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Stereospecific Rearrangements during the Synthesis of Pyrrolidines and Related Heterocycles from Cyclizations of Amino Alcohols with Vinyl Sulfones

Thomas G. Back,* Masood Parvez,† and Huimin Zhai

Department of Chemistry, University of Calgary, Calgary, AB, Canada T2N 1N4

tgback@ucalgary.ca

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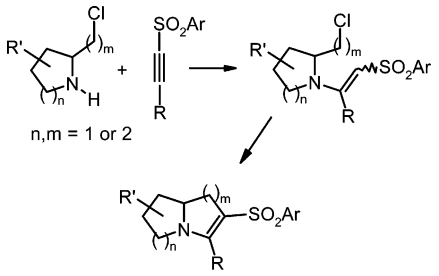
Conjugate additions of amino alcohols derived from α-amino acids to vinyl sulfones, followed by *N*-benzylation, chlorination, and intramolecular alkylation, provide a convenient route to substituted pyrrolidines. The process is accompanied by the stereospecific rearrangement of substituents from the α-position of the amine to the *β*-position of the product and takes place via the corresponding aziridinium ion intermediates. Another type of rearrangement was observed during the reaction of (2-piperidine)methanol or 2-(2-piperidine)ethanol with phenyl *trans*-1-propenyl sulfone, in which the methyl group appears to migrate from the *β*- to the α-position of the sulfone moiety. This process involves the isomerization of phenyl *trans*-1-propenyl sulfone to phenyl 2-propenyl sulfone by the addition−elimination of catalytic benzenesulfinate anion to the former vinyl sulfone, followed by conjugate addition of the amino group to the latter sulfone. Chlorination and intramolecular alkylation then afford the corresponding rearranged indolizidine and quinolizidine derivatives, respectively.

Unsaturated sulfones have proven to be versatile synthetic reagents.[1] For example, the activating and electron-withdrawing effects of the sulfone moiety enable these compounds to undergo conjugate additions and cycloadditions, as well as deprotonation and alkylation of the corresponding α-anions. Moreover, the sulfone group can be removed at the end of a synthetic sequence by a variety of reductive, alkylative, or oxidative methods, where the sulfonyl moiety is replaced by hydrogen, an alkyl group from a suitable organometallic cross-coupling reagent, or an oxygen function, respectively.[2] We recently reported the syntheses of various types of nitrogen heterocycles by conjugate additions of cyclic or acyclic amines bearing *β*- or *γ*-chloro substituents to acetylenic sulfones, followed by intramolecular alkylation.[3] The products included variously substituted pyrrolizidines, indolizidines, quinolizidines, and piperidines (e.g., see Scheme 1). These ring systems are found in myriad natural and synthetic products possessing diverse types of bioactivity.

SCHEME 1



Alternatively, ring-closure has been achieved via intramolecular acylation by incorporating ester instead of chloro substituents in the amine. Since many of the amines can be derived from natural amino acids, enantioselective syntheses of the target compounds are possible. When followed by desulfonylation and other functional group transformations, these cyclization protocols provided concise enantioselective routes to (−)-pumiliotoxin C,[4] indolizidines (−)-167B, (−)-209D, (−)-209B, and (−)-207A,[3b] as well as to (−)-lasubine II[5] (for example, see Scheme 2) and certain quinolone alkaloids found in the medicinal herb *Ruta chalepensis*.[6]

The success of the above cyclizations with use of acetylenic sulfones prompted us to investigate their extension to vinyl sulfones.[7] We now report that similar cyclizations with the latter compounds are indeed possible, but in some cases are accompanied by two types of

* Address general correspondence to this author.Phone: (403) 220-6256. Fax: (403) 289-9488.

† Address correspondence regarding X-ray structures to this author. Phone: (403) 220-5348. Fax: (403) 289−9488.

(1) For general reviews of sulfone chemistry, see: (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, UK, 1993. (b) Patai, S.; Rappoport, Z.; Stirling, C. J. M., Eds. *The Chemistry of Sulphones and Sulphoxides*; Wiley: Chichester, UK, 1988. For reviews of acetylenic and allenic sulfones, see: (c) Back, T. G. *Tetrahedron* **2001**, *57*, 5263. For vinyl sulfones, see: (d) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. For dienyl sulfones, see: (e) Bäckvall, J. E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.

(2) Nájera, C.; Yus, M. *Tetrahedron* **1999**, 55, 10547.

(3) (a) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543.

(4) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566.

(5) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779.

(6) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223.

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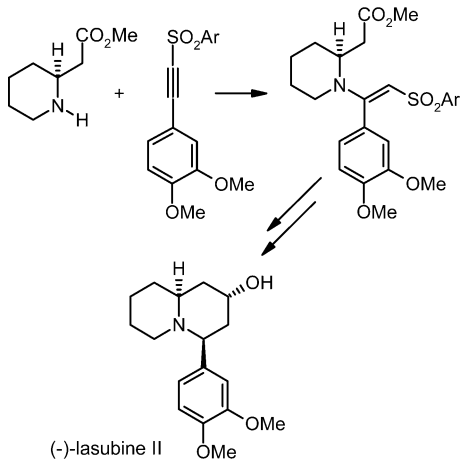
SCHEME 2



rearrangements of substituents that originate from the α-position of the amino group or *β*-position of the vinyl sulfone in the starting materials.

The amino alcohols **2a**, **2b**, and **2c** were readily obtained from (L)-alanine, (L)-phenylalanine, and (L)-valine, respectively,[8] while phenyl vinyl sulfone (**1a**)[9a] and phenyl *trans*-1-propenyl sulfone (**1b**) were obtained by literature methods.[9b] Compounds **2a**−**c**, as well as (−)-ephedrine (**7**) and the homologous racemic amino alcohols **11a** and **11b**, all reacted with sulfone **1a** by conjugate addition in refluxing 2-propanol or xylenes to afford the adducts **3a**−**c**, **8**, and **12a**,**b**, respectively (Scheme 3). To permit easier handling in subsequent steps, products **3a**−**c** were *N*-benzylated to give **4a**−**c** prior to chlorination with thionyl chloride. Alternatively, when *N*-benzylated amino alcohols were employed in the initial conjugate addition step, a more sluggish reaction was observed, leading to diminished yields of the corresponding adducts. Products **4a**−**c** were treated with thionyl chloride, followed by workup with aqueous potassium hydroxide solution. We observed that a facile rearrangement occurred during this process, leading to the stereospecific formation of the corresponding chlorides **5a**−**c**. Cyclization of the latter compounds with LDA then afforded the pyrrolidine derivatives **6a**−**c**, respectively (Scheme 3). Evidence for the rearranged structures was based on NMR evidence, including the observation of relatively downfield ^{1}H and ^{13}C NMR signals consistent with the presence of three CH_2N groups. The *trans* orientation of the methyl and benzenesulfonyl substituents in **6a** was confirmed by an NOE experiment (see the Experimental Section). In addition, reductive desulfonylation of **6a** with sodium amalgam[10] afforded the known compound (*R*)-*N*-benzyl-3-methylpyrrolidine.[11a,b] This method therefore permits the stereospecific transposition of substituents from the α-positions of the starting amines, which are readily available from the corresponding amino acids, to the less accessible *β*-positions in the pyrrolidine products.

In contrast, **8** afforded two diastereomeric products **9** and **10**, neither of which had undergone rearrangement of the *C*-methyl group under similar conditions. The structure of the major product **9** was confirmed by X-ray crystallography, while that of **10** was based on NMR evidence. Moreover, reductive desulfonylation[10] of **9** and **10** furnished the known[11c] compounds *trans*- and *cis*-*N*,2-dimethyl-3-phenylpyrrolidine, respectively. The similar cyclization of adducts **12a** and **12b** afforded the corresponding indolizidine **14a** and quinolizidine **14b**, respectively. Product **14a** was obtained as a 54:46 mixture of separable diastereomers, while **14b** was obtained as a single diastereomer. Unambiguous assignment of respective stereochemistry was not possible for **14a** and **14b**.[12]

The above rearrangements leading to **6a**−**c** can be rationalized by invoking the formation of aziridinium ion intermediates **15a**−**c** during the chlorination of **4a**−**c** with thionyl chloride (Scheme 4). The neighboring group effects of nitrogen mustards and related species are well-known to involve such intermediates.[13] Moreover, the regiochemistry of ring-opening of aziridinium species is determined by a combination of steric and electronic factors, and there is precedent for preferential reaction at the more substituted carbon atom by chloride ion.[14] Thus, attack by chloride ion at the tertiary carbon atoms of **15a**−**c** with inversion of configuration affords the rearranged products **5a**−**c**, and ultimately **6a**−**c**, respectively, after a second inversion during intramolecular alkylation of the corresponding sulfone-stabilized anion. The absence of rearranged products from (−)-ephedrine, along with the observed epimerization of the phenyl-substituted carbon atom, suggests the formation of carbocation **16** rather than aziridinium ion **17** during the chlorination step (Scheme 4).[15] Similarly, the formation of **14a** instead of the rearranged product **18** (Scheme 4) from **11a** indicates that either aziridinium ion formation

(7) For examples of other types of synthetic applications involving conjugate additions of amines to vinyl sulfones, see: (a) Caldwell, J. J.; Craig, D.; East, S. P. *Synlett* **2001**, 1602. (b) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *J. Chem. Soc., Chem. Commun.* **1997**, 2141. (c) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T.; Nemoto, H. *Tetrahedron* **1999**, *55*, 15209. (d) Iradier, F.; Arrayás, R. G. *Org. Lett.* **2001**, *3*, 2957. (e) de Vicente, J.; Arrayás, R. G.; Cañada, J.; Carretero, J. C. *Synlett* **2000**, 53. (f) Carretero, J. C.; Arrayás, R. G. *Synlett* **1999**, 49. (g) Zhou, F.; Rosen, J.; Zebrowski-Young, J. M.; Freihammer, P. M.; Detty, M. R.; Lachicotte, R. J. *J. Org. Chem.* **1998**, *63*, 5403 and references therein.

(8) Amino alcohols **2a**−**c** were prepared by the same method as reported for **2a**: Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586.

(9) For the preparation of **1a**, see: (a) Brace, N. O. *J. Org. Chem.* **1993**, *58*, 4506. (b) Sulfone **1b** was prepared by the same procedure as **1a**, using 1,2-dibromopropane as the starting material. (c) Sulfone **1c** was obtained by the method of Reich and Peake: Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888.

(10) Desulfonylation was effected via the method of Trost et al.: Trost, B. M.; Arndt, H. C.; Strege, P. E.; Vehoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(11) (a) Coldham, I.; Hufton, R. *Tetrahedron* **1996,** *52*, 12541. (b) Di Cesare, P.; Bouzard, D.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Kiechel, J. R.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J.; Desiderio, J. *J. Med. Chem.* **1992**, *35*, 4205. (c) Chelucci, G.; Saba, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 78.

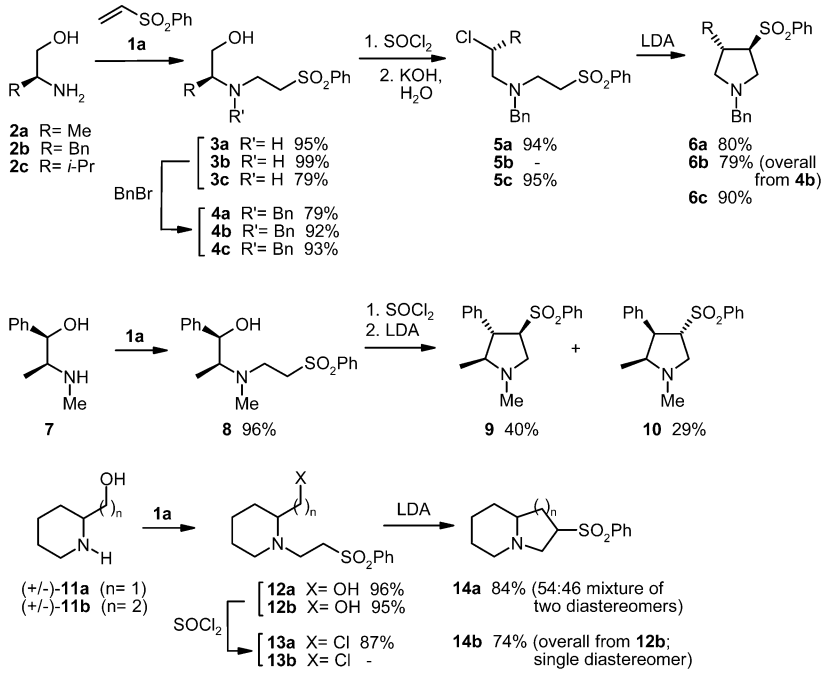
(12) Compound **14b** with unspecified stereochemistry has been reported previously: Padwa, A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 298.

(13) (a) Miller, B. *Advanced Organic Chemistry*−*Reactions and Mechanisms*; Prentice Hall: Upper Saddle River, NJ, 1998; pp 177−181. (b) Crist, D. R.; Leonard, N. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 962.

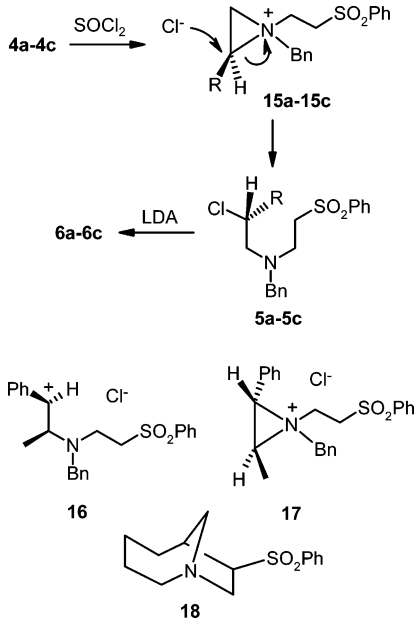
(14) (a) Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1948**, *70*, 2760. (b) Kerwin, J. F.; Ullyot, G. E.; Fuson, R. C.; Zirkle, C. L. *J. Am. Chem. Soc.* **1947**, *69*, 2961. (c) Schultz, E. M.; Sprague, J. M. *J. Am. Chem. Soc.* **1948**, *70*, 48.

(15) Alternatively, the epimerization could result from competing S_Ni and S_N2 reactions of the presumed chlorosulfite intermediate. For the regio- and stereoselectivity of other reactions of ephedrine and pseudoephedrine with nucleophiles via aziridinium ion intermediates, see: Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.

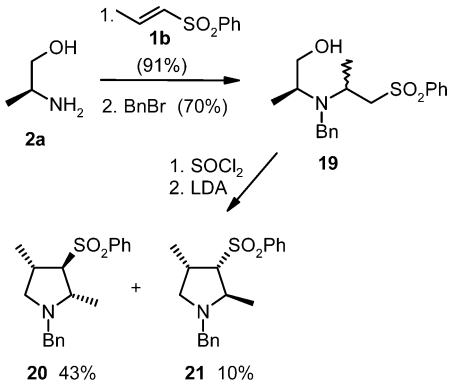
SCHEME 3



SCHEME 4



SCHEME 5



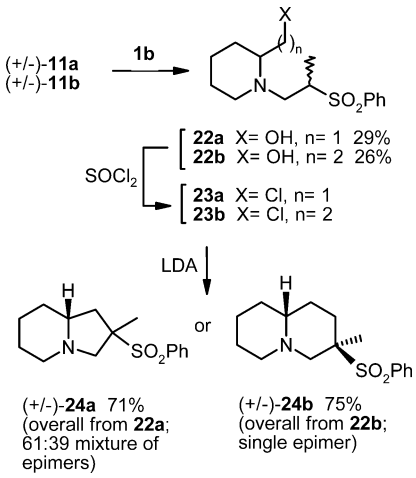
does not occur during the chlorination of **12a** or that chloride attack occurs at the less substituted aziridinium carbon atom, in contrast to the outcome with **15a**−**c**.[16]

The substituted vinyl sulfone **1b** was also investigated. The same sequence of conjugate addition, *N*-benzylation, chlorination with thionyl chloride, and cyclization with LDA was applied to amino alcohol **2a** (Scheme 5). The structures of the two main products **20** and **21** were confirmed by X-ray crystallography, which clearly indicated that rearrangement of the methyl group in **2a** had again taken place. The conjugate addition of (−)-ephedrine (**7**) to **1b** was also attempted, but gave very poor yields even after prolonged reaction times, presumably reflecting the greater steric hindrance associated with a secondary amino group and a β-substituted vinyl sulfone.

Finally, we attempted the same sequence of reactions with the cyclic amines **11a** and **11b**, and sulfone **1b**. To our surprise, the product **24a**, obtained from **11a** as a mixture of separable epimers, contained methyl groups that had rearranged from the β- to the α-position of the sulfone moiety in each isomer (Scheme 6). This was clearly evident from their ^{1}H NMR spectra, where the methyl signals appeared as singlets instead of doublets. A similar rearrangement was observed with **11b**, which afforded a single epimer **24b**, whose structure was unequivocally determined by X-ray crystallography. In both cases, the initial conjugate addition step was sluggish and afforded a poor yield of the corresponding adducts **22a** and **22b**. Further scrutiny of the crude reaction product of **11a** with **1b** revealed the presence of small amounts of the isomeric sulfones **1c** and **1d**. We therefore postulate that, under the prolonged reaction conditions required for the additions of **11a** or **11b** to **1b**, a small amount of the starting vinyl sulfone **1b** or the

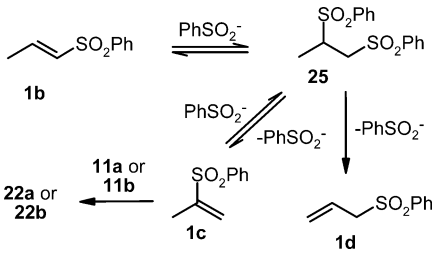
(16) For a precedent where the ring-opening of an aziridinium ion that is fused to a six-membered ring occurs at the less substituted site with chloride ion and other nucleophiles, see: Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285.

SCHEME 6



corresponding conjugate addition products first undergo elimination of benzenesulfinate anion. The latter anion then catalyzes the conversion of **1b** to **1c** and **1d** by a sequence of addition−elimination reactions proceeding via the bis-sulfone **25** (Scheme 7).[17] Although the unactivated allyl sulfone **1d** cannot undergo conjugate addition, the 2-propenyl isomer **1c** reacts preferentially with the amino alcohols **11a** or **11b** to give the observed products **22a** and **22b**, ultimately leading to **24a** and **24b**, respectively.[18] Several control experiments were performed to test this hypothesis. First, the treatment of vinyl sulfone **1b** with sodium benzenesulfinate in the absence of **11a**, under the same conditions as used for the conjugate additions, resulted in the formation of **1c** and **1d**, thus lending support for the proposed addition−elimination steps in Scheme 7. In a separate experiment, the reaction of **11a** was performed with authentic **1c**,[9c] followed by the usual cyclization protocol, to afford the same product **24a** that had been obtained from **1b**. Third, a crossover experiment was conducted in which amino alcohol **11a** and sulfone **1b** were allowed to react in the presence of added sodium *p*-toluenesulfinate, resulting in a mixture of adduct **22a** and its *p*-toluenesulfonyl analogue. These results are all consistent with the mechanism in Scheme 7. The failure to observe a similar rearrangement during the reaction of **2a** with **1b** in Scheme 5 is attributed to the fact that **2a** is a primary amine that undergoes a far more facile direct conjugate addition to **1b** than the more hindered secondary amines **11a** and **11b** in Scheme 6.[19] The latter amines fail to add

SCHEME 7



to **1b** at an appreciable rate, thus providing the opportunity for the competing isomerization of **1b** to the more reactive isomer **1c** (and the inert **1d**) to take place via Scheme 7, followed by conjugate addition to **1c**.

In conclusion, the conjugate additions of amino alcohols derived from α-amino acids to vinyl sulfones, followed by *N*-benzylation, chlorination, and intramolecular alkylation, provide a convenient route to substituted pyrrolidines. The process is accompanied by the stereospecific rearrangement of substituents from the α-position of the original amine moiety to the *β*-position of the product. A second type of rearrangement was discovered with piperidine-based amino alcohols **11a** and **11b** and the *β*-substituted vinyl sulfone **1b**, resulting in the migration of the *β*-substituent to the α-position of the sulfone.

Experimental Section

NMR spectra were recorded in $CDCl_3$ unless otherwise noted. ^{13}C NMR signals were identified as CH_3, CH_2, CH, or C by DEPT experiments. Mass spectra were obtained by EI unless otherwise noted. Chromatography refers to flash chromatography over silica gel.

Typical Procedure for Cyclizations Starting with Vinyl Sulfone 1a: (3*R*,4*S*)-3-(Benzenesulfonyl)-*N*-benzyl-4-methylpyrrolidine (6a). A solution of (*S*)-2-amino-1-propanol (**2a**) (846 mg, 11.3 mmol) and sulfone **1a** (1.895 g, 11.3 mmol) was refluxed for 2 days in 40 mL of 2-propanol and concentrated in vacuo. The residue was chromatographed (hexanes−ethyl acetate−methanol, 4:1:0.5) to afford 2.604 g (95%) of **3a** as a colorless oil, which solidified upon standing: mp 47.5−49.5 °C; IR (film) 3305, 1303, 1148 cm^{-1}; ^1H NMR (200 MHz) *δ* 7.82−7.93 (m, 2 H), 7.66−7.47 (m, 3 H), 3.49 (dd, *J* = 10.8, 3.9 Hz, 1 H), 3.30−3.16 (m, 3 H), 3.15−2.99 (m, 1 H), 2.97−2.83 (m, 1 H), 2.77−2.61 (m, 1 H), 2.59−2.29 (br s 2 H), 0.95 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (50 MHz) *δ* 139.1 (C), 133.7 (CH), 129.2 (CH), 127.7 (CH), 65.4 (CH_2), 56.2 (CH_2), 54.2 (CH), 40.3 (CH_2), 16.7 (CH_3); MS (*m*/*z*, %) 212 (10.5), 141 (33), 125 (27), 77 (51), 70 (100); HRMS calcd for $C_{10}H_{14}NO_2S$ ($M^+ - CH_2OH$) 212.0745, found 212.0748.

The amino alcohol **3a** (723 mg, 2.98 mmol), ethyldiisopropylamine (577 mg, 4.47 mmol), and benzyl bromide (612 mg, 3.58 mmol) were refluxed for 4 h in 15 mL of anhydrous acetonitrile. The mixture was concentrated in vacuo and chromatographed (50% ethyl acetate−hexanes) to give 781 mg (79%) of **4a** as a colorless oil, which solidified upon standing: mp 40−42 °C; IR (film) 3483, 1448, 1299, 1145, 1083 cm^{-1}; ^1H NMR (200 MHz) *δ* 7.86−7.72 (m, 2 H), 7.70−7.45 (m, 3 H), 7.35−7.15 (m, 5 H), 3.74 (d, *J* = 13.5 Hz, 1 H), 3.38 (d, *J* = 13.5 Hz, 1 H), 3.35 (m, 2 H), 3.15−2.74 (m, 6 H), 0.91 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz) *δ* 138.9 (C), 138.4 (C), 133.3 (CH), 128.9 (CH), 128.4 (CH), 128.1 (CH), 127.3 (CH), 126.9 (CH), 62.8 (CH_2), 56.9 (CH), 54.4 (CH_2), 53.8 (CH_2), 43.1 (CH_2), 9.4 (CH_3); MS (*m*/*z*, %) 332 ($M^+ - 1$, 1), 302 (26), 160 (29), 132 (24), 91 (100); HRMS calcd for $C_{17}H_{19}NO_2S$ ($M^+ - CH_3OH$) 301.1137, found 301.1134.

Product **4a** (2.054 g, 6.17 mmol) and thionyl chloride (1.102 g, 9.26 mmol) were refluxed for 2 h in 30 mL of chloroform.

(17) For some earlier studies of elimination−addition reactions of bis-sulfones similar to **25**, see: Kader, A. T.; Stirling, C. J. M. *J. Chem. Soc.* **1962**, 3686.

(18) The rate of addition of piperidine to sulfone **1b** is greater than that to **1c**; see: McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 351. However, these relative rates may be reversed with substituted piperidines such as **11a** and **11b** because of the additional steric interaction between the piperidine substituent and the *β*-methyl group of **1b**.

(19) We note that the additions of amines **11a** and **11b** to **1b** provided yields of only 29% and 26% of the rearranged adducts **22a** and **22b**, even after 3 and 4 days, respectively, in refluxing xylenes. Extensive decomposition of the amine starting materials was observed during this time, along with the gradual appearance of **1c** and **1d**. On the other hand, the direct addition of **2a** to **1b** was considerably more facile and proceeded even in the lower boiling solvent 2-propanol to afford 50% of **19** after refluxing for only 1 day. When refluxed in xylenes, the reaction was largely complete in less than 1 day and proceeded cleanly to form **19** in 91% yield after 2 days.

The solution was washed with 1 M aqueous KOH solution, water, and brine. The organic layer was dried, concentrated, and chromatographed (20% ethyl acetate−hexanes) to afford 2.038 g (94%) of **5a** as a light yellow oil: IR (film) 1444, 1308, 1145, 1079 cm^{-1}; ^1H NMR (200 MHz) δ 7.93−7.79 (m, 2 H), 7.69−7.49 (m 3 H), 7.32−7.16 (m, 5 H), 3.93 (sextet, J = 6.5 Hz, 1 H), 3.64 (d, J = 13.7 Hz, 1 H), 3.56 (d, J = 13.7 Hz, 1 H), 3.37−3.17 (m, 2 H), 3.05−2.92 (m, 2 H), 2.67 (m, 2 H), 1.42 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (50 MHz) δ 139.3 (C), 137.9 (C), 133.6 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 62.5 (CH_2), 59.1 (CH_2), 55.4 (CH), 53.5 (CH_2), 47.8 (CH_2), 22.9 CH_3); MS (*m*/*z*, %) 351 (M^+, 1), 314 (3), 208 (14), 144 (27), 91 (100); HRMS calcd for $C_{18}H_{22}ClNO_2S$ 351.1060, found 351.1042.

The chloroamine **5a** (503 mg, 1.43 mmol) was dissolved in 5 mL of THF and added to 2.0 mmol of LDA in 5 mL of THF at −78 °C. The mixture was stirred at −78 °C for 2 h and was then quenched by filtration through neutral alumina. The filtrate was concentrated in vacuo, and the residue was chromatographed (15% ethyl acetate−hexanes) to afford 361 mg (80%) of **6a** as a light yellow oil: IR (film) 1447, 1304, 1146, 1089 cm^{-1}; ^1H NMR (200 MHz) δ 7.96−7.83 (m, 2 H), 7.72−7.50 (m, 3 H), 7.33−7.15 (m, 5 H), 3.62 (d, J = 13.2 Hz, 1 H), 3.48 (d, J = 13.2 Hz, 1 H), 3.34−3.20 (m, 1 H), 3.02 (dd, J = 10.4, 5.6 Hz, 1 H), 2.87−2.62 (m, 3 H), 2.23 (dd, J = 8.2, 5.3 Hz, 1 H), 1.03 (d, J = 6.8 Hz, 3 H); all ^1H and ^{13}C NMR signals were assigned by COSY, DEPT, and HMQC spectra and irradiation of the **CH**$_3$CH signal at δ 1.03 enhanced the **CH**SO_2 signal at δ 3.3 by 3%, while irradiation of the latter signal enhanced that of the **CH**$_3$ group by 9%; ^{13}C NMR (50 MHz) δ 138.4 (C), 138.2 (C), 133.5 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.0 (CH), 70.1 (CH), 61.3 (CH_2), 59.3 (CH_2), 54.2 (CH_2), 34.5 (CH), 19.8 (CH_3); MS (*m*/*z*, %) 315 (M^+, 1), 173 (27), 158 (100), 145 (27), 91 (64); HRMS calcd for $C_{18}H_{21}NO_2S$ 315.1293, found 315.1312.

Typical Procedure for Cyclizations Starting with Vinyl Sulfone 1b: (±)-3-*cis*-(Benzenesulfonyl)-3-*trans*-methylquinolizidine (24b). 2-(2-Piperidine)ethanol (**11b**) (808 mg, 6.26 mmol) and 1.140 g (6.26 mmol) of vinyl sulfone **1b** were refluxed in 25 mL of xylenes for 4 days. After removal of solvent in vacuo, chromatography (hexanes−ethyl acetate−methanol = 4:1:0.5) afforded 506 mg (26%) of **22b**. The product was a light yellow oil that consisted of two diastereomers formed in the ratio of ca. 55:45 (NMR): IR (film) 3530, 1443, 1305, 1145, 1080 cm^{-1}; ^1H NMR (200 MHz, mixture) δ 7.96−7.81 (m, 2 H), 7.70−7.48 (m, 3 H), 3.85−3.50 (m, 3 H), 3.42−3.00 (m, 2 H), 3.01−2.70 (m, 1 H), 2.70−2.07 (m, 3 H), 2.07−1.75 (m, 1 H), 1.29 (d, J = 6.8 Hz, 3 H) superimposed on 1.68−1.16 (m, 7 H); ^{13}C NMR (50 MHz), major diastereomer, δ 137.7 (C), 133.5 (CH), 129.0 (CH), 128.6 (CH), 62.0 (CH_2), 59.3 (CH), 58.6 (CH), 52.9 (CH_2), 50.0 (CH_2), 31.5 (CH_2), 26.4 (CH_2), 22.2 (CH_2), 21.0 (CH_2), 12.8 (CH_3); ^3C NMR (50 MHz), minor diastereomer, δ 137.7 (C), 133.5 (CH), 129.0 (CH), 128.6 (CH), 61.6 (CH_2), 60.1 (CH), 58.8 (CH), 52.7 (CH_2), 48.6 (CH_2), 31.7 (CH_2), 27.5 (CH_2), 22.4 (CH_2), 21.5 (CH_2), 12.6 (CH_3); MS (*m*/*z*, %) 311 (M^+, 0.12), 266 (3), 124 (100), 82 (17); HRMS calcd for $C_{14}H_{20}NO_2S$ ($M^+ - C_2H_4OH$) 266.1215, found 266.1204.

A solution containing 199 mg (0.640 mmol) of **22b** and thionyl chloride (0.11 mL, 1.50 mmol) in 10 mL of chloroform was refluxed for 3 h and then concentrated in vacuo. The residue of crude **23b** was dissolved in 4 mL of THF and added to a solution of excess LDA (1.00 mmol) in 8 mL of THF at −78 °C. The mixture was stirred at −78 °C for 2 h and at room temperature for 6 h, and was then quenched by filtration through neutral alumina. The filtrate was concentrated in vacuo, and the residue was chromatographed (15% ethyl acetate−hexanes) to afford 140 mg (75%) of **24b** as a single diastereomer. Crystallization from ethyl acetate−hexanes gave light yellow crystals: mp 127−129 °C; IR (film) 1443, 1297, 1147 cm^{-1}; ^1H NMR (200 MHz) δ 7.93−7.80 (m, 2 H), 7.72−7.49 (m, 3 H), 2.80−2.56 (m, 2 H), 2.44 (d, J = 10.6 Hz, 1 H), 2.11−1.86 (m, 2 H), 1.46 (s, 3 H) superimposed on 1.72−1.10 (m, 10 H); ^{13}C NMR (50 MHz) δ 135.4 (C), 133.6 (CH), 130.4 (CH), 128.7 (CH), 62.7 (C), 62.0 (CH), 58.4 (CH_2), 56.6 (CH_2), 32.6 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 17.6 (CH_3); MS (*m*/*z*, %) 292 ($M^+ - 1$, 1.2), 150 (100), 136 (48), 94 (40); HRMS calcd for $C_{16}H_{23}NO_2S$: 293.1450, found 293.1452. Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.12; H, 8.03; N, 4.71. The structure was confirmed by X-ray crystallography.

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Supporting Information Available: Experimental procedures and characterization data for products; ^1H and ^{13}C NMR spectra of new compounds and X-ray data for **9**, **20**, **21**, and **24b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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