

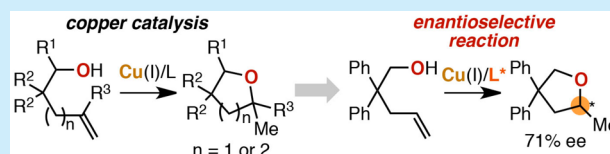
Copper(I)-Catalyzed Intramolecular Hydroalkoxylation of Unactivated Alkenes

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S 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 hydroalkoxylation 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 PPh₃ and PCy₃ gave low product yields (30% and 15%), while no reaction occurred in the absence of a ligand.

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

Scheme 1. Copper-Catalyzed Intramolecular Hydroalkoxylation

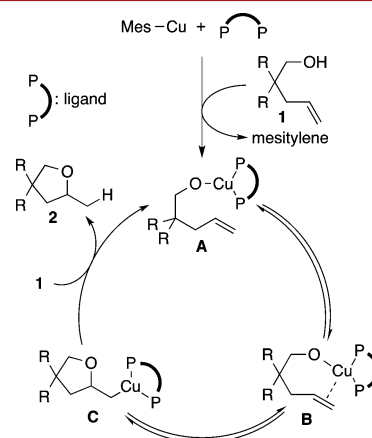
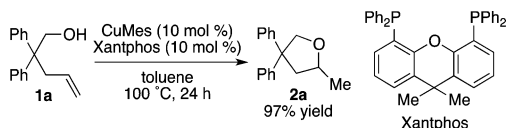


Figure 1. Possible catalytic cycle.

Received: March 16, 2015

Published: April 7, 2015

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			77 ^c
2			85 ^c
3			81 ^c
4			40
5			77
6			96 ^d
7			82
8			62
9			58
10			68
11			91

^aConditions: CuMes–Xantphos (10 mol %), **1** (0.15 mmol), toluene (0.3 mL), 100 °C, 24 h. ^bYield of the isolated product. ^cDiastereomeric ratio (3:1). ^dDiastereomeric 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).

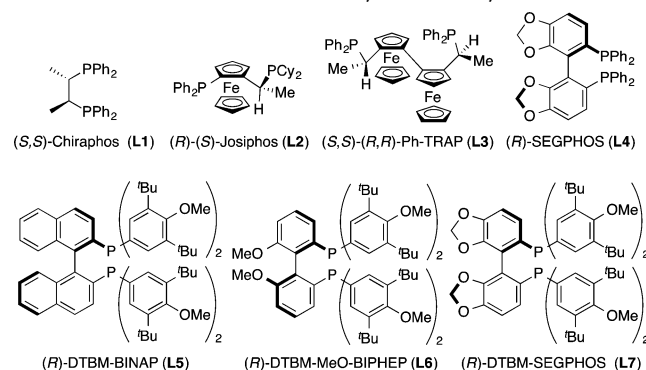
The extension of this methodology to six-membered ring formation was feasible (Table 1, entries 10 and 11). Thus, the reaction of 5-hexene-1-ol derivatives **1k** and **1l** occurred to give the corresponding tetrahydrofuran derivatives (**2k,l**) in good yields.

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	<i>t</i> -BuOH	toluene	30	30	67
10	L7	<i>t</i> -BuOH	hexane	30	39	71

^aConditions: CuMes (10 mol %), ligand (10 mol %), **1a** (0.15 mmol), solvent (0.3 mL), 24 h. ^bYield of the isolated product. ^cThe enantiomeric excess was determined by HPLC analysis.



(*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-SEGPHOS¹¹ (**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.

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>.

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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.