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ENANTIOSELECTIVE CATALYSIS WITH TRANSITION METAL COMPLEXES

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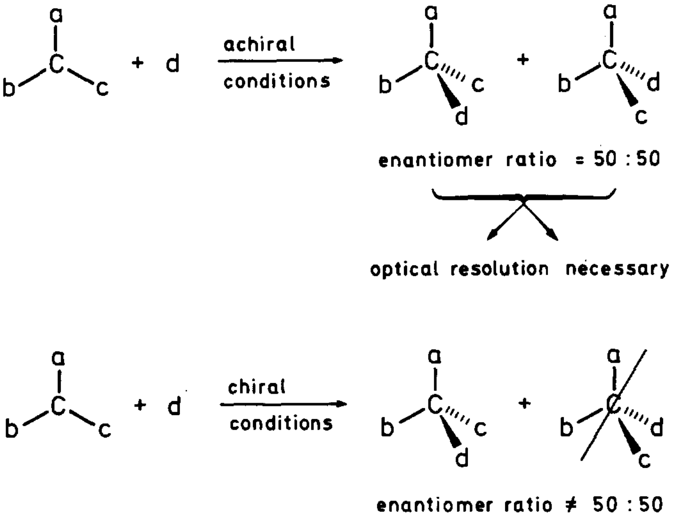
The concept of enantioselective catalysis

In the reaction of a prochiral precursor C(abc), e.g. an sp^2-hybridized carbon atom carrying three different substituents, with a reagent d an asymmetric carbon atom C(abcd) is formed (Scheme 1, upper part). Under achiral conditions attack from the front side and from the back side have equal probabilities, and the



examples for chiral conditions:

- optically active solvent
  (large quantities needed)
- a, b, c or d optically active
  (stoichiometric quantities needed)
- optically active catalyst
  (trace quantities needed)

SCHEME 1. Chiral centers from prochiral precursors.

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asymmetric product is formed as a racemic mixture. If a pure enantiomer is required a subsequent optical resolution is necessary.

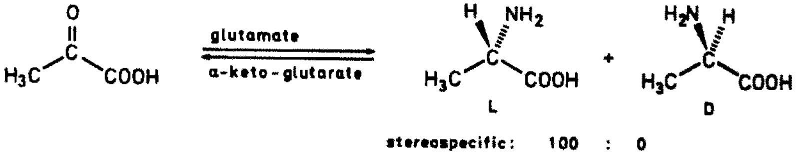
If the same reaction is carried out under chiral conditions the optically active information present in the system differentiates between front side attack and back side attack. As a consequence the enantiomer ratio will be different from 50/50. The ratio will be close to 50/50 if the chiral information is not very effective. Of course, ratios close to 100/0 in highly stereoselective or even stereospecific reactions are most desirable; this is indicated in Scheme 1 by crossing out one of the two enantiomers.

The lower part of Scheme 1 lists examples of chiral conditions for carrying out reactions, arranged in order of decreasing quantities of optically active auxiliary required. (i) Large quantities are needed for a reaction performed in an optically active solvent. As optically active solvents usually are expensive this is not a very economic approach with regard to the amount of chiral information needed. (ii) The optically active auxiliary can be a chiral substituent, either in the precursor C(abc) or in the reactant d. In this case, called asymmetric synthesis or enantioselective synthesis, a stoichiometric amount of chiral information is sufficient. (iii) If the chiral information is made part of an optically active catalyst a minimum amount is required because the catalyst re-enters each catalytic cycle with its optical activity. This concept is called enantioselective catalysis. Its application leads to a multiplication of the chiral information contained in the catalyst. Thus, in principle, with a small quantity of an optically active catalyst it should be possible to make large quantities of optically active products.

Enantiospecific catalysis with enzymes

The elegant and economic concept of enantiospecific catalysis is used by the enzymes in man, animals, and plants to produce all the optically active substances needed for life. This is demonstrated in Scheme 2 for the transamination of pyruvic acid, a prochiral precursor of type C(abc), with glutamate to give L-alanine and α-keto-glutarate. This reaction is catalyzed by the enzyme transaminase.

Enzymes are high molecular weight proteins. The transaminase in Scheme 2, isolated from pig heart, has a molecular weight of 115 000. Its chiral information, as for all the enzymes, is due to the L-amino acids which build up the peptide chain and to the folding of the protein. The enzyme is active under very mild conditions (body temperature and almost neutral pH). Its turnover number is 66 000 catalytic cycles



Typical conditions: 37°C, pH 8

mol. weight pig-heart-transaminase: 115 000

enzyme activity: turnover number 66 000 min^{-1}

SCHEME 2. Alanine by enzymatic transamination.

per minute [1,2], an average value in the range of turnover numbers covered by the enzymes [3]. Typically, the new asymmetric center in alanine is formed stereospecifically in the L-configuration, required for metabolism. Thus one enzyme molecule catalyzes the synthesis of 66000 L-alanine molecules every minute: enantioselective catalysis at its best. It is by this approach that nature produces all its optically active compounds.

However, enzymes perform these spectacularly fast and stereospecific reactions only with their natural substrates. Even for molecules closely related to the natural substrates a remarkable drop in enzymatic turnover and stereoselectivity is usually observed. In this situation the question arises whether it is possible to develop man-made enantioselective catalysts. They not only could be used to prepare natural optically active substances but also optically active products not occuring in Nature.

After this introduction into the concept of enantioselective catalysis and Nature's use of it with the enzymes I will make some historical remarks and give a short summary of the part played by optically active compounds. Then I will describe some of the contributions which my group has made to the field of enantioselective catalysis in the past six years.

Historical remarks

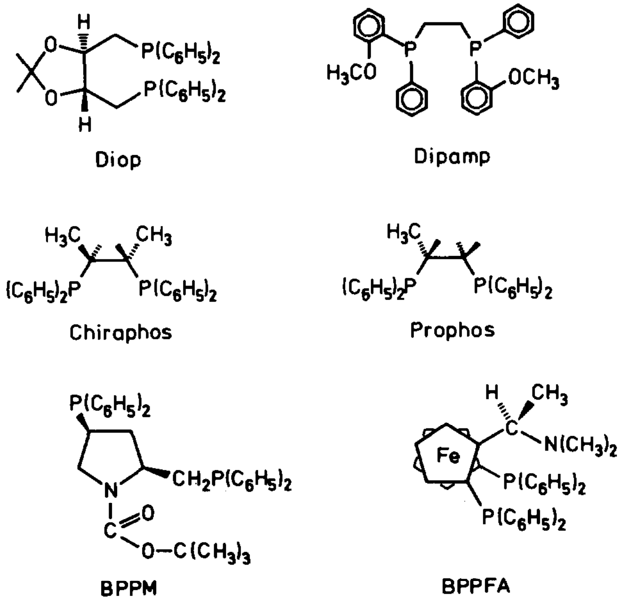
The first example of homogeneous enantioselective catalysis to appear in the literature dates back to 1966. In the reaction of styrene with ethyl diazoacetate *cis* and *trans* isomeric cyclopropane derivatives were formed, each consisting of a pair of enantiomers. For the *trans* isomers the optical induction was 6% ee (enantiomeric ratio 53/47) [4].

In 1968, Horner et al. [5] and Knowles et al. [6] independently found that prochiral olefins could be hydrogenated enantioselectively with Rh complexes of the Wilkinson type, containing optically active phosphines PMePrPh, chiral at the phosphorus atom. However, with these unidentate phosphine ligands only poor optical inductions were achieved.

Progress in the field of enantioselective hydrogenation of olefins came from the use of amino acid precursors as a new class of substrates [7]. The hydrogenation of *Z*-α-acetamidocinnamic acid to give *N*-acetylphenylalanine, shown in Scheme 5, is discussed below. The origin of the high optical inductions with dehydroamino acid substrates lies in the bidentate binding by the olefinic double bond and the acid amide oxygen atom [8].

A milestone in the development of enantioselective catalysis is Kagan's synthesis of the diphosphine Diop (Scheme 3), starting from tartaric acid [7,9]. The bidentate coordination of the ligand Diop reduces the number of possible conformations open to two unidentate ligands, thereby favouring high optical inductions [10]. Furthermore, the two phenyl rings at the phosphorus atom turned out to be good chirality transmitters from the ligand backbone, where the inducing chirality is located, to the metal coordination positions, where the prochiral substrates are converted into the optically active products. This point will be described in detail in the last paragraph. With Rh complexes of Diop, hydrogenation of *Z*-α-acetamidocinnamic acid according to Scheme 5 gave *N*-acetylphenylalanine with an enantiomer ratio of 90.5/9.5 [11].

This finding stimulated worldwide research in the synthesis of optically active



SCHEME 3. Prominent optically active diphosphines.

diphosphines [12–17]. From the variety of new ligands, five are depicted along with Diop in Scheme 3. Dipamp is the basis of the first commercial application of the concept of enantioselective catalysis [18]. With its Rh complex L-Dopa, a drug for Parkinson's disease, is produced in the Monsanto amino acid process by hydrogenation of the corresponding dehydroamino acid. Prophos [19], prepared from lactic acid, has one asymmetric center in the chelate backbone, whereas Chiraphos [20] has two. BPPM [21] is a derivative of the amino acid proline and BPPFA [22] is a ferrocene derivative.

It must be emphasized that enantioselective catalysis is usually carried out homogeneously in solution. In the homogeneous approach ligands and complexes can be tailored so that in the ideal case only one catalytically active species is present. As a surface in heterogeneous catalysis usually consists of different kinds of active sites the overall selectivity of all of them as a rule is lower than that of an optimized species in homogeneous catalysis.

Most of the work in the field of enantioselective catalysis centered around the hydrogenation of prochiral olefins especially with regard to the amino acid precursors as unsaturated substrates. But the concept is increasingly applied to other reactions due to the growing demand for optically active products.

Significance of optically active substances

The L-form of asparagine, one of the 20 amino acids which are the constituents of proteins, tastes bitter, whereas the *R*-isomer is sweet. The (+)-form of estrone is a hormone, whereas the (−)-form has no hormone activity. There are barbiturates for which one enantiomer has a narcotic effect and its mirror image isomer has a convulsive activity [23]. The *R*-isomer of thalidomide (Contergan) is a sleeping aid, whereas the *S*-isomer is teratogenic. The metabolites of (+)-benzopyrene are carcinogenic, whereas those of the (−)-isomer not. This list, which could be continued, shows that the two enantiomers of a racemic mixture behave differently in biological systems. The reason for this is that all living beings contain only L-amino acids in their proteins, D-sugars in their DNA, etc. Thus the uniform chirality of biological structures results in diastereomeric interactions with the components of a racemic mixture. If synthetic compounds are to be used as additives to food, as supplements of animal food, as parts of drugs and insecticides, etc. they should be used optically pure to avoid secondary effects and to ensure that the minimum quantity is sufficient. Some examples will demonstrate this strategy.

In the cola-mix beverages the new sweetener aspartame is used, the methyl ester of a dipeptide consisting of aspartic acid and phenylalanine. To supply the necessary quantities of L-phenylalanine, the world production had to be raised from 80 tons a year [24] to several thousand tons a year.

Animal feed based on corn is deficient in methionine and lysine. Whereas methionine can be metabolized by pigs and poultry as the racemic mixture, lysine has to be used in the L-form. About 100 000 tons of methionine and 20 000 tons of L-lysine are used each year to supplement animal feed [24].

In the list given at the beginning of this paragraph there are illustrations of the fact that the enantiomers of drugs may have completely different activities in the body. About 60% of all the pharmaceutically active compounds in the market contain chiral molecules. Of these only about 60% are used in optically pure form, most of the optically pure drugs being of natural origin. That means, about 40% of the chiral drugs, commercially available in our pharmacies, are racemic mixtures, irrespective of the fact that the pharmaceutical activity may be due to one of the two enantiomers.

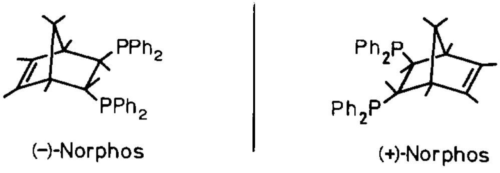
Cyclopropanes such as derivatives of chrysanthemumcarboxylic acid are insecticides, usually only one of the optical isomers displaying the biological activity. To replace the racemic mixture by the optically pure form in such cases would mean a reduction in the quantity which has to be used in fields and gardens to achieve a particular result in terms of pest control.

These examples demonstrate the broad range of application of optically active substances and the importance of designing new economic methods for their synthesis, e.g. using catalytic procedures, taking advantage of the multiplication effect involved in catalysis.

Improvement of catalysts

(a) (+)- and (−)-Norphos and the reinforced δ- and λ-conformation in their chelate rings

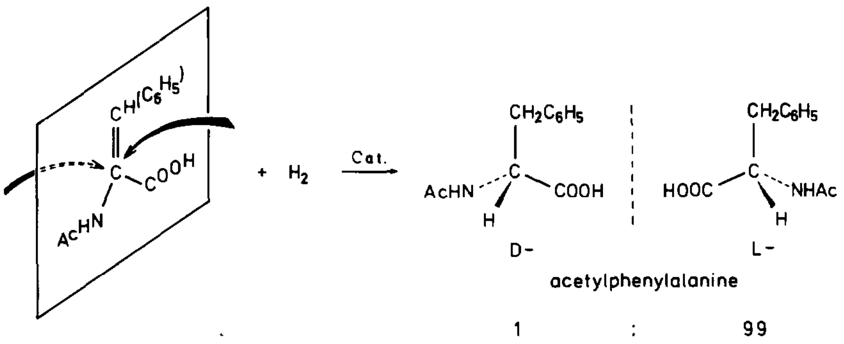
With (+)- and (−)-Norphos we added another example to the list of chelating diphosphine ligands. Prepared by a Diels–Alder reaction of cyclopentadiene and



(−)-Norphos

(+)-Norphos

SCHEME 4. (−)-(2R,3R)- and (+)-(2S,3S)-Norphos.



Typical conditions:

1g AAZ, 20 ml CH$_3$OH, 1.1 bar H$_2$, 25°C, 10 h
cat.: 7 mg [RhCl(cod-1,5)]$_2$ + 14 mg (-)-Norphos
catalyst : substrate = 1 : 200

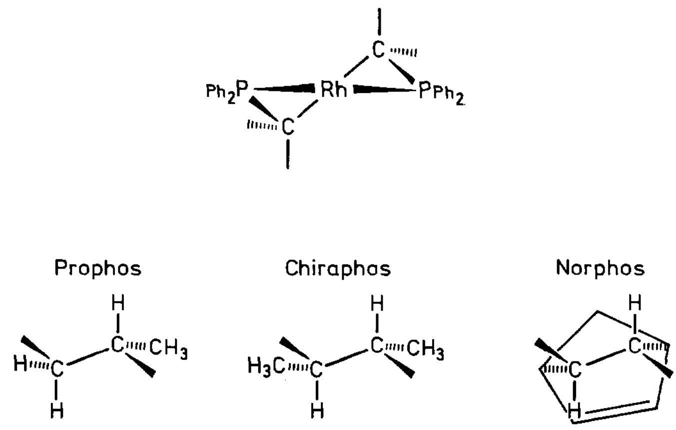
SCHEME 5. Hydrogenation of Z-α-acetamidocinnamic acid (AAZ) catalyzed by the in-situ system [Rh(cod)Cl]$_2$/(−)-Norphos.

trans-1,2-bis(diphenylphosphineoxide)ethylene [25] it is resolved at the stage of the phosphineoxide, which we call NorphosO, with (−)-dibenzoyltartaric acid [26,27]. After reduction of the phosphine oxides (+)- and (−)-NorphosO with trichlorosilane, (+)- and (−)-Norphos are obtained as white, air-stable crystals [28]. In Scheme 4, (+)- and (−)-Norphos are depicted in their correct absolute (2*S*,3*S*)- and (2*R*,3*R*)-configurations [27,29,30].

Scheme 5 shows the catalytic hydrogenation of Z-α-acetamidocinnamic acid with an in-situ catalyst consisting of [Rh(cod)Cl]$_2$ and (−)-Norphos. Typical reaction conditions are room temperature, methanol solution, and 1.1 bar H$_2$. After 10 h hydrogenation is complete, giving *N*-acetylphenylalanine in an enantiomer ratio of L/D 99/1. The multiplication factor for the conditions specified is 200. It can be increased to thousands, but on further increase there is danger of incomplete hydrogenation, a common feature of all the rhodium/optically active phosphine hydrogenation catalysts.

The two diphosphines Diop and BPPM in Scheme 3 form seven-membered chelate rings with a metal atom. For Diop complexes a number of X-ray analyses have revealed markedly different conformations of these chelate rings [31]. Prophos, Chiraphos, Dipamp (Scheme 3), and Norphos (Scheme 4) on coordination give five-membered chelate rings of a much more rigid structure. Increased rigidity is thought to be a requirement for good stereoselectivity [16].

The five-membered chelate rings of diphosphines are puckered, like the chelate rings formed by ethylenediamine type ligands. In their classical conformation analysis, Corey and Bailar [32,33] showed that because of this puckering the substituents at the carbon atoms of the ethylenediamine ligand become equatorial and axial. The same differentiation of the carbon substituents is brought about by the puckering in the five-membered chelate rings of Prophos, Chiraphos, and Norphos complexes, as indicated in Scheme 6, upper part. The stronger tendency of a methyl group than of a hydrogen atom to occupy an equatorial position controls



SCHEME 6. The puckered five-membered chelate rings in complexes of (2*S*)-Prophos, (2*S*,3*S*)-Chiraphos, and (2*S*,3*S*)-Norphos.

the puckering of the chelate rings in (2*S*)-Prophos and (2*S*,3*S*)-Chiraphos complexes as shown in the lower part of Scheme 6.

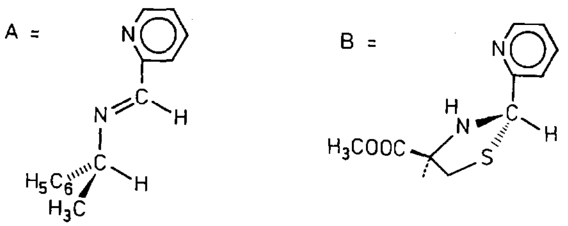
The puckered five-membered chelate ring is a chiral entity. The chirality of a given ring conformation is defined by considering the two skewed lines, the P–P connecting line and the C–C bond, as axis and tangent of a helix, the right and left handedness of which is designated δ and λ [34]. According to this definition, the chelate rings in Scheme 6 have δ-conformation.

The two ring conformations δ and λ usually interconvert rapidly. However, as methyl substituents tend to orient themselves equatorially, chelate rings with (2*S*)-Prophos and (2*S*,3*S*)-Chiraphos preferentially adopt the δ-conformation. The two carbon atoms of the chelate backbone of (2*S*,3*S*)-Norphos are part of the norbornene skeleton, the rigidity of which completely prevents the inversion of the δ-conformation. Thus the fixed ring conformation, revealed by a number of X-ray structure analyses [27,29,30,35], may be the reason for the excellent optical inductions obtained in hydrogenation reactions with Rh complexes using Norphos as the co-catalyst [26,27,29,36,37].

In spite of the rigid backbone of Norphos it was possible to prepare a number of stable chelate complexes [29,30,38]. Organometallic diastereomers differing only in the metal configuration usually have almost opposite chiroptical properties, e.g. CD-spectra [39], owing to the fact that the metal atom is the main chromophore. Surprisingly, however, the two diastereomers of $C_5H_5Fe(CO)[(-)\text{-Norphos}]^+ PF_6^-$, differing only in the Fe-configuration, exhibit nearly identical CD-spectra [38]. This result was explained by assuming similar chiroptical properties for the Fe chromophore in both diastereomers, dictated by the λ-conformation of the (−)-Norphos ligand. Corresponding behavior was observed for diastereomeric Ru complexes of Prophos [40].

(b) Nitrogen containing co-catalysts and 3d-metal pro-catalysts

The ligands most widely used in enantioselective catalysis are optically active diphosphines. However, the multistep syntheses necessary for their preparation result in prices much higher than those of the noble metal pro-catalysts. The



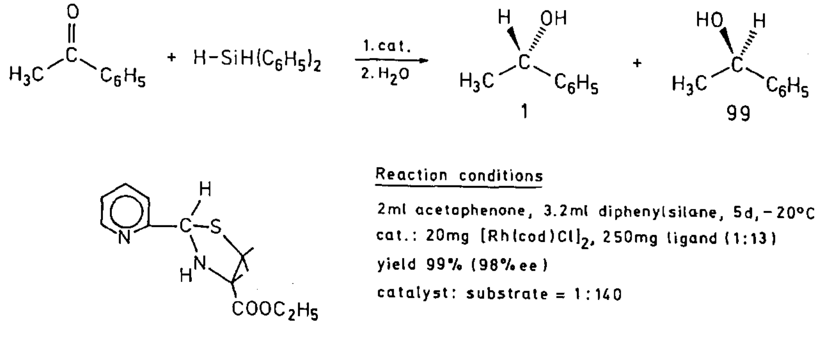
SCHEME 7. The co-catalysts pyridine imine (**A**) and pyridine thiazolidine (**B**).

cheapest co-catalyst, Diop, costs about \$ 45, Chiraphos about \$ 75, Prophos and BPPM about \$ 90, BPPFA about \$ 150, and Norphos about \$ 185 per g [28,41]. Therefore it was our aim to replace the phosphine ligands, expensive and difficult to synthesize, by nitrogen ligands, inexpensive and easy to prepare. We found such ligands with the pyridine imine **A** and the pyridine thiazolidine **B** shown in Scheme 7. Both **A** and **B** proved to be efficient co-catalysts in in-situ systems involving the pro-catalyst $[Rh(cod)Cl]_2$.

In the hydrosilylation of acetophenone with diphenylsilane the catalytic addition of the Si–H bond to the carbonyl group leads to a silyl ether, the hydrolysis of the Si–O bond of which yields 1-phenylethanol, the reduction product of acetophenone (Scheme 8). In-situ catalysts consisting of $[Rh(cod)Cl]_2$ and the pyridine imine **A** give up to 57% ee [42,43]; with the pyridine thiazolidine co-catalyst **B′** 98% ee are obtained under the reaction conditions specified in Scheme 8, lower part [44,45]. The new catalytic systems can also be used for the highly stereoselective reduction of t-butyl methyl ketone and benzyl methyl ketone by hydrosilylation with diphenylsilane followed by hydrolysis [43,45].

Co-catalysts **A**, **B**, and **B′** can be prepared by treating 2-pyridinealdehyde with (*S*)-1-phenylethylamine (**A**), L-cysteine methylester (**B**), and L-cysteine ethylester (**B′**), respectively, in one-step condensation reactions, all the starting materials being cheap chemicals. As all kinds of primary amines can be used in the synthesis of ligands of type **A**, the potential of the large number of optically active primary amines [46] can be utilized for enantioselective catalysis [43].

In the synthesis of the thiazolidines **B** and **B′**, diastereomer mixtures of 58/42



Reaction conditions

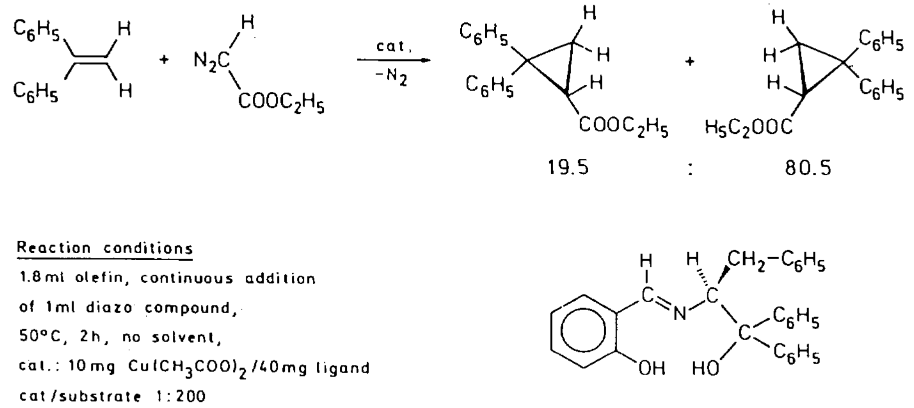
2ml acetophenone, 3.2ml diphenylsilane, 5d, −20°C

cat.: 20mg $[Rh(cod)Cl]_2$, 250mg ligand (1:13)

yield 99% (98% ee)

catalyst: substrate = 1:140

SCHEME 8. Hydrosilylation of acetophenone with diphenylsilane catalyzed by the in-situ system $[Rh(cod)Cl]_2$/pyridine thiazolidine (**B′**).



Reaction conditions
1.8 ml olefin, continuous addition
of 1 ml diazo compound,
50°C, 2 h, no solvent,
cat.: 10 mg $Cu(CH_3COO)_2$/40 mg ligand
cat/substrate 1:200

SCHEME 9. Cyclopropanation of 1,1-diphenylethylene with ethyl diazoacetate catalyzed by the in-situ system $Cu(ac)_2$/imine derived from salicylaldehyde and 1,1,3-triphenyl-3-amino-1-propanol.

and 50/50 with regard to carbon atom 2 are obtained, only one of which is depicted in Schemes 7 and 8. In both cases the two diastereomers can be separated by fractional crystallization [45]. However, the presence of a trace of an Rh complex such as $[Rh(cod)Cl]_2$, the pro-catalyst in the hydrosilylation reaction of Scheme 8, leads within seconds to complete epimerization with respect to carbon atom 2 of **B** and **B′**. It is noteworthy that a 50/50 diastereomer mixture of the pyridine thiazolidine **B′** in combination with $[Rh(cod)Cl]_2$ gives an enantiomer ratio of 99/1 in the hydrosilylation of Scheme 8.

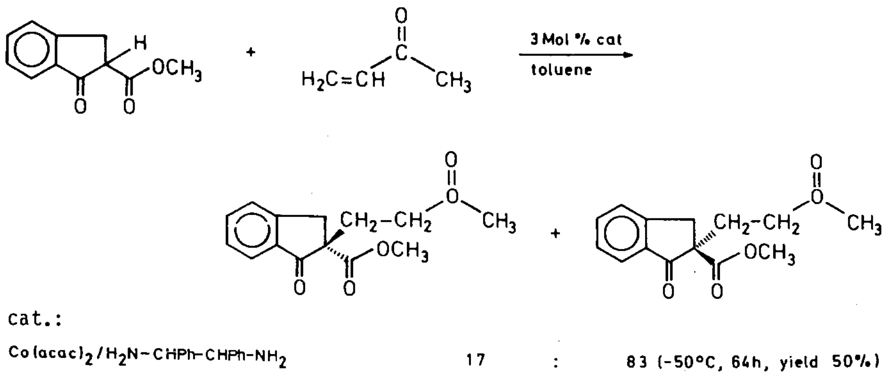
The optically active diphosphines of Schemes 3 and 4, very effective in the enantioselective hydrogenations discussed before, are not so good for the hydrosilylation of Scheme 8. The optical inductions obtained with Diop are only 25% ee [47], and with Norphos only 14% ee [48]. Thus, in the hydrosilylation reaction the nitrogen ligands **A**, **B**, and **B′** are superior to the diphosphine co-catalysts.

Inexpensive nitrogen ligands can also be used in the cyclopropanation of 1,1-diphenylethylene with ethyl diazoacetate (Scheme 9). The best results (enantiomer ratios up to 81/19) are achieved with the co-catalyst, depicted in Scheme 9, lower part, derived from salicylaldehyde and the primary amine obtained in the phenyl Grignard reaction of phenylalanine methylester [49]. It must be emphasized that in the cyclopropanation reaction of Scheme 9 not only can inexpensive and readily accessible ligands be used, but also the efficicient pro-catalyst is the 3*d* metal salt copper(II)-acetate, not a noble metal derivative.

Another example of an in-situ catalyst consisting of a 3*d* metal pro-catalyst $Co(acac)_2$, and a nitrogen ligand, 1,2-diamino-1,2-diphenylethane, is discussed in the next paragraph (Scheme 10) [50].

Extension to new reaction types and new substrates

Most of the work on enantioselective catalysis has been done in the field of hydrogenation [12–16]. A few other reactions have also been carried out enantioselectively, e.g. hydroformylation, hydrosilylation, Grignard cross coupling, cyclopropanation, epoxidation [12,16,51–54]. It would be desirable to extend the



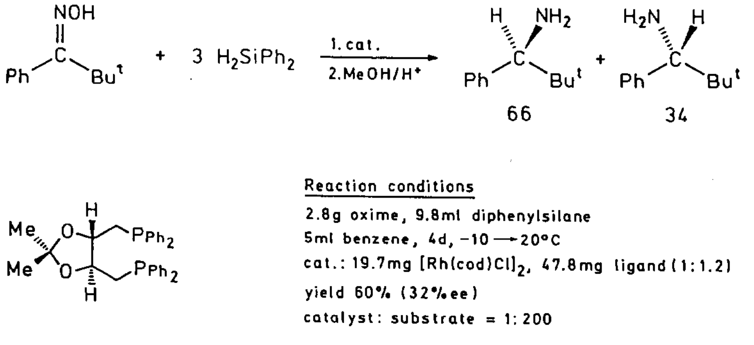
SCHEME. 10. Michael addition of methyl indanonecarboxylate and methyl vinyl ketone catalyzed by the in-situ system Co(acac)$_2$/(+)-1,2-diamino-1,2-diphenylethane.

scope of homogeneous enantioselective catalysis with transition metal complexes to reactions to which the concept hitherto has not been applied successfully.

An example of such an extension is the Michael addition of vinyl methyl ketone to methyl indanonecarboxylate shown in Scheme 10. There have been reports that such reactions can be catalyzed by Ni(acac)$_2$ [55–58], because of the mild reaction conditions the Ni(acac)$_2$ catalysis gives a better yield than the usual base catalysis.

A stereochemical variant of such a reaction requires that the central carbon atom of the 1,3-dicarbonyl system of the product does not contain a racemization-labile C–H bond. A substrate which meets this requirement is methyl indanonecarboxylate. Its addition product with vinyl methyl ketone acquires a configurationally stable quarternary asymmetric center. The specific rotation of the optically pure product is known. We developed an in-situ catalyst consisting of the two stable components Co(acac)$_2$ and (+)-1,2-diamino-diphenylethane, which at −50°C gave the Michael adduct of Scheme 10 in 50% yield with enantiomer ratio of 83/17 [50].

Another class of compounds hitherto not included in enantioselective catalysis is the oximes. We found that oximes can be reduced with diphenylsilane using an in-situ catalyst consisting of [Rh(cod)Cl]$_2$ and a chelate diphosphine [59,60]. A variation of the optically active co-catalysts showed (−)-Diop to be the most



Reaction conditions
2.8g oxime, 9.8ml diphenylsilane
5ml benzene, 4d, −10 → 20°C
cat.: 19.7mg [Rh(cod)Cl]$_2$, 47.8mg ligand (1:1.2)
yield 60% (32% ee)
catalyst : substrate = 1 : 200

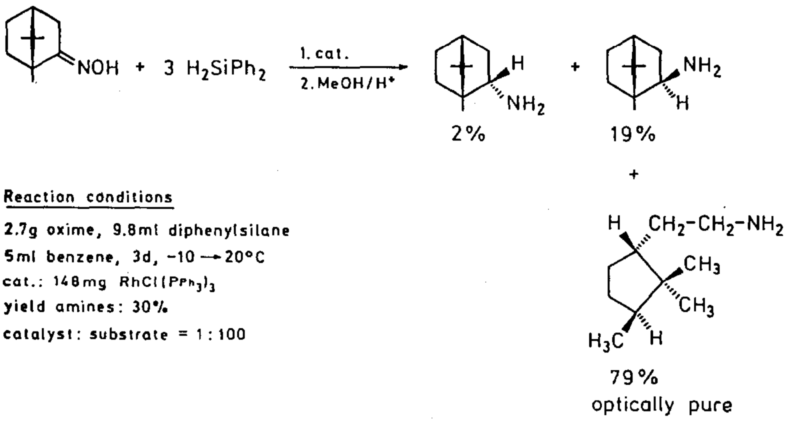
SCHEME 11. Hydrosilylation of phenyl t-butyl ketone with diphenylsilane by the in-situ system [Rh(cod)Cl]$_2$/(−)-Diop.

effective. Chemical yields are between 30 and 60%. In this reaction three moles of diphenylsilane are consumed, two of which end up as the disiloxane $Ph_2HSi–O–SiHPh_2$ and the third in the reduction product, silylamine, which can be hydrolyzed to the corresponding primary amine. Of 13 prochiral ketones examined phenyl t-butyl ketone has so far given the best optical inductions [60]. The overall reaction for the hydrosilylation of phenyl t-butyl ketone is shown in Scheme 11, along with the reaction conditions. The reaction allows the transformation of prochiral ketones into the corresponding primary amines via enantioselective catalytic hydrosilylation of their readily accessible oximes.

Use of the oxime of D-camphor in the catalytic hydrosilylation reaction gives surprising results. After hydrolysis the expected products, *endo* and *exo*-bornylamine, are found in the amine fraction in only 2 and 19% yields, respectively. In 79% yield a product is obtained the formation of which requires the hydrogenolytic cleavage of the five-membered ring in the camphor skeleton between the bridge head carbon atom and the oxime carbon atom. The product (+)-(1*R*,3*S*)-1-(2-aminoethyl)-2,2,3-trimethylcyclopentane (Scheme 12) was shown to be enantiomerically pure [61].

The imine derived from acetophenone and benzyl amine was hydrosilylated catalytically in 1975 with optical yields up to 65% ee [62]. It is surprising that this reaction has only rarely been used for the preparation of optically active secondary amines. We applied it to the 3,4-dihydro-[2*H*]-pyrrole derivative shown in Scheme 13. This compound can be prepared from acetophenone by a Mannich reaction with formaldehyde/dimethylamine, reaction of the Mannich base with KCN, and hydrogenation of the corresponding nitrile with Raney nickel, in which cyclization occurs [63].

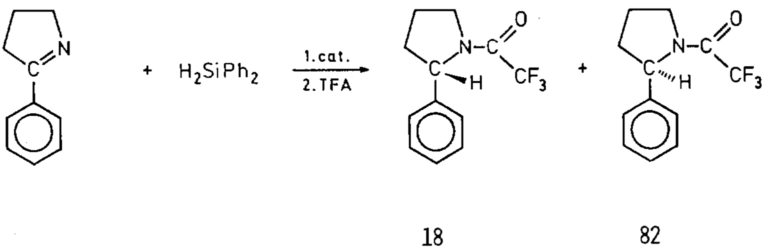
In the hydrosilylation of the cyclic imine with diphenylsilane, catalyzed by an in-situ catalyst $[Rh(cod)Cl]_2$/(−)-Diop, the Si–H bond adds to the C=N bond of the imine. The resulting silylamine is converted into the trifluoracetamide by treatment with trifluoracetic anhydride, TFA (Scheme 13). Distillation gives the product in 80–90% chemical yield, with an enantiomer ratio of 82/18, as determined by gas-chromatography using a Chirasil-L-Val column [63]. The reaction can be



Reaction conditions

2.7g oxime, 9.8ml diphenylsilane
5ml benzene, 3d, −10 → 20°C
cat.: 148mg $RhCl(PPh_3)_3$
yield amines: 30%
catalyst : substrate = 1 : 100

SCHEME 12. Hydrosilylation of D-camphor oxime with diphenylsilane by Wilkinson's catalyst.



Reaction conditions

0.4g imine, 0.8ml diphenylsilane
2ml toluene, 24h, 0 → 20°C
cat.: 10mg $[Rh(cod)Cl]_2$, 22mg Diop (1:1.1)
yield: 80%
catalyst : substrate = 1:50

SCHEME 13. Hydrosilylation of a cyclic imine with diphenylsilane by the in-situ system $[Rh(cod)Cl]_2/(-)$-Diop.

extended to imines in which the phenyl ring is OCH_3- or Br-substituted. The resulting secondary amine derivatives, readily accessible by the route given, are analogues of the alkaloid nicotine.

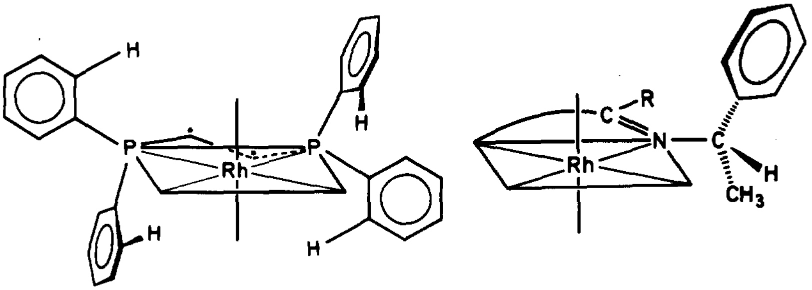
New ways of transferring chirality within the catalyst

(a) Chirality transmission in complexes of diphosphines and in nitrogen ligands containing lateral asymmetric centers

The vast majority of diphosphine ligands consist of a chiral backbone with two diphenylphosphine groups attached in such a way that stable chelate rings can be formed. The reason for this is partly because diphenylphosphine groups are easy to introduce into suitable optically active precursors. Additionally, however, each diphenylphosphine group in a complex or a catalyst is a chiral unit because the two phenyl rings adopt an axial/equatorial arrangement and a face exposed/edge exposed orientation, as can be seen in the left hand side of Scheme 14.

On the basis of the conformational analysis of five-membered chelate rings, given above, the δ- and λ-conformations are controlled by the tendency of large substituents to occupy equatorial positions. In addition, the puckering of the five-membered chelate rings influences the arrangement of the phenyl rings at the phosphorus atoms, one becoming axial and the other equatorial, as is evident from Scheme 14. Furthermore, the two phenyl rings are usually almost perpendicular to each other, one being face-exposed and one edge-exposed, also as indicated in Scheme 14. In this way the sense of chirality of the PPh_2 "ears" is enforced by the chiral centers in the ligand backbone, marked with asterisks in Scheme 14, via the puckering of the chelate ring [10,16,64,65].

The distance between the chiral centers in the diphosphine backbone and the coordination sites of the metal atom, where the prochiral substrates are converted into the optically active products, is several Å. It is mainly by transmission through the PPh_2 groups that the chiral information reaches the point where it is needed within the catalyst. The chirality transmission model of Scheme 14, left hand side,



SCHEME 14. Chirality transfer in catalysts to the metal coordination positions, where the prochiral substrates are converted into the optically active products.

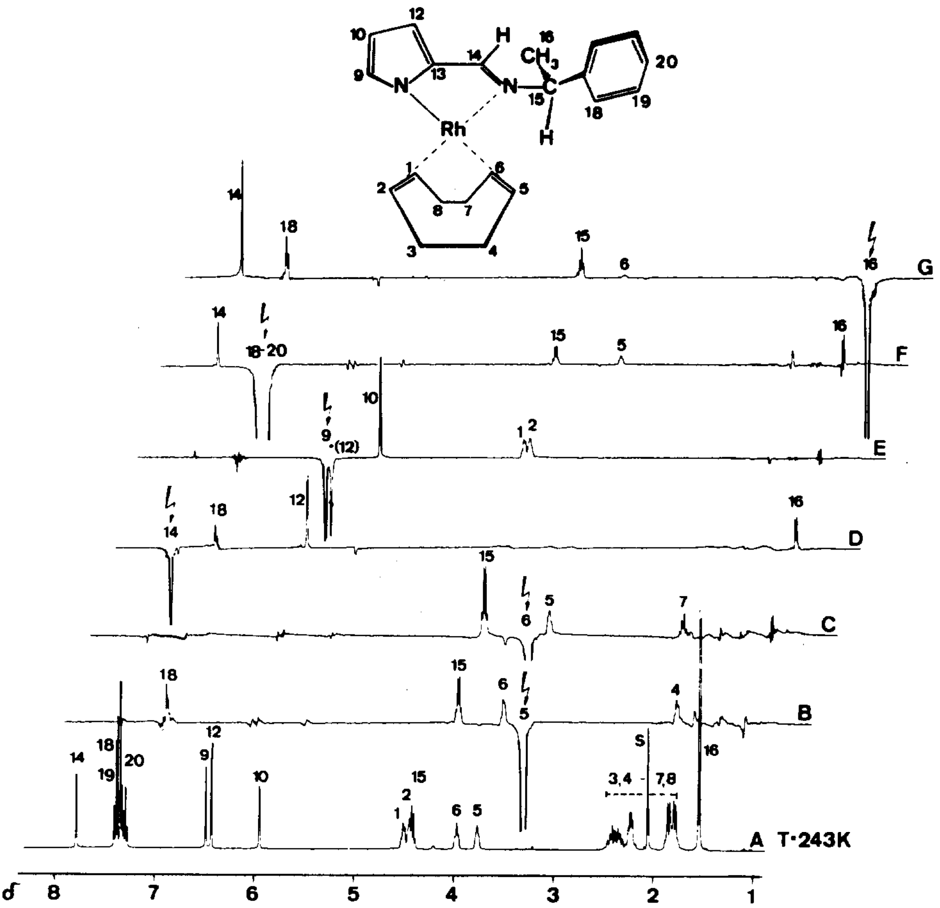
has been used to correlate the configuration of the inducing chirality in the ligand with the configuration of the amino acids formed by hydrogenation of the corresponding unsaturated precursors [64,65].

In nitrogen ligands containing lateral asymmetric centers of the general type shown in Scheme 14, right hand side, the chirality transmission is different. In such catalysts the lateral asymmetric center is at the point at which in the diphosphine ligands the chirality transmitting PPh_2 group is located. Therefore, in these systems no chirality transmitter is necessary. There is direct interaction between the inducing chirality and the metal coordination sites where the optical induction takes place [10]. The nitrogen ligands **A**, **B**, and **B′** of Schemes 7 and 8 are specific examples for the concept of nitrogen chelate ligands with lateral asymmetric centers, the efficiency of which is demonstrated by the catalysts shown in Schemes 8, 9, and 10.

(b) Conformational analysis of the lateral 1-phenylethyl group in nitrogen chelate ligands of Rh(cod) complexes

The Rh complex, depicted at the top of Scheme 15, is a catalyst in the hydrosilylation reaction shown in Scheme 8 [42,43]. Its conformation in solution was investigated by ^{1}H NMR nuclear Overhauser difference spectroscopy at 243 K in acetone-d_6 [68]. The normal 400 MHz spectrum is shown in trace A of Scheme 15. The NOE difference spectra B–G are given in stacked plot presentation, displaced to the right. The technique used gives negative signals for the protons which are saturated and positive signals for protons for which there is dipole–dipole interaction through space [66,67]. Positive signals are therefore an indication of spacial vicinity to a proton which is saturated. All the other signals in this NOE difference spectroscopy average to zero.

In spectrum B the olefinic proton 5 was saturated. As expected, the signals of the adjacent proton of the cod moiety, the olefinic proton 6, and the aliphatic protons 4, increase in intensity. The signals of proton 15 at the asymmetric center and of the *ortho* protons 18 of the phenyl ring are also enhanced. Therefore, the double bond C(5)=C(6) must be *cis* to the imine N, and both the substituents C*–H(15) and C*–Ph must be close to H(5). In spectrum C, the signal of proton 6 of the double bond C(5)=C(6) is saturated. Except for the neighboring cod protons, only the signal of H(15) increases. There is no enhancement of the *ortho* phenyl protons 18 and the integrated intensity of the methyl signal 16 is zero. These two experiments show that the C*–H(15)bond of the 1-phenylethyl substituent is oriented towards the double



SCHEME. 15. 400 MHz ^{1}H NMR spectra of the Rh complex, shown at the top, in acetone-d_6 at T 243 K. A Normal spectrum and B–G NOE difference spectra. The saturated signals are marked with arrows.

bond C(5)=C(6). Since the intensity enhancement of H(15) is larger in spectrum C, H(15) must be closer to H(6) than to H(5). Therefore, Ph(18–20) is closer to H(5) than Me(16) to H(6). In agreement, there are increases in the signals of the Ph *ortho* protons and especially of the methyl protons 16 on saturation of the imine proton 14 in spectrum D.

In spectrum F, the *ortho* protons 18 of the phenyl ring are saturated. Besides proton 15 and methyl protons 16 of the optically active substituent, imine proton 14 and cod proton 5 signals increase in intensity. On saturation of the methyl protons 16, in spectrum G, the signals of 15 and 18 as well as the signals of 14 (strongly) and 6 (weakly) are enhanced, demonstrating that methyl group 16 is in the position shown in the formula at the top of Scheme 15 [68].

The solid state conformation of the 1-phenylethyl substituent in the Rh complex of Scheme 15, determined by an X-ray structure analysis [69], turned out to be very similar. The only difference is that in solution C*–H(15) points more towards H(6) and in the solid state more towards H(5) of the C(5)=C(6) double bond [68,69]. The same tendency for the orientation of the C*–H bond towards one of the double bonds of the cod ligand has been found in Rh(cod) complexes of pyridine imine and tropolone imine ligands containing lateral 1-phenylethyl substituents [68,70].

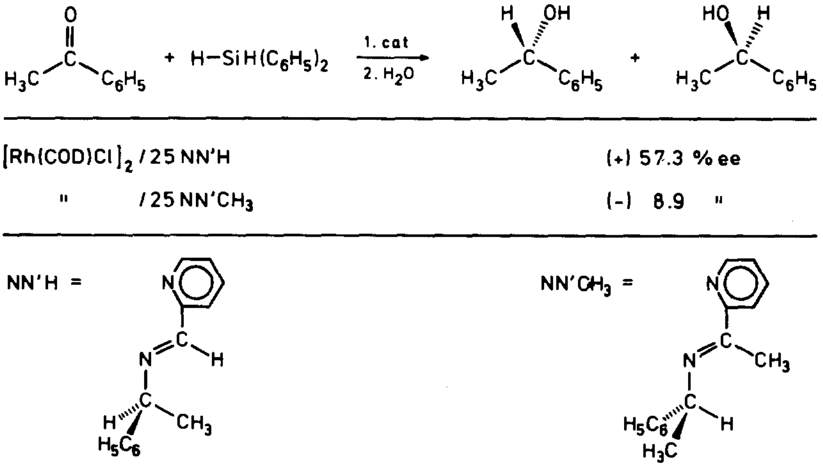
(c) Parallelism of conformational analysis and enantioselective catalysis

For the systems $C_5H_5Mo(CO)_2$-amidinate and -thioamidate a detailed conformational analysis of the arrangement of the *N*-bonded 1-phenylethyl group with respect to the four-membered chelate ring MoNCN and MoNCS was carried out [10]. It revealed that the conformation of a lateral 1-phenylethyl group is governed by the nature of the substituent at the adjacent carbon atom in the four-membered ring. If this substituent is a large group, such as methyl or phenyl, for steric reasons the C–H bond of the 1-phenylethyl group is coplanar with it [71], whereas for the small H-substituent at the adjacent carbon the methyl group of the 1-phenylethyl moiety tends to be coplanar with it [72].

Since the results of this conformational analysis have been summarized recently details will not be repeated here [10].

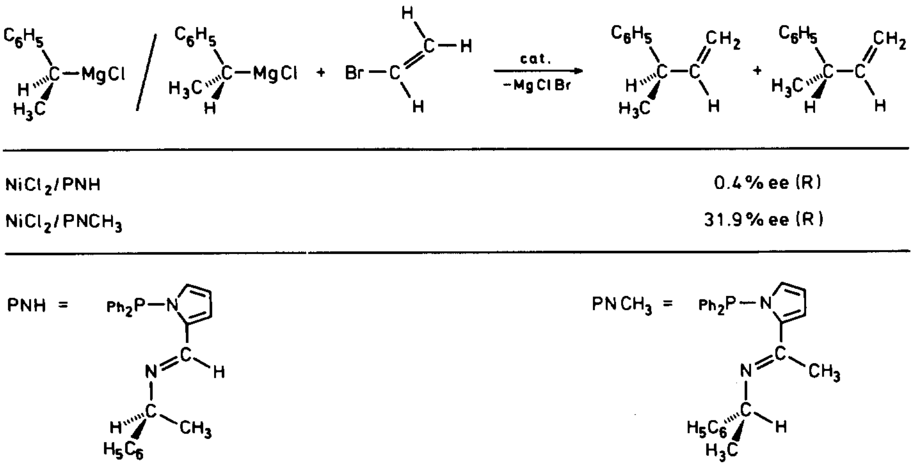
These ideas, applied to the chelate type in Scheme 14, right hand side, mean that substituents R = H and R = Me at the adjacent carbon in the chelate ring exert different control on the orientation of an *N*-bonded 1-phenylethyl group and, consequently, on its chirality transmission to the neighboring coordination sites of the metal atom. These different conformations should therefore be reflected in the results of catalytic reactions. There is accumulating evidence, exemplified by Schemes 16 and 17, for a correlation between the nature of R at the carbon atom adjacent to an *N*-bonded 1-phenylethyl group, its arrangement, and the optical induction in an enantioselective catalysis.

Scheme 16 shows the hydrosilylation of acetophenone with diphenylsilane catalyzed by $[Rh(cod)Cl]_2$ and an excess of two pyridineimine derivatives, differing only in the carbon substituents R adjacent to the lateral 1-phenylethyl group at the N atom. With the co-catalyst NN'H (R = H) (+)-1-phenylethanol is favoured with 57.3% ee, whereas with the co-catalyst $NN'CH_3$ (R = Me) (−)-1-phenylethanol is formed predominantly, with 8.9% ee [42,43].



$[Rh(COD)Cl]_2$ / 25 NN'H	(+) 57.3 % ee
" / 25 $NN'CH_3$	(−) 8.9 "

SCHEME 16. Hydrosilylation of acetophenone with diphenylsilane catalyzed by the in-situ system $[Rh(cod)Cl]_2$/pyridine imine derived from (−)-1-phenylethylamine and 2-pyridinealdehyde and 2-acetylpyridine, respectively.



$NiCl_2$/PNH	0.4% ee (R)
$NiCl_2$/$PNCH_3$	31.9% ee (R)

SCHEME 17. Cross coupling of 1-phenylethyl Grignard with vinyl bromide catalyzed by the in-situ system $NiCl_2$/imine derived from (−)-1-phenylethylamine and 1-(diphenylphosphino)-2-pyrrolaldehyde and 1-(diphenylphosphino)-2-acetylpyrrol, respectively.

Another example for the correlation of the *R*-controlled conformation of a lateral chiral substituent and the optical induction in a catalytic reaction is the cross coupling of 1-phenylethyl Grignard with vinyl bromide, catalyzed by the in-situ system consisting of $NiCl_2$ and the diphenylphosphino derivatives of the pyrrolimines shown in Scheme 17. The ligand PNH (R = H) with 0.4% ee gives an almost racemic mixture; in contrast, with the ligand $PNCH_3$ (R = Me) 31.9% ee, the highest optical inductions obtained with ligands of this kind, can be achieved [73].

Both examples demonstrate the control of optical induction in enantioselective reactions by the substituent R in the chelate ring via adjustment of the conformation of a lateral *N*-bonded 1-phenylethyl group. The parallel between conformational analysis on the one hand and enantioselective catalysis on the other hand offers promise of moving beyond the still extremely empirical nature of the art of enantioselective catalysis.

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