HETEROCYCLES, Vol. 57, No. 8, 2002, pp. 1399 - 1402, Received, 22nd May, 2002

ASYMMETRIC EPOXIDATION OF ALDEHYDES CATALYZED BY NEW C_2-SYMMETRICAL CHIRAL SULFIDE

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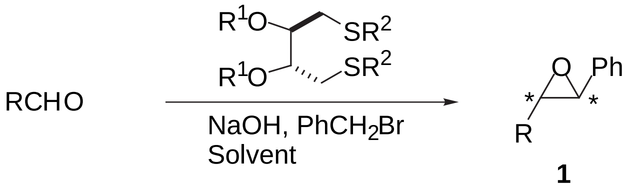
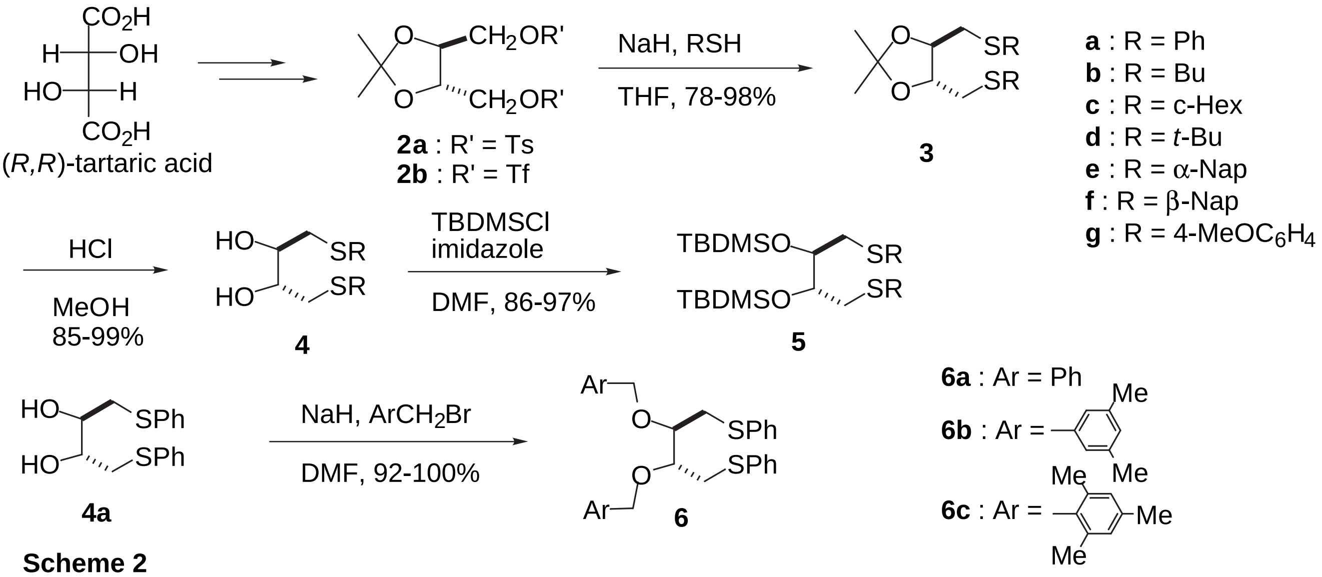
Abstract – Asymmetric synthesis of chiral epoxides from various aldehydes with benzyl bromide was investigated using new C_2-symmetrical chiral sulfides, which were readily prepared from (*R*,*R*)-tartaric acid.

Enantiomerically enriched epoxides are versatile compounds for organic synthesis and a variety of efficient methods for synthesis of chiral epoxides have been developed.[1] Among them, sulfur ylide mediated asymmetric epoxidation of aldehydes is one of the most powerful strategies for synthesis of chiral epoxides (**1**).[2-4] Thus, since the pioneering work[3a] by Furukawa in 1989, several chiral sulfides have been reported.[3,4] However, some of previously reported catalysts required multi-step synthesis and not suitable for large scale preparation. Here, we describe asymmetric epoxidation of aldehydes catalyzed by new C_2-symmetrical chiral sulfides, which were easily obtained in a large scale from (*R*,*R*)-tartaric acid (Scheme 1).



Scheme 1

Various C_2-symmetrical chiral sulfides (**3-6**)[5,6] were synthesized as follows (Scheme 2). The reaction of aromatic thiols with ditosylate (**2a**)[7] or aliphatic thiols with ditriflate (**2b**)[7] gave sulfides (**3a**,[7] **3b-g**) in 78-98% yields. Hydrolysis of actetal group in **3** afforded diols (**4a**,[7,8] **4b-g**), silylation of which furnished TBDMS ethers (**5a-g**). Several benzyl ethers (**6a-d**) were also obtained in good yields (92-100%) from phenyl sulfide (**5a**).



Scheme 2

With chiral sulfides (**3-6**) in hand, asymmetric epoxidation of benzaldehyde with benzyl bromide in the presence of NaOH as base was examined (Table 1). At first, acetal-type catalyst (**3a**, 100 mol%) was used in the reaction to give (*R*,*R*)-*trans*-stilbene oxide (**1a**) in 21% e.e. with 64% chemical yield. Since catalytic reaction[3i] using 10 mol% of sulfide (**3a**) gave **1a** with the same enantioselectivity in stoichiometric version, we employed catalytic amount of sulfide on the further investigation. Compared with aromatic sulfide, the reaction using aliphatic sulfides (**3b-d**) afforded **1a** in low e.e. Diol-type phenyl sulfide (**4a**) improved enantioselectivity to give the epoxide in 46% e.e. On the other hand, aliphatic sulfides (**4b-d**) showed only low enantioselectivity (1-6% e.e.). The highest enantioselectivity (68% e.e.) was attained using TBDMS ether (**5a**). Other aromatic sulfides (**5e-g**) were also examined in the reaction, however, enantioselectivity could not be increased.

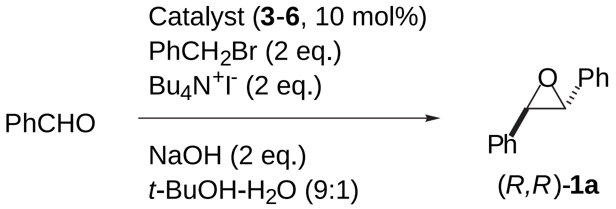
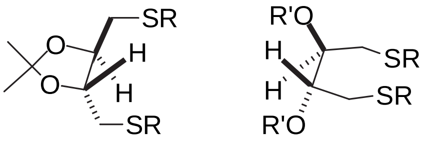


Table 1. Asymmetric epoxidation of benzaldehyde

Run	Sulfide	*trans/cis*[a]	Yield (%)[b]	E.e. (%)[a]
1[c]	**3a**	ND	64	21
2	**3a**	ND	19	21
3	**3b**	ND	32	-1
4	**3c**	ND	47	-1
5	**3d**	83 : 17	17	-7
6	**4a**	67 : 33	42	46
7	**4b**	77 : 23	60	1
8	**4c**	81 : 19	50	6
9	**4d**	85 : 15	24	2
10	**5a**	74 : 26	22	68
11	**5b**	72 : 28	63	8
12	**5c**	80 : 20	44	37
13	**5d**	80 : 20	14	35
14	**5e**	61 : 39	13	58
15	**5f**	71 : 29	19	64
16	**5g**	62 : 38	29	61
17	**6a**	67 : 33	34	48
18	**6b**	67 : 33	28	50
19	**6c**	67 : 33	27	53

a) Determined by HPLC.[3f] b) Isolated yield of *trans*-isomer. c) 100 mol% of catalyst was used.

At this stage, transition state on enantio- and diastereo-selective reaction was not clear, however, difference of ability of catalysts (**3-6**) would be rationalized by conformational change of the catalysts. Thus, two sulfide groups in acetal-type catalysts (**3**) would be placed far-away because of restricted structure by acetal group. In ether-type catalysts (**5**,**6**), such effect would not exist and steric repulsion of two ether groups[9] would cause proximity of two bulky sulfide groups, one of which might control direction of aldehyde to sulfur ylide to increase enantioselectivity.



Acetal-type (**3**) Ether-type (**5**,**6**)

Figure 1

Finally, asymmetric epoxidation of various aldehydes with stoichiometric amount of **5a** was performed to obtain epoxides in good yield (Table 2). When, the reaction of aromatic aldehydes bearing electron withdrawing group such as chloro or trifluoromethyl group gave the corresponding epoxides in lower enantioselectivity than that of benzaldehyde (Runs 2 and 3). On the other hand, epoxidation of aromatic aldehydes bearing electron-donating groups on benzene ring furnished enantioselectivity similar to that of benzaldehyde (Runs 4 and 5). The highest enantioselectivity was obtained in the reaction of *trans*-cinnamaldehyde (75% e.e., Run 7).

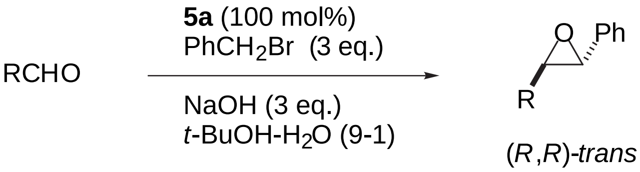


Table 2. Asymmetric Epoxidation of Various Aldehydes using **5a.**

Run	RCHO	*trans/cis*[a]	Time (d)	Yield (%)[b]	E.e. (%)[a]
1	PhCHO	70 : 30	3	67	68
2	$4\text{-ClC}_6\text{H}_4\text{CHO}$	72 : 28	3	66	63
3	$4\text{-CF}_3\text{C}_6\text{H}_4\text{CHO}$	71 : 29	1	63	55
4	$4\text{-MeC}_6\text{H}_4\text{CHO}$	71 : 29	4	68	70
5	$4\text{-MeOC}_6\text{H}_4\text{CHO}$	70 : 30	4	60	69
6	β-Naphthaldehyde	75 : 25	4	72	70
7	(E)-$\text{C}_6\text{H}_4\text{CH=CHCHO}$	80 : 20	4	75	75

a) Determined by HPLC.[3f] b) Isolated yield of *trans*-isomer.

In conclusion, we have shown convenient synthesis of new C_2-symmetrical chiral sulfides (**3-6**) and examined their catalytic ability on asymmetric epoxidation of various aldehydes. Among the catalysts, aromatic sulfides were superior to aliphatic sulfides. Furthermore, TBDMS ether (**5a**) was found to be good catalyst on asymmetric epoxidation of various aldehydes up to 75% enantioselectivity.

ACKNOWLEDGEMENTS

The authors are grateful to Mrs. F. Hasegawa of this faculty for her MS spectral measurement.

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