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Relative stereochemistry of the thermodynamic and kinetic addition of lithiated methyl phenyl sulfoxide to oxaziridine

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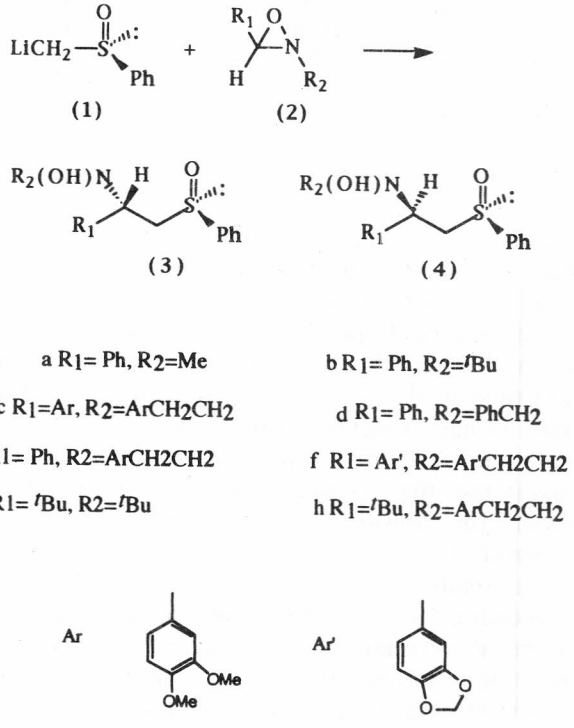
The stereochemical outcome and diastereo selectivity of the thermodynamic and kinetic reactions of lithiated methyl phenyl sulfoxide with oxaziridine is reported. The relative stereochemistry of the major diastereomeric products at thermodynamic and kinetic condition has been determined by chemical correlation with the major diastereomeric products from the reaction of lithiated racemic methyl phenyl sulfoxide with nitrones.

We have recently reported the asymmetric synthesis of chiral hydroxyamino sulfoxides from the addition of lithiated chiral sulfoxides to prochiral nitrones and oxaziridines[1,2,3]. These methods however, work best on diaryl nitrones (ArCH=N(O)Ar) or with 6, 7-dimethoxy-3, 4-dihydroisoquinoline *N*-oxide[1]. A similar trend in reactivity has been observed in the addition of other organometallic reagents to imines[4,5]. On the other hand, oxaziridines may be regarded as the isomer of nitrones which are much more reactive towards addition of organometallic reagents[6]. The thermodynamic and kinetic addition of racemic lithiated methyl phenyl sulfoxide **1** to some representative oxaziridine and the stereochemistry of the major and minor diastereomeric adducts at thermodynamic and kinetic conditions are reported.

Like lithiated sulfoxide **1**, oxaziridine **2** is also chiral and under normal conditions the reaction of **1** with **2** would be expected to give 1:1 mixture of the diastereomers of **3** and **4**. However under conditions that may allow for kinetic resolution (i.e. in which the stoichiometric ratio of 2:1 is 2:1), then these reactions may be diastereoselective[2,3].

Addition of a solution of the racemic oxaziridine **2** (2 equiv.) to a solution of **1** (1 equiv.) at −78°C in THF for 1 hr afforded a mixture of the diastereomeric and racemic β-hydroxyamino sulfoxides, **3** and **4**, in good to excellent yields after purification by simple column chromatography (Table I) (Scheme I). The product diastereoselectivities at kinetic condition, ranged from 67:33 to 75:25 (Table I) and the product diastereoselectivities at thermodynamic condition, ranged from



Scheme I

55:45 to 60:40 (Table II) as determined by ^{1}H NMR analysis on the crude reaction products.

These diastereoselectivities were in general similar to those of the analogous reactions of lithiated methyl phenyl sulfoxide with nitrones and imines.[3,4] As found previously,[3] for nitrones of the type $R_1CH=N(O)R_2$, the product diastereoselection increased, as the steric demand of the *N*-substituent of the nitrone increased, the similar

Table I—Addition of **1** to oxaziridines **2**

Entry	Oxaziridine	Yield of **3+4** (%)	Diastereoselection, 3:4
1	**2a**	83	67:33
2	**2b**	63	75:25
3	**2c**	61	68:32
4	**2d**	83	67:33
5	**2e**	79	75:25
6	**2f**	74	68:32
7	**2g**	86	60:40
8	**2h**	74	68:32

Table II—Addition of **1** to oxaziridine **2**

Entry	Oxairidine	Temp. °C/ Time, min	Yield (%)	Diastereoselection **3:4**
1	**2a**	−78/60	83	67:33
2	**2a**	−45/30	80	60:40
3	**2a**	0:5	70	55:45
4	**2d**	−78/60	83	67:33
5	**2d**	−45/30	81	62:38
6	**2d**	0/5	72	55:45
7	**2e**	−78/60	79	75:25
8	**2e**	−45/30	68	70:30
9	**2e**	0/5	61	60:40
10	**2f**	−78/60	74	68:32
11	**2f**	−45/30	68	60:40
12	**2f**	0/5	60	55:45

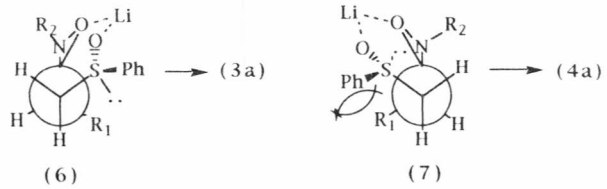
results were found for oxaziridine (Table I). The highest product diastereoselection was obtained with the oxaziridine **2b** and **2e**) (Table I).

An identical product diastereoselection was realised when the reaction was done at −78°C and then held at −45°C for 30 min or 0°C for 5 min. Longer reaction times (0.5-12h) at 0°C resulted in very poor diastereoselection (Table II), suggesting that equilibration had occurred between the diastereoisomeric adducts **3** and **4** (Scheme II).

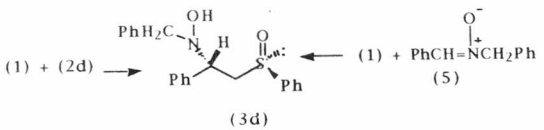
The relative (2*S**, *R***S*) stereochemistry of diastereomerically pure adduct **3d** was determined by chemical correlation. The spectral properties of this compound were identical to those of the major diastereomeric product from the reaction of **1** and the nitrone **5** (Scheme III).

The two possible chelated transition states **6** and **7** for the reaction of **1** and oxaziridines **2** are shown in Scheme II. One would expect little difference in free energy between transition states **6** and **7** and consequently the product diastereoselections are only modest to good.

In conclusion, oxaziridines offer enhanced reactivity over imines and nitrones towards addition of lithiated sulfoxides. Even the dialkyl substituted oxaziridines (**2g** and **2h**) gave products in good yield. In contrast the reaction of **1** with dialkyl



Scheme II



Scheme III

imines gives a complex mixture of products[4]. Attempts to improve the diastereoselectivity of these reactions is currently under investigation.

Experimental Section

The oxaziridines **2a-h** were prepared by oxidation of corresponding imines with oxone[7]. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 90 MHz in $CDCl_3$ solution; chemical shifts are given in ppm relative to TMS.

Reaction of **1** *with oxaziridines* **2**; *a General procedure.* Methyl phenyl sulfoxide (2.0 mmol) in anhyd. tetrahydrofuran (5 mL) was added dropwise to a cooled (−78°C), stirred solution of LDA, prepared from diisopropylamine (0.35 mL, 2.2 mmol) and *n*-butyllithium (2.4 mmol, 1.47 mL of 1.6 *M* solution in hexane) in THF (5 mL). The mixture was allowed to reach −20°C, and was then cooled again to −78°C, and treated with a solution of the oxaziridine (4 mmol) in THF (15 mL). The mixture was stirred for 30 min at −78°C and then quenched with saturated NH_4Cl. The mixture was warmed to room temperature and then extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with water, dried ($MgSO_4$) and then evaporated to dryness. The crude product was then purified by column chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent. The diastereoselection of these reactions were determined by ^{1}H NMR (400 MHz) and spectroscropic analysis of the crude reaction product.

***(R**$_S$, *1S**)-*N*-Methyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine 3a.** Oil. IR (film) 3600-3200 (br), 3300 (sharp), 1035 cm^{-1}; ^{1}H NMR : δ7.52-7.27 (10H), 4.11 (dd, *J*=6.8, 9.6 Hz, 1H), 3.72 (dd, *J*=9.6, 13.6 Hz, 1H), 3.05 (dd, *J*=6.8, 13.6 Hz, 1H); 2.55(s, Me, 3H); ^{13}C NMR : δ 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6,

123.6, 65.0, 59.1, 33.8, 20.9; MS (CI) : m/z 276 (100, $M+H^+$), 229 (32, $M+H^+$-NMeOH), 136(75), 125(100).

***(R_S^*, 1R*)-N*-Methyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine 4a.** ^1H NMR (in part): δ3.92 (dd, J=6.6, 9.6 Hz, 1H), 3.45(dd, J=9.6, 13 Hz, 1H), 2.95(dd, J=6.6, 13 Hz, 1H), 2.51(s, Me, 3H).

***(R_S^*, 1S*)-N-tert*-Butyl-*N*-(1-phenyl -2-phenylsulfinyl)ethylhydroxylamine 3b.** M.p. 144-146°C. IR (nujol) : 3520, 3330, 1030 cm^{-1}; ^1H NMR : δ8.2 (m, 1H), 7.2-7.8 (m, 9H), 4.55(dd, J=4.0, 11 Hz, 1H), 3.58(dd, J=11, 13.2 Hz, 1H), 2.94 (dd, J=4.0, 13.2 Hz, 1H), 0.981 (s, 9H); ^{13}C NMR : δ 144.6, 130.5, 129.5, 128.5, 127.3, 126.9, 126, 125, 69.3, 63.7, 28.8, 26.8. MS (CI) : m/z 318 (75, $M+H^+$), 302 (20), 262 (25) (Found: C, 68.2; H, 7.4; N, 4.4 Calcd for $C_{18}H_{23}NO_2S$: C, 68.1; H, 7.3; N, 4.4%).

***(R_S^* 1R*)-N-tert*-Butyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine 4b.** ^1H NMR (in part): δ3.64 (dd, J=10.8, 13.6 Hz, 1H), 3.01(dd, J=6.4, 13.6 Hz, 1H), 1.021 (s, 9H).

***(R_S^*, 1S*)-N*-[2-(3′, 4′-Dimethoxyphenyl)ethyl]-*N*-[1-(3′, 4'-dimethoxyphenyl)-2-phenylsulfinyl]-ethylhydroxylamine 3c.** M.p. 132-133°C. IR (nujol):3502, 3320, 1030 cm^{-1}; ^1H NMR : δ8.99-6.5 (m, 11H), 5.32(dd, J=2.8, 10.0 Hz, 1H), 3.8(4xs, 12 H), 3.35(dd, J=10, 13.2 Hz, 1H), 3.1(dd, J=2.8, 13.2 Hz, 1H); ^{13}C NMR: δ 183.3, 178.23, 170.54, 168.65, 160.24, 155.4, 148.3, 144.8, 141.6, 132.2, 126.8, 126.3, 124.5, 119.7, 117.3, 112.6, 60.2, 58.4, 57.8, 56.2, 55.6, 46.4, 34.7; MS: m/z 485.6 (100, M^+), 468, 343, 339, 202, 185 (Found: C, 64.29; H, 6.48; N, 2.85 Calcd for $C_{26}H_{31}NO_6S$: C, 64.31; H, 6.43; N, 2.88%).

***(R_S^* 1R*)-N*-(2-(3′, 4′-Dimethoxyphenyl)ethyl)-*N*-(1-(3′, 4′-dimethoxyphenyl)-2-phenylsulfinyl)-ethylhydroxylamine 4c.** ^1H NMR (in part): δ 5.14 (dd, J=2, 10.0 Hz, 1H), 3.32 (dd, J=10.0, 7 Hz, 1H), 2.99 (dd, J=7, 10.0 Hz, 1H).

***(R_S^* 1S*)-N*-Benzyl-*N*-(1-phenyl-2-phenylsulfinyl)ethylhydroxylamine 3d.** M.p. 159-160°C, IR (nujol): 3509, 3330, 2950, 1030 cm^{-1}; ^1H NMR : δ 7.2-7.8 (m, 15H) 4.36 (dd, J=5.2, 8.4 Hz, 1H), 3.84(d, J=13.6 Hz, 1H), 3.68 (d, J=13.6 Hz, 1H); 3.39 (dd, J=5.2, 13.6 Hz, 1H), 3.32 (dd, J=8.4, 13.6 Hz, 1H). MS(CI) : m/z 352 ($M+H^+$, 20), 337 (75), 230 (50), 211 (100), 197 (60), 142 (100), 127 (100), 106 (80) (Found: C, 72.0; H, 6.3; N, 4.0%. Calcd for $C_{21}H_{21}NO_2S$: C, 71.8; H, 6.0; N, 4.0%).

***(R_S^*, 1R*)-N*-Benzyl-*N*-(1-phenyl-2-phenylsulfinyl)ethyl 4d.** ^1H NMR (in part): δ 4.26 (dd, J=6.4, 10.4 Hz, 1H), 3.06 (dd, J=6.4, 13.6 Hz, 1H).

***(R_S^*, 1S*)-N*-[1-(3′, 4′-Dimethoxyphenyl)ethyl]-*N*-(2-phenyl)-2-(phenylsulfinyl)ethylhydroxylamine 3e.** M.p. 128-129°C. IR (nujol) : 3502, 3320, 1030 cm^{-1}; ^1H NMR : δ 7.99-6.8 (m, 13H), 5.22 (dd, J=2.8, 10.0 Hz, 1H), 3.9 (2xs, 6H), 3.4 (dd, J=10, 13.2 Hz, 1H), 3.2 (dd, J=2.8, 13.2 Hz, 1H); ^{13}C NMR : δ 183.3, 174.34, 171.54, 168.65, 160.24, 155.4, 148.3, 144.8, 141.6, 132.2, 126.8, 126.3, 124.5, 119.7, 117.3, 112.6, 60.2, 58.4, 57.8, 56.2, 55.6, 46.4, 34.7, MS: m/z 425.5 (100, M^+) (Found: C, 67.59; H, 6.48; N, 3.45%. Calcd for $C_{24}H_{27}NO_4S$: C, 67.74; H, 6.40; N, 3.29%).

***(R_S^* 1R*)-N*-(1-(3′, 4′-Dimethoxyphenyl)ethyl-*N*-(2-phenyl)-2-(phenylsulfinyl)ethylhydroxylamine 4e.** ^1H NMR (in part): δ 5.14 (dd, J=3.4, 10.4Hz, 1H), 3.26 (*dd*, J=3.4, 13.6 Hz, 1H).

***(R_S^*, 1S*)-N*-[2-(3′, 4′-Methylenedioxy phenyl)-ethyl]-*N*-(1-(3′, 4′methylenedioxyphenyl)-ethylhydroxylamine 3f.** M.p. 132-133°C, IR (nujol) : 3502, 3320, 1030 cm^{-1}; *^1H NMR* : δ 7.99-6.5 (m, 11H), 5.32 (dd, J=2.8, 10.0 Hz, 1H), 5.99 (2xs, 4H), 3.35 (dd, J=10, 13.2 Hz, 1H), 3.1 (dd, J=2.8, 13.2 Hz, 1H); ^{13}C NMR: δ 180.3, 176.23, 172.54, 168.65, 160.24, 155.4, 148.3, 144.8, 141.6, 132.2, 126.8, 126.3, 124.5, 119.7, 117.3, 112.6, 60.2, 58.4, 57.8, 56.2, 55.6, 46.4, 34.7. MS m/z 453.5 (100, M^+) (Found: C, 63.29; H, 5.28; N, 2.95%. Calcd for $C_{24}H_{23}NO_6S$: C, 63.56; H, 5.11; N, 3.09%).

***(R_S^* 1S*)-N*-(2-(3′, 4′-Methylenedioxy phenyl)ethyl)-*N*-(1-(3′, 4′-methylenedioxyphenyl)-ethylhydroxylamine 4f.** ^1H NMR (in part): δ 5.24 (dd, J=2, 10.0 Hz, 1H), 3.32 (dd, J=10.0, 7Hz, 1H), 2.99 (dd, J=7, 10.0 Hz, 1H).

***(R_S^* 1S*)-N-tert*-butyl-*N*-(1-phenylsulfinyl)-2-propylhydroxylamine 3g and (R_S^*, 1R*) 4g.** Oil. IR (nujol): 3700-3000 (br), 1630, 1050 cm^{-1}; ^1H NMR (on 1:1 mixture) : δ 7.7 (m, 2H), 7.5 (m, 3H), 3.82-3.66 (m, 1H), 3.13 (dd, J=10.0, 13.6 Hz, 0.5H), 3.06 (dd, J=10.4, 14 Hz, 0.5 H), 2.83 (dd, J=6.4, 14 Hz, 0.5H), 2.73 (dd, J=4, 13.6 Hz, 0.5H), 1.21 (s. 4.5H), 1.19 (s, 4.5H), 1.18 (d, J=6.4 Hz, 1.5H); ^{13}C NMR (on a 60:40 mixture, the minor isomer is shown in brackets): δ 144.6 (144.7), 130.5 (130.3), 129.0 (128.9), 124.0 (123.9), 66.4 (64.4), 58.7 (59.3), 52.2 (50.0) 27.1 (26.8), 15.0(15.2); MS(CI): m/z 251 (50, $M+H^+$), 234 (100), 169 (80), 142 (100), 127 (60), 111 (90).

***(R_S^* 1S*)-N*-(2-(3′, 4′-Dimethoxyphenyl)ethyl)-*N*-1-*tert*-butyl-2-phenylsulfinyl)ethylhydroxylamine 3h.** M.p. 132-133°C; IR (nujol) 3502, 3320, 1030 cm^{-1}; ^1H NMR: δ8.99-6.5 (m, 11H),

5.28 (dd, J=3.0, 10.4 Hz, 1H), 3.8 (2xs, 6H), 3.30 (dd, J=10.4, 13.6 Hz, 1H), 3.1 (dd, J=3.0, 13.6 Hz, 1H), 0.981 (s, 9H); ^{13}C NMR: δ 183.3, 178.23, 170.54, 144.8, 126.3, 124.5, 117.3, 112.6, 60.2, 58.4, 57.8, 56.2, 55.6, 46.4, 34.7, 27.1, 15.0, MS: m/z 405.5 (100, M^+), 368, 343, 339, 202, 185 (Found: C, 65.20; H, 7.63; N, 3.63. Calcd for $C_{22}H_{31}NO_4S$: C, 65.16; H, 7.70; N, 3.45%).

***(R*$_S$* 1R*)-N*-[2-(3′. 4′-Dimethoxyphenyl)ethyl]-*N*-1-*tert*-butyl-2-phenylsulfinyl)ethylhydroxylamine 4h**. ^{1}H NMR (in part): δ 5.14 (dd, J=2, 10.0 Hz, 1H), 3.32 (dd, J=10.0, 7 Hz, 1H), 2.99 (dd, J=7, 10.0 Hz, 1H), 9.73 (s, 9H).

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