Routes to optical activity. Catalytic stereoslective syntesis of chiral epoxides selenides and sulfides.

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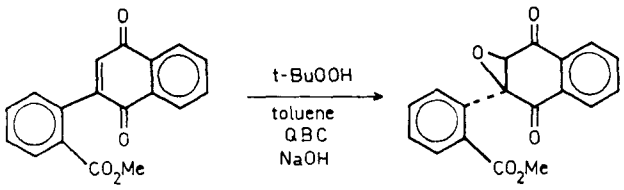
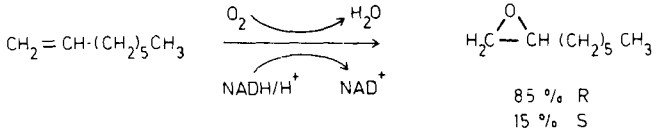


Scheme 1.9

first example was the stereospecific oxidation of 1-hexadecene to the optically pure (R)-epoxide by Coryne bacterium equi.[186]. Similarly, 1,7-octadiene can be converted with an optical yield of over 80% in 7,8-epoxy-1-octene[167]. The epoxides formed enzymatically are isolated in very low yields or not at all. Recent efforts of De Smet in our laboratory to produce and isolate larger amounts of chiral epoxide were successful in the epoxidation of 1-octene to 1,2-epoxy octane by Pseudomonas oleovorans in a two-phase system. The product showed an enantiomeric excess of 70% (Scheme 1.10)[262].



Scheme 1.10

1.4 OBJECTIVES AND SURVEY

The principal aim of the work described in this thesis was the study of catalytic enantioselective reactions and the factors which determine the extent of induction. The two reaction types studied were the Michael addition (Chapters 2, 4, and 5) and the epoxidation reaction (Chapter 3). The entire work was aimed at the optimization of the enantioselectivity.

Chapter 2 deals with the selenol addition to cycloalkenones. Pyrimidine thiols also gave optically active compounds. The results concerning e.e. and absolute configuration are treated in this chapter. The conversion of the chiral ketosulfides and especially the ketoselenides (the C-Se bond is weaker than the C-S bond) to sulfur- and selenium-free optically active compounds (*e.g.* optically active cyclohex-2-en-1-ols) is investigated. A new method for the determination of the e.e.'s concerning selenium-containing compounds is developed.

2-Methyl-1,4-naphthoquinone (vitamin K_3) can be epoxidized in a stereoselective manner in a phase-transfer reaction using optically active quarternary ammonium salts. Chapter 3 describes the enantioselective epoxidation of several other naphthoquinones with various substituents. A new synthesis of lapachol and α- and β-lapachon is discussed. The synthesis of 2-alkyl-quinone diimides is elaborated but unfortunately no epoxides of these compounds could be obtained. Very interesting is the chiral base-catalyzed quinone epoxide ring opening by means of thiols leading to chiral β-hydroxysulfides. The same ring opening method may be applied for the kinetic resolution of racemic keto-epoxides.

The work of Hiemstra led to a proposal for the mechanism of the thiol addition to cycloalkenones. According to this model the development of new catalysts based upon cinchona alkaloids has been carried out; on the one hand to verify the proposed model, on the other hand to optimize the stereoselective induction. For that purpose several transformations in cinchona alkaloids are introduced. Furthermore, a total synthesis of cinchona alkaloid analogs is carried out in order to enable variation in the quinoline part of the cinchona alkaloids. The results are discussed in Chapter 4.

In Chapter 5 the thiol addition to highly symmetrical enones (4,4-disubstituted cyclohexa-2,5-dienones, *i.e.* compounds which contain a so-called meso carbon atom) is discussed.

Finally, the synthesis of optically active 4-methyl-4-phenylcyclohex-2-en-1-one is described using either kinetic resolution or a retrograde Michael reaction.

Parts of the work described in Chapter 2[207,310] and Chapter 3[206,264] have already been published; publications concerning the research in Chapters 3, 4, and 5 are in preparation.