Direct Utilization of Naturally Occurring Sulfides for the Asymmetric Epoxidation of Aldehydes Mediated by Catalytic Ylides†

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Received May 18, 2004

Key Words : Epoxidation, Sulfide, Biotin, Sulfonium ylide

Practical and economical aspects of asymmetric synthesis are receiving increased attention.1-5 Use of a catalytic amount of the enantiomERICally ligand is now common in organometallic chemistry, but still remains a challenge for organocatalyzed reactions, in which the catalytic species is not centered on a metal atom.6

The availability of the chiral auxiliary7 is a critical parameter. A large variety of chiral auxiliaries have been prepared from the chiral pool8 or by biotechnologies, through sequences which involve several steps, often in excess of 3 to 5, leading to situations that are acceptable for preliminary exploration but definitely less for large scale applications.9,10

An ideal situation would be the use of a naturally occurring molecule directly as it is isolated. To our knowledge, there are not many molecules, which fulfill this expectation. They include:
− Tartaric acid for asymmetric Raney nickel hydrogenation.11
− Alkaloids,12 such as quinine or cinchonidine, for conjugate addition,13,14 [2+2]cycloaddition,15 sigmatropic rearrangement.16
− AminoaCids such as proline for aldolisation reaction.17

The scantiness of such molecules prompted us to explore natural chiral sulfides as auxiliaries for ylide mediated asymmetric epoxidation. We have been recently interested in achieving an enantioselective conversion of an aldehyde into an epoxide, mediated by a sulfonium ylide, and often referred as the Corey-Johnson reaction.18,19 This led us to design a \( \text{C}_5 \) symmetric sulfide 1, and to develop a catalytic simple procedure.20-22

The chiral auxiliary was prepared from (2S,5S)-hexanediol, which is accessible by enzymatic reduction23,24 of 2,5-hexanedione, and commercially available, but not cheap.

Other groups have also reported chiral sulfides for the efficient ylide epoxidation. Synthesis of the chiral sulfides required 3 to 5 synthetic steps from camphor,25-27 pulegone,28 mannitol,29 tartaric acid30 or by an enzymatic reduction,31 or a resolution.32

Our present approach was of the utmost simplicity, i.e. screen natural chiral sulfides, preferably cyclic ones. This led us rapidly to two types of structures bearing a sulfur atom in a 5-membered ring, named penicillins 2 and biotin 3.

A variety of penicillins are available commercially, as a result of the discovery of their outstanding antibiotic activity in 1929 by Fleming and their subsequent industrial production. We selected penicillin G (1, R=Ph) for its availability and low cost, as well as the apparent lack of competing functional group for the key epoxidation step.

There are three critical parameters for stereocontrol. i) Formation of a single diastereomeric sulfonium salt. ii) Control of ylide conformation. iii) Facial selectivity of the ylide.

We expected first that the concave shape of penicillin 2 would direct the first step, reaction of benzyl bromide,
towards a favored diastereomeric sulfonium salt. We anticipated that a privileged conformation of the awaited ylide would undergo attack of aldehyde on the face opposite to the hindered gem-dimethyl group. A computational study has led to demonstrate the feasibility of the thiazolidine nucleus for asymmetric epoxidation.

**Results**

The reaction was tested with the one-pot procedure, which was successful with our C₂ symmetric sulfide: use of a mixture of polar solvents, t-BuOH and H₂O, in a 9 : 1 ratio, and direct addition of stoichiometric penicillin G (R=Ph) potassium salt (1 equiv), benzyl bromide (2 equiv), benz-aldehyde (1 equiv), tetra-n-butylammonium iodide (1 equiv), and NaOH (2 equiv). Unfortunately, after a contact of one week at ambient temperature, no stilbene epoxide was detected, and the reagents were recovered. We noticed that the solubility of the penicillin was rather moderate in our solvent system. Subsequently, we performed the reaction in water, but no success was met either. We prepared the methyl carboxylate and tested it in a variety of conditions. Unfortunately, still no epoxidation occurred, which may be due to the instability of the presumed sulfonium salt.

We then investigated a second naturally occurring chiral sulfide, biotin. It is an essential co-enzyme for carboxylation, a key step in gluconeogenesis and fatty acid biosynthesis. Isolated in 1936, characterized in 1942, it is now produced industrially by synthesis for therapeutic uses and food addition to stock feeding.

In line with our purpose, it bears a thiolane ring with a stereogenic center, adjacent to the sulfur atom and bearing a 5-carbon carboxylic acid chain, potentially providing steric hindrance.

Right at the first test of epoxidation, we observed interesting results. The reaction was conducted under our standard one-pot conditions, first with a stoichiometric amount. After a period of one day, a 50% yield of stilbene oxirane was isolated. Indeed, biotin mediated the sulfur ylide reaction, with an enantiomeric excess of 50% in favor of the (S,S) enantiomer. A modest selectivity for the trans diastereomer was observed.

We attempted a catalytic use of biotin. With 0.1 equivalent, a reasonably low loading for organocatalysis, we were glad that the reaction worked, with results similar to the stoichiometric series. We noted that biotin is not much soluble in water, and less so in alcohols. Therefore, our reaction conditions might not provide optimum reaction conditions.

The reaction was performed in H₂O, instead of a mixture of t-BuOH/H₂O, but this did not give any improvement. The same yield and selectivities were observed.

We decided to improve the solubility of the chiral auxiliary, under our reaction conditions, by forming the methyl ester of biotin. At the epoxidation stage, it required the use of a non-hydrolytic base, and we selected potassium carbonate. The reaction was run with a loading of 0.1 equiv of biotin ester. After a week, stilbene oxide was isolated in a 50% yield, a diastereomeric ratio of 7 : 3, and the higher enantiomeric excess that we have met in this series, 70% (S,S).

**Discussion**

Our initial challenge has been successful. Direct utilization of a naturally occurring cyclic sulfide, biotin, readily available, is feasible for ylide-mediated epoxidation of aldehydes.

Simple experimental conditions involved mere addition of the reagents, 10% equivalent of biotin, and stirring the one-pot reaction mixture at room temperature for 6 days. The yields and e.e.’s are not reaching the present standards for general applicability, but they nicely illustrate our simple principle.

To explain the predominant formation of the (S,S) enantiomer, we propose the model depicted on Scheme 3. The

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**Table 1.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfide</th>
<th>Amount</th>
<th>Base</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>d.r.³</th>
<th>e.e.⁵ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Penicillin G</td>
<td>1</td>
<td>NaOH</td>
<td>7</td>
<td>50</td>
<td>70:30</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Methyl ester of penicillin G</td>
<td>1</td>
<td>K₂CO₃</td>
<td>70</td>
<td>50</td>
<td>70:30</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>(+)-Biotin</td>
<td>1</td>
<td>NaOH</td>
<td>1</td>
<td>50</td>
<td>67:33</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>0,1</td>
<td>NaOH</td>
<td>6</td>
<td>50</td>
<td>69:31</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Methyl ester</td>
<td>0,1</td>
<td>K₂CO₃</td>
<td>7</td>
<td>50</td>
<td>70:30</td>
<td>70</td>
</tr>
</tbody>
</table>

³Analyzed from the NMR spectrum of the crude material. ⁵Enantiomeric excess measured by HPLC using Daicel Chiralpak AD column.
alkylation of the sulfur atom would take place preferentially with the lone pair located trans to the carboxylic chain, but we believe that this might not be entirely selective and thus erode the enantiomeric excess, a situation which was avoided with our previous C2 symmetric thiolane. By subsequent deprotonation of the sulfonium salt, an anti ylide could be preferred, locating the sulfur lone pair in the same plane as the H and Ph groups on the ylidic carbon (H and lone pair anti). The approach of the aldehyde would take place backward (sí face of the ylide), to avoid steric compression with the carboxylic chain, α to the sulfonium center.

In terms of enantiomeric excess, the higher induction was observed with a simple derivative of biotin, its methyl ester, which led to 70% e.e.

The diastereoselectivity is modest (67 : 33-70 : 30) in favor of the trans isomer. It brings some information about a stereocontrol, which is not yet fully understood. Whereas the groups of Aggarwal25,19 and Cavallo-Solladié40 observed a stereocontrol, which is not yet fully understood. Whereas the on the sulfur atom, we have observed moderately hindered sulfides or with aromatic substituents related to the structural features of the sulfide. With have met several differences, which we tend to believe are experimental evidence (except for ferrocenyl sulfides41), we 90 : 10 to 60 : 40. Though, in most cases, we do not have erode the enantiomeric excess, a situation which was judged complete by thin layer chromatography (TLC). TLC plates were visualized by UV light and by treatment with a solution of 2,4-DNPH (400 mg in 100 mL of HCl 1 N). Water (5 mL) was added. The aqueous phase was extracted with diethyl ether (10 mL, 3 times); the combined organic layers were dried over MgSO4, and then concentrated to dryness. The crude product was submitted to column chromatography (silica gel, 98/2 petroleum ether/diethyl ether) to afford the stilbene oxide (49 mg, 0.25 mmol, 50% yield, d.r. : 2.2 : 1). HPLC analysis was performed on a Daicel Chiralpak AD column with a 9 : 1 hexane isopropanol eluent mixture at a flow of 1 mL/min: e.e. = 50%.

Acknowledgment. We are grateful for the financial support of the “Ministère de la Recherche et des Nouvelles Technologies” (scholarship to Jacques Zanardi and equipment), CNRS (Centre National de la Recherche Scientifique), the “Région Basse-Normandie” and the European Union (FEDER funding).

References


Conclusion

We have shown that it is feasible to use a sulfide directly from the << supplier >>, mother’s nature, to mediate conversion of aldehydes into oxiranes in a non-racemic fashion through sulfur ylides. It can be added to the very short list of natural molecules, which are directly utilized for asymmetric chemical synthesis.