Some Reactions of N-(2-Hydroxyalkyl)-p-toluenesulfonamides and N-Allyl-p-toluenesulfonamides

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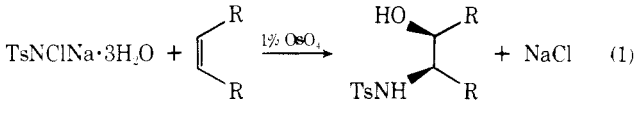
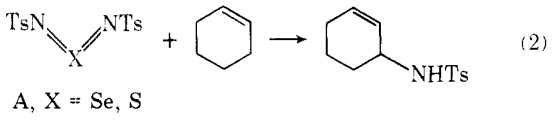
Some transformations of the products derived from oxyamination and allylic amination of olefins have been explored. Products such as **2–10** (Scheme I), *N*-tosylaziridines (**14** and **15**, Scheme II), imidazolines (**19** and **20**), and diamines (**21** and **22**) (Scheme III) are now available from olefins in a few simple steps. A syn-directive effect of the *p*-toluenesulfonamide group was observed in the epoxidation of **23** with *m*-chloroperbenzoic acid.

Recently, methods for stereospecific oxyamination[2–4] and allylic amination[5–7] of olefins have been developed. In one of the oxyamination procedures[2] it was found that the trihydrate of chloramine-T reacts with an olefin in the presence of catalytic amounts of osmium tetroxide to produce vicinal hydroxy-*p*-toluenesulfonamides (eq 1). An important aspect of the reaction is the stereospecific manner in which the oxygen and nitrogen groups are introduced (cis addition). The allylic amination was achieved by reaction of the alkene with bis(*N*-*p*-toluenesulfonyl)selenodiimide[5] (A, X = Se) or bis(*N*-*p*-toluenesulfonyl)sulfodiimide[6,7] (A, X = S). With these reagents *N*-allyl-*p*-toluenesulfonamides were obtained from olefins (eq 2). In this paper we would like to report some



(1)



(2)

A, X = Se, S

synthetic transformations of the products shown in eq 1 and 2 in order to demonstrate the utility of the oxyamination and allylic amination procedures.

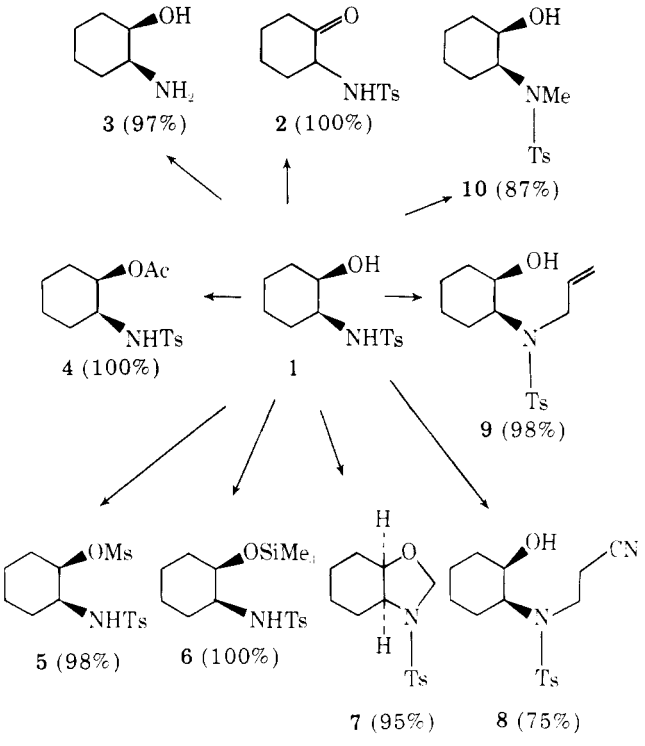
Results and Discussion

Some one-step transformations of the hydroxysulfonamide **1**, derived from cyclohexene, are shown in Scheme I. Most of the transformations take place in good to high yields. Jones oxidation of **1** to synthetically useful ketoamide **2** is quantitative, and reduction of **1** with sodium in ammonia to the *cis*-amino alcohol **3** proceeds readily. Because of the acidity of the sulfonamide hydrogen in **1**, the nitrogen can be selectively functionalized in the presence of base. Thus, alkylation (**10**) and allylation (**9**) proceed readily and the base-catalyzed conjugate addition of **1** to acrylonitrile gives **8**. Acid-catalyzed condensation of **1** with formaldehyde produces the heterocyclic compound **7** in high yield.

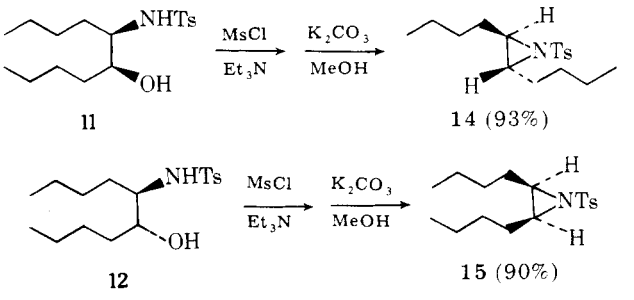
By mesylation (**5**) the oxygen of these vicinal hydroxyamides can be transformed into a leaving group, which should make further functionalization possible. One example of this is given by the intramolecular displacement of the methanesulfonyl group in the mesylates of hydroxyamides **11** and **12**, resulting in the stereospecific formation of *N*-tosylaziridines **14** and **15**, respectively (Scheme II). In this way an olefin can readily be transformed into the corresponding *N*-tosylaziridine with reversed geometry of the substituents[8] (i.e., cis olefins give *trans*-aziridines).

Some transformations of the ketoamide **2** are shown in Scheme III. Stereoselective reduction of the ketoamide **2** with lithium tri-*tert*-butoxyaluminum hydride gives *trans*-hydroxyamide **16** (quantitative, stereoselectivity >90%). The product was identical with an authentic sample prepared from the reaction of cyclohexene oxide with *p*-toluenesulfonamide sodium salt. Thus, a cyclic *cis*-hydroxyamide such as **1** may be transformed into its trans stereoisomer (**16**). Another reaction of some synthetic interest is the transformation of **2** into 5-cyanopentanal dimethyl acetal (**18**). The ketoamide was

Scheme I



Scheme II



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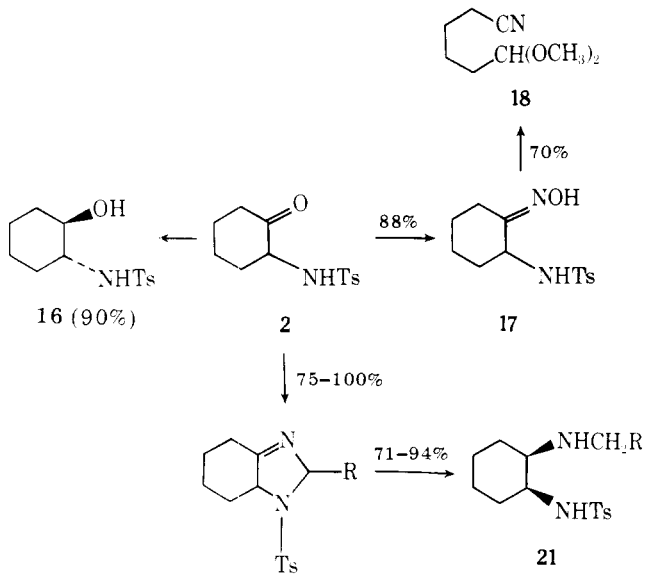
Scheme III



a, R = CH_3; b, R = C_2H_5; c, R = C_6H_5; d, R = H

transformed into the oxime **17**, which under Beckmann rearrangement conditions underwent ring opening[9] to yield **18**.

Condensation of the ketoamide **2** with an aldehyde and ammonia resulted in cyclization and gave imidazoline compounds **19** in good to high yields. The structure of the compounds **19** follows from their spectral data. The NMR spectra of these imidazoline compounds showed large long-range homoallylic couplings across nitrogen (see Experimental Section). The analogous reaction of **2** using acetone in place of the aldehyde proceeded less readily, and only 32% of the corresponding imidazoline compound could be isolated. Condensation of the acyclic ketoamide obtained from Jones oxidation of **12** with ammonia and acetaldehyde gave the analogous imidazoline compound **20** in 68% isolated yield. Thus, heterocyclic compounds like **19** and **20** can be prepared from an olefin in three simple steps (hydroxyamination–Jones oxidation–condensation) and this sequence should be useful in organic synthesis.

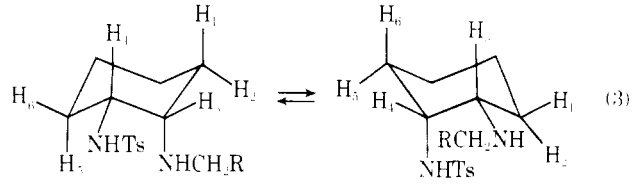
Reduction of the imidazolines **19** and **20** with $LiAlH_4$, which proceeded readily, resulted in opening of the imidazoline ring, and vicinal *N*-tosyl-*N'*-alkyldiamines **21** and **22** were isolated. The reduction of imidazoline **20** gave a mixture of the two possible diastereoisomers in an approximate ratio of 2:1, as shown by NMR analysis. On the other hand, reduction of the ring-fused imidazolidine **19** was highly stereoselective, giving only one of the two possible diastereoisomers. On the basis of NMR analyses we have assigned cis stereochemistry to diamines **21**, obtained from **19**, which is consistent with a cis-fused imidazoline intermediate in the reduction step. No trans isomer could be detected by NMR methods (<5%). The vicinal coupling constants determined for diamines **21** are given in Table I. The low value of J_{34} (3.9–4.0 Hz) together with the magnitude of the other coupling constants are only compatible with a cis configuration of the substituents, where two chair conformations are in rapid equilibrium (eq 3).[10,11] The same magnitude of coupling constants has been observed in 1,2-cyclohexanediol derivatives.[11]

We have examined the epoxidation reaction of allylic amide **23**, derived from cyclohexene according to eq 2. On epoxidation of **23** with *m*-chloroperbenzoic acid (MCPBA), the oxygen is introduced on the same side as the *p*-toluenesulfonamide group with high stereoselectivity (eq 4). In contrast, the alkylated *p*-toluenesulfonamide **24** showed a preference for anti epoxidation (eq 5). The syn-directive effects of allylic hydroxyl and allylic amido (acylamino) groups are well known in the stereoselective epoxidation of double bonds by peracids.[12] Our results demonstrate that an allylic *p*-toluenesulfonamido group also shows the same synthetically useful syn-directive effect with high stereoselectivity (96–98% syn addition). It thus appears that an allylic group with an acidic hydrogen is what is needed to obtain this directive effect in the epoxidation of olefins.

Table I. Vicinal Coupling Constants for Diamines 21[a,b]

	J_{13}	J_{23}	J_{34}	J_{45}	J_{46}
21a[c]	4.6	7.8	3.9	6.1	2.9
21b[c]	4.9	7.8	4.0	6.1	2.9
21c[d]	3.6	8.2	3.9	5.8	2.6
21d[d]	4.0	8.4	4.0	5.9	2.7

[a] Spectra were recorded on a Bruker WP-200 FT spectrometer. [b] Coupling constants were determined using spin decoupling and are given in hertz. [c] Acetone-d_6. [d] $CDCl_3$.



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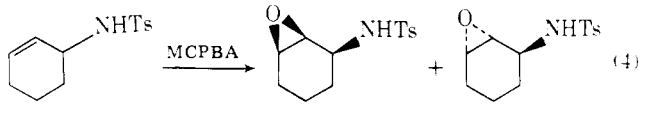
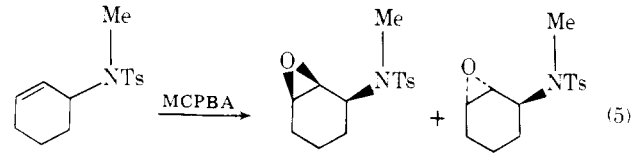


23

98:2 (in benzene, 5 °C)
96:4 (in CH_2Cl_2, 25 °C)



24

30:70 (in CH_2Cl_2, 25 °C)

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 or 257 spectrophotometer. NMR spectra were run on a Varian T-60 or a Bruker WP 200 FT spectrometer. Mass spectra were obtained using an LKB 9000 spectrometer. All olefins were obtained from Chemical Samples. MCPBA (*m*-chloroperbenzoic acid) was purchased from Aldrich. Hydroxysulfonamides **1**, **11**, and **12** were prepared according to the earlier described procedure for osmium-catalyzed oxyamination.[2] Allylic amide **23** was prepared according to ref 5. Preparative thin-layer chromatography was performed on silica gel.

Jones Oxidation of 1 to 2. To a solution of **1** (135 mg, 0.5 mmol) in acetone (10 mL) was added Jones reagent[13] under stirring until the developed yellow color remained unchanged. The resulting yellow mixture was stirred for an additional 10 min at room temperature, and then ethanol was added to destroy excess oxidizing agent. The mixture was poured into water and extracted with ether. The organic phase was dried (Na_2SO_4) and the solvent evaporated to give a crystalline compound (**2**) (134 mg, quantitative): mp 135–136 °C (hexane–chloroform) (lit.[14] 136–137 °C); NMR ($CDCl_3$) δ 7.1–7.9 (m, 4, aromatic protons), 5.82 (d, 1, NH), 3.7 (m, 1, CH–N), 2.42 (s, 3, CH_3), 1.3–2.7 (m, 8); IR (KBr) 3270, 1700 cm^{-1}.

Jones Oxidation of 12. 5-(*p*-Toluenesulfonamido)-6-decanone (13). Using the same procedure, **12** (580 mg) gave ketoamide **13** (540 mg, 94%): mp 62–63 °C (ethanol–water); IR (KBr) 3260, 2950, 1710, 1335, 1165, 1090, 810 cm^{-1}.

Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.74; H, 8.36; N, 4.30. Found: C, 63.03; H, 8.60; N, 4.17.

Reduction of 1 by Sodium in Liquid Ammonia to 3. To a solution of 1 (200 mg, 0.74 mmol) in liquid ammonia (20 mL) was added sodium (115 mg, 5 mmol) in small portions. Each addition gave a blue color which rapidly disappeared. On addition of more sodium (40 mg) the blue color reappeared, remained unchanged for 30 min, and then finally turned green after 1 h. Solid sodium acetate was added until the green color disappeared, and the ammonia was allowed to evaporate. Water (10 mL) was added to the residue, and the mixture was extracted with ethanol–chloroform (1:2, 5 × 15 mL). The organic phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a white solid (83 mg, 97%), which was identical with an authentic sample of 3 prepared according to ref 15, mp 70–71 °C (lit.[15] 71–72 °C).

Acetylation of 1 (4). The hydroxyamide 1 (135 mg, 0.5 mmol) was treated with acetic anhydride (200 mg, 2 mmol) in pyridine (10 mL) at 60 °C for 5 h. The mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with 2 N HCl solution (4 × 10 mL) and brine (2 × 10 mL) and then dried (Na_2SO_4) and concentrated to give a viscous oil (4) which was pure enough by TLC and GLC assay: NMR ($CDCl_3$) δ 7.1–7.9 (m, 4, aromatic protons), 5.90 (d, 1, NH), 4.75 (m, 1, CH–O), 3.35 (m, 1, CH–N), 2.42 (s, 3, CH_3), 2.00 (s, 3, CH_3CO), 1.1–2.0 (m, 8); IR (neat) 3290, 1760 cm^{-1}.

Mesylation of 1 (5). To a solution of 1 (538 mg, 2.0 mmol) and triethylamine in THF (20 mL) under N_2 was added methanesulfonyl chloride (274 mg, 2.4 mmol) at 0 °C under stirring. The resulting solution was stirred at 0 °C for 1 h and then at 20 °C for an additional 30 min. The reaction mixture was poured into water and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried, and concentrated to give a yellow solid (684 mg, 98%): mp 126–128 °C (hexane–chloroform); NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic), 5.66 (d, 1, NH), 4.8 (m, 1, CH–O), 3.3 (m, 1, CHN), 3.10 (s, 3, SO_2CH_3), 2.44 (s, 3, CH_3), 1.1–2.0 (m, 8); IR (KBr) 3290, 1175, 1160, 915, 890 cm^{-1}.

Trimethylsilylation of 1 (6). A solution of 1 (135 mg, 0.5 mmol) and hexamethyldisilazane (161 mg, 1.0 mmol) in THF (10 mL) was stirred at room temperature for 15 h under nitrogen. The mixture was poured into water (30 mL) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated to give a white solid (170 mg, quantitative): mp 91–93 °C (hexane–benzene); NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic), 4.93 (d, 1, NH), 3.8 (m, 1, CH–O), 3.2 (m, 1, CH–N), 2.50 (s, 3, CH_3), 1.1–2.0 (m, 8), 0.1 (s, 9, $SiMe_3$); IR (KBr) 3280, 835 cm^{-1}.

Reaction of 1 with Formaldehyde in the Presence of Hydrochloric Acid. Oxazolidine 7. Hydroxyamide 1 (489 mg, 1.82 mmol), formaldehyde (2 mL of a 37% aqueous solution), and concentrated HCl (0.2 mL) in ethanol (0.2 mL) were refluxed for 1 h. The mixture was cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried (Na_2SO_4) and concentrated to give a viscous oil which was purified by preparative TLC (ethyl acetate–hexane, 1:1): yield 485 mg (95%); mp 78–79 °C (ethanol); NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic), 4.98, 4.77 (AB quartet, 2, J_{AB} = 4.4 Hz), 3.2–4.0 (m, 2, CH–O, CH–N), 2.46 (s, 3, CH_3), 1.0–2.1 (m, 8).

Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.37. Found: C, 59.89; H, 6.82; N, 4.79; S, 11.24.

Reaction between Hydroxyamide 1 and Acrylonitrile in the Presence of Base. Preparation of 8. To a solution of 1 (250 mg, 0.93 mmol) in dioxane (10 mL) was added 2 M KOH (0.17 mL) and acrylonitrile (0.75 mL). The resulting mixture was refluxed for 5 h. A second addition of 2 M KOH (0.17 mL) and acrylonitrile (0.75 mL) was made, and the reaction mixture was refluxed for another 5 h. Extractive workup gave a dark brown oil, which was subjected to preparative TLC (ether–hexane, 60:40; two developments). The UV-active band at R_f 0.4–0.5 afforded an oil (225 mg, 75%): NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic), 4.1 (m, 1, CH–O), 3.6 (m, 1, CH–N), 3.53 (t, 2, CH_2N), 2.8–3.0 (m, 2, CH_2CN), 2.4 (s, 3, CH_3), 1.0–2.0 (m, 8); IR (neat) 3600, 2250 cm^{-1}.

N-Allylation of 1 (9). Hydroxyamide 1 (200 mg, 0.74 mmol), allyl bromide (0.26 mL, 30 mmol), and potassium carbonate (0.8 g) were refluxed in acetone (10 mL) for 15 h. Acetone was removed in vacuo, water was added, and the reaction mixture was extracted using ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Concentration of the solvent gave a crude product which was purified by preparative TLC (ethyl acetate–hexane, 40:60). The UV-active band at R_f 0.50–0.65 gave a viscous oil (225 mg, 98%): NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 5.8 (m, 1, CH=), 4.9–5.25 (m, 2, CH_2=), 3.5–4.4 (m, 4, CH_2–N, CH–O, CH–N), 2.42 (s, 3, CH_3), 1.0–2.1 (m, 8); IR (neat) 3530, 1325, 995, 910, 805 cm^{-1}.

N-Methylation of 1 (10). Hydroxyamide 1 (135 mg, 0.5 mmol), potassium *tert*-butoxide (56 mg, 0.5 mmol), and methyl iodide (0.2 mL, 3.2 mmol) were stirred in *tert*-butyl alcohol (10 mL) at 70 °C for 15 h. Extractive workup gave a crude product, which was purified by preparative TLC (ethyl acetate–hexane, 45:55): yield 123 mg (87%); mp 126–127 °C (hexane–chloroform); NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic protons), 4.2 (m, 1, CH–O), 3.7 (m, 1, CH–N), 2.95 (s, 3, N–CH_3), 2.45 (s, 3, CH_3), 2.17 (s, 1, OH), 1.0–2.0 (m, 8); IR (KBr) 3550, 1320, 1150, 900, 805, 760 cm^{-1}.

Formation of Aziridines 14 and 15. To a solution of hydroxyamide 11 (327 mg, 1.0 mmol) in THF (10 mL) was added triethylamine (120 mg, 1.2 mmol) and methanesulfonyl chloride (90 μL, 1.2 mmol) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for an additional 30 min. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated. The resulting oil was dissolved in methanol (10 mL) and treated with potassium carbonate (0.3 g) at room temperature. After stirring for 30 min, most of the solvent was evaporated and the residue extracted with ethyl acetate. Concentration of the extract gave an oil, which was submitted to preparative TLC (ethyl acetate–hexane, 1:3). The UV-active band at R_f 0.5–0.6 afforded 14 as a viscous oil (228 mg, 93%): NMR ($CDCl_3$) δ 7.2–8.0 (m, 4, aromatic), 2.63 (t, 2, CH–N–CH), 2.47 (s, 3, CH_3), 0.6–2.0 (m, 18). The same procedure gave the stereoisomeric aziridine 15 (753 mg, 90%) starting from 12 (890 mg, 2.7 mmol): NMR ($CDCl_3$) δ 7.2–8.0 (m, 4, aromatic), 2.77 (t, 2, CH–N–CH), 2.47 (s, 3, CH_3), 0.6–1.8 (m, 18).

Reduction of Ketoamide 2 with Lithium Tri-*tert*-butoxyaluminum Hydride to *trans*-Hydroxyamide 16. A solution of 2 (27 mg, 0.1 mmol) in dry ether (3 mL) was treated with lithium tri-*tert*-butoxyaluminum hydride (30 mg, 0.12 mmol) under nitrogen. After the reaction mixture was stirred for 1 h at 20 °C, water (2 drops) was added. GLC analysis showed the same retention time as an authentic sample of *trans*-*N*-tosyl-2-aminocyclohexanol (16), mp 123–125 °C (lit.[16] 128 °C) (prepared from cyclohexene oxide and the sodium salt of *p*-toluenesulfonamide), and that the stereospecificity in the reduction step was >90%.

Conversion of Ketoamide 2 to Oxime 17. To a suspension of 2 (1.07 g, 4.0 mmol) and hydroxylamine hydrochloride (500 mg, 7.0 mmol) in water (100 mL) was added 10 mL of a 2 N NaOH solution. The resulting mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water (200 mL), carefully neutralized with 1 N HCl solution, and then extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a white solid (1.0 g, 88%): mp 180–181 °C; NMR (acetone-d_6) δ 9.76 (s, 1, NOH), 7.2–7.8 (m, 4, aromatic), 6.3 (d, 1, NHTs), 3.7 (m, 1, CHN), 2.4–3.2 (m, 2), 2.37 (s, 3, CH_3), 1.0–2.3 (m, 6); IR (KBr) 3270, 1080, 895 cm^{-1}.

Conversion of 17 to 18. To a stirred solution of 17 (100 mg, 0.35 mmol) in dry THF (5 mL) was added thionyl chloride (40 μL, 0.54 mmol) at 0 °C under nitrogen. After stirring for 10 min, methanol (4 mL) was added and the reaction mixture was allowed to reach room temperature and was left for 2 h. The mixture was diluted with ethyl acetate and washed with brine. The organic phase was dried (Na_2SO_4) and concentrated to give a semisolid mass (120 mg) which was submitted to preparative TLC (ether–hexane, 2:1; two developments). The band at R_f 0.6–0.7 provided acetal 18[17] (39 mg, 70%) as an oil: NMR ($CDCl_3$) δ 4.33 (m, 1, CH), 3.34 (s, 6, OCH_3), 1.2–2.8 (m, 8); IR (neat) 2240, 1125, 1070, 950 cm^{-1}.

Formation of Imidazoline 19a. The ketoamide 2 (499 mg, 1.87 mmol), acetaldehyde (0.50 mL), and aqueous ammonia (1.2 mL, 25%) were stirred in ethanol (7 mL) for 2 h at room temperature. The mixture was poured into water (25 mL) and extracted with ether (3 × 15 mL). The organic phase was dried (Na_2SO_4) and concentrated to give white crystals of **19a** (529 mg, 97%): mp 133–134 °C (hexane–chloroform, 9:1); NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 5.40 (m, 1, N–CH_A–N, homoallylic coupling across nitrogen,[18] J_{AX} = 2.0 and J_{AY} = 2.7 Hz as determined by spin decoupling), 3.97 (m, 1, CH–NTs), 2.43 (s, 3, CH_3), 1.3–2.6 (m, 8), 1.58 (d, J = 6.1 Hz, 3, CH_3); IR (KBr) 2930, 1670, 1340, 1305, 1160, 1120, 1095, 990, 820, 810 cm^{-1}; mass spectrum, *m/e* 292 (M^+), 277, 155, 137, 91.

Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.48; H, 6.67; N, 9.31.

The same procedure was used for the preparation of the following compounds.

19b was prepared from **2**, propionaldehyde, and ammonia (reaction time 2 h): yield 100%; mp 104.5–105.5 °C (hexane); NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 5.38 (m, 1, N–CH–N), 3.98 (m, 1, CH–NTs), 2.43 (s, 1, CH_3), 1.3–2.6 (m, 10, CH_2 in ethyl group, cyclohexane protons), 0.95 (t, 3, CH_3); IR (KBr) 2940, 1670, 1340, 1165, 1100 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.65; H, 7.07; N, 8.98.

19c was prepared from **2**, benzaldehyde, and ammonia (reaction

time 2 h). The product was purified by preparative TLC (ethyl acetate–hexane, 1:2): yield 75%; mp 115–117 °C (hexane); NMR ($CDCl_3$) δ 7.2–7.7 (m, 9, aromatic), 6.39 (br t, 1, N–CH_A–N, J_{AX} = 2.1, J_{AY} = 2.8 Hz), 4.28 (m, 1, CH–NTs), 2.5–2.7 (m, 2, CH_2), 2.40 (s, 3, CH_3), 1.3–2.3 (m, 6); IR (KBr) 2930, 1655, 1165, 1095, 995 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.48; H, 6.26; N, 7.68.

19d was prepared from **2**, formaldehyde (37% aqueous solution), and ammonia at 60 °C for 4 h. The product was purified by preparative TLC (ethyl acetate–hexane, 1:2): yield 80%; mp 90–92 °C (hexane); NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic), 5.07 (m, 2, N–CH_2–N), 3.93 (m, 1, CH–NTs), 2.40 (s, 3, CH_3), 1.3–2.6 (m, 8).

Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.39; H, 6.59; N, 10.01.

1-Tosyl-2-methyl-4,5-dibutyl-2,5-dihydroimidazole (20) was prepared from ketoamide **13** (246 mg, 0.76 mmol), acetaldehyde (0.40 mL), and ammonia (0.60 mL, 25%) in ethanol (4 mL) at 60 °C for 24 h. The product was purified by preparative TLC (ethyl acetate–hexane, 1:2) to give a viscous oil (180 mg, 68%): NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 5.44 (m, 1, N–CH–N), 4.20 (m, 1, CH–NTs), 2.39 (s, 3, CH_3), 1.51 (d, 3, CH_3), 0.7–2.3 (m, 18).

Anal. Calcd for $C_{19}H_{30}N_2O_2S$: C, 65.11; H, 8.63; N, 7.99. Found: C, 65.20; H, 8.61; N, 7.82.

9-Tosyl-7,9-diaza-8,8-dimethylbicyclo[4.3.0]non-6-ene was prepared from ketoamide **2** (208 mg, 0.78 mmol), acetone (0.5 mL), and ammonia (0.5 mL, 25%) in ethanol (3 mL) at room temperature for 24 h. The product was purified by preparative TLC (ethyl acetate–hexane, 1:2): yield 75.4 mg (32%); NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 4.06 (four lines, J = 10.6, 5.7 Hz, 1, CH–NTs), 2.43 (s, 3, CH_3 tosyl), 1.74 (s, 3, CH_3), 1.56 (s, 3, CH_3), 1.2–2.7 (m, 8).

Reduction of Imidazoline 19a to Diamine 21a. The imidazoline compound **19a** (166 mg, 0.56 mmol) was treated with $LiAlH_4$ (40 mg) in dry ether (8 mL) for 1 h. The excess hydride was destroyed by adding a few drops of water and stirring for 1 h. The reaction mixture was filtered, and the inorganic precipitate was washed several times with ether. The ether phase was concentrated and the residue was treated with hexane and cooled. The crystalline material was collected by filtration (152 mg, 92%): mp 111–112 °C; NMR (acetone-d_6) δ 7.2–7.8 (m, 4, aromatic), 3.18 (m, 1, CH–NTs), 2.49 (m, 1, CH–NEt), 2.42 (s, 3, CH_3), 1.8–2.4 (m, 2, AB part of ABX_3 pattern, ΔAB = 0.34 ppm), 1.2–1.7 (m, 8, cyclohexane ring), 0.89 (t, 3, CH_3); IR (KBr) 3310, 3180, 2920, 1410, 1330, 1285, 1160, 1090, 1005, 810 cm^{-1}; mass spectrum, m/e 296 (M^+), 290, 155, 141, 124, 96, 91.

Anal. Calcd for $C_{15}H_{24}N_2O_2S$: C, 60.78; H, 8.16; N, 9.45. Found: C, 60.80; H, 8.33; N, 9.16.

The same procedure was used for the preparation of the following diamines.

21b from 19b: yield 84%; mp 96–98 °C (hexane); NMR (acetone-d_6) δ 7.2–7.8 (m, 4, aromatic), 3.19 (m, 1, CH–NTs), 2.49 (m, 1, CH–*N*-propyl), 2.43 (s, 3, CH_3), 1.80–2.00 and 2.15–2.30 (m, 2, NCH_2), 1.20–1.65 (m, 10, CH_2 in propyl group, cyclohexane ring), 0.77 (t, 3, CH_3); IR (KBr) 3320, 3280, 3190, 2930, 1330, 1165, 810 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}N_2O_2S$: C, 61.90; H, 8.44; N, 9.02. Found: C, 62.16; H, 8.71; N, 8.82.

21c from 19c: yield 94%; mp 83–84 °C (hexane); NMR ($CDCl_3$) δ 7.1–7.8 (m, 9, aromatic), 3.41, 3.28 (AB quartet, J = 13.3 Hz, 2, CH_2Ph), 3.21 (m, 1, CH–NTs), 2.51 (m, 1, CH–*N*-benzyl), 2.36 (s, 3, CH_3), 1.2–1.7 (m, 8).

Anal. Calcd for $C_{20}H_{26}N_2O_2S$: C, 67.01; H, 7.31; N, 7.81. Found: C, 67.17; H, 7.49; N, 7.78.

21d from 19d: yield 71%; mp 83–85 °C (hexane); NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 3.19 (m, 1, CH–NTs), 2.42 (s, 3, CH_3 tosyl), 2.34 (m, 1, CH–*N*-methyl), 2.02 (s, 3, CH_3–N), 1.2–1.7 (m, 8).

Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85; N, 9.92. Found: C, 59.30; H, 7.88; N, 9.59.

***N*-Tosyl-*N'*-ethyl-5,6-diaminodecane (22) from 20:** yield 90%; NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 3.17 (m, 1/3, CH–NTs in minor diastereoisomer), 3.08 (m, 2/3, CH–NTs in major diastereoisomer), 2.55 (m, 1, CH–NEt in both diastereoisomers), 2.42 (s, CH_3 in minor diastereoisomer), 2.41 (s, CH_3 in major diastereoisomer), 2.05–2.40 (m, 2, CH_2N), 1.02 (t, 3 × 2/3, CH_3 in ethylamino group), 0.96 (t, 3 × 1/3, CH_3 in ethylamino group), 0.7–1.7 (m, 18).

Anal. Calcd for $C_{19}H_{34}N_2O_2S$: C, 64.36; H, 9.67; N, 7.90. Found: C, 64.35; H, 9.75; N, 7.73.

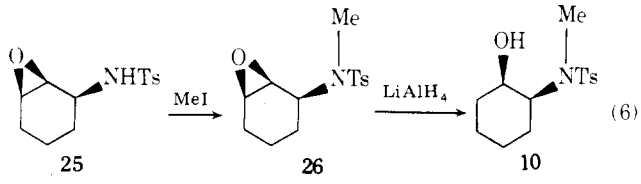
Epoxidation of Allylic Amide 23 in Benzene at 5 °C. To a stirred solution of **23** (150.6 mg, 0.6 mmol) in benzene (2.5 mL) at 5 °C was added a cold solution of MCPBA (85%, 201.2 mg, 1 mmol) in benzene (2.5 mL). The mixture was left overnight in a refrigerator (3–5 °C). The crystalline benzoic acid that formed was removed by filtration, and the resulting clear solution was treated with cold 10% Na_2SO_3 to destroy excess peracid. The organic layer was washed with saturated $NaHCO_3$, water, and brine. The organic phase was dried ($MgSO_4$) and concentrated to give 170 mg of a viscous oil (maximum theoretical 160 mg) which solidified on standing. GLC analysis (10% UCW 98) at 200 °C showed two peaks in a relative ratio of 98:2: NMR ($CDCl_3$) δ 7.2–7.9 (m, 4, aromatic), 5.25 (d, 1, NH), 3.67 (m, 1, CH–N), 3.20 (m, 1, CH–O), 2.98 (m, 1, CH–O), 2.43 (s, 3, CH_3), 1.1–2.0 (m, 6).

Epoxidation of Allylic Amide 23 in Methylene Chloride at 25 °C. The epoxidation was run in methylene chloride at 25 °C using the same procedure as above. GLC showed peaks of relative area 96:4.

Allylic Sulfonamide 24 from 23. **23** was treated with methyl iodide and potassium carbonate in refluxing acetone (cf. conversion of **1** to **9**).

Epoxidation of 24. The epoxidation was run in methylene chloride at 25 °C using the same procedure as above. GLC analysis showed peaks with a ratio of 70:30.

Configurational Assignment of Epoxysulfonamides 25 and 26. The sequence was performed as shown in eq 6.



(6)

Methylation of 25 to 26. A 0.954-g (2.0-mmol) amount of sodium hydride (50% oil dispersion) was weighed into a 25-mL round-bottom flask equipped with an N_2 inlet, a magnetic stirrer bar, and a serum cap. The sodium hydride was washed twice with dry hexane via syringe techniques, dried by passing N_2 through the flask, and then suspended in reagent DMF (5 mL). A solution of crude epoxysulfonamide **25** (obtained from epoxidation of 1 mmol of **23**) and methyl iodide (100 μL, 0.228 g, 1.6 mmol) in DMF (5 mL) was added via a cannula, and the reaction mixture was stirred for 12 h. The reaction mixture was poured into water (30 mL) and extracted with ether (3 × 20 mL). The organic phase was washed with water, dried ($MgSO_4$), and concentrated. In order to remove traces of DMF, the crude product was dissolved in benzene (20 mL) and washed with water (3 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 0.22 g (78% based on starting material) of a yellow oil. The product (**26**) showed only a single peak on GLC analysis (3% OV-17) with the same retention time as the minor product from epoxidation of **24:** NMR ($CDCl_3$) δ 7.2–7.8 (m, 4, aromatic), 4.1 (m, 1, CH–N), 2.8–3.1 (m, 2, CH–O–CH), 2.90 (s, 3, N–CH_3), 2.43 (s, 3, CH_3) 1.1–2.0 (m, 6). This product was used without further purification in the subsequent $LiAlH_4$ reduction.

Reduction of 26 to 10. To a stirred suspension of $LiAlH_4$ (35 mg) in dry THF was added a solution of *N*-methylepoxysulfonamide **26** (182 mg, 0.65 mmol) in dry THF (5 mL). The reaction mixture was refluxed for 5 h and then quenched by treatment with an excess of saturated ammonium chloride solution. The mixture was extracted with ether (3 × 30 mL), and the organic phase was dried ($MgSO_4$) and evaporated to give 155 mg (85%) of white crystals. The crude material was one component by GLC. The product was identified (NMR, GLC, and mixture melting point) as *cis*-hydroxyamide **10** by comparison with an authentic sample of **10** (vide supra).

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Registry No.—**1**, 58107-40-7; **2**, 58107-57-6; **3**, 931-15-7; **4**, 69291-75-4; **5**, 58107-58-7; **6**, 69291-76-5; **7**, 69291-77-6; **8**, 69291-78-7; **9**, 69291-79-8; **10**, 58107-59-8; **11**, 58162-20-2; **12**, 58162-19-9; **13**, 69291-80-1; **14**, 69291-81-2; **15**, 69291-82-3; **16**, 69291-83-4; **17**, 69291-84-5; **18**, 24487-23-8; **19a**, 69291-85-6; **19b**, 69291-86-7; **19c**, 69291-87-8; **19d**, 69291-88-9; **20**, 69291-89-0; **21a**, 58825-97-1; **21b**, 69291-72-1; **21c**, 69291-73-2; **21d**, 69291-74-3; **22** (isomer A), 69291-90-3; **22** (isomer B), 69291-94-7; **23**, 57981-18-7; **23** (epoxide isomer), 69291-91-4; **24**, 69291-92-5; **24** (epoxide isomer), 69291-93-6; **25**, 69350-08-9; **26**, 69350-09-0; formaldehyde, 500-00-0; acrylonitrile, 107-13-1; allyl bromide, 106-95-6; methyl iodide, 74-88-4; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; 7,9-diaza-8,8-dimethylbicyclo[4.3.0]non-6-ene, 69309-41-7.

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Chiral High-Pressure Liquid Chromatographic Stationary Phases. 1. Separation of the Enantiomers of Sulfoxides, Amines, Amino Acids, Alcohols, Hydroxy Acids, Lactones, and Mercaptans

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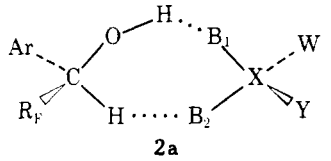
A silica gel bonded chiral fluoro alcoholic stationary phase has been prepared for the direct liquid chromatographic separation of the enantiomers of a wide assortment of solutes. The chiral fluoro alcohol utilized was selected on the basis of a rationally devised chiral recognition model that accounts for the origins of the observed separations and elution orders of the various enantiomers. More than 50 such resolutions are presented for sulfoxides, lactones, and derivatives of amines, amino acids, amino alcohols, alcohols, thiols, and hydroxy acids.

Owing to its conceptual simplicity and manifest utility, the direct liquid chromatographic separation of enantiomers upon chiral columns has been attempted many times. For most workers, the target has proven chimerical and, not withstanding the achievements of Gil-Av,[1] Lochmüller,[2] and Cram,[3] there has been little portent of the development of broad spectrum chiral stationary phases of extended scope and utility. While no single chiral stationary phase will ever suffice to separate all enantiomers, it is possible to rationally design chiral LC stationary phases that will separate the enantiomers of a wide assortment of solutes. The present paper describes one such stationary phase upon which we have to date separated the enantiomers of roughly 200 sulfoxides, lactones, amines, amino acids, amino alcohols, alcohols, hydroxy acids, and mercaptans. Insofar as this is our initial effort, we hardly consider this stationary phase to be perfected. Even so, from the high degree of latitude permissible in terms of structural variation, it is evident that literally thousands of racemic solutes can be resolved using the present stationary phase. We are confident that this is the first in a repertoire of rationally designed chiral LC stationary phases that will find widespread analytical and preparative applications.

If a chiral molecule (or stationary phase) is to have different affinities for enantiomers, it must have a minimum of three points of interaction with at least one of the enantiomers. Of these interactions, at least one must be stereochemically dependent and may be either bonding or repulsive.[4]

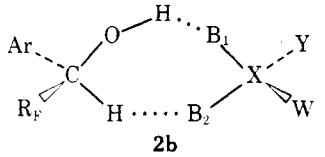
Prior NMR studies[6a–d] have shown that chiral type **1** fluoro alcohols afford two-point bonding to molecules bearing appropriate combinations of a wide variety of functional groups. Consequently, **1** interacts with enantiomers of an appropriate solute to afford diastereomeric chelate-like solvates, broadly depicted as **2a** and **2b**. These diastereomeric solvates differ in stability only if there is some mechanism whereby the alcohol substituents, R_F and W, "know" the relative locations of Y and Z. Momentarily neglecting interactions involving R_F and Y, it is obvious that a concomitant bonding interaction between W and Z will confer additional stability to **2a**, whereas repulsion between W and Z will cause **2a** to be of diminished stability. Obviously, R_F and Y are also involved in determining stability differences between solvates **2a** and **2b**. At present, these two groups seem to be relegated to rather minor roles and, as an *initial* simplifying assumption, we shall neglect whatever contributions these groups may make toward stability differences of the diastereomeric solvates. While virtually any kind of "third" interaction might be used to confer such stability differences, we initially have chosen to utilize an interaction differing in kind from the first two.

Chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol, **1a**, has previously been used as a chiral solvating agent for the NMR de-



2a

1



2b

R_F = Perfluoroalkyl
X = C, N, P, S, or a group of atoms
B_1 = hydrogen bond receptor
B_2 = carbinyl hydrogen bond receptor

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