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# An External Chiral Ligand Controlled Enantioselective Opening of Oxirane and Oxetane by Organolithiums

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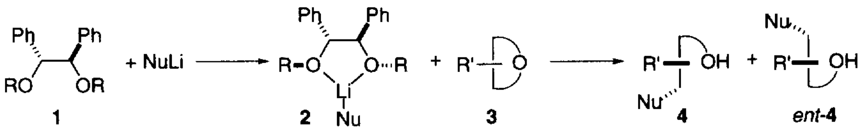
***Abstract:*** Enantioselective nucleophilic opening reactions of cyclohexene oxide and 3-phenyloxetane were achieved by the combination of an external chiral ligand and organolithiums in the presence of boron trifluoride to give the corresponding alcohols in up to 47% ee. © 1997 Elsevier Science Ltd.

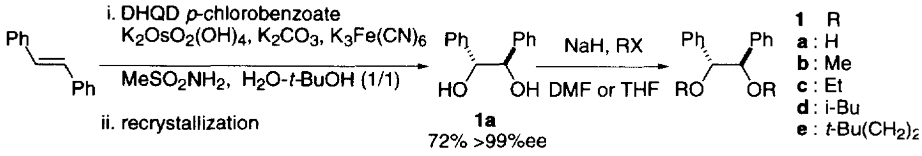
The development of asymmetric reactions of highly reactive organometallics such as organolithiums and Grignard reagents is of importance in preparation of a wide range of chiral organic compounds. The key to the success is a design of external chiral ligands that form a reactive and stereochemically ordered chelated complex with the organometallics.[1] As has been previously reported, highly efficient enantiofacial selection in a carbon-carbon bond formation was achieved through addition of organolithiums to aldimines and esters with an aid of **1** (R = Me).[2] The high enantioselectivity exhibited by the **1**-organolithium complex **2** allowed us to choose **3** as a symmetric substrate, in which selection of an enantiotopic reaction site, instead of an enantioface, is realized by the **1**-organolithium combination. It is noteworthy that, although use of chiral Lewis acids has been reported in an asymmetric opening of epoxides,[3] no efficient combination of organometallics and external chiral ligand has been developed.[4] We describe herein an approach toward an external chiral ligand-controlled enantioselective opening reaction of the prochiral oxide-ring **3** with an organolithium to afford the corresponding chiral alcohol **4**.[5]



Asymmetrization of a symmetric **3** requires differentiation of the two enantiotopic reaction sites by **2**. Our previous success in the enantioface-differentiating reaction of **2** relies on the coordination of a substrate to the lithium cation of **2** in advance to the reaction and following intra-complex and stereoselective migration of the organic group to the reaction site. However, it is not necessarily easy to propose a reasonable design for the reaction of **2** with **3**, because coordination of the oxygen atom of **3** to the lithium atom of **2** takes place on the face opposite to the nucleophile-attacking face. This implies that **2** recognizes the whole molecular structure of **3**, especially the stereochemistry of the remote part to the reaction site. To clarify this, we chose cyclohexene oxide (**5**) and 3-phenyloxetane (**6**) as a couple of model substrates.

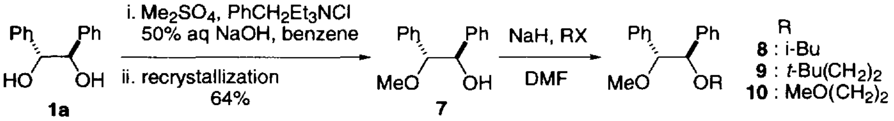
## PREPARATION OF CHIRAL LIGANDS

The chiral ligands employed in this study were readily prepared by alkylation of (*R*,*R*)-1,2-diphenylethane-1,2-diol (**1a**: R = H) obtained by the modification of the reported procedure.[6] The symmetric chiral bidentate ligands **1b-e** were prepared by direct alkylation of **1a** in good to high yields.



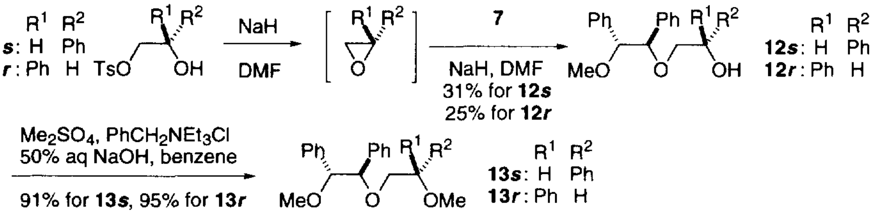
$R_2SO_4$/THF for **1b** (85%), **1c** (78%), ROTs/DMF for **1d** (67%), **1e** (99%)

The unsymmetric bidentate ligands **8** and **9**, and tridentate ligand **10** were prepared from **1a** *via* the monomethyl ether **7** which was easily obtained by phase transfer catalysis conditions.



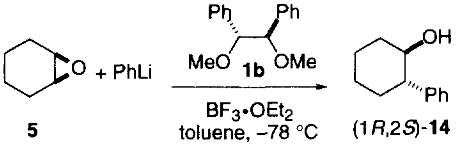
ROTs for **8** (98%), **9** (97%), and RCl for **10** (quant)

The tridentate ligands **13*s*,*r*** were prepared by the reaction of **7** with (*R*)- and (*S*)-styrene oxides that were generated *in situ* from **11**,[7] and following methylation of **12**.



## ASYMMETRIC OPENING OF CYCLOHEXENE OXIDE (5)

The reaction of **5** with phenyllithium in toluene did not proceed at the temperature ranging from −78 to 0 °C even by the aid of **1b**. However, as has been described previously,[8] upon addition of boron trifluoride diethyl etherate, the reaction proceeded smoothly at −78 °C to give the corresponding (−)-(1*R*,2*S*)-**14** in 32% ee and 99% yield. The enantioselectivity and absolute configuration of **14** were determined by a chiral HPLC analysis and specific rotation.[9]



The enantioselectivity was highly dependent on the ligand structure in a toluene solvent (Table 1). The most simple bidentate ligand **1b** having methyl groups on ether oxygens exhibits the best enantioselectivity, whereas the ligands **1c-e**, **8** and **9** having more bulky ether substituents gave the surprisingly poor selectivities. The failure in forming the complex **2** probably causes the low enantioselectivity.

**Table 1**. Ligand Effects on Enantioselectivity[a]

| entry | ligand | yield/% | ee/% |
|---|---|---|---|
| 1 | **1b** | 88 | 32 |
| 2 | **1c** | 91 | 3 |
| 3 | **1d** | 99 | 8 |
| 4 | **1e** | 99 | 5 |
| 5 | **8** | 89 | 2 |
| 6 | **9** | 99 | 3 |

a) Amounts of PhLi, ligand and $BF_3 \cdot OEt_2$ were 3.0, 3.3, and 1.5 equivalents, respectively.

**Table 2**. Solvent Effects on Enantioselectivity with use of ligand **1b**[a]

| entry | solvent | yield/% | ee/% |
|---|---|---|---|
| 1 | toluene | 99 | 32 |
| 2 | $Et_2O$ | 99 | 43 |
| 3 | THF | 90 | 0 |
| 4 | $i\text{-}Pr_2O$ | 99 | 34 |
| 5 | $Bu_2O$ | 90 | 34 |

a) Amounts of PhLi, **4** and $BF_3 \cdot OEt_2$ were 2.0, 2.1, and 1.5 equivalents, respectively.

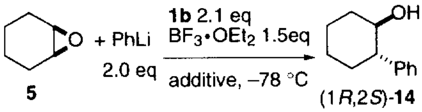
Then, we examined solvent effects on enantioselectivity in the reaction of phenyllithium with use of the ligand **1b** (Table 2). In toluene, (–)-(1*R*,2*S*)-**14** was obtained in 32% ee, whereas the selectivity was completely lost in THF, suggesting that its strong coordination to the lithium impedes the formation of **1b**-PhLi complex. The bulky ether solvents do not affect the reaction, giving the similar level of enantioselectivity to that in toluene (entries 4, 5). The enantioselectivity was improved up to 43% in $Et_2O$. We assumed that the oxygen atom of diethyl ether may coordinate to the lithium cation of the **1b**-PhLi complex (**2**).

Then, the effects of some additives of coordinating ability, LiBr, ether, THF, and HMPA were examined in toluene and ether solvents (Table 3). The presence of lithium bromide does not affect the reaction (entry 1). In toluene, the enantioselectivity goes up to 40% from 32% upon addition of 4 eq of THF. On the other hand, ee drops by the presence of 8 eq of THF and 2 eq of HMPA. In ether solvent, these additives cause the decrease of ee.

These additive effects suggest their coordination to the lithium cation of **2**. Appropriate coordination maintains the chelation of **1b**, but strong coordination destroys the chelation. It is reasonable to examine the tridentate ligands, **10** and **13**, to satisfy the coordination pattern of **2** and to form a more rigid bicyclic [3.3.0]-structure.

It is probable to expect that **10** or **13*r*** forms the bicyclic [3.3.0]-chelation (**A**) more stable than **13*s***, because the bulky phenyl group on the additional chiral center of

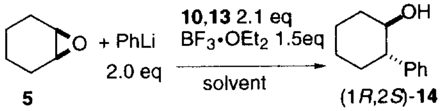
**Table 3**. Additive Effects on Enantioselectivity



| entry | solvent | additive | eq | yield/% | ee/% |
|---|---|---|---|---|---|
| 1[a] | toluene | none | | 95 | 30 |
| 2 | | none | | 99 | 32 |
| 3 | | THF | 2 | 99 | 39 |
| 4 | | THF | 4 | 99 | 40 |
| 5 | | THF | 8 | 99 | 34 |
| 6 | | HMPA | 2 | 94 | 25 |
| 7 | | $Et_2O$ | 4 | 99 | 34 |
| 8 | $Et_2O$ | none | | 99 | 43 |
| 9 | | THF | 2 | 99 | 35 |
| 10 | | THF | 4 | 99 | 28 |
| 11 | | THF | 8 | 98 | 16 |
| 12 | | HMPA | 2 | 93 | 11 |

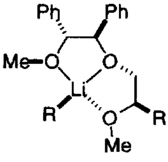
a) PhLi was prepared from PhBr and BuLi.

**Table 4**. Tridendate Ligand Effects on Selectivity

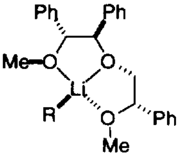


| entry | ligand | solvent | yield/% | ee/% |
|---|---|---|---|---|
| 1 | **10** | toluene | 99 | 23 |
| 2 | **10** | $Et_2O$ | 96 | 20 |
| 3 | **13*r*** | toluene | 90 | 47 |
| 4 | **13*r*** | $Et_2O$ | 93 | 38 |
| 5 | **13*s*** | $Et_2O$ | 99 | 26 |

**13*s*** occupies the concave face of the bicyclo[3.3.0]-chelation (**B**). Expectedly, the reaction with **13*r*** gave **14** in 47% ee, higher selectivity compared with 23 and 26% ees by **10** and **13*s***, respectively (Table 4). It is worthy to note that enantioselectivity dependency on solvent is minimized, probably due to the formation of more rigid bicyclo[3.3.0]-chelation structure through an intramolecular coordination (**A**).



**A** (R = H or Ph)

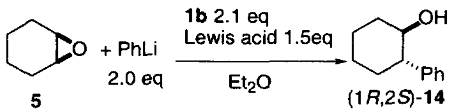


**B**

Since the presence of $BF_3{\bullet}OEt_2$ is essential in opening of the oxide ring of **5**, the effects of some Lewis acids on the enantioselectivity were examined (Table 5). Both $BF_3{\bullet}OMe_2$ and $BF_3{\bullet}OBu_2$ showed slightly higher enantioselectivity of up to 47% compared with 43% induced by $BF_3{\bullet}OEt_2$.[10] 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 **5** on the opposite face to the attacking phenyllithium.

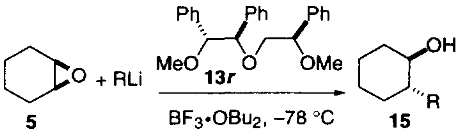
The present reaction is applicable to other organolithiums to give the corresponding alcohols in moderate ees (Table 6).

**Table 5**. Enantioselectivity Dependence on Lewis Acid



| entry | Lewis acid | yield/% | ee/% |
|---|---|---|---|
| 1 | $BF_3{\bullet}OMe_2$ | 99 | 45 |
| 2 | $BF_3{\bullet}OEt_2$ | 99 | 43 |
| 3 | $BF_3{\bullet}OBu_2$ | 99 | 47 |
| 4 | $BBu_2OTf$ | 99 | 6 |

**Table 6**. Asymmetric Opening of **5**



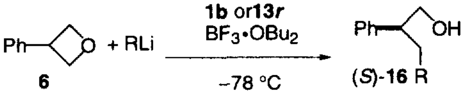
| RLi | solvent | yield/% | ee/% |
|---|---|---|---|
| Ph | toluene | 90 | 47 |
|  | $Et_2O$ | 93 | 38 |
| Bu | toluene | 68 | 26 |
| PhC≡C | toluene | 93 | 22 |
| 2-Naph | $Et_2O$ | 96 | 37 |

## ASYMMETRIC OPENING OF 3-PHENYLOXETANE (6)

The present enantioselective opening reaction is applicable to the other oxide ring, oxetane (**6**) giving **16** (Table 7). The ligand **1b** afforded (*S*)-**16** (R = Ph) in 20% ee.[11] Although the ligand **13*s*** exhibited rather poor enantioselectivity to give nearly racemic **16**, fortunately **13*r*** afforded (*S*)-**16** (R = Ph) in 47% ee. Butyllithium and lithium phenylacetylide gave the corresponding alcohols in low ees.

Although enantioselectivities obtained in these reactions are primitive and further studies are required, we believe that the selection of enantiotopic reaction site may be realized by this methodology.

**Table 7**. Asymmetric Opening of **6**



| 1b, 13r | RLi | solvent | yield % | ee % |
|---|---|---|---|---|
| **1b** | Ph | toluene | 99 | 20 |
| **13*r*** |  | $Et_2O$ | 92 | 47 |
| **1b** | Bu | toluene | 93 | 37 |
| **13*r*** |  | toluene | 85 | 27 |
| **1b** | PhC≡C | toluene | 78 | 13 |
| **13*r*** |  | toluene | 87 | 15 |

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## EXPERIMENTAL[12]

**(1*R*,2*R*)-1,2-Bis(2-methylpropoxy)-1,2-diphenylethane (1d).** To a suspension of NaH (60% oil dispersion, 1.2 g, 30.0 mmol) in 5 ml of DMF was added dropwise a solution of (*R*,*R*)-**1a**[6] (2.1 g, 10.0 mmol) in 5 ml of DMF. The mixture was stirred for 1 h at 60 °C and allowed to cool to rt. A solution of isobutyl tosylate[13] (5.0 g, 22.0 mmol) in 3 ml of DMF was added dropwise over 20 min. After stirring for 3 h and 25 h, NaH (60% oil dispersion, 400 mg, 10.0 mmol) and tosylate (2.3 g, 10.0 mmol) were added, respectively. After 36 h stirring, the mixture was cooled to 0 °C and quenched with 20 ml satd. $NH_4Cl$. The mixture was extracted with ethyl acetate (150 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (80 g, hexane/AcOEt = 30/1) gave **1d** as a colorless oil (2.3 g, 72%). $[\alpha]^{25}_D$ –52.6 °(c 0.985, $CHCl_3$). PMR: 0.85 (12H, d, *J* = 7.5 Hz, $CH_3$), 1.85 (2H, h, *J* = 7.5 Hz, CH), 3.11 (4H, d, *J* = 7.5 Hz, $CH_2$), 4.39 (2H, s, CH), 6.78-7.47 (10H, m, ArH). CMR: 19.4, 28.7, 76.3, 85.8, 127.1, 127.4, 127.8, 139.2. IR (neat): 1450, 1100 $cm^{-1}$. Rf 0.23 (PhH/ hexane = 1/4). MS *m/z*: 326 ($M^+$). Anal: Calcd. for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.66; H, 9.43.

**(1*R*,2*R*)-1,2-Bis(3,3-dimethylbutoxy)-1,2-diphenylethane (1e).** Prepared in 99% yield from **1a** by the same procedure for **1d** using homoneopentyl tosylate[14]. Purification through silica gel column chromatography (20 g, hexane/AcOEt = 40/1) gave **1e** as a colorless oil (753 mg, 99%). $[\alpha]^{25}_D$ –17.3 °(c 1.52, $CHCl_3$). PMR: 0.86 (18H, s, $CH_3$), 1.50 and 3.42 (each 4H, t, *J* = 7.5 Hz, $OCH_2CH_2$), 4.36 (2H, s, CH), 6.81-7.42 (10H, m, ArH). CMR: 29.6, 29.8, 43.1, 67.1, 84.1, 127.1, 127.5, 127.8, 139.2. IR (neat): 1470, 1360, 1200, 1100 $cm^{-1}$. Rf 0.17 (PhH/hexane = 1/3). MS *m/z*: 380 ($M^+$-2). Anal: Calcd. for $C_{26}H_{38}O_2$: C, 81.63; H, 10.01. Found: C, 81.52; H, 9.85.

**(1*R*,2*R*)-1,2-Diphenyl-2-methoxyethanol (7).** To a solution of NaOH (28.0 g, 0.2 mol) in 28 ml of water was added 350 ml of benzene, (*R*,*R*)-**1a** (15.0 g, 70.0 mmol), and benzyltriethylammonium chloride (3.2 g, 14 mmol). After stirring for 15 min, dimethyl sulfate (7.9 ml, 84.0 mmol) was added dropwise. After stirring for 1.5 h at rt, 100 ml of water was added and the mixture was extracted with benzene (150 ml). The combined organic layers were washed with brine, and dried over $MgSO_4$. Concentration and crystallization from 10 ml of hexane gave **7** (10.2 g, 64%) as colorless plates of mp 68-69 °C. $[\alpha]^{25}_D$ +53.3 °(c 1.50, $CHCl_3$). PMR: 3.31 (3H, s, $OCH_3$), 3.50 (1H, s, OH), 4.14 and 4.67 (each 1H, d, *J* = 7.5 Hz, $CHOCH_3$ and CHOH), 6.78-7.42 (10H, m, ArH). CMR: 56.9, 78.6, 89.2, 127.3, 127.67, 127.72, 127.8, 128.03, 137.2, 137.9. IR (nujol): 3400, 1260 $cm^{-1}$. Rf 0.20 (hexane/AcOEt = 9/1). MS *m/z*: 227 ($M^+$-1). Anal: Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.09; H, 6.99.

**(1*R*,2*R*)-1-(2,2-Dimethylpropoxy)-2-methoxy-1,2-diphenylethane (8).** To a suspension of NaH (60% oil dispersion, 23 mg, 0.6 mmol) in 0.1 ml of DMF was added dropwise a solution of **7** (109 mg, 0.48 mmol) in 0.2 ml of DMF. The mixture was stirred for 30 min at 50 °C and then a solution of isobutyl tosylate (131 mg, 0.58 mmol) in 1 ml of DMF was added dropwise over 5 min. After stirring for 3 h at 50 °C, NaH (23 mg, 0.58 mmol) and tosylate (65 mg, 0.29 mmol) were added. After 6.5 h stirring, the mixture was cooled to 0 °C and quenched with 10 ml of satd. $NH_4Cl$. The mixture was extracted with benzene (30 ml), and the combined organic layers were washed with brine and dried over $MgSO_4$. Concentration and purification of the residue through silica gel column chromatography (10 g, hexane/AcOEt = 14/1) gave **8** as a colorless oil (134 mg, 98%). $[\alpha]^{25}_{D}$ –49.2 °(c 1.53, $CHCl_3$). PMR (270 MHz): 0.84 and 0.85 (each 3H, d, *J* = 7.4 Hz, $CH_3$), 1.87 (1H, h, *J* = 7.4 Hz, CH), 3.10 (2H, d, *J* = 7.4 Hz, $CH_2$), 3.29 (3H, s, $OCH_3$), 4.32 and 4.38 (each 1H, d, *J* = 7.4 Hz, CHPh), 6.94-7.23 (10H, m, ArH). CMR: 19.3, 19.4, 28.5, 57.5, 76.3, 85.8, 87.5, 127.26, 127.34, 127.56, 127.60, 127.8, 138.6, 139.1. IR (neat): 2900, 1500, 1450, 1100 $cm^{-1}$. Rf 0.62 (hexane/AcOEt = 4/1). MS *m/z*: 284 ($M^+$). Anal: Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.11; H, 8.43.

**(1*R*,2*R*)-1-(3,3-Dimethylbutoxy)-2-methoxy-1,2-diphenylethane (9)**. Prepared by the same procedure for **8** from **7** and homoneopentyl tosylate in 97% yield. Purification through silica gel column chromatography (hexane/PhH = 20/1 and then PhH) gave **9** as a colorless oil. $[\alpha]^{25}_{D}$ –35.3 °(c 1.37, $CHCl_3$). PMR (270 MHz): 0.82 (9H, s, $CH_3$), 1.39-1.71 (2H, m, $CH_2$), 3.26 (3H, s, $OCH_3$), 3.29-3.45 (2H, m, $CH_2$), 4.32 and 4.39 (each 1H, d, *J* = 7.4 Hz, CHPh), 6.90-7.23 (10H, m, ArH). CMR: 29.5, 29.7, 42.9, 57.3, 66.8, 85.9, 87.6, 127.3, 127.4, 127.6, 127.7, 127.8, 138.4, 139.0. IR (neat): 2900, 1500 $cm^{-1}$. Rf 0.50 (hexane/AcOEt = 8/1). MS *m/z*: 312 ($M^+$). Anal: Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.90; H, 8.92.

**(1*R*,2*R*)-1-Methoxy-2-(2-methoxyethoxy)-1,2-diphenylethane (10)**. Prepared by the same procedure for **8** from **7** and methoxyethyl chloride in quantitative yield. Purification through silica gel column chromatography (hexane/acetone = 9/1) gave **10** as a colorless oil. $[\alpha]^{25}_{D}$ –25.6 °(c 1.56, $CHCl_3$). PMR: 3.28 and 3.33 (each 3H, s, $OCH_3$), 3.53 (4H, s, $CH_2$), 4.33 and 4.47 (each 1H, d, *J* = 7.4 Hz, CHPh), 6.78-7.39 (10H, m, ArH). CMR: 57.2, 58.8, 68.5, 71.8, 86.3, 87.4, 127.4, 127.67, 127.76, 127.79, 138.3, 138.4. IR (neat): 2900, 1450, 1200, 1100 $cm^{-1}$. Rf 0.14 (hexane/AcOEt = 4/1). MS *m/z*: 287 ($M^{+}$+1). Anal: Calcd. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.32; H, 7.51.

**(1*R*,2*R*)-1-[(*S*)-2-Hydroxy-2-phenylethoxy]-2-methoxy-1,2-diphenylethane (12*s*)**. To a suspension of NaH (60% oil dispersion, 1.2 g, 28 mmol) in 10 ml of DMF was added dropwise a solution of (*S*)-**11*s*** (4.7 g, 16 mmol), prepared from (*S*)-mandelic acid, in 10 ml of DMF over 30 min at –40 °C. The mixture was allowed to warm up to rt gradually. After checking the conversion of tosylate to epoxide by tlc, the mixture was cooled to –40 °C again and a solution of **7** (1.8 g, 8.0 mmol) in 10 ml of DMF was added over 20 min. The whole was stirred for 17 h at 70 °C and was added with 20 ml of satd. $NH_4Cl$. The mixture was extracted with ethyl acetate (100 ml). The combined organic layers were washed with brine and dried over $Na_2SO_4$, and then concentrated. Distillation gave **7** (180-200 °C/3 mmHg) and the residue which was purified through silica gel column chromatography (BW 200, 50 g, hexane/AcOEt = 6/1) to afford **12*s*** as a colorless oil (190 mg, 31%). $[\alpha]^{25}_{405}$ –5.5 °(c 1.1, PhH). PMR: 3.28 (1H, dd, *J* = 10.0, 10.0 Hz, $OCH_2CHPh$) 3.33 (3H, s, $OCH_3$), 3.56 (1H, brs, OH) 3.75 (1H, dd, *J* = 2.5, 10.0 Hz, $OCH_2CHPh$), 4.36 (1H, d, *J* = 7.5 Hz, PhCHCHPh), 4.53 (1H, d, *J* = 7.5 Hz, PhCHCHPh), 4.97 (1H, dd, *J* = 2.5, 10.0 Hz, PhCHOH), 6.81-7.50 (15H, m, ArH). CMR: 57.2, 73.7, 76.5, 88.1, 88.4, 127.1, 127.5, 127.6, 127.7, 127.9, 128.0, 128.2, 137.7, 138.4, 139.8. IR (neat): 3000, 1100 $cm^{-1}$. Rf 0.43 (hexane/AcOEt = 7/3). MS *m/z*: 347 ($M^{+}$-1). Anal: Calcd. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.39; H, 6.69.

**(1*R*,2*R*)-1-Methoxy-2-[(*S*]-2-methoxy-2-phenylethoxy]-1,2-diphenylethane (13*s*)**. To a solution of NaOH (5.0 g, 12.5 mmol) in 5 ml of water was added bezyltriethylammonium chloride (114 mg, 0.5 mmol) and a solution of **12*s*** in 5 ml of benzene . After stirring for 30 min at rt, dimethyl sulfate (0.36 ml, 3.8 mmol) was added, and the mixture was stirred for 30 min. Then 20 ml of water was added, and the mixture was extracted with benzene (50 ml). The combined organic layers were washed with brine, and dried over $Na_2SO_4$. Concentration and purification through silica gel column chromatography (BW 200, 50 g, hexane/AcOEt = 4/1) gave **13*s*** as a colorless oil (820 mg, 91%). $[\alpha]^{25}_{D}$ +3.1 °(c 1.03, $CHCl_3$). PMR: 3.21 and 3.29 (each 3H, s, $OCH_3$), 3.43 (1H, dd, *J* = 5.0, 12.5 Hz, $OCH_2CHPh$), 3.50 (1H, dd, *J* = 7.5, 12.5 Hz, $OCH_2CHPh$), 4.31 (1H, dd, *J* = 5.0, 7.5 Hz $PhCHCH_2O$), 4.35 and 4.60 (1H, d, *J* = 6.3 Hz, PhCHCHPh), 6.81-7.56 (15H, m, ArH). CMR: 57.0, 57.4, 74.0, 83.4, 86.7, 87.3, 126.9, 127.3, 127.4, 127.6, 127.7, 127.8, 127.9, 128.2, 138.5, 138.7, 139.3. IR (neat): 3000, 1100 $cm^{-1}$. Rf 0.60 (hexane/AcOEt = 4/1). MS *m/z*: 361 ($M^+$-1). Anal: Calcd. for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.25; H, 7.10.

**(1*R*,2*R*)-1-[(*R*)-2-Hydroxy-2-phenylethoxy]-2-methoxy-1,2-diphenylethane (12*r*).** Prepared by the same procedure for **12*s*** from **7** and (*R*)-**11*r*** (4.7 g, 16.0 mmol), prepared from (*R*)-mandelic acid, as a colorless oil in 25% yield. $[\alpha]^{25}_{405}$ +24.9 °(c 1.59, PhH). PMR: 3.33 (3H, s, $OCH_3$), 3.50 (1H, brs, OH) 3.50 and 3.53 (each 1H, brd, *J* = 2.5 Hz, $CH_2CHPh$), 4.53 and 4.88 (each 1H, d, *J* = 7.5 Hz, PhCHCHPh), 4.97 (1H, dd, *J* = 5.0, 7.5 Hz, PhCHOH), 6.81-7.47 (15H, m, ArH). CMR: 57.1, 71.1, 74.4, 85.2, 87.7, 126.1, 127.5, 127.7, 127.8, 127.9, 128.2, 137.7, 137.9, 140.2. IR (neat): 3520, 1180 $cm^{-1}$. Rf 0.30 (hexane/AcOEt = 7/3). MS *m/z*: 347 ($M^+$-1). Anal: Calcd. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.28; H, 6.73.

**(1*R*,2*R*)-1-Methoxy-2-[(*R*)-2-methoxy-2-phenylethoxy]-1,2-diphenylethane (13*r*).** Prepared from **12*r*** by the same procedure for **13*s*** as a colorless oil in 95% yield. $[\alpha]^{25}_{D}$ −95.1 °(c 1.17, $CHCl_3$). PMR: 3.25 and 3.31 (each 3H, s, $OCH_3$) 3.42 (1H, dd, *J* = 5.0, 10.0 Hz, $OCH_2CHPh$), 3.64 (1H, dd, *J* = 7.5, 10.0 Hz, $OCH_2CHPh$), 4.39 and 4.47 (each 1H, d, *J* = 7.5 Hz, PhCHCHPh), 4.39 (1H, dd, *J* = 5.0, 7.5 Hz, $CH_2CHOMe$), 6.69-7.42 (15H, m, ArH). CMR: 57.0, 57.4, 74.2, 82.9, 86.4, 87.4, 127.2, 127.3, 127.4, 127.7, 127.8, 127.9, 128.2, 138.3, 138.5, 139.4. IR (neat): 1100 $cm^{-1}$. Rf 0.56 (hexane/AcOEt = 7/3). MS *m/z*: 361 ($M^+$-1). Anal: Calcd. for $C_{24}H_{26}O_3$:1/4$H_2O$. C, 78.55; H, 7.28. Found: C, 78.26; H, 7.08.

**Reaction of 5 with phenyllithium using 1b giving (1*R*,2*S*)-14 (Table 5, entry 3).** To a solution of **1b** (510 mg, 2.1 mmol) in 17 ml of ether at −78 °C was added dropwise a solution of phenyllithium (1.3 ml, 2.0 mmol) in cyclohexane-ether. The mixture was stirred for 20 min at −78 °C and then **5** (0.1 ml, 1.0 mmol) was added. Successively, to the mixture was added dropwise a solution of boron trifluoride dibutyl etherate (0.31 ml, 1.5 mmol) in 2 ml of ether over 5 min. After stirring for 30 min at −78 °C, 20 ml of satd. $NaHCO_3$ was added. The mixture was extracted with benzene, and the combined organic layers were washed with 10% aq. NaOH and brine, then dried over $Na_2SO_4$. Concentration and purification through silica gel column chromatography (BW 200, 50 g, hexane/AcOEt = 8/1) gave **1b** (510 mg, quantitative recovery) and (1*R*,2*S*)-**14** (170 mg, 99%) of 47% ee as colorless needles. $[\alpha]^{31}_{D}$ −22.4 °(c 1.56, PhH). Optical purity is 47% based on $[\alpha]^{31}_{D}$ +47.6 °(c 1.56, PhH) for optically pure compound. HPLC analysis indicated 47% ee (Daicel Chiralcel OD, hexane/i-PrOH = 30/1, 1.0 ml/min, 250 nm, rt (min) con (%), 20.28 (27.603) and 22.44 (72.396)). PMR: 1.00-2.67 (10H, m), 3.67 (1H, m, CHOH), 6.94-7.53 (5H, m, ArH). IR (nujol): 3400, 1300 $cm^{-1}$. Rf 0.37 (PhH/AcOEt = 9/1).

**Reaction of 5 with butyllithium using 1b giving (−)-15 (R = Bu).** The same procedure for **14** above, but using $BF_3$•$OEt_2$, gave (−)-**15** (R = Bu) in 12% ee and 85% yield. $[\alpha]^{25}_{D}$ −6.0 °(c 1.08, $CHCl_3$). The ee was determined to 12% by HPLC analysis of the corresponding phenyl carbamate[15] (Chiralcel OD, i-PrOH/hexane = 1/50, 1.0 ml/min). PMR: 0.58-2.17 (19H, m), 3.03-3.58 (1H, m, CHOH).[16] IR (neat): 3300, 1440, 1350 cm$^{-1}$. Rf 0.27 (hexane/AcOEt = 9/1).

**Reaction of 5 with methyllithium using 1b giving (+)-15 (R = Me).** The same procedure for **14** above, but using $BF_3{\cdot}OEt_2$, gave (+)-**15** (R = Me) in 12% ee and 54% yield. $[\alpha]^{20}_D$ –2.8 °(c 1.04, MeOH). The ee was determined to 12% by HPLC analysis of the corresponding phenyl carbamate (Chiralcel OD, i-PrOH/hexane =1/50, 1.0 ml/min). PMR $\delta$: 0.69-2.25 (13H, m), 3.11 (1H, m, CHOH); IR (neat): 3700-3000, 2900 cm$^{-1}$. Rf 0.30 (hexane/AcOEt = 8/1).

**Reaction of 5 with 1-naphthyllithium using 1b giving (+)-(1*S*,2*R*)-15 (R = 1-Naph).** 1-Naphthyllithium was prepared from 1-naphthyl bromide and butyllithium in the presence of **1b** in toluene for 3 h at –40 °C. The same procedure for **14** above, but using $BF_3{\cdot}OEt_2$, gave (+)-(1*S*,2*R*)-**15** (R = 1-Naph) in 15% ee and 96% yield. $[\alpha]^{25}_D$ +8.5 °(c 1.41, $CHCl_3$). The absolute configuration was determined based on $[\alpha]^{25}_D$ +78.7 °(c 1.0, $CHCl_3$) for (1*S*,2*R*)-**15** (R = 1-Naph).[17] The ee was confirmed by HPLC analysis (Daicel Chiralcel OD, i-PrOH/hexane = 1/10, 0.5 ml/min, 250 nm, rt/min (con (%)): 19.14 (41.925) and 26.69 (56.486)). PMR: 1.00-2.44 (9H, m), 3.42 (1H, m, CHOH), 4.03 (1H, m, CH-Naph), 7.33-8.44 (7H, m, ArH). CMR: 25.1, 26.3, 33.8, 34.7, 46.6, 74.1, 122.6, 123.2, 125.6, 125.6, 126.0, 127.0, 128.9, 132.2, 134.1, 139.4. IR (nujol): 3300, 1180 cm$^{-1}$. Rf 0.24 (hexane/AcOEt = 4/1). MS *m/z*: 226 (M$^+$).

**Reaction of 5 with 2-naphthyllithium using 1b giving (+)-15 (R = 2-Naph).** 2-Naphthyllithium was prepared from 2-naphthyl bromide and butyllithium in the presence of **1b** in ether at –40 °C for 1 h. The same procedure for **14** above gave (+)-**15** (R = 2-Naph) in 33% ee and quantitative yield. $[\alpha]^{25}_D$ –7.8 °(c 1.05, $CHCl_3$). The ee was determined by HPLC analysis (Daicel Chiralcel OD, i-PrOH/hexane = 1/10, 0.5 ml/min, 250 nm, rt/min (con (%)): 16.72 (33.518) and 18.39 (65.967)). PMR: 1.00-2.50 (9H, m), 3.39 (1H, m, CHOH), 4.97 (1H, m, CH-Naph), 7.08-8.44 (7H, m, ArH). CMR: 25.0, 26.0, 33.2, 34.4, 53.3, 74.2, 125.5, 125.9, 126.1, 126.7, 127.6, 128.5, 132.5, 133.5, 140.6. IR (nujol): 3300, 1040 cm$^{-1}$. Rf 0.27 (hexane/AcOEt = 4/1). MS *m/z*: 226 (M$^+$).

**Reaction of 5 with phenylethynyllithium using 1b giving (+)-15 (R = PhC≡C).** The same procedure for **14** above, but using $BF_3{\cdot}OEt_2$, gave (+)-**15** (R = PhC≡C) in 23% ee and 85% yield. $[\alpha]^{25}_D$ -22.3 °(c 1.445, $CHCl_3$). The ee was determined by HPLC analysis (Daicel Chiralcel OD, i-PrOH/hexane = 1/30, 0.5 ml/min, 250 nm, rt/min (con (%)): 24.60 (38.349) and 26.85 (61.613)). PMR: 0.97-2.78 (10H, m), 3.28-3.78 (1H, m, CHOH), 7.03-7.78 (5H, m, ArH.). CMR: 24.2, 24.8, 30.9, 33.1, 39.5, 73.5, 82.6, 90.8, 123.2, 127.8, 128.2, 131.6. IR (nujol): 3400, 2240, 1600, 1170 cm$^{-1}$. Rf 0.5 (hexane/AcOEt = 3/1). MS *m/z*: 200 (M$^+$).

**Reaction of 6 with phenyllithium using 13*r* giving (+)-(*S*)-16 (R = Ph) (Table 7).** To a solution of **13*r*** (398 mg, 1.1 mmol) in 6 ml of ether at –78 °C was added dropwise a solution of phenyllithium (1.1 ml, 1.03 mmol) in cyclohexane-ether. The mixture was stirred for 20 min at –78 °C and then a solution of **6**[18] (67 mg, 0.5 mmol) in 1 ml of ether was added. Successively, to the mixture was added dropwise a solution of boron trifluoride dibutyl etherate (0.16 ml, 0.75 mmol) in 1 ml of ether over 5 min. After stirring for 30 min, 20 ml of satd. aq. $NaHCO_3$ was added. The mixture was extracted with benzene, and the combined organic layers were washed with 10% aq. NaOH and brine, then dried over $Na_2SO_4$. Concentration and purification through silica gel column chromatography (BW 200, 50 g, hexane/AcOEt = 8/1) gave **13*r*** (390 mg, 98% recovery) and (+)-(*S*)-**16** (R = Ph) (97 mg, 92%) in 47% ee of $[\alpha]^{20}_D$ +50.2 °(c 4.25, ether). The absolute configuration was determined based on $[\alpha]^{20}_D$ +107.6 °(c 4.18, ether) for the reported (*S*)-**16**. The ee was confirmed to 47% by HPLC analysis (Daicel Chiralcel OD, hexane/i-PrOH = 30/1, 0.5 ml/min, 250 nm rt/min (con (%)): 34.0 (26.393) and 38.74 (73.341)). PMR: 1.33 (1H, brs, OH), 2.72-3.33 (3H, m, CHPh), 6.94-7.56 (10H, m, ArH). IR (neat): 3400 cm$^{-1}$. Rf 0.40 (hexane/AcOEt = 7/3).

**Reaction of 6 with butyllithium using 1b giving (+)-16 (R = Bu) (Table 7).** The same procedure for **16** (R = Ph) above, but using **1b**, gave (+)-**16** (R = Bu) in 37% ee and 93% yield $[\alpha]^{25}_D$ +6.9 °(c 1.57, $CHCl_3$). The ee was determined to 37% by HPLC analysis (Daicel Chiralcel AS, hexane/i-PrOH = 30/1, 0.5 ml/min, 250 nm rt/min (con (%)): 14.84 (67.272) and 15.97 (31.118)). PMR: 0.83 (3H, t, $J$ = 7.5 Hz, $CH_3$), 1.00-2.00 (9H, m, $CH_2$, OH), 2.56-3.00 (1H, quint., PhCH), 3.78 (2H, d, $J$ = 7.5 Hz, $CH_2O$), 6.94-7.56 (5H, m, ArH). CMR: 14.0, 22.5, 26.9, 31.9, 32.0, 48.7, 67.6, 126.7, 128.1, 128.6, 142.3. IR (neat): 3400 cm$^{-1}$. Rf 0.30 (hexane/AcOEt = 7/2). MS *m/z*: 192 ($M^+$).

**Reaction of 6 with phenylethynyllithium using 1b giving 16 (R = $PhC\equiv C$) (Table 7).** The same procedure for **16** (R = Ph) above, but using **1b**, gave (+)-**16** (R = $PhC\equiv C$) in 13% ee and 78% yield. $[\alpha]^{25}_D$ +5.5 °(c 1.10, $CHCl_3$). The ee was determined to 13% by HPLC analysis (Daicel Chiralcel OD, hexane/i-PrOH = 30/1, 0.5 ml/min, 250 nm, rt/min (con (%)): 46.00 (56.334) and 55.50 (43.635)). PMR: 1.61 (1H, s, OH), 2.83 (2H, dd, $J$ = 2.5, 6.3 Hz, $CH_2$), 3.13 (1H, quint., $J$ = 6.3 Hz CHPh), 4.00 (2H, dd, $J$ = 2.5, 6.3 Hz, $CH_2O$) 7.06-7.44 (10H, m, ArH). CMR: 14.0, 22.5, 26.9, 31.9, 32.0, 48.7, 67.6, 126.7, 128.1, 128.6, 142.3. IR (neat): 3400 cm$^{-1}$. Rf 0.30 (hexane/AcOEt = 7/2). MS *m/z*: 236 ($M^+$). Anal. Calcd. for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.20; H, 6.81.

**Reaction of 6 with 2-naphthyllithium using 1b giving (+)-16 (R = 2-Naph) (Table 7).** The same procedure for **16** (R = Ph) above gave (+)-**16** (R = 2-Naph) in 27% ee and 85% yield. mp 76-78 °C. $[\alpha]^{25}_D$ +28.0 °(c 0.59, $CHCl_3$). The ee was determined to 27% by HPLC analysis (Daicel Chiralcel OD, hexane/i-PrOH = 30/1, 0.5 ml/min, 250 nm, rt/min (con (%)): 59.20 (63.445) and 86.18 (36.326)). PMR: 1.44 (1H, s, OH), 2.97-3.36 (3H, m, $PhCHCH_2$), 3.83 (2H, d, $J$ = 6.3 Hz $CH_2O$), 7.00-8.00 (12H, m, ArH). CMR: 14.0, 22.5, 26.9, 31.9, 32.0, 48.7, 67.6, 126.7, 128.1, 128.6, 142.3. IR (neat): 3400 cm$^{-1}$. Rf 0.32 (hexane/AcOEt = 7/3). MS *m/z*: 262 ($M^+$). Anal: Calcd. for $C_{19}H_{18}O{:}1/5H_2O$: C, 85.81; H, 6.97. Found: C, 85.87; H, 6.80.

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