyl allylic ethers are found in natural products and are versatile substrates and building blocks in organic synthesis.¹ The most widely used method for formation of ethers, the Williamson ether synthesis, is seldom useful for preparing tertiary ethers, as elimination reactions tend to be favored when tertiary alkoxides or tertiary halides are used.² Despite recent advances, a mild, efficient, and general method for the synthesis of alkyl *tert*-allylic ethers still remains a challenging topic for synthetic chemists.³

An atom-economical solution to the problem would be to develop a regioselective intermolecular hydroalkoxylation of 1,1-disubstituted allenes (**1**→**3**, Scheme 1). Stoichiometric amounts of toxic mercury(II) salts have been known to

Scheme 1. Gold(I)-Catalyzed Hydroalkoxylation of Allenes



mediate such transformations,⁴ but no modern, catalytic method exists.⁵ Gold(I) is a superb carbophilic Lewis acid⁶ and is thus an obvious candidate for catalyzing **1**→**3**.

However, all reported procedures, notably by the groups of Widenhoefer and Yamamoto, show that gold(I) catalyzes the intermolecular hydroalkoxylation of **1** regioselectively to provide *primary* allylic ethers **2** instead of *tertiary* allylic ethers **3** (Scheme 1).^{7–9} While carrying out mechanistic

(1) For selected examples of biologically relevant molecules and natural products with alkyl *tert*-allylic ether moieties, see: (a) Evidente, A.; Andolfi, A.; Fiore, M.; Boari, A.; Vurro, M. *Phytochemistry* **2006**, *67*, 19. (b) Matsumoto, F.; Idetsuki, H.; Harada, K.; Nohara, I.; Toyoda, Y. *J. Essent. Oil Res.* **1993**, *5*, 123. (c) Bohlmann, F.; Singh, P.; Jakupovic, J. *Phytochemistry* **1982**, *21*, 157. (d) Olagnier, D.; Costes, P.; Philippe, B.; Berry, A.; Linas, M.-D.; Urrutigoity, M.; Dechy-Cabaret, O.; Benoit-Vical, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6075. (e) Giannouli, A. L.; Kintzios, S. E. *Med. Aromat. Plants—Ind. Profiles* **2000**, *14*, 69.

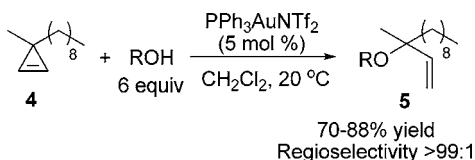
(2) (a) Assabumrungrat, S.; Kiatkittipong, W.; Sevitoon, N.; Praserttham, P.; Goto, S. *Int. J. Chem. Kinet.* **2002**, *34*, 292. (b) Shi, B.; Davis, B. H. *J. Catal.* **1995**, *157*, 359.

(3) For example, see: (a) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882. (b) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (c) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359. (d) Corma, A.; Renz, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 298, and references cited therein.

investigations into gold(I)-catalyzed alcohol additions to cyclopropenes, we gathered compelling evidence that it is possible to completely switch the regioselectivity of allene hydroalkoxylation to provide the more challenging *tert*-allylic ethers **3**. Herein, we report our successful attempt at developing a regioselective gold(I)-catalyzed method for hydroalkoxylation of allenes to provide alkyl *tert*-allylic ethers **3**.

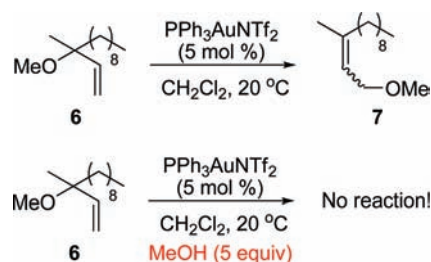
We recently disclosed a highly regioselective, facile, and mild gold(I)-catalyzed addition of alcohols to cyclopropenes **4** to form alkyl *tert*-allylic ethers **5** (Scheme 2).¹⁰ An *excess*

Scheme 2. Previous Results: Regioselective Gold(I)-Catalyzed Alcohol Additions to Cyclopropenes¹⁰



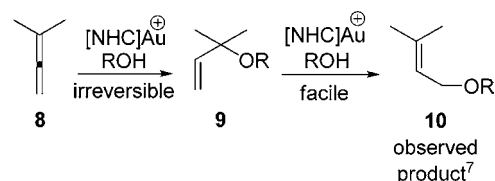
of alcohol is crucial to ensure high regioselectivity for the tertiary (vs primary) ether. Suspecting isomerization between ethers **3** and **2**, *tert*-allylic ether **6** was subjected to gold(I) catalysis¹¹ in the absence and presence of excess alcohol (Scheme 3). The tertiary ether **6** does indeed isomerize to the primary ether **7** under gold(I) catalysis, but addition of excess alcohol retards this isomerization. We postulated that the latter observation is the key to the high regioselectivities observed in Scheme 2.

Scheme 3. Gold(I)-Catalyzed Isomerization of *tert*-Allylic Ethers to Primary Allylic Ethers: Excess Alcohol Retards Isomerization



We were thus highly intrigued by a recent report on DFT calculations regarding the intermolecular hydroalkoxylation of allenes.¹² Various groups have demonstrated that gold-catalyzed hydroalkoxylation of 1,1-disubstituted allenes such as **8** produces the primary allyl ethers **10** regioselectively (Scheme 4).⁷

Scheme 4. DFT Calculations by Paton and Maseras Suggest that Facile Isomerization is Responsible for Selectivity of **10**¹²

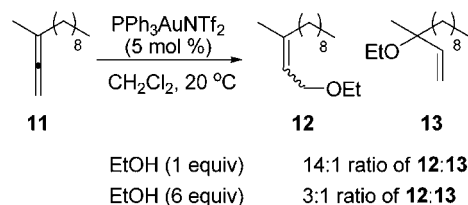


- (4) Waters, W. L.; Kiefer, E. F. *J. Am. Chem. Soc.* **1967**, *89*, 6261.
- (5) *Intramolecular* hydroalkoxylation of allenes, however, has been realized using a variety of different metals, including Au(I) and Au(III). For representative examples, see: (a) Winter, C.; Krause, N. *Green Chem.* **2009**, *11*, 1309. (b) Deutsch, C.; Gockel, B.; Hoffmann-Röder, A.; Krause, N. *Synlett* **2007**, 1790. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (d) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519. (e) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. (f) Erdsak, J.; Krause, N. *Synthesis* **2007**, 3741. (g) Alcaide, B.; Almendros, P.; Martinez del Compo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6684. (h) Zhang, A.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (i) Zhang, Z.; Widenhofer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283. (j) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485.
- (6) For selected reviews on gold catalysis, see: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.
- (7) (a) Zhang, Z.; Widenhofer, R. *Org. Lett.* **2008**, *10*, 2079. (b) Nishina, N.; Yamamoto, Y. *Tetrahedron* **2009**, *65*, 1799. (c) Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 4908. (d) Cui, D.-M.; Yu, K. R.; Zhang, C. *Synlett* **2009**, 1103. (e) Cui, D.-M.; Zheng, Z.-L.; Zhang, C. *J. Org. Chem.* **2009**, *74*, 1426.
- (8) The first report on Au(I)-catalyzed reaction of alcohols and allenes involves the sequential addition of two molecules of methanol to the central carbon of the allene: Schulz, M.; Teles, J. H. (BASF AG), WO-A1 9721648, 1997. *Chem. Abstr.* **1997**, *127*, 121499.
- (9) For a review on gold-catalyzed reaction of alcohols, see: Muzart, J. *Tetrahedron* **2008**, *64*, 5815.
- (10) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405.
- (11) For development of PPh₃AuNTf₂, see: Mézailles, N.; Richard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.
- (12) Paton, R. S.; Maseras, F. *Org. Lett.* **2009**, *11*, 2237.
- (13) For a review on applications of NHC–Au complexes, see: Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776.

DFT calculations, however, suggest that the tertiary allyl ether **9** should be the kinetic product, and subsequent gold-catalyzed isomerization possibly occurs to produce the observed (and more stable) primary allylic ether **10**.

Bearing in mind our discovery in Scheme 3, we became excited at the possibility of switching the regioselectivity of the gold-catalyzed hydroalkoxylation of allenes by simply *retarding the subsequent isomerization process*, presumably with excess alcohol. Such a switch in regioselectivity will produce the much harder-to-access *tert*-allyl ethers **3** over the primary allyl ethers **2**. Our proof-of-concept study clearly shows that an excess of alcohol changes the **2:3** selectivity of the reaction (Scheme 5). Although a **3:1** ratio of **12:13** is far from selective, the change in ratio nevertheless gave us

Scheme 5. Initial Studies: Effect of Excess Alcohol on the Gold(I)-Catalyzed Hydroalkoxylation of Allenes

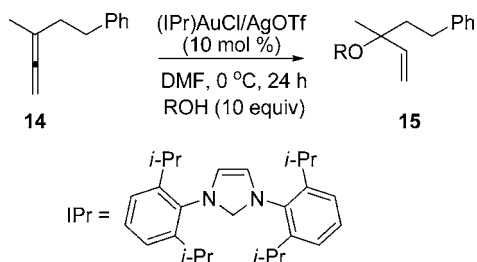


confidence that following optimization studies, a complete switch of regioselectivity could be achieved.

Following ligand, counterion, solvent, concentration, equivalents of alcohol, and temperature screening (see Supporting Information), we successfully developed conditions to produce alkyl *tert*-allylic ethers **3** through hydroalkoxylation of allenes in excellent regioselectivity and good yields (Table 1). It is necessary to switch to the NHC gold catalyst [(IPr)AuCl/AgOTf]^{13,14} in DMF and excess alcohol at 0 °C to produce the desired regioselectivity.¹⁵ It is of interest to note that of all the solvents screened only DMF produced the desired regioselectivity and conversion (see Supporting Information).¹⁶ Even running the reaction in neat alcohol produced only a ~1:1 ratio of **2**:**3**.

The intermolecular hydroalkoxylation of allene **14** with a range of alcohols is presented in Table 1. A wide range of

Table 1. Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of **14** with a Range of Alcohols



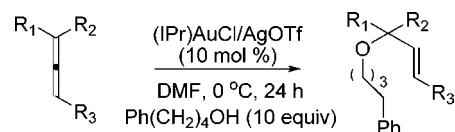
entry	R	product	3 : 2 ^a	yield (%) ^b
1	Et	15a	99:1	83
2	-(CH ₂) ₄ Ph	15b	99:1	86
3	-(CH ₂) ₂ CH=CH ₂	15c	99:1	74
4	-(CH ₂) ₂ Ph	15d	99:1	85
5	-CH ₂ CH(Ph)(Me)	15e	99:1	85
6	-CH ₂ C(CH ₃) ₃	15f	99:1	81
7	-CH ₂ CH=CHPh	15g	99:1	82
8	<i>i</i> Pr	15h	3:1	20
9	<i>t</i> Bu	15i	N/A	0

^a Determined by ¹H NMR analysis of the crude mixture. ^b Isolated yield of product **15**.

primary alcohols add to allenes to produce the *tert*-allylic ethers **15** in good to excellent selectivities and good isolated yields (entries 1–7). In particular, even more sterically encumbered primary alcohols such as 2-phenylpropan-1-ol (entry 5) and neopentyl alcohol (entry 6) add with excellent regioselectivities. Secondary and tertiary alcohols, however, are not efficient nucleophiles under these conditions (entries 8 and 9). Isopropanol reacts rather sluggishly to produce only 20% of **15h** after 24 h, with a 3:1 regioselectivity of the tertiary and primary allylic ethers (entry 8). Unsurprisingly, *tert*-butanol does not react at all even under prolonged reaction times (entry 9).

Next, we carried out scope and generality studies with a range of allenes (Table 2). Allenes **16** and **11** undergo

Table 2. Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of a Range of Allenes



entry	allene	product	3 : 2 ^a	yield (%) ^b
1	16	17	99:1	82
2	11	18	99:1	70
3	19 OTBDPS	20 OTBDPS	99:1	82
4	14	15b	99:1	86
5	21	22	90:10	66
6 ^c	23	24	85:15	45
7	25	26	99:1	55

^a Determined by ¹H NMR analysis of the crude mixture. ^b Isolated yield. ^c This reaction was carried out with 15 mol % catalyst for 48 h.

hydroalkoxylation smoothly to provide the corresponding *tert*-allylic ethers **17** and **18** regioselectively (99:1, entries 1

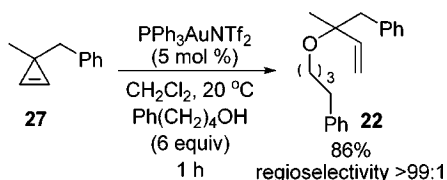
(14) A control with AgOTf as the catalyst resulted in no reaction.

(15) Under these optimized conditions, no isomerization of tertiary ethers **3** to primary ethers **2** is observed, regardless of the presence of excess alcohol. The excess alcohol, however, is still necessary to suppress the formation of other byproducts. See Supporting Information for more details.

and 2). Gratifyingly, even trisubstituted allene **19** produces *tert*-allylic ether **20** regioselectively and stereoselectively (99:1, *E*-selectivity, entry 3). Entries 4–6 investigate the effect of bringing the Ph ring progressively closer to the reactive center. While reaction with allene **14** proceeds smoothly (entry 4), allene **21** with a benzyl substituent produces slightly lower regioselectivity (90:10, entry 5). The regioselectivity drops again with bulkier allene **23** (85:15, entry 6). Nevertheless, the *tert*-allylic ether product is still favored over the primary in all of the cases studied. Finally, reaction with exocyclic allene **25** produces **26** regioselectively, and the acetal moiety is tolerated under these conditions (entry 7).

Since the hydroalkoxylation of allene **21** produced only a 9:1 ratio of **3**:**2**, we were intrigued to compare this reaction with the gold(I)-catalyzed addition of alcohol to the corresponding cyclopropene **27** (Scheme 6). To our delight, *tert*-

Scheme 6. Preparation of *tert*-Allylic Ether **22** through Gold(I)-Catalyzed Alcohol Addition to Cyclopropene **27**



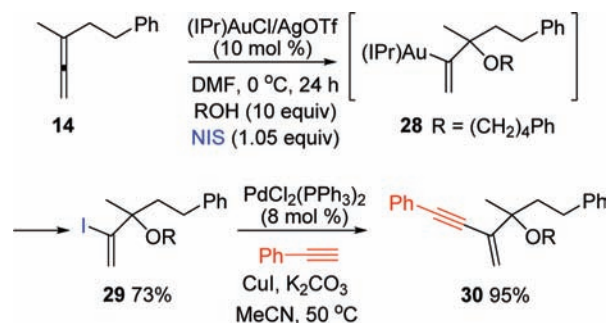
allylic ether **22** is formed regioselectively (>99:1) and in good yield (86%) from cyclopropene **27**. We believe that this example exemplifies the complementarity of the two approaches toward *tert*-allylic ethers.

Finally, it is possible to trap the putative vinylgold intermediate (e.g., **28**) with NIS to produce iodoalkene **29**

(16) For a review on DMF: much more than a solvent, see: Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

(17) For examples of capture of vinylgold intermediates with iodine, see: (a) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7927. (b) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310. (c) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727. (d) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (e) Yu, M.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147. (f) Alcaide, B.; Almendros, P.; del Campo, T. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 6684. (g) Liu, L.-P.; Hammond, J. B. *Chem. Asian J.* **2009**, *4*, 1230.

Scheme 7. Further Functionalizations



(Scheme 7).^{17,18} The iodoalkene is a good handle for further functionalization at the alkene. For example, Sonogashira coupling with phenylacetylene successfully produces **30** in 95% yield (Scheme 7).

In summary, we present a method for regioselective formation of alkyl *tert*-allylic ethers via gold-catalyzed hydroalkoxylation of allenes. It is thus now possible to achieve either regioselective formation of primary allylic ethers **2**⁷ or tertiary allylic ethers **3** via gold-catalyzed hydroalkoxylation of allenes simply by switching the reaction conditions. The method presented in this communication is complementary to our previous approach involving gold-catalyzed additions of alcohols to cyclopropenes.¹⁰ Future work will focus on the extension of these reactions to enantioselective methods.

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

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(18) A control reaction with NIS as the reagent (without any gold catalyst) results in <5% of **29** being formed.