4 Optically active β-ketosulfoxides in asymmetric synthesis
G. SOLLADIÉ

4.1 Introduction

During the 1980s, organic sulfur compounds have become increasingly useful and important in organic synthesis. Sulfur, incorporated into an organic molecule, stabilizes a negative charge on an adjacent carbon atom, a property which has been especially important in the development of new ways to form carbon–carbon bonds. With respect to sulfides and sulfones, the sulfoxide group is of special interest because of its chirality and the presence of three different kinds of substituent, from a steric and stereoelectronic point of view: the lone pair of electrons, the oxygen atom and two aryl or alkyl groups give a special efficiency to sulfoxides in asymmetric synthesis.

The purpose of this chapter will be limited to asymmetric syntheses from β-ketosulfoxides. After a general overview on the different ways to introduce an optically active sulfoxide group on a target molecule, the asymmetric reduction of β-ketosulfoxides will be described. Finally, several applications in total synthesis of natural products will be presented.

4.2 Optically active sulfoxide preparations

Until now, optimally active sulfoxides have been obtained in many different ways: optical resolution, asymmetric synthesis, kinetic resolution and stereospecific synthesis.

Optical resolution could be achieved, following the pioneering work of Harrison,1 by means of an acidic or basic group present in the molecule. The resolution of ethyl p-tolyl sulfoxide was also achieved in 1966, through the formation and separation of the diastereoisomeric complexes with trans-dichloroethylene platinum(II) containing optically active α-phenyl-ethylamine as a ligand.2 The more recent work on optical resolution was reviewed in detail by Mikolajczyk et al.3

Asymmetric oxidation of sulfides with optically active peracids was first reported by Montanari4 and Balenovic,5 though their products were of low enantiomeric purity, generally not higher than 10%. More recently Kagan6 reported that high enantioselectivities could be obtained with a modified Sharpless reagent [Ti(O-i-Pr)₄/DET/t-BuOOH/H₂O]; ee values in the range of 80 to 90% were obtained (see Chapter 17) in the case of simple alkyl aryl
sulfides. Enzymatic oxidation of sulfides also gave very good results in a few cases.\textsuperscript{3,7}

New approaches starting from cyclic disulfides\textsuperscript{8} or oxazolidinones\textsuperscript{9} were also reported.

However, all these methods, which give good results with specific substrates, are not yet general enough. A great achievement in the stereochemistry of organosulfur compounds was the stereoselective synthesis of optically active sulfoxides, originally proposed by Gilman\textsuperscript{10a} and developed later by Andersen\textsuperscript{10b}. This approach to sulfoxides of high optical purity, still most important and widely used, is based on the reaction of the diastereoisomerically pure \((-\)-(S)-menthyl \(p\)-toluenesulfinate (1)* with Grignard reagents. \((+)-(R)\)-Ethyl \(p\)-tolyl sulfoxide (2) was the first optically active sulfoxide obtained by this method (Scheme 4.1).\textsuperscript{10b} The reaction proceeds with complete inversion of configuration at sulfur. This was demonstrated by chemical correlation\textsuperscript{11–13} and ORD studies.\textsuperscript{11, 13–16} A Cotton effect was observed between 235 and 255 nm for alkyl aryl sulfoxides and near 200 nm for dialkyl sulfoxides, characteristic of the absolute configuration at sulfur. The absolute configuration of \((-\)-(S)-menthyl \(p\)-toluenesulfinate was previously established\textsuperscript{14} by correlation with that of \((--\)-menthyl \((--\)-\(p\)-iodobenzene sulfinate determined by X-ray diffraction.\textsuperscript{16}

The Andersen sulfoxide synthesis is general in scope and its application to the synthesis of complex optically active sulfoxides will be shown later. However, a major drawback in this reaction is the requirement for optically pure \((-\)-(S)-menthyl \(p\)-tolyl sulfinate (1). In the numerous examples reported by Andersen,\textsuperscript{10b,15,17} Mislow\textsuperscript{14,16,18} and others,\textsuperscript{11,12,19} \((--\)-(S)-1) was obtained from the reaction of \(1\)-menthol with \(p\)-toluenesulfinyl chloride followed by fractional crystallization of the mixture of the two diastereoisomers. This esterification reaction showed no particular stereoselectivity, giving a 1:1 diastereomeric mixture. The process can be improved and the fractional crystallization of the diastereoisomers avoided by using the acid-catalysed

\* An ambiguity arises in the configurational designation of sulfinate esters because the prefixes \((R)\) and \((S)\) are reversed according to whether the \(S-O\) bond is regarded as a single or as a double bond. We followed a previously established custom and considered for nomenclatural purposes the \(S-O\) bond as a single bond.