Amino acid modified phosphine ligands for the development of artificial transition metalloenzymes

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The discovery of new routes for the preparation of enantiomerically pure compounds of interest for industrial production is one of the most actively pursued goals in synthetic chemistry. Target molecules comprise pharmaceuticals, vitamins, agrochemicals and flavorants. Enantioselective catalysis, either biocatalytic or chemocatalytic, is one of the most efficient ways to synthesize enantiopure compounds.

In biocatalysis, the use of enzymes for organic transformations finds more and more applications, primarily owing to the excellent activity, chemoregio- and enantioselectivity displayed by enzymes. Enzymes are capable of combining molecular recognition for substrate orientation with catalytic centers. In the field of chemocatalysis, a large number of chemical transformations make use of homogeneous organometallic catalysts. The key to their success lies in the relative ease of catalyst modification by changing the ligand environment. Both the transition metal center and the large variety of ligands around it determine the properties of the catalyst.

Biocatalysis and chemocatalysis are often seen as complementary in terms of substrate scope, reaction conditions and reaction medium. The synergy of both fields is therefore an intriguing development. The synthesis of bioinspired transition metal catalysts and artificial metalloenzymes has received much attention. In particular, the design of enantioselective transition metal catalysts which make use of secondary interactions between the ligand and the substrate, aiming at enzyme-like behavior, is an interesting development. This thesis deals with the development of new bioinspired transition metal catalysts and artificial transition metalloenzymes and their evaluation in several types of asymmetric catalytic reactions. The first part of Chapter 1 presents examples of bioinspired transition metal catalysts with a focus on phosphine ligands. The combination of phosphorus donor atoms with peptide fragments as a chiral entity in close proximity of the metal center can result in enantioselective catalysts. In the second part of Chapter 1, important examples in the development of artificial metalloenzymes are presented. With the aim to combine the best of both homogeneous
catalysis and biocatalysis, artificial metalloenzymes can be constructed by the insertion of (non)-chiral metal catalysts into the active site of a host protein.

The synthesis of a series of chiral amino acid-functionalized diphosphine ligands is described in Chapter 2. The meta or para position of the diphenylphosphino groups of Xantphos and DPEphos were functionalized with relatively small peptide fragments in order to create sterically demanding ligand systems that allow non-covalent secondary interactions between functionalized substrates and the ligand. NMR studies showed that the new xanthene-based ligands display metal coordination behaviour typical of Xantphos-type ligands and no direct influence of the amino acid residues was observed on complex formation.

The ligands were tested in the rhodium-catalyzed asymmetric hydroformylation of vinyl acetate. The peptide fragments influenced the stereo- and enantioselective outcome of the reaction. In terms of enantioselectivity, the rigid xanthene-based ligands gave better results than the ligand with the flexible diphenyl ether backbone. In addition, the use of dipeptide-containing Xantphos derivatives had a more pronounced effect on the enantioselectivity than its shorter monopeptide-functionalized analogues, and enantiomeric excesses up to 13 % were achieved. Almost no enantioselective induction was observed in the hydroformylation of the substrate styrene, which contains no heteroatoms. In the Rh-catalyzed hydrogenation of dimethyl itaconate enantioselectivities up to 7 % were obtained with the dipeptide-functionalized ligands. Thus, these results illustrate that it is possible to influence the enantiomeric outcome of asymmetric catalytic reactions by making use of non-covalent secondary interactions between amino acid-functionalized ligands and prochiral substrates, although the ee values obtained so far are disappointing. In order to fully exploit these interactions, other better defined ligand systems need to be developed.

A well-defined ligand system is presented in Chapter 3. Cyclic double bridged diphosphines in which the two phosphine lone pairs have a syn orientation form a class of ligands in which the metal embracement is particularly effective. The two phosphorus atoms are bridged by two backbones and the third substituent is forced to reside at the front side of the metal center. Chapter 3 describes a stereoselective route to cyclic double bridged diphosphine ligands based on two xanthene backbones. The
reaction of dilithio-xanthene with dichlorophenylphosphine gave cyclic bisxantphos as a single stereoisomer. X-ray crystal structure analysis revealed that the phosphorus bridging groups are arranged in a syn-disposition. The route is flexible in the choice of aryldichlorophosphine and should permit a range of substituents to be introduced on the phosphorus atoms. The ligand displays trans-coordination upon complexation to [Pt(cod)Cl₂]. The new bisxantphos ligand together with the structurally related P-bridged [1.1]ferrocenophane were modified with amino acid fragments on the third substituent of the phosphorus atoms in order to create a chiral enzyme-like pocket upon coordination of the ligands to a metal center.

The cyclic bisxantphos ligand showed a low activity and regioselectivity in the hydroformylation of 1-octene and a high percentage of octene isomers was formed during the reaction. The chiral amino acid-functionalized P-bridged [1.1]ferrocenophanes were active in the Pd-catalyzed allylic amination of 1,3-diphenylallyl acetate displaying enantioselectivities of up to 10 %. Despite the low enantiomeric excesses obtained in this reaction, the observed chiral induction is unusual since the stereogenic centers on the ligands are not situated close to the metal center (as is usually the case in chiral transition metal catalysts), but rather at the substrate side of the catalytic metal center.

A different approach towards amino acid-functionalized diphosphine ligands is described in Chapter 4. The amino acid-fragments are not introduced at the diphenylphosphino groups, as was done with the ligands presented in Chapters 2 and 3, but at the backbone of the ligands.
Four bidentate phosphorus ligands with a nitrogen atom in the backbone were modified with amino acid-fragments at an appropriate distance from the phosphorus atoms which allows non-covalent secondary interactions between functionalized substrates and the ligand. The palladium catalysts, which were prepared in situ by mixing the amino acid-modified ligands and [Pd(η₃-C₃H₅)Cl]₂, were examined for catalytic activity and enantioselectivity in the asymmetric allylation of 2-acetylcyclohexanone with cinnamyl acetate. The observed enantioselectivity was attributed to secondary interactions between the nucleophile and the amino acid fragments on the ligand. The catalysts may be regarded as artificial enzyme-like catalysts, as the catalysts interact with the electrophile (allyl acetate) and the nucleophile (sodium enolate) simultaneously.

In addition to the synthesis of bioinspired transition metal catalysts, the use of artificial metalloenzymes as catalysts for asymmetric transformation reactions of non-natural substrates is an intriguing development. A strategy for the preparation of artificial transition metalloenzymes by site-selective incorporation of metal-binding phosphine ligands into the active site of the Photoactive Yellow Protein (PYP) is presented in Chapter 5. Photoactive Yellow Protein is a water-soluble protein with a relatively low molecular weight that features a hydrophobic chromophore-binding pocket with a highly nucleophilic cysteine residue, Cys69. The thiol group of Cys69 in protein mutant R52G is highly reactive towards activated carboxylates. Using the nucleophilic thiol group, carboxylate-containing phosphine ligands and their corresponding transition metal complexes were coupled to PYP-R52G. The successful coupling was shown by ³¹P NMR spectroscopy and ESI mass spectroscopy. The new hybrid catalysts were tested in hydrogenation, hydroformylation and allylic substitution reactions. The new artificial metalloenzymes were active in rhodium-catalyzed hydrogenation and palladium-catalyzed allylic amination. However, in both reactions organic cosolvents were required to obtain reproducible conversions. We assume that under fully aqueous conditions the metal center in the R52G adducts are not accessible for substrates. The addition of organic solvents denaturates the protein which results in a more accessible metal center. This also disrupts the tertiary structure of the protein which can explain the lack of induction of enantioselectivity. The new artificial metalloenzymes were not active in the aqueous biphasic hydroformylation of styrene. The relatively high temperature and pressure of syngas required for this reaction appear to be too harsh for the PYP-adducts.