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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.



Although no opening of 2 with phenyllithium in toluene took place even by the aid of 1, upon an addition of boron trifluoride etherate⁵ the reaction proceeded smoothly at -78 °C to give the corresponding (-)-(1R,2S)-3⁶ 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 Et₂O.

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.

$$Ph \rightarrow O + PhLi \rightarrow Ph \rightarrow OH$$

6 S-7 Ph

entry	2/6	1/4/5	solvent	Lewis acid	yield (%)	ee (%)
1	2	1	toluene	BF ₃ OEt ₂	99	32
2	2	1	Et ₂ O	BF ₃ OEt ₂	99	43
3	2	1	THF	BF ₃ OEt ₂	90	0
4	2	1	Et ₂ O	BF ₃ OMe ₂	99	45
5	2	1	Et ₂ O	BF ₃ OBu ₂	99	47
6	2	1	Et ₂ O	BBu ₂ OTf	99	6
7	2	4	toluene	BF ₃ OBu ₂	90	47
8	2	4	Et ₂ O	BF ₃ OBu ₂	93	38
9	2	5	Et ₂ O	BF ₃ OBu ₂	99	26
10	6	1	Et ₂ O	BF ₃ OBu ₂	98	16
11	6	4	Et ₂ O	BF ₃ OBu ₂	98	47
12	6	5	toluene	BF ₃ OBu ₂	92	1

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

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- 7. Repeated reactions showed the dependency of enantioselectivity on BF3 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 BF₃OBu₂ (0.31 mL, 1.5 eq) for 5 min. After stirring at -78 °C for 30 min, sat. NaHCO₃ 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%). [α]_D³¹ -22.3 (c 1.56, benzene).6
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