Design, synthesis, and use of (chiral) ligands for transition metal (catalyzed) reactions
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In this thesis the design and synthesis of chiral ligands for transition-metal catalyzed asymmetric reactions are described. The focus lies more on the design and synthesis of the ligands, rather than on a wide scope of reactions. One reaction, known from the literature, the cross-coupling of racemic 1-phenylethylmagnesium chloride (1) and vinyl bromide (2) to afford 3-phenyl-butene-1 (3), was used to test the newly developed ligands. This reaction, carried out with a catalytic amount of NiCl₂ and a catalytic amount of a chiral ligand, may lead to asymmetric induction in the product. This results in an enantiomeric excess (e.e.) of one of the two enantiomers.

A literature survey of the use of organometallic catalysts in asymmetric syntheses is given in Chapter 1. A conclusion that can be drawn immediately from this is that thus far chiefly chiral phosphines or amiphosphines have been designed, synthesized and used as ligands for the transition-metal catalyzed asymmetric reactions.

Stimulated on the one side by examples drawn from Nature, and on the other by a desire to broaden the scope of available ligands we designed some nonphosphine ligands, namely chiral macrocycles containing several heteroatoms (sulfur and/or nitrogen). The synthetic strategy to these macrocycles proceeds via the cesium salt method. This method, using Cs₂CO₃ in the solvent dimethylformamide, has been used in Chapter 2, where the synthesis of (chiral) macrocyclic amines (6) is described.

This new synthetic approach is used in the synthesis of macrocycle 7. The macrocycle, designed as a new ligand for platinum, was designed and synthesized to influence the reaction behaviour of the arylplatinum
compound 8. The results are described in Chapter 3.

Chapter 4 describes the design and synthesis of several chiral sulfur and sulfur/nitrogen containing ligands and their results in the asymmetric synthesis of the reaction leading to product 3. The crucial ring-closure step in the synthesis of the macrocyclic ligands is achieved via the cesium salt method. The new macrocycles are chemically very efficient in the nickel-catalyzed reaction, as seen from high chemical yields of reaction product, and give e.e.'s considerably higher than their open-chain counterparts. Ligand 12, designed with the aid of CPK models, with
four sulfur atoms within the macrocyclic framework, gave the highest e.e. An analysis of a possible route to the enantiomer obtained in excess in this ligand in the cross-coupling reaction is given. Chapter 4 ends with some speculations of possible improvement of this class of ligands.

A need for more insight into the sulfur-containing ligands led to an investigation of ligands containing three heteroatoms, sulfur, nitrogen, and phosphorus. Starting from the sulfur-containing amino acids, cysteine, methionine, and homomethionine, Chapter 5 describes how several ligands, trisubstituted with diphenylphosphino, dialkylamino, and sulfide appendages, have been designed, synthesized, and tested. Optically pure homomethionine (13, n = 3, R = CH₃) was obtained from racemic material via resolution by means of a peptidase isolated from Pseudomonas putida or via a chiral phosphoric acid. X-Ray structures of palladium with methphos (14, n = 2, R = CH₃), and homomethphos (14, n = 3, R = CH₃), established that the transition metal was coordinated with nitrogen and phosphorus. All new ligands gave nearly quantitative yields of product 3 in the cross-coupling reaction. The observation of increasing values for the e.e. with increasing length of the sulfur side arm led us to postulate an intramolecular sulfur participation in the mechanism leading to product 3. The observations are in agreement with theoretical calculations on the "associative mechanism" for reductive elimination, studied by others. Homomethphos, again designed with the aid of CPK models, therefore, not only was of great practical value (leading to the highest e.e. ever reported for this reaction), but also proved its usefulness in the understanding of some mechanistic aspects of the cross-coupling reaction.

The successful design and synthesis of chiral ligands for this nickel-catalyzed reaction may be summarized in other words, paraphrasing a commercial:

"The ligands were selected, and so was the metal"