

H, aliph CH₂), 2.68 (t, 12 H, CH₂N), 3.30-3.90 (m, 23 H, CH₂O).

Acknowledgment. We thank the National Institutes of Health for grants GM 33940 (physical studies) and GM 36262 (syntheses) which supported this work.

Supplementary Material Available: 60-MHz ¹H NMR spectra of compounds A, C, D, 1, and 2; infrared spectra for compounds C, D, and 1; and 100-MHz ¹³C NMR spectra for compound 1 (9 pages). Ordering information is given on any current masthead page.

Reactions and Diastereoselectivity of *N*¹-Arylsulfonyl Amidine Anions

Philip Magnus*¹ and John Moursoundis

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Received July 11, 1990

Cyclic *N*¹-alkyl-*N*²-sulfonyl amidine anions undergo stereoselective aldol reactions to give the syn diastereoisomer as the major product. The ratio of syn to anti aldol products decreases as the size of the *N*¹-alkyl increases. This is interpreted as a change in the transition state from an open-aldol to a closed-Zimmerman-Traxler-type transition state.

Compared to the extensive investigations of the alkylation and aldol chemistry of cyclic ketones, cyclic amides (lactams) have received considerably less attention.² Part of our alkaloid research program required alkylation of the amide enolate (endo-*E* enolate) 2 derived from the tetra-cyclic amide 1.³ While we could not successfully alkylate 1, the derived thioamide 3 underwent thio-Claisen rearrangement, as described by Takano⁴ to give 4. Thioamides exhibit increase diastereoselectivity in the aldol reaction compared to amides. For example, *N*-methylthio-pyrrolidone 5 gave the syn and anti aldol products 5a and 5b, respectively, in a 19:81 ratio, whereas *N*-methyl-pyrrolidone 6 gave the syn and anti aldol products 6a and 6b, respectively, in a 1:1 ratio (Scheme I).⁵

If the oxygen atom of an amide is replaced by a functional group that could exert either a steric or electronic effect, or a combination of both, changes in the diastereoselectivity might result. With this in mind we have examined some reactions of *N*¹-alkyl-*N*²-*p*-tolylsulfonyl amidine anions (Scheme II). It is somewhat surprising that the chemistry of these anions has not been previously explored.

For Scheme II, *N*-Ts geometry in 7 is *E* (X-ray crystallographic structural data on aldol adducts 51, 52, and 65). The *N*-lithio derivative 8 should undergo C-alkylation to give 9. The alkyl group R in 9 should assume an axial conformation, at least for a six-membered ring (A^{1,3} strain).⁶ It is difficult to predict the diastereoselectivity

of the reaction between the lithio derivative 8 and an aldehyde. On the one hand the prior literature shows that cyclic ketone enolates react with aldehydes under kinetic control (no demonstrable equilibration) to give the anti aldol product as the major diastereoisomer.² As mentioned above, the same situation is true for lactam enolates. A Zimmerman-Traxler-type transition state for an *E* enolate (cyclic amidine) predicts the anti diastereoisomer, whereas the so-called open transition state for an *E* enolate leads to the syn diastereomer.⁷ The *N*-lithio derivative 8, in a conformation where the *N*¹-alkyl group and *N*²-Ts group are *Z* (syn), in a Zimmerman-Traxler transition state 11, leads to the anti diastereoisomer 12, and the rotamer 13 leads to the syn diastereoisomer 14 (Scheme III).

An open transition state such as shown in Scheme IV leads to a reversal of the diastereoisomers for a particular orientation of the aldehyde. This simple analysis is severely complicated by the various steric interactions of the NTs group with the NR group and the R group in the aldehyde. These various manifestations of A^{1,3} steric strain will no doubt play important roles in transition states such as 11/13 (NTs, NR A^{1,3} strain) and 15 (NTs, R A^{1,3} strain), but before the fact it is difficult to make significant predictions regarding the preferred, if any, diastereoselectivity. Although two reasonable predictions are possible, the newly formed carbon-carbon bond in either *syn*-10 or *anti*-10 should be axial (for a six-membered ring) and remain axial 17. Conformational relaxation to the equatorial conformer 18 should be prevented by the A^{1,3} strain that develops when, and if, the stereochemical relationship between the NR and NTs functionality is *E*. This will depend upon the size of R, and as a consequence, there should be a trend in the extent of diastereoselectivity as a function of the bulk of R. There should also be a change in the diastereoselectivity as the size of the Ts group is altered (trisyl, for example). We have not examined this possibility.

The synthesis of *N*¹,*N*¹-dialkyl-*N*²-*p*-tolylsulfonyl amidines 7 was accomplished in a straightforward manner, using a reaction described in 1960 by King.⁸ Treatment

(1) Address correspondence to this author at The Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712.

(2) Evans, D. A. Stereoselective Alkylation Reactions of Chiral Metal Enolates In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press Inc.: 1984; Vol. 3, p 1. Heathcock, C. H. The Aldol Addition Reaction In Morrison, J. D., Ed.; *Asymmetric Synthesis*; Academic Press Inc.: 1984; Vol. 3, p 111.

(3) Magnus, P.; Ladlow, M.; Kim, C. S.; Boniface, P. *Heterocycles* 1989, 28, 951. Magnus, P.; Ladlow, M.; Elliott, J.; Kim, C. S. *J. Chem. Soc., Chem. Commun.* 1989, 518.

(4) Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* 1981, 1153. Takano, S.; Hirama, M.; Araki, T. K.; Ogasawara, K. *J. Am. Chem. Soc.* 1976, 98, 7084.

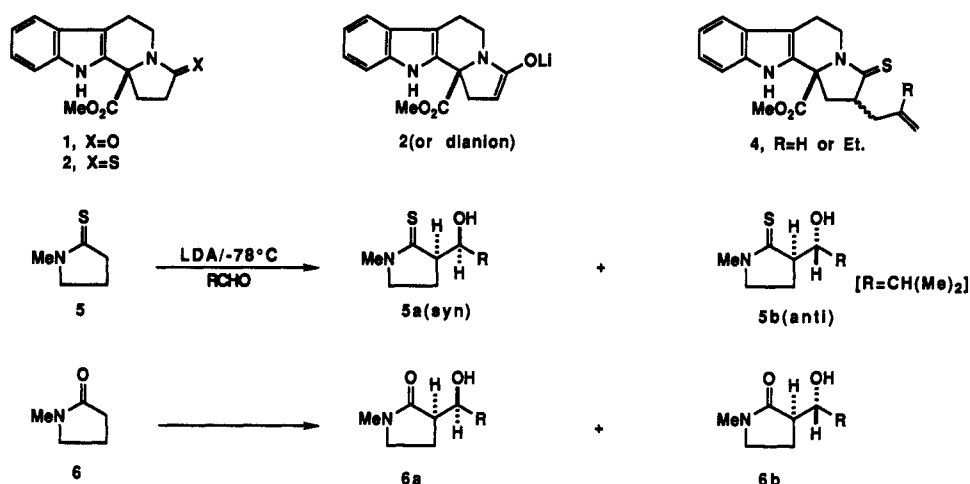
(5) Tamura, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* 1980, 102, 7808.

(6) Johnson, F. *Chem. Rev.* 1968, 68, 375. Hoffmann, R. W. *Chem. Rev.* 1989, 89, 1841.

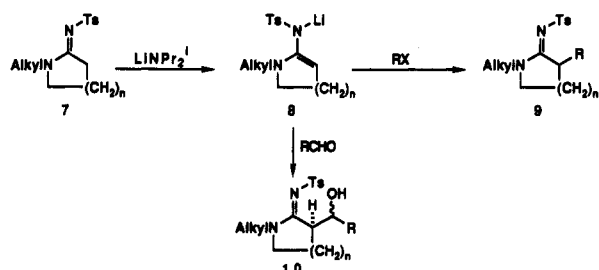
(7) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* 1957, 79, 1920.

(8) King, C. *J. Org. Chem.* 1960, 25, 352.

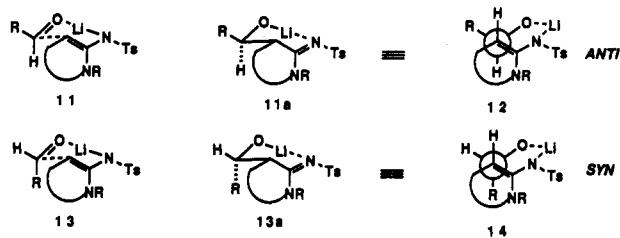
Scheme I



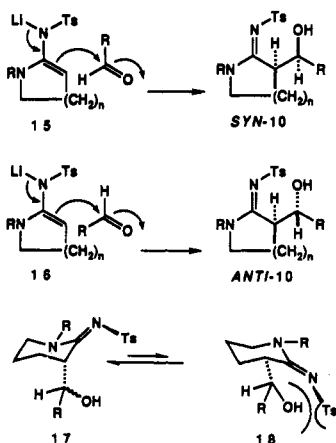
Scheme II



Scheme III

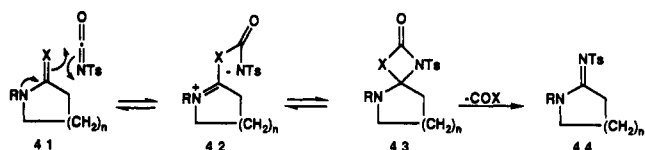


Scheme IV

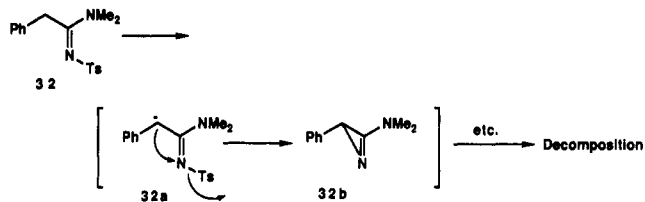


of amides with *p*-tolylsulfonyl isocyanate at room temperature gave the derived *N*¹-*p*-tolylsulfonyl amidines in excellent yields (ca. 90%) (Table I). While thioamides (entries 1, 2, 3, and 8) react more rapidly with *p*-tolylsulfonyl isocyanate, it offers no real advantages since they have to be made from the corresponding amide. In all cases the amidines 31 through 40 were isolated as a single stereoisomer, and on the basis of the X-ray data (for

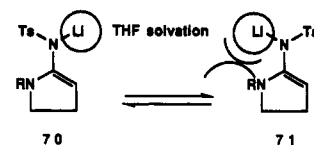
Scheme V



Scheme VI



Scheme VII



compounds 51, 52, and 65) they are presumably the *E* geometrical isomers. Scheme V shows a plausible mechanism for the conversion of amides 41 (X = O) and thioamides 41 (X = S) into their corresponding NTs amidines 44 via the dipolar intermediate 42 and the extrusion of CO₂ or COS from 43.

Before proceeding to examine the diastereoselectivity of the amidate anions derived from the amidines 33 through 40 in the aldol reaction, we investigated some simple alkylation reactions. Table II summarizes the results. The amidate anions derived from treatment of 32/33 and 37 with lithium diisopropylamide at -78 °C in tetrahydrofuran underwent clean monoalkylation. No dialkylation products could be detected. The amidate anion derived from the acyclic substrate 32 was not stable above approximately -20 °C. It has the potential to enter into Neber-type rearrangement chemistry, Scheme VI, and this may be the cause of its instability.⁹

Quenching of the amidate anions derived from the cyclic amidines with aldehydes at -78 °C gave high yields of the aldol adducts (Table III). Comparing the examples 5/6 (Scheme I) and the general tendency for *E* enolates (in cyclic systems) to give the anti aldol as the major product,

(9) O'Brien, *C. Chem. Rev.* 1964, 64, 81.

Table I

entry	substrate	conditions	NTs amidine	yield (%)
1		TsNCO/20 °C/THF/2 h		84%
2		TsNCO/20 °C/THF/5 h		80%
3		TsNCO/20 °C/THF/5 h		90%
4		TsNCO/20 °C/THF/18 h		92%
5		TsNCO/20 °C/THF/18 h		91%
6		TsNCO/20 °C/THF/18 h		89%
7		TsNCO/20 °C/THF/18 h		91%
8		TsNCO/20 °C/THF/5 h		91%
9		TsNCO/20 °C/THF/18 h		84%
10		TsNCO/20 °C/THF/2 h		90%
11		TsNCO/20 °C/THF/5 h		79%
12		TsNCO/20 °C/THF/5 h		83%

the contrast is substantial. Entries 1 and 2 show that the major diastereomer is the syn adduct. The relative stereochemistry of 51 and 52 was determined by single-crystal X-ray crystallography.¹⁰ The vicinal methine ¹H coupling in the syn diastereomers (49, 51, 55, 57, 59, and 61) is in the range of 9.0–9.9 Hz, and for the anti diastereomers (52, 56, 58, 60, and 62) this coupling is smaller, 4.5–5.7 Hz. Increasing the steric bulk of the N¹-alkyl group from Me (entry 1, syn:anti 86:14), Et (entry 5, syn:anti 64:36), *i*-Pr (entry 6, syn:anti 57:43), through to *t*-Bu (entry 7, syn:anti, 50:50) in the pyrrolidine series of compounds could be interpreted as changing the rotamer population, 70 versus 71 (Scheme VII). The predominance of the syn isomer in the aldol reaction of 33 (entry 1, Table III) is ascribed to the reaction of the anion via an open transition state involving the rotamer 71, rather than 70.

The rotamer 71 can react with an aldehyde in an open transition state to give the syn adducts (Scheme IV), whereas the rotamer 70 can adopt a Zimmerman-Traxler-type transition state that would lead to the anti adducts. The lithium atom is solvated by the tetrahydro-

Table II

entry	substrate	conditions	product	yield (%)
1	32	LDA/-78 to 0 °C/THF/MeI		62%
2	33	LDA/-78 to 0 °C/THF/MeI		70%
3	33	LDA/-78 to 0 °C/THF/H ₂ C=CHCH ₂ Br		90%
4	37	LDA/-78 °C/THF/Br-(CH ₂) ₄ Br		60%

furan and should be bulkier than the *p*-tolylsulfonyl group.¹¹ Therefore as the size of the N¹-alkyl group increases (Me → Et → *i*-Pr → *t*-Bu) so does the A^{1,3} steric interaction between Li-THF_{*n*}. This will favor the rotamer 70 and give increased amounts of the anti adducts. The same effect was seen in the piperidine series. Treatment of the anion derived from 37 (entry 10) with benzaldehyde 39 (entry 11) gave both the syn and anti adducts, 66/67 (1:1). The stereochemistry of 65 was established by single-crystal X-ray crystallography, and also clearly shows that the newly formed carbon-carbon bond is axial (see 17/18).¹⁰ The only electrophiles we have examined other than benzaldehyde are *t*-BuCHO and PhCOMe (entries 3 and 4, Table III), and in both cases a single diastereomer was isolated (53 and 54 respectively).

Experimental Section

General procedure for the synthesis of *N*-(4-methylphenyl)sulfonyl amidines 31 through 40.

p-Tolylsulfonyl isocyanate (1.0 equiv) was slowly added dropwise to a solution of the amide or thioamide (1.0 equiv) in tetrahydrofuran at 0 °C. The mixture was warmed to 20 °C, stirred for 16–30 h, and cooled to 0 °C to cause the direct crystallization of the amidines. In some cases crystallization was difficult; therefore, the solvent was evaporated in vacuo and the residue triturated with ether/pentane (1:1) or chromatographed over silica gel, eluting with ethyl acetate/hexane (1:1) to give the *N*-(4-methylphenyl)sulfonyl amidines.

3-Phenyl-1-(((4-methylphenyl)sulfonyl)imino)-*N,N*-dimethylpropylamine (31): mp 109–110 °C (from hexane/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 2.39 (3 H, s), 3.00 (3 H, s), 3.04 (3 H, s), 3.05–3.01 (2 H, m), 3.24–3.17 (2 H, m), 7.25 (2 H, d, *J* = 7.8 Hz), 7.30 (5 H, m), 7.87 (2 H, d, *J* = 7.8 Hz). Anal. Calcd for C₁₈H₂₂N₂O₂S: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.33; H, 6.75; N, 8.30.

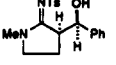
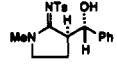
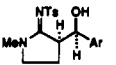
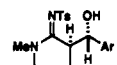
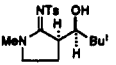
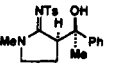
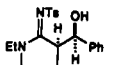
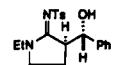
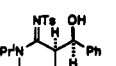
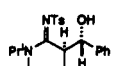
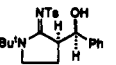
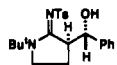
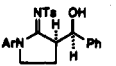
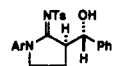
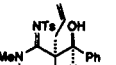
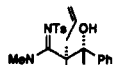
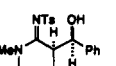
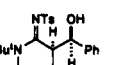
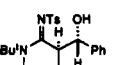
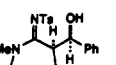
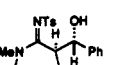
2-Phenyl-1-(((4-methylphenyl)sulfonyl)imino)-*N,N*-dimethylethylamine (32): mp 124–125 °C (from hexane/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 2.32 (3 H, s), 2.82 (3 H, s), 3.05 (3 H, s), 4.40 (2 H, s), 7.20 (5 H, m), 7.26 (2 H, d, *J* = 7.8 Hz), 7.85 (2 H, d, *J* = 7.8 Hz). Anal. Calcd for C₁₇H₂₀N₂O₂S: C, 64.55; H, 6.33; N, 8.86. Found: C, 64.50; H, 6.20; N, 8.71.

1-Methyl-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (33). **Typical Example.** *p*-Tolylsulfonyl isocyanate (9.13 mL, 0.06 mol) and 1-methylpyrrolidin-2-one (5.75 mL, 0.06 mol) in

(10) The complete details of the crystallographic data for 51, 52, and 65 are given in the supplemental material. Dr. John C. Huffman, Molecular Structure Center, Indiana University, IN 47405, is thanked for the X-ray analyses.

(11) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* 1985, 68, 1373. Seebach, D. *Angew. Chem., Int. Ed.* 1988, 27, 1624. Willard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* 1987, 109, 5539.

Table III^a

entry	substrate	reagent	products (syn/anti)	ratio (¹ H NMR/HPLC)	yield (%)	
1	33	PhCHO	 49	 50	86:14/82:18	88%
2	33	4-MeOC ₆ H ₄ CHO	 51	 52	88:12/87:13	87%
3	33	Bu/CHO	 53		100:0/100:0	86%
4	33	PhCOMe	 54		100:0/100:0	91%
5	34	PhCHO	 55	 56	64:36/76:33	90%
6	35	PhCHO	 57	 58	54:43/55:45	84%
7	36	PhCHO	 59	 60	50:50/48:52	81%
8	38	PhCHO	 61	 62	68:32/68:32	69%
9	47	PhCHO	 63	 64	50:50/56:44	68%
10	37	PhCHO	 65		100:0/100:0	82%
11	39	PhCHO	 66	 67	50:50/48:52	84%
12	40	PhCHO	 68	 69	68:32/67:33	77%

^a Yields refer to material after purification by chromatography. The ratios were measured before chromatography. Ar = 4-MeOC₆H₄CH₂.

dry tetrahydrofuran (15 mL) at 20 °C were stirred together for 18 h. Evaporation of the solvent in vacuo and crystallization of the residue from dichloromethane/*n*-hexane (1:1) gave **33** (13.6 g 92%): mp 163–164 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.08 (2 H, dt, *J*_s = 8.4 and 7.8 Hz), 2.43 (3 H, s), 3.00 (3 H, s), 3.10 (2 H, t, *J* = 8.4 Hz), 3.49 (2 H, t, *J* = 7.8 Hz), 7.29 (2 H, d, *J* = 8.1 Hz), 7.85 (2 H, d, *J* = 8.1 Hz); IR (CHCl₃) 1600 cm⁻¹. Anal. Calcd for C₁₂H₁₆N₂O₂S: C, 57.14; H, 6.35; N, 11.11. Found: C, 57.07; H, 6.21; N, 10.98. Similarly the thioamide **21** gave **33** in 90% yield.

1-Ethyl-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (34): mp 107–108 °C (CHCl₃/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.10 (3 H, t, *J* = 7.8 Hz), 2.01 (2 H, m), 2.37 (3 H, s), 3.00 (2 H, t, *J* = 7.5 Hz), 3.40–3.47 (5 H, m), 7.28 (2 H, d, *J* = 7.8 Hz), 7.78 (2 H, d, *J* = 7.8 Hz); IR (CHCl₃) 1580 and 1140 cm⁻¹. Anal. Calcd for C₁₄H₂₀N₂O₂S: C, 59.97; H, 7.19; N, 10.00. Found: C, 59.71; H, 7.14; N, 9.76.

1-Isopropyl-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (35): mp 90–91 °C (CHCl₃/hexane); ¹H NMR (300

MHz, CDCl₃) δ 1.13 (6 H, d, *J* = 7.5 Hz), 2.00 (2 H, quintet, *J* = 7.5 Hz), 2.39 (3 H, s), 3.03 (2 H, t, *J* = 7.5 Hz), 3.38 (2 H, t, *J* = 7.5 Hz), 4.55 (1 H, m), 7.24 (2 H, d, *J* = 9.0 Hz), 7.80 (2 H, d, *J* = 9.0 Hz); IR (CHCl₃) 1580 and 1140 cm⁻¹. Anal. Calcd for C₁₄H₂₀N₂O₂S: C, 59.97; H, 7.19; N, 10.00. Found: C, 59.71; H, 7.14; N, 9.76.

1-tert-Butyl-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (36): mp 91–92 °C (CHCl₃/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.14 (9 H, s), 1.87–1.98 (2 H, m), 2.38 (3 H, s), 3.07 (2 H, t, *J* = 8.1 Hz), 3.53 (2 H, t, *J* = 6.9 Hz), 7.23 (2 H, d, *J* = 9 Hz), 7.78 (2 H, d, *J* = 9 Hz). Anal. Calcd for C₁₅H₂₂N₂O₂S: C, 61.19; H, 7.54; N, 9.52. Found: C, 61.25; H, 7.67; N, 9.55.

1-Methyl-2-(((4-methylphenyl)sulfonyl)imino)piperidine (37): mp 109–110 °C (CHCl₃/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.75–1.79 (4 H, m), 2.39 (3 H, s), 3.02 (3 H, s), 3.04 (2 H, t, *J* = 6.3 Hz), 3.34 (2 H, t, *J* = 5.7 Hz), 7.24 (2 H, d, *J* = 8.4 Hz), 7.82 (2 H, d, *J* = 8.4 Hz). Anal. Calcd for C₁₃H₁₈N₂O₂S: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.37; H, 6.63; N, 10.27.

1-(4-Methoxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (38): mp 139–140 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.93–2.04 (2 H, m), 2.41 (3 H, s), 3.08 (2 H, t, *J* = 8.1 Hz), 3.32 (2 H, t, *J* = 7.2 Hz), 3.79 (3 H, s), 4.52 (2 H, s), 6.82 (2 H, d, *J* = 8.4 Hz), 7.14 (2 H, d, *J* = 8.4 Hz), 7.26 (2 H, d, *J* = 8.1 Hz), 7.83 (2 H, d, *J* = 8.1 Hz). Anal. Calcd for C₁₉H₂₂N₂O₃S: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.42; H, 5.90; N, 7.55.

1-tert-Butyl-2-(((4-methylphenyl)sulfonyl)imino)piperidine (39): mp 81–83 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.43 (9 H, s), 1.61–1.81 (4 H, m), 2.40 (3 H, s), 3.13 (2 H, t, *J* = 6.3 Hz), 3.38 (2 H, t, *J* = 6.0 Hz), 7.25 (2 H, d, *J* = 7.8 Hz), 7.80 (2 H, d, *J* = 7.8 Hz). Anal. Calcd for C₁₆H₂₄N₂O₂S: C, 62.31; H, 7.85; N, 9.09. Found: C, 62.64; H, 8.08; N, 9.24.

1-Methyl-2-(((4-methylphenyl)sulfonyl)imino)hexahydroazepine (40): mp 109–111 °C (ether/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.61–1.72 (6 H, m), 2.39 (3 H, s), 3.09 (3 H, s), 3.12–3.14 (2 H, m), 3.46–3.50 (2 H, m), 7.25 (2 H, d, *J* = 10.2 Hz), 7.83 (2 H, d, *J* = 10.2 Hz). Anal. Calcd for C₁₄H₂₀N₂O₂S: C, 59.97; H, 7.19; N, 10.00. Found: C, 60.13; H, 7.37; N, 10.14.

General Procedure for the Preparation of ((4-Methylphenyl)sulfonyl)imino *N,N*-Dialkyl Anions and Their Quenching with Alkylation Reagents and Carbonyl Compounds. A solution of lithium diisopropylamide in tetrahydrofuran (0.71 M, 2.0 mL, 1.42 mmol) at –78 °C was added dropwise to a solution of the amidine (1.0 mmol) in tetrahydrofuran (10–15 mL) at –78 °C. The mixture was stirred at –78 °C for 0.5 h and the electrophile (2 mmol) added. The resulting solution was stirred until thin layer chromatography (SiO₂, ethyl acetate) indicated complete consumption of the starting amidine (10 to 120 min). Water (10 mL) was added to the reaction mixture (at –78 °C) and the resulting slurry warmed to room temperature (ca. 25 °C). The solution was extracted with diethyl ether (3 × 10 mL), and the combined extracts were washed with saturated brine and dried (MgSO₄). Evaporation of the extract in vacuo gave the products, which were purified by direct crystallization or chromatography over silica gel, eluting with ethyl acetate–hexane. Diastereomer ratios were determined by ¹H NMR (300 MHz, CDCl₃) and analytical HPLC analysis of the crude unfractionated material prior to purification.

2-Phenyl-1-(((4-methylphenyl)sulfonyl)imino)-*N,N*-dimethylpropylamine (45): mp 159–160 °C (hexane/CH₂Cl₂); ¹H NMR (90 MHz, CDCl₃) δ 1.57 (3 H, d, *J* = 7.0 Hz), 2.35 (3 H, s), 2.70 (3 H, b), 2.90 (3 H, b), 5.48 (2 H, q, *J* = 7.0 Hz), 7.20 (7 H, b), 7.85 (2 H, d, *J* = 9.0 Hz). Anal. Calcd for C₁₈H₂₂N₂O₂S: C, 65.45; H, 6.67; N, 8.48. Found: C, 65.60; H, 6.60; N, 8.30.

1,3-Dimethyl-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (46): mp 75–76 °C (hexane/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 1.35 (3 H, d, *J* = 7.8 Hz), 2.39 (3 H, s), 2.94 (3 H, s), 3.33 (1 H, dt, *J*'s = 9.9 and 1.2 Hz), 3.59 (1 H, m), 3.75 (1 H, dt, *J*'s = 7.8 and 7.5 Hz), 7.42 (2 H, d, *J* = 7.8 Hz), 7.83 (2 H, d, *J* = 7.8 Hz). Anal. Calcd for C₁₃H₁₈N₂O₂S: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.40; H, 6.61; N, 10.48.

1-Methyl-3-allyl-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (47): mp 76–77 °C (hexane/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 1.85–1.94 (1 H, m), 2.00–2.16 (1 H, m), 2.20–2.30 (1 H, m), 2.36 (3 H, s), 2.62–2.64 (1 H, m), 2.90 (3 H, s), 3.29 (1 H, dt, *J*'s = 13 and 2 Hz), 3.34–3.53 (1 H, m), 3.70 (1 H, dt, *J*'s = 11 and 3 Hz), 5.03–5.09 (2 H, m), 5.66–5.80 (1 H, m), 7.21 (2 H, d, *J* = 10 Hz), 7.80 (2 H, d, *J* = 10 Hz). Anal. Calcd for C₁₅H₂₀H₂O₂S: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.53; H, 6.81; N, 9.68.

1-Methyl-3,3-tetramethylene-2-(((4-methylphenyl)sulfonyl)imino)piperidine (48): mp 144–145 °C (hexane/CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.40–1.60 (8 H, m), 1.60–1.68 (2 H, m), 1.76–1.86 (2 H, m), 2.14–2.26 (2 H, m), 2.38 (3 H, s), 3.45 (3 H, s), 7.20 (2 H, d, *J* = 7.8 Hz), 6.80 (2 H, d, *J* = 7.8 Hz). Anal. Calcd for C₁₇H₂₄N₂O₂S: C, 63.72; H, 7.55; N, 8.74. Found: C, 63.66; H, 7.45; N, 8.60.

rel-(3*S*,1'*R*)-1-Methyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (49): mp 178–179 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.71–1.89 (1 H, m), 2.05–2.16 (1 H, m), 2.39 (3 H, s), 2.87 (1 H, bs), 2.98 (3 H, s), 3.24 (1 H, ddd, *J*'s = 9.6, 8.7, and 1.2 Hz), 3.65 (1 H, q, *J* = 8.7 Hz), 3.98 (1 H, d, *J* = 9.6 Hz), 5.93 (1 H, s), 7.22–7.28 (3

H, m), 7.36 (2 H, dd, *J*'s = 7.8 and 7.5 Hz), 7.55 (2 H, d, *J* = 8.1 Hz), 7.86 (2 H, d, *J* = 8.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 19.99 (t), 21.41 (q), 32.31 (q), 50.63 (d), 51.93 (t), 73.54 (d), 125.54 (d), 126.05 (d), 127.01 (d), 128.21 (d), 129.08 (d), 141.32 (s), 141.78 (s), 142.44 (s), 169.35 (s); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₁₉H₂₂N₂O₃S: C, 63.94; H, 6.19; N, 7.82. Found: C, 63.78; H, 6.20; N, 7.70.

rel-(3*S*,1'*S*) diastereomer 50: mp 169–170 °C (CHCl₃/hexane); HRMS calcd for C₁₉H₂₂N₂O₃S 358.1251, found *m/e* 358.1321.

rel-(3*S*,1'*R*)-1-Methyl-3-(1'-hydroxy-4'-methoxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (51): mp 166–167 °C (CHCl₃/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.78–1.83 (1 H, m), 1.91–2.03 (1 H, m), 2.40 (3 H, s), 2.78 (1 H, bs), 2.98 (3 H, s), 3.24 (1 H, ddd, *J*'s = 9.8, 9.3, and 1.4 Hz), 3.61 (1 H, q, *J* = 9.3 Hz), 3.81 (3 H, s), 3.94 (1 H, d, *J* = 9.8 Hz), 5.87 (1 H, s), 6.89 (2 H, d, *J* = 8.4 Hz), 7.24 (2 H, d, *J* = 9.0 Hz), 7.45 (2 H, d, *J* = 9.0 Hz), 7.87 (2 H, d, *J* = 8.4 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₂₀H₂₄N₂O₄S: C, 61.83; H, 6.23; N, 7.22. Found: C, 61.69; H, 6.40; N, 7.14.

rel-(3*S*,1'*S*) diastereomer 52: mp 199–200 °C (CHCl₃/pentane); ¹H NMR (300 MHz, CDCl₃) δ 1.98–2.09 (1 H, m), 2.14–2.20 (1 H, m), 2.32–2.44 (1 H, m), 2.40 (3 H, s), 2.74 (3 H, s), 2.97 (1 H, t, *J* = 9.0 Hz), 3.09 (1 H, d, *J* = 4.5 Hz), 3.79 (3 H, s), 4.10 (1 H, t, *J* = 4.5 Hz), 5.48 (1 H, bs), 6.48 (2 H, d, *J* = 9.0 Hz), 7.27 (2 H, d, *J* = 7.5 Hz), 7.32 (2 H, d, *J* = 7.5 Hz), 7.89 (2 H, d, *J* = 9.0 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₂₀H₂₄N₂O₄S: C, 61.83; H, 6.23; N, 7.22. Found: C, 61.56; H, 6.40; N, 7.32.

rel-(3*S*,1'*R*)-1-Methyl-3-(1'-hydroxy-2',2'-dimethylpropyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (53): mp 161–162 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.05 (9 H, s), 1.94 (1 H, dd, *J*'s = 12.9 and 5.7 Hz), 2.19–2.24 (1 H, m), 2.40 (3 H, s), 2.96 (3 H, s), 3.25–3.31 (2 H, m), 3.68–3.81 (2 H, m), 7.26 (2 H, d, *J* = 7.8 Hz), 7.83 (2 H, d, *J* = 7.8 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₁₇H₂₆N₂O₃S: C, 60.33; H, 7.75; N, 8.38. Found: C, 59.99; H, 7.95; N, 8.23.

rel-(3*S*,1'*R*)-1-Methyl-3-(1'-hydroxy-1'-methylbenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (54): mp 184–185 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.81–1.93 (1 H, m), 1.84 (3 H, s), 2.00–2.11 (1 H, m), 2.41 (3 H, s), 2.71–2.78 (2 H, m), 2.77 (3 H, s), 4.00 (1 H, d, *J* = 9.3 Hz), 4.70 (1 H, s), 7.26–7.30 (5 H, m), 7.45–7.48 (2 H, m), 7.88 (2 H, d, *J* = 8.1 Hz). Anal. Calcd for C₂₀H₂₄N₂O₃S: C, 64.49; H, 6.50; N, 7.53. Found: C, 64.14; H, 6.25; N, 7.74.

rel-(3*S*,1'*R*)-1-Ethyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (55): mp 158–159 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.13 (3 H, t, *J* = 7.8 Hz), 1.73–1.88 (1 H, m), 2.05–2.13 (1 H, m), 2.40 (3 H, s), 2.50 (1 H, bs), 3.26 (1 H, ddd, *J*'s = 2.3, 9.3, and 2.4 Hz), 3.36–3.46 (1 H, m), 3.48–3.59 (1 H, m), 3.65 (2 H, q, *J* = 7.8 Hz), 3.99 (1 H, d, *J* = 9.6 Hz), 5.93 (1 H, s), 7.24–7.28 (3 H, m), 7.36 (2 H, dd, *J*'s = 7.2 Hz), 7.54 (2 H, d, *J* = 7.2 Hz), 7.87 (2 H, d, *J* = 8.4 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₂₀H₂₄N₂O₃S: C, 64.49; H, 6.50; N, 7.53. Found: C, 64.37; H, 6.51; N, 7.62.

rel-(3*S*,1'*S*) diastereomer 56: mp 139–140 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 0.85 (3 H, t, *J* = 6.6 Hz), 1.95–2.09 (1 H, m), 2.22–2.38 (1 H, m), 2.40 (3 H, s), 2.95 (1 H, dd, *J* = 9.9 and 9.6 Hz), 3.09–3.19 (1 H, m), 3.21–3.37 (3 H, m), 4.15 (1 H, dd, *J* = 9.0 and 4.5 Hz), 5.58 (1 H, d, *J* = 5.1 Hz), 7.25–7.29 (5 H, m), 7.43 (2 H, dd, *J* = 6.9 and 2.4 Hz), 7.88 (2 H, d, *J* = 9 Hz); IR (CHCl₃) 3300 and 1602 cm⁻¹. Anal. Calcd for C₂₀H₂₄N₂O₃S: C, 64.49; H, 6.50; N, 7.53. Found: C, 64.42; H, 6.58; N, 7.69.

rel-(3*S*,1'*R*)-1-Isopropyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (57): mp 185–186 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.11 (3 H, d, *J* = 6.6 Hz), 1.18 (3 H, d, *J* = 6.6 Hz), 1.67 (1 H, bs), 1.72–1.81 (1 H, m), 2.05–2.18 (1 H, m), 2.40 (3 H, s), 3.27 (1 H, ddd, *J* = 10.5, 9.3, and 1.8 Hz), 3.53 (1 H, q, *J* = 9.0 Hz), 4.01 (1 H, d, *J* = 9.9 Hz), 4.55 (1 H, s, *J* = 6.6 Hz), 5.93 (1 H, s), 7.25–7.29 (3 H, m), 7.37 (2 H, t, *J* = 7.8 Hz), 7.54 (2 H, d, *J* = 7.5 Hz), 7.87 (2 H, d, *J* = 8.1 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₂₁H₂₆N₂O₃S: C, 65.26; H, 6.79; N, 7.25. Found: C, 65.26; H, 6.68; N, 7.14.

rel-(3*S*,1'*S*) diastereomer 58: mp 161–163 °C. Anal. Calcd for C₂₁H₂₈N₂O₃S: C, 65.26; H, 6.79; N, 7.25. Found: C, 65.08; H, 6.76; N, 7.44.

rel-(3*S*,1'*R*)-1-*tert*-Butyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (59): mp 187–188 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.41 (9 H, s), 1.68–1.76 (1 H, m), 1.93–2.01 (1 H, m), 2.32 (1 H, m), 2.39 (3 H, s), 3.43 (1 H, ddd, *J* = 10.8, 9.3, and 2.4 Hz), 3.67 (1 H, q, *J* = 9.0 Hz), 4.02 (1 H, ddd, *J* = 10.5 Hz), 5.95 (1 H, bs), 7.22–7.26 (3 H, m), 7.35 (2 H, ddd, *J*'s = 8.1, 5.4, and 2.7 Hz), 7.54 (2 H, d, *J* = 8.4 Hz), 7.84 (2 H, ddd, *J*'s = 8.4 and 2.7 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₂₂H₂₈N₂O₃S: C, 65.97; H, 7.05; N, 7.00. Found: C, 65.71; H, 7.22; N, 6.83.

rel-(3*S*,1'*S*) diastereomer 60: mp 125–126 °C (CHCl₃/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.24 (9 H, s), 1.41 (1 H, m), 1.93–2.04 (1 H, m), 2.11–2.18 (1 H, m), 2.41 (3 H, s), 2.51–2.60 (1 H, m), 3.23 (1 H, dd, *J*'s = 11.1 and 9.9 Hz), 4.17 (1 H, dd, *J*'s = 9.0 and 5.7 Hz), 5.49 (1 H, d, *J* = 5.4 Hz), 7.26–7.32 (5 H, m), 7.48 (2 H, dd, *J*'s = 7.8 and 1.2 Hz), 7.87 (1 H, d, *J* = 8.1 Hz); IR (CHCl₃) 3300 and 1600 cm⁻¹. Anal. Calcd for C₂₂H₂₈N₂O₃S: C, 65.97; H, 7.05; N, 7.00. Found: C, 65.58; H, 7.06; N, 6.69.

rel-(3*S*,1'*R*)-1-(4-Methoxybenzyl)-3-(1-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (61): colorless foam; ¹H NMR (300 MHz, CDCl₃) δ 1.68–1.79 (1 H, m), 2.03–2.10 (1 H, m), 2.40 (3 H, s), 2.75 (1 H, bs), 3.17 (1 H, ddd, *J*'s = 11.7, 10.5, and 1.2 Hz), 3.55 (1 H, q, *J* = 8.7 Hz), 3.77 (3 H, s), 4.04 (1 H, d, *J* = 9.3 Hz), 7.11 (2 H, d, *J* = 9.3 Hz), 7.24–7.28 (3 H, m), 7.35 (2 H, dd, *J*'s = 7.8 and 5.4 Hz), 7.55 (2 H, d, *J* = 7.8 Hz), 7.87 (2 H, d, *J* = 9.0 Hz); IR (CHCl₃) 3300 and 1604 cm⁻¹. Anal. Calcd for C₂₆H₂₈N₂O₄S: C, 67.22; H, 6.09; N, 6.03. Found: C, 67.04; H, 5.89; N, 5.90.

rel-(3*S*,1'*S*) diastereomer 62: colorless foam; ¹H NMR (300 MHz, CDCl₃) δ 1.51–2.05 (1 H, m), 2.13–2.31 (2 H, m), 2.42 (3 H, s), 2.88 (1 H, dd, *J*'s = 9.9 and 9.6 Hz), 3.50 (1 H, br), 3.77 (3 H, s), 4.05 and 4.51 (2 H, AB q, *J* = 14.4 Hz), 4.20 (1 H, dd, *J*'s = 5.7 and 5.4 Hz), 5.52 (1 H, d, *J* = 4.5 Hz), 6.73 (2 H, d, *J* = 8.7 Hz), 6.93 (2 H, d, *J* = 8.7 Hz), 7.22–7.29 (5 H, m), 7.40 (2 H, dd, *J*'s = 6.9 and 3.3 Hz). Anal. Calcd for C₂₆H₂₈N₂O₄S: C, 67.22; H, 6.09; N, 6.03. Found: C, 67.15; H, 5.98; N, 5.85.

rel-(3*S*,1'*R*)-1-Methyl-3-(1-hydroxybenzyl)-3-(2-propenyl)-2-(((4-methylphenyl)sulfonyl)imino)pyrrolidine (63): mp 153–154 °C (CHCl₃/pentane); ¹H NMR (300 MHz, CDCl₃) δ 1.67–1.77 (1 H, m), 2.10–2.25 (2 H, m), 2.31 (1 H, dd, *J*'s = 13.5 and 9.0 Hz), 2.41 (3 H, s), 2.61–2.69 (1 H, m), 2.98 (1 H, dd, *J*'s = 13.5 and 5.7 Hz), 3.14 (3 H, s), 3.16–3.25 (1 H, m), 3.76 (1 H, bs), 5.08–5.18 (2 H, m), 5.66–5.87 (1 H, m), 7.26–7.30 (5 H, m), 7.41 (2 H, dd, *J*'s = 7.8 and 2.7 Hz), 7.89 (2 H, d, *J*'s = 8.1 Hz). Anal. Calcd for C₂₂H₂₈N₂O₃S: C, 66.30; H, 6.58; N, 7.03. Found: C, 66.23; H, 6.52; N, 7.20.

rel-(3*S*,1'*S*) diastereomer 64: mp 125–125 °C (CHCl₃/pentane); ¹H NMR (300 MHz, CDCl₃) δ 1.53–1.61 (1 H, ddd, *J*'s = 12.6, 8.1, and 4.2 Hz), 2.00–2.07 (1 H, m), 2.38–2.48 (1 H, m), 2.41 (3 H, s), 2.99–3.12 (2 H, m), 3.07 (3 H, s), 3.24–3.33 (1 H, m), 7.26–7.39 (7 H, m), 7.91 (2 H, d, *J* = 8.1 Hz). Anal. Calcd for

C₂₂H₂₈N₂O₃S: C, 66.30; H, 6.58; N, 7.03. Found: C, 66.41; H, 6.68; N, 7.03.

rel-(3*S*,1'*R*)-1-Methyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)piperidine (65): mp 173–174 °C (CHCl₃/pentane); ¹H NMR (300 MHz, CDCl₃) δ 1.32–1.43 (1 H, m), 1.52–1.61 (1 H, m), 1.68–1.78 (1 H, m), 2.21–2.31 (1 H, m), 2.40 (3 H, s), 2.55 (1 H, d, *J* = 4.2 Hz), 3.10 (3 H, s), 3.24–3.33 (1 H, m), 3.49–3.56 (1 H, m), 4.01–4.06 (1 H, m), 6.09 (1 H, t, *J* = 3.6 Hz), 7.22–7.28 (3 H, m), 7.36 (2 H, dd, *J*'s = 7.8 and 6.9 Hz), 7.59 (2 H, d, *J* = 7.5 Hz), 7.88 (2 H, d, *J* = 8.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 166.86 (s), 142.14 (s), 141.34 (s), 128.93 (d), 128.04 (d), 126.89 (d), 125.77 (d), 125.67 (d), 75.00 (d), 51.16 (t), 44.03 (d), 39.25 (q), 21.33 (q), 20.21 (t), 19.71 (t); IR (CHCl₃) 3300 and 1570 cm⁻¹. Anal. Calcd for C₂₀H₂₄N₂O₃S: C, 64.49; H, 6.50; N, 7.53. Found: C, 64.33; H, 6.74; N, 7.52.

rel-(3*S*,1'*R*)-1-*tert*-Butyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)piperidine (66): mp 209–210 °C (CH₂Cl₂/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.40 (9 H, s), 1.61–1.73 (2 H, m), 1.81–1.91 (1 H, m), 2.40 (3 H, s), 2.44–2.51 (1 H, m), 3.30 (1 H, ddd, *J*'s = 15.0, 11.4, and 3.6 Hz), 3.41–3.46 (1 H, m), 4.19 (1 H, ddd, *J*'s = 11.4, 8.7, and 2.7 Hz), 5.98 (1 H, dd, *J*'s = 3.6 and 3.3 Hz), 7.24–7.27 (3 H, m), 7.35 (2 H, dd, *J*'s = 7.8 and 7.8 Hz), 7.61 (2 H, d, *J* = 7.5 Hz), 7.84 (2 H, d, *J* = 8.4 Hz). Anal. Calcd for C₂₃H₃₀N₂O₃S: C, 66.03; H, 7.30; N, 6.76. Found: C, 66.48; H, 7.47; N, 6.53.

rel-(3*S*,1'*S*) diastereomer 67: mp 178–179 °C (CHCl₃/hexane). Anal. Calcd for C₂₃H₃₀N₂O₃S: C, 66.03; H, 7.30; N, 6.76. Found: C, 66.61; H, 7.45; N, 6.90.

rel-(3*S*,1'*R*)-1-Methyl-3-(1'-hydroxybenzyl)-2-(((4-methylphenyl)sulfonyl)imino)hexahydroazepine (68): mp 156–157 °C (ether/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.19–1.37 (2 H, m), 1.41–1.56 (1 H, m), 1.59–1.63 (1 H, m), 1.71–1.81 (2 H, m), 2.39 (3 H, s), 3.01 (1 H, d, *J* = 3.3 Hz), 3.11 (1 H, ddd, *J*'s = 12.0, 8.1, and 3.9 Hz), 3.18 (3 H, s), 4.16 (1 H, dd, *J* = 8.7 and 1.2 Hz), 4.37 (1 H, ddd, *J*'s = 7.8, 3.9, and 3.9 Hz), 5.68 (1 H, s), 7.21–7.26 (3 H, m), 7.34 (2 H, dd, *J*'s = 7.8 and 6.9 Hz), 7.56 (2 H, d, *J* = 7.2 Hz), 7.84 (2 H, d, *J* = 8.1 Hz). Anal. Calcd for C₂₁H₂₆N₂O₃S: C, 65.26; H, 6.79; N, 7.25. Found: C, 64.92; H, 6.80; N, 7.36.

rel-(3*S*,1'*S*) diastereomer 69: mp 170–171 °C (ether/hexane); ¹H NMR (300 MHz, CDCl₃) δ 1.21–1.31 (1 H, s), 1.52–1.87 (5 H, m), 2.41 (3 H, s), 3.16 (3 H, s), 3.37 (1 H, d, *J* = 15.3 Hz), 4.05 (1 H, ddd, *J*'s = 15.3, 13.2, and 2.1 Hz), 4.53–4.60 (1 H, m), 4.90–5.05 (2 H, m), 7.26–7.34 (3 H, m), 7.39 (2 H, dd, *J*'s = 7.2 and 7.2 Hz), 7.55 (2 H, d, *J* = 7.2 Hz), 7.88 (2 H, d, *J* = 8.1 Hz). Anal. Calcd for C₂₁H₂₆N₂O₃S: C, 65.26; H, 6.79; N, 7.25. Found: C, 64.89; H, 6.88; N, 6.97.

Acknowledgment. The National Institutes of Health are gratefully thanked for their support of this research.

Supplementary Material Available: Crystallographic data and ORTEP drawings for **51**, **52**, and **65** (39 pages). Ordering information is given on any current masthead page.