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Author's Review

Separation of Enantiomers by Chromatography as a Vehicle for Chiral Catalysis. Abridged Review*

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Abstract. Chiral, or asymmetric catalysis is the most efficient approach to chiral molecules in the enantiomerically enriched form. Organocatalysis and organometallic catalysis are nowadays the methods of choice in this field. In the first case enantiomerically pure chiral organic molecules of different symmetry classes exhibit catalytic effect, in the second one chiral organic molecule acts as the ligand in the organometallic complex that exerts catalytic activity. In both cases small amount, milligrams or grams, of enantiopure organic or organometallic catalyst suffice to produce substantial amounts, grams or tons, of chiral products of academic or commercial interest. Due to the need for limited quantities of chiral organic molecules in the optically pure form to act as the catalysts or be the part of the catalytic systems, preparative chromatographic separation, and in particular simulated moving bed (SMB) chromatographic resolution of racemic material, represent valuable approach. Examples of separation of racemates by chiral chromatography and SMB technology to catalytically useful enantiomers are presented, and application of enantiomers from different symmetry classes in efficient catalytic processes is highlighted.

Keywords: separation of enantiomers by cromatography, simulated moving bed (SMB) technology, chiral catalysis

INTRODUCTION

Effective transfer of scientific results from academic research into technical, problem-solving sphere of industrial R&D is ever more demanding process. This stays in particular for the results of research in chemistry, where any larger-scale experimentation requires expensive equipment, and consumption of row materials under huge pressure of prices and ambiental-protection requirements. Even when these tasks are solved from the financial, ecological and organizational aspects, newly developed technology will meet harsh requirements for competitive position on the global market.

Western and Eastern World are responding to these challenges by founding new, science-based (biotech) companies in the chemical industry.[1] Among them are companies dealing with the development of new catalysts, production of new HPLC columns with chiral stationary phases (CSPs) for the separation of pharmaceuticals, their intermediates, and last not the least, for separation of chiral compounds that will serve as organocatalysts or as the parts of organometallic catalytic complexes. Ready accessibility of optically pure organocatalysts and ligands is one of the most critical factors when a practical methodology for asymmetric catalysis is emerging. Their availability in homochiral, optically pure form from racemic, easily available, compounds by "chiral chromatography" makes novel catalytic processes possible.

Such complex research was traditionally performed in academic laboratories, nowadays however it is shifted to "start-up companies" or "innovation companies", or "biotech companies".[2] Some own results presented in this abridged review are obtained in early period at CATBIO Laboratory (www.spider.irb.hr/CatBio.htm), more recently at Chirallica Ltd., (www.chiralica.hr.com), spin-off company, both at "Ruđer Bošković" Institute, Zagreb.

* Dedicated to Professor Emeritus Drago Grdenić, Fellow of the Croatian Academy of Sciences and Arts, on the occasion of his 90th birthday.

APPLICATION OF OPTICALLY PURE COMPOUNDS AS THE CATALYSTS AND CHROMATOGRAPHIC ENANTIOSEPARATION OF THEIR RACEMATES

Chirality of the Catalytic Molecules and Ligands

Effective catalytic production of chiral molecules in the enantiomerically enriched form generally does not depend on the symmetry group to which catalytically active chiral molecule belongs. Chiral molecule do not posses 2nd order elements of chirality; alternating axis of symmetry of the second order (S_n), center of symmetry (i), or plane of symmetry (σ).[3,4] Alternating axes, centers and planes of symmetry are elements that correspond to "symmetry operations of the second kind" which cannot be performed on chiral molecules. Chiral molecules belong to C_n and D_n point groups; in the former C_n axis is the only symmetry element, the later are characterized by n C_2 axis perpendicular to the main C_n axis.[3] They are usually named centro-chiral, axial-chiral and planar-chiral molecules; representatives of chiral molecules (**1**–**7**) and one achiral molecule (**8**) active as organocatalysts or ligands are given in the Figure 1.

As will be exemplified in the next chapters, there are many representatives of above classes of chiral molecules that are highly effective organocatalysts or ligands in organometallic complexes. It is still an art in synthetic chemistry to design an effective chiral catalyst for specific organic reaction, as *e.g.* C–C, C–H, C–N and C–O bond-forming reactions, or skeletal rearrangements under formation of a new stereogenic center. There is an important practical aspect that differentiates three classes of chiral molecules in the Figure 1; their availability from the "chiral pool" of Nature. Nature regularly creates chiral molecules with C_1 symmetry, and almost exclusively in one enantiomeric form.[5] Such C_1 symmetric molecules are often submissive to further chemical modifications to give catalytic and non-catalytic auxiliary agents in synthetic organic chemistry, with already mentioned limitation that only one enantiomer is usually available. The first two molecules (**1**,**2**) in the Figure 1 are natural compounds, the third chiral molecule with C_1 symmetry (**3**) is an unnatural structure, prepared in the laboratory to act as monodentate ligand, see section *Centro-chiral Ligands*.

What about availability of axial-chiral, as exemplified by C_2 and C_3 symmetric molecule in the Figure 1, and planar-chiral molecules? They can be prepared either in the enantiomerically pure form, often a difficult task, or as racemate and then submitted to separation of single enantiomers. It is this last approach that is so attractive for preparation of chiral catalysts, in particular when completed by chromatographic separation on chiral stationary phases (CSPs). This method affords both enantiomers with high optical purity and in quantities sufficient for testing in the enantioselective catalytic reaction. If one enantiomer proves effective, but specific target molecule is obtained with "wrong" configuration, application of the second enantiomer as catalyst elegantly resolves the problem.

Some axially chiral enantiomers are characterized by relatively low configurational stability, based on the hindered rotation around C–C bond which is perpendicular to C_2 axis. Low configurational stability characterizes also some planar-chiral molecules, as will be discussed in the section *Planar-chiral Complexes*.

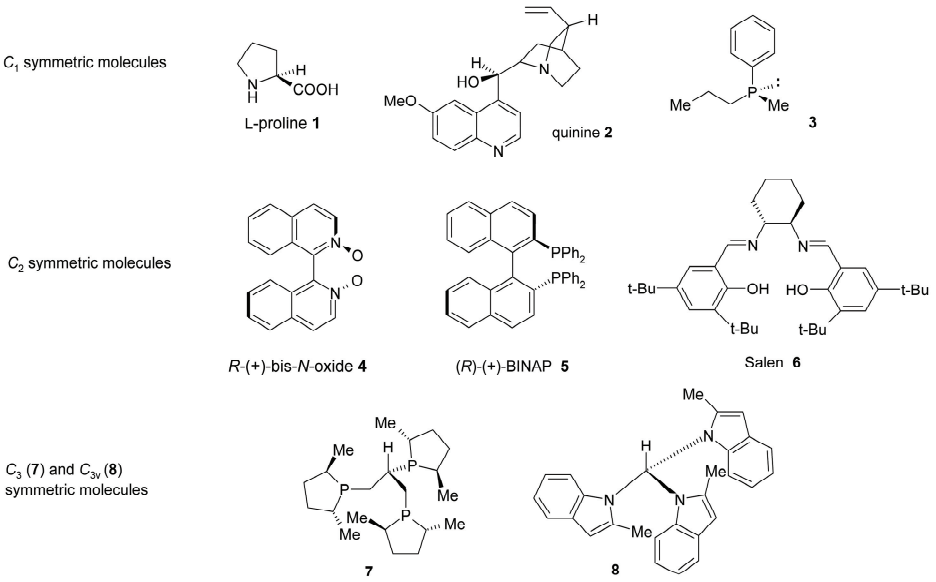


Figure 1. Examples of catalytically active molecules and ligands that belong to various symmetry groups.

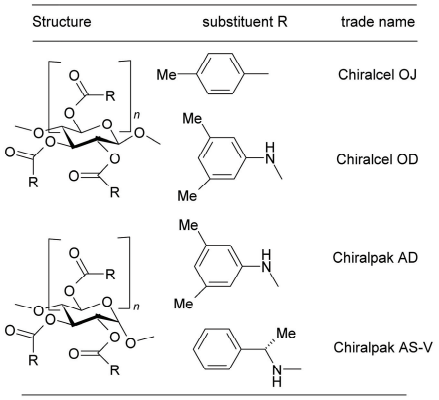


Figure 2. Four most important polysaccharide-based chiral selectors ("golden four").

There is one peculiarity related to the molecules possessing C_3-axis. They are chiral if no element of the second order (i, S_n, σ) is present, as represented by tripodal phosphane **7** in the Figure 1. In the molecule **8** three σ-planes are present, it is achiral and belongs to C_{3v} (D_3) symmetry group. On coordination to Pd, however, the whole complex adopts planar chirality.

Rarity of chiral organic molecules in Nature with axial and planar symmetry, but their availability in both enantiomeric forms by chromatographic separation of racemic mixtures on CSPs, has created productive interaction between chromatographic and synthetic methods. This review is prompted by some spectacular results in asymmetric catalysis due to interplay of these two methodologies.

Techniques of Preparative Separation of Enantiomers by Chromatography

Chromatographic separation of enantiomers on chiral stationary phases (CSPs) is discussed in details in the recent monographs and reviews.[6–10] We published an author-review related to our research on novel CSPs in this Journal,[11] and informative overviews in the technology oriented journal.[12,13] Mechanism of chiral recognition by various CSPs, specific application of the biopolymer-based CSPs, polysaccharide-type and protein-type being the most important ones, and brush-type CSPs, will not be discussed and interested reader is directed to consult the above references. For the purpose of easier following of discussion in the next chapters, only two aspects of chiral chromatography will be shortly commented here; *types of chiral selectors* (CS) nowadays in the common use, and *elementary thermodynamics of chromatographic enantioseparation*.

Two important elements distinguish two main types of CS; molar mass and type of binding to silica. According to molar mass CS are either derived from chiral polymers, usually from polysaccharides or proteins, or they are small chiral molecules, often designed on purpose for separation of specific racemate, and named "brush-type" or "Pirkle type", according to the inventor of such CSPs.[14] Polysaccharide based CS represent over 90 % of the market, and in even higher percentage considering the number of reported separation of racemates. Four of them, called "golden four", practically cover this market, two of them are based on cellulose (Chiralcel), and the other two on amylose (Chiralpak), are repeatedly cited in this review, Figure 2. Financial dimension of the world market of chiral technologies is worth of mentioning; it was *ca.* 5 billion $ in 1999, and is expected to more then triple in 2009.[15]

According to type of binding, CS can either be non-covalently adsorbed, as usual for polymer-based CS, or covalently bound to the activated surface of silica gel. Number of the reported "brush-type" or "Pirkle-type" CS nowadays presumably exceeds 1000. This is

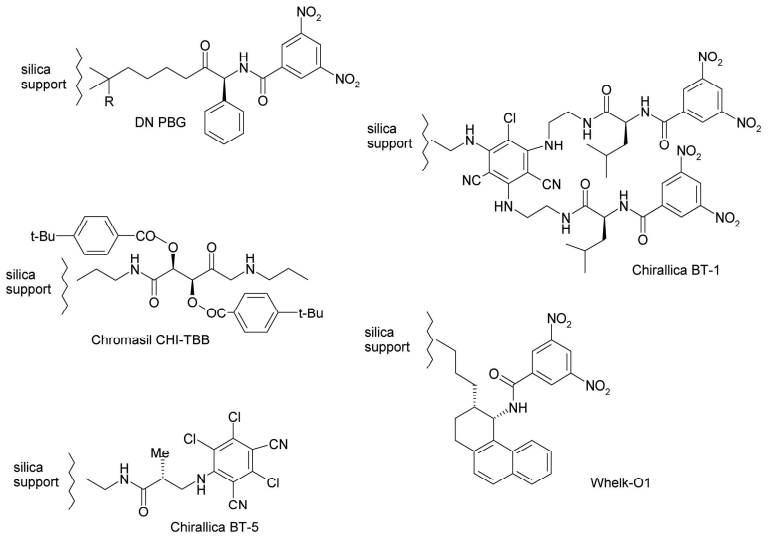


Figure 3. Five selected commercial brush-type CSPs.

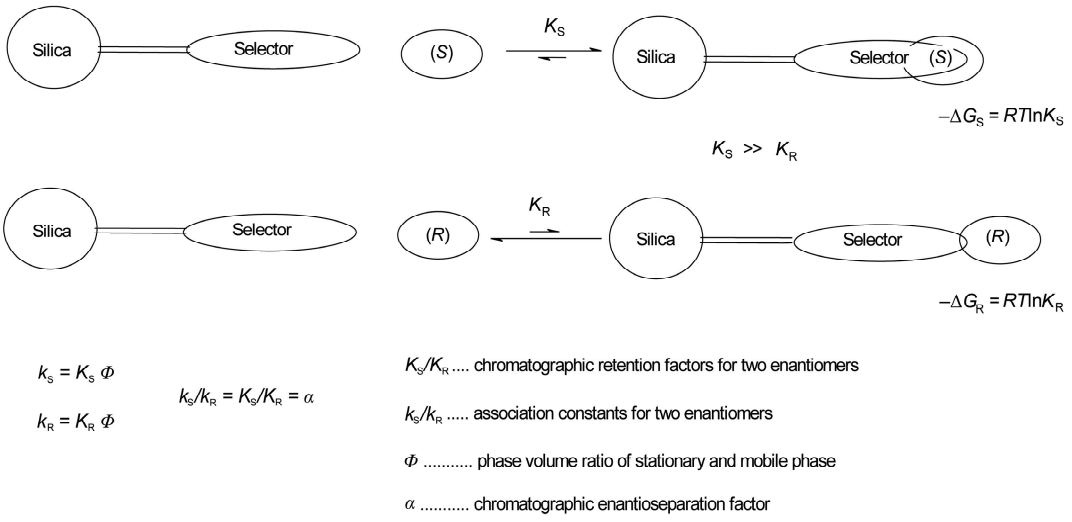


Figure 4. Model of chromatographic enantioseparation and thermodynamics that describe the process.

because of the relative easy conceptual creation and synthetic approach to such selectors, and straight-forward methods for their covalent binding on the modified silica gels.[16] There is still need for new covalent binding modes of both, polymer-based and small-molecule, or "brush-type" CSPs. Figure 3 presents the structures of five selected, commercial "brush-type" selectors.

Thermodynamics of enantioseparation is based on the simple model of equilibrium between free and bound analyte, *i.e.* two enantiomers to be separated, Figure 4.

It is important to note that α is experimentally easily available parameter, and is usually used as comparison parameter for efficacy of enantiosepartion on specific CSPs.[17]

Simulated moving bed (SMB) chromatography represents most effective technique for separation of enantiomers. It is reported in the literature as the method of choice for obtaining practical quantities of commercially important compounds and their intermediates.[18–21] SMB technology is developed for separation of *rac.* BINOL, on the route to enantiomerically pure BINAP, see sections *Axial-chiral Organocatalysts*, and patents are claimed by Merck[22] and GreatLakes/Monsanto[23] companies.

Detailed description of the SMB cycles and their optimization is reported in the recent literature.[24–26] This method is characterized by programmed opening of the valves, which simulates moving of the stationary phase, although fixed in the set of the columns, Figure 5.

Two inlet lines, eluent and feedstock, permit continuous injection of racemic mixture as a feedstock and the eluent. Two outlet lines, extract and raffinate, allow for withdrawal of the separated enantiomers. By programmed rotating inlet/outlet points in the direction of eluent flow, a counter-current movement of the stationary phase is simulated. Herewith suffice to mention that optimization of the process requires application of the software packages which beside chromatographic parameters of enantioseparation (retention times, separation capacity terms k and α), takes into account dimension and pore-diameters of the particles, inside flows, turnover-times, and cycles.[25,26]

SMB technology is claimed as the method of choice for separation of protected amino acids.[27] In view of their simple conversion to amino alcohols, and incorporation of the later in the mono- and bidentate ligands, this technology opens the route to novel organo-metallic catalytic complexes, see also section *Axial-chiral Organocatalysts*.

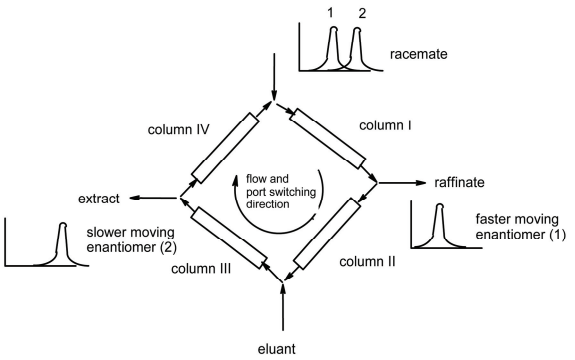
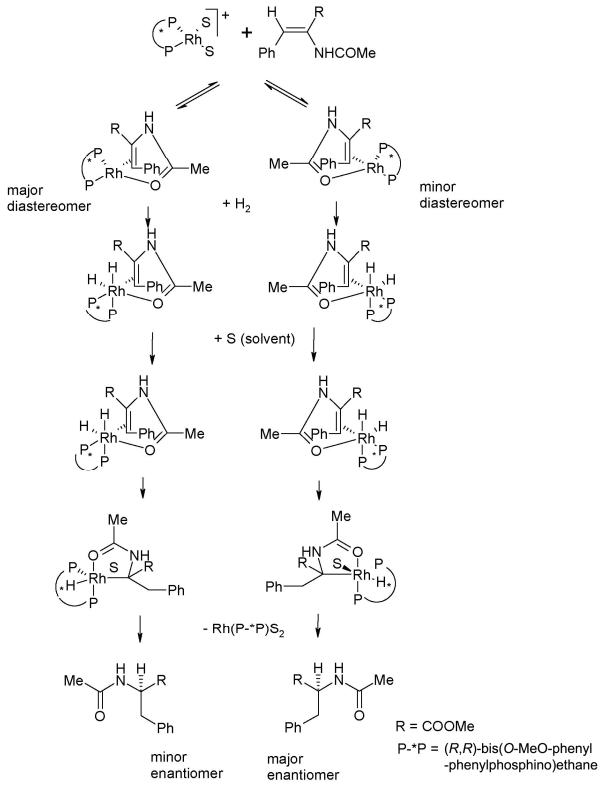


Figure 5. Principle of simulated bed chromatography.

Organometallic Catalysis

Representative Mechanisms in Enantioselective Organometalic Catalysis

In this introductory paragraph short comments on the mechanistic aspects of selected enantioselective *orga-*



Scheme 1. Mechanism of enantioselective hydrogenation of *α*-acetylamino carboxylic acids by the Rh^{I} complex of diphosphine.

nometallic catalytic reactions are given, and in the next section *Respective Mechanisms in Enantioselective Organocatalysis* mechanistic considerations of selected *organocatalysed* reactions are given. For both catalytic methodologies chiral chromatography often represents a trigger, producing enantiopure organic molecules which are the part of organometallic catalytic complex or can act as the catalyst. Organometallic catalysis is discussed in some review articles,[28–32] and monographs,[33–37] organocatalysis is more recently recognized as a general topic. Some aspects of organocatalysis are reviewed,[38] an extensive monograph appears recently.[39]

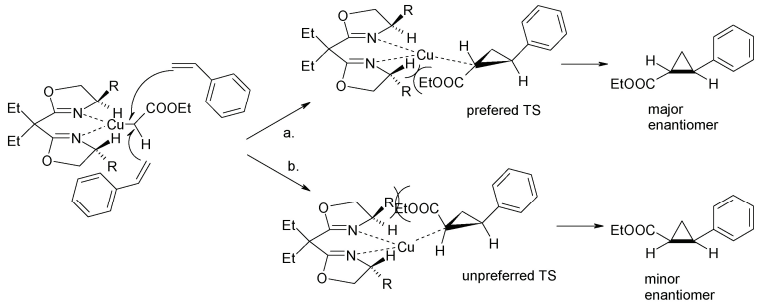
Generally, mechanism of organometallic catalysis comprises catalytic cycle wherein coordination of the substrate and reagent to central metal ion involves d-π or d-σ electronic interactions, initiating formation of a new bond in the product. Departure of the product from the catalytic cycle is promoted by its weaker binding to the central metal ion then affected by the reactants. As an example, a mechanism proposed by Halpern for enantioselective hydrogenation of enamide C=C bond is presented in the Scheme 1.[40]

There are important peculiarities inherent to this mechanistic proposal. First characteristic of this cycle is bidentate binding of *N*-acetyl-*α*-amino acid *via* π-electrons of C=C bond and n-electrons of amide oxygen to Rh(I), oxidative addition of H_2, and stepwise transfer of activated hydrogen from Rh^{III} to C=C bond, followed by reductive elimination of the product. Second, more stable complex on the route to transition state was crystallized and its structure determined by X-ray single crystal analysis. Surprisingly, it proved to be "unproductive" complex, since major enantiomer was formed from the less stable diastereomeric complex.[40] Chiral topology of the whole complex is controlled by the bidentate phosphine ligand, see section *Representative Mechanisms in Enantioselective Organometallic Catalysis*.

Second illustrative mechanistic example relates to C–C bonds forming cyclopropanation reaction.[41] According to Pfaltz the stereochemistry of the predominating *trans* product is determined by the more favourable styrene attack form direction *a*; in the formed TS the bulky ester group faces a "small" hydrogen atom. In contrast, the attack from direction *b* produces the less stable transition state due to steric repulsion between large substituent on the bis(oxazoline) stereogenic center and the ester group. Consequently, *trans*-diastereomer with defined absolute configurations on both stereogenic centers prevails, Scheme 2.[41]

This reaction is characterized by coordination to metal of the carbene (substrate) only, whereas alkene (reagent) is oriented to carbene from the less hindered side by topology of the ligand.

It is important to emphasize that the mechanism of *organometallic catalysis* corresponds by its very nature



Scheme 2. Mechanism of Cu^{I} catalyzed cyclopropanation.

to that of the catalysis performed by *metaloenzymes*.[42] Particularly important practical aspect represents nearly 100 % enantioselectivity achieved in many reactions catalyzed by organometallic complexes, approaching values recorded for enzyme catalyzed transformations.

Centro-chiral Ligands

This type of the ligands belong to C_1 symmetry group and differ in the position of the stereogenic center. Stereogenic center can be found either on the heteroatom that coordinates to metal, which is often phosphorous, or on the carbon atom, closer or farther from the coordinating heteroatom. In the pioneering period of organometallic catalysis a belief existed that most effective chiral catalysts should have stereogenic center on, or close to the atom coordinated by the metal.[33,34] Soon it was discovered that effective chirality transfer, *i.e.* high enantioselectivity in catalytic reaction, requires well defined *chiral topology* of the transition states, preferring energetically (for *ca.* 9.2 kJ/mol) the more stable one.[43,44]

Figure 1 shows C_1-symmetric ligand **3**, which was the first explored chiral monophosphine in Rh-catalyzed hydrogenation of C=C bond in arylalkenes.[45] Low enantioselectivity, *ca.* 8 % enantiomeric excess (e.e.), was later explained by improper selection of unsaturated substrate, 2-phenylpropene, without additional coordinating group. Highly effective ligands with C_1 symmetry were developed later, when hydrogenation of *α*-acetylamino-cinnamic acid was selected as the model reaction; *N*-*α*-acetylamino-alanine was obtained with 98–99 % e.e.

In Figure 6 representatives of monodentate P-ligand with stereogenic centers on carbons (**9**), bidentate *P*,*P*-ligands with stereogenic center on carbon (**10**), and monodentate *P*-ligands with stereogenic center on phosphorous are given (**11**).

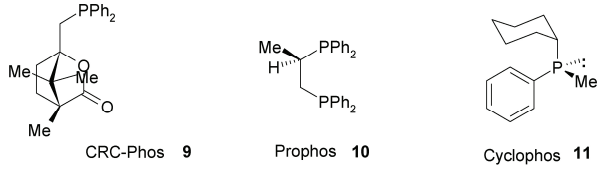
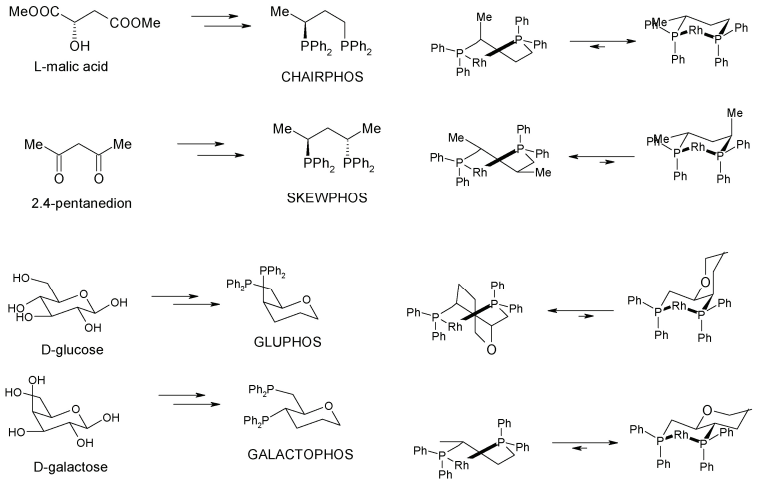


Figure 6. C_1 Symmetric phosphine ligands, effective in hydrogenation of *α*-acetylamino-cinnamic acid.

When stereogenic center is on the carbon, ligands are usually derived from homochiral products from the Nature. Thus, CRC-Phos **9** is derived from camphor *via* camphanic acid,[46,47] Prophos **10** from lactic acid.[44] Separation of enantiomers is required for C_1 ligands when stereogenic center appears at phosphorus, as in Cyclophos **11**.[48,49] Though quite different in their structures and location of the center of chirality, all these ligands catalyze hydrogenation of C=C bond with very high e.e., nicely demonstrating that design of an effective catalysts is limited only by serendipity and creativity of the chemist.

There is an important aspect of enantioselective organometallic catalysis related to the symmetry group of the ligand and chiral topology of the activated complex. As already mentioned, efficacy of the chirality transfer, *i.e.* enantioselectivity of the catalytic process is not correlated to the symmetry group of the catalytic species. It is *chiral topology of the transition-state*, which rises difference in the free energies of the two transition-state species, determining enantioselective bias of the catalytic process.[50,51]

The importance of conformational characteristics for organometallic catalysts will be exemplified analyzing set of four bidentate phosphines, ligands in enantioselective catalytic hydrogenation. Ligands presented in the Scheme 5 are 1,5-diphosphines and can form six-



Scheme 3. 1,5-Bidentated diphosphines, their starting materials and two preferred conformations of their 6-membered Rh^I chelates.

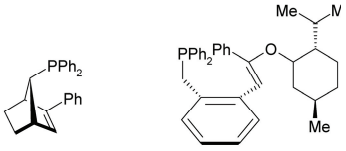


Figure 7. Two representatives of phosphane alkene (PAL) ligands.

membered chelate ring with Rh^I. It is conformation of the chelate ring that defines topology of the whole complex, in particular mutual position of the four phenyl rings in the two Ph_2P groups. These ligands may differ by the "local symmetry" of the stable conformer in the chiral complex. Stable conformations of the 6-membered chelate posses *pseudo-σ* plane or *pseudo-*C_2 axis. High "local symmetry" of conformers with *pseudo-σ* plane renders the whole complex less effective in the chirality transfer, *i.e.* in enantioselective hydrogenation. This was first observed by Bosnich *et al.*, for two bidentate ligands of extreme simplicity, named by the authors CHAIRPHOS and SKEWPHOS.[52,63] The first is available from L-malic acid, while the route to enantiopure form of the second requires resolution of racemic *trans*-diol available form 2,4-pentandione, Scheme 3.

Two chiral diphosphines are demonstrated by CD measurements to differ in that SKEWPHOS adopts chiral skew conformation of the chelate ring whereas CHAIRPHOS adopts an achiral chair conformation.[53] As a consequence the former complex gives high optical yields in hydrogenation of *α*-acylamino–*α*,*β*-unsaturated carboxylic acids, generally above 90 % e.e., whereas with the later where surprisingly low (10–20 % e.e.).

Approximately at the same time we have reported significant difference in the hydrogenation of *α*-acylamino-cinnamic acid with 1,5-bidentate ligands GLUPHOS and GALACTOPHOS, derived from D-glucose and D-galactose, Scheme 3.[54–57] In this case skew conformation of the chelate is preferred for GLUPHOS, whereas achiral chair conformation predominates in the Rh^I complex of GALACTOPHOS, as shown by the CD spectra.[56,57] The origin for preference of chair conformation in GALACTOPHOS complex stays in equatorially annelated tetrahydrofurane ring, in the former complex this ring is axially annelated, instead. Higher e.e. (50–70 %) obtained with the former then with the later (10–18 % e.e.), is expected consequence of difference in topology of the two complexes.

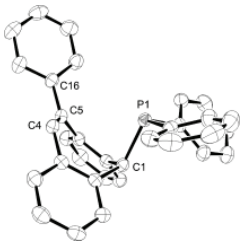


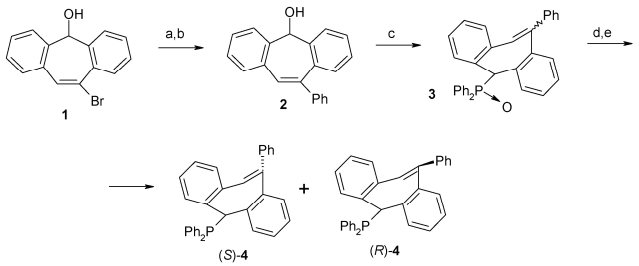
Figure 8. ORTEP of the (*S*) enantiomer of **4**. The thermal ellipsoids are drawn at the 50 % probability level. (Reproduced with permission from Ref. 62.)

A class of C_1-symetric monophosphines with additional ethylene group, named phosphane-alkene ligands (PAL), are emerging as important steering ligands.[58–60] Two selected structures are presented in the Figure 7. These concave-shaped structures are particularly interesting due to their topological relation to tridentate, or tripodal, six-electron donor ligands (see section *Axial-chiral Ligands*), but serve only as four-electron donors.[61]

These rigid, concave-shaped molecules are usually available as racemates and require enantioseparation prior to application as homochiral ligands. Exemplary synthesis of racemic **4** and its chromatographic enantioseparation is presented in the Scheme 4.[62]

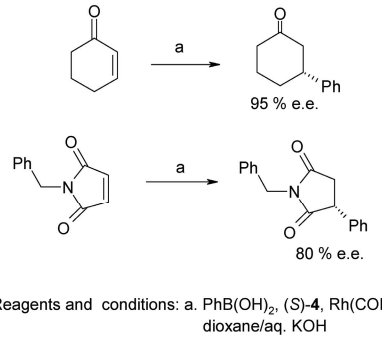
Separation of *rac.* **4** was completed on Chiralcel OD-H with hexane/2-PrOH (98:2) as eluent; at 0.8 mL/min flow retention time R_t for (–)-**4** 8.0 min, R_t for (+)-4 10.4 min. Structure and absolute configuration of (–)-**4** was determined by using X-ray crystallography, Figure 8.[62]

PAL ligands proved most effective in enantioselective arylation by 1,4-arylboronic acid addition to



Reagents and conditions: a. $PhB(OH)_2$, 2.5 mol % $Pd(PPh_3)_4$; b. Na_2CO_3 aq./DMF/EtOH, c. Ph_2PCl, TFA/THF; d. HPLC resoln. on Chiralcel OD-H e. $HSiCl_3$/toluene, 90 °C.

Scheme 4. Synthesis of chiral PAL **3** and HPLC separation into enantiomers of **4**.



Scheme 5. Enantioselective Hayashi-Miyaura reactions using PAL-type ligand (*S*)-**4**.

α,*β*-unsaturated carbonyl compounds, known as Hayashi-Miyaura reaction.[63] In the Scheme 5 are presented two examples of successful application of Rh^{I} complex of (*S*)-**4** in enantioselective *β*-arylation.[62]

Axial-chiral Ligands

C_2*-symmetric Ligands*. This symmetry group is frequently present in the ligands of organometallic complexes applied in various enantioselective reactions. Ligands with C_2-symmetry are usually of bidentate nature, able to form chelates of various ring-size with central metal atom. Generally, ring-size of chelates is not decisive for high enantiosectivity of catalytic reaction. As already mentioned, enantioselectivity is governed by chiral topology of the reactive complex.[50,51] Four hereafter selected examples illustrate important enantioselective reactions catalyzed by organometallic complexes of various C_2-symmetric ligands; *a. hydrogenation*, *b. cyclopropanation*, *c. allylic alkylation*, and *d. epoxidation*, all catalyzed by C_2-symmetric complexes of Ru, Cu, and Pd.

- *Hydrogenation* of prochiral ketones and alkenes, *i.e.* polar C=O and non-polar C=C bond, by Ru complexes of chiral biphenyl diphosphines was studied in big-pharma companies and in academies. The following structurally related ligands are developed by Takasago Int. Co (SEGPHOS)[64] and by academic laboratory in Paris (DIFLUORPHOS, SYNPHOS), Figure 9.[65,66]

Intermediary, racemic bis-*P*-oxide of DIFLUOROPHOS was separated into enantiomers by preparative HPLC using Chirose C3 column, with cyclodextrin-based CSP, and transformed into final diphosphine by

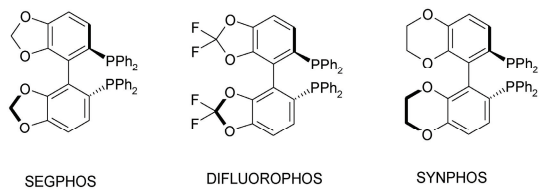


Figure 9. Dioxolo- and anysil-biphenyl diphosphines.

standard reduction with $HSiCl_3$ / Bu_3N in xylene. SYNPHOS, instead was separated by crystallization with (+)-tartaric acid derivative.[66]

These ligands are selected to demonstrate successful design, based on accumulated knowledge in the field. Stereoelectronic feature renders them capable to hydrogenate both polar C=O and unpolar C=C bond. Such "bivalent" reductive capacity results from high electron density on P-atom due to *para*-situated electron-donating oxygen atoms, while high enantioselectivity is tuned by the proper dihedral angles of the biaryl backbone.[66] With standard *β*-ketoacids as substrates up to 99 % e.e. were recorded for *β*-hydroxy acids, the same or higher than obtained with BINAP and some other bidentate ligands already in use on the large-scale hydrogenations of other substartes.[67,68]

An improved process is claimed for preparation of asymmetrically substituted biaryldiphosphines *via* chromatographic separation of enantiomers, and their use as ligands for transition metal-catalyzed asymmetric hydrogenation.[69]

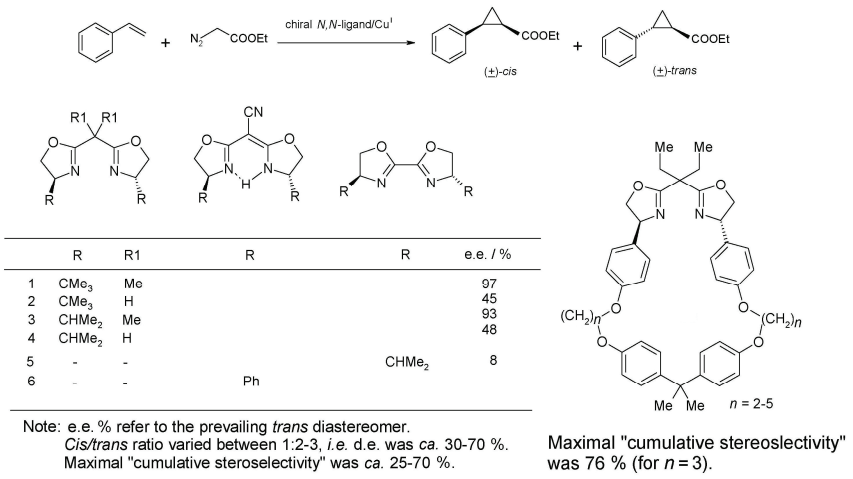
- *Enantioselectivity* of chiral *N*,*N*/Cu complex as the catalysts *in cyclopropanation* is usually tested with a couple styrene/carbene derived from diazoacetic acid according to the general scheme in the Figure10.

In this reaction two stereogenic centers are formed affording *cis*- and *trans*-racemates, and a formidable task represents stereoselective preparation of the targeted one of four possible stereoisomers. Studies of the mechanism of cyclopropanation, and successful application of C_1 and C_2 symmetric ligands are reviewed.[70] Chiral chromatography is particularly related to effective monitoring of cyclopropanation, since four stereoisomers, two racemic pairs, should be resolved on the same column. Effective chiral columns for separation of all stereoisomers have been reported in many synthetic papers.[71–74]

Representative dinitrogen ligands with C_2 symmetry are presented in the Figure 10, along with e.e. % and cumulative selectivities achieved for the prevalent diastereomer in cyclopropanation according to the scheme.

It is interesting to note that the highest cumulative stereoselectivity, expressed as the product of *cis*/*trans* and enantioselectivity, is obtained with macrocyclic, supramolecular ligands in the Figure 1, for which an effect of "chiral cleft" has been envoked.[74–76]

In all bis-oxazoline ligands from the Figure 10 enantiopure *α*-amino alcohols are incorporated by double cyclisation of malonate or oxalate diesters. Preparation of enantiopure *α*-amino alcohols by chromatographic resolution of racemic material is often a method of choice. Thus, preparation of optically-active 4-amino-



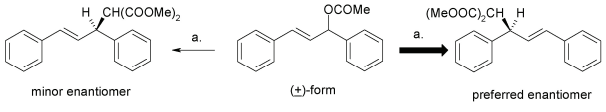
	R	R1	R	R	e.e. / %
1	CMe_3	Me			97
2	CMe_3	H			45
3	$CHMe_2$	Me			93
4	$CHMe_2$	H			48
5	-	-		$CHMe_2$	8
6	-	-	Ph		

Figure 10. Representative bidentate bis-oxazolines,[71–73] and supramolecular bis-oxazolines,[74] and % e.e. obtained in Cu^I catalyzed cyclopropanation.

2-methylbutan-1-ol by derivatization and chromatographic separation of enantiomers is claimed as the basis for production of various bidentate ligands.[77] An isopropanol solution of the dibenzoyl derivative of this alcohol was charged onto a Chiralcel OD column and eluted with hexane/isopropanol to give (*S*)- and (*R*)-enantiomers at resolution factor $\alpha = 3.2$.

Chromatographic methods for separation of racemic α-, β- and γ-amino acids, both natural and synthetic, are claimed.[78] Enantiopure form of these amino acids are rich source of amino-alcohols, amino-phosphines, and other bidentate ligands. For enantioseparation of unnatural amino acids specific CSPs are developed, such as macrocyclic glycopeptide resorcitin A,[79] or Chirobiotic T and Chirobiotic TAG, chiral CSPs based on native teicoplanin and teicoplanin aglycone.[80] Some standard CSPs, like Chiralcel OD proved effective in enantioseparation of α-methyl-α-amino acids.[81] Representative of brush-type CSPs effective in enantioseparation of secondary amino acids, particularly important precursors for *sec* amino alcohols, valuable ligands in stoichiometric enantioselective hydroboration and other asymmetric syntheses, was reported by Antal *et al.*,[82] and for α-amino acid separations are developed chiral crown-ether derivatives by H. Han *et al*.[83]

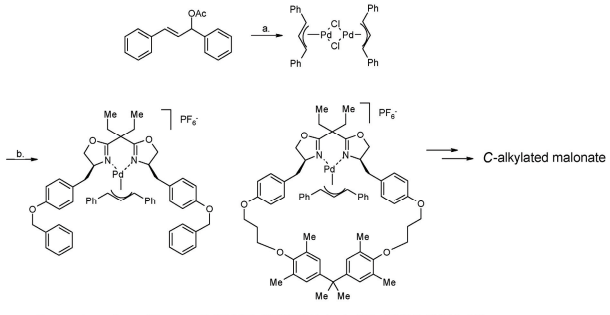
- *Allylic alkylation* is an important C–C bond-forming reaction catalyzed by Pd^{II} complexes of various ligands, including C_2 symmetric *N*,*N*-bidentate ligands.[84] Alkylation of diethylmalonate anion as nucleophile by allylacetate is schematically presented in the Scheme 6.



Scheme 6. Schematic presentation of enantioselective allylic alkylation.

In this reaction racemic allyl ester is transformed into preferred enantiomer of malonate derivative. Mechanism of this reaction involves formation of Pd^{II}/allyl-cation complex which first coordinates bidentate ligand, then alkylates malonate anion. Structure and topology of such complexes are repeatedly studied.[85–89] Formation of the precatalytic, bridged complex **1**, and coordination of acyclic (**2**) and macrocyclic (**3**) bis-nitrogen ligands is outlined in the Scheme 7. Conformation of these complexes has been spectroscopically studied in detail.[88]

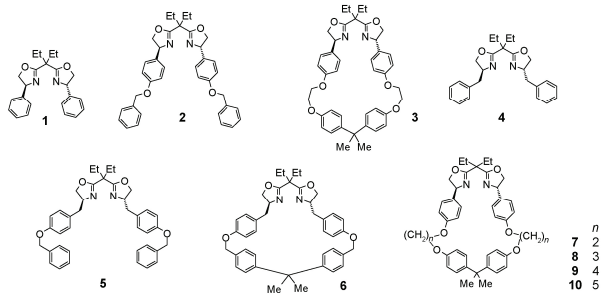
Enantioselectivity of this model-reaction are usually higher then with other allylic systems, in particular with the cyclic ones.[87] Still, this reaction serves as a good model for efficacy and enantioselectivity of the catalytic complexes, as illustrated for the ligands **1**–**10** in the Table 1.[88]



Scheme 7. Formation of C_2-symmetric catalytic complexes in *C*-allylation.

Table 1. Results of asymmetric alkylation of *rac*-1,3-diphenyl-3-acetoxy-prop-1-ene with diethyl malonate catalyzed by Pd^{II}/**1**-**10** complexes

Ligand	yield / %	e.e. / %	config.
1	49	84.9	*R*
2	98	92.0	*R*
3	14	79.8	*R*
4	93	86.0	*R*
5	98	87.5	*S*
6	98	65.0	*S*
7	74	80.8	*S*
8	39	83.8	*S*
9	41	79.9	*S*
10	22	84.0	*S*



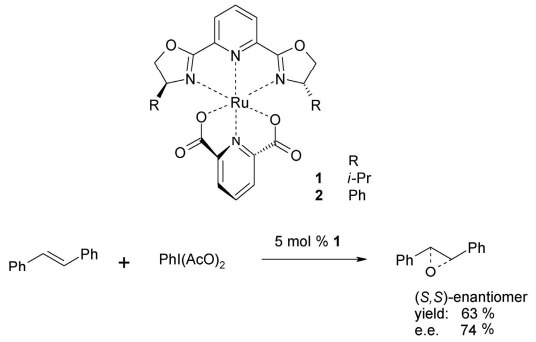
For only moderate variation of enantioselectivity with the length and ring size of the ligand a rationale was offered on the bases of combined 2D NMR and CD study.[88]

Concluding this section on one of the most important enantioselective C–C bond forming reactions, it is worth of mentioning that Pd^{II} complexes of the ligands other then bidentate *N*,*N* are reported. Most of them contain only one P-atom, either as monodentate,[90–92] or within *P*,*N*,[93,94] *P*,*S*,[95,96] or *P*,*O*[97,98] bidentate ligands. SciFinder search does not reveal any example of application of *P*,*P*-bidenate ligand in Pd^{II} complex that promote allylic alkylation.

- *Epoxidation* of C=C bond can be completed in the enantioselective manner by various catalytic systems.[99] As a representative example of C_2 symmetric tridentate (*N*,*N*,*N*) ligands here are selected pyridine-bisoxazolines (pybox) which form catalytic complexes (*S*,*S*)-**1** and (*S*,*S*)-**2** with Ru-pyridinedicarboxylate as the second ligand, Scheme 8.[100]

Epoxidation is promoted by bis(acetoxy)iodobenzene as an oxygen donor, and proves dependent on the rigidity of chiral bis-(oxazolinyl)pyridine ligands.

An interesting example of design of chiral hybrid spiro-bis-(isoxazoline) ligands (SPRIXs) represent com-



Scheme 8. C_2-symmetric tridentate ligands in catalytic epoxidation.

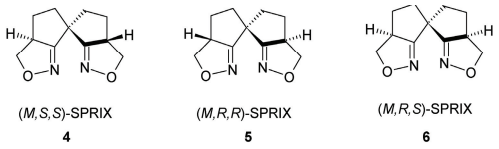
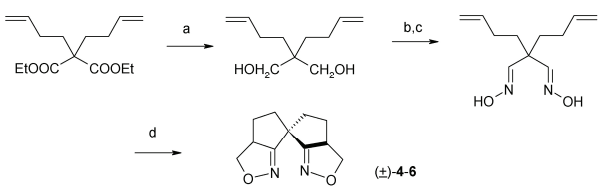


Figure 11. Structures of three diastereomeric SPRIX ligands.

pounds **4**–**6**.[101] These three racemic diastereomers posses three stereogenic centers, one at spiro-carbon and two lateral ones, Figure 11.

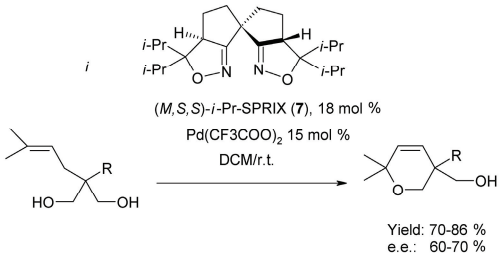
Crowded and strained carbon framework in **4**–**6** is surprisingly easy available in the laboratory from diethylmalonate derivative in four steps, Scheme 9. Three diastereomeric racemates are first separated on silica gel column, and afforded pure enantiomers by preparative chromatographic separation on chiral stationary phase Chiralpak OD.[102] Using ethanol as eluent on the preparative column (dimensions 2×25 cm) at flow rate 3 mL/min retention times for the enantiomers **4**–**6** were as follows: **4**; 21 min/29 min, **5**; 30 min/66 min, **6**; 33 min/49 min. Complete separation enabled the use of enantiomerically pure **4**–**6** as the ligands in some catalytic reactions.[101–103] Here is presented catalytic cyclization effected by Pd-complexes of *i*-Pr-SPRIX **7**, Scheme 10. It is based on activation of olefins towards enantioselective tandem cyclization of an alkenyl alcohol (Wacker-type cyclization).[102]

Concluding this section it is proper to state that bidentate ligands, mostly with C_2 symmetry, represent



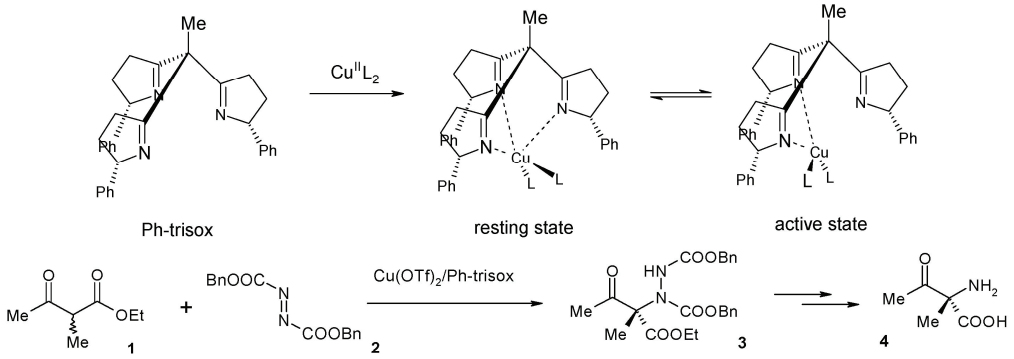
Reagents and conditions: a. LAH/THF; 94 %, b. $(COCl_2)$, DMSO/Et_3N, DM-78 °C, c. NH_2OH×HCl, Py; 87 %, d. NaOCl, DCM 74 %

Scheme 9. Synthesis of spiro-bis-oxazoline ligands (SPRIXs).



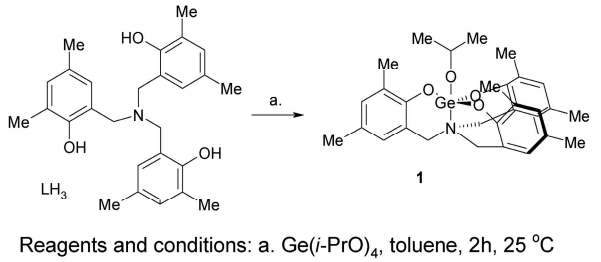
Scheme 10. Catalytic asymmetric Wacker-type cyclization.

C_3-symmetric Ligands. Though C_3-symmetry is intriguing and rare in organic chemistry, application of C_3-symmetric compounds in asymmetric catalysis is repeatedly reported.[104,105] Tridentate ligands are trifunctional molecules with C_3 symmetry and can have different topologies.[104] In these molecules the presence of a center of chirality is common requirement, in order to distroy D_3 symmetry. C_3-symmetric molecules usually behave as tridentate ligands and form octahedral complexes reducing the number of possible diastereomeric transition states, matching an important requirement for high enantioselectivity. Three examples serve to illustrate this fascinating field of organometallic chemistry and chiral catalysis.



Entry	Catalyst loading / %	Yield / %	e.e. of **3** / %
1	10	91	99
2	1	91	99
3	0.1	72	99
4	0.01	49	48

Scheme 11. Enantioselective α-amination of ethyl 2-methylacetoacetate with dibenzylazodicarboxylate catalyzed by [Ph-trisox/Cu(OTf)$_2$].

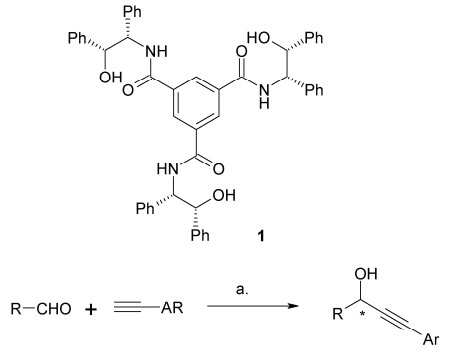


Scheme 12. Formation of chiral C_3 symmetric Ge^{IV} complex.

most frequent unit in organometallic catalytic complexes; additional examples are spread over this and cited reviews. In spite of their seemingly artificial structure, their efficacy based on the bidentate nature, and their avaliabilty from natural chiral compounds by incorporation of two C_1-symmetric molecules of the same chirality into dimeric structure, or by chromatographic separation of racemic ligands with C_2-symmetry, makes them highly attractive for further exploration in academic and industrial laboratories.

Cu^{II} complex of tripodal trisoxazolines (Ph-trisox), prepared according to the Scheme 11, is reported as highly efficient ligand in catalysis of α-amination.[106] Intermediary diazo-dicarboxylate, obtained with 99 % e.e., can easily be transformed into valuable *S*-α-methyl-α-amino-β-ketoacid.

Chiral Ge^{IV} complex **1**, in spite of its strange-looking structure, is easily obtainable from amine-trisphenolate ligand LH_3, Scheme 12, and proved effective in catalysis a polymerization process of extreme inudstrial and ecological importance.[107] This is ring-opening polymerization of lactide (LA) in polylactide (PLA), a biodegradable aliphatic polyester, which proceeds in the presence of **1** stereoselectively, in a highly heterotactic mode. In view of comercial impact of stereoregular PLA,[108] mechansim of this stereoregular reaction, best completed under solvent-free conditions, is under intensive investigation.



Reagents and conditions: a. Et_2Zn, 20 mol % **1**, $Ti(O\text{-}i\text{-}Pr)_4$, hexane/DCM (1:4)
e.e. % determined on Chiralcel OD

Scheme 13. Ti^{IV} complex of **1** in enantioselective alkynilation of aldehydes.

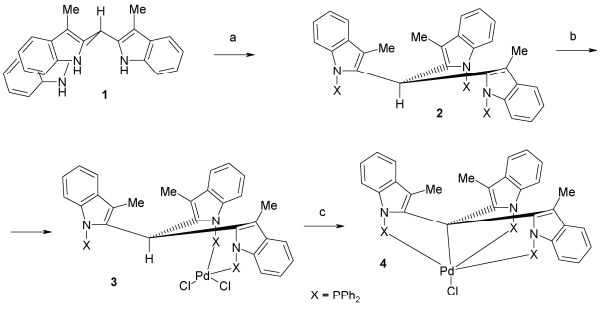
The current state of the art in asymmetric catalysis with complexes of C_3-symmertic ligands is typified by the use if Ti^{IV} complex of the ligand **1** to catalyze enantioselective alkynilation of aldehydes with up to 92 % e.e., Scheme 13.[109] Other molecules with C_3-symmetry whose design is inspired by the Nature are recently presented in a short review.[110]

Planar-chiral Complexes

Chirality in the complexes with achiral C_{3v}-symmetric ligands can be achieved by conformational restriction posed on complexation by the metal. Such pyramidal complexes are chiral, and enantiomers can be separated if configurational stability of the metal atom is high enough. Nice example of such structure offers Pd complex **4**, obtained from tridentate ligand **2** as in the Scheme 14.[111]

Racemization in such complexes occurs due to pyrimidal inversion, whereby ligand formally passes through the chiral plane. Real process, however, requires bond-braking and bond-making steps from the metal to the coordinated atom(s).

Complex **4** is formed from triphosphine **2** by coordination of the third P-atom in the intermediary **3** to



Reagents and conditions: a. NaH/THF, r.t., Ph_2PCl; b. $PdCl_2$/THF; c. $AgBF_4$, r.t.

Scheme 14. Synthesis of tripodal ligand **2** and its palladium complexes **3** and **4**.

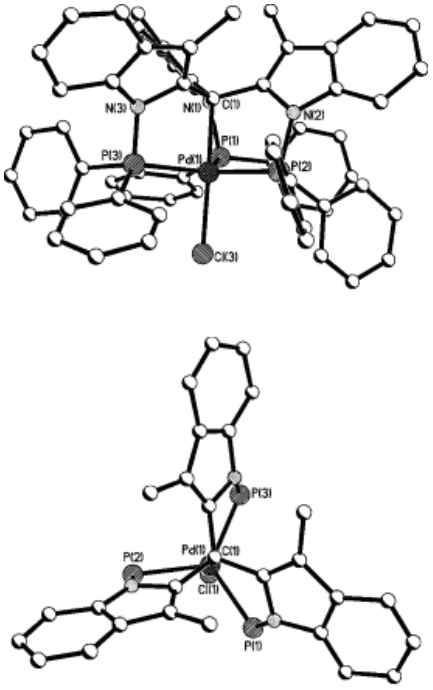
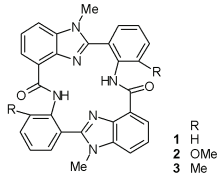


Figure 12. Molecular structure of palladium complex 4, bottom projection is along the virtual threefold axis. Hydrogen atoms and the phenyl rings attached to the phosphorus atoms are omitted for clarity (Reproduced with permission from Ref. 111.)

Pd^{II}. C_3-symmetry of the complex **4** in the solid-state as confirmed by X-ray analysis, Figure 12. After having confirmed that axial chirality of the complex is retained in solution, the authors have separated enantiomers by chiral HPLC. To this aim Chirobiotic T stationary phase, based on teicoplanin, proved most effective when EtAc/hexane (3:1) was used as eluent. Separated enantiomers of **4** did not racemize on heating under reflux in THF for 15 h, as clear evidence of their configurational stability under the reaction conditions. First reported catalytic reaction, Suzuki cross-coupling between 1-iodo-2-methoxynaphthalene and 1-naphthylboronic acid lead to axially chiral binaphthyl derivative with low enantioselectivity (7 % e.e.).

Non-planar distortion of polyazamacrocyclies (PAMs) makes their planar-chiral complexes effective catalysts in some enantioselective catalytic reactions.[112,113] These ligands form toplogically novel chiral transition metal complexes, as exemplified by cyclic bis(benzimidazole)-based amides **1**–**3**, Figure 13.[113]

Lactames **1**–**3** are chiral due to inherent ruffling, alternate displacement of the *meso* carbons above and



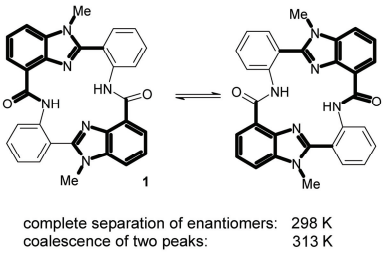


Figure 13. Macrocyclic inversion for enantiomers of cycli amide **1**.

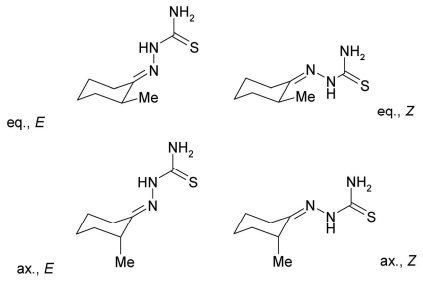


Figure 14. Diastereomeric forms of 2-methyl cyclohexanone thiosemicarbazone.

below the mean macrocyclic plane. As shown for the solid-state structure of **1**, the four aromatic units are alternately tilted above and below the mean 4N-plane. Compounds **1**–**3** are configurationally unstable and racemize at the rather different rates, as determined by dynamic HPLC on the chiral stationary phase.[113]

For the compound **1** half-life for racemization at r.t. was determined as 16.6 min, whereas for sterically more hindered derivatives **2** and **3** much slower racemization process was observed. Thus, when enantiomerically enriched sample of **2** was kept in solution at r.t. for 7 h optical purity was halved, decreasing from 84 % e.e. to 42 % e.e. Still, this ligand racemizes *ca.* 90 times faster then its Me-flanked counterpart **3**, revealing larger steric congestion by Me group as compared to MeO group.

Temperature-dependent enantiomerization process of **1**, as monitored by chiral HPLC, has revealed coalescence temperature of two separated peaks at approx. 313 K.

Due to their configurational instability ligands **1**–**3** cannot transfer chiral information during catalytic process. Their Ni^{II} complexes proved configurationally stable, however, and their separation by chiral chromatography succeeded on Chiralpak OD columns. Effective separation of both is achieved on polysaccharide based columns at r.t. Ni complex of **1** proved configurationally much more stable than the free ligand; it racemizes at the rate of *ca.* 1 % e.e./day. It was estimated that ligand **1** racemizes at r.t. *ca.* 10^4 faster than its Ni^{II} complex. Therefore enantiomers of Ni^{II} complex of PAM ligands **1**–**3** are expected to act as chiral organometallic catalysts in epoxidation of *E*-alkenes, known to be "difficult" substrates for enantioselective epoxidation.[114] As yet only Cr^{V}-salen complex proved highly enantioselective in this reaction.[115]

In the context of enantioseparation of configurationally unstable compounds it is important to note that chiral chromatography offers unique possibility of direct converting the racemic form of chiral compound with controlled, low configurational stability into one enantiomer. To this aim separation process is immediately followed by racemization of the undesired enantiomer. Chiral chromatography serves double scope; determination of kinetic and thermodynamic parameters of enantiomerization, and separation of enantiomers. The former data serve to define chromatographic conditions (eluent, temperature) where effective separations is achieved, and racemization conditions (solvent, temperature, acid or base catalyst) where fast and clean racemization of the "wrong" enantiomer takes place.

This concept exemplifies work of Cirilli *et al.*[116] The authors have completed LC separation of enantiomers and diastereomers of 2-methylcyclohexanone thiosemicarbazone (MCET), Figure 14.

All MCET isomers are interesting intermediates on the route to chiral heterocycles, in particular 1,3-thiazoles, which can act as ligands in organometallic catalysis. Their separation has been completed by combining separation on Chiralpak IA and on Chiralpak AS-H, both CSPs based on modified amylose. Since *E*/*Z* diastereomers comprise enantiomeric pairs due to stereogenic center on C(2), complete separation is expected to give two pairs of peaks of the same intensity. Unequal ratio of *E*/*Z* isomers reflects fast *E*-*Z* on-column isomerization process leading to acumulation of the more stable *E*-racemate. To enhance the rate of isomerization and racemization process, acid catalysis

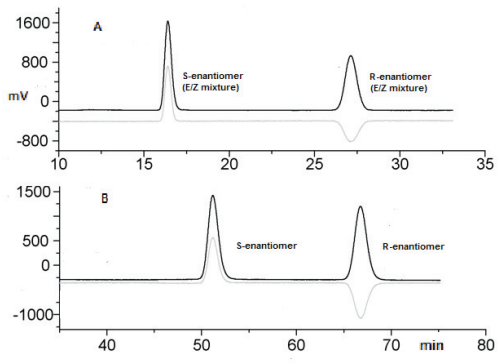


Figure 15. Enantioseparation of 2-MCET on Chiralpak AS-H under conditions of A: fast *E*-*Z* isomerization, B: slow *R*-*S* enantiomerization. (Modified from Ref. 117)

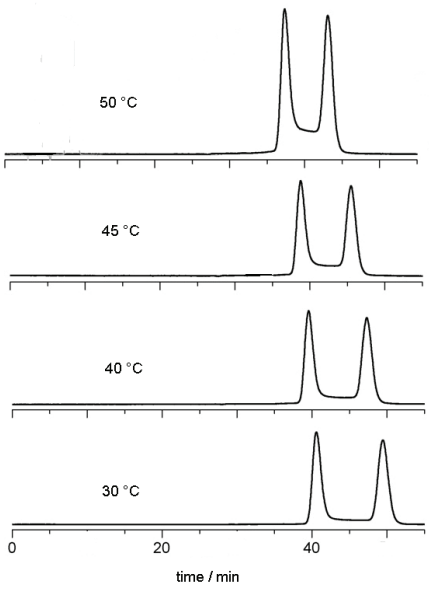


Figure 16. Temperature-dependent chromatograms of 2-MCET on Chiralpak IA, eluent EtAc/TFA (100:0.1). (Modified from Ref. 117)

by 0.001 % to 0.1 % of TFA added to the eluent was effective, Figure 15.[117]

These data, along with data for off-column enantio-merization, enabled semipreparative HPLC separation and deracemization of 2-MCET.

Figure 16 shows chromatograms that reveal temperature dependent rates of racemization, which served as the bases for estimation of thermodynamic parameters of enantiomerization, based on iterative comparison of simulated and dynamic experimental elution profiles.[117,118] This process allowed production of only one (selected) enantiomer from racemic 2-MCET on the semipreparative column (250×10 mm) with *ca.* 80 mg/h productivity.

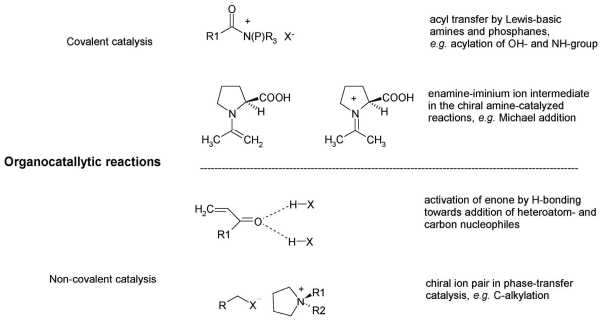
Organocatalysis

Representative Mechanisms in Enantioselective Organocatalysis

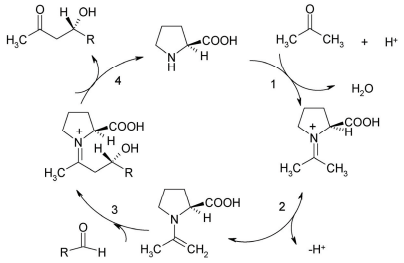
Organocatalysts can be regarded as a "minimum version" of *metal-free enzymes*, and catalytic reactions can be explained by mechanistic considerations inherent to biocatalysis.

Since catalytic effect and the rate acceleration in organocatalysis depends on the interactions between two or more organic molecules, two general mechanistic schemes can be distinguished, Scheme 15.

In the absence of d-electrons from the metal orbitals, two types of bonding interactions between organocatalyst and reactants may be operative; *formation of covalent adducts* and *non-covalent interactions*. Typical



Scheme 15. Examples of covalent and non-covalent organocatalysis.



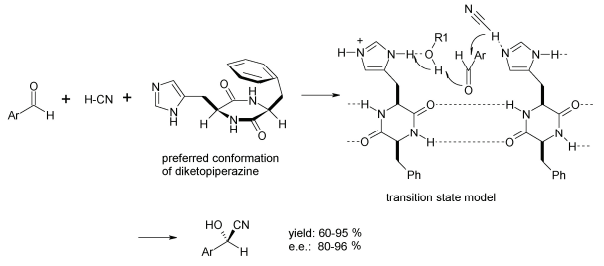
Scheme 16. Catalytic cycle and mechanism of L-proline-catalyzed enantioselective addition of aldehydes to acetone (aldol reaction).

examples of *covalent intermediates* and *non-covalent bonding* interactions are given in the Scheme 15.

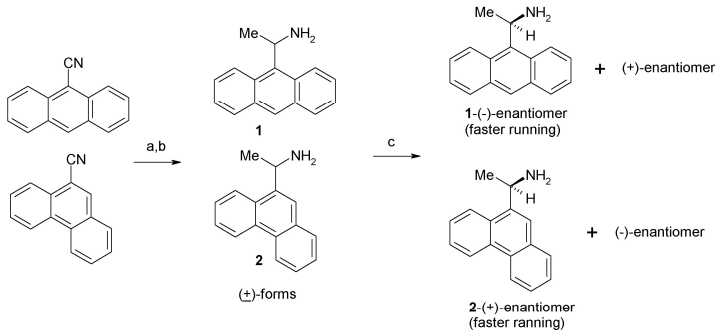
To exemplify covalent catalysis, the catalytic cycle in the L-proline-catalyzed aldol reaction is given in the Scheme 16.[119]

Formation of chiral enamine of L-proline as electron donor corresponds to formation of enamine with L-lysine in the class I aldolases, enzymes that catalyze C-C bond forming reactions *in vivo*. Fascinating aspect of this reaction is that L-proline alone mimics chiral environment of the aldolase active site so effectively that enantiomeric excesses obtained in these reactions are often close to 100 %!

Another example of non-covalent organocatalysis is given in the next section, Scheme 17, some others can



Scheme 17. Mechanims of hydrocyanation catalyzed by diketopiperazine.



Reagents and conditions. a. MeMgI, THF; b. $NaCNBH_3$/THF; c. for **1**: Chiralpak AD. MeOH/Et_2NH (100:0.01) for **2**: Chiralcel OD MeCN/Et_2NH (100:0.1).

Scheme 18. Preparation and enantioseparation of 1-anthrylethylamines **1** and **2**.

be found in the section devoted to phase-transfer organocatalysis.

Centro-chiral Organocatalysts

Selected example of C_1-chiral organocatalytic reactions refers to various origins of organocatalysts. In the first example it is a dimer obtained on cyclization of two homochiral amino acids into 1,4-diketopyperazine derivative, in the second non-natural α-arylethylamines acts as chiral modifiers in heterogeneous catalysis, and the third type of organocatalysts belong to complex natural products, alkaloids quinine and quinidine.

First example of non-covalent organocatalysis is given in the Scheme 17.[120] It outlines one of the most thoroughly studied mechanisms in organocatalysis; enantioselective nucleophilic addition of hydrogen cyanide to a carbonyl group catalyzed by chiral diketopiperazine.[121,122] Diketopiperazine acts as heterogeneous catalysts, the active site being a gel which forms in benzene or toluene. Therefore its preferred conformation in the solid-state has been studied by computational and spectroscopic methods.[123,124] Conformation in solution was studied by NMR in the mixture of benzene and mandelonitrile, thus mimicking reaction conditions.[125] From these studies mechanistic model emerged that invokes diketopiperazine dimer as a catalytic species that promotes proton-relay properties of imidazole unit. Cyanhydrines are obtained in (*R*)-configuration when L-Hys-L-Phe dimer acts as the catalyst, regularly with high yield and over 90 % e.e.[126]

Second example refers to enantiomerically pure 1-arylethylamines, important chiral auxiliaries in stoichiometric and catalytic reactions,[127,128] and for enantiorecognition in CSPs.[129]

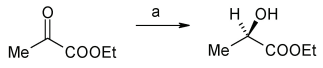
Successful application of preparative chromatographic resolution of racemic 1-arylethylamines on the road to chiral catalytic modifiers is reported by Solladie-Cavallo *et al*.[130] Polycondensed 1-arylethylamines **1** and **2** are characterized by strong steric shielding of stereogenic center by the aromatic units, promoting an effective in chirality transfer and enantiorecognition. Both compounds are prepared in the racemic form, and on gram-scale separated on two polysaccharide based stationary phases, Scheme 18.[130] For anthryl derivative **1** Chiralpak AD was used on both analytical and preparative scale, for phenantryl derivative **2**, however, Chiralcel OD proved more effective.

Enantiomeric purities of both enantiomers of **1** and **2** were over 99 %, except for (–)-**1** (95 % e.e.). It is interesting to note that prior to this publication separation of enantiomers of **1** and **2** was reported and in 8 and 10 % yield, *via* diastereomeric salts with (*R*)-mandelic acid.[131] Later we have reported an improved process for crystallization that afforded (*R*)-(+)-**1** in 56 % yield and 98.6 % e.e.[132]

Pure (+)-enantiomers of **1** and **2** were used as chiral modifiers for catalytic heterogeneous hydrogenation of ethyl pyruvate according to the Scheme 19.[130]

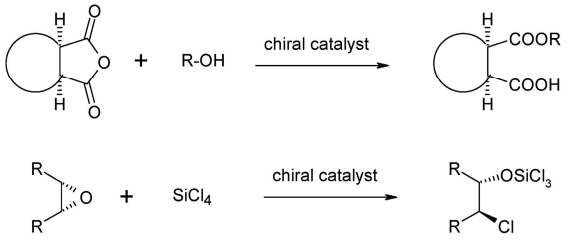
Although enantiomeric purity of ethyl lactate did not exceed ca 40 % e.e., it represents an interesting achievement in view of generally low e.e. often obtained with chiral modified heteroegenous catalysts.[133]

Final example of organocatalytic reaction represents desymmetrization of meso-compounds by C_1 organocatalysts. Meso-anhydrides and meso-epoxides are prochiral building blocks which on desymmetrization became chiral since mirror-image relationship between



Reagents and conditions: a. 5 % Pt/Al_2O_3, chiral modifier (+)-**1** or (+)- **2** (*ca.* 0.01 %), 10-40 × 10^5 Pa H_2/AcOH

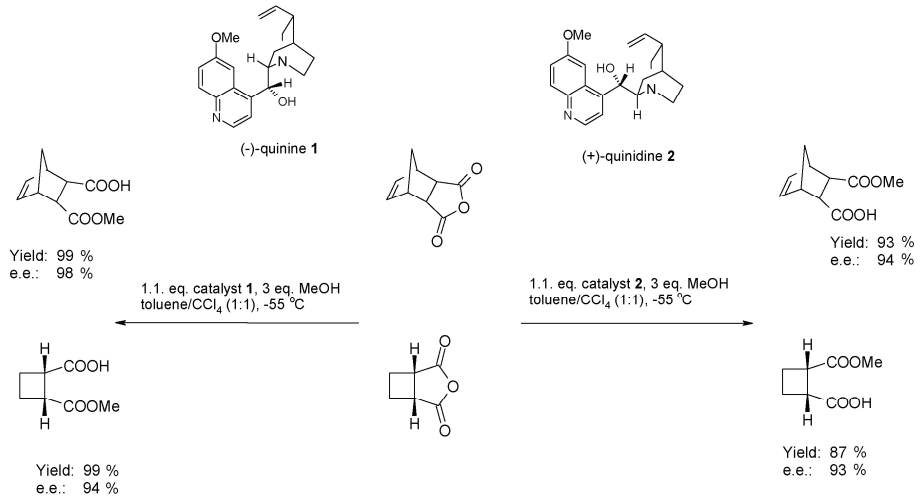
Scheme 19. Enantioselective hydrogenation of pyruvic acid in the presence of chiral modifiers (+)-**1** and (+)-**2**.



Scheme 20. General scheme for desymmetrization of cyclic meso-anhydrides and meso-epoxides.

present in the two enantiomers,[136,137] which results with kinetic resolution of racemate.

Desymmetrization of meso-anhydrides may be successfully completed by solvolysis, usually alcoholysis, catalyzed by the chiral bases. Among most effective organocatalysts for desymmetrization belong cynchona alkaloids (cinchonine, quinine, quinidine), due to concerted binding interactions with substrate by aromatic (quinoline) unit and bidentate *β-tert*-amino-alcohol functionality.[138,139]



Scheme 21. Opposite enantioselectivites in desymmetrization of meso-anhydrides by methanolysis.

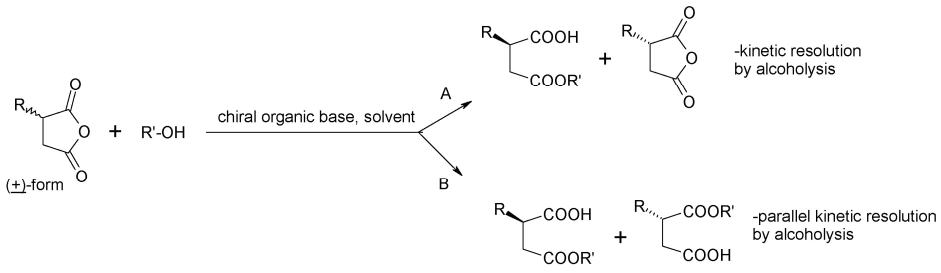
two stereogenic centers is eliminated. This transformation can be generally presented as in the Scheme 20.

It is important to note that two chemically equivalent units in anhydrides and epoxides, C=O and *R*-(CH-O) group respectively, are stereochemically non-equivalent. They are «enantiotopic through internal comparison» according to Mislow and Raban.[134,135] This relation is revealed by reflection through the mirror-plane that bisects meso-compounds. Internal enantiotopicity has the consequence that chiral catalyst can selectively effect transformation at only one of the two units. This situation corresponds to preference of one of the groups «enantiotopic through external comparison»,

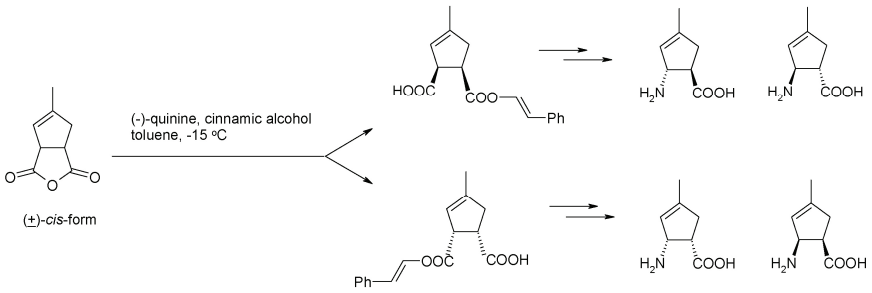
Two interesting aspects of this chiral catalytic process are worth of mentioning. First, two related alkaloids, quinine and qunidine, regularly catalyze alcoholysis of meso-anhydrides with opposite enantioselectivity, as exemplified by the Scheme 21.[140,141] Two enantiomeric hemiesters are obtained with high optical purity, amenable to efficient conversion into more complex products.

Second, the same alkaloids as chiral organic bases catalyze enantioselective alcoholysis of enantiotopic groups in racemic anhydrides, Scheme 22.

However, this process is not yet effected as a simple kinetic resolution (route A), rather as a parallel ki-



Scheme 22. Kinetic resolution and parallel kinetic resolution of racemic anhydride.



Scheme 23. Parallel kinetic resolution of cyclopentene-anhydride on the route to isomeric, enantiopure *β*-amino acids.

netic resolution (route B), that is two enantiomers of the anhydride are converted to regioisomeric esters.[140,141] The following example shows quinine mediated parallel kinetic resolution on the route to novel alicyclic *β*-amino acids, congeners of antifungal agent Icofungipen, Scheme 23.[142]

Complex chiral organic bases of natural origin have proven effective catalysts in desymmetrization and parallel kinetic resolution of anhydrides, as well as in desymmetrization of some other meso-compounds. Many impressive examples demonstrate how effective non-covalent interactions in the organocatalytic process lead to valuable products with high optical purity. Moreover, this type of organocatalysis has revealed all importance of weak interactions in the catalytic processes, and is strong contribution to famous statement of Linus Pauling, that the end of the 20th century will see the progress of chemistry mainly due to deeper understanding of the weak interactions.[143]

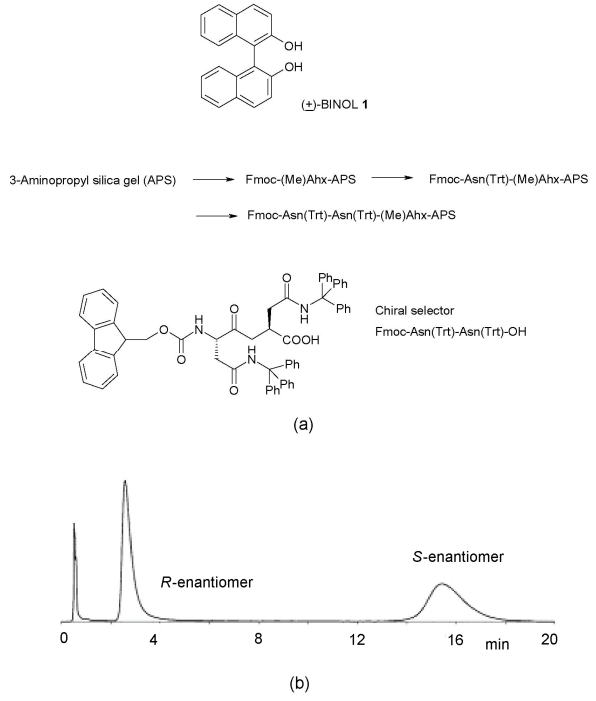


Figure 17. (a) Preparation of Fmoc-Asn (Trt)-Ahx- $Nh(CH_2)_3$-silica CSP for separation of *rac.* **1**; (b) chromatographic resolution of *rac*. BINOL (**1**) on the prepared CSP.

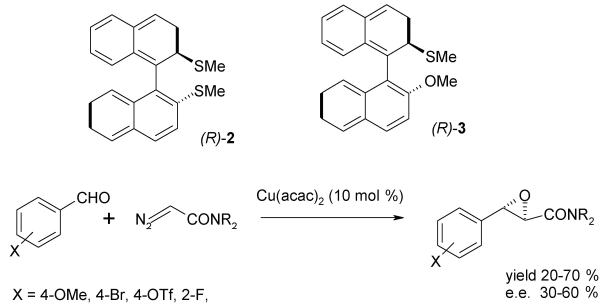
Concluding this section we can state that requirements for effective organic chiral ligands in organometallic catalysis and organocatalytically active chiral molecules are in continuous upgrowith. Chiral liquid chromatography is the methodology that offers access to structurally sophisticated, enantiomerically pure chiral ligands and chiral organic molecules as catalysts. There is a solid bridge appearing between these two fields of organic chemistry and technology; this review is intended as an information source and an insight intoboth fast developing areas.

Axial-chiral Organocatalysts

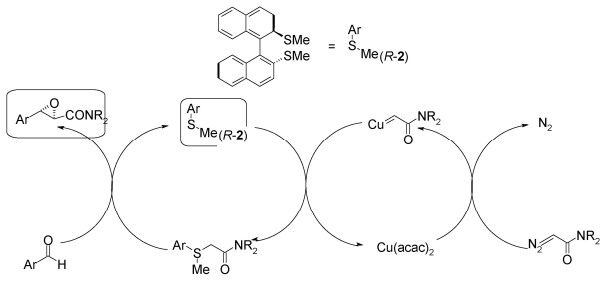
Resolution and Application of BINOL. 1,1'-Bi-2-naphthol (BINOL, **1**) may be considered as prototype of the larger class of atropisomeric chiral molecules with C_2-symmetry and is starting material for preparation of several derivatives of high catalytic efficiency and versatility, as demonstrated in the section *Axial-chiral Ligands*.

First published methods for resolution of racemic BINOL involved separation of diastereomeric salts,[144,145] or thiophosphoramidate derivatives[146] by crystallization. More recently racemic BINOL became one of the most popular analytes in chiral separation and has been studied extensively. Due to its strong π-basic (π-electron donor) properties BINOL is well resolved on brush-type CSPs containing π-acidic 3,5-dinitrobenzoyl (DNB) group within chiral selector, or filler.[147–151] In the recent study efficient resolution of BINOL was effected by a number of peptide-like selectors containing π-basic unit.[152] Most effective selectors were identified by screening a library consisting of 121 members. Impressive resolution is obtained with Fmoc-Asn (Trt)-Ahx-$Nh(CH_2)_3$-silica as the stationary phase. Preparation of this phase and chromatographic separation of racemic **1** is presented on the Figures 17a and 17b.[152]

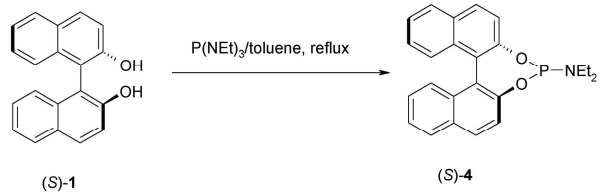
Application of optically pure BINOL derivatives as organocatalysts and ligands is an important contri-



Scheme 24. Application of BINOL congeners (*R*)-**2** and (*R*)-**3** in Cu^{II} catalyzed epoxidation.



Scheme 25. Catalytic cycle for enantioselective addition of sulphur-ylides to aryl aldehydes.



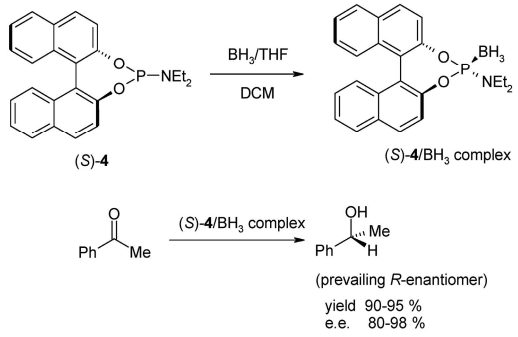
Scheme 26. Synthesis of *S*-**4** from (*S*)-BINOL.

bution to the concept which may be defined as "chiral separation triggers chiral catalysis". Two examples should illustrate catalytic utility of BINOL derivatives.

Transformation of (*R*)-BINOL into bis-dimethylsulfide congener (*R*)-**2** and methylsulfide-methoxy-congener (*R*)-**3** was completed in three steps,[146,153] both are used in sulfur-ylide promoted addition to aryl-aldehydes obtaining glycidic amides.[153] Enantioselective formation of epoxides is presented in the Scheme 24, and some details of the catalytic cycle in the Scheme 25.[153]

As discussed for cyclopropanation in the section *Axial-chiral Ligands*, formation of epoxide comprises formation of *cis*/*trans* racemic pairs; yields and e.e. cited in the Scheme 24 refer to the prevailing *trans*-stereoisomer.

Second example relates to enantioselective reduction of prochiral ketones. Chiral phosphorus catalyst *S*-**4**



Scheme 27. Formation of the reactive (*S*)-4/BH_3 complex and hydrogenation of acetophenone by borane.

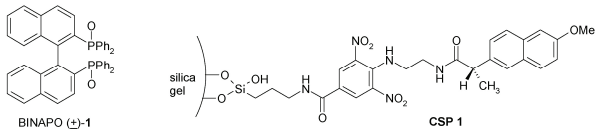


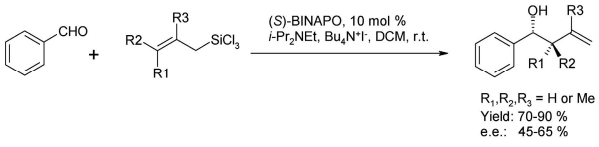
Figure 18. Racemic BINAPO (**1**) and structure of CSP **1**.

was derived from (*S*)-BINOL and triethylaminophosphorus, Scheme 26.[154]

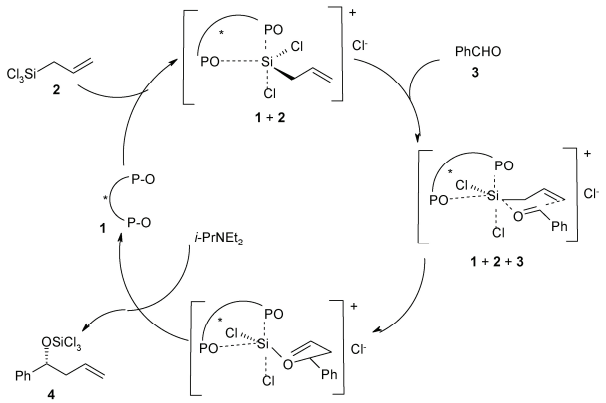
C_2-symmetric (*S*)-**4** contains a stereogenic trivalent P-atom which can donate a lone pair of electrons to borane, and efficiently catalyze the borane reduction of ketone with high enantiomeric excess, Scheme 27.[154]

Resolution and application of BINAPO. BINAPO (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl-bisoxide, **1**) is one of the best-known C_2 symmetric ligands with axial chirality. This bis-P-oxide is separated on the analytical columns filled with brush-type stationary phases.[155–157] We recently reported its separation on specifically designed brush-type CSP-**1**, Figure 18.[158] Application of this stationary phase in SMB technology has enabled multigram separation of (+)-BINAPO and (–)-BINAPO.[159,160]

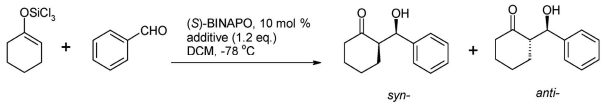
Enantiomerically pure BINAPO (> 99 % e.e.) has found application in many organocatalytic and organometal catalyzed syntheses of chiral target compounds in the enantiomerically pure form. Thus, (*S*)-BINAPO has been used as chiral organocatalyst in enantioselective allylation of aldehydes with allyltrichlorosilane, Scheme 28.[161]



Scheme 28. Allylation of aldehydes with allyltrichlorosilanes catalyzed by (*S*)-BINAPO.



Scheme 29. Proposed reaction mechanism for bis-*P*-oxide catalyzed allylation of aldehydes.

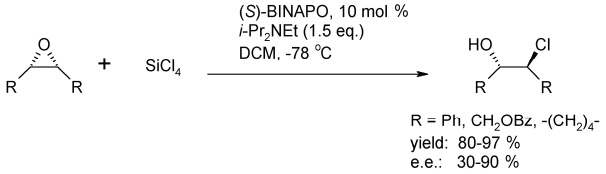


Scheme 30. Asymmetric aldol reaction catalyzed by (*S*)-BINAPO.

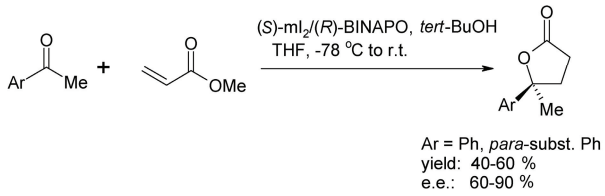
Characteristic of this reaction is formation of one C–C bond and two stereogenic centers, along with migration of the double C=C bond to the terminal position. Plausible reaction mechanism is presented in the Scheme 29.[162]

Asymmetric aldol reaction represents another C–C bond-forming reaction catalyzed by (*S*)-BINAPO as the Lewis-base, Scheme 30.[162,163] In this reaction two stereogenic centers are also formed contemporaneously, therefore diastereoselectivity (*syn*/*anti*) ratio is an additional issue. With *i*-Pr_2NEt as additive, alone or in combination with quartenary ammonium salt, *syn*/*anti* ratio up to 1:14, *i.e.* 93 % diastereomeric excess (d.e.) was achieved along with 87 % e.e. for the prevailing *anti* isomer.[163]

Asymmetric ring opening of meso-epoxides is also catalyzed by (*S*)-BINAPO, Scheme 31.[164] For the mechanistic reasons only *trans*-chlorohydrine can be formed on the ring opening by the activated chlorosilane; fine tuning of the reaction conditions led to 94 % yield and 90 % e.e. of *trans*-isomer with R = Ph.



Scheme 31. Asymmetric ring opening of meso-epoxides catalyzed by (*S*)-BINAPO.



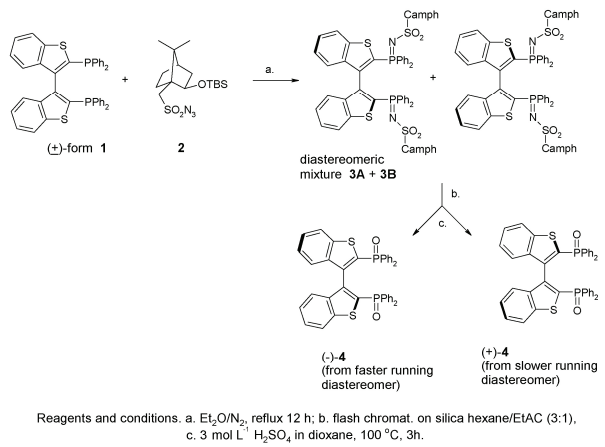
Scheme 32. Reductive coupling of arylketones with methylacrylate.

Chiral Lewis-base character of (*R*)-BINAPO has been explored in reductive coupling of ketones with *α,β*-unsaturated esters to *γ*-lactones promoted by Sm^{II} complex, Scheme 32.[165]

Although this reaction is neither catalytic in SmI_2 nor in (*R*)-BINAPO, both are required in 100 % molar exces, it has great synthetic potential enabling construction of biologically important *γ*-butyrolactones.

Final example in this section is devoted to preparation and separation of BINAPO congener BITIANP-O (**4**), bis-diphenylphosphine oxide derived from benzothiophen.[166] The route outlined in the Scheme 33 elegantly solves the problem of site-selective oxidation of phosphine units into phosphine-oxides in the presence two thioether units prone to form sulphoxide. To this aim Staudinger reaction of *rac.* **1** with chiral, camphor derived sulphonyl azide **2**, afforded diastereomeric phosphinimines **3A**/**3B**, which are separated by flash chromatography on silica. On hydrolysis faster running diastereomer afforded (–)-**4**, and slower running (+)-**4**, both enantiomers are amenable for application in chiral catalysis.

In conclusion, above examples demonstrate high utility of the tendem technology; SMB separation of racemic BINAPO and its congener, and application as bidentate ligand in organocatalyzed or organometal



Reagents and conditions. a. Et_2O/N_2, reflux 12 h; b. flash chromat. on silica hexane/EtAC (3:1), c. 3 mol L^{-1} H_2SO_4 in dioxane, 100 °C, 3h.

Scheme 33. Preparation of enantiomers of bis-phosphin-oxide **4**.

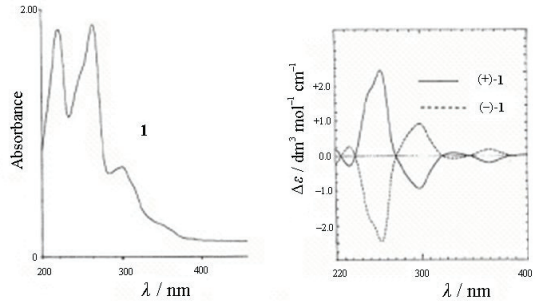
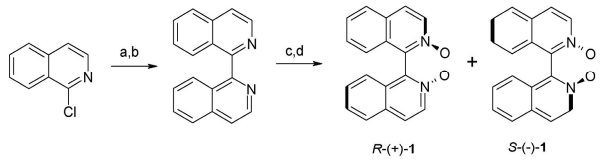


Figure 19. UV Spectrum of *rac*. **1** and CD spectra of its enantiomers.



Scheme 34. Synthesis and enantioseparation of *rac*. **1**.

complex-catalyzed reactions.

Resolution and Application of C_2 *Symmetric Chiral* N-*oxides*. Bis-*N*-oxides with axial chirality can be separated into enantiomers by chromatographic and non-chromatographic methods. First chromatographic separation was completed with racemic bis-isoqionoline *N*-oxide (**1**).[167] Using Chiralcel OD preparative column and hexane/ethanol (7:3) as eluting system two enantiomers were separated with huge retention times 52.55 min and 64.16 min, respectively. CD and UV spectra of the enantiomers of **1** have nicely revealed that the two main transition moments extended along the long axis of the two isoquinoline nuclei interact with each other to give exciton coupling (EC) in the CD spectrum, Figure 19.

Interestingly, two extrema at 299 nm and 263 nm form negative couplet for (+)-**1** and positive couplet for (–)-**1**. The whole concept of preparation and separation of (+)-**1** and (–)-**1** is outlined in the Scheme 34, demon-

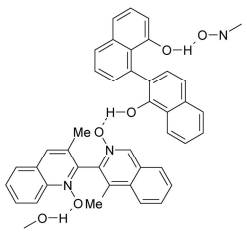
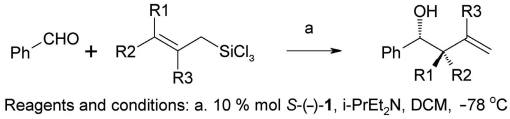


Figure 20. Two-dimensional presentation of the network of hydrogen bonds in the continuous chain formed by (*S*)-BINOL and bis-*N*-oxide **2**.



Scheme 35. Enantioselective allylation of aldehydes catalyzed by (–)-**1**.

strating simplicity of the road to C_2-symmetric, optically pure, catalytically valuable structure.[167]

An imaginative non-chromatographic method of enantioseparation of *rac.* bis-*N*-oxide **2** derived from bis-quinoline comprises complexation with (*S*)-BINOL (chromatographically seprated on CSP!), as outlined in the Figure 20.[168]

Two distereomeric complexes are formed, and (*R*)-**2**/(*S*)-BINOL complex crystallizes from DCM/hexane forming continuous chains of hydrogen bonded species. *N*-oxide units act as electron-pair donors, *i.e.* proton acceptors, with a short (1.7 Å) hydrogen bond distance.[168] Additional stabilization of the complex is achieved by edge-to-face orientation of the naphthyl and quinolyl aromatic units along the chain. This complex is additionally purified by chromatography on silica gel, and for the separated (*R*)-**2** be > 99 % e.e. was determined using Chiralcel OD stationary phase. Again, (*S*)-**2** and (*R*)-**2** were eluted with huge difference in retention times, 17.7 min and 33.8 min, respectively, when a mixture hexane/2-propanol (3:1) was used as eluent.

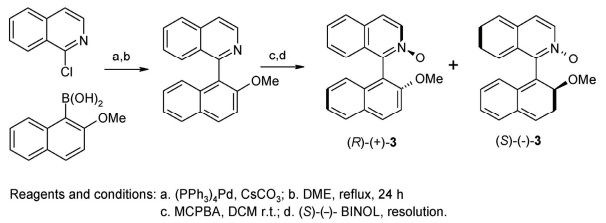
Catalytic activity of axial-chiral bis-*N*-oxides was first reported by Nakajima *et al.*,[160] who used (*S*)-(–)-**1** and (*S*)-(–)-**2** as chiral catalysts in enantioselective allylation of aldehydes according to the Scheme 35.

The importance of this one-step catalytic reaction stays in the contemporaneous formation of new C–C bond, migration of the old C=C bond, elongation of carbon framework, and formation of one or two stereogenic centers in enantioselective fashion. As an illustration, set of the data for the reaction in the Scheme 26 are presented in the Table 2.

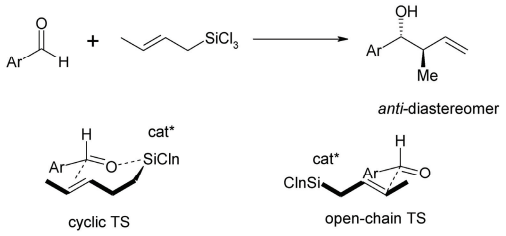
Preferred formation of *anti*-diastereomers when R1#R2 is explained in the more recent paper of Kochovsky *et al.*[170] These authors have prepared axial-

Table 2. Enantioselective alkylation of benzaldehyde with allyltrichorosilanes catalyzed by (*S*)-**1**

entry	R1	R2	R3	yield / %	e.e. / %	config.
1	H	Me	H	68	86	(1*R*,2*R*)
2	Me	H	H	64	84	(1*R*,2*S*)
3	Me	Me	H	52	78	(*R*)
4	H	H	Me	70	50	(*R*)



Scheme 36. Preparation and resolution of racemic **3**.



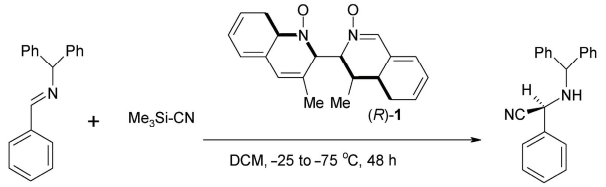
Scheme 37. Proposed transition-states for *N*-oxide catalyzed alkylation of aldehydes.

chiral mono-isoquinolyl-*N*-oxide (*R*)-(+)-**3**, by resolving racemic **3** with (*S*)-BINOL, Scheme 36.

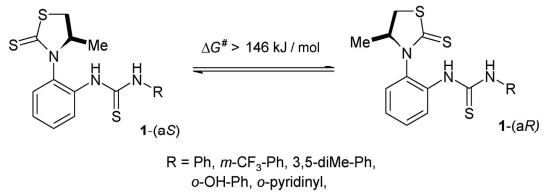
Applying (*R*)-(+)-**3** in the same reaction as in the Scheme 27, the authors obtained the same or even higher e.e., revealing that the second N–O functionality is not a prerequisite for high asymmetric induction. Exclusive or prevalent formation of *anti*-diastereomer is compatible with a generally accepted cyclic transition state, whereas formation *anti*/*syn* mixtures suggest participation of the open-chain transition state, Scheme 37.

Due to latent capacity of *N*-oxides to coordinate silicon atom, cyano group can also be transferred from tralkylsilylcyanides to C=N double bond, an electronically similar process to the transfer of allyl-anionic species from allyltrichlorosilane to C=O double bond. Such Strecker-type cyanation of an imine bond is catalyzed by bis-*N*-oxide (*R*)-**1**, used in the stoichiometric amount, Scheme 38.[171] The reaction was pushed nearly to completeness, but only 58 % e.e. of phenylglycine nitrile was achieved.

There are other useful synthetic reactions completed in enantioselective fashion with pyridine-type *N*-oxides as catalysts. Worth of mentioning are conjugate additions of the Michael-type, epoxidations of olefins, desymmetrization of epoxides, and reductions



Scheme 38. Strecker-type asymmetric cyanation of imine.



Scheme 39. Conformational, atropisomeric equilibrium for thioereas.

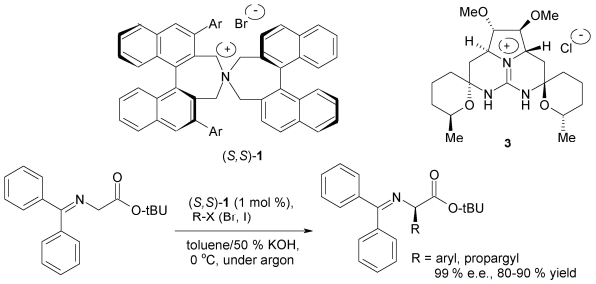
of ketones; a report on application *N*-oxides as asymmetric catalysts has recently appeared.[172]

Resolution and Application of Axially Symmetric Thiourea Derivatives. Enantioseparation of a series of nonracemic, atropisomeric thioureas, is reported in respond to continuous need for enantiopure thioureas, recently introduced as highly effective chiral organocatalysts,[173–175] and neutral, enantioselective anion receptors.[176] Equilibrium between atropisomeric chiral thioureas is given in the Scheme 39, and barrier to rotation in **1** was estimated to be larger than 146 kJ/mol, allowing separation into configurationally stable enantiomers.[177]

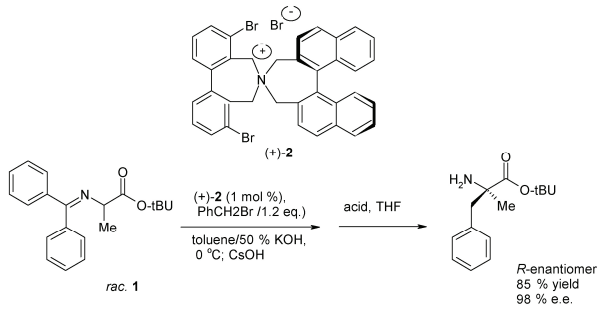
Structure of the urea **1** (R = Ph) obtained by X-ray diffraction analysis revealed that conformation of the urea group in the crystal is suitable to provide a double H-bond donating site, whereas NOESY assignement in solution revealed that (*Z*,*E*) conformation is largely preferred. Chromatographic enantioseparations of thioureas **1** was completed on the (*S*,*S*)-Whelk O1 CSP using hexane/2-PrOH (8:2) as eluent; α-values varied between 1.34 and 1.75.[177]

C_2 *Symmetric Quaternary Ammonium Ions in the Phase-transfer Organocatalysis*. Dimeric quarternary ammonium ions with spiro-nitrogen, derived from binaphthyl-2,2'-carboxylic acids represent specific group of C_2 symmetric organocatalysts, They are highly effective in phase-transfer catalyzed (PTC) enantioselective alkylations. Thus, (*S*,*S*)-**1** was found effective in enantioselective alkylation of benzophenon-imines derived from glycine ester, Scheme 40.[178,179]

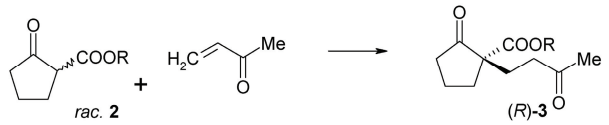
Even more effective C_2 symmetric quarternary



Scheme 40. Enantioselective PTC alkylation of prochiral glycin-imine.



Scheme 41. PTC enantioselective alkylation of *rac*. alanyl-imine.



Scheme 42. PTC Michael addition to *rac*. α-ketoesters.

organocatalyst (+)-**2** contains one conformationally flexible biphenyl subunit and catalyses alkylation of glycinate ester with 95 % yield and 92 % e.e.[180]

Catalytic power of quaternary PTC (+)-**2** was proved when alkylation of otherwise unreactive *tert*. C atom in *rac.* **1** was completed with 85 % yield and 98 % e.e., Scheme 41.[181]

It is important to note that imino derivative of *rac.* alanine, was benzylated into *R*-enantiomer with quartenary carbon due to stabilization of one enantiomer of otherwise configurationally unstable carbonum ion.

Similarly unreactive *tert.* C atom in α-keto ester **2** undergoes Micahel addition to methyl-vinyl ketone (MVK) affording (*R*)-**3** with 80–90 % e.e. and in 85–90 % yield, Scheme 42.[182]

The Nagasawa group demonstrated that C_2-symmetric guanidine **3**, due to its strong basicity can act as chiral bases in PTC alkylations of the glycinate according to the Scheme 40.[183] Eantioselectivities ranged between 80–90 % e.e. and yields between 55–80 %.

Planar-chiral Organocatalysts

Ferrocenyl-azoles, DMAP Congeners. This group of catalysts are enlightening example of how an effective achiral catalyst, 4-dimethylamino-pyridine (DMAP), well know for its activating effect in acyl-transfer,[184]

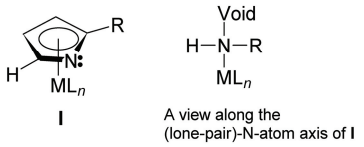


Figure 21. Planar-chiral (π-heterocycle) ML_n complex.

prompted development of chiral catalytic assembly. The rationale behind design of such planar-chiral DMAP derivatives is given in the Figure 21.[185,186]

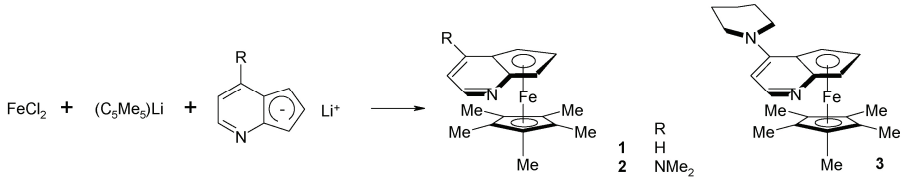
Planar chirality is created by incorporation of ferrocenyl unit in the vicinity of the nucleophilic N atom. Large steric demand on the bottom side leaves top-side for the approach of the reagent, and cyclopentadienyl unit serves to distinguish right (R, occupied) from the left (H, free) space for this approach. Simple route to such apparently complex molecules is exemplified by synthesis of racemic planar-chiral compounds **1**–**3**, Scheme 43.[187]

It is important to note that in these organometallic compounds ferrocenyl unit acts only as the steric perturber. Fe ion not engaged in any covalent or non-covalent interactions during the catalytic processes, and therefore such structures may be classified as organocatalysts. Racemic compounds **1**–**3** are successfully separated on Chiralcel OD column, "the method of choice for resolving our planar-chiral heterocycles, at least during the catalyst-development stage", as stated by the author.[186]

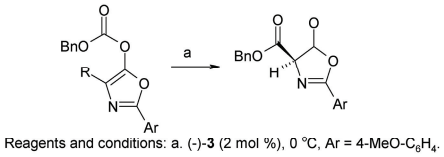
Large difference in the retention times (R_t) are achieved also for the analogs of **2**. During semi-preparative separation of 4-pyrrolidinyl derivative racemic **3**, (+)-enantiomer was collected between 7.08 and 8.50 min, and (–)-enantiomer from 14.4 to 19.3 min (Chiralcel OD column, 1 cm × 25 cm, EtOH/hexane/ Et_2NH (50:50:0.4), 3.0 mL/min).[186]

An example of enantioselective catalysis effected by (–)-**3** is given in the Scheme 44, where on acyl migration quaternary stereocenter is constructed in the enantioselective fashion with e.e. regularly over 90 %.[187]

Synthesis and enantioseparation of ferrocenyl(alkyl)azoles **1**–**4** represents another case of successful tandem "racemic synthesis-chromatographic enantioseparation". Synthesis of racemic **1**–**4** was com-



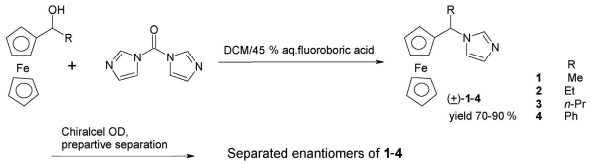
Scheme 43. Synthesis of racemic **1**–**3**.



Reagents and conditions: a. (-)-**3** (2 mol %), 0 °C, Ar = 4-MeO-C_6H_4.

Entry	R	*e.e.* / %	*yield* / %
1	Me	91	94
2	Et	90	93
3	$PhCH_2$	90	93
4	allyl	91	93
5	isobutyl	92	95
6	CH_2CH_2SMe	88	94

Scheme 44. Enantioselective *O*,*C*-acyl migration in azlactones catalyzed by planar-chiral organocatalyst (–)-**3**.

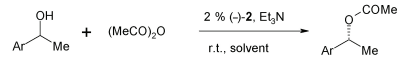


Scheme 45. Synthesis and enantioseparation of racemic planar-chiral ligands **1**–**4**.

pleted in high yields from racemic α-ferrocenylcarbinols and activated azoles in boiling dichloromethane (DCM), according to the Scheme 45.[188]

It is important to note that **1**–**4** have only central chirality, no planar chirality. Due to high structural resamblence to planar chiral ferocenes, and exemplary chromatographic separation of their enantiomers they are discussed wihin this section. Separation of racemic **1**–**4** was achieved on Chiralcel OD, with *n*-hexane/*i*-PrOH (100:4) as eluent. Favorable chromatographic parameters for **1**–**4** (α 1.14–1.37, K_1' 5–9, and K_2' 7–10) enabled effective separation of enantiomers on preparative scale. Applications of such ferrocene-based ligands is repeatedly reported, some examples are given in this section.

Planar-chiral DMAP congeners proved rather versatile catalysts. Beside *intramolecular* C–C bond-forming reactions,[187] they are effective in catalysis of *intermolecular* C–O and C–N bond-forming reactions, *e.g.* in acyl-transfer to alcohols and amines. When performed on racemic substrates, both reactions represent non-enzymatic kinetic resolution, affording one prevalently acylated enantiomer. Traditionally, kinetic resolutions by enantioselective acylation of racemic alcohols and amines were completed by enzymes, and this topic is repeatedly reviewed.[189,190] In this context we would like to mention our contribution to the studies of the conformational effects in acyclic,[191,192] and cyclic[193–196] racemates on the efficacy of kinetic resolution. Efficacy of such processes is measured by selectivity factor, which is defined as ***s***-value or as *E*-value calculated according to



Solvent	conversion after 1 h / %	***s***-value
DMF	6	3.4
MeCN	10	3.6
DCM	14	7.0
***t*-amyl alcohol**	**36**	**27.0**

Entry	unreacted alcohol, major enantiomer		***s***-value Et_2O/*t*-amyl alcohol
1		14	**43** (99 % e.e. 55 % conv.)
2		52	**95** (96 % e.e. 51 % conv.)
3		22	**71** (99 % e.e. 53 % conv.)
4		22	**65** (95 % e.e. 52 % conv.)

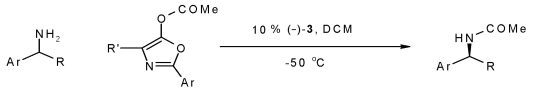
Scheme 46. Examples of enantioselective acylation of 1-aryl carbinols catalyzed by (–)-**2**.

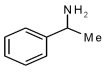
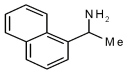
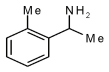
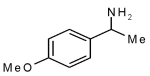
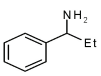
Sih *et al.*,[197] and is defined by the ratio of the rates for fast-reacting and slow-reacting enantiomer.

Kinetic resolution of racemic arylalkyl carbinols by chiral DMAP-ferrocene derivative (–)-**2** is outlined in the Scheme 46, effects of the solvent and large groups in the substrate are summarized in the tables.[198]

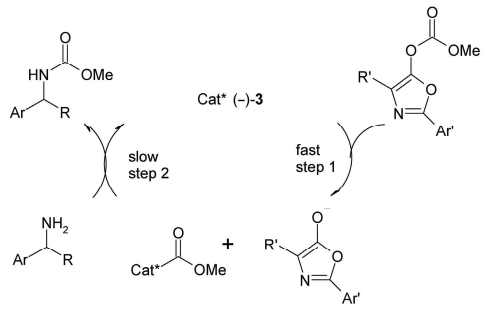
The ***s***-values obtained with (–)-**2** in *tert*-amylalcohol as the solvent approach the best ones obtained by *enzymatic kinetic resolutions*,[189,190] and enables isolation of both alcohol and acetate with excellent enantiomeric purities.

Compound (–)-**3** in combination with *O*-acylated azlactone as acyl donor was reported as the first effective catalyst for non-enzymatic acylation of amines, Scheme 47.[199] High ***s***-values are obtained only with azlactones at low temperatures and at 10 % loading of



Amine	***s***-value
	12
	27
	16
	11
	16

Scheme 47. Kinetic resolution of 1-arylalkylamines catalyzed by (–)-**3**.



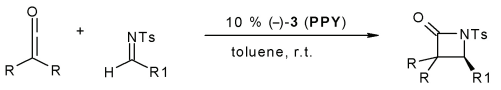
Scheme 48. Proposed mechanism of acylation catalyzed by (–)-**3**.

the catalyst, whereas with traditional acylating agents, anhydrides, vinyl esters and acyl chlorides, essentially no enantioselection was obtained in the presence of (–)-**3**. The authors explain this specific kinetic resolution by the catalytic cycle outlined in the Scheme 48.

Catalyst reacts rapidly with acylating agent to produce an ion pair, which has high steady-state concentration, *i.e.* represents resting state of the cycle. In the stereochemistry-determining step transfer of methoxycarbonyl group to the amine take place furnishing enantiomerically enriched carbamate and (–)-**3** for recycling.

In view of easy acylation of planar-chiral DMAP derivatives, it is not surprising that they interact with ketenes in enantioselective addition reactions. First was described addition of alcohols to ketenes,[200] and more recently formation of *β*-lactames in enantioselective fashion, Scheme 49.[201]

The above reaction, known as Staudinger reaction,



R	R1	e.e. / %	yield / %
-$(CH_2)_6$-	-Ph	81	84
-$(CH_2)_6$-		92	90
-$(CH_2)_6$-		91	82
-$(CH_2)_6$-		94	89
-$(CH_2)_6$-		94	76
Et		92	93
Et		92	83

Scheme 49. Catalytic enantioselective Staudinger reaction catalyzed by (–)-**3**.

represents 2+2 cycloaddition of ketene to an imine, and provides an efficient route to biologically important enantiopure *β*-lactames. Data from the Scheme 48 reveal that catalyst (–)-**3** couples symmetric ketenes with a diverse set of aldimines affording *β*-lactames with e.e. mostly above 90 %.

CONCLUSIONS AND PROSPECTIVE

Catalytic production of enantiomerically pure compounds is becoming the most explored field in organic synthetic chemistry. "Chiral variants" of many synthetic reactions, used over the last century to produce racemic mixtures, are nowadays developed to the level of producing > 99 % pure enantiomers, and mostly in the catalytic fashion. Many of these reactions are scaled-up to multi-ton production of commercial products, some examples are given in this review. However, there is still need for cheaper, less complex and more selective catalytic systems, in particular for more stable catalytic complexes under variety of reaction conditions, *e.g.* in aqueous media and at elevated temperatures and pressures. There is also need for more effective catalysts enantioselective catalysis, with high turn-over number (TON) and low catalyst loading. All these unmet aspects of chiral catalysis prompt present research of both, effective chromatographic separation methods for obtaining optically pure compounds to serve as organocatalysts or as ligands in organometallic catalytic complexes, and their application in novel, more effective catalytic reactions.

Acknowledgements. This overview is stimulated by the many-year long collaboration with friends and colleagues at CAT-BIO Laboratory and Chirallica Ltd. The former unit is presently headed by Dr. Z. Hameršak and Dr. V. Vinković the later by Dr. M. Roje; to all of them I am particularly indebted. The names of many other valuable collaborators appear in the cited papers; my gratitude goes to all of them for their enthusiastic collaboration and support.

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SAŽETAK

Separacija enantiomera kromatografijom kao pokretač kiralne katalize. Premostni pregled

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Kiralna ili asimetrična kataliza je najdjelotvorniji pristup kiralnim molekulama u enantiomerno obogaćenom obliku. Danas su metode izbora na ovom području organokataliza i organometalna kataliza. U prvom primjeru enantiomerno čiste organske molekule različitih simetrijskih klasâ pokazuju katalitičko djelovanje, u drugom organska molekula djeluje kao ligand u organometalnom kompleksu koji pokazuje katalitičku aktivnost. U oba je slučaja mala količina, miligrami ili grami, enantiomernog čistog organskog ili organometalnog katalizatora dovoljna za pripravu znantnih količina, grama ili tona, kiralnog produkta od akademskog ili komercijalnog interesa. Budući da su potrebne ograničene količine kirlanih organskih molekula u optički čistom obliku da bi djelovale kao katalizatori ili bile dio katalitičkog sustava, to resolucija racemičnog materijala preparativanom kromatografijom, naročito kromatografijom simuliranih pokretnih čestica (engl. simulated moving bed, SMB), predstavlja vrijedan pristup. Izneseni su primjeri separacije racemata kiralnom kromatografijom i SMB tehnologijom u katalitički primjenjive enantiomere te primjene enantiomera različitih simetrijskih klasa u djelotvornim katalitičkim procesima.