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Regio- and Stereoselective Synthesis of Aziridino Epoxides from Cyclic Dienes

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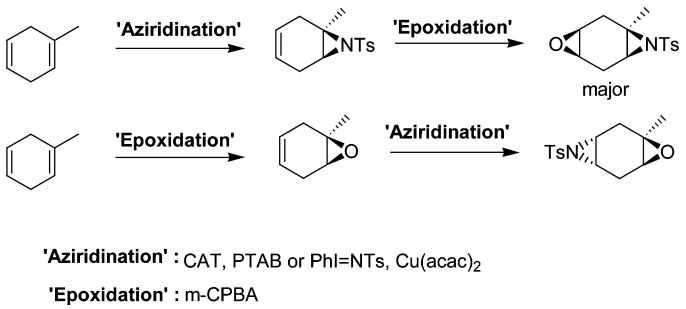
Received November 15, 2005



Two different routes for the regio- and stereoslective synthesis of aziridino epoxides from cyclic dienes have been explored. The first strategy involves regiospecific aziridination of cyclic diene derivatives and subsequent epoxidation with *m*-CPBA to yield *cis*-aziridino epoxides as major products. The second strategy utilizes regiospecific epoxidation of cyclic diene derivatives followed by Sharpless aziridination to provide exclusively *trans*-aziridino epoxides. Synthesis of both enantiomers of *cis*-aziridino epoxides from (*R*)-(−)- and (*S*)-(+)-carvones are also reported.

Introduction

Aziridino epoxides[1] are useful intermediates in organic synthesis which warrant systematic study and development of new methodologies for stereoslective synthesis. Recently, aziridino epoxides **1** and **2** (Figure 1) were used as key intermediates to synthesize the cytotoxic compound (+)-bromoxone[2] and the positional isomer of 7-deoxypancratistatin,[3] respectively, in a stereoselective fashion. Aziridino epoxides are potential synthons

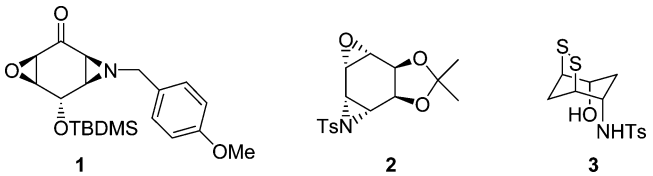


FIGURE 1.

for the synthesis of enantiomerically enriched aziridino allylic alcohols[4] by chiral amide base-mediated rearrangement. Additionally, it is possible to synthesize functionalized amino alcohols by carrying out aziridine ring opening as well as epoxide ring opening either stepwise or in a one-pot operation. Using this strategy, we recently reported the synthesis of conformationally locked bridged disulfide[5] **3** from *cis*-aziridino epoxide **6a** in a single step operation.

Herein, we report a systematic study of the synthesis of aziridino epoxides derived from cyclic 1,3-, 1,4-, and 1,5-dienes

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(1) (a) Viehe, H. G.; Merenyi, R.; Francotte, E. *J. Am. Chem. Soc.* **1977**, *99*, 2340−2342. (b) Zipperer, B.; Mueller, K. H.; Gallenkamp, B.; Hildebrand, R.; Fletschinger, M.; Burer, D.; Pillat, M.; Hunkler, D.; Knothhe, L.; Fritz, H.; Prinzbach, H. *Chem. Ber*. **1998**, *121*, 757. (c) Francotte, E.; Merenyi, R.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 936−937. (d) Francotte, E.; Merenyi, R.; Coyette, B. V.; Viehe, H. G. *Helv. Chim. Acta* **1981**, *64*, 1208−1218. (e) Sana, M.; Leroy, G.; Vaerman, J. L.; Viehe, H. G. *Can. J. Chem*. **1990**, *68*, 1625−1628. (f) Vaerman, J. L.; Viehe, H. G. *Tetrahedron* **1989**, *45*, 3183−3188. (g) Prinzbach, H.; Mueller, K. H.; Kaiser, C.; Hunkler, D. *Tetrahedron Lett.* **1980**, *21*, 3475−3478. (h) Vogel, E.; Klug, H. H.; Schaefer-Ridder, M. *Angew. Chem*. **1976**, *88*, 268. (i) O'Brien, P.; Pilgram, C. D. *Tetrahedron Lett.* **1999**, *40*, 8427−8430.

(2) Barros, M. T.; Mathias, P. M.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321−4323.

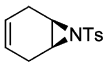
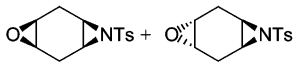
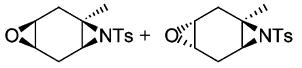
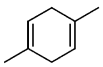
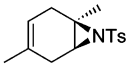
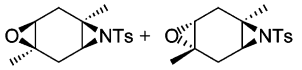
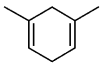
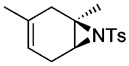
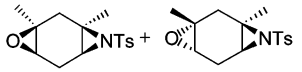
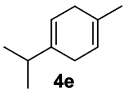
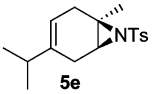
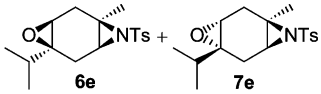
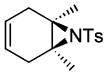
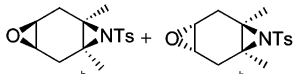
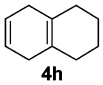
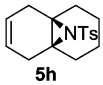
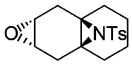
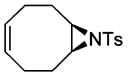
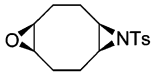
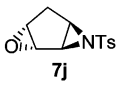
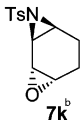
(3) (a) Schilling, S.; Rinner, U.; Chan, C.; Ghiviriga, I.; Hudlicky, T. *Can J. Chem*. **2001**, *79*, 1659−1667. (b) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem*. **2002**, *67*, 8726−8753.

(4) O'Brien, P.; Pilgram, C. D.*Org. Biomol. Chem.* **2003**, *1*, 523−534.

(5) Sureshkumar, D.; Koutha, S.; Chandrasekaran, S. *J. Am. Chem. Soc*. **2005**, *127*, 12760−12761.

10.1021/jo052357x CCC: $33.50
Published on Web 01/27/2006

TABLE 1. Aziridination Followed by Epoxidation of Cyclic Dienes

Entry	Cyclic dienes	Aziridino cyclohexenes	Yield (%) Method A	Yield (%) Method B	Cyclic Aziridino-epoxides	cis : trans ratio[a]	Yield (%)
1	 **4a**	 **5a** Na	60	60	 **6a** + **7a**	52 : 48	95
2	 **4b**	 **5b**	70	65	 **6b** + **7b**	65 : 35	92
3	 **4c**	 **5c**	66	55	 **6c** + **7c**	80 : 20	91
4	 **4d**	 **5d**	65	58	 **6d** + **7d**	75 : 25	90
5	 **4e**	 **5e**	55	55	 **6e** + **7e**	85 : 15	93
6	 **4f**	 **5f**	67	55	 **6f**[b] + **7f**[b]	60 : 40	94
7	 **4g**	No reaction	-	-	-	-	-
8	 **4h**	 **5h**	50	45	-	 **7h**	-	81
9	 **4i**	 **5i**	45	0	 **6i**	-	-	79
10	 **4j**	 **5j**	0	80	-	 **7j**	-	82
11	 **4k**	 **5k**	0	60	-	 **7k**[b]	-	86

[a] Determined from the ^{1}H NMR of the crude products. [b] The stereochemistry of **6f** and **7f** was assigned on the basis of analogy with other aziridino epoxides **6** and **7**; the stereochemistry of **7k** was assigned on the basis of the similarity to the ^{1}H NMR of **7j**.

using *m*-CPBA for epoxidation and the Sharpless method (method A)[6] or Yamada reagent, PhI═NTs (method B)[7] for aziridination. We also report a two-step synthesis of both enantiomers of *cis*-aziridinoepoxycarvones from (*R*)-(−)- and (*S*)-(+)-carvones.

Results and Discussion

Two synthetic strategies were employed in our study. In the first approach, aziridination was effected followed by epoxidation to obtain aziridino epoxides. Initially, a wide range of cyclic 1,4-hexadienes **4a**−**h** were prepared using Birch reduction[8] of the corresponding aromatic substrates. Aziridination of alkenes **4a**−**i** was carried out using the Sharpless aziridination protocol[6] [chloramine-T trihydrate ($TsNClNa\cdot 3H_2O$; 3.3 mmol), phenyltrimethylammonium tribromide ($PhMe_3N^+Br_3^-$; 0.3 mmol), CH_3CN, rt, 12 h], which yielded aziridinocyclohexenes **5a**−**i**, respectively (Table 1), in 45−70% yield (Scheme 1, method A).

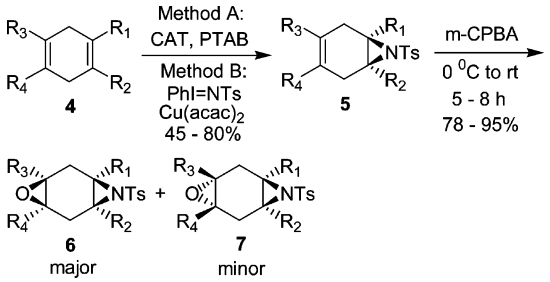
As anticipated, in all cases, aziridination occurred at the more substituted double bond in a regiospecific manner (Table 1, entries 2, 6, and 8). However, in the case of γ-terpinene **4e,**

(6) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845.

(7) (a) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, *4*, 361−362. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744−6746. (c) Knight, J. G.; Muldowney, M. P. *Synlett* **1995**, 949−951.

(8) (a) Last, L. A.; Fretz, E. R.; Coates, R. M. *J. Org. Chem.* **1982**, *47*, 3211−3219. (b) *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 467; *Org. Synth.* **1972**, *49*, 62.

SCHEME 1. Aziridination Using the Sharpless or Yamada Method Followed by Epoxidation



aziridination occurred regiospecifically on the sterically less hindered double bond. Since the Sharpless method of aziridination failed in the case of 1,3-cyclohexadienes, we adopted $Cu(acac)_2$-catalyzed aziridination using Yamada reagent, PhI═NTs[7] as the nitrene source as an alternate method (method B). Aziridination of 1,3-cyclohexadienes **4j** and **4k** by method B afforded the corresponding aziridines **5j** and **5k** in moderate to good yields (entries 10 and 11). Regiospecific aziridination of 1,4-cyclohexadienes by method B also resulted in the formation of corresponding aziridines with the same efficiency (entries 1−6 and 8).

In the next stage, epoxidation of aziridinocyclohexenes **5a**−**k** was carried out under standard conditions [1.5 equiv of m-CPBA/ $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 5−8 h followed by workup with aq Na_2SO_3] (Table 1). These epoxidations were generally *cis*-selective. In the case of substrates **5b**−**f**, the *cis*-aziridino epoxides **6b**−**f** were found to be the major products (entries 2−6). It is pertinent to note that in the case of bicyclic aziridines **5h** and allylic aziridines **5j**−**k**, exclusive formation of the corresponding *trans*-aziridino epoxides **7h** and **7j**−**k** was observed (Table 1). But, aziridinocyclooctene **5i** gave *cis*-aziridinocyclooctane epoxide **6i** as the only product (Figure 2).

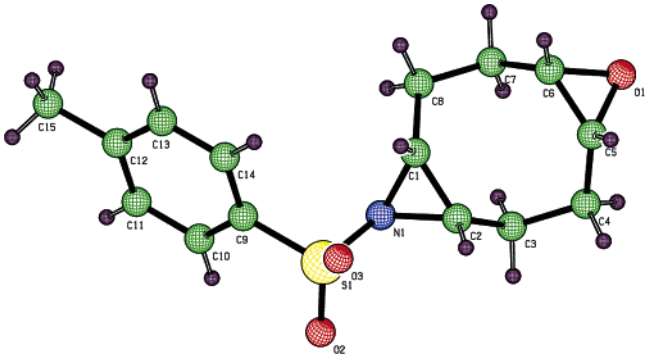


FIGURE 2. Solid-state structure of compound **6i**.

In general, the *cis*-selectivity in the epoxidation of aziridinocyclohexenes **5b**−**f** can be explained on the basis of hydrogen bond assisted interaction[9] (Figure 3). Introduction of substituents on the alkene further increases the *cis*-selectivity. However in the case of **5h**, **5j**, and **5k**, the *trans*-stereoselectivity is governed by lack of hydrogen-bonding and steric factors. Further, the stereo- and regiochemistry of the products were confirmed by single-crystal X-ray analysis (see the Supporting Information).

Our next approach was to synthesize aziridino epoxides via epoxidation followed by aziridination (Scheme 2). This strategy

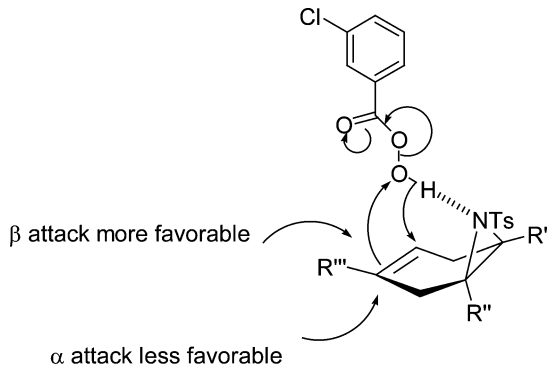
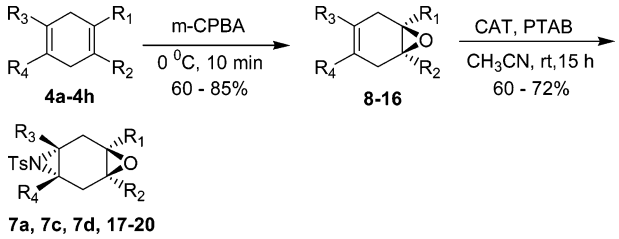


FIGURE 3. Hydrogen bond assisted *cis*-selective epoxidation of **5**.

SCHEME 2. Epoxidation Followed by Aziridination Using the Sharpless Method



involved regiospecific epoxidation[10] of cyclic 1,4-dienes **4a**−**h** (Table 2) [1.0 equiv of *m*-CPBA at −15 °C, CH_2Cl_2 for 10−15 min followed by workup with aq Na_2SO_3] to afford the corresponding mono-epoxy derivatives **8**−**16** as the major products (Table 2), respectively, in good yields. However, in the case of **4e** (entry 5, Table 2), it resulted in a mixture of regioisomers **12** and **13** in a 1:1 ratio. Aziridination of cyclohexene oxides **8**−**16** by Sharpless aziridination procedure (Method A) gave selectively *trans*-aziridino epoxides **7a**, **7c**, **7d**, and **17**−**20**, respectively, in good yields (Table 2). Attempted aziridination of compounds **12** and **13** was not successful. Aziridination of cyclohexene oxides **4a**−**h** using method B failed to give the corresponding aziridino epoxides. Since formation of bromonium ion is the first step in the Sharpless aziridination procedure,[6] in the case of epoxycyclohexene **8**, the formation bromonium ion[11] **I** occurs selectively in a *cis* fashion and chloramine-T opens up the bromonium ion **I** from the α-face followed by Br−Cl elimination to generate intermediate **III**, which upon intramolecular cyclization forms *trans*-aziridinoepoxide **7a** (Scheme 3). The stereo- and regiochemistry of compounds **17**, **19**, and **20** were confirmed by single-crystal X-ray analysis (see the Supporting Information).

This methodology was also extended to study the reactivity of carvone. Both optically pure enantiomers of *cis*-aziridino epoxides **21d** and **22d** were synthesized in two steps from (*R*)-(−)- and (*S*)-(+)-carvones **21a** and **22a,** respectively. Synthesis of epoxycarvones **21b** and **22b** was achieved according to the literature procedure,[12] which were then subjected to the Sharpless aziridination (method A) to furnish diastereomeric mixtures of aziridino epoxides **21c**−**d** and **22c**−**d,** respectively, in high

(9) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. *Org Lett.* **2003**, *5*, 4955−4957.

(10) (a) Mehta, G.; Ramesh, S. S.; Bera, M. K. *Chem. Eur. J.* **2003**, *9*, 2264−2272. (b) Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Catal.* **2004**, *224*, 224−228. (c) Thummel, R. P.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 4250−4254.

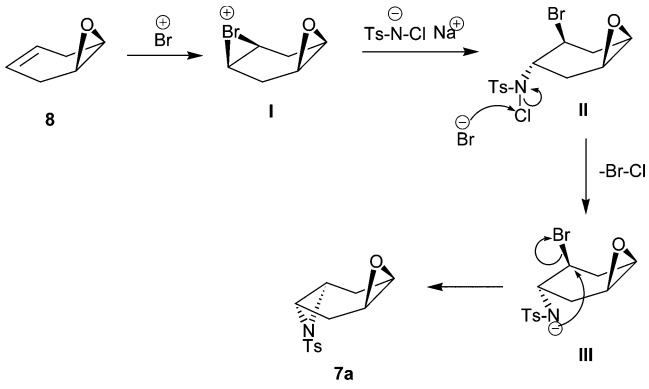
(11) *cis*-Bromonium ion **I** is 2.35 kcal/mol more stable than the corresponding *trans*-bromonium ion (see the Supporting Information).

(12) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091−1099.

TABLE 2. Epoxidation Followed by Aziridination Using the Sharpless Method

Entry	Cyclic dienes	Cyclic Epoxides	Yield (%)	Cyclic aziridino-epoxides	Yield (%)
1	**4a**	**8**	60	**7a**	64
2	**4b**	**9**	70	**17**	67
3	**4c**	**10**	68	**7c**	61
4	**4d**	**11**	71	**7d**	63
5	**4e**	**12** + **13**	85	-	-
6	**4f**	**14**	65	**18**	60
7	**4g**	**15**	68	**19**	70
8	**4h**	**16**	72	**20**	72

SCHEME 3. Tentative Mechanism for the Formation *trans*-Aziridino Epoxides by the Sharpless Aziridination

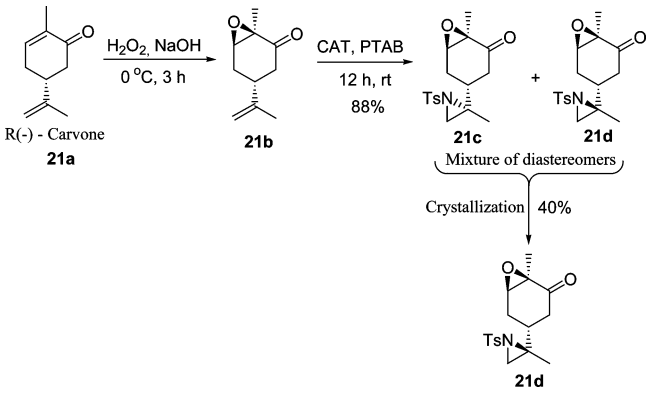


yield. Recrystallization of this diastereomeric mixture (ethyl acetate−hexane) gave colorless crystals of *cis*-aziridino epoxides **21d**[5] and **22d** in optically pure form in 40% yield (Schemes 4 and 5). Both compounds **21d** and **22d** were characterized by single-crystal X-ray analysis to confirm the stereochemistry of aziridine and epoxide. This reaction could be successfully scaled up (10 g) without any difficulty.

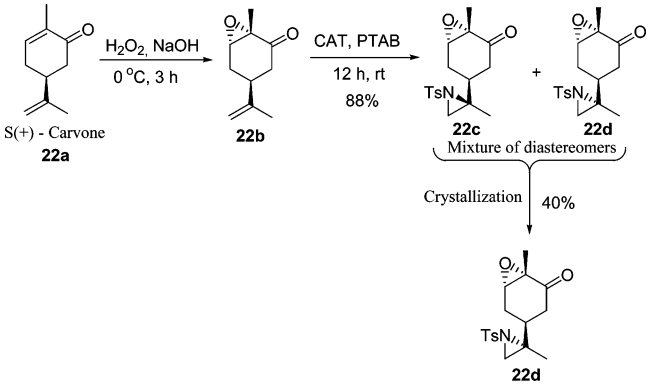
Conclusion

In summary, two complementary routes toward the synthesis of *cis*- and *trans*-aziridino epoxides from cyclic dienes have been studied, and the stereo- and regiochemistry of aziridino epoxides have been established by single-crystal X-ray analysis. Mono- and disubstituted alkenes have been shown to undergo stereospecific aziridination as well as epoxidation in good yields.

SCHEME 4. Aziridino Epoxide 21d Derived from (*R*)-(−)-Carvone



SCHEME 5. Aziridino Epoxide 22d Derived from (*S*)-(+)-Carvone



Further, both of the enantiomers of *cis*-aziridino epoxides **21d** and **22d** were synthesized from enantiomers of carvones using this methodology.

Experimental Section

General Procedure for the Sharpless Aziridination (Method A).[6] To a mixture of an appropriate cyclic diene **4** (3 mmol) and $TsNClNa\cdot 3H_2O$ (CAT) (0.930 g, 3.3 mmol) in CH_3CN (15 mL) was added phenyltrimethylammonium tribromide (PTAB) (0.113 g, 0.3 mmol) at 28 °C. After 12 h of vigorous stirring, the reaction mixture was concentrated and filtered through a short column of silica gel and eluted with 10% EtOAc in hexanes. After evaporation of solvent, the resultant solid was purified by flash column chromatography to yield the corresponding aziridines in good yield.

General Procedure for Aziridination Using PhI═NTs[7] (Method B). PhI═NTs (9.0 mmol) was added portionwise to a stirred solution of freshly distilled appropriate cyclic diene **4** (18.2 mmol) and $Cu(acac)_2$ (240 mg, 0.9 mmol) in CH_3CN (10 mL) at 0 °C under N_2. After being stirred for 15 min, the reaction was allowed to warm to rt and stirred for a further 45 min. Then, the reaction mixture was poured into NaOH (aq) (1 M, 200 mL). Et_2O (50 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give the corresponding cyclic aziridines in 45−80% yield.

Compound 5b: $R_f = 0.70$ (EtOAc/hexanes, 1:4); yield 0.553 g, 70%; mp 124 °C; IR (neat) 1314, 1153, 1089, 950, 898 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.40−5.37 (m, 1H), 3.18 (s, 1H), 2.58 (d, J = 18.3 Hz, 1H), 2.39 (s, 3H), 2.32 (bs, 1H), 2.24 (bs, 1H), 2.15 (d, J = 18.3 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3,

138.6, 129.3, 126.7, 122.2, 120.8, 49.3, 46.1, 31.5, 24.1, 21.3, 19.7; HR-MS *m*/*z* calcd for $C_{14}H_{17}NO_2S$ [M + Na^+] 286.0878, found 286.0888. Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32; S, 12.18. Found: C, 63.95; H, 6.42; N, 5.22; S, 12.23.

General Procedure for Epoxidation of Aziridinocycloalkene Derivatives. Sodium hydrogen carbonate (2 equiv) and *m*-CPBA (2 equiv, approximately 70% pure material) were added in portions to a stirred solution of the cyclic diene **4** (0.8 mmol) in CH_2Cl_2 (10 mL) at room temperature under nitrogen. After the mixture was stirred for 16 h at room temperature, 20% aqueous sodium sulfite solution (10 mL) was added, and the mixture was further stirred for 20 min. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts was washed with 20% aqueous sodium sulfite solution (20 mL), saturated aqueous sodium hydrogen carbonate solution (20 mL), and water (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude aziridino epoxide, which was further purified by flash column chromatography.

Note: The same procedure was used for the stereospecific epoxidation[10a] of cyclic dienes **4a**−**h** at −15 °C for 15−20 min, and in the next step these crude epoxycycloalkenes **8**−**16** were used directly for the Sharpless aziridination (method A).

Compound 6b: R_f = 0.20 (EtOAc/hexanes, 3:7); yield 0.167 g, 60%; mp 107 °C; IR (neat) 1455, 1301, 1154, 1082, 967, 903, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 3.05−2.07 (m, 4H), 2.42−2.29 (m, 1H), 2.40 (s, 3H), 2.17 (td, J = 17.0 Hz, 1H), 2.02 (dd, J = 17.0, 3.0 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.6, 129.2, 126.7, 49.2, 48.2, 46.7, 43.9, 29.6, 22.3, 21.3, 20.1; HR-MS *m*/*z* calcd for $C_{14}H_{17}NO_3S$ [M+Na^+] 302.0827, found 302.0826. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 60.08; H, 6.30; N, 5.21; S, 11.35.

Synthesis of *cis*-Aziridino Epoxide 21d. Synthesis of epoxycarvone **21b** was achieved according to the literature procedure,[12] which was then subjected to the Sharpless aziridination (method A) to furnish a diastereomeric mixture of aziridino epoxides **21c** and **21d** after flash chromatography. The diastereomeric mixture was recrystallized using EtOAc and hexanes to afford aziridinoepoxycarvone **21d** as colorless crystals: R_f = 0.50(EtOAc/hexanes, 3:7); yield 0.402 g, 40%; mp 121 °C; $[\alpha]^{27}_D$ = +48.00 (c = 1.0, $CHCl_3$); IR (neat) 1708, 1319, 1159, 846, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 3.42 (d, J = 3.3 Hz, 1H), 2.63 (s, 1H), 2.57−2.50 (m, 1H), 2.44 (s, 3H), 2.36−2.29 (m, 1H), 2.24 (s, 1H), 2.13−1.95 (m, 2H), 1.88−1.79 (m, 1H), 1.66 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 144.0, 137.5, 129.5, 127.3, 60.7, 58.7, 50.9, 40.3, 39.0, 35.3, 25.5, 21.5, 15.2, 15.1; HR-MS *m*/*z* calcd for $C_{17}H_{21}NO_4S$ [M + Na^+] 358.1089, found 358.1098. Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18; S, 9.56. Found: C, 60.68; H, 6.2336; N, 4.02; S, 9.55.

Acknowledgment. D.S. thanks CSIR, New Delhi, for a senior research fellowship. We also thank DST, New Delhi, for CCD X-ray facility.

Supporting Information Available: ^1H and ^{13}C spectra for all new compounds and X-ray structures of compounds **5b**,**c**, **6b**,**c**,**e**,**i**, **7b**,**d**,**h**,**j**, **17**−**20**, **21d**, and **22d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052357X