Substituent Effect on the Enantioface-Differentiating Reaction of (*R*)-[Lithiomethyl *p*-Tolyl Sulfoxide] with *m*- or *p*-Substituted Acetophenones

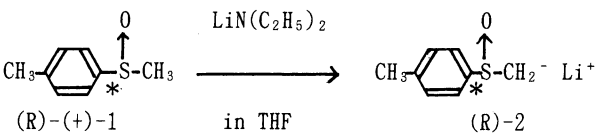
Norio KUNIEDA,* Junzo NOKAMI,† and Masayoshi KINOSHITA
Department of Bioapplied Chemistry, Faculty of Engineering,
Osaka City University, Sumiyoshi-ku, Osaka 558
†Okayama University of Science, Radai, Okayama 700
(Received January 16, 1991)

When lithiomethyl *p*-tolyl sulfoxide derived from (*R*)-(+)-[methyl *p*-tolyl sulfoxide] was allowed to react with acetophenones which have a variety of *m*- or *p*-substituents, the corresponding diastereometic mixture of β-hydroxy sulfoxides (R_sS_c and R_sR_c) was produced. The degree of enantioselectivity was affected by the nature of the substituent on benzene ring. The logarithms of the R_sS_c/ R_sR_c values thus obtained gave a good correlation with Hammett's σ values, affording a negative straight line. The results have been discussed in view of the stereochemical cource of the reaction.

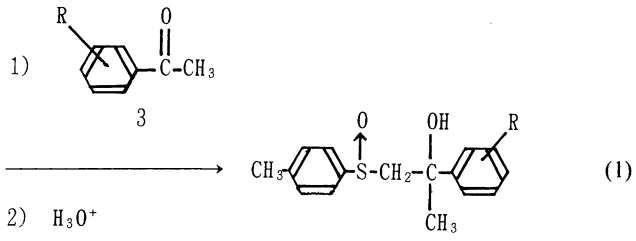
Recently electronic effects, as well as steric bulk, have been discussed as an important factor which controls the stereochemical course of the asymmetric induction in certain asymmetric reactions.[1] During the course of our research concerned with the asymmetric induction by chiral sulfinyl group, recently, we have found that the enantiomer-differentiating reaction[2] of racemic lithiomethyl *p*-tolyl sulfoxide with *m*- or *p*-substituted (−)-[(*R*)-menthyl benzoate]s is markedly affected by the polar effect of the substituent on benzene ring.[3b] This finding prompted us to investigate the enantioface-differentiating reaction[2] of lithiomethyl *p*-tolyl sulfoxide, derived from (*R*)-(+)-[methyl *p*-tolyl sulfoxide] and lithium diethylamide, with *m*- or *p*-substituted acetophenones. We have now found that the present reaction is also affected by the nature of the substituent on benzene ring. In order to discuss the polar effect of the substituents on the stereochemistry, in this paper, we compile substantial amounts of date of this enantioface-differentiating reaction.

Results and Discussion

Treatment of lithiomethyl *p*-tolyl sulfoxide ((*R*)-**2**), derived from (*R*)-(+)-[methyl *p*-tolyl sulfoxide] (**1**) and lithium diethylamide, with 1.04 equivalents of acetophenones (**3**) in tetrahydrofuran (THF) at −78 °C displayed the feature of an enatioface-differentiating reaction, affording the corresponding diastereomeric mixture of β-hydroxy sulfoxide (**4**) in good yields (>99%) (Eq. 1).[4]



(R)-(+)-1 (R)-2



(1)

4 (R_sS_c and R_sR_c)

(The star indicates chiral center)

3 and **4**

a R=*p*-CH_3O	**b** R=*p*-*t*-C_4H_9	**c** R=*p*-CH_3
d R=*m*-CH_3	**e** R=H	**f** R=*m*-CH_3O
g R=*p*-Cl	**h** R=*p*-Br	**i** R=*m*-Cl
j R=*p*-CF_3	**k** R=*p*-CN	

The ratio of the diastereoisomers in **4** (R_sS_c-**4** and R_sR_c-**4**) was supported by the ^{1}H NMR spectrum which exhibited resonances at δ=1.51—1.64 and δ=1.88—1.95 due to two kinds of diastereotropic methyl groups. In a typical example, the ^{1}H NMR spectrum of the mixture of diastereoisomers of **4e** showed the resonances at δ=1.59 and 1.91. By integration of the respective signals, the percent ratio of the diastereoisomers was found to be 25 : 75.

In order to determine the configuration of the predominant diastereoisomer, we have tried two examinations. When 1-(*p*-tolylsulfinyl)-2-phenyl-2-butanol (**5**), derived from the reaction of ethyl phenyl ketone with (*R*)-**2**, was treated with Raney nickel[5] in ethanol at 50 °C for 30 min, the dextrorotatory 2-phenyl-2-butanol ($[\alpha]_D^{20}$ +5.3° (acetone)) was obtained. Since the specific rotation of (*R*)-2-phenyl-2-butanol is reported to be $[\alpha]_D^{27}$ +17.45° (neat),[6] the absolute configuration of the predominant diastereoisomer should be R_sS_c. In the similar manner, treatment of 2-(*p*-tolylsulfinyl)-1-cyclohexyl-1-phenylethanol, derived from the reaction of cyclohexyl phenyl ketone with (*R*)-**2**, with Raney

Table 1. Results of the Enantioface-Differentiating Reaction of (*R*)-[Lithiomethyl *p*-Tolyl Sulfoxide] ((*R*)-**2**) with Substituted Acetophenones (**3**)[a]

Acetophenones (**3**) R		Ratio of diastereoisomers R_sS_c : R_sR_c[b]	$\Delta\Delta G^{\ddagger}$ kJ mol^{-1}	$\Delta\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta\Delta S^{\ddagger}$ J K^{-1} mol^{-1}
p-CH_3O (**3a**)	**4a**	87 : 13	3.08		
p-*t*-C_4H_9 (**3b**)	**4b**	85 : 15	2.81		
p-CH_3 (**3c**)	**4c**	80 : 20	2.26	−2.69	−2.23
m-CH_3 (**3d**)	**4d**	78 : 22	2.06		
H (**3e**)	**4e**	75 : 25	1.78	−2.28	−2.54
m-CH_3O (**3f**)	**4f**	74 : 26	1.70		
p-Cl (**3g**)	**4g**	69 : 31	1.30	−1.70	−2.03
p-Br (**3h**)	**4h**	67 : 33	1.15		
m-Cl (**3i**)	**4i**	62 : 38	0.80		
p-CF_3 (**3j**)	**4j**	60 : 40	0.66		
p-CN (**3k**)	**4k**	53 : 47	0.20		

a) In THF at −78 °C. b) Average values of 2—6 experiments.

nickel yielded (*R*)-rich 1-cyclohexyl-1-phenylethanol ($[\alpha]_D^{20}$ +15.2° (acetone)),[7] suggesting that the absolute configration of the predominant diastereoisomer is R_sS_c. On the basis of these experiments, we considered that the methyl signal of ^{1}H NMR spectrum at the lower field (δ=1.88—1.95) showed the methyl group of the R_sS_c diastereoisomer. The results for the reaction of (*R*)-**2** with eleven acetophenones (**3**) possessing a variety of *m*- or *p*-substituents are summarized in Table 1.

The degree of the enantioselectivity of the reaction was sensitive to the reaction temperature. The decrease in temperature favored the formation of the predominant diastereoisomer (R_sS_c-**4**). The diagram correlating log R_sS_c/R_sR_c against $1/T$ showed a linear positive slope over 78° temperature range (from 0 to −78 °C). The $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values obtained from the reactions from the **3c**, **3e**, and **3g** are also listed in Table 1. These exhibited small negative values.

As shown in Table 1, the ratio of R_sS_c-**4** vs. R_sR_c-**4** obtained was markedly affected by the nature of the substituent R. The ratio varies from 87 : 13 to 53 : 47. In general, the electron-releasing substituents trend to increase the enantioselectivity. The best result has been obtained from the reaction of (*R*)-**2** with **3a**(R=*p*-CH_3O), affording R_sS_c-**4a** in a 74% optical yield.

When the logarithms of the R_sS_c/R_sR_c values thus obtained were plotted against Hammett's σ values,[9] a negative straight line was obtained as shown in Fig. 1, with the correlation coefficient r=0.981. This fact clearly indicates that the enantioselectivity on the present reaction of (*R*)-**2** with **3** should be affected by the polar effect of the substituent R.

In our previous report concerning the enantiomer-differentiating reaction of racemic lithiomethyl *p*-tolyl sulfoxide with (−)-[(*R*)-menthyl benzoate]s,[3] we proposed a six-membered cyclic transition state which was assisted by an electrophilic assistant (a chelation) of the lithium cation on the α-lithio sulfoxide toward the electrophile as proposed by Marquet et al.[10] and Biellmann et al.[11] Actually, the reaction of (*R*)-**2** with **3** was tried in the presence of 4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]eicosane (Kryptofix 211)[13] as an trapping agent of the lithium cation. The results are listed in Table 2. The addition of 1.1 equivalents of Kryptofix 211 to the reaction of (*R*)-**2** with **3a** or **3g** drastically decreases the ratio of the diastereoisomers obtained. This result seems to support our prediction described above.

Table 2. Results of the Reaction of (*R*)-**2** with **3a** and **3g** in the Presence of a Lithium Cation Trapping Agent[a]

Acetophenones (**3**)	Ratio of R_sS_c-**4** and R_sR_c-**4**	
	None	Kryptofix 211[b]
3a	**4a** 87 : 13	66 : 34
3g	**4g** 69 : 31	53 : 47

a) In THF, at −78 °C. b) 1.1 Equivalents based on (*R*)-**2**.

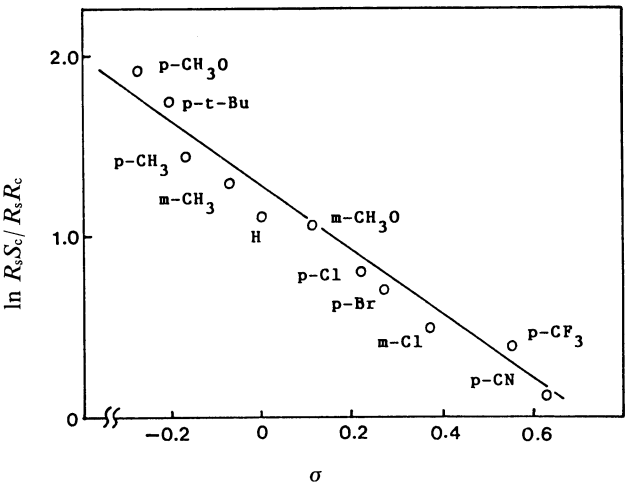
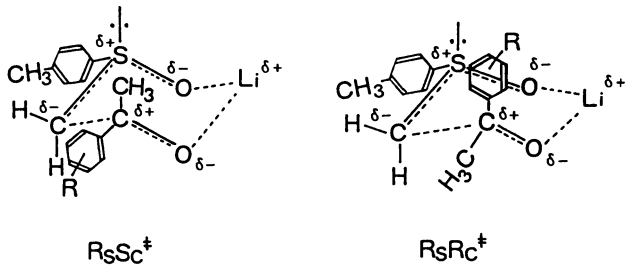


Fig. 1. Relationship between ln R_sS_c/R_sR_c values and Hammett's σ values.

According to this proposal, as well as the steric requirements,[12] the reaction of (*R*)-**2** with **3** affording R_sS_c-**4** preferentially takes a transition state $R_sS_c^{\ddagger}$ in Scheme 1. The results for the direction of enantioselec-



Scheme 1.

tivity of this reaction agree fairly well with this prediction. However, the change of the degree of enantioselectivity owing to the substituent R on benzene ring can not be interpreted on the basis of this prediction. We suppose that the two alternative transition states, $R_sS_c^*$ and $R_sR_c^*$, may be postulated according to the polar character of the substituent R.

The reaction of (*R*)-**2** with **3** which has the electron-releasing substituent proceeds through the transition state $R_sS_c^*$ which forms the chelations by lithium cation, because the electron-releasing substituent should contribute to the formation of a rigid transition state. On the other hand the reaction of (*R*)-**2** with **3** which has the electron-withdrawing substituent seems to proceed through the transition state $R_sR_c^*$. In the case of the transition state $R_sR_c^*$, we have now considered that an interaction between the electron-deficient phenyl group and the lone pair of the chiral *p*-tolyl sulfinyl group would be effected to from a tight transition state. Namely, a gradual change of the transition state from $R_sS_c^*$ to $R_sR_c^*$ with the increase of the electron-withdrawing character of the substituent R is considered.

In summary, the enantioface-differentiating reaction of (*R*)-**2** with **3** was markedly affected by the nature of the substituent. We suppose at present that the apparent difference in the mode of the transition states, $R_sS_c^*$ and $R_sR_c^*$, arises from the polar effect exserted by the substituent R. Further investigations are now underway in an effort to obtain more detailed knowledge of the stereochemistry of this reaction.

Experimental

General. The ^{1}H NMR spectra were measured with a JASCO PS-100 type or a PX-400 type spectrometer; the chemical shifts are reported in δ units, using tetramethylsilane as the internal reference. The optical rotation obtained were determined by using a JASCO DIP-360 type polarimeter. The mass spectra were taken on a JEOL JMS 06 spectrometer.

Starting Material. (*R*)-(+)-[Methyl *p*-tolyl sulfoxide] (**1**) was prepared from (−)-menthyl (*S*)-*p*-toluenesulfinate, mp 107—107.5 °C $[\alpha]_D^{25}$ −200° (*c* 0.520, acetone),[14] with methylmagnesium iodide according to the method developed by Andersen;[16] mp 74.5 °C, $[\alpha]_D^{20}$ +146° (*c* 0.460, acetone) [lit,[17] mp 73—74.5 °C, $[\alpha]_D$ +145.5° (acetone)]. (−)-Menthol of commercial grade (Hoei Chemical, Osaka) was used without further purification. Acetophenones (**3a**—**3k**) of commercial grade (Tokyo Kasei Co., Ltd. and Aldrich) were distilled freshly each time. Tetrahydrofuran (THF) was purified by fresh distillation from a solution of sodium benzophenone ketyl before use in all reactions. Butyllithium was purchased as a 1.56 mol dm^{-3} solution in hexane (Mitsuwa Chemical Co., Ltd., Osaka). Kryptofix 211 was obtained from Merck and used without further purification.

Preparation of (*R*)-[Lithiomethyl *p*-Tolyl Sulfoxide] ((*R*)-2). Into a 50 cm^3 two-necked, round-bottomed flask equipped with a rubber septum, a magnetic stirring bar, and a nitrogen-inlet tube were placed 10 cm^3 of dry THF, 3.13 mmol of butyllithium in hexane, and 0.33 ml (3.13 mmol) of diethylamine through the rubber septum via a syringe under nitrogen at 0 °C. The flask was cooled to −78 °C, a solution of 2.59 mmol of (*R*)-(+)-[methyl *p*-tolyl sulfoxide] in 3 cm^3 of dry THF was added, and the solution was stirred vigorously for 1 h at 0 °C.

Reaction of (*R*)-2 with Methyl *p*-Methoxyphenyl Ketone (3a). A solution of methyl *p*-methoxyphenyl ketone (**3a**) (2.70 mmol) in 2 cm^3 of dry THF was injected via a syringe, drop by drop, into the solution of (*R*)-**2** at −78 °C with vigorous stirring. The stirring was continued for 1 h at −78 °C. To the reaction mixture 5 cm^3 of saturated aqueous ammonium chloride solution was added and then 30 cm^3 of water and extracted with chloroform(3×30 cm^3). The extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The acetophenone remaining in the residue was removed under a high diminished pressure, giving the analytically pure diastereomeric mixture of β-hydroxy sulfoxides (**4a**) in a 99.4% yield, which was subjected to ^{1}H NMR spectroscopic measurement. ^{1}H NMR ($CDCl_3$) δ=1.51, 1.88 (d, 3H, $-CH_3$), 2.38 (s, 3H, $-CH_3$), 3.84 (s, 3H. $-OCH_3$), 4.07, 4.20 (dd, *J*=14 Hz, 2H, $-CH_2-$), 6.90—7.95 (m, 8H, aromatic). This compound exhibited the following mass and elemental analysis data. MS: 304 (M^+). Found: C, 67.12; H, 6.70%. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H. 6.62%.

Reaction of (*R*)-2 with the Other Substituted Acetophenones (3b—3k). In the manner similar to that used for the preparation of **4a** the treatment of 2.59 mmol of (*R*)-**2** with 2.70 mmol of the substituted acetophenone (**3b**—**3k**) afforded the corresponding β-hydroxy sulfoxides (**4b**—**4k**) in a good yield (>99%). These β-hydroxy sulfoxides exhibited the follwing properties.

4b; ^{1}H NMR ($CDCl_3$): δ=1.31 (s, 9H,$-(CH_3)_3$), 1.52, 1.90, (d, 3H, $-CH_3$), 2.37(s, 3H, $-CH_3$), 4.07, 4.21 (dd, *J*=14 Hz, $-CH_2-$), 7.10—7.84 (m, 8H. aromatic). MS: 330(M^+).

Found: C, 72.80; H, 7.89%. Calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93%.

4c; ^{1}H NMR ($CDCl_3$) δ=1.53, 1.91 (d, 3H, $-CH_3$), 2.39 (s, 6H, 2×$-CH_3$), 4.07, 4.22 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.17—7.90 (m, 8H, aromatic). MS: 288(M^+).

Found: C, 70.77; H, 6.93%. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99%.

4d; ^{1}H NMR ($CDCl_3$) δ=1.53, 1.92 (d, 3H, $-CH_3$), 2.38 (s, 6H, 2×$-CH_3$), 4.08, 4.22 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.17—7.83 (m, 8H, aromatic). MS: 288(M^+).

Found: C, 70.83; H, 7.03%. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99%.

4e; ^{1}H NMR ($CDCl_3$) δ=1.59, 1.91 (d, 3H, $-CH_3$) 2.35 (s, 3H, $-CH_3$), 4.08, 4.22 (dd, *J*=14 Hz, 2H, $-CH_2$), 7.15—7.85 (m. 8H, aromatic). MS: 274 (M^+).

Found: C, 70.14; H, 6.68%. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61%.

4f; ^{1}H NMR ($CDCl_3$) δ=1.60, 1.92 (d, 3H, $-CH_3$), 2.38 (s, 3H, $-CH_3$), 3.85 (s, 3H, $-CH_3$), 4.08, 4.22 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.00—7.95 (m, 8H, aromatic). MS: 304(M^+).

Found: C, 67.18; H, 6.73%. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62%.

4g; ^{1}H NMR ($CDCl_3$) δ=1. 60, 1.93 (d, 3H, $-CH_3$), 2.37 (s, 3H, $-CH_3$), 4.09, 4.22 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.17—7.90 (m, 8H, aromatic). MS: 309(M^+).

Found: C, 62.45; H, 5.66%. Calcd for $C_{16}H_{17}O_2SCl$: C, 62. 23; H, 5.55%.

4h; ^{1}H NMR ($CDCl_3$) δ=1.61, 1.93 (d, 3H, $-CH_3$), 2.38 (s, 3H, $-CH_3$), 4.10, 4.24 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.21—7.89 (m, 8H, aromatic). MS: 353(M^+).

Found: C, 54.53; H, 4.97%. Calcd for $C_{16}H_{17}O_2SBr$: C, 54.40; H, 4.85%.

4i; ^{1}H NMR ($CDCl_3$) δ=1.62, 1.93 (d, 3H, $-CH_3$), 2.39 (s, 3H, $-CH_3$), 4.11, 4.25 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.24—7.85 (m, 8H aromatic). MS: 309 (M^+).

Found: C, 62.33; H, 5.62%. Calcd for $C_{16}H_{17}O_2SCl$: C, 62.23; H, 5.55%.

4j; ^{1}H NMR ($CDCl_3$) δ=1.62, 1.94 (d, 3H, $-CH_3$), 2.40 (s, 3H, $-CH_3$), 4.11, 4.26 (dd, *J*=14 Hz, 2H, $-CH_2-$), 7.24—7.87 (m, 8H, aromatic). MS: 342 (M^+).

Found: C, 59.39; H, 5.12%. Calcd for $C_{17}H_{17}O_2SF_3$: C, 59.64; H, 5.01%.

4k; ^{1}H NMR ($CDCl_3$) δ=1.64, 1.95 (d, 3H, $-CH_3$), 2.41 (s, 3H, $-CH_3$), 4.12, 4.26 (dd, *J*=14 Hz, 2H,$-CH_2-$), 7.25—7.90 (m, 8H, aromatic). MS: 299(M^+).

Found: C, 68.51; H, 5.79%. Calcd for $C_{17}H_{17}O_2SN$: C, 68.20; H, 5.72%.

Reductions of 1-(*p*-Tolylsulfinyl)-2-phenyl-2-butanol (5) and 2-(*p*-Tolylsulfinyl)-1-cyclohexyl-1-phenylethanol (6) by Raney Nickel. The diastereomeric mixture of **5** or **6** (1 mmol) was treated with Raney nickel[5] in dry ethanol at 50 °C for 30 min. The reaction mixture was filtered cautiously, and the filtrate was evaporated in vacuo. The oily residue was passed through the column packed with 5 g of 200 mesh activated alumina using methylene dichloride as the eluent. The analytically pure dextrorotatory 2-phenyl-2-butanol, $[\alpha]_D^{20}$ +5.3° (*c* 1.00, acetone), and 1-cyclohexyl-1-phenylethanol, $[\alpha]_D^{20}$ +15.2° (*c* 1.00, acetone), were obtaind in an 82.5% and an 80.7% yields, respectively. The structural assignments of these alcohols were confirmed by mass spectrometer and elemental analysis.

2-Phenyl-2-butanol; MS: 150(M^+). Found: C, 79.79; H, 9.40%. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39%.

1-Cyclohexyl-1-phenylethanol; MS: 204(M^+). Found: C, 82.50; H, 9.66%. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87%.

References

1) For example: H. B. Kagan and J. G Fiaud, "New Approaches in Asymmetric Synthesis, " in "Topics in Stereochemistry," ed by E. L. Eliel and N. Allinger, Interscience Publ. New York, N. Y. (1978), Vol. 10, p. 175; and references cited therein.

2) Y. Izumi, *Angew. Chem., Int. Ed. Engl.*, **10**, 871 (1971); "Chemistry of Asymmetric Reaction," Kagaku Sosetsu-4, Chem. Soc. Jpn., Tokyo (1974).

3) a) N. Kunieda, A. Suzuki, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **54**, 1143 (1981); b) N. Kunieda, T. Nakanishi, and M. Kinoshita, *ibid.*, **62**, 2229 (1989).

4) a) G. Tsuchihashi, S. Iriuchijima, and M. Ishibashi, *Tetrahedron Lett.*, **1972**, 4605; b) G. Tsuchihashi, S. Iriuchijima, and K. Maniwa, *ibid.*, **1973**, 3389; c) N. Kunieda, M. Kinoshita, and J. Nokami, *Chem. Lett.*, **1977**, 289.

5) W-4 type Raney nickel (prepared from 2 g of nickel-aluminium (45% nickel) and 2.5 g of sodium hydroxide).

6) H. H. Zeiss, *J. Am. Chem. Soc.*, **73**, 2391 (1951).

7) (*S*) -1-Cyclohexyl-1-phenylethanol showed the levorotatory optical activity, $[\alpha]_D$ −20.6° ($CHCl_3$).[8]

8) T. D. Inch, G. J. Levis, G. L. Sainsburg, and D. J. Sellews, *Tetrahedron Lett.*, **1969**, 3657.

9) The σ value used here is that reported by Jaffe; B. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

10) G. Chassaing, R. Lett, and A. Marquet, *Tetrahedron Lett.*, **1978**, 471; G. Chassaing and A. Marquet, *Tetrahedron*, **34**, 1399 (1978).

11) J. F. Biellmann and J. J. Vicens, *Tetrahedron Lett.* **1987**, 467.

12) J. M. Lehn and J. P. Sauvage, *J. Chem. Soc., Chem. Commun.*, **1971**, 440.

13) V. Prelog, *Helv. Chim. Acta*, **36**, 708 (1953); D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); T. J. Leitereg and D. J. Cram, *ibid.*, **90**, 4019 (1968).

14) (−)-Menthyl (*S*)-*p*-toluenesulfinate was prepared by the reaction of (−)-menthol, $[\alpha]_D^{20}$ −50° (EtOH), with *p*-toluenesulfinyl chloride according to the method developed by Phillips.[15]

15) H. Pillips, *J. Chem. Soc.*, **127**, 2552 (1925).

16) K. K. Andersen, *Tetrahedron Lett.*, **1962**, 93.

17) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A.L. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 858 (1965).