Organic LETTERS

Letter

pubs.acs.org/OrgLett

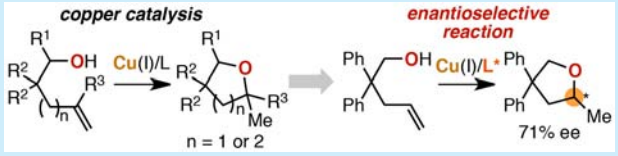
Copper(I)-Catalyzed Intramolecular Hydroalkoxylation of Unactivated Alkenes

Hiroaki Murayama, Kazunori Nagao, Hirohisa Ohmiya,* and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

Supporting Information

ABSTRACT: A Cu(I)−Xantphos system catalyzed the intramolecular hydroalkoxylation of unactivated terminal alkenes, giving five- and six-membered ring ethers. This system is applicable to both primary and secondary alcohols. A reaction pathway involving the addition of the Cu−O bond across the C−C double bond is proposed. A chiral Cu(I) catalyst system based on the (*R*)-DTBM-SEGPHOS ligand promoted enantioselective reaction with moderate enantioselectivity.

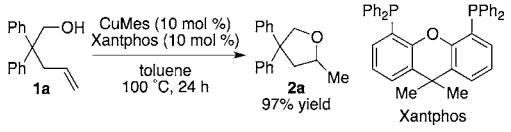


Oxygen-containing heterocyclic compounds are found in many biologically active natural products and pharmaceuticals.[1] Metal-catalyzed intramolecular hydroalkoxylation of unactivated alkenes is a straightforward method for the preparation of *O*-heterocycles.[2] To date, these types of reactions have been realized by using various catalysts with different metals such as Pt(II), Au(I), Ag(I), Al(III), Fe(III), Ru(II), and Cu(II).[3,4] Notably, all of these reactions were achieved through electrophilic activation of hydroxyalkenes at the C−C double bond by π Lewis acid metals that promote outer-sphere nucleophilic addition of the hydroxy group to the alkene.

Herein, we report that a Cu(I)−Xantphos catalyst system promotes the intramolecular hydroalkoxylation of unactivated terminal alkenes to give five- or six-membered ring ethers.[5,6] This new copper catalysis should be mechanistically different from the previously reported intramolecular hydroalkoxylations of unactivated alkenes. Instead, addition of the Cu−O bond of an alkoxocopper(I) intermediate across the C−C double bond followed by alcoholysis of the Cu−C bond is proposed. A chiral Cu(I) catalyst system based on the (*R*)-DTBM-SEGPHOS ligand promoted enantioselective reaction with moderate enantioselectivity.

Our ligand screening for the reaction of 2,2-diphenyl-4-penten-1-ol (**1a**) revealed that Xantphos, featuring an extraordinary large bite angle, was the most effective. The reaction of **1a** in the presence of mesitylcopper(I) (10 mol %) and Xantphos (10 mol %) in toluene at 100 °C over 24 h afforded five-membered ring ether **2a** in 97% yield (Scheme 1).[7] DPPF was also effective, but the product yield was slightly decreased (82%). DPPE was much less effective, giving only 18% yield. Monophosphines such as PPh_3 and PCy_3 gave low product yields (30% and 15%), while no reaction occurred in the absence of a ligand.

Scheme 1. Copper-Catalyzed Intramolecular Hydroalkoxylation



It is well-known that σ-bond metathesis between the Cu−C bond of mesitylcopper(I) and the O−H bond of alcohols produces the corresponding copper(I) alkoxides, which are generally poor Lewis acids.[8] Accordingly, a π Lewis acid mechanism involving outersphere nucleophilic addition of the hydroxy group to the alkene should be ruled out for the present Cu(I)-catalyzed intramolecular hydroalkoxylation. Instead, we propose a mechanism involving the insertion of the alkene into the Cu−O bond of the copper(I) alkoxide as illustrated in Figure 1. The catalytic cycle would be initiated by the reaction between the mesitylcopper−Xantphos complex and the H−O bond of the substrate (**1**) to form copper alkoxide **A**. Subsequently, the terminal alkene forms Cu−alkene π-complex **B**. Next, the intramolecular addition of the Cu−O bond across

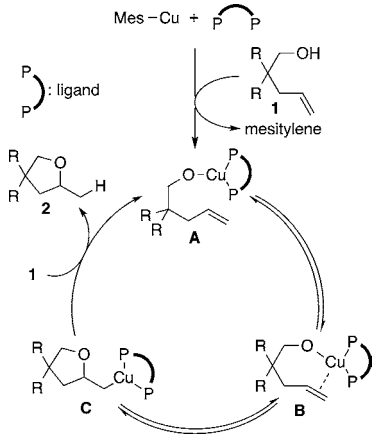


Figure 1. Possible catalytic cycle.

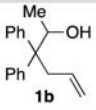
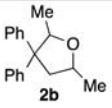
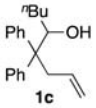
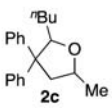
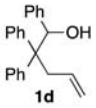
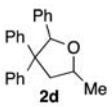
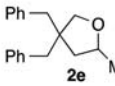
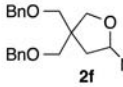
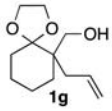
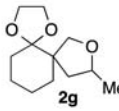
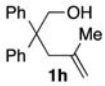
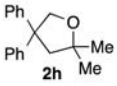
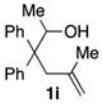
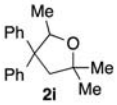
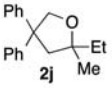
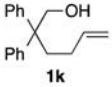
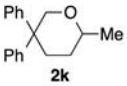
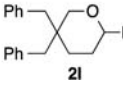
Received: March 16, 2015
Published: April 7, 2015

DOI: 10.1021/acs.orglett.5b00758
Org. Lett. 2015, 17, 2039−2041

the C−C double bond affords alkylcopper intermediate **C** with an oxygen heterocycle. Finally, protonolysis of the Cu−C bond of **C** with the H−O bond of **1** gives the product (**2**).

We examined various hydroxyalkenes as substrates for the Cu-catalyzed hydroalkoxylation for preparing tetrahydrofuran derivatives (Table 1). The Cu(I)−Xantphos catalyst system

Table 1. Substrate Scope[a]

entry	substrate	product	yield (%)[b]
1	 **1b**	 **2b**	77[c]
2	 **1c**	 **2c**	85[c]
3	 **1d**	 **2d**	81[c]
4	 **1e**	 **2e**	40
5	 **1f**	 **2f**	77
6	 **1g**	 **2g**	96[d]
7	 **1h**	 **2h**	82
8	 **1i**	 **2i**	62
9	 **1j**	 **2j**	58
10	 **1k**	 **2k**	68
11	 **1l**	 **2l**	91

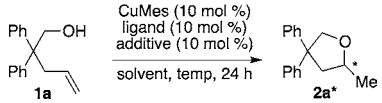
[a]Conditions: CuMes−Xantphos (10 mol %), **1** (0.15 mmol), toluene (0.3 mL), 100 °C, 24 h. [b]Yield of the isolated product. [c]Diastereomeric ratio (3:1). [d]Diastereomeric ratio (1:1).

was also effective for the reaction of secondary alcohols (**1b−d**) (entries 1−3), tolerating various substituents such as Me, *n*-Bu, and Ph groups at the position α to the hydroxy group. The hydroxyalkenes with a dibenzylmethylene (**1e**) or a di(benzyloxymethyl)methylene (**1f**) inserted in the linker chain underwent the reaction in moderate yields (entries 4 and 5). Spirocyclization of the cyclohexanone acetal derivative **1g** proceeded efficiently and cleanly with the acetal moiety untouched (entry 6). The geminally disubstituted alkenes **1h−j** also underwent the hydroalkoxylation to construct a quaternary carbon center (entries 7−9). The hydroalkoxylation of a 1,2-disubstituted alkene did not proceed at all (data not shown).

The extension of this methodology to six-membered ring formation was feasible (Table 1, entries 10 and 11). Thus, the reaction of 5-hexene-1-ol derivatives **1k** and **1l** occurred to give the corresponding tetrahydrofuran derivatives (**2k,l**) in good yields.

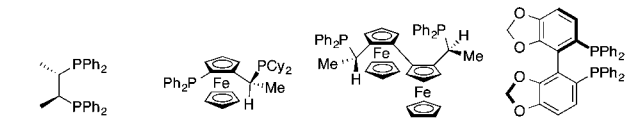
Next, we explored the catalytic enantioselective hydroalkoxylation. Copper complexes prepared from mesitylcopper (10 mol %) and various chiral bisphosphine ligands were examined in the reaction of **1a** in toluene at 60 °C for 24 h (Table 2). The catalyst prepared from (*S,S*)-Chiraphos (**L1**) or

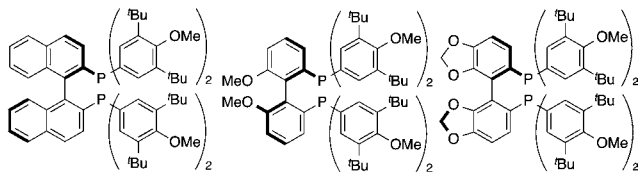
Table 2. Enantioselective Reaction[a]



entry	ligand	additive	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	**L1**	none	toluene	60	0	
2	**L2**	none	toluene	60	0	
3	**L3**	none	toluene	60	22	9
4	**L4**	none	toluene	60	23	4
5	**L5**	none	toluene	60	7	51
6	**L6**	none	toluene	60	60	51
7	**L7**	none	toluene	60	94	51
8	**L7**	none	toluene	30	46	62
9	**L7**	*t*-BuOH	toluene	30	30	67
10	**L7**	*t*-BuOH	hexane	30	39	71

[a]Conditions: CuMes (10 mol %), ligand (10 mol %), **1a** (0.15 mmol), solvent (0.3 mL), 24 h. [b]Yield of the isolated product. [c]The enantiomeric excess was determined by HPLC analysis.


(*S,S*)-Chiraphos (**L1**) (*R*)-(*S*)-Josiphos (**L2**) (*S,S*)-(*R,R*)-Ph-TRAP (**L3**) (*R*)-SEGPHOS (**L4**)


(*R*)-DTBM-BINAP (**L5**) (*R*)-DTBM-MeO-BIPHEP (**L6**) (*R*)-DTBM-SEGPHOS (**L7**)

(*R,S*)-Josiphos (**L2**) did not promote the reaction at all (entries 1 and 2). (*S,S*)-(*R,R*)-Ph-TRAP (**L3**)[9] and (*R*)-SEGPHOS (**L4**) induced only low catalytic activity and enantioselectivity (entries 3 and 4). Further screening of chiral ligands revealed that introducing 3,5-di-*tert*-butyl-4-methoxyphenyl (DTBM) substituents on the phosphorus atoms of chiral bisphosphines was important not only for enantiocontrol but also catalytic activity (entries 5−7).[10] Thus, (*R*)-DTBM-BINAP (**L5**) induced a moderate enantioselectivity, albeit with a poor product yield (entry 5). The use of DTBM-MeO-BIPHEP (**L6**) increased product yield, but this change did not improve the enantioselection (entry 6). The use of (*R*)-DTBM-SEGPHOS[11] (**L7**) led to a significant improvement in the product yield with the enantioselectivity unchanged (entry 7). To our knowledge, this is the first metal-catalyzed enantioselective intramolecular hydroalkoxylation of unactivated alkenes.

DOI: 10.1021/acs.orglett.5b00758
Org. Lett. 2015, 17, 2039−2041

The enantioselection could be improved to 62% ee by carrying out the reaction at 30 °C, but with a serious reduction of the yield (Table 2, entry 8). Interestingly, the enantioselectivity could be increased to 67% ee by adding a catalytic amount of *t*-BuOH (10 mol %), also with a reduction of the yield (30%) (entry 9). The enantioselectivity was further improved to 71% ee using hexane as a solvent with an increase in the product yield (39%) (entry 10).[12] This result suggested the reversibility of the Cu−alkene π-complex **B** and alkylcopper intermediate **C** (see Figure 1).

In summary, the Cu−Xantphos system catalyzed the intramolecular hydroalkoxylation of unactivated terminal alkenes, giving five- and six-membered ring ethers. This system is applicable to both primary and secondary alcohols. A reaction pathway involving the addition of the Cu−O bond across the C−C double bond is proposed. A chiral Cu(I) catalyst system based on the (*R*)-DTBM-SEGPHOS ligand promoted enantioselective reaction with moderate enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ohmiya@sci.hokudai.ac.jp.
*E-mail: sawamura@sci.hokudai.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Young Scientists (A) and Challenging Exploratory Research, JSPS to H.O., and CREST, JST, to M.S. K.N. thanks JSPS for scholarship support.

■ REFERENCES

(1) (a) Elliott, M. C. *J. Chem. Soc., Perkins Trans. 1* **2000**, 1291. (b) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkins. Trans. 1* **2001**, 2303. (c) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

(2) For a review, see: Patil, N. T.; Kavthe, R. D.; Shinde, V. S. *Tetrahedron* **2012**, *68*, 8079.

(3) (a) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (b) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553. (c) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (d) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553. (e) Coulombel, L.; Rajzmann, M.; Pons, J.-M.; Olivero, S.; Duñach, E. *Chem.—Eur. J.* **2006**, *12*, 6356. (f) Kamiya, I.; Tsunoyama, H.; Tsukuda, T.; Sakurai, H. *Chem. Lett.* **2007**, *36*, 646. (g) Komeyama, K.; Morimoto, T.; Nakayama, Y.; Takaki, K. *Tetrahedron Lett.* **2007**, *48*, 3259. (h) Ohta, T.; Kataoka, Y.; Miyoshi, A.; Oe, Y.; Furukawa, I.; Ito, Y. *J. Organomet. Chem.* **2007**, *692*, 671. (i) Ito, Y.; Kato, R.; Hamashima, K.; Kataoka, Y.; Oe, Y.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2007**, *692*, 691. (j) Adrio, L. A.; Quek, L. S.; Taylor, J. G.; Hii, K. K. *Tetrahedron* **2009**, *65*, 10334.

(4) For lanthanide-catalyzed intramolecular hydroalkoxylation of alkenes, see: Dzudza, A.; Marks, T. J. *Org. Lett.* **2009**, *11*, 1523.

(5) For a Cu-catalyzed intramolecular hydroamination of unactivated alkenes from our groups, see: (a) Ohmiya, H.; Moriya, T.; Sawamura, M. *Org. Lett.* **2009**, *11*, 2145. (b) Ohmiya, H.; Yoshida, M.; Sawamura, M. *Synlett* **2010**, 2136.

(6) For Cu(II)-catalyzed intramolecular carboalkoxylation of alkenes, see: (a) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149. (b) Bovino, M. T.; Liwosz, T. W.; Kendel, N. E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6383. For asymmetric Cu(I) catalysis involving intramolecular oxycupration of allenes, see: (c) Kawai, J.; Chikkade, P. K.; Shimizu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7177.

(7) All copper-catalyzed reactions were carried out under nitrogen atmosphere. See the Supporting Information.

(8) Stollenz, M.; Meyer, F. *Organometallics* **2012**, *31*, 7708.

(9) Sawamura, M.; Hamashima, H.; Sugawara, M.; Kuwano, R.; Ito, Y. *Organometallics* **1995**, *14*, 4549.

(10) For discussion on the effect of the DTBM groups in the enantioselective Cu-catalyzed hydrosilylation of aryl ketones, see: Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779.

(11) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(12) The absolute configuration of **2a*** was not determined.

DOI: 10.1021/acs.orglett.5b00758
Org. Lett. 2015, 17, 2039−2041