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A New Chiral Organosulfur Catalyst for Highly Stereoselective Synthesis of Epoxides

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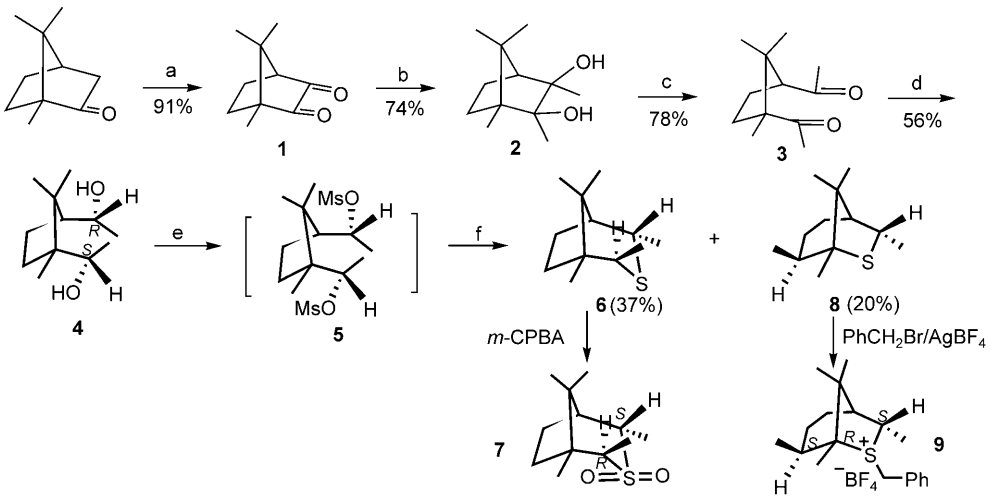
Abstract: A new chrial organosulfide was synthesized through an unexpected Wagner–Meerwein rearrangement. This organosulfide could catalyze the epoxidation reaction of various aromatic aldehydes smoothly with benzyl bromide to give *trans*-diaryl epoxides in satisfactory yields (60–84%) with excellent diastereoselectivities (*trans:cis* = 95:5–100:0) and good to excellent enantioselectivities (86–96% *ee*).

Keywords: chiral organosulfides; diastereoselectivity; enantioselectivity; epoxidation; organocatalysis

In the last decade, organocatalysis has undergone great advances and become a powerful tool for the synthesis of important optically active building blocks.[1] It is well known that chiral epoxides are one of the most important synthetic building blocks owing to their versatile chemical transformations and significant biological activities. Recently, the chiral ylide route has become one of the most important strategies for optically active epoxides because it combines the formation of a carbon-carbon bond and an epoxidation into one reaction.[2–6] Although there are many reports on employing chiral sulfides to catalyze epoxidation reactions *via* sulfonium ylides, very successful cases are still limited.[2a,3–6] Aggarwal et al. found that chiral sulfonium ylides could be formed by the reaction of sulfides with diazo compounds under the catalysis of $Cu(acac)_2$ or $Rh_2(OAc)_4$, affording an elegant synthesis of *trans*-diaryl epoxides in high yields with excellent distereoselectivities and enantioselectivities (up to 94% *ee*).[3] In these processes, although novel sulfides were used as organocatalysts, metal complexes were also neccessarily employed.[1b,2a,3] Dai's group reported a camphor-derived sulfide as an organocatalyst to undergo the epoxidation reaction, furnishing *trans*-stilbene oxides with moderate enantiometric excesses (about 74% *ee*).[4] Metzner et al. successfully developed epoxidations catalyzed by C_2-symmetrical thiolanes to give *trans*-diaryl epoxides with excellent enantioselectivities (up to 96% *ee*).[5] However, the diastereoselective excesses are 66–88% in most cases.[5] Goodman's group also utilized C_2-symmetrical chiral sulfides to catalyze asymmetric epoxidation, and a couple of good examples, the *trans*-2,3-diphenyl epoxide with 97% *ee* and *trans*-2-(4-fluorobenzenyl)-3-phenyl epoxide with 98% *ee* were obtained.[6] Neverthless, the yields of the two epoxides are only 41% and 19%, respectively. Therefore, it is still a challenge to find new organosulfur catalysts for epoxidations to achieve not only excellent enantioselectivities but also excellent diastereoselectivities.

Initially, cheap D-camphor was chosen as a starting material to undergo oxidation with selenium dioxide, reaction with methylmagnesium iodide, and another oxidation with lead tetraacetate, leading to diketone **3** in a satisfactory yield similar to that reported in the literature (Scheme 1).[7] Then it was found that diketone **3** could react stereoselectively with sodium borohydride to give diol **4** as major product in a reasonable yield. After the mesylation of **4** and the successive nucleophilic substitution of dimesylate **5** with sodium sulfide nonahydrate in DMSO at 100–105 °C, we isolated desired chiral organosulfide **6** in 37% yield as major product and an unkown liquid. The configurations of the two carbons connected with two hydroxy groups, respectively, in diol **4** should be opposite to the configurations of that connected to sulfur in organosulfide **6** due to the S_N2 reaction initiated by sulfide anion.[5] The structure of organosulfide **6** was deduced from its oxide **7** by single crystal X-ray diffraction.[8a] Because the spot of the unkown liquid on TLC after exposure to iodine vapor is very close to the spot of organosulfide **6**, the ^1H NMR spectrum of the liquid



(a) SeO_2, Ac_2O, reflux; (b) CH_3MgI, Et_2O, 0 °C to r.t.; (c) $Pb(OAc)_4$, AcOH, r.t.;
(d) $NaBH_4$, MeOH, 0 °C to r.t.; (e) $MeSO_2Cl$, pyridine, 0 °C; (f) Na_2S 9 H_2O, DMSO, 100 – 105 °C.

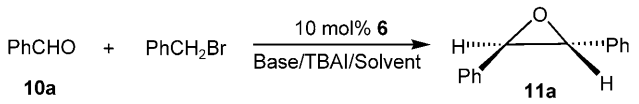
Scheme 1. Synthesis of chiral organosulfide **6**.

is analogous to that of **6** and the molecule weight of the liquid is equal to that of **6** according to mass spectra data, we presumed that the liquid might be an isomer of organosulfide **6**. Thus, the reaction of the liquid with benzyl bromide and silver tetrafluoroborate was perfomed at room temperature, and the expected sulfonium salt **9** was obtained in 87% yield. Finally, the unkown liquid was determined to be organosulfide **8** by single crystal X-ray diffraction of its salt **9**.[8b]

By lowering the temperature in the reaction of dimesylate **5** with sodium sulfide from 100–105 °C to 65–70 °C,[5c] the yield of organosulfide **6** was increased to 55%. With the novel organosulfide **6** in hand, we examined the epoxidation reaction of benzaldehyde **10a** with benzyl bromide under the catalysis of organosulfide **6**. It was found that when sodium hydroxide or potassium hydroxide and tetrabutylammonium iodide (TBAI) were employed, respectively, as a base and an additive for halogen exchange and phase-transfer catalysis,[5b] organosulfide **6** could catalyze the epoxidation reaction smoothly in MeCN-H_2O (9:1 v/v) at room temperature to give desired diphenyl epoxide **11a** in good yields with excellent *trans* diastereoselectivities (entries 5 and 6, Table 1). However, the enantioselectivities were rather low under various reaction conditions. (Table 1).

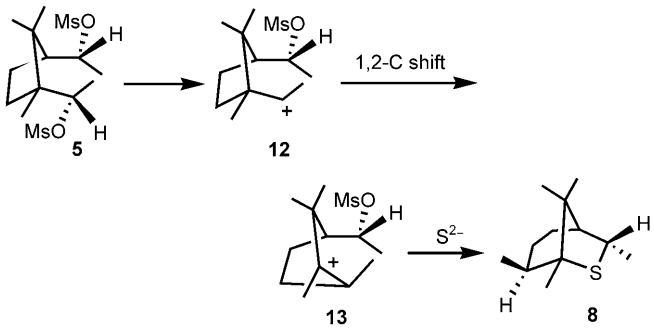
Owing to the poor enantioselectivities of the epoxidation catalyzed by chiral organosulfide **6**, we turned our attention to chiral organosulfide **8**. The organosulfide **8** was a Wagner–Meerwein rearrangement product from dimesylate **5**. The quartenary carbon adjacent to the secondary carbon cation in **12** might promote a 1,2-carbon shift to form a more stable tertiary carbon cation as in **13** (Scheme 2). We improved the rearrangement reaction by raising the reaction temperature and decreasing the amount of sodium sulfide in the nucleophilic substitution, and found that when the reaction of dimesylate **5** with sodium sulfide nonahydrate was performed in DMF at 140–150 °C and the amount of sodium sulfide nonahydrate was decreased from about 2 equiv. to about 1 equiv., the organosulfide **8** could be obtained as major product in a yield of 41% with the organosulfide **6** in 13% yield in the two-step sequence (Scheme 3).

Table 1. Optimization of the asymmetric epoxidation catalyzed by organosulfide **6**.[a]

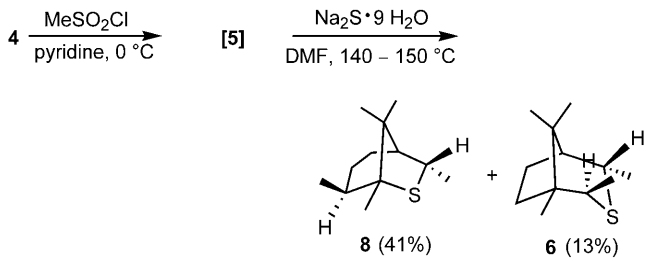


Entry	Solvent (9:1 v/v)	Base	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	*t*-BuOH/H_2O	NaOH	54	98:2	9
2	*i*-PrOH/H_2O	NaOH	50	98:2	11
3	MeCN/H_2O	Cs_2CO_3	trace	–[e]	–[e]
4	MeCN/H_2O	K_2CO_3	trace	–[e]	–[e]
5	MeCN/H_2O	NaOH	78	99:1	19
6	MeCN/H_2O	KOH	80	99:1	15

[a] Reaction temperature was 20–25 °C and reaction time was 40 h. Other conditions are similar to the general procedure for epoxides in Experimental Section.
[b] Isolated yields.
[c] Determined by ^{1}HNMR or GC.
[d] Enantiomeric excesses of trans isomers were determined by chiral HPLC using a Chiracel OD-H column.
[e] Not determined.



Scheme 2. Simplified scheme of the rearrangement to form organosulfide **8**.



Scheme 3. Synthesis of chiral organosulfide **8**.

With the new organosulfide **8** in hand, we chose benzaldehyde **10a** as a model substrate to probe the reaction conditions for asymmetric epoxidation. When *t*-BuOH/H_2O (9:1 v/v), sodium hydroxide and TBAI were employed as solvent, base and additive, respectively, we were pleased to find that organosulfide **8** could catalyze the epoxidation reaction of benzaldehyde **10a** readily with benzyl bromide to give the desired diphenyl epoxide **11a** in a moderate yield with excellent diastereoselectivity and good enantioselectivity (entry 1, Table 2). Encouraged by this result, we examined other solvents in the reaction. Using *i*-PrOH/H_2O (9:1 v/v) as solvent led to similar yield, diastereoselectivity and enantioselectivity (entry 2, Table 2). To our delight, when MeCN/H_2O (9:1 v/v) was employed as a solvent, both the yield and the enantioselectivity were improved remarkably (entry 3, Table 2). The effect of bases on yields was also studied. Using potassium hydroxide led to a similar yield, diastereoselectivity and enantioselectivity as those using sodium hydroxide (entries 3 and 4, Table 2). When weak bases such as cesium carbonate and potassium carbonate were employed, only a trace amount of *trans*-diphenyl epoxide **11a** was obtained (entries 5 and 6, Table 2). As compared to the 10 mol% loading, using 20 mol% of organosulfide **8** led to a slight decrease of enantioselectivity while there was a slight increase in yield (compare entries 3 and 8, Table 2). When the reaction temperature was decreased from room temperature to 0 °C, the epoxidation reaction proceeded slowly, and no significant increase of the *ee* value was observed (entry 9, Table 2). It was further found that without TBAI, both the yield and enantioselectivity of the epoxidation were decreased (compare entries 3 and 10, Table 2). Thus, the optimal reaction conditions were as follows: the reaction was performed at room temperature, the solvent was CH_3CN/H_2O (9:1 v/v), the base was sodium hydroxide, TBAI was employed as an additive and the amount of organosulfide **8** was 10 mol%.

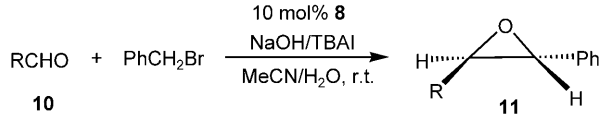
Table 2. Optimization of the asymmetric epoxidation catalyzed by organosulfide **8**.[a]

Entry	Mol% **8**	Solvent/H_2O[b]	Base	Yield [%][c]	*trans*/*cis*[d]	*ee* [%][e]
1	10	*t*-BuOH	NaOH	51	98:2	88
2	10	*i*-PrOH	NaOH	48	98:2	87
3	10	MeCN	NaOH	70	99:1	93
4	10	MeCN	KOH	71	99:1	91
5	10	MeCN	Cs_2CO_3	trace	–[f]	–[f]
6	10	MeCN	K_2CO_3	trace	–[f]	–[f]
7	5	MeCN	NaOH	58	98:2	92
8	20	MeCN	NaOH	74	99:1	90
9[g]	10	MeCN	NaOH	63	99:1	93
10[h]	10	MeCN	NaOH	60	99:1	88

[a] Reaction temperature was 20–25 °C and reaction time was 40 h. Other conditions are similar to the general procedure for epoxides in Experimental Section.
[b] Solvent/H_2O: v:v = 9:1.
[c] Isolated yields.
[d] Determined by ^{1}HNMR or GC.
[e] Enantiomeric excesses of trans isomers were determined by chiral HPLC using a Chiracel OD-H column.
[f] Not determined.
[g] Reaction temperature: 0 °C.
[h] No TBAI was used.

After the optimal reaction conditions were established, various aromatic aldehydes **10a–i** were examined in the asymmetric epoxidation. It was found that organosulfide **8** at 10 mol% loading could catalyze the epoxidation of aromatic aldehydes **10a–i** smoothly with benzyl bromide *via* a chiral sulfonium ylide, giving the desired *trans*-diaryl epoxides **11a–i** with satisfactory yields (60–84%) in 40 h (entries 1–9, Table 3). Almost solely *trans* isomers of epoxides were obtained in most cases for the aromatic aldehydes **10a–i**. Moreover, various aromatic aldehydes could result in good to excellent enantioseletivities (88–96% *ee*) and among them, 4-methylbenzaldehyde led to the highest enantioselectivity (entries 1–9, Table 3). For the asymmetric epoxidation of bezaldehyde **10a** with benzyl bromide, the chiral sulfide **8** as an organocatalyst could result in both excellent enantioselectivity (93% *ee*) and excellent diastereoselectiv-

Table 3. Scope of the epoxidation of aldehydes **11** under the catalysis of orgaosulfide **8**.[a]



Entry	R	11	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]	Configuration
1	C_6H_5	**a**	70	99:1	93	*R,R*
2	4-$CH_3C_6H_4$	**b**	67	99:1	96	*R,R*
3	4-$CH_3OC_6H_4$	**c**	60	98:2	90	*R,R*
4	4-ClC_6H_4	**d**	78	100:0	94	*R,R*
5	2-ClC_6H_4	**e**	65	96:4	93	*R,R*
6	4-BrC_6H_4	**f**	84	100:0	88	*R,R*
7	4-FC_6H_4	**g**	76	100:0	88	*R,R*
8	2,4-$Cl_2C_6H_3$	**h**	80	97:3	90	*R,R*
9	4-$NO_2C_6H_4$	**i**	71	98:2	86	*S,S*
10	2-Furyl	**j**	68	95:5	86	*S,R*
11	E-Styryl	**k**	65	99:1	85	*R,R*
12	Cyclohexyl	**l**	53	87:13	85	*R,R*
13[e]	$CH_3(CH_2)_3$	**m**	57	75:25	73	*R,R*
14[e]	$(CH_3)_2CHCH_2$	**n**	51	80:20	71	*R,R*

[a] For detailed reaction conditions, see the general procedure for epoxides in Experimental Section.
[b] Isolated yields.
[c] Determined by ^{1}HNMR or GC.
[d] Enantiomeric excesses of *trans* isomers were determined by chiral HPLC using a Chiracel OD-H column.
[e] 15 mol% of **8** was employed and the reaction time was 48 h.

ity (98% *de*), which was rarely reported in the literature.[10] The absolute configurations of the epoxides **11a–n** were assigned by comparison of the results of optical rotation and chiral HPLC with those of known compounds and all (*R*, *R*)-isomers of **11a–h** are dextrorotatory in EtOH.[3d,4] Furyl aldehyde **10j** as a heteroaromatic aldehyde also underwent the epoxidation reaction readily, giving a similar yield, diastereoselectivity and enantioselctivity (entry 10, Table 3). The configuration of 2-(4-nitrophenyl)-3-phenyl epoxide **11i** was reversed and the configuration of 2-(2-furyl)-3-phenyl epoxide **11j** is the same as that in most diaryl epoxides **11a–h** although it was designated (2*S*,3*R*) (entries 9 and 10, Table 3).[3d,9]

As compared to many epoxidations of aromatic aldehydes, only a small amount of examples involved aliphatic aldehydes. In order to examine the new chiral organosulfide **8** more extensively, we studied the epoxidation of aliphatic aldehydes. It was found that organosulfide **8** could also catalyze the epoxidation of aliphatic aldehydes smoothly with benzyl bromide to furnish 2-alkyl-3-phenyl epoxides **11l–n** in reasonable yields with moderate diastereoselectivities (entries 12–14, Table 3). Among them, cyclohexanecarboxaldehyde led to good enantioselectivity, and valeraldehyde or isovaleraldehyde led to moderate enantioselectivities.

In conclusion, we have synthesized two new chiral organosulfides **6** and **8** using cheap D-camphor as starting material. Among them, the chiral organosulfide **8** was synthesized through an unexpected Wagner–Meerwein rearrangement. It was found that the organosulfide **8** could catalyze the epoxidation reaction of various aromatic aldehydes smoothly with benzyl bromide to give *trans*-diaryl epoxides in satisfactory yields (60–84%) with excellent diastereoselectivities (*trans*:*cis* = 95:5–100:0) and good to excellent enantioselectivities (86–96% *ee*). Therefore, organosulfide **8** has better catalytic functions in comparison with the other organosulfides summarized in ref.[10] The studies on the utility of the chalcogenides having a novel structure like **8** in organocatalyzed epoxidations, cyclopropanations and aziridinations with excellent diastereoselectivies and enantioselectivies are underway.

Experimental Section

General Procedure for Epoxides

To the solution of chiral organosulfide **8** (6.0 mg, 0.03 mmol) in MeCN/H_2O (3 mL, 9:1v/v) was added aldehyde (0.30 mmol), benzyl bromide (77 mg, 0.45 mmol), *n*-Bu_4NI (108 mg, 0.30 mmol) and NaOH (24 mg, 0.60 mmol).The reaction mixture was stirred at 20–25 °C for 40 h. Filtration and evaporation gave a residue that was purified by preparative TLC or column chromatography, affording the desired epoxide **11a–n**.

Supporting Information

Preparations, analytical data, ^{1}H and ^{13}C NMR spectra of **3**–**6**, **8**, **9** and **11a–n** and chiral HPLC diagrams of **11a–n** are available as Supporting Information.

Acknowledgements

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[10] See Chart 1 on p 5844 of ref.[2a]

