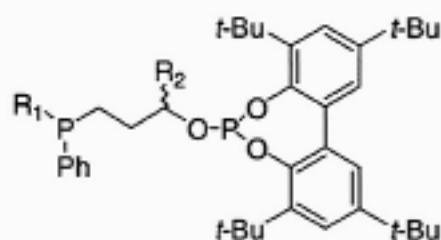


## Summary

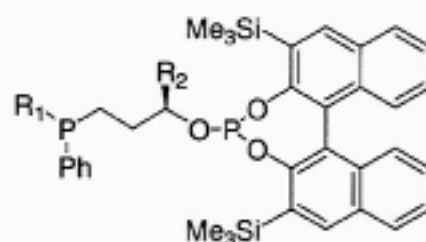
This thesis describes the development and application of new chiral phosphine-phosphite ligands in asymmetric homogeneous catalysis. The introduction (Chapter 1) explains the importance of chiral compounds in nature. Asymmetric catalysis is a very elegant and clean way of introducing a chiral center in an organic molecule, since in the ideal case no undesirable side products are formed that result in chemical waste. Furthermore, asymmetric synthesis gives easy access to both the natural product analogues and their "unnatural" enantiomers. The chiral products can be used as building blocks for the synthesis of *e.g.* pharmaceuticals, agrochemicals, human food additives and animal food supplements.

Asymmetric homogeneous catalysis is a widely applied method to introduce a chiral center in an organic molecule. The actual catalyst is a metal complex containing one or more chiral ligands. Modification of the chiral ligand and thus the chiral catalyst influences the outcome of the catalytic reaction; a higher (enantio)selectivity may be obtained, but also activity, catalyst stability and chemoselectivity can be modified. The majority of the chiral ligands reported in literature can be divided into two groups: ligands providing 1)  $C_2$ -symmetric metal complexes and 2)  $C_1$ -symmetric metal complexes. In the family of  $C_2$ -symmetric diphosphine ligands the chirality originates from a chiral backbone, stereogenic phosphorus atoms, or both. Whereas  $C_2$ -symmetric ligands containing phosphines having stereogenic phosphorus atoms have been examined frequently, only little research has been done on ligands containing a stereogenic phosphine moiety that lack this  $C_2$ -symmetry.

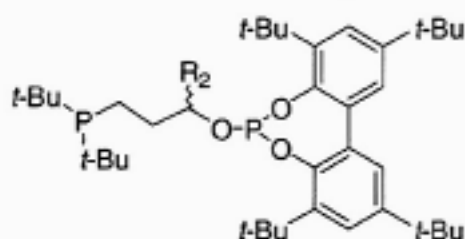
In order to elucidate the effects of ligand structure on the enantioselectivity in the catalytic reactions studied we designed a new class of diastereomeric phosphine-phosphite ligands with a stereogenic phosphine moiety, a chiral backbone and a bulky biphenyl phosphite moiety. This type of ligands has the advantage that many structural variations can be made. Systematic variation of the different chiral centers in the ligand can provide information about the origin of the stereochemistry of the reaction. These ligands have been successfully tested in several transition metal catalyzed reactions.



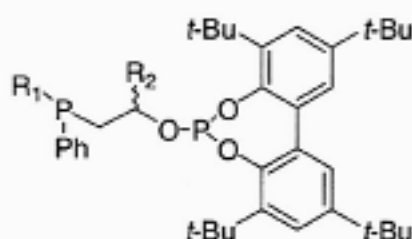
**(S<sub>P</sub>, S<sub>C</sub>)** R<sub>1</sub>=1-Napht, R<sub>2</sub>=Ph  
**(S<sub>P</sub>, S<sub>C</sub>)** R<sub>1</sub>=2-Anisyl, R<sub>2</sub>=Ph  
**(S<sub>P</sub>, R<sub>C</sub>)** R<sub>1</sub>=1-Napht, R<sub>2</sub>=Ph  
**(R<sub>P</sub>, S<sub>C</sub>)** R<sub>1</sub>=*t*-Bu, R<sub>2</sub>=Ph  
**(R<sub>P</sub>, R<sub>C</sub>)** R<sub>1</sub>=*t*-Bu, R<sub>2</sub>=Ph  
**(R<sub>P</sub>)** R<sub>1</sub>=*t*-Bu, R<sub>2</sub>=Ph  
**(R<sub>P</sub>, S<sub>C</sub>)** R<sub>1</sub>=*t*-Bu, R<sub>2</sub>=Me  
**(S<sub>C</sub>)** R<sub>1</sub>=Ph, R<sub>2</sub>=Me  
**(S<sub>C</sub>)** R<sub>1</sub>=Ph, R<sub>2</sub>=Ph



**(S<sub>P</sub>, S<sub>C</sub>, R)** R<sub>1</sub>=1-Napht, R<sub>2</sub>=Ph  
**(S<sub>P</sub>, S<sub>C</sub>, S)** R<sub>1</sub>=1-Napht, R<sub>2</sub>=Ph  
**(R)** R<sub>1</sub>=Ph, R<sub>2</sub>=H  
**(S)** R<sub>1</sub>=Ph, R<sub>2</sub>=H



**(S<sub>C</sub>)** R<sub>2</sub>=Ph



**(R<sub>P</sub>, R<sub>C</sub>)** R<sub>1</sub>=*t*-Bu, R<sub>2</sub>=Ph  
**(R<sub>P</sub>, S<sub>C</sub>)** R<sub>1</sub>=*t*-Bu, R<sub>2</sub>=Ph

The synthesis of the ligands is described in Chapters 2 and 3. The ligands containing a stereogenic phosphorus atom were synthesized via two routes. The method published by Jugé and Genet using ephedrine as a chiral auxiliary was utilized for the preparation of (diaryl)monophosphines. Monophosphines containing *tert*-butyl groups were synthesized applying the method described by Livinghouse using (–)-sparteine as a chiral resolving agent. In this way a large series of systematically varied phosphine–phosphite ligands was synthesized having one, two or three stereogenic moieties.

Hydroformylation is one of the largest scale processes of homogeneous organometallic catalysis. In Chapter 2 the use of these ligands in the rhodium–catalyzed hydroformylation of styrene is described. The structure of the important intermediate  $\text{RhH}(\text{CO})_2(\text{P}_1\text{–P}_2)$  species has been elucidated by means of high pressure NMR and IR techniques. Compared to Takaya's BINAPHOS, the present ligands coordinate in different fashion in the trigonal bipyramidal  $\text{RhH}(\text{CO})_2(\text{P}_1\text{–P}_2)$  species, *i.e.* the phosphite donor occupies an equatorial and the phosphine donor an apical position. Under mild reaction conditions enantiomeric excesses

up to 63 % and regioselectivities up to 92 % towards 2-phenylpropanal were obtained (25–60 °C, 20 bar of syn gas CO:H<sub>2</sub> [1:1]).

Another important reaction is the palladium-catalyzed allylic substitution reaction of *rac*-1,3-diphenyl-2-propenyl acetate, which is described in Chapters 3 (alkylation) and 4 (amination). Enantioselectivities up to 83 % were obtained (25 °C) using dimethyl malonate as a nucleophile. The allylic amination reaction using benzylamine as a nucleophile resulted in moderate to high ee's up to 94 %. From the x-ray crystal study of an allylpalladium(P<sub>1</sub>-P<sub>2</sub>) complex we observed a longer palladium-carbon bond distance *trans* to the phosphine moiety. This indicates that the attack of the nucleophile takes place at the carbon *trans* to the phosphine moiety, which is indeed the experimental outcome of the reaction. As a consequence, the phosphine moiety did not affect the enantioselectivity directly. For the allylic amination a cooperative effect between the stereogenic phosphine and the stereocenter in the backbone was observed. Since this was not observed for the alkylation reaction it was concluded that the reaction mechanism is different for carbon and nitrogen nucleophiles.

Chapter 5 describes the nickel-catalyzed hydrocyanation reaction of styrene. Excellent selectivity toward the branched product and low enantioselectivity up to 34 % were obtained. Most often this reaction is catalyzed by nickel complexes modified by phosphites or phosphines with large bite angles. Intermediates in the catalytic cycle have been detected by <sup>31</sup>P{<sup>1</sup>H} NMR, including Ni(P<sub>1</sub>-P<sub>2</sub>)(cod) and Ni(P<sub>1</sub>-P<sub>2</sub>)(styrene). Electron-withdrawing ligands enhance the reaction rate. In contrast to the accepted idea that the Ni(P<sub>1</sub>-P<sub>2</sub>)(allyl)CN complex is the resting state of the reaction, we found that for the present system the Ni(P<sub>1</sub>-P<sub>2</sub>)(styrene) species is the resting state of the reaction.

The enantioselective rhodium-catalyzed hydrogenation reaction of dehydroamino acids is described in Chapter 6. Intermediate cationic rhodium complexes were observed with <sup>31</sup>P{<sup>1</sup>H} NMR. Substrate coordination in the hydrogenation reaction is controlled by the difference in electronic character between the phosphine and phosphite moiety. The carbonyl donor of the acrylic acid derivatives is coordinated *trans* to the phosphite. Absence of a rhodium hydride species indicated that first the substrate coordinates, followed by oxidative addition of dihydrogen. This is confirmed by kinetic studies that revealed a zeroth order dependency of the reaction rate on the substrate concentration. The rate of the formation of hydrogenation products is linearly proportional to the rhodium precursor concentration. Electron-donating ligands increase the catalyst activity by enhancing the oxidative addition

of dihydrogen. The structure of the substrate-coordinated species was studied by NMR spectroscopy. Even though only one major diastereomer was observed, a minor complex, which might be present under the detection limit of NMR, could also react to form the observed product. The enantioselectivity of the hydrogenation reaction has been explained by the rotation mechanism. Substrate coordination is determined by the electronic and steric character of the ligand. Due to the steric hindrance of the ligand the required rotation of the coordinated substrate to form the product is preferentially in one direction, resulting in the observed major enantiomer. At room temperature under 1 bar of hydrogen the highest enantiomeric excess obtained was 99 %.

In all the catalytic reactions the carbon stereocenter of the backbone is mainly responsible for the enantioselectivity induced by the ligand. Since the substituent of the carbon stereocenter is not in close vicinity to the coordinated substrate, we anticipated that the bisphenol adopts a configuration, which is controlled by this stereocenter. The configuration was fixed when enantiomerically pure bisnaphthol based phosphites were incorporated. The phosphine moiety has no direct influence on the enantioselectivity, but the electronic character is very important for the rate of reaction. In some reactions a cooperative effect was observed between the stereogenic phosphine moiety and the carbon stereocenter in the backbone, resulting in an increase of the enantioselectivity. The bisphenol moiety is in close vicinity to the substrate and determines the enantioselectivity.