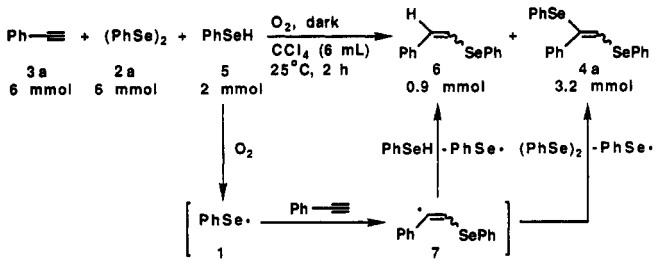
Scheme I



NMR (68 MHz, $CDCl_3$) δ 125.99 (p), 127.37 (p), 127.41 (p), 128.23 (m and =CH), 128.60 (o), 129.13 (m), 129.22 (m), 130.51 (ipso), 130.65 (ipso), 131.16 (ipso), 132.06 (o), 133.03 (o), 139.54 (=*C*); ^{77}Se NMR (51.5 MHz, $CDCl_3$) δ 406.35 (J_{Se-Se} = 27.6 Hz), 508.94 (J_{Se-Se} = 27.6 Hz); IR (NaCl) 3052, 1576, 1475, 1438, 1070, 1021, 736, 689 cm^{-1}; MS (EI) *m/e* = 416 (M^+, 71). Anal. Calcd for $C_{20}H_{16}Se_2$: C, 57.99; H, 3.89. Found: C, 57.71; H, 4.07. ***Z* isomer**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.06–7.57 (m, 16 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 126.61 (p), 127.27 (m), 127.49 (p), 127.84 (p), 128.26 (m), 129.09 (m), 129.38 (o), 130.33 (ipso), 130.86 (o), 131.00 (ipso), 131.49 (ipso), 133.20 (o), 136.04 (=*C*H), 140.52 (=*C*); ^{77}Se NMR (51.5 MHz, $CDCl_3$) δ 390.11 (J_{Se-Se} = 80 Hz), 436.35 (J_{Se-Se} = 80 Hz); IR (NaCl) 3055, 1577, 1476, 1438, 1022, 733, 690 cm^{-1}; MS (EI) *m/e* = 416 (M^+, 71). Anal. Calcd for $C_{20}H_{16}Se_2$: C, 57.99; H, 3.89. Found: C, 58.07; H, 4.05.

Radical Cyclization of Enyne 3h Induced by the Phenylseleno Radical. In a Pyrex glass tube were placed enyne **3h** (0.5 mmol), diphenyl diselenide **2a** (0.5 mmol), and benzene (1 mL). The tube was sealed under reduced pressure. The mixture was irradiated with a tungsten lamp (500 W). The solvent was then evaporated in vacuo. The residue was purified by preparative TLC on silica gel (*n*-hexane/Et_2O, 10:1) to provide 197 mg (70%) of cyclic **4h′** along with 22 mg (8%) of the adduct **4h**. **4h′**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.21 (t, 3 H, *J* = 7.0 Hz), 1.24 (t, 3 H, *J* = 7.0 Hz), 2.11 (dd, 1 H, *J* = 9.5, 13.1 Hz), 2.78 (dd, 1 H, *J* = 5.8, 11.9 Hz), 2.87–3.22 (m, 5 H), 4.17 (q, 2 H, *J* = 7.0 Hz), 4.19 (q, 2 H, *J* = 7.0 Hz), 6.33 (s, 1 H), 7.22–7.29 (m, 6 H), 7.41–7.51 (m, 4 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.92 (OCH_2CH_3), 13.96 (OCH_2CH_3), 32.05 (J_{C-Se} = 32.4 Hz, CH_2SePh), 40.26, 40.45, 43.96, 58.16 (O=C*C*C=O), 61.58 (OCH_2CH_3), 61.61 (OCH_2CH_3), 112.10 (C=*C*H), 126.80 (p), 127.02 (p), 129.03 (m), 129.13 (m), 129.98 (ipso), 131.08 (ipso), 131.82 (o), 132.92 (o), 147.43 (*C*=CH), 171.13 (*C*=O), 171.23 (C=*O*); IR (NaCl) 3056, 2980, 2933, 1731, 1578, 1477, 1438, 1250, 1179, 1022, 737, 691 cm^{-1}; MS (EI) *m/e* = 552 (M^+, 0.6). Anal. Calcd for $C_{25}H_{28}O_4Se_2$: C, 54.60; H, 5.13. Found: C, 54.46; H, 5.46.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan. Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining NMR and mass spectra with JEOL JNM-GSX-400 and JEOL JMS-DX303 instruments, respectively. We thank Mr. Ryoichi Obayashi at Osaka University for experimental assistance.

Registry No. **2a**, 1666-13-3; **3a**, 536-74-3; **3b**, 693-02-7; **3c**, 107-19-7; **3d**, 1066-54-2; **3e**, 4250-81-1; **3f**, 1942-45-6; **3g**, 78-80-8; **3h**, 101268-55-7; **3i**, 133788-02-0; **3j**, 51580-41-7; (*E*)-**4a**, 132330-37-1; (*Z*)-**4a**, 7392-13-4; (*E*)-**4a′**, 134904-95-3; (*Z*)-**4a′**, 134904-96-4; (*E*)-**4b**, 134904-97-5; (*Z*)-**4b**, 101349-67-1; (*E*)-**4c**, 134904-98-6; (*Z*)-**4c**, 134904-99-7; (*E*)-**4d**, 134905-00-3; (*Z*)-**4d**, 134905-01-4; (*E*)-**4e**, 134905-02-5; (*Z*)-**4e**, 134905-03-6; (*E*)-**4f**, 134905-04-7; (*Z*)-**4f**, 134905-05-8; (*E*)-**4g**, 134905-06-9; (*Z*)-**4g**, 134905-07-0; **4h**, 134905-09-2; **4h′**, 134905-08-1; **4i**, 134905-11-6; **4i′**, 134905-10-5; **4j**, 134905-13-8; **4j′**, 134905-12-7; **6**, 96983-85-6; (*n*-BuSe)$_2$, 20333-40-8.

Supplementary Material Available: Analytical data on the compounds prepared (IR, ^{1}H NMR, ^{13}C NMR, and mass spectra; elemental analyses) (12 pages). Ordering information is given on any current masthead page.

Regiospecific Ortho Lithiation of *o*-Halophenyl *p*-Tolyl Sulfoxides and Synthesis of Meta-Substituted Optically Active Aryl Alcohols

Satoshi Ogawa and Naomichi Furukawa*

Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

Received March 28, 1991

The regiospecific introduction of substituents onto aromatic rings has been an important objective in synthetic organic chemistry. Electrophilic substitution is one of the common procedures to give various substituted aromatic compounds, but this method is not suited to some substitution patterns.[1] Recently, regiospecifically directed metalation of aromatic rings has attracted attention, and many functional groups that orient the lithiation to the ortho position of the aromatic ring have been reported.[2] During studies on the lithiation reactions of pyridyl sulfoxides, we found that regiospecific ortho lithiation of aryl pyridyl sulfoxides afforded the corresponding aryl ortho-substituted pyridyl sulfoxides in moderate yields.[3] In this note, we report a new ortho-lithiation reaction of diaryl sulfoxides that allows the arylsulfinyl group to be easily removed after introduction of enantiomerically enriched alcohol groups onto the benzene ring with optically active sulfoxides.

Results and Discussion

When diphenyl sulfoxide was allowed to react with lithium diisopropylamide (LDA) at −78 °C in THF and subsequently with acetaldehyde, 2-(1-hydroxyethyl)phenyl phenyl sulfoxide was obtained in 60% yield, which was found to be a mixture of two diastereomers in the ratio of 63:37. However, similar treatment of phenyl *p*-tolyl sulfoxide with LDA and acetaldehyde gave mixtures of three sulfoxides, one of which was found to be alkylated at the ortho position of phenyl group, another at the ortho position of *p*-tolyl group, and the other at the methyl group of *p*-tolyl group. In the course of further studies on the regiospecific lithiation of diaryl sulfoxides and also asymmetric induction in the reactions of the lithiated intermediates with aldehydes, *o*-halophenyl *p*-tolyl sulfoxides (**1a**, X = Cl; **1b**, X = Br; **1c**, X = I) together with optically active sulfoxides (*S*)-(−)-**1a** and (*S*)-(−)-**1b** were synthesized.[4] When the sulfoxides **1a–c** were treated with organolithium reagents and then with acetaldehyde, the products changed dramatically depending on the sulfoxide and organolithium reagents employed. Namely, the sulfoxide **1a** gave solely the sulfinyl transfer product **4**, which was racemized completely, while the sulfoxide **1b** gave a

(1) (a) Norman, R. O. C.; Taylor, R. *Electrophilic Substitution in Benzenoid Compounds*; Elsevier: Amsterdam, 1965. (b) Olah, G. A. *Friedels-Crafts and Related Reaction*; Interscience: New York, 1963. (c) Pearson, D. E.; Buehler, C. A. *Synthesis* **1972**, 533. (d) Effenberger, F. *Ibid.* **1980**, 151.

(2) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Katritzky, A. R.; Lue, P. *J. Org. Chem.* **1990**, *55*, 74. (c) Negishi, E.; Zhang, Y.; Shimoyama, I.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018. (d) Alabaster, R. J.; Cottrell, I. F.; Hands, D.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *Synthesis* **1989**, 598. (e) Lee, D.; Still, W. C. *J. Org. Chem.* **1989**, *54*, 4715. (f) Mills, R. J.; Taylor, N. J.; Snieckus, V. *Ibid.* **1989**, *54*, 4372. (g) Mills, R. J.; Snieckus, V. *Ibid.* **1989**, *54*, 4386. (h) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (i) Beak, P.; Snieckus, V. *Ibid.* **1982**, *15*, 306.

(3) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1989**, *30*, 7091.

(4) (a) Anderson, K. K. *Tetrahedron Lett.* **1962**, 93. (b) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637. (c) Herbrandson, H. F.; Dickerson, R. T., Jr.; Weinstein, J. *Ibid.* **1959**, *81*, 4102.

0022-3263/91/1956-5723$02.50/0

Scheme I

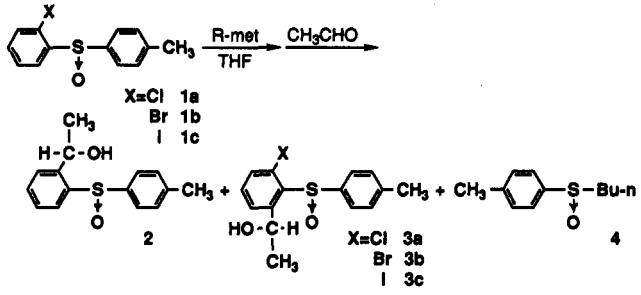


Table I. Reactions of *o*-Halophenyl *p*-Tolyl Sulfoxides (1a–c) with *n*-BuLi or LDA

X	R-met	yield % 2	3	4	diastereomer ratio
Cl[a]	*n*-BuLi			90[c]	
Cl[a]	LDA		94		69:31
Br[b]	*n*-BuLi	40		34[c]	65:35
Br[b]	LDA		95		71:29
I	*n*-BuLi	92			65:35
I	LDA		59		72:28[d]

[a] $[\alpha]^{25}_D$ −142.0° (optical purity 100%). [b] $[\alpha]^{25}_D$ −112.6° (optical purity 58%). [c] $[\alpha]^{25}_D$ 0°. [d] Determined by ^{1}H NMR.

Table II. Reactions of Lithiated *o*-Chlorophenyl *p*-Tolyl Sulfoxide with Electrophiles

aldehyde	product	yield (%)	diastereomer ratio
C_6H_5CHO	**5a**	95	66:34
p-$CH_3C_6H_4CHO$	**5b**	96	65:35
p-$CH_3OC_6H_4CHO$	**5c**	96	65:35
p-$CF_3C_6H_4CHO$	**5d**	91	63:37

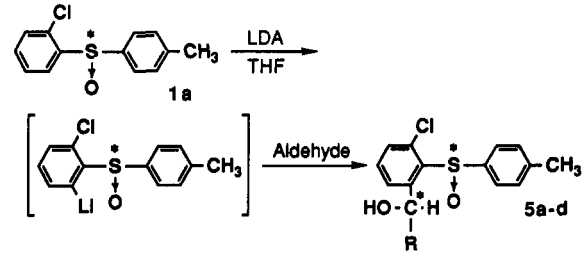
mixture of diastereomeric alcohols **2** and racemized **4**. On the other hand, sulfoxide **1c** afforded only the same diastereomeric mixture of alcohols. When the sulfoxides **1a–c** were treated with LDA at −78 °C, lithiation was found to take place regiospecifically at the 6-position on the *o*-halophenyl ring to give the alcohols **3a–c**, respectively, as diastereomeric mixtures in the ratio of about 7:3. No racemization was observed at the sulfur center of the alcohols **3a** or **3b**. This diastereomeric mixture **3** can be easily separated by silica gel column chromatography. The results are shown in Scheme I and are summarized in Table I. Characterization of the diastereomeric isomers of the alcohol **3a** and **3b** was performed by mp, ^{1}H NMR, IR, mass, and elemental analysis.

Thus, the present results demonstrate that the regiospecific lithiation of *o*-halophenyl sulfoxides can be accomplished by using LDA, but butyllithium induces racemization of the diaryl sulfoxides via a facile ligand exchange reaction at the sulfinyl sulfur atom.[5]

The reactions of the optically pure (*S*)-(−)-**1a** with several aldehydes were carried out following the procedures described above and gave ortho-substituted products **5a–d** in good yields (Scheme II and Table II). The diastereomers were separated quite easily by column chromatography, and their ratios were determined to be from 66:34 to 63:37. The results indicate that diastereomeric selectivity is not significantly influenced by the electronic effect of the substituents on the aldehydes.

After the separation, the sulfinyl group of each diastereomer of **3a** and **5b** could be removed easily by reaction with Grignard or organolithium reagents to afford optically pure 1-chloro-3-(1-hydroxyethyl)benzene (**6**) and 3-chloro-4′-methylbenzhydrol (**7**) in good yields as shown in Scheme III and Table III.

Scheme II



Scheme III

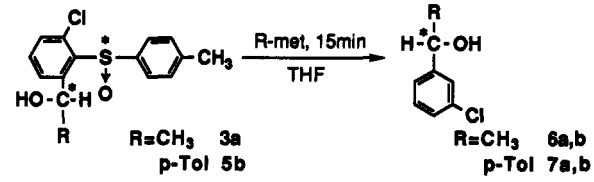


Table III. Desulfinylation Reactions of Sulfoxides 3a and 5b with Grignard or Organolithium Reagents

substrate	R-met	temp (°C)	product	yield (%)	op (%)	config
3a, major	EtMgBr	0	**6a**	91	100	*R*
3a, minor	EtMgBr	0	**6b**	89	100	*S*
3a, major	PhMgBr	0	**6a**	72	99	*R*
3a, major	*n*-BuLi	−78	**6a**	84	100	*R*
3a, major	PhLi	−78	**6a**	70	99	*R*
5b, major	EtMgBr	0	**7a**	93	100	
5b, minor	EtMgBr	0	**7b**	91	100	

These procedures involving preparation of optically active sulfoxides, separation of diastereomers, and removal of the sulfinyl group by substitution reaction, provide a new synthetic approach to optically active arylcarbinols via ortho-directed lithiation of diaryl sulfoxides.

Experimental Section

General. All melting points are uncorrected. Optical rotation was measured on a digital polarimeter. All reagents were obtained from Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Co. Solvents (ether, THF) were further purified and dried by general methods.[6]

(*S*)-(−)-*o*-Chlorophenyl *p*-Tolyl Sulfoxide (1a). A solution of *l*-menthyl *p*-toluenesulfinate[4c] (5.00 g, 17.0 mmol) in ether (100 mL) was treated dropwise with 0.72 M (2-chlorophenyl)magnesium bromide (50 mL, 36 mmol) for 1 h at 0 °C. The mixture was added to saturated aqueous NH_4Cl until the inorganic salts precipitated, leaving a clear ether solution. The inorganic residue was extracted with ether (3 × 150 mL). The combined ether solution was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent, hexane/EtOAc = 7/3) to give 3.62 g (85%) of sulfoxide **1a**. Recrystallization from hexane gave colorless crystals: mp 90.5–91 °C; ^{1}H NMR (500MHz, $CDCl_3$) δ 2.35 (s, 3 H, CH_3), 7.24, 7.61 (ABq, J = 8.1 Hz, 4 H, TolH), 7.32 (dd, J = 7.8, 1.0 Hz, 1 H, 3-ArH), 7.38 (td, J = 7.8, 1.5 Hz, 1 H, 4-ArH), 7.50 (td, J = 7.8, 1.0 Hz, 1 H, 5-ArH), 8.07 (dd, J = 7.8, 1.5 Hz, 1 H, 6-ArH); IR (KBr) 1049 cm^{-1} (SO); MS (m/z) 250 (M^+); $[\alpha]^{25}_D$ − 142.0° (c = 2.0, acetone); op (optical purity) = 100%. Anal. Calcd for $C_{13}H_{11}ClOS$: C, 62.27; H, 4.42. Found: C, 61.97; H, 4.35. Optical purity was calculated on the basis of the optical rotation of ethyl *p*-tolyl sulfoxide, which was obtained by the reaction of the sulfoxide **1a** with ethylmagnesium bromide.

(*S*)-(−)-*o*-Bromophenyl *p*-Tolyl Sulfoxide (1b). The title sulfoxide was prepared from *l*-menthyl *p*-toluenesulfinate and

(5) The results have been submitted. Furukawa, N. *Heteroatom Chemistry*; Block, E., Ed.; Verlag: New York, 1990; pp 165.

(6) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

(2-bromophenyl)magnesium bromide at −105 °C by the same procedure as **1a**. **1b**: yield 3.81 g (76%); mp 88–89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H, CH_3), 7.22, 7.63 (ABq, J = 8.1 Hz, 4 H, TolH), 7.29 (td, J = 7.8, 1.7 Hz, 1 H, 4-ArH), 7.49 (dd, J = 7.8, 1.0 Hz, 1 H, 3-ArH), 7.54 (td, J = 7.8, 1.0 Hz, 1 H, 5-ArH), 8.06 (dd, J = 7.8, 1.7 Hz, 1 H, 6-ArH); IR (KBr) 1050 cm^{-1} (SO); MS (m/z) 294 (M^+); $[\alpha]^{25}_D$ −112.6° (c = 2.0, acetone); op = 58%. Anal. Calcd for $C_{13}H_{11}BrOS$: C, 52.89; H, 3.76. Found: C, 52.96; H, 3.71. Optical purity was determined by the same procedure as **1a**.

(±)-*o*-Iodophenyl *p*-Tolyl Sulfoxide (1c). *o*-Iodophenyl *p*-tolyl sulfide was prepared from 2-chloronitrobenzene and *p*-thiocresol via diazonium salt.[7] To a stirred solution of the sulfide (5.55 g, 17.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added 85% *m*-chloroperoxybenzoic acid (3.45 g, 17.0 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at 0 °C for 10 h and treated with anhydrous ammonia. The resulting solid was separated by filtration and the filtrate was evaporated under reduced pressure to afford crude sulfoxide, which was purified by column chromatography (silica gel; eluent, hexane/EtOAc = 7/3) to give 5.29 g (91%) of sulfoxide **1c**. Recrystallization from hexane gave colorless crystals: mp 82–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3 H, CH_3), 7.23, 7.65 (ABq, J = 8.1 Hz, 4 H, TolH), 7.16 (td, J = 7.7, 1.6 Hz, 1 H, 4-ArH), 7.58 (td, J = 7.7, 1.0 Hz, 1 H, 5-ArH), 7.78 (dd, J = 7.7, 1.0 Hz, 1 H, 3-ArH), 8.00 (dd, J = 7.7, 1.6 Hz, 1 H, 6-ArH); IR (KBr) 1040 cm^{-1} (SO); MS (m/z) 342 (M^+). Anal. Calcd for $C_{13}H_{11}IOS$: C, 45.63; H, 3.24. Found: C, 45.69; 3.20.

Reaction of *o*-Halophenyl *p*-Tolyl Sulfoxides (1a–c) with *n*-Butyllithium and Acetaldehyde. In a typical run, to a stirred solution of *o*-bromophenyl *p*-tolyl sulfoxide (**1b**, 400 mg, 1.4 mmol) in THF (15 mL) at −78 °C was added 1.58 M *n*-butyllithium (0.89 mL, 1.4 mmol) in hexane solution under N_2 at −78 °C for 15 min. Then to this mixture was added acetaldehyde (0.23 mL, 4.2 mmol). The mixture was stirred for 30 min, treated with water, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under vacuum to afford the crude products. The crude products were separated by column chromatography (silica gel; eluent, hexane/EtOAc = 3/2) to give the two diastereomers of 2-(1-hydroxyethyl)phenyl *p*-tolyl sulfoxide (**2**) in 40% yield and butyl *p*-tolyl sulfoxide (**4**) in 34% yield. **2** (major diastereomer): mp 116–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (d, J = 6.4 Hz, 3 H, CH_3), 2.32 (s, 3 H, $TolCH_3$), 4.34 (br s, 1 H, OH), 5.17 (q, J = 6.4 Hz, CH), 7.15–7.75 (m, 7 H, TolH, 3,4,5-ArH), 7.83 (dd, J = 7.8, 1.3 Hz, 6-ArH); IR (KBr) 3360 (OH), 1056 cm^{-1} (SO); MS (m/z) 242 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −1.9° (c = 1.4, $CHCl_3$). Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19. Found: C, 69.28; H, 6.24. **2** (minor diastereomer): mp 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, J = 6.4 Hz, 3 H, CH_3), 2.31 (s, 3 H, $TolCH_3$), 4.12 (br s, 1 H, OH), 5.28 (q, J = 6.4 Hz, 1 H, CH), 7.15–7.75 (m, 7 H, TolH, 3,4,5-ArH), 7.78 (dd, J = 7.8, 1.3 Hz, 1 H, 6-ArH); IR (KBr) 3360 (OH), 1055 cm^{-1} (SO); MS (m/z) 242 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −16.8° (c = 0.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{16}O_2S$; C, 69.20; H, 6.19. Found: C, 69.56; H, 6.25. **6**: mp 88–89 °C (lit.[8] mp 89.5–90 °C); ^{1}H NMR ($CDCl_3$) δ 0.70–3.00 (m, 9 H, Bu), 2.40 (s, 3 H, CH_3), 7.30, 7.54 (ABq, J = 8 Hz, 4 H, TolH); MS (m/z) 196 (M^+); $[\alpha]^{25}_D$ 0° (c = 0.5, acetone).

Reactions of *o*-Halophenyl *p*-Tolyl Sulfoxides (1a–c) with LDA and Acetaldehyde. A typical experimental procedure is as follows. To a stirred solution of sulfoxide **1a** (250 mg, 1.0 mmol) in THF (10 mL) at −78 °C under N_2 was added 1.0 M LDA (1.0 mL, 1.0 mmol) in THF solution. The mixture was stirred for 15 min at −78 °C, and acetaldehyde (0.17 mL, 3.0 mmol) was added. The mixture was stirred for 30 min at −78 °C and treated with water. After hydrolysis and extraction with CH_2Cl_2 (3 × 20 mL), the extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified with column chromatography (silica gel; eluent hexane/EtOAc = 3/2) to give each diastereomer of **3a**. **3a** (major diastereomer): yield 191 mg (65%); mp 171–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (d, J = 6.4 Hz, 3 H, CH_3), 2.33 (br s, 1 H, OH), 2.38 (s, 3 H, $TolCH_3$), 5.68 (q, J = 6.4 Hz, 1 H, CH), 7.27, 7.47 (ABq, J = 8.2 Hz, 4 H, TolH), 7.35 (dd, J = 7.9, 1.0 Hz, 1 H, 3-ArH), 7.44 (t, J = 7.9, 1 H, 4-ArH), 7.63 (dd, J = 7.9, 1.0 Hz, 1 H, 5-ArH); IR (KBr) 3416 (OH), 1040 cm^{-1} (SO); MS (m/z) 278 ($M^+ - O$), 276 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −163.5° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{15}ClO_2S$: C, 61.12; H, 5.13. Found: C, 60.90; H, 5.36. **3a** (minor diastereomer): yield 86 mg (29%); mp 169–170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3 H, CH_3), 2.39 (s, 3 H, $TolCH_3$), 4.49 (br s, 1 H, OH), 5.38 (q, J = 6.5 Hz, 1 H, CH), 7.28, 7.49 (ABq, J = 8.2 Hz, 4 H, TolH), 7.39 (dd, J = 7.9, 1.3 Hz, 1 H, 3-ArH), 7.44 (t, J = 7.9, 1 H, 4-ArH), 7.53 (dd, J = 7.9, 1.3 Hz, 1 H, 5-ArH); IR (KBr) 3378 (OH), 1023 cm^{-1} (SO); MS (m/z) 278 ($M^+ - O$), 276 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −178.2° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{15}ClO_2S$: C, 61.12; H, 5.13. Found: C, 60.76; H, 5.03. **3b** (major diastereomer) yield 229 mg (68%); mp 167–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (d, J = 6.3 Hz, 3 H, CH_3), 2.26 (br s, 1 H, OH), 2.36 (s, 3 H, $TolCH_3$), 5.67 (q, J = 6.3 Hz, 1 H, CH), 7.25, 7.46 (ABq, J = 8.1 Hz, 4 H, TolH), 7.35 (t, J = 7.9 Hz, 1 H, 4-ArH), 7.55 (dd, J = 7.9, 1.0 Hz, 5-ArH), 7.63 (dd, J = 7.9, 1.0 Hz, 1 H, 3-ArH); IR (KBr) 3374 (OH), 1048 cm^{-1} (SO); MS (m/z) 322 ($M^+ - O$), 320 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −110.5° (c = 3.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{15}BrO_2S$: C, 53.10; H, 4.46. Found: C, 53.20; H, 4.41. **3b** (minor diastereomer): yield 93 mg (27%); mp 163–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 3 H, CH_3), 2.38 (s, 3 H, $TolCH_3$), 4.51 (br s, 1 H, OH), 5.40 (q, J = 6.3 Hz, 1 H, CH), 7.28, 7.49 (ABq, J = 8.1 Hz, 4 H, TolH), 7.36 (t, J = 7.9 Hz, 4-ArH), 7.58 (d, J = 7.9 Hz, 1 H, 5-ArH), 7.59 (d, J = 7.9 Hz, 1 H, 3-ArH); IR (KBr) 3378 (OH), 1025 cm^{-1} (SO); MS (m/z) 322 ($M^+ - O$), 320 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −116.4° (c = 1.2, $CHCl_3$). Anal. Calcd for $C_{15}H_{15}BrO_2S$: C, 53.10; H, 4.46. Found: C, 53.26; H, 4.43. **3c** (diastereomeric mixture): yield 228 mg (59%); colorless liquid; IR (KBr) 3358 (OH), 1046 cm^{-1} (SO); MS (m/z) 368 ($M^+ - H_2O$). The diastereomeric ratio (72:28) was determined by 500-MHz ^{1}H NMR with $CDCl_3$ as a solvent. Major diastereomer: δ 1.47 (d, J = 6.3 Hz, 3 H, CH_3), 2.37 (s, 3 H, $TolCH_3$), 5.64 (q, J = 6.3 Hz, 1 H, CH), 7.20 (t, J = 7.8 Hz, 1 H, 4-ArH), 7.27, 7.46 (ABq, J = 8.1 Hz, 4 H, TolH), 7.72 (d, J = 7.8 Hz, 1 H, 5-ArH), 7.82 (d, J = 7.8 Hz, 1 H, 3-ArH). Minor diastereomer: δ 1.46 (d, J = 6.3 Hz, 3 H, CH_3), 2.35 (s, 3 H, $TolCH_3$), 5.56 (q, J = 6.3 Hz, 1 H, CH), 7.24–7.74 (m, 7 H, ArH).

Reactions of Optically Active *o*-Lithio-(*S*)-(−)-*o*-chlorophenyl *p*-Tolyl Sulfoxide with Several Aldehydes. To a stirred solution of sulfoxide **1a** (250 mg, 1.0 mmol) in THF (10 mL) at −78 °C under N_2 was added 1.0 M LDA (1.0 mL, 1.0 mmol) in THF solution. The mixture was stirred for 15 min at −78 °C, and benzaldehyde (0.30 mL, 3.0 mmol) was added. The mixture was stirred for 30 min at −78 °C and treated with water. After hydrolysis and extraction with CH_2Cl_2 (3 × 20 mL), the extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified with column chromatography (silica gel; eluent, hexane/EtOAc = 7/3) to give each diastereomer of **5a**. **5a** (major diastereomer): yield 224 mg (63%); mp 86–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3 H, CH_3), 4.98 (br s, 1 H, OH), 6.45 (br s, 1 H, CH), 6.89–7.35 (m, 8 H, ArH), 7.26, 7.51 (ABq, J = 8.0 Hz, 4 H, TolH); IR (KBr) 3246 (OH), 1033 cm^{-1} (SO); MS (m/z) 340 ($M^+ - O$), 338 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −261.8° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{20}H_{17}ClO_2S$: C, 67.31; H, 4.80. Found: C, 67.03; H, 4.81. **5a** (minor diastereomer): yield 115 mg (32%); mp 82–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3 H, CH_3), 3.83 (br s, 1 H, OH), 6.74 (br s, 1 H, CH), 7.07–7.52 (m, 12 H, ArH, TolH); IR (KBr) 3362 (OH), 1025 cm^{-1} (SO); MS (m/z) 340 ($M^+ - O$), 338 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −40.2° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{20}H_{17}ClO_2S$: C, 67.31; H, 4.80. Found: C, 67.33; H, 4.76. **5b** (major diastereomer): yield 231 mg (62%); mp 176–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3 H, 4′-CH_3), 2.40 (s, 3 H, CH_3), 4.78 (d, J = 3.9 Hz, 1 H, OH), 6.38 (d, J = 3.9 Hz, 1 H, CH), 6.82, 7.02 (ABq, J = 7.9 Hz, 4 H, 2′,3′,5′,6′-ArH), 6.93 (dd, J = 7.8, 1.0 Hz, 1 H, 5-ArH), 7.26 (td, J = 7.8, 1.0 Hz, 1 H, 4-ArH), 7.29, 7.53 (ABq, J = 8.0 Hz, 4 H, TolH), 7.35 (d, J = 7.8 Hz, 1 H, 3-ArH); IR (KBr) 3178 (OH), 1021 cm^{-1} (SO); MS (m/z) 354 ($M^+ - O$), 352 ($M^+ - H_2O$); $[\alpha]^{25}_D$ −293.1° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_2S$: C, 68.01; H, 5.16. Found: C, 67.89; H, 5.03. **5b** (minor diastereomer): yield 125 mg (34%); mp 165–166 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3 H, 4′-CH_3), 2.31 (s, 3 H, CH_3), 3.79 (br s, 1 H, OH), 6.68 (br s, 1 H, CH),

(7) Tarbell, D. S.; Todd, C. W.; Paulson, M. C.; Lindstrom, E. G.; Wystrach, L. P. *J. Am. Chem. Soc.* **1948**, 70, 1381.
(8) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1965**, 87, 1958.

7.03-7.52 (m, 11 H, ArH, TolH); IR (KBr) 3234 (OH), 1023 cm^{-1} (SO); MS (m/z) 354 ($M^+ - O$), 352 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -19.7° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_2S$: C, 68.01; H, 5.16. Found: C, 67.84; H, 5.15. **5c** (major diastereomer): yield 241 mg (62%); mp 134-135 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 4.87 (br s, 1 H, OH), 6.37 (br s, 1 H, CH), 6.75, 6.86 (ABq, J = 8.6 Hz, 4 H, 2',3',5',6'-ArH), 6.95 (t, J = 7.8 Hz, 1 H, 5-ArH), 7.27 (t, J = 7.8 Hz, 1 H, 4-ArH), 7.28, 7.52 (ABq, J = 8.1 Hz, 4 H, TolH), 7.35 (d, J = 7.8 Hz, 1 H, 3-ArH); IR (KBr) 3326 (OH), 1031 cm^{-1} (SO); MS (m/z) 370 ($M^+ - O$), 368 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -295.8° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_3S$: C, 65.19; H, 4.95. Found: C, 64.76; H, 5.00. **5c** (minor diastereomer): yield 130 mg (34%); mp 122-124 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 3.90 (br s, 1 H, OH), 6.66 (br s, 1 H, CH), 6.75-7.58 (m, 11 H, ArH, TolH); IR (KBr) 3306 (OH), 1021 cm^{-1} (SO); MS (m/z) 370 ($M^+ - O$), 368 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -21.7° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_3S$: C, 65.19; H, 4.95. Found: C, 64.68; H, 4.92. **5d** (major diastereomer): yield 244 mg (57%); mp 116-117 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3 H, CH_3), 4.65 (br s, 1 H, OH), 6.59 (br s, 1 H, CH), 6.97 (d, J = 7.9 Hz, 1 H, 5-ArH), 6.99, 7.40 (ABq, J = 8.2 Hz, 4 H, 2',3',5',6'-ArH), 7.24, 7.47 (ABq, J = 8.1 Hz, 4 H, TolH), 7.31 (t, J = 7.9 Hz, 1 H, 4-ArH), 7.38 (d, J = 7.9 Hz, 1 H, 3-ArH); IR (KBr) 3330 (OH), 1039 cm^{-1} (SO); MS (m/z) 408 ($M^+ - O$), 406 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -233.8° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{16}F_3ClO_2S$: C, 59.37; H, 3.80. Found: C, 58.90; H, 3.80. **5d** (minor diastereomer): yield 143 mg (34%); mp 101-102 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3 H, CH_3), 4.38 (br s, 1 H, OH), 6.70 (br s, 1 H, CH), 7.10-7.46 (m, 11 H, ArH); IR (KBr) 3372 (OH), 1039 cm^{-1} (SO); MS (m/z) 408 ($M^+ - O$), 406 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -54.9° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{16}F_3ClO_2S$: C, 59.37; H, 3.80. Found: C, 58.89; H, 3.76.

Desulfinylation Reactions of 3a and 5b with Grignard or Organolithium Reagents. In a typical run, to a stirred solution of major diastereomer of sulfoxide **3a** (200 mg, 0.68 mmol) in THF (10 mL) at 0 °C was added 1.0 M EtMgBr (1.36 mL, 1.36 mmol) in THF solution under N_2 at 0 °C for 15 min. Then this mixture was treated with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtrated, and concentrated under reduced pressure. The crude products were separated by column chromatography (silica gel; eluent hexane/EtOAc = 3/2) to give 96.9 mg (91%) of optically active 1-chloro-3-(1-hydroxyethyl)benzene (**6a**) and 112 mg (98%) of optically active ethyl p-tolyl sulfoxide. **6a**: bp 116-118 °C (20 Torr); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, J = 6.5 Hz, 3 H, CH_3), 3.00 (br s, 1 H, OH), 4.76 (q, J = 6.5 Hz, 1 H, CH), 7.17-7.27 (m, 3 H, 4,5,6-ArH), 7.33 (s, 1 H, 2-ArH); IR (neat) 3338 cm^{-1} (OH), MS (m/z) 156 (M^+); $[\alpha]^{25}_D$ +38.6° (c = 1.5, acetone). Anal. Calcd for C_8H_9ClO: C, 61.35; H, 5.79. Found: C, 61.20; H, 5.85. **6b**: yield 94.8 mg (89%); bp 116-117 °C (19 Torr); ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, J = 6.5 Hz, 3 H, CH_3), 2.59 (br s, 1 H, OH), 4.80 (q, J = 6.5 Hz, 1 H, CH), 7.14-7.25 (m, 3 H, 4,5,6-ArH), 7.31 (s, 1 H, 2-ArH); IR (neat) 3338 cm^{-1} (OH); MS (m/z) 156 (M^+); $[\alpha]^{25}_D$ -39.0° (c = 1.2, acetone). Anal. Calcd for C_8H_9ClO: C, 61.35; H, 5.79. Found: C, 61.20; H, 5.84. Optical purities of the alcohols **6a** and **6b** were determined by ^1H NMR in $CDCl_3$ using $Eu(tfc)_3$ as a chiral shift reagent. Absolute configurations of the alcohols **6a** and **6b** were determined on the basis of the rotation of optically active 1-phenylethanol, which was obtained by the reaction of alcohol **6a** or **6b** with lithium. Ethyl p-tolyl sulfoxide: ^1H NMR ($CDCl_3$) δ 1.77 (t, J = 7 Hz, 3 H, CH_3), 2.40 (s, 3 H, $TolCH_3$), 2.80 (q, J = 7 Hz, 2 H, CH_2), 7.29, 7.52 (ABq, J = 8 Hz, TolH); $[\alpha]^{25}_D$ -202.1° (c = 1.0, acetone). Optical purity and absolute configuration were 100% and S, respectively. **7a**: yield 117 mg (93%); colorless liquid; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H, $TolCH_3$), 5.74 (br s, 1 H, CH), 7.13-7.25 (m, 7 H, 4,5,6-ArH, TolH), 7.39 (s, 1 H, 2-ArH); IR (neat) 3392 cm^{-1} (OH); exact mass calcd for $C_{14}H_{13}ClO$ 232.0655, found 232.0614; $[\alpha]^{25}_D$ +43.1° (c = 2.0, acetone). **7b**: yield 114 mg (91%); colorless liquid; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H, $TolCH_3$), 5.74 (br s, 1 H, CH), 7.13-7.26 (m, 7 H, 4,5,6-ArH, TolH), 7.38 (s, 1 H, 2-ArH); IR (neat) 3412 cm^{-1} (OH); exact mass calcd for $C_{14}H_{13}ClO$ 232.0655, found 232.0617; $[\alpha]^{25}_D$ -42.9° (c = 2.0, acetone). Optical purities of the alcohols **7a** and **7b** were determined by the same procedures as **6a** and **6b**.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 02453018) from the Ministry of Education, Science and Culture of Japan.

Registry No. **1a**, 20268-16-0; **1b**, 135145-16-3; **1c**, 135145-17-4; **2** (isomer 1), 135145-18-5; **2**(isomer 2), 135145-19-6; **3a** (isomer 1), 135145-20-9; **3a** (isomer 2), 135145-21-0; **3b** (isomer 1), 135145-22-1; **3b** (isomer 2), 135145-23-2; **3c** (isomer 1), 135145-24-3; **3c** (isomer 2), 135145-25-4; **4**, 67529-36-6; **5a** (isomer 1), 135145-26-5; **5a** (isomer 2), 135145-27-6; **5b** (isomer 1), 135145-28-7; **5b** (isomer 2), 135145-29-8; **5c** (isomer 1), 135145-30-1; **5c** (isomer 2), 135145-31-2; **5d** (isomer 1), 135145-32-3; **5d** (isomer 2), 135145-33-4; **6a**, 120121-01-9; **6b**, 135145-34-5; **7a**, 135145-35-6; **7b**, 135145-36-7; CH_3CHO, 75-07-0; C_6H_4CHO, 100-52-7; p-$CH_3C_6H_4CHO$, 104-87-0; p-$CH_3OC_6H_4CHO$, 123-11-5; p-$CF_3C_6H_4CHO$, 455-19-6; EtMgBr, 925-90-6; PhMeBr, 100-58-3; n-BuLi, 109-72-8; PhLi, 591-51-5.

Selective Ether Cleavage Reactions of 4,6-Dialkoxy-2-(trifluoromethyl)pyridine Mono- and Dicarboxylates

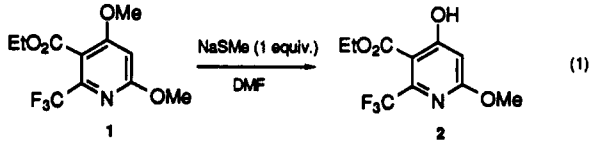
Shridhar G. Hegde

New Products Division, Monsanto Agricultural Company, A Unit of Monsanto Company, St. Louis, Missouri 63167

Received April 16, 1991

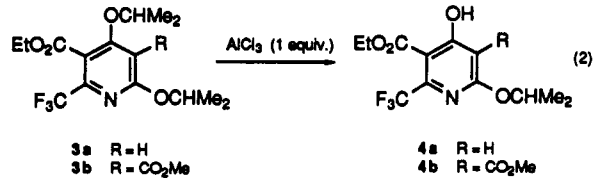
Recent reports from these laboratories have disclosed the synthesis[1,2] and utility[2] of 4,6-dialkoxy-2-(trifluoromethyl)pyridine-3-carboxylates and 4,6-dialkoxy-2-(trifluoromethyl)pyridine-3,5-dicarboxylates as herbicides or herbicide intermediates. Although a variety of 4,6-dialkoxypyridine-3-carboxylates were derived from the corresponding dihydroxypyridines by alkylation with an excess amount of alkyl halides, the methodology permitted the synthesis of only those dialkoxy derivatives wherein the two alkoxy groups are identical. For a complete structure-activity correlation study we required examples of dialkoxypyridines with nonidentical alkoxy groups. In this paper, we describe the regioselective partial ether cleavage reactions of some symmetrical 4,6-dialkoxy-2-(trifluoromethyl)pyridine mono- and dicarboxylates to the corresponding monoalkoxy derivatives and their subsequent elaboration to the unsymmetrical dialkoxypyridines.

The reaction of dimethoxypyridine **1** with 1 equiv of sodium methanethiolate in DMF at 80 °C resulted in clean conversion to the methoxypyridinol **2** in 76% yield (eq 1).



1 2 (1)

Likewise, the diisopropoxypyridines **3a** and **3b** underwent selective cleavage of one of the isopropoxy groups when treated with a stoichiometric amount of anhydrous aluminum chloride at 0 °C to provide isopropoxypyridinols **4a** and **4b** in 83% and 80% yield, respectively (eq 2).[3]



3a R = H
3b R = CO_2Me
4a R = H
4b R = CO_2Me (2)

(1) Lee, L. F.; Normansell, J. E. *J. Org. Chem.* 1990, *55*, 2964.
(2) Lee, L. F. Eur. Pat. Appl. EP 181 311, 1986; U.S. Patent 4 609 399, 1986; *Chem. Abstr.* 1986, *105*, 97334.

0022-3263/91/1956-5726$02.50/0