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

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Practical and economical aspects of asymmetric synthesis are receiving increased attention.[1-5] Use of a catalytic amount of the enantioenriched 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 auxiliary[7] is a critical parameter. A large variety of chiral auxiliaries have been prepared from the chiral pool[8] 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]

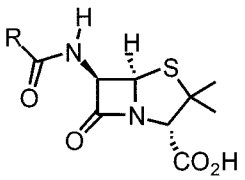
An ideal situation would be the use of a naturally occurring molecule directly as it is isolated. To our knowledge, there are not many molecules, which fulfill this expectation. They include:

– 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 C_2 symmetric sulfide **1**, and to develop a catalytic simple procedure.[20-22] The chiral auxiliary was prepared from (2*S*,5*S*)-hexanediol, which is accessible by enzymatic reduction[23,24] 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 acid[30] 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**.



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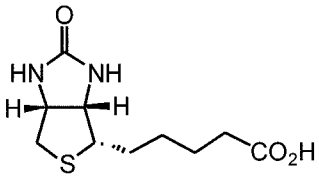

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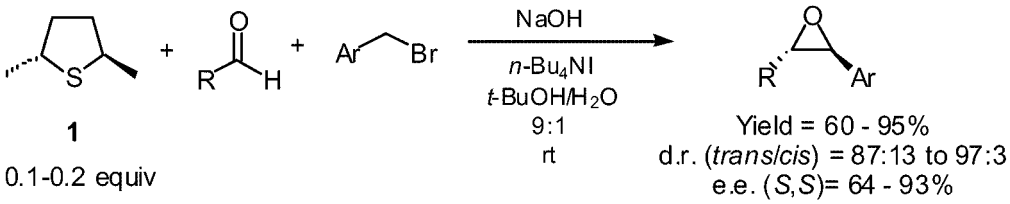
A variety of penicillins are available commercially, as a result of the discovery of their outstanding antibiotic activity in 1929 by Fleming and their subsequent industrial production. We selected penicillin G (**1**, R=Ph) for its availability and low cost, as well as the apparent lack of competing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



Scheme 1

†Dedicated to Prof. Yong Hae Kim, for his commitment to the synthetic organic chemistry of sulfur, superb achievements, and friendship all over the years.

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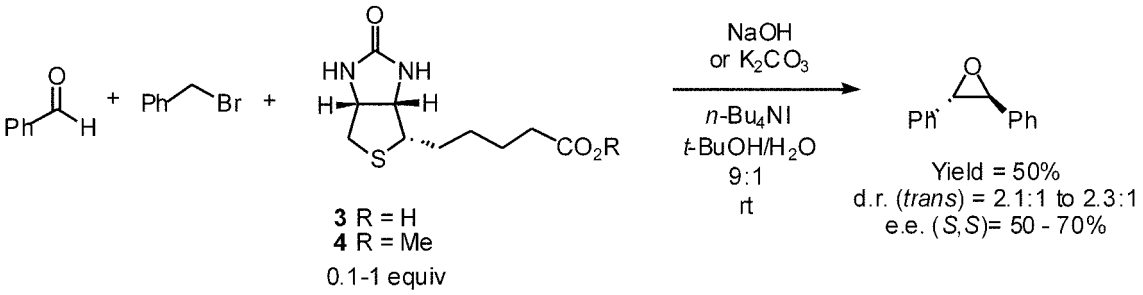


Scheme 2

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[33] has led to demonstrate the feasibility of the thiazolidine nucleus for asymetric epoxidation.

Results

The reaction was tested with the one-pot procedure,[20] which was successful with our C_2 symmetric sulfide: use of a mixture of polar solvents, *t*-BuOH and H_2O, in a 9 : 1 ratio, and direct addition of stoichiometric penicillin G **2** (R=Ph) potassium salt (1 equiv), benzyl bromide (2 equiv), benzaldehyde (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[34] 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.[35]

We then investigated a second naturally occurring chiral sulfide, biotin **3**.[36] 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[22,37-39] of biotin. With 0.1 equivalent, a reasonably low loading for organocatalysis,[6,39] 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.

Table 1.

Entry	Sulfide	Amount	Base	Time (d)	Yield (%)	d.r.[b] *trans*/cis	e.e.[c] (%) (*S*,*S*)
1	Penicillin G	1	NaOH	7	0		
2	Methyl ester of penicillin G	1	K_2CO_3	7	0		
3	(+)-Biotin	1	NaOH	1	50	67:33	50
4		0,1	NaOH	6	50	69:31	53
5	Methyl ester	0,1	K_2CO_3	7	50	70:30	70

[b]Analyzed from the NMR spectrum of the crude material. [c]Enantiomeric excess measured by HPLC using Daicel Chiralpak AD column.

The reaction was performed in H_2O, instead of a mixture of *t*-BuOH/H_2O, but this did not give any improvement. The very same yield and selectivities were observed.

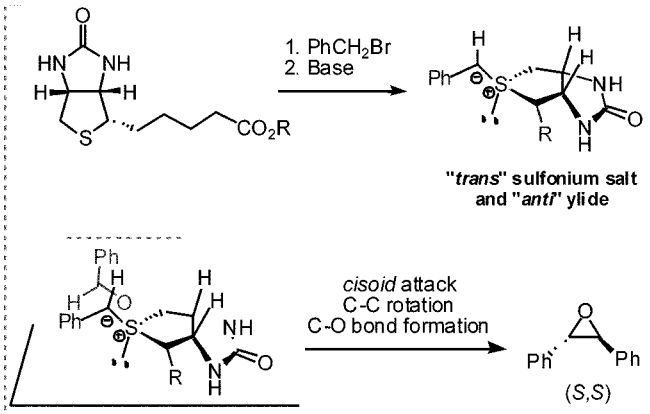
We decided to improve the solubility of the chiral auxiliary, under our reaction conditions, by forming the methyl ester of biotin. At the epoxidation stage, it required the use of a non-hydrolytic base, and we selected potassium carbonate.[21] The reaction was run with a loading of 0.1 equiv of biotin 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[20] the model depicted on Scheme 3. The



Scheme 3

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 C_2 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 (*si* 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 Aggarwal[25,19] and Cavallo-Solladié[40] observed a marked selectivity in favor of the *trans* stilbene oxirane, we have met several differences, which we tend to believe are related to the structural features of the sulfide. With moderately hindered sulfides or with aromatic substituents on the sulfur atom, we have observed *trans/cis* ratios from 90 : 10 to 60 : 40. Though, in most cases, we do not have experimental evidence (except for ferrocenyl sulfides[41]), we propose a marked kinetic control, compatible with the model proposed by Aggarwal.[42,43] With moderately hindered sulfides, the formation of the << *syn* >> betaine is less reversible (easier C-C bond rotation) than with hindered sulfides and thus leads to more *cis* oxirane.

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.

Experimental Part

Typical procedure. To a solution of (+)-biotin (24 mg, 0.05 mmol, 0.1 eq.) in 1 mL of a mixture of *t*-BuOH/H_2O 9/1 were added benzyl bromide (120 µL, 1 mmol, 2 eq.), powdered NaOH (40 mg, 1 mmol, 2 eq.), *n*-tetrabutylammonium iodide (185 mg, 0.5 mmol, 1 eq.) and benzaldehyde (53 mg, 0.5 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 6 days. The reaction 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 $MgSO_4$, 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%.

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