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Novel stereoselective sulfur ylide epoxidation reaction catalyzed by ferrocenylsulfide*

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Abstract: A range of ferrocenyl sulfides are synthesized and screened. Among them 1-α-methysulphoferrocenyl ethyl acetate and 1-α-methysulphoferrocenyl alcohol are found to be unexpected catalysts, which is first reported mediating in sulfur ylide epoxidation reactions, furnishing a novel approach for highly stereoselective synthesis of oxiranes with 98%~100% *trans*-isomer. The protocol also has excellent yield, convenient workup and recycled starting material. The reason of high *trans*-selectivity is due to the bulky ferrocenyl sulfide group, which stabilizes the intermediates and determines the trans priority. A possible catalytic mechanism is also proposed.

Keywords: Ferrocenylsulfide, Catalytic ylide epoxidation, Stereoselectivity
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INTRODUCTION

Ferrocenyl compounds have found wide applications in organic synthesis and related areas since Wilkinson *et al*.(1952) characterized ferrocene as Sandwich structure. The versatile utilizations (Hayashi *et al*., 1998; Masdeu-Bulto *et al*., 2003) of ferrocene and its derivatives, chiral ferrocenyl compounds in asymmetric catalysis (Colacot, 2003) and agrochemicals industry (Moser *et al*., 1982) stimulated much attention. Our aim is to design and synthesize ferrocene-based chiral sulfides which can be used in stereoselective and/or enantioselective epoxidation and other asymmetric process. It is well known that ferrocenylsulfides are used as ligands (Masdeu-Bulto *et al*., 2003; Moser *et al*., 1982) in transition metal-catalyzed asymmetric synthesis. However, to the best of our knowledge, the sulfur ylide epoxidation reaction via ferrocenylsulfides has not reported in the literature until now.

Stereoselective and/or enantioselective reactions are most challenging problems in modern organic synthesis. Some research groups (Winn *et al*., 2002; Li *et al*., 2003; Julienne and Metzner, 1998; Aggarwal *et al*., 2004) have described their approaches for the synthesis of oxiranes via ylide routes. In these cases (Winn *et al*., 2002; Julienne and Metzner, 1998), although the enantiomeric excess were high, the ratio of *trans*/*cis* products needs to be increased; as to vinyl epoxides, neither *cis*- nor *trans*-oxiranes has priority (Li *et al*., 2003). An effective method for highly stereoselective synthesis of oxiranes is still lacking. We have reported (Wang and Huang, 2003) synthesis of *trans*-oxiranes via telluronium ylides. It should be noted that in this case, the ratio of *trans*/*cis*-oxiranes ranged from 92/8 to 60/40. The low ratio reported might be due to the fact that the steric hindrance from the group close to the sulfur or telluronium atom was not strong enough to prevent attack from the *syn* face (Aggarwal *et al*., 1996; Li *et al*., 1996). So it was necessary to design new sulfides to improve the stereoselectivity (*trans*/*cis*). Here we wish to report

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our results via racemic sulfides 1 and 2 to form diaryl oxiranes with 98%~100% *trans*-isomer (Fig.1).

The ferrocenyl sulfides 1 and 2 were synthesized using modified methods described in (Togni *et al*., 1994). Considering the satisfying steric hindrance of the ferrocenyl group, we hope to get highly stereoselective effect (*trans*/*cis*).

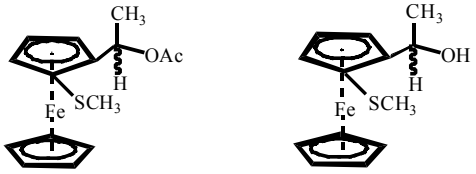
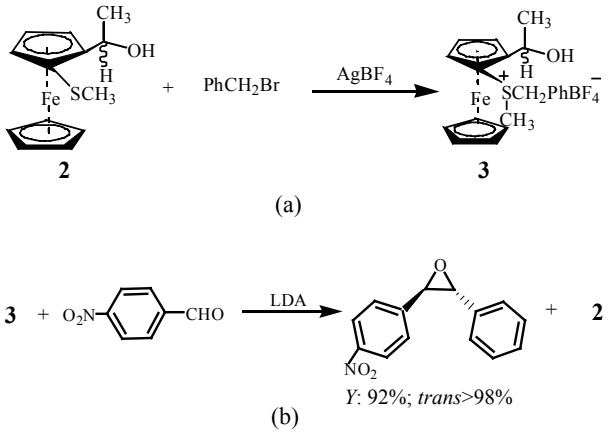


Fig.1 Racemic ferrocenyl sulfides used in catalytic epoxidation reactions

The initial attempt to employ 1 or 2 with benzyl bromide to form the sulfonium salt failed due to the bulky vicinal group and the weak nucleophilicity of the sulfur atom. Then we treated 2, in the presence of silver tetrafluroborate, reacting benzyl bromide to furbish the sulfonium salt 4 (Scheme 1) in almost quantitative yield. Fortunately, it was found that the salt 3, after deprontonation by LDA in situ, could react with *para*-nitrobenzaldehyde to afford 2-(4-nitrophenyl)-3-phenyl oxirane 5 with high stereoselectivity (>98% *trans*-isomer) in 92% yield (Scheme 1). We observed that the sulfide 2 could be recovered with 95% amount suggesting the possibility of catalytic sulfur ylide epoxidation.



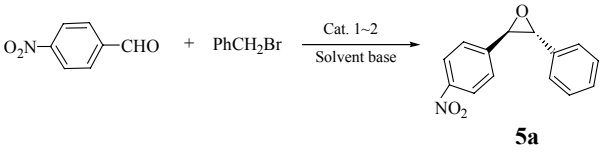
Scheme 1 Two steps for the synthesis of oxirane: formation of the sulfonium salt (a) and sulfur ylide epoxidation in situ (b)

Encouraged by the above result we investigated the simplified procedure. Primarily we intended to use a one-pot reaction involving all the reagents mixing together. The reaction of sulfide 2 (1 equiv), benzyl bromide (1.5 equiv) and *para*-nitrobenzaldehyde (1.0 equiv) was carried out with a mineral base (1.5~2.0 equiv) at room temperature (Scheme 2, Table 1).

Table 1 Effects of reaction conditions on the sulfides 1 and 2 mediated sulfur ylide epoxidation

Entry	Cat.	Solvent	Base	*Trans* /*cis*[b]	Yield (%)[c]
1	2	dry CH_2Cl_2	NaOH	/	0
2	2	dry THF	NaOH	/	0
3	2	THF+PTC[a]	NaOH	>98:2	84
4	2	CH_3CN+PTC[a]	NaOH	>99:1	99
5	2	*i*-BuOH+PTC[a]	NaOH	>98:2	77
6	2	CH_3CN+PTC[a]	KOH	>99:1	99
7	2	CH_3CN+PTC[a]	K_2CO_3	>99:1	47
8	1	CH_2Cl_2+PTC[a]	KOH	>98:2	50
9	1	THF+PTC[a]	KOH	>98:2	43
10	1	CH_3CN+PTC[a]	KOH	>99:1	67

[a] In this case, 0.1 g TBAB was used with 50% aqueous NaOH 1.0 ml; [b] The ratio of *trans*/*cis* was determined by ^{1}HNMR according to its coupling constant; [c] Isolated yields



Scheme 2 One-pot reaction mediated by sulfides 1 and 2

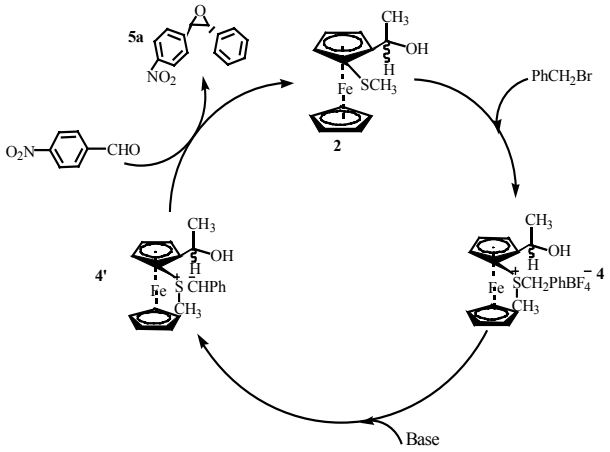
As shown in Table 1 (Entries 1~5), the reaction was found to be much solvent-dependent. Experiments in low or moderately polar solvent (Entries 1~2, Table 1) yielded no products. If tetrabutyl ammonium bromide (TBAB) was added as phase transfer catalyst, the reaction carried out smoothly (Entries 3~4, Table 1) with excellent yield. After the reaction was completed the sulfide 2 was isolated and recovered. Even under the careful workup the sulfide 1 could not be recovered in these cases (Entries 8~10, Table 1), but sulfide 2 yield obtained was 90%~95% (calculated from 1). This must be due to the fact that the acetyl ester group in sulfide 1 was sensitive to basic conditions and subject to hydrolysis during the extraction procedure.

Using the optimized conditions we further investigated the scope and limitation of the reaction by utilizing a series of structurally different aldehydes (Table 2) and found that the aromatic aldehydes worked well, had high stereoselectivity, and excellent yields. A heteroatomatic aldehyde (Entry 6, Table 1) also performed satisfactorily and a good yield. Another attractive feature of the reaction was that the initial sulfide 2 could be recovered in high yield (Entries 1~5, Table 1). Only in one case, furfural (Entry 6, Table 1), sulfide 2 was obtained in 92% yield due to the longer reaction time.

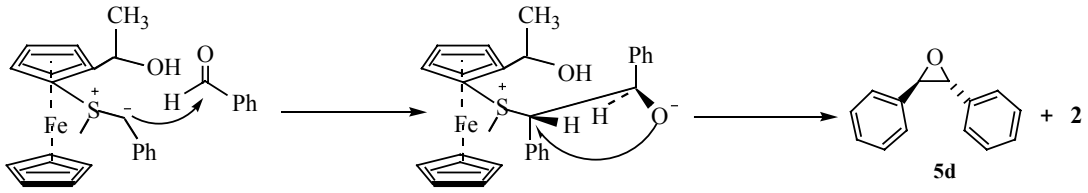
So that a catalytic process was induced by the use of 0.2 equiv of sulfide 2 for the epoxidation of *para*-nitrobenzaldehyde (1.0 equiv) with benzyl bromide (1.2 equiv). The reaction was completed in 17 d (detected by disappearance of aldehyde) and the yield (95%) of *trans*-isomer was excellent. No *cis*-isomer was detected. A possible catalytic mechanism was proposed (Scheme 3). The *trans*-selectivity of the epoxidation reaction is presented in Scheme 4.

CONCLUSION

We have developed a novel protocol for highly stereoselective synthesis of oxiranes with excellent



Scheme 3 A possible mechanism of sulfide 2 mediated catalytic sulfur ylide epoxidation reaction



Scheme 4 The *trans*-selectivity of sulfide 2 mediated sulfur ylide epoxidation reaction

Table 2 Results of epoxidation studies[a] using sulfide 1 and a range of aldehydes

Entry	Aldehyde	Time (d)	*Trans*/*cis*[b]	Yield (%)[c]	Sulfide recovered (%)
1	*p*-$NO_2C_6H_4CHO$	0.5	>99:1	99 (**5a**)	98
2	*p*-ClC_6H_4CHO	1.5	>99:1	99 (**5b**)	98
3	*p*-BrC_6H_4CHO	2	>99:1	96 (**5c**)	98
4	C_6H_4CHO	2	>99:1	85 (**5d**)	97
5	*p*-MeC_6H_4CHO	2.5	>98:2	87 (**5e**)	98
6	Furfural	3.5	>98:2	68 (**5f**)	92

[a] In this table, benzyl bromide, aldehydes were employed in 1.0 equiv, and NaOH in 1.2 equiv; [b] The ratio of *trans*/*cis* was determined by ^{1}HNMR according to its coupling constant; [c] Isolated yields after column chromatography

yields by using sulfides 1~2 which can be recycled after reactions. The approach has the advantage of mild reaction conditions, convenient procedure and available starting material. The asymmetric version via chiral 1 or 2 will be reported later.

References

Aggarwal, V.K., Ford, J.G., Thompson, A., Jones, R.V.H., Standen, M.C.H., 1996. Direct asymmetric epoxidation of aldehydes using catalytic amounts of enantiomerically pure sulfides. *J. Am. Chem. Soc*., **118**:7004.

Aggarwal, V.K., Charmat, J., Dudin, L., Porcelloni, M., Richardson, J., 2004. Effect of sulfide structure on enantioselectivity in catalytic asymmetric epoxidation of aldehydes: Mechanistic insights and implications. *Proc. Nat. Acad. Science (U.S.A.)*, **101**:5467-5471.

Colacot, T.J., 2003. A concise update on the application of

chiral ferrocenyl phosphines in homogeneous catalysis leading to organic synthesis. *Chem. Rev.*, **103**:3101-3118.

Hayashi, T., Tomioka, K., Yonemitsu, O., 1998. Asymmetric Synthesis Graphical Abstracts and Experimental Methods. Gordon and Breach Science Publishers, Amsterdam, p.76-88.

Julienne, K., Metzner, P., 1998. A simple C_2 symmetrical sulfide for a one-pot asymmetric conversion of aldehydes into oxiranes. *J Org Chem*, **63**:4532.

Li, A.H., Dai, L.X., Hou, X.L., Huang, Y.Z., Li, F.W., 1996. Preparation of enatiomerically enriched (2*R*,3*R*)- or (2*S*, 3*S*)-*trans*-2,3-diaryloxiranes via camphor-derived sulfonium ylides. *J Org Chem*, **61**:489.

Li, K., Huang, Z.Z., Tang, Y., 2003. An efficient catalytic ylides route to vinyl epoxides. *Tetrahedron Lett*., **44**:4137.

Masdeu-Bulto, A.M., Dieguez, M., Martin, E., Gomez, M., 2003. Chiral thioether ligands: coordination chemistry and asymmetric catalysis. *Coord Chem Rev*, **242**:159-201.

Moser, H., Rihs, G., Sauter, H., Naturforsch. Z., 1982. Ciba-Geigy Ltd, 37b 451; 1972, Ciba-Geigy Ltd, U.S. Pats., 3 937 730 and 4 022 611.

Togni, A., Breutel, C., Schnyder, A., Spindler, F., Lander, H., Tijani, A., 1994. A novel easily accessible chiral ferrocenyldiphosphine for highly enantioselective hydrogenation, allylic alkylation, and hydroboration reactions. *J Am Chem Soc*, **116**:4062.

Wang, L., Huang, Z.Z., 2003. Highly stereoselective synthesis of *trans*-diaryl Epoxides via semi-stabilized telluronium ylides. *J Chem Res(S)*, **2003**(5):305-306.

Wilkinson, G., Rosenblum, M., Whiting, M.C., Woodward, R.B., 1952. The structure of iron *bis*-cyclopentadienyl. *J. Am Chem Soc*, **74**:2125.

Winn, C.L., Bellenie, B.R., Goodman, J.M., 2002. A highly enatioselective one-pot sulfur ylide epoxidation reaction. *Tetrahedron Lett*., **43**:5427.