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Chiral Ligand Controlled Enantioselective Opening of Oxirane and Oxetane

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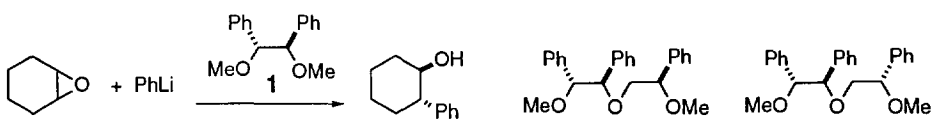
Abstract: Enantioselective opening of oxide ring was achieved by the combination of a chiral ether and phenyllithium in the presence of boron trifluoride to give the corresponding alcohol in 47% ee. Copyright © 1996 Published by Elsevier Science Ltd

We have been involved in the development of asymmetric reactions using a combination of external chiral ligands and highly reactive organometallics such as organolithiums and Grignard reagents.[1] As has been previously reported, highly efficient enantiofacial selection in a carbon-carbon bond formation was achieved through addition of organolithiums to α,β-unsaturated imines and esters with an aid of **1**.[2] The high enantioselectivity exhibited by **1** allowed us to choose **2** as a substrate, in which selection of enantiotopic reaction site, instead of enantioface, is realized by an organolithium-**1** combination. It is noteworthy that, although use of some chiral Lewis acids has been reported in asymmetric opening of epoxides,[3] no efficient combination of organometallics and external chiral ligand has been developed.[4] We describe here the approach toward a ligand-controlled enantioselective opening of the prochiral oxide-ring with phenyllithium.



2 **1*R*,2*S*-3** **4** **5**

Although no opening of **2** with phenyllithium in toluene took place even by the aid of **1**, upon an addition of boron trifluoride etherate[5] the reaction proceeded smoothly at -78 °C to give the corresponding (-)-(1*R*,2*S*)-**3**[6] in 32% ee and 99% yield. Enantioselectivity and absolute configuration were determined by chiral HPLC (DAICEL CHIRALCEL OD) and specific rotation.[6] The enantioselectivity was dependent on solvent (Table 1, entries 1-3). In toluene, **3** was obtained in 32% ee, whereas the selectivity was completely lost in THF, suggesting that its strong coordination to lithium impedes the formation of PhLi-**1** complex. The enantioselectivity was improved up to 43% in Et_2O.

Since the presence of Lewis acid such as BF_3OEt_2 is essential in opening of oxide ring of **2**, the effects of some Lewis acids on the enantioselectivity were examined (entries 4-6). Both BF_3OMe_2 and BF_3OBu_2 showed slightly higher enantioselectivity compared with that induced by BF_3OEt_2.[7] On the other hand, the selectivity assisted by more bulky BBu_2OTf was almost marginal. It is quite interesting in that these Lewis acids exert definite effects on enantioselectivity, in spite of their coordination to the oxygen of **2** on the back face to the attacking PhLi.[8]

We have also examined tridentate ligands, **4** and **5**, which have an additional coordinating oxygen to form a more rigid bicyclic [3.3.0] structure. It is reasonable to expect that **4** forms the bicyclic chelation more stable than **5**, due to a bulky phenyl group on the additional chiral center. Expectedly the reaction with **4** gave **3** in 47% ee, higher selectivity compared with 26% ee by **5** (entries 7-9).

The present enantioselective opening reaction is applicable to the other oxide rings, oxetane **6** giving **7**

(entries 10-12). The ligand **1** afforded *S*-**7** in 16% ee.[9] Although the ligand **5** exhibited rather poor enantioselectivity to give nearly racemic **7**, fortunately **4** afforded **7** in 47% ee.

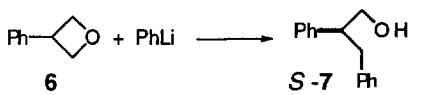


Table 1. Enantioselective Opening of **2** and **6** with PhLi-Chiral Ligand Combination

entry	2 / 6	1 / 4 / 5	solvent	Lewis acid	yield (%)	ee (%)
1	**2**	**1**	toluene	BF_3OEt_2	99	32
2	**2**	**1**	Et_2O	BF_3OEt_2	99	43
3	**2**	**1**	THF	BF_3OEt_2	90	0
4	**2**	**1**	Et_2O	BF_3OMe_2	99	45
5	**2**	**1**	Et_2O	BF_3OBu_2	99	47
6	**2**	**1**	Et_2O	BBu_2OTf	99	6
7	**2**	**4**	toluene	BF_3OBu_2	90	47
8	**2**	**4**	Et_2O	BF_3OBu_2	93	38
9	**2**	**5**	Et_2O	BF_3OBu_2	99	26
10	**6**	**1**	Et_2O	BF_3OBu_2	98	16
11	**6**	**4**	Et_2O	BF_3OBu_2	98	47
12	**6**	**5**	toluene	BF_3OBu_2	92	1

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7. Repeated reactions showed the dependency of enantioselectivity on BF_3 used.
8. Table 1, entry 5: To a stirred solution of **1** (510 mg, 2.1 eq) in ether (17 mL) at -78 °C was added of PhLi (2.0 eq). After 20 min, **2** (0.1 mL, 1 mmol) was added to the solution, followed by addition of BF_3OBu_2 (0.31 mL, 1.5 eq) for 5 min. After stirring at -78 °C for 30 min, sat. $NaHCO_3$ was added and the reaction mixture was extracted with benzene. Concentration and column chromatography on silica gel (hexane/EtOAc=9/1) gave **3** (170 mg, 99%). $[\alpha]_D^{31}$ -22.3 (c 1.56, benzene).[6]
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