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ALKYLATION OF 2-PHENYLSULFINYLETHANOL

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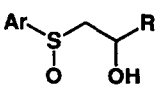
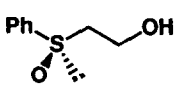
Summary: Alkylation of 2-phenylsulfinylethanol resulted syn-diastereomer as the major products, although the ratio of syn/anti isomers varied depending on the alkyl groups. By application of this procedure to the chiral sulfoxides, optically active epoxides have been obtained in good yields.

Chiral sulfoxides play an important role in asymmetric synthesis, because the chirality of S-O group can be transfered to carbons.[1] One example is the alkylation of β-hydroxyalkyl sulfoxides. The substrates so far examined have an alkyl group on β-position (**1**).[2] Accordingly the asymmetric induction in alkylation was controlled by the chirality of both S-O and C-O group, and the reported results indicate that the effect of the latter overcome the one of the former.[2] In this paper, we would like to disclose the net effect of the sulfoxide group via alkylation of (R)-2-phenylsulfinylethanol (**2**), which is available by microbial oxidation in optically pure form.[3]

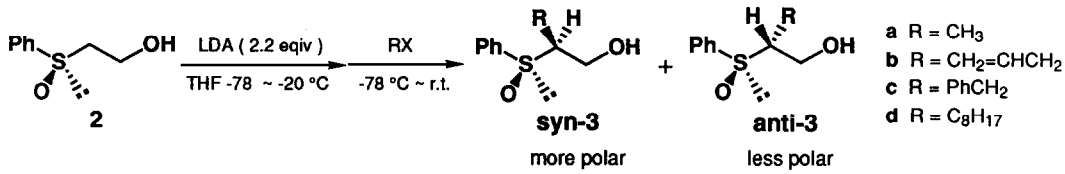


1



2

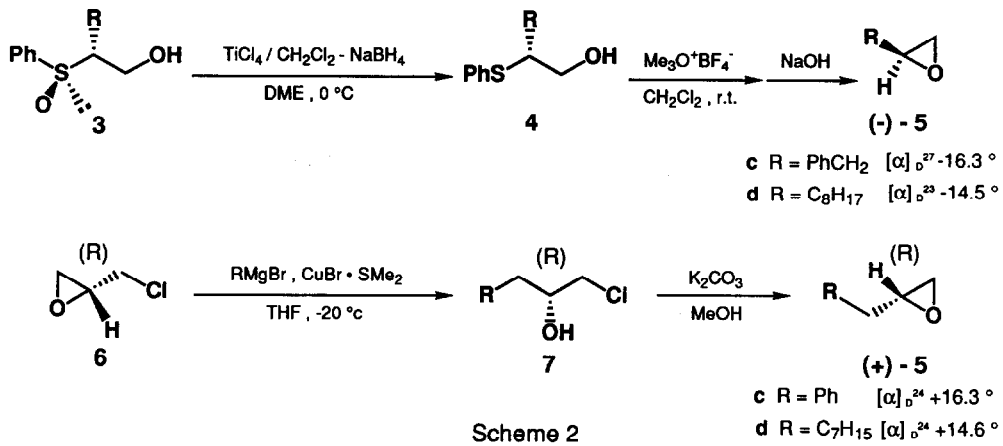
To a solution of **2**[4] in THF was added 2.2 equiv of lithium diisopropyl amide stirring at -78 °C. The reaction mixture was warmed to -20 °C, kept at that temperature for 2 h, and cooled again to -78 °C. Then, an alkyl halide was added dropwise and the resulting solution was gradually warmed to the ambident temperature during 1 h. The usual work-up afforded 2-alkyl-2-phenylsulfinylethanol in good yield (Scheme 1 and Table I). In all cases two possible diastereomers were formed, and the ratios were determined by ^{1}H-NMR. In case of **3a** the signals due to the methyl group were observed as two doublets (δ 0.92 ppm for syn, 1.19 ppm for anti). Concerning the others ^{1}H-NMR spectra were measured after acetylation and the two stereoisomers were identified by acetyl protons: **3b**; 2.04 and 1.85, **3c**; 2.03 and 1.84, **3d**; 2.03 and 1.82 ppm for syn and anti isomer, respectively. The configuration of the newly introduced asymmetric carbon (α to sulfinyl group) was determined as follows. In the case of R = $PhCH_2$ and R = C_8H_{17},



Scheme 1

Table I. Alkylation of 2-Phenylsulfinylethanol

Run	Base	RX	Yield(%)	syn:anti
1	LDA	CH_3I	85	7:1
2	LDA	$CH_3OSO_2CF_3$	95	6.9:1
3	n-BuLi	CH_3I	59	6.7:1
4	LDA	$CH_2=CHCH_2Br$	78	6.9:1
5	LDA	$PhCH_2Br$	85	6.6:1
6	LDA	$C_8H_{17}I$	64	1:1.7



Scheme 2

the two diastereomers were separated by TLC and the less polar ones were derived to epoxides as shown in Scheme 2. Reduction of sulfoxide to sulfide (**4**) by $TiCl_4/NaBH_4$,[5] formation of sulfonium salt by the aid of Meerwein reagent followed by treatment with a base resulted in the formation of (-)-1,2-epoxy-3-phenylpropane[6] (**5c**) $[\alpha]_D^{27}$ -16.3° (c 0.37, Et_2O) and (-)-1,2-epoxydecane (**5d**)[7] $[\alpha]_D^{23}$ -14.5° (c 0.47, Et_2O), respectively. On the other hand, (+)-(R)-epichlorohydrin (**6**) $[\alpha]_D^{23}$ -31.6° (c 1.33, MeOH)[8] was converted to the same epoxides (**5**),[9] which exhibited the opposite sign of specific rotation, indicating that the absolute configuration of (-)-**5** is S. Thus it is concluded that the absolute configuration of asymmetric carbons of less polar **3c** and **3d** are R, relative configuration being anti. Concerning

the methylation product (**3a**), the major isomer was assigned to be syn by comparing the ^{1}H-NMR with that of an authentic specimen.[10] As for **3b** (R = allyl), the relative configuration of two stereoisomers have been estimated by comparing the chemical shifts of acetylated derivatives with those of **3c** and **3d**. Thus it can be concluded that in most cases, electrophiles substituted pro-(S) proton of the α-methylene of **2**, although the selectivity of the reaction of octyl iodide is opposite.

The stereochemistry of the reaction can be interpreted as follows. The first one equiv of the base will react with the hydroxyl proton of **2** to form lithium alkoxide, which will form a six-membered ring by chelation.[11] Then the second molecule of the base attacks the methylene group α to sulfinyl to form the dianion. Although, four isomers (**A** - **D**) are possible for the anion as illustrated in Fig. 1, two of which (**C** and **D**) are negligible, because the sterically bulky phenyl group occupies the axial position. Thus the conformers **A** and **B** will decide the fate of the dianion. It is well documented that the alkyl halides attack the anion from the backside of the C-Li bond.[12] Thus, **A** and **B** will afford syn and anti isomer, respectively. The faster the reaction of the dianion with the alkylating reagent, more exactly the ratio of products reflect the ratio of intermediary isomer **A** and **B**. The fact that the syn-alkylated products **syn-3** are dominant in the case of reaction of relatively reactive electrophiles (Run 1 to 5), indicates that the more favorable configuration of the dianion is **A**. This conclusion is consistent to the generally accepted proposal that the configuraion of carbanion is preferentially controlled by the electronic demand of the chirality of sulfinyl group, i.e., the anionic orbital being

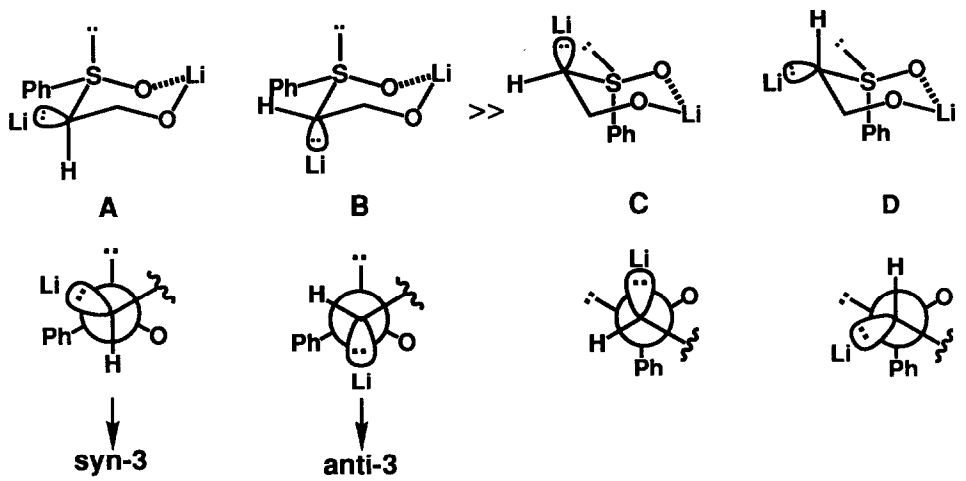


Fig.1 Possible Conformations for the Dianion of 2 - Phenylsulfinylethanol

trans to the sulfinyl oxygen.[13] On the other hand, anion **B** is supposed to be more reactive than **A**, because the electrophile can approach the reaction center from the less hindered exo site of the ring in the case of **B**. Thus, when the steric bulkiness of the alkyl halides are large, the contribution of **B** would become relatively important. These assumptions well explain the low stereoselectivity of the reaction of octyl iodide.

In conclusion, the stereochemistry of the alkylation of 2-phenylsulfinylethanol is well accounted for by thermodynamic stability and reactivity of six-membered chelation intermediate.

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