mp 144-144.5 °C): IR (KBr) 3400 cm^{-1} (NH); ^1H NMR δ 1.2 (s, 4 H), 4.95 (br s, 2 H, disappeared upon addition of D_2O), 6.64-6.88 (m, 6 H), 7.15-7.3 (m, 4 H); MS m/z 225 ($M^+ + 1$, 2.44), 224 (M^+, 14.5), 132 ($M^+ - C_6H_5NH$, 100). Anal. Calcd for $C_{15}H_{16}N_2$: MW, 224; C, 80.35; H, 7.14; N, 12.50. Found: MW by vapor-pressure osmometry, 220; C, 80.25; H, 7.30; N, 12.42.

The third fraction gave 2 g of an oil that was extracted (10 × 25 mL) with boiling petroleum ether (30-60 °C). Cooling the combined extracts to -10 °C for 2 d gave **10** (53 mg, 1%), mp 79-80 °C. Recrystallization from petroleum ether (30-60 °C) gave white crystalline **10**, mp 80-81 °C (lit.[14] mp 80-81 °C): IR (KBr) 3150, 3050, 2920, 1600 cm^{-1}; NMR δ 2.42 (s, 3 H), 7.4-7.8 (m, 6 H); UV (C_2H_5OH) λ_{max} 250 nm (ϵ 0.97 × 10^4); MS m/z 159 (M^+, 3), 131 ($M^+ - N_2$, 53), 77 (100). An authentic sample[14] gave IR and NMR spectra, TLC behavior, and a mixed mp that were identical.

The combined fourth and fifth fractions gave a dark, brown oil (2.3 g) that was extracted (10 × 25 mL) with petroleum ether (30-60 °C). The cooled (-10 °C) extracts yielded 32 mg (0.6%) of **8**, mp 60-62 °C. It was recrystallized from petroleum ether (30-60 °C), mp 62-63.5 °C (lit.[22] mp 64 °C): IR (KBr) 3100, 1600 cm^{-1}; NMR δ 2.38 (s, 3 H), 7.35 (s, 1 H), 7.5-7.65 (m, 5 H); UV (C_2H_5OH) λ_{max} 223 nm (ϵ 1.4 × 10^4). An authentic sample[22] gave IR and NMR spectra, TLC behavior, and a mixed mp that were identical.

When **2a** (4.0 g, 0.034 mol), 20 mL of benzene, and **6** (4 g, 0.1 mol) were heated at 100 °C for 1 week and the gas phase (2.4 L at 25 °C) was passed through the K_2HgI_4 reagent, no precipitate was observed. The reaction was also carried out in sealed, heavy-wall Pyrex tubes using xylene in place of benzene at 100 °C for 1 week, 70 °C for times ranging from 1 to 3 weeks, and at 50 °C for 2 weeks. Similar results were obtained from all reactions (e.g., the TLC and NMR of the crude reaction product mixtures were virtually identical). Since **6** was sometimes passed over NaOH pellets before use in a reaction, it was tested by passing through the K_2HgI_4 reagent both before and after NaOH exposure. No precipitate was observed in either case.

Heating 6 with *N*-Methylaniline. *N*-Methylaniline (3.64 g, 0.034 mol), benzene (15 mL), and **6** (8 g, 0.2 mol) were heated in an autoclave at 105 + 5 °C for 7 d. After being cooled to room temperature, the gas was passed through the K_2HgI_4 reagent (no precipitate formed) and collected (4.0 L at room temperature).

Reaction of 2a with Methylacetylene (19). In an autoclave, **2a** (4.0 g, 0.034 mol), benzene (20 mL), and condensed (-78 °C) **19** (10 g, 0.25 mol) were combined and heated at 100 + 2 °C for 3 d. A dark brown oil was obtained (5.6 g) that showed no IR band for phenyl azide (2130 cm^{-1}). The ^1H NMR exhibited sharp singlets at δ 2.37 and 2.42 as well as resonance in the aromatic region. No resonance at δ 1.2 (**18**) was detected. Silica gel TLC showed two spots and a silica gel column chromatographic separation was undertaken. The first fraction gave 2.46 g (46%) of a white solid, mp 78-80 °C. Recrystallization from petroleum ether (30-60 °C) yielded colorless crystalline **10** (1.8 g, 34%), mp 80-81 °C. The IR, NMR, UV, TLC, mp, and mixed mp of this and an authentic sample[14] of **10** were identical.

The second fraction yielded 3.0 g of a viscous liquid that was short-path distilled and the major fraction collected at 125 °C (2 mm). This material solidified at -10 °C but remained liquid at room temperature: IR (neat) 3450, 3100, 2900, 1600 cm^{-1}; NMR δ 2.37 (s, 3 H), 7.3 (m, 6 H), 7.7 (m, 4 H), 8.08 (s, 1 H). Addition of D_2O to the NMR sample did not effect the spectrum. The elemental analysis gave a high nitrogen value (27.76%). The TLC behavior and the NMR singlet at δ 2.37 are the same as for **8** but the IR is quite different. All attempts to obtain **8** from this material were unsuccessful. A repetition of this experiment produced the same results.

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Asymmetric Reactions of Thioacetals and Their *S*-Oxides Derived from 1,1'-Binaphthalene-2,2'-dithiol[1]

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The chiral dithiepine **3** was selectively oxidized to all possible oxides: the sulfoxide **9**, the sulfone **16**, the sulfone-sulfoxide **20**, the disulfoxide **21**, and the disulfone **22**. The sulfinyl oxygens of **9**, **14**, **20**, and **21** are always in the pseudoaxial configuration, as shown by the X-ray structure determination of **11a**. Reaction of the anions of **3**, **9**, and **16** with methyl iodide, benzaldehyde, or acetophenone occurs efficiently. The stereoselectivity of the processes is high and maximized in sulfoxide **9**, where the contributions of the chiral binaphthyl residue and the sulfoxide appear to occur synergistically. The alcohols derived from reaction of the anions of **3**, **9**, and **16** with benzaldehyde and acetophenone were also prepared in high yield and stereoselectivity via reduction or methylation of the phenyl ketone **8** and of its oxidized homologues **14** and **19**. Alcohol **6a**, prepared in 8:2 ratio in the reaction of **3** with benzaldehyde, was obtained as a single diastereoisomer in the reduction of **8** with lithium aluminum hydride.

"Umpolung" of the carbonyl group via the thioacetal[4] is a powerful tool for the synthesis of a variety of functionalized molecules. However, asymmetric variants, making use of thioacetals derived from chiral thiols, remain to be explored. Work has been done with related molecules

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(3) Author to whom inquiries concerning the X-ray crystallographic analysis should be directed.

(4) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

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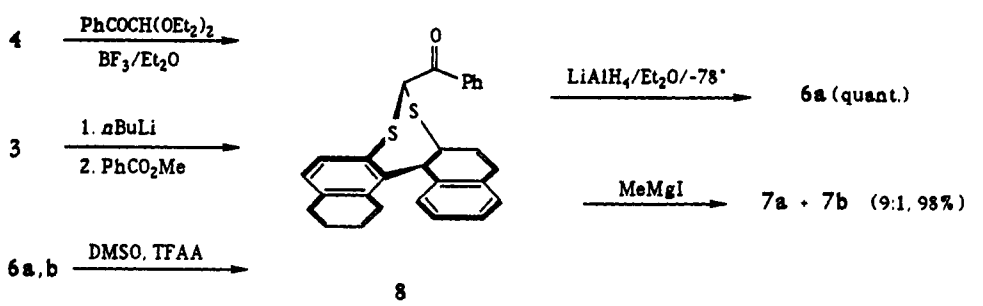
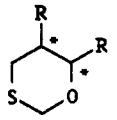
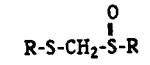
Scheme I



such as the oxathianes 1[5] and with asymmetric thioacetal *S*-monoxides 2.[6]



1

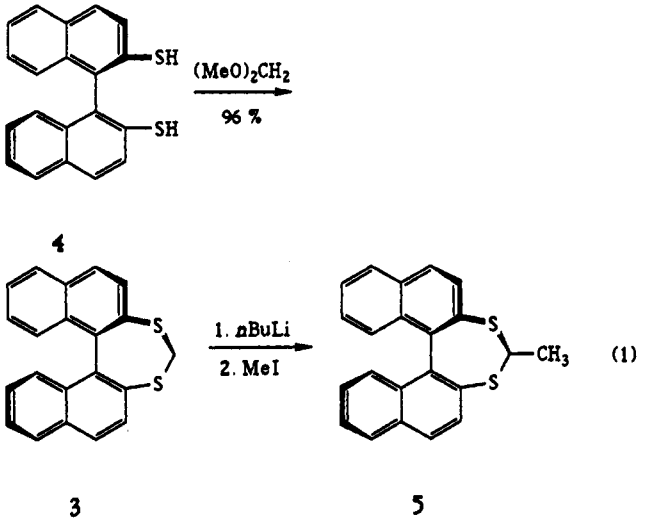


2 R = Tol, Ph, Me, $-(CH_2)_2-$, $-(CH_2)_3-$, etc.

We report a study on the degree of diastereoselection obtainable with the C_2-symmetric chiral thioacetal 3 and related molecules and a rationalization of the factors influencing diastereoselectivity.

Results and Discussion

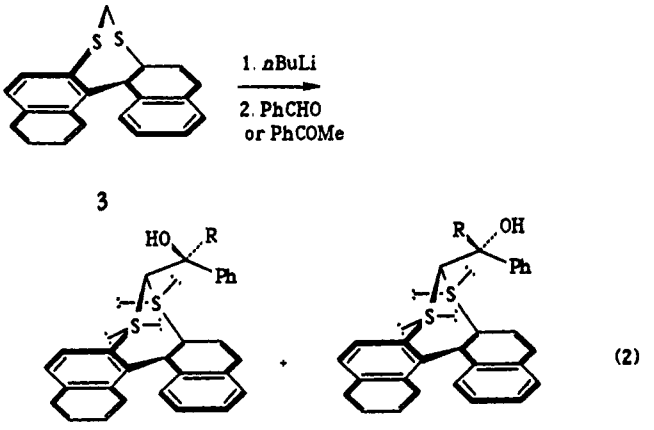
Dithiepine 3 is readily available from the C_2-chiral binaphthodithiol 4 via Lewis acid catalyzed condensation with dimethoxymethane (eq 1). Thiepine 3 and all the derived compounds are crystalline.[7]



(1)

3 5

Methylation of the anion of 3, generated by *n*-BuLi in THF, affords the monomethylated product 5 (no stereochemistry implied).[8] Reaction of the anion of 3 with benzaldehyde yielded the two possible diastereoisomers **6a** and **6b** in 8:2 ratio, while the reaction with benzophenone resulted in a slightly lower selectivity, giving rise to a 7:3 mixture of diastereoisomers **7a** and **7b** (eq 2). The



(2)

R = H **6a** **6b**
R = Me **7a** **7b**

stereochemistry shown for **6a** and **6b** was deduced as described below. All the alcohols are crystalline and could be readily separated by silica gel column chromatography or fractional crystallization.

Alcohols 6 and 7 could also be formed via reduction or methylation of phenyl ketone 8.[9,10] Ketone 8 was synthesized via the three routes indicated in Scheme I. The highest yield route was the condensation of dithiol 4 with diethoxyacetophenone, although nucleophilic substitution of the anion of 3 with benzoic acid derivatives gave comparable yields under proper reaction conditions[10,11] and/or with suitable esters.[12]

Reduction of 8 with lithium aluminum hydride in ether smoothly and cleanly produced a single diastereoisomeric alcohol identical with **6a**, i.e. the major isomer of the aldol reaction of 3 with benzaldehyde. Addition of methylmagnesium iodide to 8 occurred with good selectivity, giving rise to a 9:1 mixture of diastereoisomers **7a** and **7b**.

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(7) The crystals, however, often included solvent that was difficult to remove, preventing correct elemental analysis.

(8) Alkylation of the parent dithiepine has been reported: Breslow, R.; Mohacsi, E. *J. Am. Chem. Soc.* **1963**, *85*, 431. Semmelhack, C. L.; Chiu, I.-C.; Grohmann, K. G. *Tetrahedron Lett.* **1976**, 1251.

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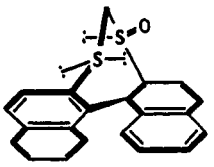
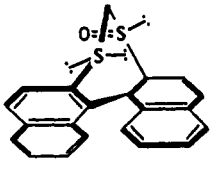
(12) Namm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

The oxidation of **3** with 1 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) led to a single diastereomeric sulfoxide with the pseudoequatorial stereochemistry **9**, as confirmed



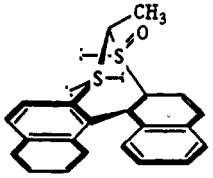
9 (pseudo-equatorial)



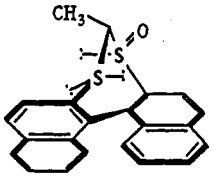
9' (pseudo-axial)

by the X-ray structure of **11a** (vide infra). This finding constitutes an advance over previously reported methods for the preparation of diastereomerically pure sulfoxides from chiral sulfides,[13] hydroxy sulfides,[14] or amino and imino sulfides.[15]

Standard generation of the anion of **9** with *n*-BuLi in THF, followed by methylation, afforded a single pure diastereoisomer to which we assigned the stereochemistry **10a**, in accord with the benzaldehyde adduct **11a**.

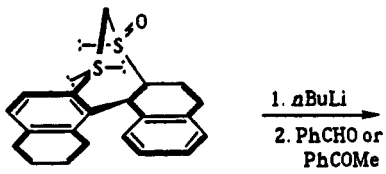


10a

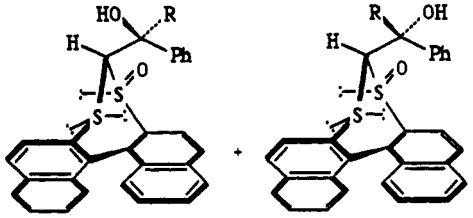


10b

Reaction of the anion of **9** with benzaldehyde afforded only the diastereomeric alcohol **11a** (eq 3). In this case,



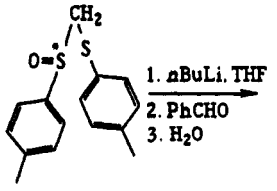
9



(3)

R = H	**11a**	(10 : 0)	**11b**
R = Me	**12a**	(>10 : 1)	**12b**

three contiguous chiral centers were stereoselectively constructed, relying on the chirality of the binaphthyl residue. This finding compares favorably with the reaction of the open-chain analogue (eq 4), whose reaction with benzaldehyde gave variable amounts of all four possible diastereoisomers.[16]



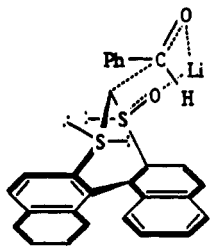
(4)

diastereomeric ratio: 50:35:15:0[1]

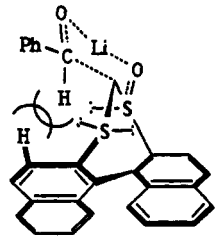
" " 50:26:15:9[2]

An X-ray structure determination (Figure 1 in the supplementary material) established the stereochemistry of adduct **11a**. The hydrogen bonding between the sulfoxide sulfur and the hydroxy group is significant.

The configuration of **11a** is that expected from analysis of the transition states **11'** and **11"**, which are similar to those proposed in the reaction of acyclic dithioacetal oxides.[16] Of the two representations in which the phenyl group is in an equatorial position, the first is preferred because the aldehyde hydrogen enters from the most open part of the molecules.



11'

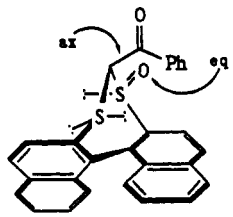


11"

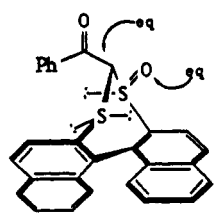
Reduction of the sulfoxide group of **11a** afforded a dithioacetal identical with **6a**, establishing the stereochemistry shown in eq 2.

The reaction of the anion of **9** with acetophenone gave a >10:1 mixture of the two diastereoisomers **12a** and **12b**, whose stereochemistry was tentatively based on analogy with the reaction of **9** with benzaldehyde.

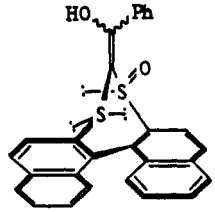
Of the two possible sulfinyl ketones **14a** and **14b**, which may be interconvertible by a tautomeric equilibrium via the enols **15**, only a single crystalline sulfoxide (presumably **14b** in which the benzoyl group is pseudoequatorial) was obtained. This result occurred with any of the following



14a



14b



15

(13) Swindell, C. S.; Blase, F. R.; Carroll, P. J. *Tetrahedron Lett.* **1990**, *31*, 5405.

(14) Arai, Y.; Hayashi, K.; Koizumi, T.; Shiro, M.; Kuriyama, K. *Tetrahedron Lett.* **1988**, *29*, 6143. Eschler, B. M.; Haynes, R. K.; Kremmydas, S.; Ridley, D. D. *J. Chem. Soc., Chem. Commun.* **1988**, 137. Goodridge, R. J.; Hambley, T. W.; Haynes, R. K.; Ridley, D. D. *J. Org. Chem.* **1988**, *53*, 2881. Pyne, S. G.; Bloem, P.; Griffith, R. *Tetrahedron* **1989**, *45*, 7013. De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457; **1989**, *54*, 3245. De Lucchi, O.; Buso, M.; Modena, G. *Tetrahedron Lett.* **1987**, *28*, 107. De Lucchi, O.; Lucchini, V.; Marchioro, C.; Modena, G. *Ibid.* **1985**, *26*, 4539.

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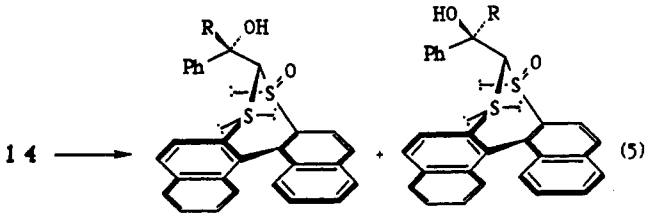
procedures: (1) oxidation of dithiepine 8 with 1 equiv of *m*-CPBA, (2) quenching of the anion of 9 with benzoyl chloride or methyl benzoate, and (3) Swern oxidation of **11a**.

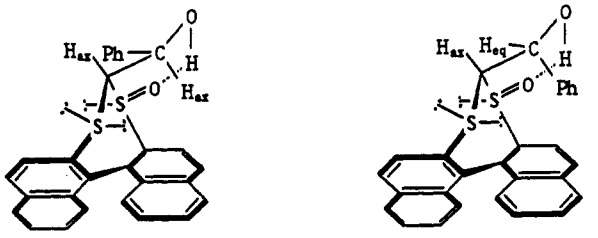
Reduction of the sulfoxide ketone **14** with 1 mol of lithium aluminum hydride afforded a >20:1 mixture[17] of two diastereomeric sulfinyl alcohols, both with ^{1}H NMR spectra different from **11a**. The configurations **11c** and **11d** (eq 5) are suggested because reduction of the sulfoxide



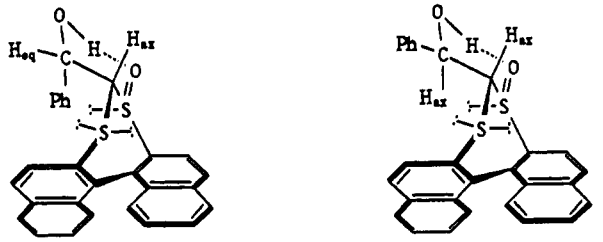
(5)

R = H **11c** **11d**
R = Me **12c** **12d**

function of the major isomer **11c** with more lithium aluminum hydride gave alcohol **6a**, which is the same alcohol obtained by reduction of the sulfoxide function of **11a**. This observation shows that the configuration of the alcoholic carbon of **11c** is the same as in **6a**, while the configuration of the thioacetalic carbon is opposite. The minor product **11d** afforded **6b** upon reduction of the sulfoxide function, hence it could be either **11b** or **11d**. On the basis



11a **11b**



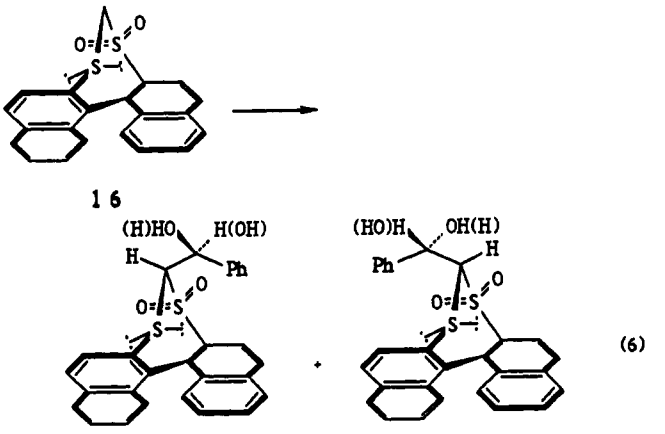
11c **11d**

of the coupling constants between the two aliphatic protons (J = 8.5 Hz), we assigned the structure **11d** because the thioacetalic and the alcoholic protons are in an axial–axial relationship, forming a dihedral angle close to 180°.[18] In **11b**, the axial–equatorial proton dihedral angle is close to 90°, which should lead to a much smaller coupling constant, comparable to that in **11c** (J = 2.1 Hz).[18]

The prevalent formation of **11c** in the reduction of **14** supports the hypothesis that the structure of the ketone is **14b** rather than **14a**, although the latter could be inferred from the Swern oxidation of **11a**. Nevertheless, the hypothesis that a lithium aluminum hydride induced tautomerization precedes the reduction cannot be dismissed.

Reaction of **14** with methylmagnesium iodide (eq 5) afforded the two alcohols **12c** and **12d**, both with a configuration different from that observed in the direct aldol addition of **9** to acetophenone. The stereochemistry shown is suggested by similarity to the benzaldehyde adduct.

The sequence of reactions described in the preceding paragraphs was also performed with the monosulfone **16**, which was obtained in good yield by permanganate oxidation[19] of the sulfoxide **9** (Scheme II). Methylation of the anion of **16** with methyl iodide afforded a mixture of the two diastereomeric derivatives **17a,b** in a 7:3 ratio (eq 6). The reaction with benzaldehyde also had poor



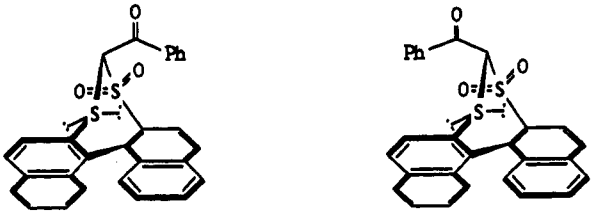
(6)

16

R = Me **17a** **17b**
R = CH(OH)Ph **18a(b)** **18c(d)**

diastereoselectivity, giving rise to a mixture of the four possible diastereoisomers **18** in variable ratios depending on the reaction conditions. Independent experiments showed that the sulfonyl alcohols **18** are interconvertible under basic conditions.

Ketone **19** was prepared from the anion of **16** with methyl benzoate in a 1:4 ratio of isomers. In similarity to the sulfinyl ketones **14**, we assume that the pseudoequatorial isomer **19b** is the major isomer. Reduction of **19**



19a **19b**

with lithium aluminum hydride gave virtually a single diastereoisomer which, again in similarity to sulfoxide **11c** (eq 5), should possess configuration **18c**. This assignment is, however, tentative because the coupling constant between the aliphatic protons is large (J = 9.2 Hz) and indicative of an axial–axial relationship. Such an arrangement is consistent with hydrogen bonding of the hydroxy group with the axial oxygen atom of the sulfonyl group. The formation of a single diastereoisomer by reduction of the 4:1 mixture of **19** suggests that the isomers interconvert under the reaction conditions. The alcohols **18** are precursors of arylpropionic acids.[20]

(17) Reduction with sodium borohydride in a water–methanol solution containing triethylamine afforded lower diastereoselection, as observed by Guanti et al. (ref 10), suggesting a shift in the tautomeric equilibrium between the two sulfoxides **14**.

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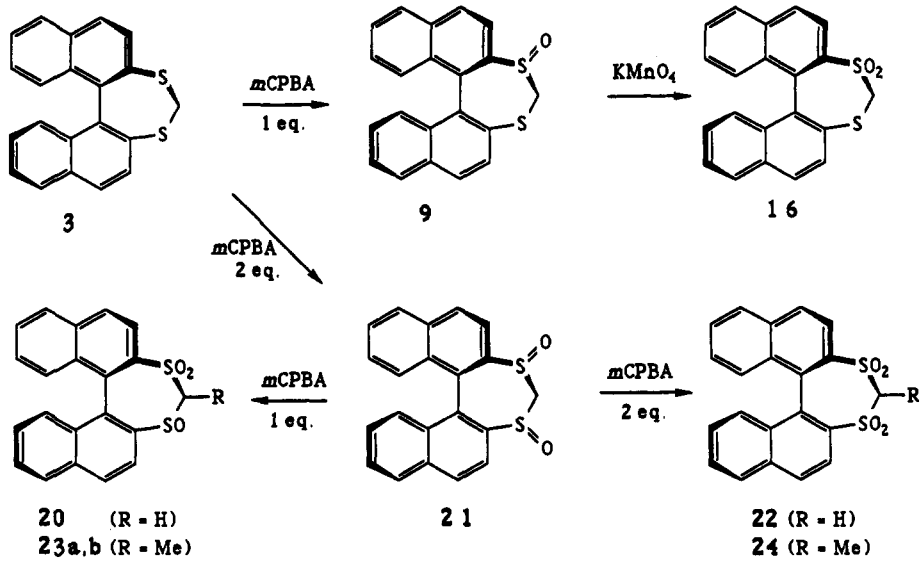
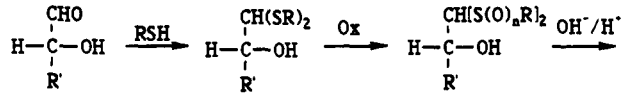
Scheme II



The other possible oxides derivable from **3**, i.e. the sulfone–sulfoxide **20**, the disulfoxide **21**, and the disulfone **22**, were synthesized by standard methods (Scheme II). Methylation of the anion of **20** gave an 8:2 mixture of the diastereoisomers **23a,b** while **22** gave **24**, no stereochemistry being implied. None of the systems investigated gave acceptable results in the reaction of their anions with benzaldehyde, as might have been expected from the absence of literature data on analogous reactions. Significantly, there are examples of using the retro process (eq 7) as a way of shortening sugar derivatives.[21]



$$R'CHO + CH_2[S(O)_nR]_2 \quad (7)$$

n = 1 or 2

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 200.13 MHz, with tetramethylsilane as internal standard and $CDCl_3$ as solvent. The diastereomeric composition of the crude reaction mixtures was determined by ^1H NMR. Tetrahydrofuran and ether were purified by distillation from sodium wire in an argon atmosphere. Diisopropylamine and dimethyl sulfoxide were freshly distilled and stored under argon. Commercially available *m*-chloroperbenzoic acid (Aldrich) and trifluoroacetic anhydride (TFAA) were used without further purification. All other chemicals were commercial grade and were purified by distillation. Petroleum ether refers to the 40–70 °C boiling fraction.

Dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine (3). To a solution of **4**[22] (9.3 g, 29.2 mmol) and dimethoxymethane (2.3 g, 29.2 mmol) in 150 mL of dry dichloromethane was added dropwise, under argon and at 0 °C, boron trifluoride etherate (4.15 g, 29.2 mmol). The reaction mixture was stirred for 4 h at 0 °C and for 3 h at room temperature. The solution was washed with 5% KOH (2 × 20 mL) and water (3 × 10 mL) and dried over anhydrous sodium sulfate. Concentration of the filtrate in vacuo provided a colorless solid (8.6 g, 89%): mp 158 °C (*i*-PrOH/MeOH); ^1H NMR δ 4.35 (s, 2 H), 7.11 (dm, 2 H, *J* = 8.5 Hz), 7.23 (m, 2 H), 7.48 (m, 2 H), 7.80 (d, 2 H, *J* = 8.5 Hz), 7.95 (br d, 2 H, *J* = 8.5 Hz), 7.98 (d, 2 H, *J* = 8.5 Hz); MS *m/z* (M^+) calcd 330.0534, obsd 330.0531.[23]

Dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*-Oxide (9). A dichloromethane solution of *m*-CPBA (85%, 3.04 g, 15 mmol) was added dropwise to a stirred and cooled (−10 °C, ice–salt bath) solution of dithiepine **3** (4.95 g, 15 mmol) in the same solvent. The reaction temperature was kept at −10 °C for 1 h, and the resulting white suspension was washed with aqueous sodium sulfite and 5% sodium carbonate. The organic layer was dried over anhydrous sodium sulfate and evaporated. Pure material was obtained by flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (1:1) (4.76 g, 92%): mp 199–200 °C (*i*-PrOH/MeOH); IR (KBr) 3051, 2973, 1044 cm^{-1}; ^1H NMR δ 3.61 (d, 1 H, *J* = 10.7 Hz), 5.09 (d, 1 H, *J* = 10.7 Hz), 7.22 (d, 2 H, *J* = 8.2 Hz), 7.31 (td, 1 H, *J* = 6.8, 1.5 Hz), 7.33 (td, 1 H, *J* = 8.2, 1.5 Hz), 7.54 (td, 1 H, *J* = 8.2, 1.5 Hz), 7.59 (td, 1 H, *J* = 8.2, 1.5 Hz), 7.85 (d, 1 H, *J* = 8.2 Hz), 7.96 (d, 1 H, *J* = 8.2 Hz), 7.99 (d, 1 H, *J* = 8.2 Hz), 8.06 (d, 1 H, *J* = 8.2 Hz), 8.22 (d, 1 H, *J* = 8.8 Hz), 8.29 (d, 1 H, *J* = 8.8 Hz).

Dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*-Dioxide (16). To a solution of **9** (400 mg, 1.15 mmol) in 10 mL of acetone containing 860 mg of suspended magnesium sulfate was added dropwise at −25 °C a solution of potassium permanganate (1.25 g, 7.89 mmol) in 12 mL of acetone. The brown slurry was stirred for 2 h at −20 °C and then warmed to room temperature. After filtration through Celite and concentration in vacuo, a colorless solid was obtained (410 mg, 98%): mp 233–4 °C (AcOEt/MeOH); IR (KBr) 3057, 2973, 1300, 1124 cm^{-1}; ^1H NMR δ 4.21 (d, 1 H, *J* = 13.1 Hz), 4.75 (d, 1 H, *J* = 13.1 Hz), 7.10 (br d, 1 H, *J* = 8.6 Hz), 7.19 (br d, 1 H, *J* = 8.6 Hz), 7.29 (td, 1 H, *J* = 10.0, 1.5 Hz), 7.33 (td, 1 H, *J* = 10.0, 1.5 Hz), 7.56 (td, 1 H, *J* = 8.6, 1.5 Hz), 7.64 (td, 1 H, *J* = 8.6, 1.5 Hz), 7.96 (dd, 2 H, *J* = 9.0 Hz), 8.00 (dd, 2 H, *J* = 9.0 Hz), 8.20 (d, 1 H, *J* = 9.0 Hz), 8.29 (d, 1 H, *J* = 9.0 Hz); MS *m/z* (M^+) calcd 362.0432, obsd 362.0437.

Dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*,*S*′-trioxide (20) was prepared in 80% yield by oxidation of **9** with *m*-CPBA and was purified via flash chromatography, eluting with petroleum ether/ethyl acetate: mp 260–1 °C (*i*-PrOH); IR (KBr) 3057, 2966, 1322, 1124, 1054 cm^{-1}; ^1H NMR δ 4.45 (d, 1 H, *J* = 11.9 Hz), 5.11 (d, 1 H, *J* = 11.9 Hz), 7.15–8.39 (m, 12 H).

Dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*′-dioxide (21) was prepared by oxidation of **3** with 2 equiv of *m*-CPBA as described for **9**. Purification by flash chromatography (petroleum ether/ethyl acetate) afforded colorless material (80%): mp 285–6 °C (AcOEt/MeOH); IR (KBr) 3064, 2966, 1060, 1055 cm^{-1}; ^1H NMR δ 4.70 (s, 2 H), 7.23–8.46 (m, 12 H); MS *m/z* (M^+) calcd 362.0492, obsd 362.0430.

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Dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*,*S*′,*S*′-Tetraoxide (22). To a solution of **3** (500 mg, 1.51 mmol) in 5 mL of dichloromethane was added dropwise at room temperature a 4% solution of *m*-CPBA (1.04 g, 5.1 mmol) in the same solvent. The resulting mixture was stirred at room temperature for 2 h or until disappearance of the dithiepine (TLC). The reaction mixture was washed with aqueous sodium sulfite and sodium carbonate, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was recrystallized from methanol to yield a crystalline solid (583 mg, 98%): mp 321–2 °C; IR (KBr) 3057, 2975, 1325, 1129 cm^{-1}; ^1H NMR δ 4.97 (s, 2 H), 7.18 (d, 1 H, J = 8.5 Hz), 7.25 (d, 1 H, J = 8.5 Hz), 7.40 (td, 2 H, J = 8.5 Hz), 7.70 (td, 2 H, J = 8.5 Hz), 8.04 (d, 2 H, J = 8.5 Hz), 8.25 (s, 4 H); MS m/z (M^+) calcd 394.0330, obsd 394.0327.

General Procedure for the Generation of the Carbanion and Reaction with Electrophiles. To a solution of substrate (1 mmol) in dry THF (2 mL), cooled at −78 °C under argon, was added dropwise via syringe *n*-BuLi (1.6 M in hexane, 1.2 mmol). The red solution was stirred at −78 °C for 2 h, and an equimolar quantity of the electrophile (methyl iodide, benzaldehyde, or acetophenone) was added. After being stirred at −78 °C for an additional 2 h, the solution was slowly warmed to −40 °C over 3 h. Acetic anhydride and/or saturated ammonium chloride was added, and the mixture was warmed slowly to room temperature. The residue was taken up in dichloromethane, dried (Na_2SO_4), concentrated, and recrystallized or flash chromatographed through silica, eluting with petroleum ether/ethyl acetate.

Quenching with Methyl Iodide. 2-Methyldinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine (5) (99%): mp 200–1 °C (MeOH); ^1H NMR δ 1.55 (d, 3 H, J = 6.7 Hz), 4.94 (q, 1 H, J = 6.7 Hz), 7.08–7.29 (m, 4 H), 7.37–7.52 (m, 2 H), 7.79 (d, 2 H), 7.90–8.00 (m, 4 H); MS m/z (M^+) calcd 344.0690, obsd 344.0709.

2-Methyldinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*-oxide (10a) (95%): mp 214–6 °C (*i*-PrOH); ^1H NMR δ 1.28 (d, 3 H, J = 6.8 Hz), 5.03 (q, 1 H, J = 6.8 Hz), 7.10–8.25 (m, 12 H).

2-Methyldinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*-Dioxide (17a,b). Obtained as a colorless solid diastereomeric mixture of sulfones (70:30) (85%). **17a** (major): ^1H NMR δ 1.52 (d, 3 H, J = 6.5 Hz), 4.75 (q, 1 H, J = 6.6 Hz), 7.01–8.31 (m, 12 H). **17b** (minor): ^1H NMR δ 1.72 (d, 3 H, J = 6.5 Hz), 4.42 (q, 1 H, J = 6.6 Hz), 7.01–8.31 (m, 12 H).

2-Methyldinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*,*S*′-Trioxide (23a,b). Obtained as a 84:16 mixture. **23a** (major): ^1H NMR δ 1.32 (d, 3 H, J = 7.0 Hz), 4.85 (q, 1 H, J = 7.0 Hz), 7.23–8.38 (m, 12 H). **23b** (minor): ^1H NMR δ 1.07 (d, 3 H, J = 7.0 Hz), 4.27 (q, 1 H, J = 7.0 Hz), 7.23–8.38 (m, 12 H).

2-Methyldinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*,*S*′,*S*′-tetraoxide (24) (95%): mp 252–4 °C (CH_2Cl_2/petroleum ether); ^1H NMR δ 1.75 (d, 3 H, J = 7.0 Hz), 4.75 (q, 1 H, J = 7.0 Hz), 7.19–8.32 (m, 12 H).

Quenching with Benzaldehyde. 2-(1-Phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine (6a,b). Obtained from **3** as a 8:2 mixture of diastereoisomers (90%). **6a** (major): mp 218–9 °C; ^1H NMR δ 4.37 (d, 1 H, J = 8.8 Hz), 4.97 (d, 1 H, J = 8.8 Hz), 7.08–8.08 (m, 17 H, two diast.); MS m/z (M^+) calcd 436.0951, obsd 436.0966. **6b** (minor): mp 104–5 °C; ^1H NMR δ 4.93 (d, 1 H, J = 7.5 Hz), 5.20 (d, 1 H, J = 7.5 Hz), 7.08–8.08 (m, 17 H, two diast.).

2-(1-Phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*-Oxide (11a). Obtained from **9** as a single diastereoisomer (92%): mp 190–2 °C (*i*-PrOH); ^1H NMR δ 5.00 (dd, 1 H, J = 0.9, 9.2 Hz), 5.34 (d, 1 H, J = 9.2 Hz), 5.95 (d, 1 H, J = 0.9 Hz, OH), 7.20–8.44 (m, 12 H).

2-(1-Phenyl-1-hydroxymethyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*′-Dioxide (18). Obtained from **16** as a variable mixture of four diastereoisomers (85%): mp 253–5 °C (one diast.); ^1H NMR δ 4.41 (d, 1 H, J = 2.1 Hz, one diast.), 4.64 (d, 1 H, J = 9.8 Hz, one diast.), 4.75 (d, 1 H, J = 9.2 Hz, one diast.), 4.96 (d, 1 H, J = 2.1 Hz, one diast.), 5.04 (d, 1 H, J = 9.2 Hz, one diast.), 5.13 (d, 1 H, J = 9.8 Hz, one diast.), 5.85 (d, 1 H, J = 2.1 Hz, one diast.), 5.93 (d, 1 H, J = 2.1 Hz, one diast.), 7.02–8.40 (m, 17 H, four diast.).

Quenching with Acetophenone. 2-(1-Phenyl-1-hydroxyethyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine (7a,b). A diastereomeric mixture (87:13) was obtained (85%). **7a** (major): ^1H NMR δ 1.66 (s, 3 H), 5.16 (s, 1 H), 7.01–8.03 (m, 17 H, two diast.). **7b** (minor): ^1H NMR δ 1.82 (s, 3 H), 5.27 (s, 1 H), 7.01–8.03 (m, 17 H, two diast.).

2-(1-Phenyl-1-hydroxyethyl)dinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*-Oxide (12a,b). A diastereomeric mixture (92:8) was obtained (68%). **12a** (major): ^1H NMR δ 1.80 (s, 3 H), 5.49 (s, 1 H), 6.01 (s, 1 H), 7.02–8.42 (m, 17 H, two diast.). **12b** (minor): ^1H NMR δ 1.72 (s, 3 H), 5.76 (s, 1 H), 5.89 (s, 1 H), 7.02–8.42 (m, 17 H, two diast.).

2-Benzoyldinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine (8). Method A. A solution of boron trifluoride etherate (965 mg, 6.8 mmol) in 20 mL of chloroform was treated dropwise at 65 °C with **4** (1 g, 3.14 mmol) and 2,2′-diethoxyacetophenone (708 mg, 3.4 mmol) dissolved in 20 mL of chloroform. After being stirred for 2 h at the same temperature the mixture was cooled. The crude product was washed with 30 mL of 20% aqueous sodium bicarbonate and purified by flash chromatography eluting with petroleum ether/dichloromethane to give **8** as yellow solid (1.1 g, 90%): mp 178–80 °C (CH_2Cl_2/EtOH); IR (KBr) 3050, 2921, 1673 cm^{-1}; ^1H NMR δ 6.26 (s, 1 H), 7.12–8.04 (m, 17 H).

Method B. A 10% solution of **3** (350 mg, 1.06 mmol) in dry THF was cooled at −78 °C and treated with *n*-BuLi (1.6 M, 1.16 equiv). After 2 h, methyl benzoate (0.144 mL, 1.16 mmol) was added. The reaction mixture was stirred at the same temperature for 2 h and then at −40 °C for 3 h. A cool 10% ammonium chloride solution was added, and the reaction mixture was warmed to ambient temperature. The crude was taken up in dichloromethane, dried (Na_2SO_4), and concentrated to give a solid (96 mg, 20%).

Method C. In a typical run, TFAA (0.05 mL, 0.386 mmol) in dry dichloromethane (1 mL) was added dropwise at −78 °C to a solution of DMSO (30 mg, 0.382 mmol) in dry dichloromethane over 10 min. After 10 min, a solution of alcohol **6** (130 mg, 0.3 mmol) in the same solvent was added via syringe. After 12 h at −78 °C the reaction mixture was slowly warmed to −50 °C and triethylamine (0.08 mL) was added. The solution was stirred at room temperature for 45 min, poured into water, and extracted with dichloromethane. The organic phase was treated sequentially with dilute hydrochloric acid and dilute sodium bicarbonate. The organic extract was dried ($CaCl_2$), and the solvent was removed under vacuum to provide the ketone **8** (43 mg, 33%).

2-Benzoylbinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*-Oxide (14). Method A. From **8**, via the standard oxidative procedure described for **9** (98%): mp 174 °C; IR (KBr) 3053, 2921, 1671, 1059 cm^{-1}; ^1H NMR δ 5.35 (s, 1 H), 7.25–8.12 (m, 17 H).

Method B. A solution of **9** (500 mg, 1.44 mmol) in 10% dry THF was cooled at −78 °C and treated with *n*-BuLi (1.6 M, 0.5 equiv), and benzoyl chloride (532 mg, 3.788 mmol) was added in four portions. The reaction mixture was stirred at the same temperature for 2 h and then at −40 °C for 3 h. Cool 10% ammonium chloride solution was added, and the reaction mixture was warmed to room temperature. The crude was taken up in dichloromethane, dried (Na_2SO_4), and concentrated to give a solid (144 mg, 23%): mp 174 °C.

Method C. To a solution of diisopropylamine (83 mg, 0.829 mmol) in dry THF (1 mL) was added via syringe *n*-BuLi (1.6 M, 0.829 mmol) at −78 °C under argon. The mixture was stirred for 30 min at −78 °C and a few minutes at room temperature. The solution was cooled again to −78 °C, and compound **9** (0.721 mmol) in dry THF (1 mL) was added via syringe. After 2 h at −78 °C, methyl benzoate was added and the mixture was warmed slowly to −38 °C. After 10 h at this temperature, the reaction mixture was treated with a cool 10% ammonium chloride solution and the residue was flash chromatographed (1,2-dichloroethane–acetone).

Method D. Compound **14** was obtained (30% yield) by Swern oxidation of alcohol **11a** with DMSO and TFAA in dry dichloromethane as described in method C in the preparation of ketone **8**.

2-Benzoylbinaphtho[2,1-*d*:1′,2′-*f*][1,3]dithiepine *S*,*S*-Dioxide (19a,b). Obtained from **16** (200 mg, 0.55 mmol) with *n*-BuLi (1.6 M, 0.5 mL) in THF (2 mL) and methyl benzoate (0.1 mL, 0.80 mmol) as electrophile. An 8:2 ratio (variable) of diastereoisomers was obtained (230 mg, 90%): IR (KBr) 3047, 2922, 1670, 1314, 1132 cm^{-1}. **19b** (major): ^1H NMR δ 6.08 (s, 1 H), 7.07–8.44 (m, 17 H, two diast.). **19a** (minor): ^1H NMR δ 6.40 (s, 1 H), 7.07–8.44 (m, 17 H, two diast.); MS (mixture of diastereoisomers)

m/z (M^+) calcd 466.0693, obsd 466.0682.

General Procedure for the Reduction of 8, 14, and 19 with Lithium Aluminum Hydride. To a suspension of lithium aluminum hydride (2 equiv) in 2% dry ether was added a 2.5% solution of substrate in dry THF at -78 °C under argon. The mixture was stirred for 45 min at the same temperature, treated with a 4% HCl, and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated in vacuo.

6a. Reduction of 8 with lithium aluminum hydride, following the procedure described above, gave one diastereomer (98% yield).

11c,d. Via the procedure described above, reduction of 14 gave a diastereomeric mixture (96:4) of alcohols (93% yield). **11c** (major): ^1H NMR δ 4.18 (d, 1 H, J = 2.0 Hz), 5.67 (d, 1 H, J = 2.0 Hz), 7.19-8.34 (m, 17 H, two diast.). **11d** (minor): ^1H NMR δ 4.27 (d, 1 H, J = 8.5 Hz), 5.47 (d, 1 H, J = 8.5 Hz), 7.19-8.34 (m, 17 H, two diast.).

18c. Reduction of 19 with lithium aluminum hydride, following the procedure described above, gave one diastereomer (98%) and traces of the other isomers: ^1H NMR δ 4.75 (d, 1 H, J = 9.2 Hz), 5.04 (d, 1 H, J = 9.2 Hz), 7.02-8.40 (m, 17 H); MS m/z (M^+) calcd for $C_{28}H_{20}O_3S_2 \cdot H_2O$ 450.0744, obsd 450.0751.

General Procedure for the Reaction of 8 and 14 with Methylmagnesium Iodide. A 3% solution of the substrate in dry THF/ether (1:2.5) under argon was cooled to -78 °C. Methylmagnesium iodide (5 equiv) was added dropwise via syringe. The reaction mixture was treated with water and saturated aqueous ammonium chloride. The combined organic extracts were dried over anhydrous sodium sulfate. The product was purified by flash chromatography, eluting with the specified solvent.

7a,b. Via the procedure described above, alkylation of 8 with methylmagnesium iodide gave a diastereomeric mixture (87:13) of alcohols (95% yield). The crude product was purified by flash chromatography, eluting with a gradient of petroleum ether-dichloromethane.

12a,b. As described above, a single diastereoisomer was obtained from the reaction of methylmagnesium iodide with 14 (64% yield) as a light yellow solid after flash chromatography (dichoromethane): ^1H NMR δ 2.25 (s, 3 H), 4.18 (s, 1 H), 6.75-8.31 (m, 17 H).

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Supplementary Material Available: X-ray crystallographic data including an ORTEP drawing (Figure 1) and tables of fractional coordinates, anisotropic thermal parameters, bond distances, and bond angles for compound 11a (Tables I-IV), ^1H NMR spectra for all title compounds in the Experimental Section, and HRMS data for selected compounds. (29 pages). Ordering information is given on any current masthead page.

Diastereoselective Cycloaddition of N-Lithiated Azomethine Ylides to (*E*)-α,β-Unsaturated Esters Bearing a C_2-Symmetric Imidazolidine Chiral Controller

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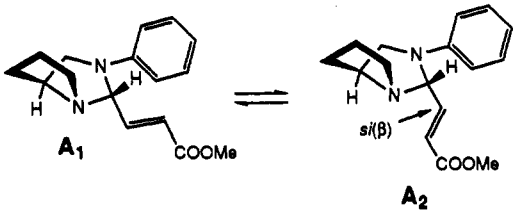
The 1,3-dipolar cycloaddition of N-metalated azomethine ylides to chiral (*E*)-3-(1,3-disubstituted 4,5-diphenylimidazolidin-2-yl)propenoates proceeded highly diastereoselectively. The previously unknown absolute configuration of optically pure 1,2-dianilino-1,2-diphenylethane was determined from the absolute configuration of the cycloadducts. What diastereotopic olefin face of the α,β-unsaturated ester was attacked by the ylide was found to depend dramatically upon the nature of N substituents of the chiral controller as well as upon the bulkiness of the ester moiety of the ylide.

Introduction

Despite its potentially great utility in the synthesis of heterocycles, asymmetric 1,3-dipolar cycloaddition has been the subject of few reports.[1] Nitrones and nitrile oxides are among the 1,3-dipoles that have been relatively widely applied synthetically.[2,3] Because few examples of efficient Lewis acid catalyzed stereocontrol of 1,3-dipolar cycloaddition are known,[1] the only way to achieve a high degree of asymmetric induction in 1,3-dipolar cycloaddition is by employing suitably designed chiral dipoles and dipolarophiles.

α,β-Unsaturated carbonyl compounds bearing a chiral controller are attractive intermediates for use in synthetic chemistry because they can not only be utilized as acceptor molecules in nucleophilic carbon-carbon bond-forming reactions but also serve as activated olefinic dipolarophiles

Scheme I



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