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Sulfonium ylide epoxidation reactions: methylene transfer

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Received (in Cambridge, UK) 22nd December 2003, Accepted 10th March 2004
First published as an Advance Article on the web 1st April 2004

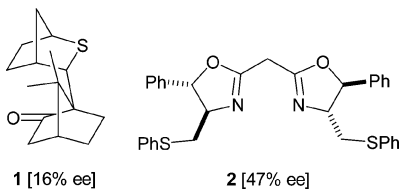
Using a D-mannitol derived chiral sulfide, terminal epoxides are formed in up to 76% ee; the first example of double asymmetric induction in a sulfonium methylide epoxidation is reported and an improved method of generating sulfonium ylides is detailed.

The synthesis of terminal epoxides in high enantiomeric excess has proven very challenging. A kinetic resolution step is normally required to achieve high enantioselectivity.[1] The reaction of sulfonium ylides with carbonyl compounds offers a great deal of potential for forming this important functionality,[2] however in general low enantiomeric excesses have been obtained. Aggarwal's variant of the sulfur ylide epoxidation reaction, using Simmons–Smith conditions to directly form the sulfur ylide from the sulfide *via* a carbene addition, has led to the highest enantioselectivities observed to date for the formation of styrene oxide by methylene transfer: 16% ee using sulfide **1** and 47% ee using disulfide ligand **2** (Fig. 1).[3]

Crystalline, odour-free sulfide **3**[4] has been shown to mediate aryl transfer epoxidation reactions in reasonable yield and high enantiomeric excess.[5] Diaryl epoxides are of limited synthetic utility and so it was desirable to extend this work to the more synthetically useful monosubstituted epoxides. Treatment of **3** with methyl iodide then base did not produce the product. The Aggarwal/Simmons–Smith conditions were used successfully in reactions with sulfide **3** and preliminary results are detailed here.

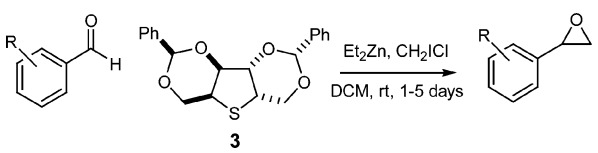
The reaction of sulfide **3** (2 eq.) with chloroiodomethane (2 eq.), benzaldehyde (1 eq.) and diethylzinc (1 eq.) led to the formation of styrene oxide after 2 days stirring at room temperature (Scheme 1), with an isolated yield of 61%. Recovery of sulfide is straightforward: the reaction is quenched with water, extracted with dichloromethane and extracts are filtered through a short silica column. Epoxide and remaining aldehyde are rapidly eluted; as sulfide **3** is considerably more polar, it can be recovered simply by washing the column with further dichloromethane. Where the reaction did not go to completion, flash chromatography was necessary to separate epoxide from starting aldehyde.

The enantiomeric excess of this, and the other examples detailed below, was determined by chiral shift NMR using the (+) isomer of Eu(hfc)$_3$. Low field NMR spectrometers (200 or 250 MHz) were used to minimise signal broadening. Enantiomeric excess of 48% was observed. According to the literature for the optical rotation of styrene oxide in chloroform,[6] the major isomer was assigned as *S*. This is consistent with chiral shift NMR.[7]



1 [16% ee] **2** [47% ee]

Fig. 1 Enantioselectivities achieved in the formation of styrene oxide.[3]



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Scheme 1 Terminal epoxidation mediated by sulfide **3**.

A range of aromatic aldehydes were investigated as substrates for this reaction (Table 1). Most enantioselectivities obtained are in the range of 34–49%, similar to those obtained by Aggarwal using disulfide **2**.[3] The more sterically demanding 2,4-dichlorobenzaldehyde was found to be comparatively very reactive under these conditions—reaction was complete after just one day stirring at ambient temperature, and gave isolated epoxide in almost quantitative yield. The enantioselectivity of this reaction was found to be much higher than for the other cases studied, 78% being obtained on the first attempt. Repeating this reaction gave consistently high levels of enantioselectivity—between 72% and 80%.

Reducing the reaction temperature to 0 °C had a small beneficial effect on selectivity: 53% ee was obtained for the formation of *para*-nitrostyrene oxide. Reactivity was reduced, with a yield of 62% being observed.

One major disadvantage of this protocol is the use of two equivalents of the chiral sulfide. This problem is minimised by the ease of recovery of sulfide. Between 70% and 100% of sulfide is recovered from the reaction; the amount of sulfide recovered decreases where a longer reaction time is required. Recycled sulfide appears to work just as selectively as freshly prepared, giving an ee of 75% in the formation of *ortho*,*para*-dichlorostyrene oxide.

The possible active species proposed for the Simmons–Smith epoxidation reaction are noted to be unstable at room temperature.[8] This means that the addition of all reagents at the start of an extended reaction time is unlikely to be the best method for formation of epoxide product. The addition of dimethoxyethane was found to stabilise zinc complexes, and extend the lifetime of the active species. Also, generating the active species continually by syringe-pump addition in the presence of dimethoxyethane allows considerably shorter reaction times than previously reported. The reaction of chloroiodomethane (3 eq.), tetrahydrothiophene (1 eq.) and aldehyde (1 eq.) in dimethoxyethane (1 eq.), and dichloromethane, with addition of diethylzinc (1.2 eq.) by syringe pump over 2.5 h gives complete conversion of aldehyde to styrene oxide. This compares favourably with previously observed reaction times of one to two days,[2,3] and only one equivalent of sulfide is required. However, the use of the syringe pump is less convenient than leaving the reaction to stir.

The use of diethylzinc has also been problematic. Diethylzinc was used as a solution in hexane : diethylzinc solution from

Table 1 Yield and enantioselectivity observed using different aldehydes

R (**R**CHO)	Isolated yield of epoxide	Enantiomeric excess of epoxide
Phenyl	61%	48%
2-Naphthyl	54%	34%
4-Nitrophenyl	86%	49%
3,4-Dichlorophenyl	48%	49%
2,4-Dichlorophenyl	96%	76%
2,6-Dichlorophenyl	92%	47%

DOI: 10.1039/b316653h

different suppliers, and in some cases different batches from the same supplier has led to inconsistent yields and reactivities.

The use of an isolable and analysable zinc complex removes the inconsistencies between different supplies of diethylzinc. Stable halomethylzinc complexes have been found by Charette *et al.* to be effective in cyclopropanation reactions and in the alkylation of sulfur.[9] Therefore, the use of a stable complex in epoxidation reactions was investigated.

Bis(chloromethyl)zinc : bipyridine **4** was prepared by addition of a solution of 2,2′-dipyridyl to a solution of bis(chloromethyl)zinc,[9] formed *in situ* from a 3 : 1 mixture of chloroiodomethane : diethylzinc at low temperature (Scheme 2).

The bis(chloromethyl)zinc : bipyridyl complex **4** was found to be effective in forming ylides for the sulfonium ylide epoxidation reaction.† When 1.2 equivalents of complex **4** were used with one equivalent of tetrahydrothiophene, styrene oxide was formed in 60% yield in just two hours. Disappointingly, no further reaction was observed after this time indicating that all of the reagent has been used up or decomposed. The use of two equivalents of the bis(chloromethyl) complex **4** led to complete conversion in under 14 h. It is unclear why two equivalents of this reagent are required.

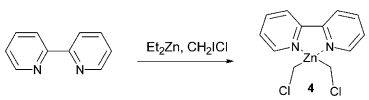
To investigate the possibility that this reaction may work catalytically, 0.2 eq. of tetrahydrothiophene were used. Only 18% yield was obtained, indicating that stoichiometric sulfide is required under these conditions. Nevertheless, this is an improvement on the two equivalents required for this reaction using the previous protocol.[3]

The use of complex **4** also proved effective in epoxidation reactions with chiral sulfide **3** (Scheme 3), although reaction times were longer than for tetrahydrothiophene. For the reaction involving benzaldehyde, 56% yield was obtained after 20 hours, and enantiomeric excess for styrene oxide formation was 57%. This is the highest reported enantioselectivity for the direct formation of styrene oxide by a sulfonium methylide epoxidation reaction.

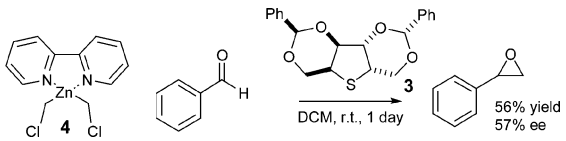
To further test the effectiveness of the terminal epoxidation conditions developed, they were applied to the synthesis of a useful reaction intermediate. Amino acid-derived epoxide **5** is an intermediate in the synthesis of the protease inhibitor amprenavir.[2,9–11]

Aldehyde **6** was formed from phenylalanine, using the synthetic route developed by Reetz.[12] This material was used immediately in the epoxidation reactions described below (Scheme 4). Using a racemic sulfide (tetrahydrothiophene) and literature epoxidation conditions,[2,3] the desired epoxide was found to be formed in a 5 : 1 *syn* : *anti* ratio, in agreement with published work.[2] Using sulfide **3**, a mixture of epoxides was formed in 57% conversion—a pleasing result indicating that this sulfide is reactive in the formation of aliphatic as well as aromatic epoxides. The ratio of *syn* and *anti* epoxides (calculated by integration of an NMR sample of the crude mixture) was 12 : 1.

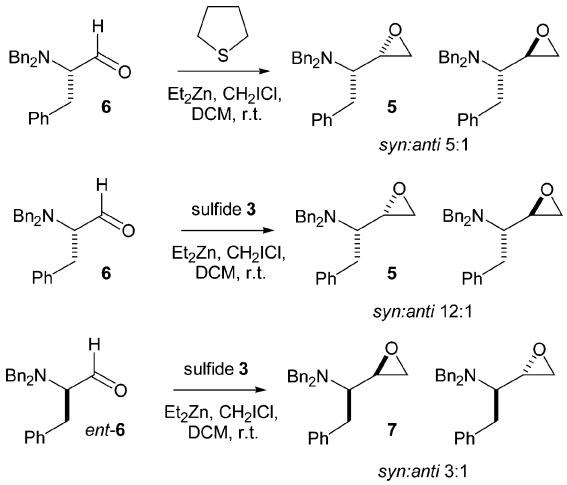
To investigate whether this is a genuine double stereoinductive effect and not merely an artefact of the increased steric bulk of the



Scheme 2 Formation of an isolable bis(chloromethyl)zinc complex.



Scheme 3 Terminal epoxidation using sulfide **3** and complex **4**.



Scheme 4 Combination of substrate and reagent control in epoxidation reactions using sulfide **3**.

sulfide used, the enantiomer of aldehyde **6** was synthesised, again using the Reetz protocol[12] but starting with the unnatural D-(*R*)-phenylalanine. 45% conversion to product **7** was observed, with a diastereomeric ratio of 2.7 : 1 (*syn* : *anti*). This case is 'mismatched', with the stereochemical induction of the sulfide working against the substrate bias. The *syn* epoxide is the major product, indicating that the reagent control is not powerful enough to overturn the substrate selectivity. The use of preformed zinc complex **4** was again more effective: 76% conversion to epoxides was observed, in a similar ratio of 3.3 : 1.

To our knowledge, this is the first example of double asymmetric induction in a sulfonium ylide epoxidation reaction, and further demonstrates the potential utility of chiral sulfide **3** in the synthesis of useful epoxide intermediates.

Notes and references

† Sample experimental procedure for epoxidation using zinc complex: To a suspension of complex **4** (2 eq.) in dichloromethane (10 mL/mmol aldehyde) was added sulfide (1 eq.) and aldehyde (1 eq.). The mixture was stirred at 20 °C under argon for 2–24 h. Water (10 mL/mmol aldehyde) was added, and the mixture extracted with dichloromethane (3 × 7 mL/mmol aldehyde). Organic phases were filtered through a short plug of silica and solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, 1 : 1 dichloromethane : hexane).

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