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Synthesis and Application of Easily Recyclable Thiomorpholines for Use in Sulfur Ylide Mediated Asymmetric Epoxidation of Aldehydes

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: Chiral nonracemic thiomorpholines have been synthesized in four to six steps from limonene or achiral alkenes using α-methylbenzylamine to control absolute stereochemistry. These aminosulfides have been used to generate sulfur ylides, which have been applied in the asymmetric epoxidation of aldehydes as easily recoverable catalysts. Excellent yields (up to 98%), enantioselectivities (up to 97:3 e.r.), and diastereoselectivities (≥98:2 *trans*/*cis*) were achieved in these epoxidations and the sulfides were easily recovered in high yield (up to 97%) by simple acid/base extraction.

Keywords: asymmetric epoxidation · enantioselectivity · sulfur · thiomorpholines · ylides

Introduction

The use of sulfur ylides as reagents for the asymmetric epoxidation of carbonyl compounds is now well established and there are a number of chiral sulfides that give greater than 90% *ee* in epoxidations (Figure 1) and other related reactions.[1–4] Both catalytic and stoichiometric processes have been developed, the latter showing broader substrate scope.[5] For example, we have developed sulfide **1**, which can be synthesized on a large scale in four steps and 56% yield from camphorsulfonyl chloride;[6] it is an effective and selective catalyst for epoxidation of a wide variety of carbonyl compounds.[5a] However, with this and all other sulfides shown in Figure 1, column chromatography is required to separate the product epoxide from the sulfide, which is unattractive for large-scale applications. We have therefore sought sulfides that are easier to separate, which additionally improves their recyclability. With this in mind, we have focused on thiomorpholines and in this paper we describe the synthesis of a series of such molecules and their use in asymmetric epoxidations.

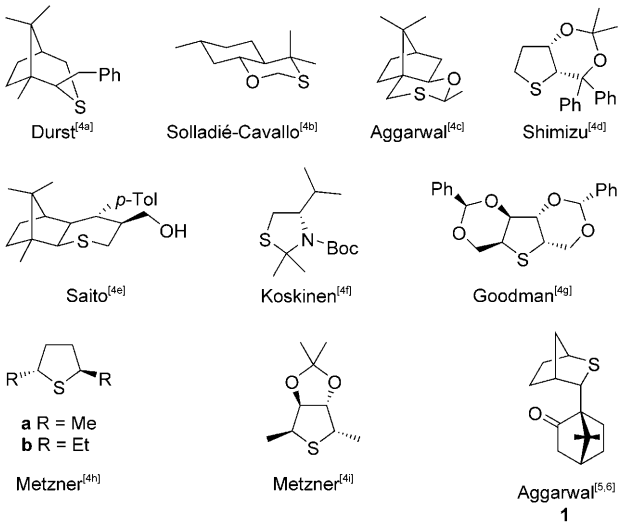

Figure 1. Sulfides which give greater than 90% *ee* in epoxidations.[4–6]

Potential sulfides were designed bearing in mind that the enantioselectivity in sulfide-mediated epoxidations is governed by four main factors:[2]

a) Alkylation of the sulfide should lead to a single diastereomer of ylide, and so in non-C_2-symmetric sulfides only one lone pair should be reactive.

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b) The conformation of the ylide must be well controlled.
c) The ylide should show a high level of face selectivity in reaction with the carbonyl compound.
d) The *anti*-betaine should be formed nonreversibly; the steric bulk of the sulfide can affect this.

It was envisaged that the pseudo-chair conformation of the six-membered ring of thiomorpholines would make a good core for the design of aminosulfide targets. The amino group would allow the sulfide to be easily recovered from the reaction mixture by a simple acid/base extraction. Although amines are generally more nucleophilic than sulfides, by adding significant steric hindrance around the nitrogen atom we expected the normal pattern of reactivity to be reversed. Appropriate placement of substituents should allow control of the lone-pair alkylation, the ylide conformation, and the face selectivity of the ylide (Figures 2 and 3). For example, the thiomorpholines **2** should show good selectivity in alkylation of the less hindered, equatorial lone pair. The ylide conformation would be controlled by *syn*-pentane interactions between the axial C–H bonds of the thiomorpholine and the C-H versus C-Ph groups of the ylide. Ylide face selectivity would be expected to be well controlled as there is a C substituent directly in front of the ylidic carbon atom. *cis*-2,3-Disubstituted thiomorpholines **4** and **5** were also selected since it was expected that a bulky N substituent might force the adjacent substituent into an axial position, thus enhancing the selectivity in alkylation of the sulfide. Similarly **6** would be expected to show very high selectivity in sulfide alkylation and very high selectivity in ylide conformation.

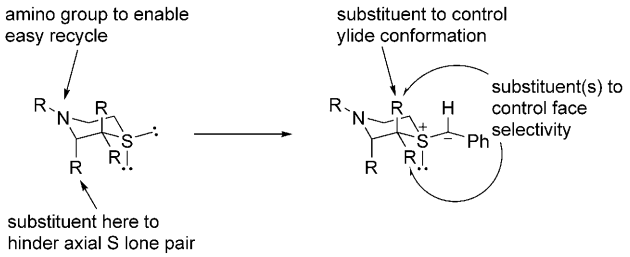

Figure 2. Design elements in target sulfides.

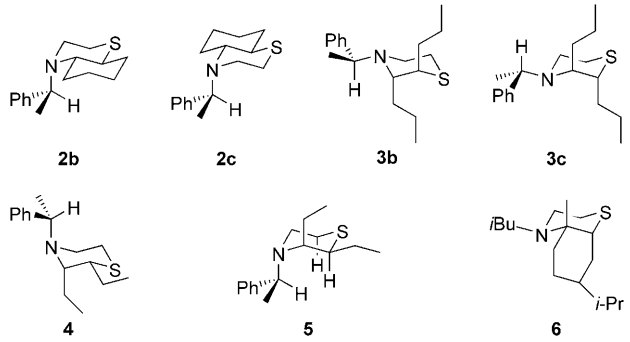

Figure 3. Target thiomorpholines **2**–**6**.

The main uncertainty was ylide face selectivity, which no longer has a substituent directly flanking the ylidic carbon atom in the case of **6**, but does have a carbon substituent in the case of **4**/**5**. For completeness we decided to test the conformationally flexible *trans*-2,3-disubstituted thiomorpholines **3** since both conformationally flexible and locked *cis* substrates (**4, 5**, and **6**) had been targeted together with the conformationally locked *trans*-2,3-substituted thiomorpholines **2**. The synthesis of thiomorpholines **2**–**6**, a family of highly selective and recoverable catalysts for asymmetric epoxidation of aldehydes, is described below.

Results and Discussion

The synthesis of **2**–**5** from commercially available alkenes is outlined in Scheme 1. Reaction of sulfuryl chloride with disulfide **7**[7] generated the corresponding sulfenyl chloride,[8] which was treated in situ with the appropriate alkene to give β-chlorosulfides **11a**–**13a** (**Caution!**). The racemic β-chlorosulfides **11a**–**13a** were used rapidly as they are potentially hazardous and somewhat unstable on storage. Reaction with cheap and commercially available (*S*)-α-phenylethylamine gave the desired aminosulfides **11b,c**, **12b,c**, **13b,c** as a mixture of two diastereomers in each case (1:1 by ^{1}H NMR of the crude product) which were separable by column chromatography.[9] Treatment of the diastereomerically pure β-aminosulfides **11c**, **12**-d1 (diastereomer 1 of **12**), **13b**, and **13c** with hydrochloric acid followed by triacetoxyborohydride gave the desired thiomorpholines **2**–**5**.[10,11]

Sulfide **6** was synthesized starting from inexpensive (*R*)-limonene (Scheme 2), taking advantage of a new route to thiomorpholines from aminothiols developed in our group.[12] Selective hydrogenation of the external double bond gave (*R*)-menthene.[13] Reaction of menthene with iodine and thiocyanogen yielded a 2:1 mixture of diastereomers **16** and **17** in which the iodo and isothiocyanato groups have a *trans* relationship as expected from the analogous reaction of 4-*tert*-butyl-1-methylcyclohexene.[14] The regioselectivity observed is as expected for the ring opening of iodonium ions having *cis* and *trans* relationships to the isopropyl group to yield diaxial iodo and thiocyanato groups in chair conformations. Addition of MeMgI to the mixture of diastereomers converted **16** into thiazoline **18** in low yield (unoptimized).[15] Products from the minor diastereomer **17** were not isolated. Hydrolysis with hydrochloric acid gave only low conversion after 7 days at reflux.[16] However, it was found that after 13 h of microwave irradiation the desired aminothiol **19** was obtained cleanly in excellent yield. Application of our recently developed methodology for the synthesis of thiomorpholines[12] gave **20** (90%), which furnished sulfide **6** (79%) after reductive amination.

Sulfide Alkylation

The conformers of **2c**, **4**, **5**, and **3**-d1 (diastereomer 1 of **3**) shown in Scheme 3 were predicted to be the lowest-energy

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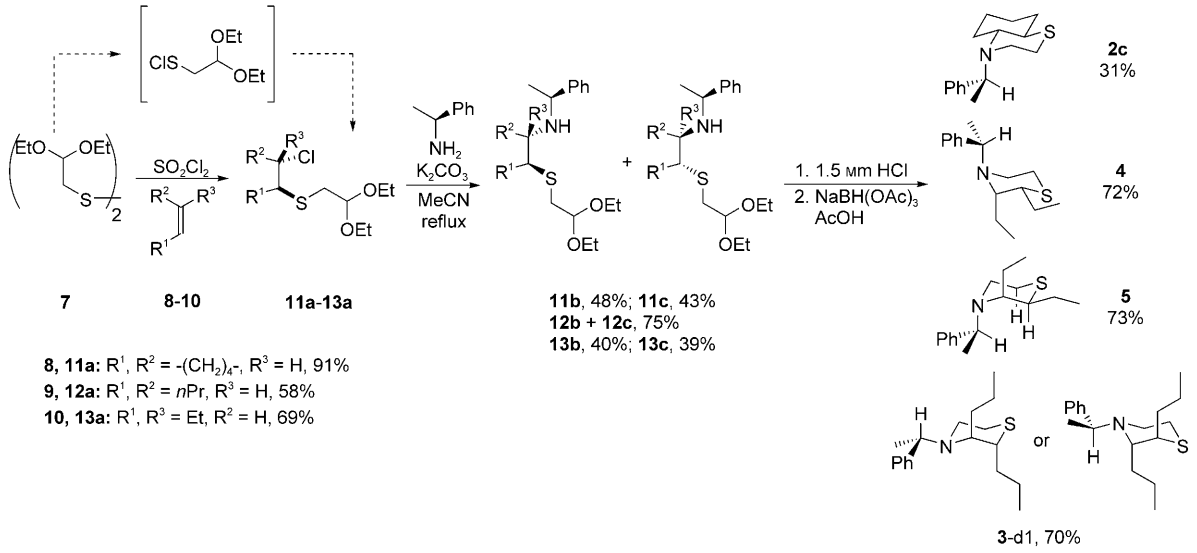
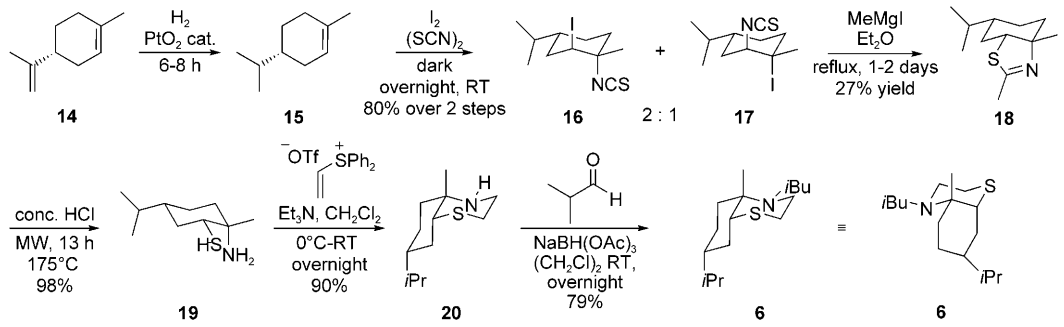


Scheme 1. Synthesis of thiomorpholines **2**–**5**. The absolute stereochemsitry of **3**-d1 has not been established.



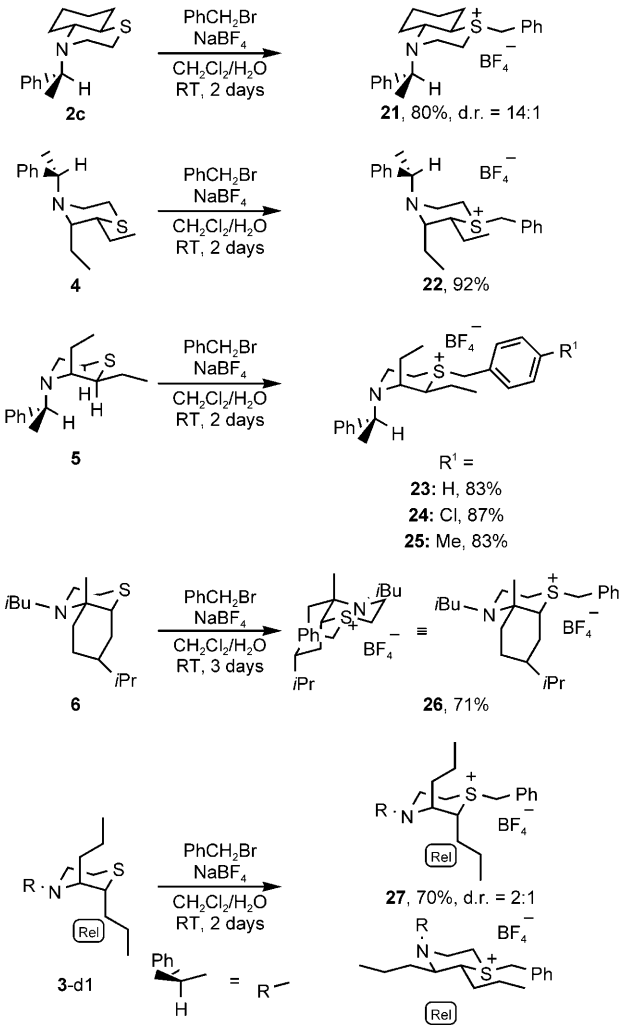
Scheme 2. Synthesis of **6** from (*R*)-limonene **14**. MW = microwave.

conformations using molecular mechanics modelling.[17] The preference for the N substituent to sit pseudoaxial for **2c**, **4**, and **5** and pseudoequatorial for **3-**d1 was quite pronounced (conformers with the N substituent in the alternate position were more than 11 kJ mol^{-1} higher in energy compared to the lowest-energy conformer). The following rationalization for the preferred conformations is proposed: The need for the N substituent to avoid a steric clash with the alkyl substituent on the adjacent carbon atom outweighs the 1,3-diaxial interactions with axial hydrogen substituents in sulfides **2c**, **4**, and **5**. The propyl groups in **3-**d1 have a strong preference to sit in *trans*-diaxial positions so as to avoid gauche interactions with each other.[18] Thus in this case the N substituent sits in a pseudoequatorial position as the 1,3-diaxial interaction with the propyl chain is a more severe interaction than the interaction with the axial propyl group on the adjacent carbon atom.

As expected **4**, **5**, and **6**, gave single diastereomers upon alkylation with BnBr because in each case the axial lone pair is severely hindered by an axial substituent in the 3-position (Scheme 3).[19] An X-ray structure of **23** (Figure 4) proved the relative stereochemistry, from which we were able to deduce the stereochemistry of **4** and **5**. The high selectivity in alkylation of **4/5** is a consequence of the need for the bulky N substituent to be as far away from the adjacent C substituent, forcing it and the C3 substituent into pseudoaxial positions. The axial C substituent then blocks the axial sulfide lone pair, leading to high selectivity. Evidently, without the axial substituent the diastereoselectivity in alkylation is moderate as shown in example **2c** (d.r. = 14:1). In the case of **3-**d1 we believe that the poor selectivity in alkylation is due to slow alkylation of the major (diaxial) conformer and rapid alkylation of the minor (diequatorial) conformer.

Epoxidation Reactions

Sulfonium salts **21**, **22**, **23**, and **26** were tested in the asymmetric epoxidation of benzaldehyde (Table 1). Using EtP_2 base ($[Me_2N]_3P{=}NP(=NEt)[NMe_2]_2$) at −78 °C in CH_2Cl_2 (method A) high diastereo- and enantioselectivities and good yields were obtained (Table 1, entries 1–3, 5). However, attempted recovery of the sulfides by acid/base extraction did not give clean material. In contrast, use of KOH at



Scheme 3. Synthesis of sulfonium salts **21**–**27**. The relative stereochemistry of dipropyl groups is *trans* but the absolute stereochemistry is not known.

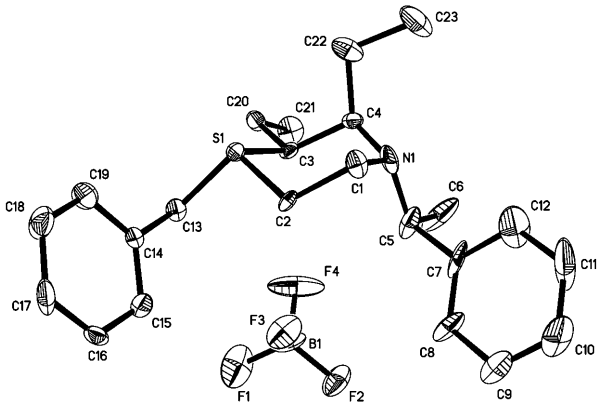
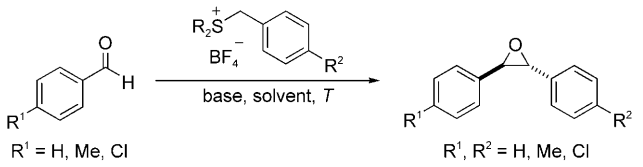


Figure 4. Solid-state structure of **23**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms and cocrystallized dichloromethane solvent have been omitted for clarity.

Table 1. Results obtained in the asymmetric epoxidation of aldehydes with sulfonium salts **21**–**26**.



Entry	Sulfonium salt	Method[a]	R^1, R^2	Yield [%][b]	*trans*/*cis*[c]	e.r.[d]	Recovered sulfide [%]
1	**21** (14:1 **a**/**b**)	A	H, H	79	≥98:2	85.5:14.5 (*R*,*R*)	–
2	**22**	A	H, H	74	≥98:2	93:7 (*R*,*R*)	–
3	**26**	A	H, H	86	≥98:2	79:21 (*S*,*S*)	–
4	**26**	B	H, H	60	97:3	80:20 (*S*,*S*)	83
5	**23**	A	H, H	79	≥98:2	97:3 (*S*,*S*)	–
6	**23**	B	H, H	95	86:14	96:4 (*S*,*S*)	97
7	**23**	B	Cl, H	89	94:6	96:4 (*S*,*S*)	90
8	**24**	B	H, Cl	92	98:2	97:3 (*S*,*S*)	93
9	**23**	B	Me, H	94	89:11	96:4 (*S*,*S*)	96
10	**25**	B	H, Me	73	78:22	95:5 (*S*,*S*)	94

[a] Method A: EtP_2 base (1.1 equiv), aldehyde (1.1 equiv), −78 °C, 1.5–2 h, CH_2Cl_2, sulfide not recovered. Method B: KOH (2 equiv), aldehyde (2 equiv), 0 °C, 3 h, MeCN/H_2O (9:1). [b] Combined yield of isolated *cis*- and *trans*-stilbene oxide. [c] Determined by ^1H NMR of crude product. [d] Determined by chiral HPLC; see the Supporting Information for details. [e] 8 h.

0 °C in MeCN/H_2O (9:1; method B) did allow clean recovery of the sulfides in good to excellent yield through acid/base wash (Table 1, entries 4 and 6). The enantioselectivity remained high and was not affected significantly by the change in conditions although a decrease in diastereoselectivity was observed when using salt **23** (Table 1, entries 5 and 6). Sulfonium salt **23** performed best in epoxidations of benzaldehyde and was tested in epoxidations of *p*-chloro- and *p*-methylbenzaldehyde, which also gave excellent results (Table 1, entries 7 and 9). In addition salts **24** and **25** derived from sulfide **5** were also tested in the epoxidation of benzaldehyde and gave good results (Table 1, entries 8 and 10). In all cases the sulfide **5** was reisolated by a simple acid/base wash in high yield.

The small changes in diastereoselectivity observed with different solvents, and with different substituents on the benzylide and aldehyde groups, can be explained in terms of their effect on the reversibility of the reaction between the ylide and the aldehyde. Reducing the reversibility of the betaine formation leads to more *cis*-epoxide being produced.[2,5a] Changing the solvent from CH_2Cl_2 to MeCN/H_2O makes the initial reaction between the ylide and aldehyde to form *syn*- and *anti*-betaines less reversible. This leads to more *cis*-epoxide being produced in MeCN/H_2O than in CH_2Cl_2 (see Table 1, entry 5 vs. 6). The reaction between the ylide derived from **23** and *p*-chlorobenzaldehyde is expected to be less reversible than the reaction between the ylide de-

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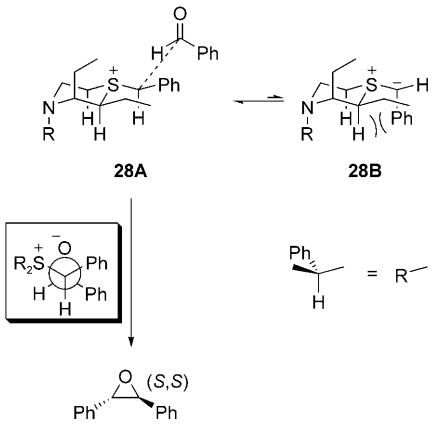
rived from **24** and benzaldehyde and therefore produces more *cis*-epoxide (Table 1, entry 7 vs. 8). Similarly, the methyl substituent on **25** is expected to lower the stability of the corresponding ylide and make the reaction with benzaldehyde less reversible than the reaction between the ylide derived from **23** and *p*-methylbenzaldehyde (Table 1, entry 9 vs. 10), again leading to lower diastereoselectivity. Thus, for the diastereoselective synthesis of substituted stilbene oxides it is preferable to have the more electron-withdrawing substituents on the ylide component and the more electron-donating substituents on the aldehyde.

The formation of *trans*-epoxides with good to excellent enantioselectivity can be understood by considering the ylide conformation and facial selectivity of the *anti*-betaine formation.[3] Deprotonation of **23** gives ylide **28** (Scheme 4).

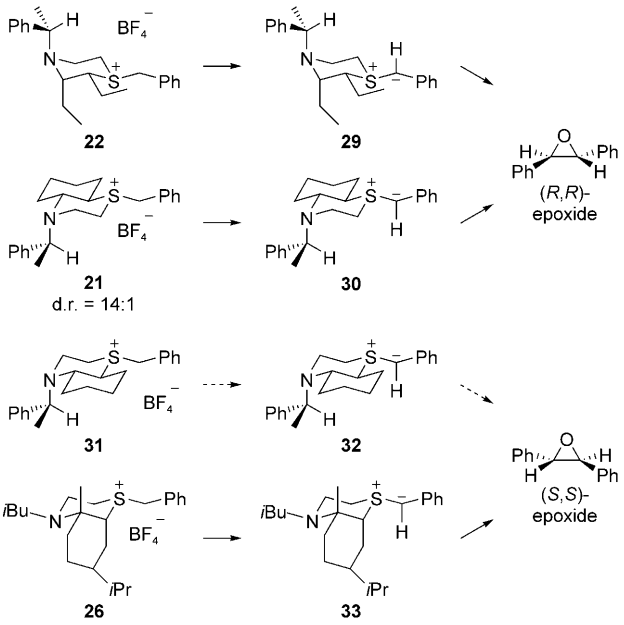


Scheme 4. Model for the enantioselectivity observed in the reaction of ylide **28** derived from **23**.

Conformer **28A** is favored over **28B** owing to unfavorable interactions between the axial protons on the thiomorpholine ring and the phenyl group in **28B**. The ethyl substituent blocks the approach of the aldehyde to the *Re* face of the ylide and thus the aldehyde approaches to the *Si* face. The *anti*-betaine thus formed would give the (*S*,*S*)-epoxide, as is observed. The difference in enantioselectivity obtained with **22** versus **23**, although small, shows that there is communication between the stereocenter on the methylbenzylamine all the way to the ylide, leading to a small match/mismatch effect.

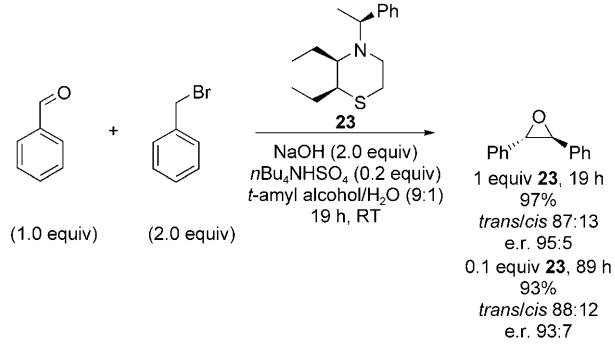
Application of the model described above allows the major enantiomer obtained from epoxidations involving ylides **29** and **33** to be explained (Scheme 5). Using the same model, it was deduced that **21** must give rise to **30** rather than **32**. This then allows the assignment of the absolute stereochemistry of the stereocenters at the 2,3-positions of **21** and its precursors. It is suggested that the lower enantioselectivity obtained with **26** is due to the poorer ability of an axial substituent on the carbon atom α to sulfur to control facial selectivity compared to an equatorial substituent.

Epoxidation protocols involving the generation of sulfonium salts in situ by alkylation of sulfide **23** were also attempt-



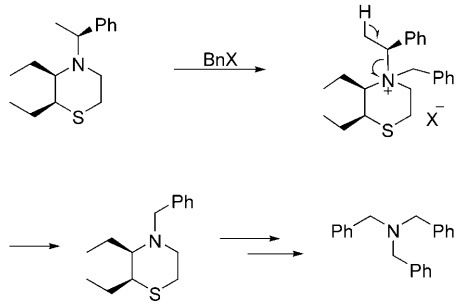
Scheme 5. Predicted major conformer of ylides **29**–**33** and prediction of the major enantiomer of epoxide that should be obtained in the epoxidation of benzaldehyde with each ylide.

ed (Scheme 6). Initially one equivalent of sulfide **23** was used with nBu$_4$NHSO$_4$ (0.2 equiv) as an additive.[20] In acetonitrile/H_2O the formation of 8% tribenzylamine was ob-



Scheme 6. Asymmetric epoxidation of benzaldehyde using an in situ sulfide alkylation protocol.

served. This can be explained by a decomposition pathway in which the aminosulfide is *N*-benzylated to give an ammonium salt which is degraded by Hofmann elimination (Scheme 7). Repetition of these steps leads to the formation of NBn_3. Fortunately in alcoholic solvents this pathway was suppressed and excellent results were obtained. Following experimentation with solvents a 9:1 mixture of *tert*-amyl alcohol and water was found to be the best solvent combination (Scheme 6). Reducing the sulfide loading to 10 mol% gave slower reactions and some sulfide decomposition was noted.



Scheme 7. Proposed degradation pathway for in situ alkylation reaction conditions in MeCN/H_2O.

Conclusions

In summary, we have synthesized a family of enantiomerically pure thiomorpholines in four to six steps and tested their potential in sulfur ylide mediated epoxidations. From this study, the *cis*-2,3-diethyl-substituted thiomorpholine **5** emerged as the optimum. It gave complete selectivity in sulfide alkylation and gave high enantioselectivity (96:4) in subsequent epoxidations. The sulfide could also be employed in substoichiometric amounts (10%) in a catalytic epoxidation process with similar selectivity. Furthermore, the sulfide could be separated from the product epoxide, reisolated, and reused by a simple acid/base wash.

Experimental Section

Sample epoxidation procedure: Method B: Powdered KOH (25 mg, 0.44 mmol) was added to a solution of the sulfonium salt **23** (0.22 mmol) and the corresponding aldehyde (0.22 mmol) in MeCN/H_2O 9:1 (1.0 mL) at 0 °C without preclusion of air. The reaction mixture was stirred for 3 h at 0 °C. The organic solvent was removed under reduced pressure, and the residue was redissolved in Et_2O (10 mL) and extracted with aqueous HCl solution (1 M, 2×5 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The diastereomeric ratio of the crude epoxide was determined by ^1H NMR spectroscopy. Purification of the crude product by flash chromatography (silica; EtOAc/PE 1:50) afforded the epoxides as colorless solids.

Recovery of sulfide: The combined aqueous phases were basified by addition of aqueous NaOH solution (3 M) to pH 11 and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The sulfide **5** thus recovered was shown to be pure by ^1H and ^{13}C NMR spectroscopy.

Full experimental data for the synthesis of all compounds described, including NMR spectra, are supplied in the Supporting Information. CCDC 684971 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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