

## Some Examples of Non-catalytic, Catalytic and Biocatalytic Preparations of Chiral Molecules

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Practical solutions for the preparation of enantiomerically pure compounds (EPC) by enantioselective synthesis have now been found for most important organic reactions, and for a number of economically important classes of organic compounds. This author-review, therefore, covers only representative examples of those methods to which the author's group made some contribution.

*Non-catalytic* preparation of chiral molecules can be achieved either by separation of racemic mixtures, or by enantioselective synthesis using stoichiometric quantities of a chiral auxiliary agent. Examples of various separations of racemic 1,4-benzodiazepines will be given. Non-catalytic enantioselective preparation of specific  $\alpha$ -amino acids and some therapeutically important compounds, will exemplify the use of chiral auxiliaries, derived from the »chiral pool« of Nature.

*Biocatalytic* transformations of chiral molecules that are not natural substrates of the enzymes, represent a rapidly growing field of application of enzymes and microorganisms in organic synthesis. Recently, we successfully used microbial lipases for enantioselective hydrolysis of some precursors of C<sub>3</sub> and C<sub>4</sub> chiral synthons, for kinetic resolution of *rac* 3-(2-nitrophenoxy) butanoates, precursors for 1,5-benzoxazepin-4(5H)-ones with ACH inhibitory activity, and also in chemoenzymatic synthesis of *S*-fenpropimorph, the biologically active enantiomer of a commercially important fungicide. Complete stereoselectivity in the hydrolysis and acylation of resorcylic acid macrocyclic lactones, intermediates in the production of  $\alpha$ -zeaxanol, a commercially important growth-promoting agent, catalyzed by microbial lipases, prompted us to propose a new »helical model« for interaction of substrates with the *Pseudomonas sp.* lipase active site.

*Catalytic* transformation of prochiral substrates into enantiomerically pure products is the most economical chiral method. It is based on the ap-

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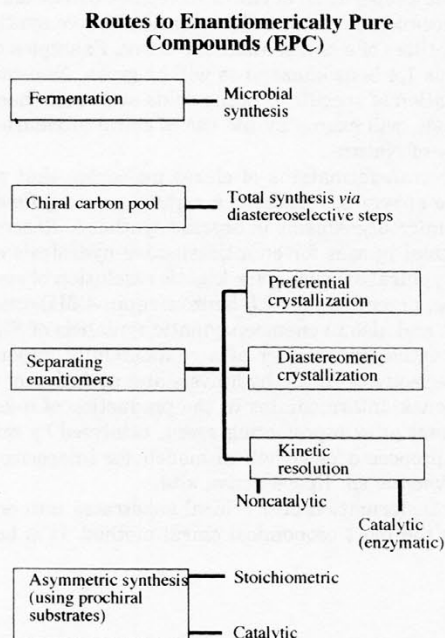
plication of organometallic complexes with chiral ligands as catalysts. Success of the enantioselective catalyst depends on the nature of the metal, and the structure and electronic properties of the chiral ligand. Examples will be given of the preparation of Rh(I) complexes with chiral monophosphine derived from camphor, and chiral diphosphites and diphosphines, bidentate ligands derived from the most widespread monosaccharides, and their efficacy in enantioselective hydrogenation. Synthesis, structural and chiroptical investigations, and catalytic activity of some recently prepared Rh(I) and Cu(I) complexes of chiral bidentate nitrogen ligands will be reported, as well.

## INTRODUCTION

The main reasons for producing optically pure materials include: *a*) biological activity is often associated with only one enantiomer, *b*) enantiomers may exhibit different types of activity, one may be beneficial and the other undesirable, *c*) an unwanted enantiomer enhances production costs if recycled, otherwise it represents economical ballast, *d*) the unwanted enantiomer also represents »ecological ballast«. Therefore, all conceivable methods for the preparation of optically pure chiral compounds are nowadays intensively studied both on the laboratory and industrial scale.<sup>1-5</sup>

The general scheme of practical methods for the preparation of enantiomerically pure compounds (EPC) is presented in Scheme I.

Strictly speaking, enantioselective syntheses are only those that start from prochiral substrates and transform them preferentially into one enantiomer. As indicated in Scheme I, they can be stoichiometric or catalytic. Syntheses from chiral carbon



Scheme 1. Routes to enantiomerically pure compounds

pool, known as asymmetric syntheses in the broader sense, are multistep processes that are in any single step diastereoselective, transforming chiral, optically pure, material into one diastereomer preferentially.

Nowadays, chirality emerges as the key issue in pharmaceutical and fine-chemicals industry. A monograph »Chirality in Industry« has recently appeared,<sup>3</sup> there are also increasing numbers of statements on the development of »chiral technology« for large-scale industrial processes.<sup>6-8</sup> Upcoming regulations in the USA and EC for the development and marketing of chiral drugs, which account for *ca* 30% of total drug production, are expected to effect research policies in many synthetic, biological and pharmacological industrial and non-industrial laboratories. There is a trend named »racemic switch«: single enantiomers are redeveloped from older chiral drugs, originally marketed as racemates.<sup>7,8</sup>

All these events prompted intensive laboratory research on the methods for production of chiral molecules in optically (enantiomerically) pure form. This review is by no means exhaustive, and it is mainly oriented to the examples of the principal methods of preparing chiral compounds in the enantiomerically pure form, where the author's group made some contribution. Fast progress of this field is recorded in recent monographs, review articles, specialist conferences, and even in new journals dedicated to asymmetry, chirality and stereoselection. Most recent monographs, reviews, and representative articles for any particular methodology are cited, expecting they will be a guide for the reader interested in a thorough overview of this particular topic.

#### NON-CATALYTIC METHODS FOR THE PREPARATION OF CHIRAL MOLECULES IN THE ENANTIOMERICALLY PURE FORM

These methods can be divided into two main groups:

1. *Separation of racemate by crystallization or chromatography*
2. *Preparation of enantiomerically pure compounds using a stoichiometric quantity of the chiral auxiliary agent.*

Where as the former method makes use of racemic material, the latter starts from prochiral or chiral non-racemic material, usually found in the »chiral pool« of Nature, Scheme 1.

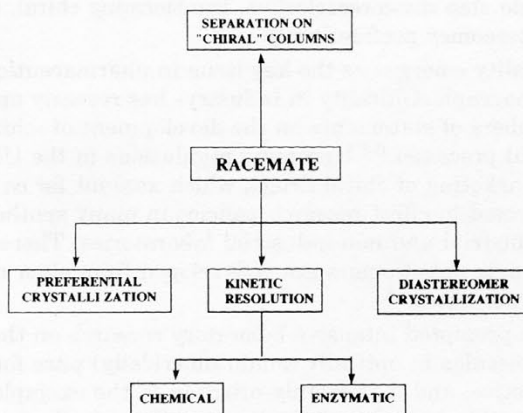
The resolution of racemates still constitutes a valuable method for industrial synthesis of pure enantiomers; it can be divided into four types, Scheme 2.

- 1.1. *direct preferential crystallization*
- 1.2. *crystallization of diastereomeric salts*
- 1.3. *chromatographic separation*
- 1.4. *kinetic resolution*

#### *Separation of Racemate by Crystallization or Chromatography*

*Direct preferential crystallization.* – Racemates can be divided into conglomerates and true racemic compounds on the basis on their solid state properties. Direct preferential crystallization of an enantiomer, also referred to a resolution by entrainment, is possible only with conglomerates and depends on the difference in the rate of crystallization of the two enantiomers.

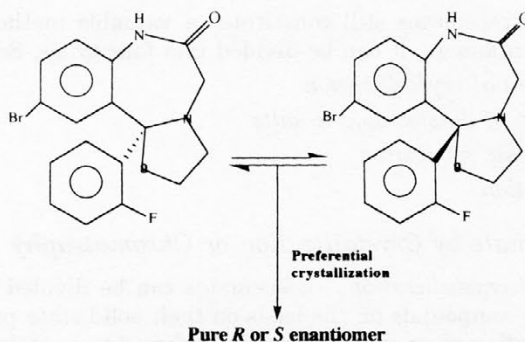
## Methods for Resolution of Racemates



Scheme 2. Methods for resolution of racemates

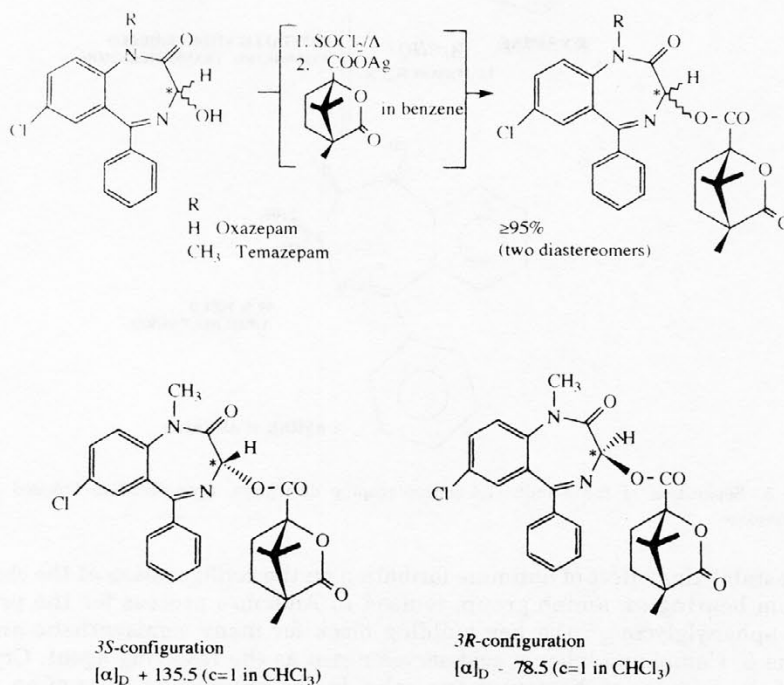
Promoted racemization during crystallization, based on the low optical stability of the chiral center of chiral compounds within racemic mixture, makes this method particularly attractive. This property, although not generally recognized, makes resolution by preferential crystallization still widely used on industrial scale. Preferential crystallization accompanied by spontaneous *in situ* racemization allows for as theoretical 100% yield of one enantiomer. This process is also referred to as crystallization-induced asymmetric transformation. Okada *et al.*<sup>9,10</sup> have reported separation of *R*- and *S*-enantiomers of 1,4-benzodiazepino-oxazole derivative, a compound with CNS activity, by preferential crystallization of racemate accompanied by spontaneous *in situ* racemization, resulting in an over 90% yield of one enantiomer, Scheme 3.

During our early study of stereochemical and chiroptical properties of 1,4-benzodiazepines, we observed optical instability of 3-hydroxy-1,4-benzodiazepines. Indirect separation of their enantiomers<sup>11</sup> was performed by acylation with silver salt



Scheme 3. Resolution of 1,4-benzodiazepino-oxazol by preferential crystallization

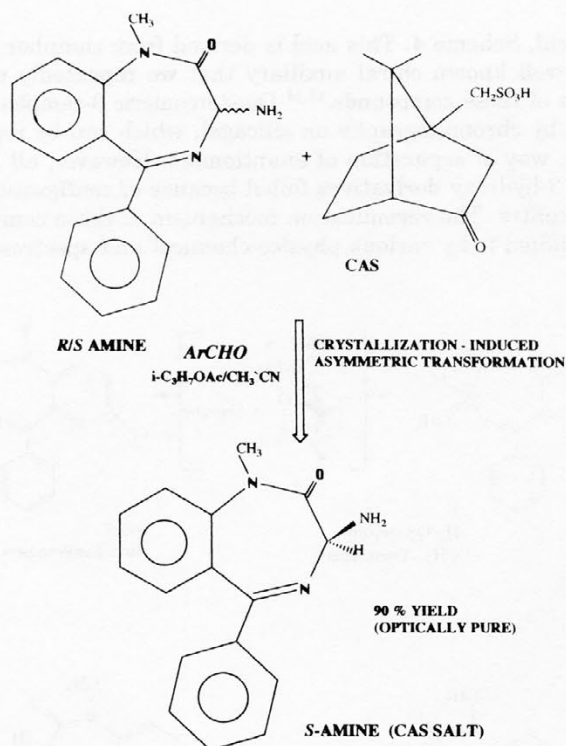
of camphanic acid, Scheme 4. This acid is derived from camphor in a few steps and represents the well known chiral auxiliary that we repeatedly used in our stereochemical studies of these compounds.<sup>12-14</sup> Diastereomeric 3-camphanoyloxy derivatives were separated by chromatography on silicagel, which can be regarded as another, though indirect, way of separation of enantiomers. However, all attempts to obtain optically active 3-hydroxy derivatives failed because of configurational instability of the C(3) chiral centre. The racemization mechanism of these compounds is peculiar, and we have studied it by various physico-chemical and spectroscopic methods.<sup>15</sup>



Scheme 4. Camphanic acid derivatives of 3-hydroxy-1,4-benzodiazepines

Recently described procedure for separation of 3-amino-1,4-benzodiazepines makes use of configurational instability of the C(3) chiral centre.<sup>16</sup> It is related to our study of optical instability of 3-hydroxy-1,4-benzodiazepin-2-ones,<sup>15,17-19</sup> Scheme 5.

Crystallization of diastereomeric salts of the racemic C(3) amino derivative with camphor sulphonic acid in the presence of trace of an aldehyde as the epimerization catalyst afforded *S*-1,4-benzodiazepine camphorsulphonate in 90% yield. Racemization is promoted by transitory formation of benzaldimine, *i.e.* by the appearance of the third double bond flanking the C(3) chiral centre. We made use of a similar acidity enhancement of C(3)-H in stereoselective C(3) alkylation of some chiral 1,4-benzodiazepines (Chapter 1.2.)

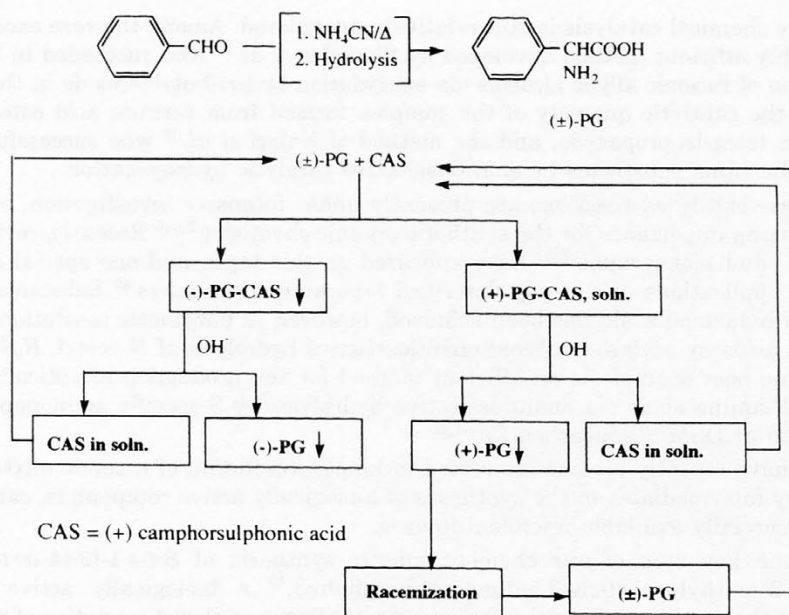


Scheme 5. Separation of *R,S*-3-amino-1,4-benzodiazepine derivative, crystallization induced asymmetric transformation

Destabilizing effect of aldimine formation on the configuration at the chiral carbon atom bearing an amino group, is used in Andeno's process for the production of D-(-)-phenylglycine,<sup>20</sup> the key building block for many semisynthetic antibiotics, Scheme 6. Camphorsulphonic acid serves again as the resolving agent. Crystallization of the mixture of diastereomeric salts, in the presence of trace of an aldehyde as racemization catalyst, afforded D-(-) aminoacid salt in 90% yield in a single crystallization. Transitory formation of an aldimine makes the chiral centre of  $\alpha$ -amino acid configurationally unstable.

*Crystallization of diastereomeric salts.* – Four out of five racemates are true racemic compounds, *i.e.* a homogeneous solid phase of the two enantiomers co-existing in the same unit cell. Such compounds may be separated by diastereomeric crystallization, which generally involves reaction of the racemate with an optically pure acid or base as resolving agent to give a mixture of two diastereomeric salts whose physical properties are different. We used diastereomeric crystallization for separation of racemic 3-methoxy-1,4-benzodiazepines.<sup>17</sup>

Separation of enantiomers of the commercially important product fenpropimorph (see Scheme 8 for the formula) *via* crystallization of camphorsulphonic or tartaric acid salts, is another example of the use of this classical method.<sup>21</sup> The obvious drawback of this method, particularly for the production of optically stable products, is the waste of half of the material as a »wrong« enantiomer.



Scheme 6. Production of D-phenylglycine by DSM/Andeno process

*Chromatographic separation.* – Separation of racemates by chromatography on a chiral support is nowadays the most widely used analytical method for determination of the optical purity of enantiomerically enriched compounds, *i.e.* for determination of enantiomeric excess, (e.e.%). As yet, it has not found any large-scale application, mainly because of the extremely high price of chiral packing in such columns. Following the GLC methods for enantiomer separation,<sup>22</sup> HPLC is entering the field with a growing number of chiral supports.<sup>23-25</sup> In this context, it is interesting to mention that biopolymers, polysaccharides (cyclodextrins) and proteins are among the most frequently used chiral supports in both types of chromatography. Hundreds of papers on enantioselective syntheses and kinetic resolutions published in the last decade cite direct chromatographic determination of enantiomeric excess on the columns with chiral stationary phases, either by the GLC or HPLC methods.

In the late 1970's, we studied the binding of various types of chiral 1,4-benzodiazepines on human serum albumine (HSA).<sup>26-28</sup> Quite different binding constants for two enantiomers were obtained. This work was a contribution to the development of chromatographic techniques for analytical separation of this class of pharmacologically important compounds.<sup>29-31</sup>

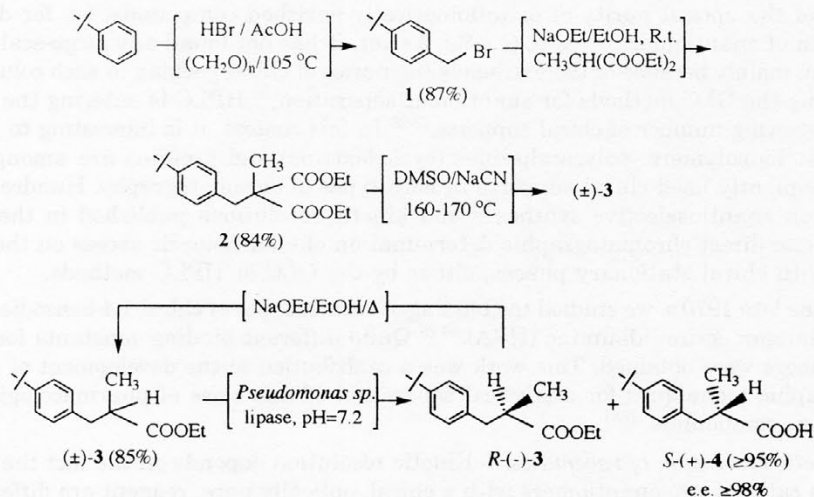
*Kinetic resolution of racemates.* – Kinetic resolution depends on the fact that the reaction rates of two enantiomers with a chiral, optically pure, reagent are different. This chiral reagent can either be a small organic molecule or biomacromolecule, usually enzyme. Preferably, the chiral agent should function in catalytic quantities, as the enzymes do. Stoichiometric quantities of the chiral agent are usually required when resolution is performed with small organic molecules. The area of kinetic reso-

lution by chemical catalysis is still relatively unexplored. Among the rare exceptions is a highly efficient method developed by Sharples *et al.*<sup>32</sup> who succeeded in kinetic resolution of racemic allylic alcohols *via* epoxydation by *tert*-butylperoxide in the presence of the catalytic quantity of the complex formed from tartaric acid esters and titanium tetra-isopropoxyde, and the method of Nojori *et al.*<sup>33</sup> who successfully resolved the same substrates by enantioselective catalytic hydrogenation.

Lipase catalyzed reactions are presently under intensive investigation, and are of increasing importance for the synthetic organic chemistry.<sup>34,35</sup> Recently, review articles<sup>36,37</sup> and monographs<sup>38,39</sup> have appeared on this topic, and one special edition enables applications of a newly described laboratory procedures.<sup>40</sup> Substantial progress on industrial scale has been achieved, however, in enzymatic resolution of *rac*  $\alpha$ -amino acids by acylase-catalyzed enantioselective hydrolysis of *N*-acetyl, *R,S*-amino acids. The best example is an efficient method for the production of optically pure *S*- and *R*-amino acids *via* enantioselective hydrolysis by *S*-specific aminopeptidase, developed at DSM/Stamicarbon Co.<sup>41,42</sup>

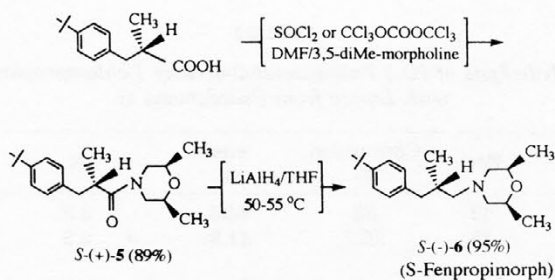
We have recently become interested in kinetic resolution of racemic mixtures of some key intermediates in the syntheses of biologically active compounds, catalyzed by commercially available microbial lipases.

In the key step of our chemoenzymatic synthesis of *S*-(-)-1-[3-(4-*tert*-butylphenyl)-2-methylpropyl-cis-3,5-dimethylmorpholine],<sup>43</sup> a biologically active enantiomer of the systematic fungicide fenpropimorph, lipase catalyzed resolution of racemic 3-*tert*-butylphenyl-2-methylpropionic acid ethylester was accomplished with over 98% enantioselectivity. Base-catalyzed racemization and recycling of the *R*-ester gives to this approach the appearance of a cost-effective method, which can extend the production range of single enantiomer agrochemicals, Schemes 7 and 8.



Scheme 7. Chemoenzymatic synthesis of *S*-(-)-fenpropimorph I

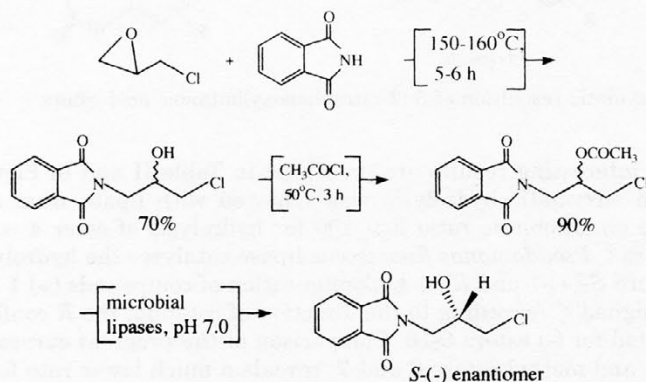


Scheme 8. Chemoenzymatic synthesis of *S*-(-)-fenpropimorph II

Regarding this synthesis, it is interesting to note that already in 1980 Himmele and Pommer<sup>44</sup> reported a much higher fungicidal activity of the *S*-(-) enantiomer as compared to the *R*-(+) enantiomer, and its absolute configuration was determined by X-ray structure analysis. In spite of this fact, the racemic mixture is still commercialized, demonstrating how difficult the »racemic switch« is for the companies that have racemic products well established on the market.

Separation of the enantiomers, intermediates in a multi-step synthesis of the optically active target molecule, should be performed at an early stage, in order to avoid unnecessary manipulation of a wrong enantiomer. Having this in mind, we studied<sup>45</sup> the separation of *rac*-3-phthalimido-2-acetoxy-1-chloropropane. Enantiomerically pure alcohol is a valuable chiral  $C_3$  synthon for the preparation of  $\beta$ -adrenergic blocking agents. After one-carbon chain elongation, *e.g.* by substitution of chlorine by cyano group, it becomes chiral  $C_4$  synthon, precursor of *R*-(+)- $\gamma$ -amino- $\beta$ -hydroxybutyric acid (GABOB), and carnitine (vitamine  $B_{12}$ ). Racemic intermediate is available in two steps from the commodity product *rac* 1-chloro-epoxypropane, Scheme 9.

A series of Amano lipases was screened,<sup>45</sup> and best results were obtained with *Pseudomonas sp.* lipase, Table I.

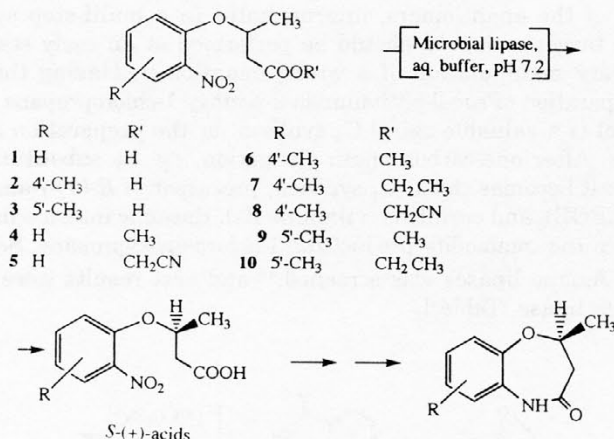


Scheme 9. Enzymatic resolution of 3-phthalimido-2-acetoxy-1-propane

TABLE I  
Hydrolysis of ( $\pm$ )-3-Phthalimido-2-acetoxy 1-chloropropane  
with Lipase from *Pseudomonas* sp.

S:E / mg	t/h	T/°C	Conversion %	e.e. %	E	Organic solvent added to buffer
100:100	44	42	32	<b>44.3</b>	3.2	
100:10	48	45	26.2	<b>41.3</b>	2.8	10% od dioxane
100:150	28	42	51	<b>99.0</b>	>1000	10% od ethanol
100:100		42	40	<b>92.5</b>	48.3	
100:33	48	45	26	<b>94.4</b>	48.0	10% of acetone
100:10		45	9.8	<b>96.0</b>	70.5	

We developed<sup>46</sup> a similar approach for resolution of some 3-(2-nitrophenoxy) butanoic acid esters (**1-10**), chiral precursors of 2,3-dihydro-1,5-benzoxazepin-4(5H)-ones, with ACE inhibitory activity, Scheme 10.



Scheme 10. Enzymatic resolution of 3-(2-nitrophenoxy)butanoic acid esters

The most interesting results are presented in Table II and in Figure 1. Highly enantioselective enzymatic hydrolysis was achieved with lipase from *Pseudomonas fluorescens*, the enantiomeric ratio E > 100 for hydrolysis of ester **4** was calculated according to Sih.<sup>47</sup> *Pseudomonas fluorescens* lipase catalyzes the hydrolysis of S-form of *rac*-**4** to afford S-(+)-**1** and R(-)-**4**. Configuration of compounds (+) **1** and (-) **4** was previously assigned.<sup>48</sup> According to the direction of rotation, the R configuration can also be predicted for (-) esters **6-10**. Comparison of the progress curves for ethyl esters **9** and **10**, and methyl esters **6** and **7**, reveals a much lower rate for esters with methyl substituent in the 4'-position of the aromatic ring; 5'-methyl substituted ester **9** was hydrolyzed at the highest rate,, Figure 1. Optically purity of the faster hydrolyzed esters **9** and **10** was 85% and  $\geq 99\%$ , respectively, Table II.

TABLE II  
*Enantioselective Hydrolysis of 3-Nitrophenoxy-butanoic acid Esters*

Substrate	Lipase	Reaction time / h	Yield ester	Yield acid	e.e. ester %
10	<i>P. fluorescens</i>	19	48	41	>99
10	<i>P. Sp.</i>	19	47	31	>99
7	<i>P. fluorescens</i>	46 <sup>c</sup>	48	38	>99
7	<i>P. sp.</i>	28,5	42	37	88
4	<i>P. fluorescens</i>	26,5	46	34	88
4	<i>P. fluorescens</i>	6,5	52	23	90
6	<i>P. fluorescens</i>	26	37	60	72
6	<i>P. fluorescens</i>	24	53	22	69
8	<i>P. fluorescens</i>	2	56	42	76
9	<i>P. fluorescens</i>	5,5	54	26	85

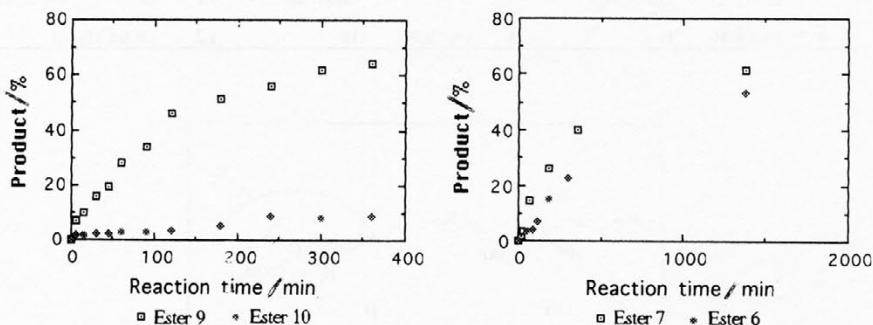


Figure 1. Progress curves for kinetic resolution of 3-nitrophenoxy butanoic acid esters.

These results reveal an unexpected effect of the remote methyl group on the kinetic resolution of *rac* carboxylic acid esters. This can be explained by conformational perturbations of the remote methyl group on the side chain bound on the active site.

However, it is difficult to confirm such a hypothesis experimentally. We were fortunate to join at the same time a project that contributed substantially to this concept of the control of stereoselectivity in lipase catalyzed reactions by *absolute conformation* of the substrate. Lipase catalyzed kinetic separation of diastereomers proved highly effective in the case of macrocyclic lactone derivatives.  $7\alpha,\beta$ -O-acyl *trans*-zearelanols (**3,4**) and  $7\alpha,\beta$ -O-acyl zearanol (**11,12**).<sup>49,50</sup> Stereochemically pure  $7\alpha$ -alcohol (zearanol, **9**) is a well known growth promoting factor.<sup>51</sup> It is interesting to note that the chiral centre C(7) in compounds **1-12** is flanked by two chains of at least three methylenic groups, which separate the chiral centre from the remote perturbing groups. This situation resembles that in the open-chain *sec* acetates (**I**), where the least satisfactory resolution by lipases is obtained.<sup>52,53</sup> These compounds possess two conformationally flexible alkyl groups with similar sterical requirements. This situation could drastically change in cyclic carbinols, however, since rotation of the two side chains around the chiral center is restricted by their connection into macrocyclic structure (**II**). High stereoselectivity in lipase catalyzed hydrolysis<sup>54,55</sup> and esterification<sup>55,56</sup> of the substrates with small rings, substituted near the chiral center, suggests such possibility.



TABLE IV  
 Stereoselective acylation of zearalenon derivatives **1**, **2**, **6**, and **9**, **10**

Substrate	Solvent	log <i>P</i>	<i>t</i> /h	Conversion (%)	<i>v</i> <sub>o</sub> /nM s <sup>-1</sup>	Product configuration	d.e. (%)
<b>1,2</b>	n-heptane	4.0	30	42.9	144.9	3 <i>S</i> ,7 <i>S</i> (7β)	100
	n-hexane	3.5	30	25.7	41.6		
	cyclohexane	3.2	48	21.4	18.5		
	diisopropyl ether	2.8	30	37.0	70.1		
	dichlormethan	1.25	48	10.3	8.08		
	tetrahydrofuran	0.49	48	6.7	6.08		
	aceto	-0.23	30	6.4	7.54		
	acetonitrile	-0.33	30	11.5	24.3		
1,4-dioxane	-1.1	48	0	0			
<b>6</b>	n-heptane	4.0	30	97.2 <sup>1</sup>	821.8	3 <i>S</i> ,7 <i>S</i> (7β)	
	acetonitrile	-0.33	30	32.0 <sup>a</sup>	71.49		
<b>9,10</b>	n-heptane	4.0	28	21.0	88.2	3 <i>S</i> ,7 <i>S</i> (7β)	100
	diisopropyl ether	2.8	24	49.9	283.0		86.1
	chloroform	2.0	30	0	0		—
	acetone	-0.23	29	32.1	65.4		100
	acetonitrile	-0.33	30	45.9	102.0		90.6
	1,4-dioxane	-1.1	29	9.52	6.7		100

<sup>a</sup>Transesterification of the mixtures of *cis/trans*-7α-(75% of *cis*-7α, **5** and 25% of *trans*-7α, **1**) and *cis/trans*-7β-zearalenols (75% of *cis*-7β, **6** and 25% of *trans*-7β, **2**) have shown complete inertness of 7α-diastereomers.

First, it was observed that lipases from *Pseudomonas sp.* and *Pseudomonas fluorescens* selectively hydrolyze 7β-diastereomers **4** and **12**, with known 3*S*,7*S* absolute configuration.<sup>57,58</sup> The unsaturated substrate **4** was hydrolyzed faster than **12**, with complete diastereoselectivity, Table III. Lipase from *Candida cylindracea* was less active with diastereomeric mixture **3,4**, whereas lipases from *Aspegillus niger* and *Rhizopus oryza* exhibited a very low activity, but retaining complete β-diastereoselectivity. Lipases from *Pseudomonas sp.* and *Pseudomonas fluorescens* slowly deacylate a mixture of saturated congeners **11,12** with *ca.* 80% diastereoselectivity.

TABLE V  
 Kinetic Parameters for transesterification of *trans*-7β-Zearalenol (**2**), *cis*-7β-Zearalenol (**6**) and 7β-Zearanol (**10**) in *n*-Heptane and Acetonitrile

Substrate	Solvent	<i>K</i> <sub>N</sub> /mM	<i>V</i> <sub>max</sub> /μM s <sup>-1</sup>	<i>V</i> <sub>max</sub> / <i>K</i> <sub>M</sub> /ms <sup>-1</sup>
<b>2</b>	<i>n</i> -heptane	3.1	0.57	0.184
	acetonitrile	12.5	0.12	0.001
<b>6</b>	<i>n</i> -heptane	15.5	2.23	0.144
	acetonitrile	10.4	0.12	0.012
<b>10</b>	<i>n</i> -heptane	7.6	0.98	0.129
	acetonitrile	46.5	0.85	0.018

The same high stereoselectivity was then achieved for a reverse reaction, acylation of  $7\alpha,\beta$ -alcohols with vinylacetate in organic solvents.<sup>59,60</sup> Table IV and V show the dependence of enzyme reactivity on the polarity of the solvent, but nearly constant stereoselectivity in the broad range of the solvents.

To account for the selective hydrolysis of  $7\beta$ -O-acyl derivatives **4** and **12**, and acylation of alcohols **2** and **10**, we should first recall two simple models, recently proposed for predicting which substrate will be effectively resolved by lipases,<sup>56,81</sup> Figure 2a,b. Both are nearly two-dimensional, and do not take into account the conformational characteristics of the substrate. The latter parameter, however, seems to be of decisive importance in explaining the lipase stereoselectivity with macrocyclic O-acyl derivatives.

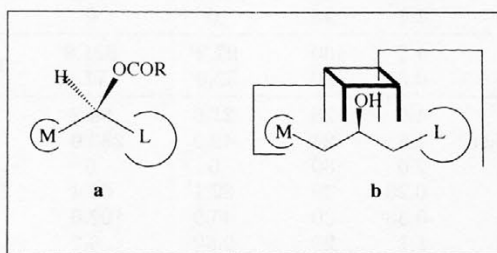


Figure 2. An extension of Prelog's rule to hydrolases, more reactive enantiomer presented (according to Ref. 61), b. representation of the enzyme active site with canopy for recognition of the hydroxyl functionality of the substrate (according to Ref. 56).

Conformational properties of most representatives of the 14-membered macrocyclic lactones **1-12** are known; solution conformation of the series of  $7\alpha$ - and  $7\beta$  diastereomers and the parent ketones has been studied by NMR and CD. These studies reveal substantially different solution conformations for  $7\alpha$ -derivatives **1, 5, 9**, and **11**, as compared to  $7\beta$ -isomers **2, 6, 10** and **12**.<sup>58,62</sup> As X-ray data for two  $7\alpha$ -O-acetyl derivatives, **1** and **5**, and the series of  $7\beta$ -congeners reveal, there is a helical arrangement of the two trimethylene side chains on the hydroxymethine chiral center C(7), Figure 3.

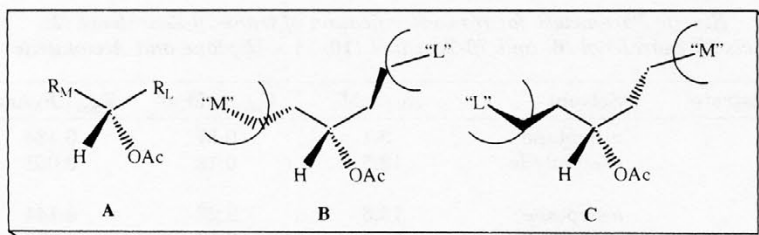


Figure 3. Helical arrangement of trimethylene chain, the right-sided, bulky, L chain effects the approach of nucleophile<sup>49,60</sup>.

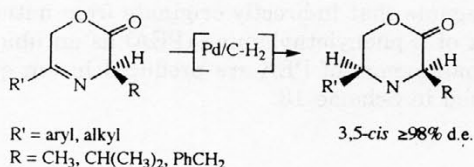
The right hand side of this chain is protracted outside the vertical plane which bisects C(6) and C(8) and, therefore, strongly perturbs the nucleophile on its approach to the acyloxy group on C(7), whereas the left-hand chain is placed on the near side of the same plane and leaves open space to the nucleophilic group that approaches the active site of the enzyme. One can see that sterical requirements in  $7\alpha$ -diastereomer correspond to those in the non-reactive open chain substrates outlined in Figure 3, whereas  $7\beta$ -diastereomers possess »matching« absolute conformation.

### Preparation of Enantiomerically Pure Compounds Using Stoichiometric Quantities of a Chiral Auxiliary Agent

This method is also known as asymmetric induction, or utilization of chiral pool materials, or »second generation asymmetric synthesis«.<sup>63</sup> The chiral pool customarily refers to relatively inexpensive, readily available optically active, enantiomerically pure natural products. This section is concerned with some examples of the use of »chiral pool« substances as building blocks. They are usually incorporated into the target structure, after necessary transformations in order to achieve the desired chiral features. However, they are often split off the target molecule and recycled.

Amino acids and sugars are among the most explored chiral pool materials in this context. The recent monograph of Coppola and Schuster<sup>64</sup> and the review of Reetz<sup>65</sup> cover the important topic of the construction of chiral molecules using amino acids, the monograph of Hanessian<sup>66</sup> reviews the application of monosaccharides in asymmetric syntheses, while Tse-Lok Ho collected enantioselective syntheses of natural products from terpenes.<sup>67</sup>

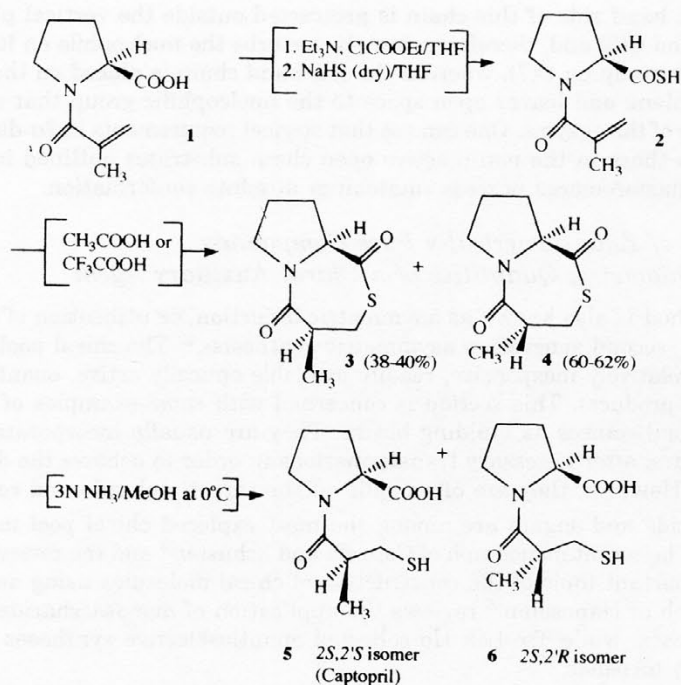
Herewith I would like to give some examples of our own work. Effective cyclic induction was realized in our study on asymmetric hydrogenation of endocyclic azomethine bond.<sup>68</sup> A number of 2,3-dihydro-6*H*-1,4-oxazino-2-ones, chiral at the C(3) atom, have been prepared from various  $\alpha$ -amino acids and hydrogenated to 4,5-dihydro analogues, Scheme 11. Over 98% stereoselectivity was regularly achieved, and relative 2,5-*cis* configuration in the product was confirmed by X-ray structure analysis.<sup>69</sup>



Scheme 11. Asymmetric induction in hydrogenation of 2,3-dihydro-6*H*-1,4-oxazino-2-ones

Another type of asymmetric induction has been investigated in relation to the original stereoselective synthesis of captopril,<sup>70</sup> a well known antihypertensive agent.<sup>71</sup> Earlier methods regularly required separations of diastereomeric intermediates by crystallization; our approach is outlined in Scheme 12.

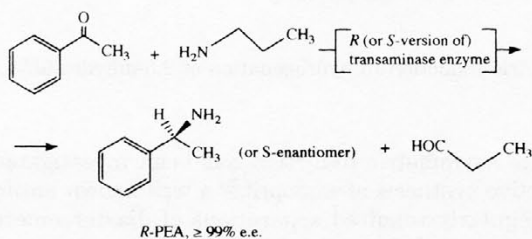
Starting from *N*-methacryloyl-*L*-proline **1**, acyclic thioacid **2** was prepared. It afforded, in the cyclization step, the »wrong diastereomer« (**4**) in 20 – 25% diastereomeric



Scheme 12. Stereoselective synthesis of captopril

excess. On the basis of  $^1\text{H}$ -,  $^{13}\text{C}$ -NMR, and CD data, we explained the relatively low asymmetric induction in the cyclization step by a nearly equal population of *E/Z* conformers around the amide bond in the acyclic precursor **2**.

The use of chiral agents that indirectly originate from nature can be best illustrated by development of  $\alpha$ -phenylethylamine (PEA) as an ubiquitous chiral auxiliary. Optically pure enantiomers of PEA are produced in ton quantities by the industrial method outlined in Scheme 13.



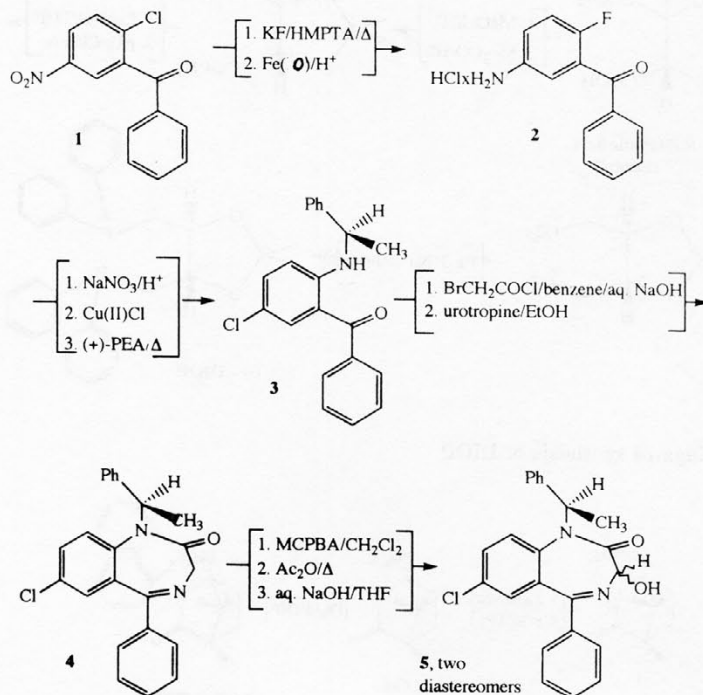
Scheme 13. Production of optically pure (+) and (-) PEA



Synthesis of either enantiomer of PEA begins from acetophenone as substrate, a large excess of a low-cost amine donor such as propylamine, and either the *R*- or *S*-version of transaminase enzyme.<sup>8</sup> The transaminase mediates conversion of the reactants to propionaldehyde and an almost 100% yield of *R*- or *S*- $\alpha$ -phenylethylamine in over a 99% enantiomeric excess. This technology was developed by USA high-tech company Celgene at Warren, N.J.<sup>8</sup> It is worth mentioning that an older method, resolution of *rac* PEA with tartaric acid,<sup>72,73</sup> makes use of another chiral auxiliary from nature to obtain the target chiral auxiliary agent.

We used (+)-PEA as chiral auxiliary in preparation of 1,4-benzodiazepines as templates for stereoselective synthesis of  $\alpha$ -aminoacids. First, the nitrogen atom of (+)-PEA was incorporated into the conformationally rigid 7-membered ring in **4**, as outlined in Scheme 14. This compound was transformed into 3-hydroxy derivatives **5**, needed for the study of kinetics and mechanism of configurational inversion at C(3).<sup>13,15</sup>

During this study, we noticed the high conformational stability and defined the absolute conformation of the 7-membered ring in the intermediary compound **4**. This indicated that, according to the known mechanism of alkylation of carbanions,<sup>74-76</sup> coordination of Li cation could favour a front-side attack of the alkylating agent on C(3), leading to products with *R*-absolute configuration. Among the products of stereoselective alkylation at prochiral center C(3), the most interesting was the 3-carbomethoxy derivative, precursor of 3-fluoromethyl derivative, the intermediate in our original



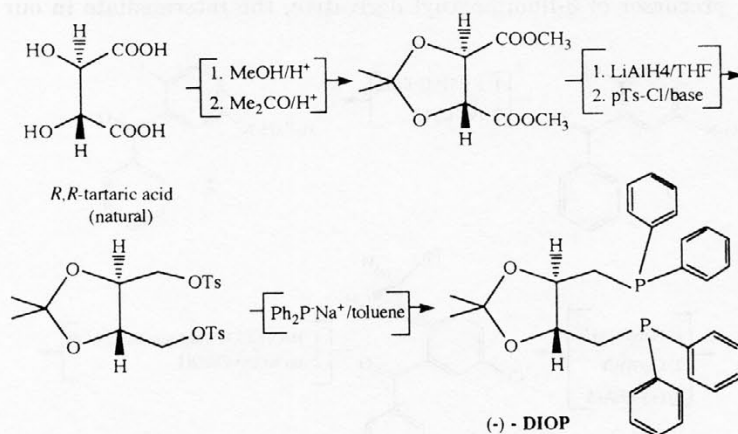
Scheme 14. Preparation of chiral 1,4-benzodiazepines with incorporated (+)-PEA

synthesis of *S*- $\alpha$ -deutero- $\beta$ -fluoroalanine.<sup>77</sup> This compound was obtained with 85% stereoselectivity, as a consequence of the »rearrangement of the second order«, *i.e.* of equilibration between two diastereomers *via* ester enolate.

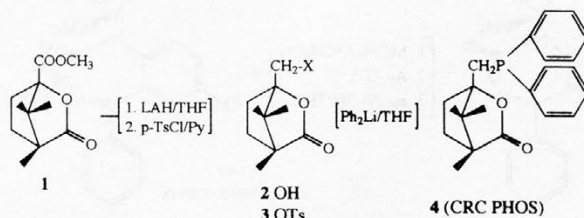
### CATALYTIC METHODS FOR THE PREPARATION OF OPTICALLY PURE COMPOUNDS

Many examples of this methodology are described in Morrison's monograph<sup>78</sup> and recent review articles.<sup>79,80</sup> Our original interest was oriented towards preparation of Rh(I) complexes with chiral P-bidentate ligands, while recently we turned attention to the preparation of various bisnitrogen ligands, as more advantageous from technological and ecological aspects. Versatility of their complexes in catalytic reactions was reviewed by Gladiali, Mestroni *et al.*<sup>81</sup>

Impressed already in 1972/73 by Kagan's results in asymmetric catalytic hydrogenation achieved with Rh(I) complex of (+)-DIOP as chiral bidentate ligand available from (+)-tartaric acid in a few synthetic steps,<sup>82,83</sup> Scheme 15, I had the opportunity in 1980 to complete the preparation of chiral phosphine ligand CRC-PHOS (4),<sup>84,85</sup> derived from camphor, *via* camphanic ester (1); the free acid is a well known chiral auxiliary agent,<sup>86,87</sup> Scheme 16.



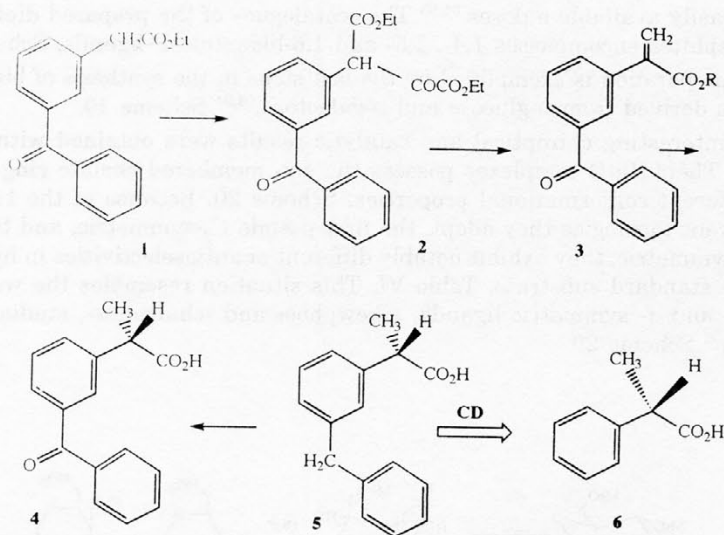
Scheme 15. Kagan's synthesis of DIOP



Scheme 16. Synthesis of CRC-PHOS

Although certain bidentate nature of **4** was expected on the basis of complexation to LIS NMR reagents, as determined by computer assisted »search for the metal«,<sup>85</sup> *i.e.* determination of the position of the lanthanide cation in the complex, its Rh(I) complex did not exhibit any remarkable enantioselectivity in hydrogenation of some standard substrate.

In the same period, we studied chiroptical and biological properties of *S*-(-)-ketoprofen,<sup>88-90</sup> where racemic form is a well known antiinflammatory agent. We first separated the enantiomers *via* their (+)-PEA amides, and studied some *in vitro* properties.<sup>88</sup> At the same time, we attempted enantioselective hydrogenation of the prochiral precursor (**3**) of ketoprofen, Scheme 17. Kagan's DIOP also exhibited, with this substrate, superior *e.e.*'s. as compared to CRC-PHOS. We also determined the *S*-absolute configuration of (-)-enantiomer by CD correlation of the non-conjugated chromophore in **5** with *S*-(-)-hydratropic acid (**6**).<sup>90</sup>



Scheme 17. Preparation of *S*-(-)-ketoprofen and CD correlation of absolute configuration

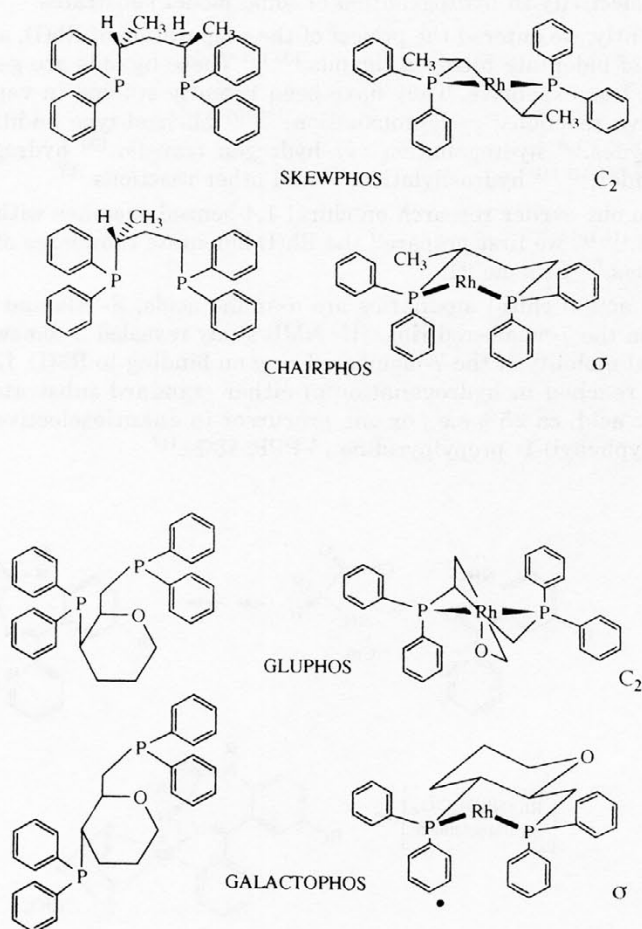
It is worth mentioning that in 1993, nearly 20 years after we separated and described the enantiomers of ketoprofen, *S*-(-)- enantiomer was introduced into the market in some EC countries. It is expected, however, that the »racemate switch« of ketoprofen will occur world-wide, and that optically pure *S*-ketoprofen will completely substitute the racemic form after 25 years of its marketing.

We superated unsatisfactory results in hydrogenation with CRC-PHOS by some bidentate ligands derived from the most widespread monosaccharides. This project envisaged preparation of the »catalogue« of chiral bidentate phosphites and phosphi-



Based on the subtle structural difference, »skewphos«, which possesses one methyl group more than »chairphos«, adopts a completely different conformation, as confirmed by an elegant CD study by the same authors.<sup>97</sup> The Rh(I) complex of the former reduced the standard substrate,  $\alpha$ -acetylaminocinnamic acid, to  $\alpha$ -N-acetyl phenylglycine with over 90% e.e., whereas the Rh(I) complex of the latter ligand exhibits  $\geq 10\%$  enantioselectivity, Table VI.

Monosaccharides were also used as the chiral pool for the preparation of bidentate phosphites by Selke and Pracejus.<sup>98,99</sup> Their approach consisted of the preparation of selectively O-protected monosaccharides, whereby the protecting groups determine the sites for the introduction of diphenylphosphine group and define the



Scheme 20. Chiral 1,3-diphosphines and structures of their Rh(I) complexes with local  $C_2$ - and  $\sigma$ -symmetry

TABLE VI

*Enantioselective Hydrogenation of Z- $\alpha$ -Acetamidocinnamic acid with Rh(I) Complexes of Skewphos, Chairphos, and Gluphos, Galactophos*

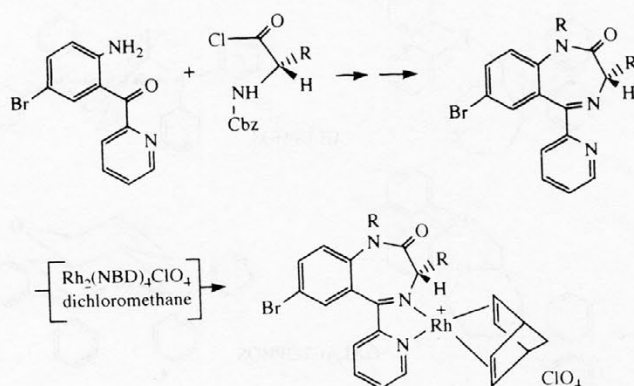
Ligand	Product	e.e. / %	Ref.
Skewphos	R-Ac-Phe	<b>94</b>	93
Chairphos	R-Ac-Phe	<b>7</b>	93
Gluphos	S-Ac-Phe	<b>73</b>	90
Galactophos	S-Ac-Phe	<b>17</b>	90

chiral topology of the ligand. The ligands designed by these authors exhibited up to 97% enantioselectivity in hydrogenation of some model substrates.

More recently, we entered the project of the preparation of Rh(I), and other metal complexes of bidentate nitrogen ligands.<sup>100-103</sup> These ligands are generally easily available and less expensive. They have been recently studied in various catalytic enantioselective reactions; cyclopropanation,<sup>104-106</sup> Michael-type addition,<sup>107</sup> alkylation of aldehydes,<sup>108</sup> hydrogenation *via* hydrogen transfer,<sup>109</sup> hydrogenation with complex hydrides,<sup>110,111</sup> hydrosilylation,<sup>112</sup> and other reactions.<sup>113</sup>

Related to our earlier research on chiral 1,4-benzodiazepines with incorporated  $\alpha$ -amino acids,<sup>114-116</sup> we first prepared the Rh(I) bidentate complexes of 5-pyrido-1,4-benzodiazepines,<sup>100</sup> Scheme 21.

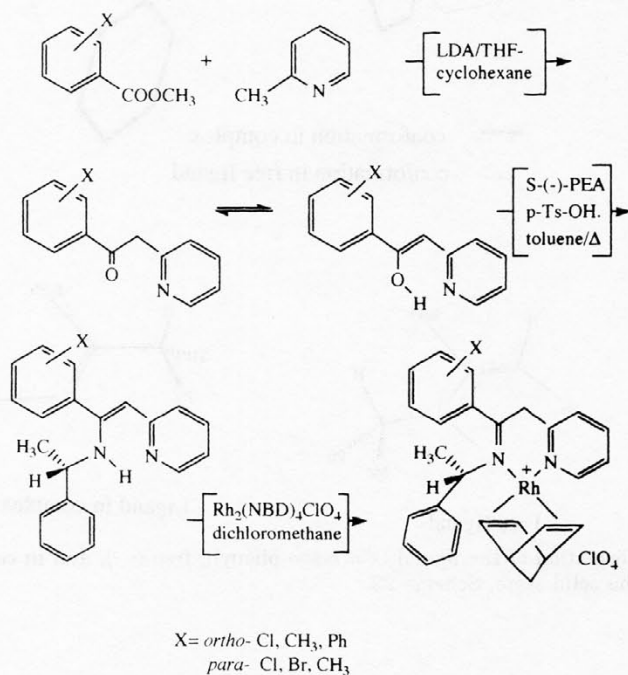
Here, the actual chiral auxiliaries are  $\alpha$ -amino acids, *S*-Ala and *S*-Phe, which are »hidden« in the 7-membered ring. <sup>1</sup>H-NMR study revealed a somewhat enhanced conformational mobility of the 7-membered ring on binding to Rh(I). Low enantioselectivity was reached in hydrogenation of either standard substrate, *Z*- $\alpha$ -acetamidocinnamic acid, ca 25% e.e., or one precursor in enantioselective synthesis of *S*-3-(3-hydroxyphenyl)-1-propylpyridine (3-PPP, 18%).<sup>117</sup>



Scheme 21. Preparation of Rh(I) complexes of 5-pyrido-1,4-benzodiazepines

We explored (+)-PEA also as a chiral auxiliary in the preparation of 1,5-bidentate nitrogen ligands and examination of catalytic activity of the metal complexes, Scheme 22.<sup>103</sup>

The X-ray crystal structure and CD data corroborated our assumption that the whole chiral topology of the ligands is strongly twisted. An interesting »inversion« of the absolute conformation of the ligands takes place on binding to Rh(I) as the result of the double-bond shift from C=C bond in the ligand to C=N in the Rh(I) complex. Strong non-bonding interactions of 1,5-dinitrogen ligand and diene (NBD) in the complex were confirmed by X-ray (Figure 4), <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR shows two



Scheme 22. Preparation of 1,5-bidentate nitrogen ligands with (+)-PEA, and their Rh(I) complexes<sup>103</sup>

conformations, one of the free ligand (X=*ortho*-phenyl), and the other of the same ligand in the Rh(I) complex.

We also prepared in situ the Cu(I) complexes of chiral ligands presented in Scheme 22. They exhibited a rather low enantioselectivity in cyclopropanation of styrene; it was somewhat higher for *ortho*- than for *para*-phenyl substituted ligands.<sup>103</sup>

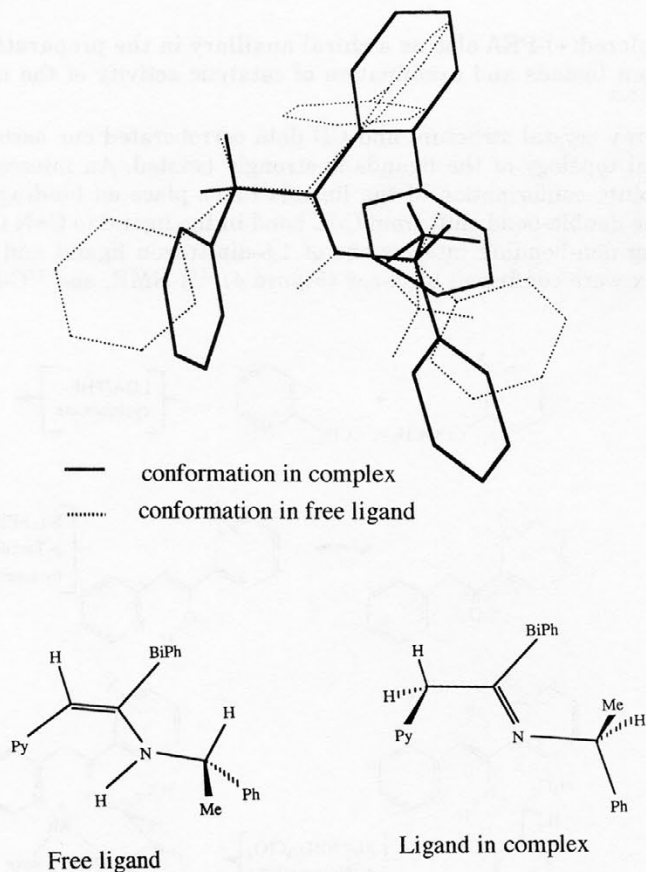


Figure 4. Conformation of the ligand ( $x = \text{ortho-phenyl}$ ), free (.....), and in complex (—), determined for the solid state, Scheme 22.

*Acknowledgement.* – My thanks are due to all the colleagues and collaborators who have contributed to this work over many years. Their names appear in the papers cited herewith. Professor V. Prelog is a teacher who revealed to me the three-dimensional world of organic molecules, and the late Professor G. Snatzke was a dear friend who, over 20 years, continued in helping me to understand the electronic and spectroscopic background of chiral molecules.

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## SAŽETAK

### Neki primjeri nekatalitičkih, katalitičkih i biokatalitičkih priprava kiralnih molekula

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Danas su nađena praktična rješenja za pripremu enantiomerno čistih spojeva (engl. EPC) enantioselektivnim varijantama najvažnijih organskih reakcija, te se ovim metodama proizvodi čitav niz komercijalno značajnih skupina organskih spojeva. Ovaj autorski pregled stoga sadrži samo primjere enantioselektivnih metoda gdje je autorova skupina dala neki doprinos.

*Nekatalitička* priprava kiralnih molekula može se postići bilo separacijom racemičnih smjesa ili enantioselektivnom sintezom uz uporabu stehiometrijskih količina kiralnog pomoćnog sredstva. Dani su primjeri raznih separacija racemičnih 1,4-benzodiazepina. Nekatalitičke sinteze specifičnih  $\alpha$ -aminokiselina i nekih terapijski značajnih spojeva poslužit će kao primjeri za uporabu kiralnih pomoćnih sredstava izvedenih iz »kiralnog spremnika« Prirode.

*Biokatalitičke* transformacije kiralnih molekula koje nisu prirodni supstrati enzima predstavljaju područje primjene enzima i mikroorganizama u organskoj sintezi koje se posebno brzo razvija. Nedavno smo uspješno primijenili mikrobne lipaze za enantioselektivnu hidrolizu nekih prekursora  $C_3$  i  $C_4$  kiralnih sintona, zatim za kinetičku rezoluciju racemičnih 3-(2-nitrofenoksi)butanoata, prekursora 1,5-benzoksepinan-4(5H)-ona, spojeva s inhibitorским djelovanjem na enzim ACH, te realizirali prvu kemoenzimsku sintezu S-fenpropomorfa, biološki aktivnog enantiomera komercijalno važnog fungicida. Kompletna stereoselektivnost u hidrolizi i acilaciji makrocikličkih laktona rezorcilne kiseline, intermedijara u produkciji komercijalnog produkta  $\alpha$ -zearanola, faktora rasta, potakli su nas da predložimo novi »helikalni model« za interackiju enantiomernih supstrata s aktivnim mjestom lipaze iz *Pseudomonas sp.*

*Katalitička* transformacija prokiralnih supstrata u enantiomerno čiste produkte najekonomičnija je metoda sa stajališta kiralnosti. Zasniva se na primjeni kovinskih kompleksa s kiralnim ligandima kao katalizatorima. Uspješnost enantioselektivne katalize ovisi kako o prirodi kovine, tako i o strukturi i elektronskim svojstvima kiralnih liganada. Pokazani su primjeri pripreve kompleksa Rh(I) s kiralnim monofosfinom izvedenim iz kamfora, pripreve kiralnih difosfita i difosfina, bidentatnih liganada izvedenih i najrasprostranjenijih monosaharada, te je istraživana njihova efikasnost u enantioselektivnim hidrogenacijama. Također se opisuje sinteza, struktura i kiroptička svojstva, te katalitička aktivnost nedavno pripremljenih kompleksa Rh(I) i Cu(I) s bidentatnim dušikovim ligandima.