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Copper-Catalyzed Enantioselective Propargylic Etherification of Propargylic Esters with Alcohols

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Supporting Information

ABSTRACT: Enantioselective propargylic etherification of propargylic esters with not only aliphatic alcohols but also phenols in the presence of a catalytic amount of copper-Pybox complex gives the corresponding propargylic ethers in good to high yields with a high to excellent enantioselectivity (up to 99% ee). The result described here provides the first successful example of enantioselective propargylic etherification

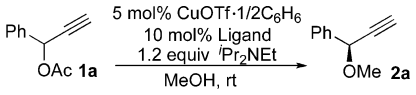
Propargylic skeleton bearing a terminal alkyne moiety is one of the most versatile intermediates for organic transformations because the terminal alkyne moiety can be readily converted into various functional groups in a single step. For example, Huisgen cycloaddition between azides and terminal alkynes to afford the corresponding 1,2,3-triazoles in high yields with an excellent selectivity is widely used as a synthetic tool for the construction of target molecules in many research areas including material science and medical science.[1]

Since the first report of ruthenium-catalyzed enantioselective propargylic alkylation of propargylic alcohols with acetone as a carbon-centered nucleophile,[2] our research group and many others have found the ruthenium- and copper-catalyzed enantioselective propargylic substitution reactions of propargylic alcohols and their derivatives with various carbon- and nitrogen-centered nucleophiles to give the corresponding propargylic alkylated products, propargylated aromatic compounds, and propargylic amines with a high enantioselectivity.[3−9] Unfortunately, the transition-metal-catalyzed enantioselective propargylic etherification of propargylic alcohol derivatives with alcohols has not yet been reported until now, although propargylic etherification with alcohols as oxygen-centered nucleophiles in the presence of various transition-metal complexes as catalysts has already been reported to afford the corresponding propargylic ethers in high yields.[3]

As an extension of our study, we have now found the copper-catalyzed enantioselective propargylic etherification of propargylic esters with not only alcohols but also phenols as oxygen-centered nucleophiles to give the corresponding propargylic ethers in good to high yields with a high to excellent enantioselectivity (up to 99% ee). In this reaction system, Me-Pybox (**L1**) has been found to work as the best optically active ligand. This is the first successful example of transition-metal-catalyzed enantioselective propargylic substitution reactions with oxygen-centered nucleophiles. Herein, we describe preliminary results.

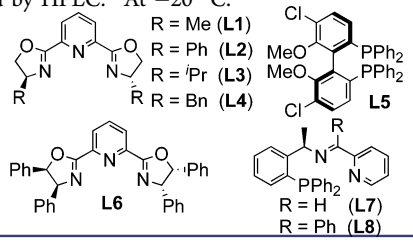
Treatment of 1-phenylprop-2-ynyl acetate (**1a**) with 1.2 equiv of *N*,*N*-diisopropylethylamine in the presence of 5 mol % of CuOTf·1/2C_6H_6 and 10 mol % of (*S*)-Me-Pybox **L1** in methanol at room temperature for 4 h gave methyl 1-phenylprop-2-ynyl ether (**2a**) in 77% yield with 43% ee (*R*) (Table 1, run 1). The use

Table 1. Copper-Catalyzed Enantioseletive Propargylic Etherification of 1-Phenylprop-2-ynyl acetate (1a) with Methanol[a]



run	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	**LI**	4	77	43 (*R*)
2	**L2**	4	92	38 (*R*)
3	**L3**	4	54	29 (*R*)
4	**L4**	4	61	2 (*R*)
5	**L5**	4	0	-
6	**L6**	4	89	1 (*R*)
7	**L7**	8	25	26 (*S*)
8	**L8**	6	19	72 (*S*)
9[d]	**L1**	72	72	71 (*R*)

[a]Reactions of **1a** (0.20 mmol) with ^{i}Pr$_2$NEt (0.24 mmol; 1.2 equiv) in the presence of CuOTf·1/2C_6H_6 (0.010 mmol) and ligand (0.020 mmol) in methanol (2 mL) at room temperature. [b]Isolated yield. [c]Determined by HPLC. [d]At −20 °C.



of other Pybox ligands such as (*S*)-Ph-Pybox (**L2**), (*S*)-^{i}Pr-Pybox (**L3**), and (*S*)-Bn-Pybox (**L4**) as optically active ligands gave **2a** with a lower enantioselectivity (Table 1, runs 2−4). (*R*)-Cl-MeO-BIPHEP (**L5**) and diPh-Pybox (**L6**), which were reported to work as effective optically active ligands toward the copper-catalyzed enantioselective propargylic amination,[5,6] did not give satisfactory results (Table 1, runs 5 and 6). Recently, Hu et al. have reported the copper-catalyzed enantioselective propargylic alkylation by using optically active tridentate PNN-ligands (**L7**

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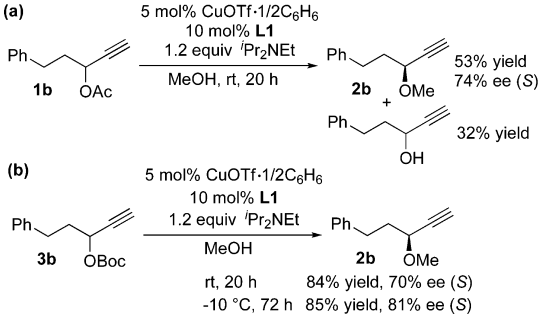
and **L8**).[7] However, the propargylic etherification by using these tridentate PNN-ligands did not proceed smoothly under the same reaction conditions, and **2a** (*S*) was obtained in only low yields (Table 1, runs 7 and 8). When the reaction by using **L1** was carried out at −20 °C for 72 h, **2a** was obtained in 72% yield with 71% ee (Table 1, run 9).

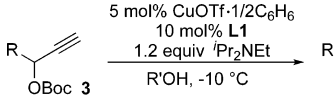
Next, we investigated a similar reaction of 5-phenylpent-1-yn-3-yl acetate (**1b**) in methanol at room temperature for 20 h in the presence of 5 mol % of CuOTf·1/2C_6H_6 and 10 mol % of **L1**. The products were methyl 5-phenylpent-1-yn-3-yl ether (**2b**) (53% yield, 74% ee (*S*)) and 5-phenylpent-1-yn-3-ol (32% yield) (Scheme 1a). On the other hand, the use of *tert*-butyl 5-phenylpent-1-yn-3-yl carbonate (**3b**) in place of **1b** as a substrate under the same reaction conditions resulted in the formation of only **2b** in 84% yield in 70% ee without any formation of the propargylic alcohol (Scheme 1b). A higher enantioselectivity (81% ee) was achieved when the reaction of **3b** was carried out at −10 °C for 72 h (Scheme 1b).

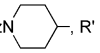
Scheme 1. Copper-Catalyzed Propargylic Etherification of Propargylic Esters with Methanol



Based on the result of Scheme 1, reactions of other propargylic carbonates were carried out by using **L1** as an optically active ligand at −10 °C in methanol or ethanol. Typical results are shown in Table 2. Reactions of *tert*-butyl 6-phenylhex-1-yn-3-yl carbonate (**3c**) and *tert*-butyl 7-phenylhept-1-yn-3-yl carbonate (**3d**) in methanol at −10 °C for 72 h in the presence of 5 mol % of CuOTf·1/2C_6H_6 and 10 mol % of **L1** gave methyl 6-phenylhex-1-yn-3-yl ether (**2c**) and methyl 7-phenylhept-1-yn-3-yl (**2d**) in 89% (78% ee) and 88% (79% ee) yields, respectively (Table 2, runs 2 and 3). The reaction of propargylic carbonate lacking a phenyl group (**3e**) similarly proceeded under the same reaction conditions (Table 2, run 4).

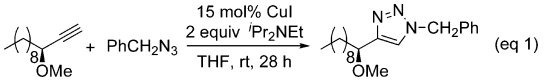
Table 2. Copper-Catalyzed Enantioseletive Propargylic Etherification of *tert*-Butyl Propargylic Carbonates with Alcohols.[a]



run	2 or 4	time (h)	yield (%)[b]	ee (%)[c]
1	R = $PhCH_2CH_2$, R' = Me (**2b**)	72	85	81
2	R = $PhCH_2CH_2CH_2$, R' = Me (**2c**)	72	89	78
3	R = $PhCH_2CH_2CH_2CH_2$, R' = Me (**2d**)	72	88	79
4	R = $CH_3(CH_2)_8$, R' = Me (**2e**)	96	91	80[d]
5	R = $PhCH_2$, R' = Me (**2f**)	72	65	94
6	R = 4-$MeOC_6H_4CH_2$, R' = Me (**2g**)	72	73	95
7	R = 4-$BrC_6H_4CH_2$, R' = Me (**2h**)	72	72	95
8	R = 2-$MeC_6H_4CH_2$, R' = Me (**2i**)	72	89	99
9	R =  , R' = Me(**2j**)	72	83	90
10	R = $PhCH_2CH_2$, R' = Et (**4b**)	120	63	80
11	R = $PhCH_2$, R' = Et (**4f**)	168	57	93

[a]Reactions of **3** (0.20 mmol) with ^{i}Pr$_2$NEt (0.24 mmol; 1.2 equiv) in the presence of CuOTf·1/2C_6H_6 (0.010 mmol) and **L1** (0.020 mmol) in alcohols (2 mL) at −10 °C. [b]Isolated yield. [c]Determined by HPLC. [d]Determined by HPLC after the conversion into the corresponding 1,2,3-triazole (eq 1).

A higher enantioselectivity (94% ee) was achieved in the reaction of propargylic carbonate bearing a benzylic moiety at the propargylic position (**3f**) under the same reaction conditions (Table 2, run 5). Introduction of a substituent such as a methoxy or bromo group at the *para*-position of the benzene ring of the propargylic carbonates (**3g** and **3h**) gave a similar high enantioselectivity (95% ee) (Table 2, runs 6 and 7). The presence of a methyl group at the *ortho*-position of the benzene ring of the propargylic carbonate (**3i**) gave the highest enantioselectivity (99% ee) (Table 2, run 8). The reaction of propargylic carbonate bearing a cyclic ring at the propargylic position (**3j**) in methanol proceeded smoothly to afford the corresponding propargylic ether (**2j**) in 83% yield with 90% ee (Table 2, run 9). The produced propargylic ethers can be readily converted into the corresponding 1,2,3-triazoles by Huisgen cycloaddition. In fact, the reaction of propargylic ether bearing only an alkyl moiety **2e** with benzyl azide and *N,N*-diisopropylethylamine in the presence of 15 mol % of CuI in THF at room temperature for 28 h gave the corresponding 1,2,3-triazole in 93% isolated yield (eq 1).



The propargylic etherification of propargylic carbonates (**3b** and **3f**) with ethanol also proceeded smoothly to afford the corresponding ethyl propargylic ethers (**4b** and **4f**) in 63% (80% ee) and 57% (93% ee) yields, respectively (Table 2, runs 10 and 11), although a longer reaction time (120 and 168 h) was necessary to complete the reaction. These results indicate that other oxygen-centered nucleophiles are available under the same reaction conditions.

To obtain more information on the reactive species of copper catalyst in the catalytic reaction, we prepared a new dinuclear copper-pybox complex $[Cu_2(\mathbf{L2})_2][OTf]_2$[10] (**5**) from the reaction of CuOTf·1/2C_6H_6 with 1 equiv of **L2** in CH_2Cl_2 at room temperature for 1 h (Scheme 2a). The molecular structure of **5** is unambiguously characterized by X-ray crystallography, and an ORTEP drawing of cationic part of **5** is shown in Scheme 2a.[11] Then, we carried out the catalytic reaction by using **5** as a catalyst as shown in Scheme 2b. The catalytic activity is almost the same as that of the copper complex formed in situ from CuOTf·1/2C_6H_6 and **L2** under the present catalytic reaction conditions. This result indicates that the dinuclear copper complex bearing 2 equiv of Pyboxs such as **5** may work as a reactive species.

A proposal of dicopper complex **5** as a reactive species in the present propargylic etherification is also supported by a nonlinear relationship[12] between the ee value of optically active ligand **L1** and the ee value of propargylic ether (**2b**), which is produced by treatment of **3b** with methanol at −10 °C for 72 h in the presence of 5 mol % of CuOTf·1/2C_6H_6 and 10 mol % of **L1** as shown in Scheme 2c. This result provides direct evidence that

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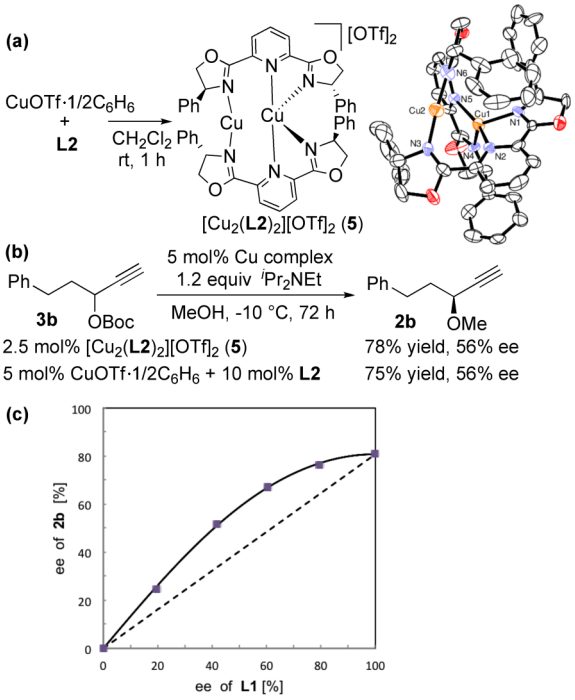
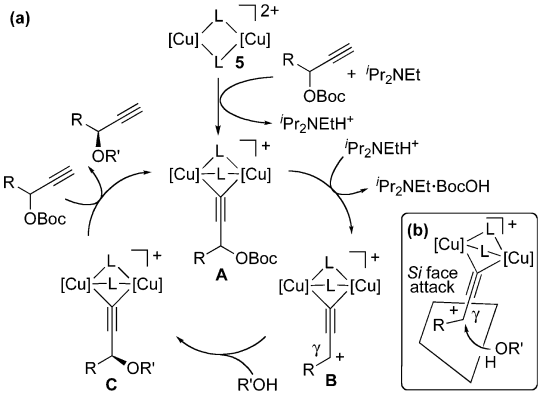
Scheme 2. Preparation of Dinuclear Copper Complex Bearing Pybox Ligands and Its Catalytic Activity



a dinuclear copper complex works as key reactive species in the propargylic etherification.

In addition to the experimental results shown above, we separately confirmed that no reaction took place at all in the reaction of propargylic carbonate bearing an internal alkyne moiety with methanol under the same reaction conditions. Based on all experimental results, a proposed reaction pathway for the present catalytic etherification is shown in Scheme 3a. First,

Scheme 3. Proposed Reaction Pathway and Transition State of Copper-Allenylidene Complex

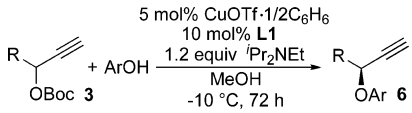


dicopper-acetylide complex[10c] (**A**) is formed from the dicopper complex **5** and propargylic carbonate.[13−15] Then, dicopper-allenylidene complex (**B**) may be formed by the elimination of a carbonate moiety from **A**. Alcohol attacks the complex **B** to afford the corresponding dicopper-acetylide complex (**C**). Finally, the complex **C** is converted into the starting complex **A** by liberating product propargylic ether by the ligand exchange with another propargylic carbonate.

To account for the enantioselective formation of propargylic ethers, we propose a transition state involving the dicopper-allenylidene complex as shown in Scheme 3b. The absolute configuration at the propargylic position in **2** indicates that the attack of alcohol on the cationic γ-carbon in the dicopper-allenylidene complex occurs from the *Si* face to the allenylidene ligand.

The successful results of the propargylic etherification with simple alcohols such as methanol and ethanol prompted us to investigate the propargylic etherification with various phenols as oxygen-centered nucleophiles by using **L1** as an optically active ligand. Typical results are shown in Table 3. The reaction of

Table 3. Copper-Catalyzed Enantioseletive Propargylic Etherification of *tert*-Butyl Propargylic Carbonates with Phenols[a]



run	6	yield of 6 (%)[b]	ee of 6 (%)[c]
1	R = $PhCH_2$, Ar = 4-$MeOC_6H_4$ (**6a**)	76	97
2	R = 2-$MeC_6H_4CH_2$, Ar = 4-$MeOC_6H_4$ (**6b**)	69	98
3	R = 2-$MeC_6H_4CH_2$, Ar = Ph (**6c**)	66	99
4	R = $PhCH_2CH_2$, Ar = 4-$MeOC_6H_4$ (**6d**)	88	91
5	R = $CH_3(CH_2)_8$, Ar = 4-$MeOC_6H_4$ (**6e**)	69	93
6	R = $PhCH_2$, Ar = Ph (**6f**)	82	97
7	R = $PhCH_2$, Ar = 2-$MeOC_6H_4$ (**6g**)	71	97
8	R = $PhCH_2$, Ar = 3-$MeOC_6H_4$ (**6h**)	66	96
9	R = $PhCH_2$, Ar = 4-^{t}BuC_6H_4 (**6i**)	50	94
10	R = $PhCH_2$, Ar = 4-PhC_6H_4 (**6j**)	88	96
11	R = $PhCH_2$, Ar = 4-BrC_6H_4 (**6k**)	57	98

[a]Reactions of **3** (0.20 mmol) with phenols (0.40 mmol; 2.0 equiv) and ^{i}Pr$_2$NEt (0.24 mmol; 1.2 equiv) in the presence of CuOTf·1/2C_6H_6 (0.010 mmol) and **L1** (0.020 mmol) in methanol (2 mL) at −10 °C for 72 h. [b]Isolated yield. [c]Determined by HPLC.

propargylic carbonate bearing a benzylic moiety at the propargylic position (**3f**) with 2 equiv of *p*-methoxyphenol and 1.2 equiv of *N*,*N*-diisopropylethylamine in methanol at −10 °C for 72 h in the presence of 5 mol % of CuOTf·1/2C_6H_6 and 10 mol % of **L1** gave 4-methoxyphenyl 1-phenylbut-3-yn-2-yl ether (**6a**) in 76% yield with 97% ee (Table 3, run 1). Here, various propargylic carbonates are available as substrates as shown in Table 3, runs 2−4. It is noteworthy that the propargylic etherification of propargylic carbonate lacking a phenyl group with 4-methoxyphenol proceeded smoothly with a high enantioselectivity (93% ee) (Table 3, run 5).

Further, a variety of phenols can be applicable as oxygen-centered nucleophiles. The propargylic etherification with phenol, 2-methxoyphenol, 3-methxoyphenol, 4-*tert*-butylphenol, 4-phenylphenol, and 4-bromophenol proceeded smoothly to give the corresponding propargylic ethers in good to high yields with a high enantioselectivity (Table 3, runs 6−11). After one recrystallization of the crude propargylic ether, the enantiomerically pure **6k** was isolated, and its absolute configuration was determined by X-ray crystallography.[11] This result supports the proposed reaction pathway shown in Scheme 3b, where the attack of oxygen-centered nucleophiles favors *Si* face of the allenylidene ligand in the dicopper complex.

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In summary, we have found that the copper-catalyzed enantioselective propargylic etherification of propargylic carbonates with not only simple alcohols such as methanol and ethanol but also phenols as oxygen-centered nucleophiles to give the corresponding propargylic ethers in good to high yields with a high to excellent enantioselectivity (up to 99% ee). This is the first successful example of the transition-metal-catalyzed enantioselective propargylic etherification. Propargylic carbonate was revealed to be a substrate of choice. It is noteworthy that a variety of propargylic carbonates bearing an alkyl substituent at the propargylic position are applicable as substrates in the present reaction system. Further studies on the transition-metal-catalyzed enantioselective propargylic substitution reactions with other nucleophiles are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and X-ray data (CIF). 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.

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(11) See SI for details.

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