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Practical and Highly Selective Sulfur Ylide Mediated Asymmetric Epoxidations and Aziridinations Using an Inexpensive, Readily Available Chiral Sulfide. Applications to the Synthesis of Quinine and Quinidine

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Although it has been demonstrated *in principle* that asymmetric sulfur ylide mediated epoxidation[1] could be a complementary method to asymmetric epoxidations of alkenes, it is rarely used.[2] This can be attributed to two factors: (1) limited scope — while 1,2-diaryl epoxides can be formed with high diastereo- and enantioselectivity, the synthetically much more useful 1,2-arylalkyl or α,β-unsaturated epoxides[3] cannot; (2) lack of availability — sulfides that give high selectivity require multistep syntheses.[4] Herein we report a sulfide that addresses both of these issues and that should change sulfur ylide mediated epoxidation into a scaleable, mainstream practical method. We report a chiral sulfide that is accessible in one step from a cheap, readily available chiral pool precursor (itself available in both enantiomeric forms) which delivers high enantio- and diastereoselectivity and demonstrate its application in the synthesis of the complex natural products, quinine and quinidine.

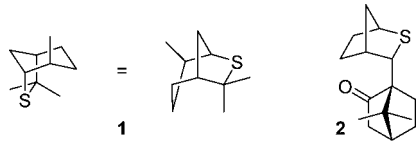
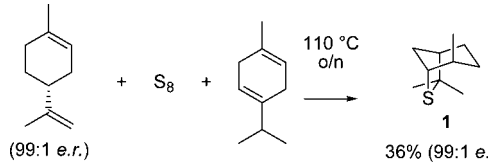


Figure 1. Structure of sulfide catalysts.

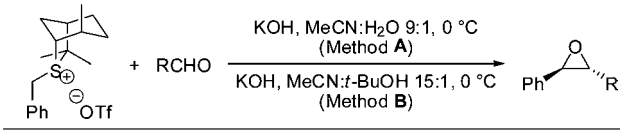
Isothiocineole **1** was investigated due to its well-defined rigid architecture and somewhat close resemblance to our previous successful sulfide **2**[4h] which had delivered high levels of enantioselectivity (Figure 1). This sulfide was prepared by the solvent-free reaction between elemental sulfur and limonene[5] in the presence of γ-terpinene[6] at 110 °C (Scheme 1). Simple distillation of the crude reaction mixture furnished essentially pure isothiocineole in 36% yield and with high er (99:1 *e.r.*). With such inexpensive reagents,[7] a simple protocol and facile isolation, (+) or (−)-isothiocineole is very easily obtained on a large scale.[8]

Scheme 1. Synthesis of Isothiocineole



With substantial quantities of sulfide **1** in hand we explored a series of representative reactions associated with sulfur ylides. Reactions of the benzyl sulfonium salt[9] with aromatic and unsaturated aldehydes all worked spectacularly well in all cases, furnishing high yields and perfect levels of diastereo- and enantioselectivity (Table 1, entries 1−4). Aliphatic aldehydes are traditionally problematic in this process, but nevertheless conditions were found

Table 1. Reactions of Benzyl Sulfonium Salt with Aldehydes



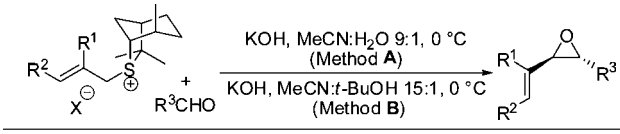
entry	aldehyde	method	yield (%)	*d.r.*[a]	*e.r.*[b]
1	benzaldehyde	A	77	>95:5	99:1
2	(*E*)-PhCH=C(Me)CHO	A	84[c]	>95:5	98:2
3	(*E*)-cinnamaldehyde	A	88[c]	>95:5	99:1
4	(*E*)-crotonaldehyde	A	86[c]	>95:5	97:3
5	*c*-$C_6H_{11}CHO$	B	62	93:7	99:1
6	*n*-C_4H_9CHO	B	56	91:9	99:1

[a] *Trans/cis*. [b] Determined by chiral HPLC; see Supporting Information (SI) for details. [c] Determined by ^{1}H NMR with an internal standard.

that delivered 1,2-arylalkyl epoxides with the highest levels of diastereoselectivity and enantioselectivity to date (entries 5−6).[10]

Allylic sulfonium salts also worked extremely well in this process provided they were substituted by an α-substituent ($R^1 \neq H$) furnishing α,β-unsaturated epoxides in high yields as well as high diastereo- and enantioselectivities, even with aliphatic aldehydes (Table 2). This process represents the most selective and direct route to these useful intermediates.[11]

Table 2. Reactions of Allylic Sulfonium Salts with Aldehydes



R^1	R^2	R^3	method	yield (%)[a]	*d.r.*[b]	*e.r.*
H[c]	Ph	Ph	A	65	80:20	85:15[d]
Me[c]	Ph	Ph	A	97	>95:5	99:1[d]
Me[e]	H	Ph	A	80	>95:5	99:1[d]
Me[c]	Ph	*c*-C_6H_{11}	B	77	>95:5	98:2[d]
Me[e]	H	*c*-C_6H_{11}	B	77	>95:5	97:3[f]

[a] Determined by ^{1}H NMR with an internal standard. [b] *Trans/cis*. [c] X = BF_4. [d] Determined by chiral HPLC. [e] X = OTf. [f] Determined by chiral GC; see SI for details.

The benzyl sulfonium salt was also tested in aziridinations (Table 3), and again high yields and perfect enantioselectivities were obtained.[12] Again, the most notable aspect of the process is the record levels of diastereoselectivity observed which was essentially complete in the case of the cinnamaldehyde-derived imine (entry 5). The reactions in entries 5 and 6 were easily conducted on a 12/14 mmol scale, and the sulfide was reisolated in 95% yield.

The stereochemical outcome of the reactions can be rationalized by considering the conformation and face selectivity of the ylide

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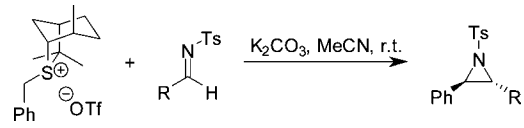
Table 3. Reaction of Benzyl Sulfonium Salt with Imines

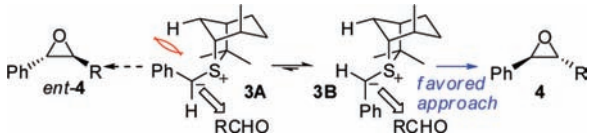


	R	yield (%)	*trans/cis*	*e.r.*[a]
1	Ph	72	85:15	99:1
2	*p*-MeC_6H_4	63	86:14	99:1
3	*p*-ClC_6H_4	65	75:25	99:1
4	*p*-$MeOC_6H_4$	80	83:17	99:1
5	(*E*)-PhCH=CH	78	>99:1	98:2
6	(*E*)-TMSCH=CH	78	87:13	99:1

[a] Determined by chiral HPLC; see SI for details.

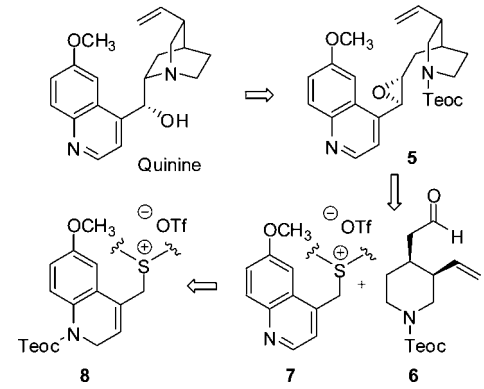
intermediate.[13] Of the two conformers, ylide **3B** will be favored over **3A** due to nonbonded steric interactions (Scheme 2), and this will react with electrophiles on its *Re* face since the *Si* face is blocked by a flanking methyl group. We believe that the minor enantiomer *ent*-**4** originates from reaction of the minor conformer **3A** again reacting with high facial selectivity.

Scheme 2. Rationalization of the Reaction Selectivity



We have applied this methodology to a short synthesis of the cinchona alkaloids, quinine and quinidine, molecules with a long and important history spanning folklore, medicine, synthesis, and catalysis.[14] We envisaged that the target molecule could be constructed via epoxide **5**, a strategy which had been employed previously. In such a strategy the epoxide had either been obtained nonselectively[15] or selectively by Sharpless dihydroxylation of the corresponding alkene.[16] The alkene itself was ultimately obtained from N-protected meroquinene aldehydes similar to **6**.[16,17] The sulfur ylide disconnection had never been applied to epoxides related to **5**, even though it provides access in one step from aldehyde **6**. Furthermore, as the molecule is divided into two more equal parts (quinoline **7** and piperidine **6**) (Scheme 3) the synthesis becomes significantly more convergent and significantly more direct.

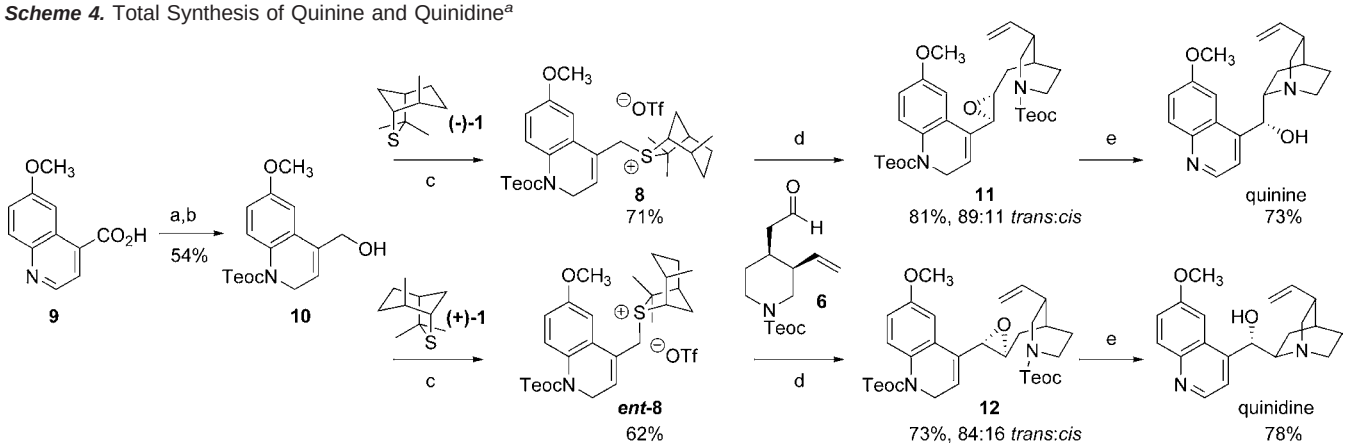
Scheme 3. Retrosynthesis of Quinine Molecule



As sulfonium salts are not usually compatible with nucleophilic substituents within the same molecule because of a tendency toward polymerization, we decided to mask the quinoline nitrogen in **7** as a carbamate and, in particular, chose the trimethylsilylethyloxycarbamate (Teoc) group **8**.[18] It was envisaged that, in the final step, treatment with fluoride would initiate a cascade reaction sequence involving simultaneous deprotection of the two amino functionalities, air oxidation to the quinoline ring, and cyclization of the amino epoxide.

Thus, sulfonium salt **8** was our initial target and was prepared as shown in Scheme 4. Reduction of the known quinoline carboxylic acid **9**[19] with BH_3·THF followed by carbamate formation and subsequent reduction with $NaBH_4$ gave alcohol **10**. Activation of the alcohol with Tf_2O followed by treatment with sulfide (+)-**1** gave sulfonium salt **8**.[20] Reaction of the sulfonium salt **8** with aldehyde **6**[21] under the standard conditions for aliphatic aldehydes (Table 1, method B) gave epoxide **11** as a 89:11 separable mixture of *trans*/*cis* epoxides which were the only two diastereoisomers detected by NMR. As high *trans*-selectivity is only usually observed in reactions between hindered aliphatic aldehydes (or aromatic aldehydes) and more stabilized sulfur ylides, the reaction between an unhindered aliphatic aldehyde and a moderately stabilized sulfur ylide (an allylic sulfonium salt) presents an extremely challenging case. Nevertheless, good levels of *trans*-selectivity were observed in this example highlighting the effectiveness of the new sulfide in promoting *diastereoselective* reactions in especially challenging cases. Subsequent treatment with CsF in DMF for 15 min under microwave conditions triggered the reaction cascade involving

Scheme 4. Total Synthesis of Quinine and Quinidine[a]



[a] Reagents and conditions: (a) BH_3·THF, THF, r.t. 16 h, 69%; (b) $TMS(CH_2)_2OH$, triphosgene, K_2CO_3, THF, r.t. 1 h, followed by $NaBH_4$, H_2O, r.t. 4 h, 79%; (c) 2,6-di-*tert*-butylpyridine, Tf_2O, sulfide (−)-**1**, CH_2Cl_2, −45 °C to r.t. 16 h, 71% (**8**), and sulfide (+)-**1**, 62% (***ent*-8**); (d) KOH, CH_3CN/*t*-BuOH 15:1, 0 °C, 24 h, 81%, 89:11 *trans*/*cis*, (**11**), 73%, 84:16 *trans*/*cis* (**12**); (e) CsF, DMF, MW, 180 °C, 15 min, then stir under O_2, r.t. 24 h, 73% quinine, 78% quinidine.

deprotection of the piperidine and quinoline rings and cyclization,[22] but apparently oxidation of the quinoline ring was slow. However, simply stirring the crude reaction mixture under an atmosphere of O_2 overnight effected oxidation and gave quinine in 73% yield over four steps.

Quinidine, which is an epimer of quinine at C8 and C9, was easily made simply by using the opposite sulfide enantiomer *ent*-**1**. In the key step, reaction of sulfonium salt *ent*-**10** with aldehyde **6** gave epoxide **12** as an 84:16 mixture of *trans*/*cis* epoxides which, again, were the only two isomers detected by NMR. Since both epoxides **11** and **12** had been isolated and their differences identified by NMR, it was clear that they had been formed exclusively in the epoxidation step, showing that the sulfide is able to deliver perfect enantiocontrol. As before, treatment with CsF in DMF under microwave conditions initiated a reaction cascade which, after stirring over O_2, gave quinidine in 78% yield.

In conclusion, we have developed a facile synthesis of isothiocineole, a sulfide which has been found to be highly effective in asymmetric epoxidation and aziridination reactions. The straightforward synthesis of the sulfide, broad scope of epoxidations and aziridinations especially in the synthesis of synthetically useful 1,2-arylalkyl and α,β-unsaturated epoxides and aziridines, and simple reaction conditions now allow the asymmetric sulfur ylide mediated transformations to be routinely employed for everyday use and larger scale applications in synthesis. This has been demonstrated in a convergent and stereoselective synthesis of each of the diastereoisomers of the cinchona alkaloids, quinine and quinidine.

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Supporting Information Available: Synthesis and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Although the original procedure by Weitkamp had been optimized and operated on a >100 gallon scale, it still resulted in low yield and erosion in er and required a difficult separation of the product isothiocineole from various side products. By adding γ-terpinene a much improved synthesis was achieved without erosion of er and with simple isolation. Full details on its role will be reported in due course.

(7) (*R*)-Limonene is an extremely cheap chiral pool material, available in bulk quantities. Sulfide (−)-**1** costs <$1/g to synthesize based on Aldrich's current UK prices. (*S*)-Limonene is also available in bulk but is normally available as a 90:10 mixture of enantiomers. In this case, two successive low temperature (−50 °C) recrystallizations from pentane furnished enantiopure (+)-isothiocineole.

(8) We have scaled up the reaction uneventfully to an ~1 mol scale. This material is commercially available from TCI (T2578 and T2579).

(9) This was prepared by alkylation of the sulfide with BnBr and required 24 h at 20 °C. The alkylation of sulfides with flanking *gem*-dimethyl groups, e.g. 1,4-oxathianes (see 4k) or 1,3-thioacetals [Solladié-Cavallo, A.; Diep-Vohuule, A.; Šunjiç, V.; Vinkovic, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1783.] is usually difficult. In the event, alkylation proved to be facile, presumably because of the lack of heteroatoms within the ring which, in the case of 1,4-oxathianes or 1,3-thioacetals, reduce the nucleophilicity of the sulfide through inductive effects.

(10) See page S14 in the SI for a comparison with sulfide **2**.

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