4. Summary

This thesis presents new applications of enzymes in the synthesis of chiral non-racemic heteroorganic compounds bearing a stereogenic center on a sulfur or phosphorus atom. Enzymatic syntheses of such compounds were carried out under the conditions of kinetic resolution of the racemic substrates or desymmetrization of the prochiral substrates, having a hydroxy group as the center of reaction. The enantiomerically pure precursors thus obtained were functionalized by introducing into a molecule enantiomerically pure acyclic amines and aziridines to give tridentate ligands which were used as chiral catalysts in an asymmetric synthesis.

Sulfinyl derivatives containing the hydroxy group and stereogenic centers located on the sulfinyl sulfur atom and on the carbon atom in the chiral amine substituent were successfully used in the asymmetric Mannich reaction and in the Simmons-Smith reaction. In the asymmetric Mannich reaction the highest chemical yield (97%), enantiomeric excess (97%) and diastereomeric excess (20:1) of the products were obtained when the ligand bearing (+)-(*R*)-1-(1'-naphthyl)ethylamine moiety was used. In turn, in the asymmetric Simmons-Smith cyclopropanation of allylic alcohols the most effective was the ligand containing (-)-(*S*)-2-isopropylaziridine group (product yields up to 95%, ee up to 94%).

These ligands were used also in the asymmetric allylation of aromatic aldehydes and the asymmetric addition of diethylzinc to α-nitroalkenes. Unfortunately, in these cases they were not effective as catalysts. The products were obtained in moderate chemical yields and with very low enantiomeric excesses or were even racemic.

In order to check the influence of each functional group (the sulfinyl group, the hydroxy group and the amine moiety) in the ligands on the enantioselectivity of the catalyzed reactions, a series of derivatives were obtained, in which the functional groups were replaced and/or protected. As a model reaction, the nitroaldol Henry reaction was selected. It was found that the absolute configuration of the stereogenic center located in the amine moiety exerted the decisive influence on the stereochemical outcome of the reaction. When the hydroxy group in the ligand was acetylated, an acetylated analogue of lower catalytic activity was obtained. Replacement of the hydroxy group by a second enantiomeric amine moiety led to the

products with higher enantiomeric excess. However, removal of the sulfinyl group (by its reduction to the sulfide or oxygenation to the sulfone) caused a significant decrease of the catalytic activity of all derivatives. This may be taken as proof that all the three functional groups in the ligands have a significant impact on their catalytic activity and the stereochemistry of the resulting product and, consequently, that the ligands are tridentate.

It was attempted to synthesize the corresponding ligands in which the sulphur atom has been replaced by phosphorus atom. As a result of a series of trials, appropriate procedures were developed for highly stereoselective enzyme-promoted kinetic resolution of racemic 2-hydroxymethylphenyl(methyl)phenylphosphine oxide. This allowed to obtain both enantiomerically pure forms of the substrate, which were planned as precursors of bidentate ligands. The enantiomers were fully characterized and their absolute configurations were determined by X-ray analysis. The appropriate conditions to achieve a highly stereoselective enzyme-promoted desymmetrization of the prochiral bis(2-hydroxymethylphenyl)methylphosphine oxide were also developed, which resulted in the preparation of enantiomerically pure (2-acetoxymethylphenyl)-(2'-hydroxymethylphenyl)methylphosphine oxide, the precursor of the planned tridentate ligands. It was fully characterized and its absolute configuration was determined by a chemical correlation and X-ray analysis.

It should be stressed that the use of enzymes gave the opportunity to obtain in one step the desired precursors (both sulphinyl and phosphoryl) in high chemical yield and almost enantiomerically pure. Such a result would not be possible to achieve by chemical methods. It is worth emphasizing that in all the cases described above, a very high stereoselectivity of the enzymatic reaction was observed for the substrates, in which the distance between heteroatom stereogenic or prostereogenic centers and the center of the chemical reaction (OH group) is equal to four bonds.

As in the case of the sulfinyl ligands, the enantiomerically pure phosphoryl precursors were functionalized by introducing into the molecule enantiomerically pure acyclic amines and aziridines giving bidentate and tridentate ligands. The ligands were checked for their catalytic activity in the nitroaldol (Henry) reaction and asymmetric addition of diethylzinc to benzaldehyde. Unfortunately, it turned out that these ligands were not effective catalysts for the reactions. The products were obtained in moderate chemical yields and their enantiomeric excesses did not exceed 16%.

During the synthesis of these ligands significant difficulties were encountered due to a partial racemization of the precursors at the stage of mesylation reaction, which preceded introduction of a chiral amine moiety. The proposed mechanism of racemization assumed the existence of an equilibrium between the hydroxymethylphosphine oxide and the cyclic form containing pentacoordinated phosphorus atom. However, attempts to prove the existence of such a cyclic hypervalent phosphorus compound failed.