Summary and Evaluation

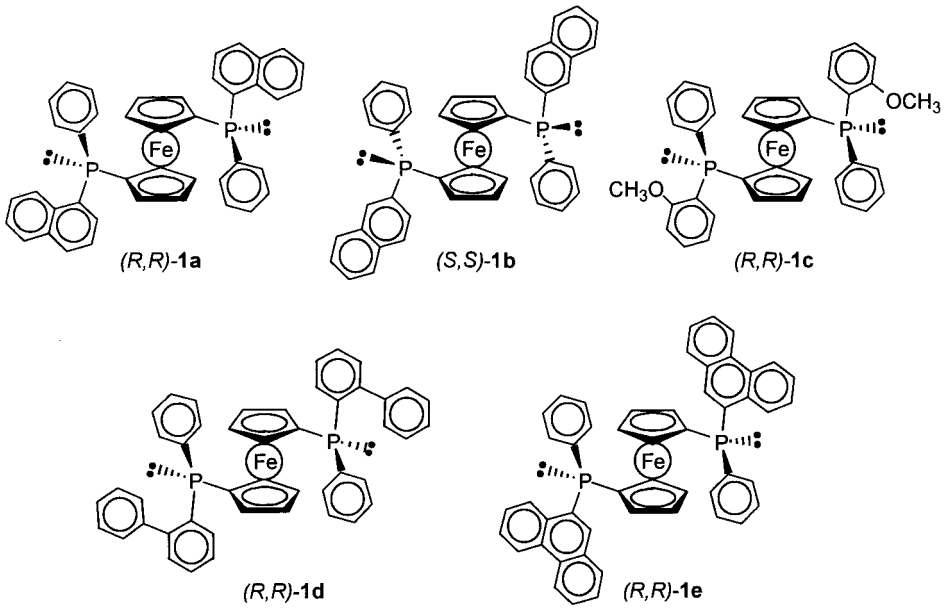
The main objectives of the present thesis were the development of novel, P-chiral, propeller-shaped diphosphines as ligands for enantioselective catalysis. In first instance, their application focused on asymmetric hydroformylation, a reaction cleanly transforming alkenes in possibly chiral, high value-added aldehydes, which are of industrial interest as building blocks in the manufacture of agrochemicals and pharmaceuticals. Thus, ligand design focused on specific structural features such as wide bite angle frameworks incorporating stereogenic phosphorus donors. The C_2-type symmetry of the active catalyst complexes resulting thereof was believed to promote good stereoselectivities.

The synthetic goals of the research project were successfully met by establishing a stereoselective route to phosphorus-chiral enantiopure diphosphine ligands. The new approach is characterized by its tolerance towards bulky residues, allowing the attachment of three sterically demanding aryl substituents onto a given phosphorus atom. Flexibility and easy modification of the multistep synthesis enabled the preparation of in total 12 novel P-chiral diphosphines, simultaneously exploiting new levels of stereocontrol on asymmetrically substituted phosphorus centers. In view of the ever-growing request for new "tailor-made" ligand structures for specific (industrial) applications, the disclosed approach might as well prove useful in related ligand syntheses by offering considerably improved access to enantiopure (di)phosphine donors.

Concerning the application of the new ligands in rhodium catalyzed asymmetric hydroformylation, it was shown that several factors determining enantiodiscrimination are not sufficiently governed by the mentioned concepts of P-chirality and C_2-type symmetry. While e.e. values obtained in the hydroformylation of styrene rank among the highest reported for propeller-shaped diphosphines, the performance of other types of catalyst modifiers, such as diphosphites or phosphine-phosphites could not be equalled. Nevertheless, the investigations undertaken contribute to a deeper understanding of mechanistic aspects of the hydroformylation reaction and provide useful information concerning future ligand design. A generally promising and structurally interesting class of diphosphine ligands has been added to the chiral toolbox and might find applications in other catalytic transformations in the future. A step into this direction was already made by employing the new diphosphines in enantioselective hydrogenation and allylic substitution reactions, of which the results represent an integral part of this PhD research.

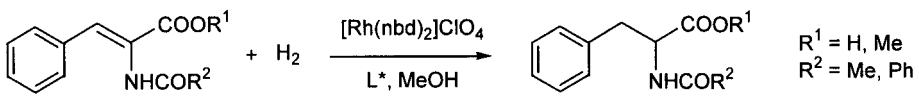
Chapter 2 describes the synthesis of five new P-chiral, C_2-symmetrical diphosphines, based on a stereoselective route developed by Jugè et al. Extending this approach to bulky aromatic dilithioferrocene reagents gave the dppf-analogue ligands **1a-e** in good overall yields and excellent enantioselectivities (Scheme 1). The stereochemical course of the multistep nucleophilic substitution sequence was confirmed by crystal structure analyses of ligands **1a**, **1b** and **1d**.

Scheme 1



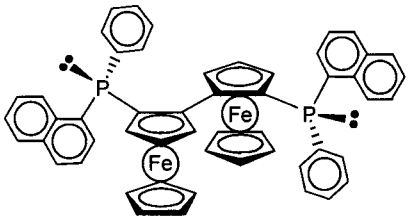
For a first evaluation, the potential of the new ligands was tested in rhodium-catalyzed asymmetric hydrogenation reactions of cinnamic acid derivatives (Scheme 2). Catalysts derived from ligands **1b** and **1d** revealed insufficient reactivities or enantiodiscriminating abilities. In contrast, remarkable enantioselectivities could be obtained employing diphosphines **1a**, **1c** and **1e**, whereby especially the latter donor excelled, giving e.e. values of up to 98.7%.

Scheme 2

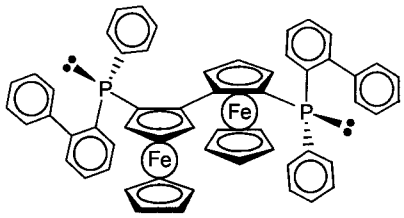


As described in *Chapter 3*, the mentioned multistep approach was utilized in the synthesis of diphosphine ligands **2a,b** bearing biferrocenyl skeletons and incorporating four adjacent stereocenters (Scheme 3). Chirality on phosphorus provided efficient means for the preparation of diastereomerically pure compounds, whereby enantiopure ferrocenyl phosphine oxides served as key intermediates. In the case of 2-biphenylylphenylphosphinoxyferrocene, *ortho*-magnesiation was found to proceed stereoselectively, after quenching with I_2 affording the *ortho*-iodo product in 94% d.e. (Scheme 4). The absolute configuration of the diphosphine ligands was confirmed by a solid state structure of a platinum(II) dichloride complex of **2a**, constituting the first example of a crystallographically characterized metal complex ligated by a biferrocenyl diphosphine donor.

Scheme 3

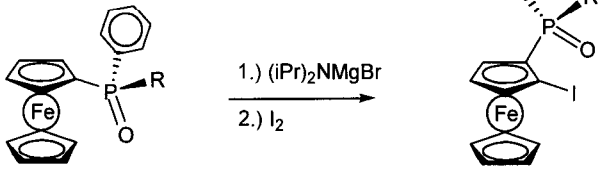


(S_P,R_m,R_m,S_P)-**2a**



(S_P,R_m,R_m,S_P)-**2b**

Scheme 4

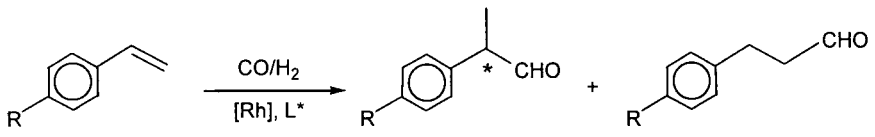


(*R*) (R_P,S_m)

R = 2-biphenylyl: 94% d.e.

Chapter 4 deals with the synthesis of electronically varied ligands **3a-c**, derived of diphosphine **1a** by *para*-methoxy- and/or *para*-trifluoromethyl substitution of the phenylphosphine rings. Their use in rhodium catalyzed asymmetric hydroformylation was described, whereby styrene, 4-methoxystyrene and 4-chlorostyrene were tested as substrates (Scheme 5). The solution structures of dicarbonyl rhodium hydride precursor complexes incorporating the respective ligands were investigated by high pressure IR and NMR techniques, revealing high preferences for the bisequatorial coordination mode in trigonal bipyramidal complexes. Thus, the intended C_2-type symmetry was realized; however, enantioselectivities remained moderate (up to 51% e.e.). While ligand electronic variations were shown to affect enantiodiscrimination to some extent, substrate electronic perturbations had a greater impact on regio- as well as stereoselectivity.

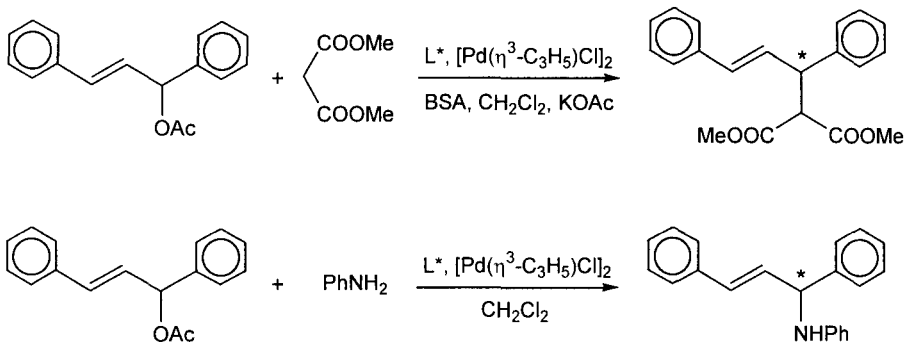
Scheme 5



R = H, Cl, MeO

In *Chapter 5* an investigation on the performance of the phosphorus-chiral auxiliaries, including the new 1,1'-bis(ferrocenylphenylphosphino)ferrocene in palladium-catalyzed asymmetric allylic substitution reactions, is described. Linear and cyclic pro-C_s-type substrates were tested under various reaction conditions; the best results were obtained employing 1,3-diphenylpropenyl acetate in combination with dimethylmalonate or benzylamine nucleophiles (Scheme 6). Ligands **2a** and **1d** were found best suited as catalyst modifiers for above mentioned reactions the latter effecting e.e. values of up to 99%. A crystal structure analysis of a 1,3-diphenyl-η^3-allyl palladium complex, ligated by diphosphine **1a** showed a marked distortion of the allyl moiety with respect to the phosphorus-palladium-phosphorus coordination plane. The assumption of the hereby more heavily dislocated allyl carbon terminus as target of nucleophilic attack was found in agreement with the outcome of the reaction.

Scheme 6


OAc
COOMe
COOMe
L*, [Pd(η3-C3H5)Cl]2
BSA, CH2Cl2, KOAc
MeOOC
COOMe
OAc
PhNH2
L*, [Pd(η3-C3H5)Cl]2
CH2Cl2
NHPh