Summary

The use of homogeneous transition metal catalysis in synthetic chemistry has attractive features. Generally, it accounts for more selective processes, therewith lowering the waste-formation. In addition, it allows synthesis of compounds that are otherwise difficult to prepare. Using asymmetric catalysis, the selective preparation of one single enantiomer comes within reach, avoiding tedious separation procedures. In spite of these advantages, still limited numbers of enantioselective, transition metal catalyzed reactions are applied in industrial processes. This is mainly due to the lack of suitable catalysts for the specific conversions of interest and the time-to-market pressure limiting the time to find a proper one. Since only small energy differences in the free energies of activation in the pathways giving the R- and S-product account for high ee, prediction of suitable catalysts for a certain process is impossible. The availability of large and diverse ligand libraries for the formation of chiral transition metal complexes would considerably facilitate the incorporation of economically benign homogeneous steps in synthesis routes by allowing the identification of active and selective catalysts by screening. Nowadays, libraries of many different ligands are available, especially of monodentate phosphite- and phosphoramidite ligands. However, due to intrinsic synthetical difficulties, libraries of chiral bidentate phosphorus ligands, especially those containing phosphine ligands, are relatively scarce. The use of supramolecular chemistry, in which bidentate ligands are assembled from smaller building blocks by attractive interactions such as met-to-ligand interactions and hydrogen bonds, can be an elegant solution to this problem.

The aim of the work described in this thesis was to develop a large and versatile bidentate phosphorus ligand library using the supramolecular strategy. In addition, we aimed to apply this library in different homogenously catalyzed reactions in order to show the applicability of the approach. In this thesis we describe the use of specific metal-ligand interactions to form supramolecular bidentate ligands (Figure 1: schematic representation). We make use of the Supraphos technology as developed previously in our group. In this approach metallo-porphyrin acceptor- and nitrogen donor- building blocks are used to selectively form heterobidentate ligands (Figure 2).

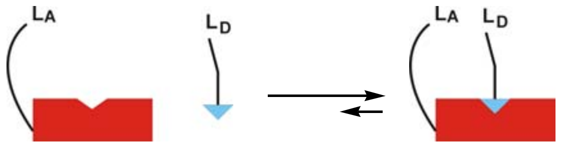

Figure 1: Schematic representation of the formation of a supramolecular bidentate ligand by the use of a complementary binding motif.

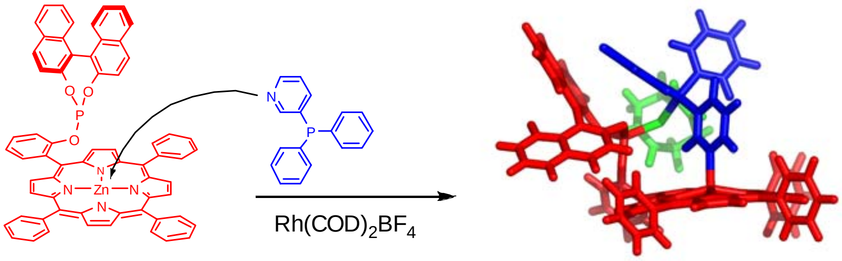

Figure 2: Formation of a rhodium catalyst with a Supraphos phosphine-phosphite ligand by mixing of the components.

In *Chapter 2* the development of a large and diverse ligand library is described. The synthesis of zinc(II) porphyrin phosphites and zinc(II) porphyrin phopshoramidites and the preparation of a variety of nitrogen donor –phosphines, -phosphites and phosphoramidites is discussed. By mixing these components, bidentate phosphite-phosphine, phosphite-phosphoramidite, hetero-bisphosphite, phosphoramidite-phosphine and bisphosphoramidite ligands are available. With 41 building blocks (14 zinc(II) porphyrin modified ligands and 27 nitrogen donor functionalized ligands) a 378-membered bidentate ligand library (14 × 27) becomes accesible.

In *Chapter 3* the results with ruthenium(II) porphyrin as a template are described. The binding of pyridine to ruthenium(II) porphyrin is stronger and less dynamic than the binding to zinc(II) porphyrin, thus providing an interesting tool for the evalution of the influence of the binding motif on the catalytic performance. In contrast to the zinc analogues, however, the binding of phosphine- and phosphite ligands to ruthenium(II) porphyrins is significant. While pyridine and pyrrolidine are preferred by ruthenium(II) tetraphenylporphyrin above triphenylphosphite, these nitrogen donors can not compete with the phosphite in the dimeric phosphite ruthenium(II) porphyrin assemblies (Figure 3, left). This complicates the use of these porphyrins as building blocks for Supraphos catalysts. In contrast, 5-(4-

(diphenylphosphite)phenyl)-10,15,20-trisphenyl ruthenium(II) porphyrins can be used as building blocks for supramolecular catalysts by using ditopic nitrogen donor ligands, allowing the formation of sandwich-type ligands (Figure 3, right).

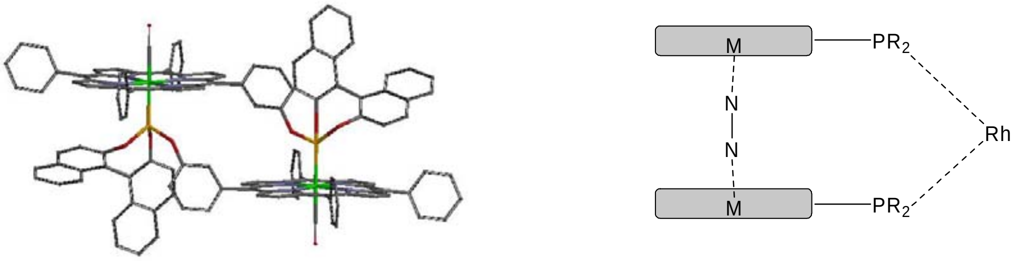

Figure 3: *left*: Dimeric assembly of phosphite ruthenium(II) porphyrin. *Right*: Sandwich-type ligand assembly of phosphite ruthenium porphyrin with ditopc nitrogen ligands.

In *Chapter 4* the use of Supraphos ligands in the rhodium-catalyzed hydrogenation of enamide substrates is discussed. Using the robot-facilities at DSM, a large library of ligands was investigated, providing a new catalyst based on a Supraphos phosphite-phosphine ligand for the hydrogenation of *N*-(3, 4-dihydro-2-naphthalenyl)-acetamide (Figure 4) that yields the product with unprecedented high ee, 94%. The importance of high-throughput screening was evident from the fact that the second best ee obtained with the Supraphos library was only 56%.

The same ligand that rendered *N*-(3, 4-dihydro-2-naphthalenyl)-acetamide in 94% ee, provided the hydrogenated product of *N*-(3, 4-dihydro-2-naphthalenyl)-phenylamide with over 90% ee. On the contrary, this catalyst provided the product of *N*-(3,4-dihydro-1-naphthalenyl)-acetamide with approximately 19% ee, demonstrating the substrate-sensitivity of the catalyst.

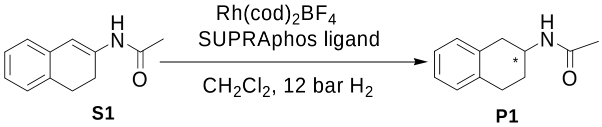

Figure 4: Asymmetric hydrogenation of *N*-(3, 4-dihydro-2-naphthalenyl)-acetamide. The catalyst that provides the product with 94% ee is displayed in Figure 2.

Chapter 5 shows the application of a part of the ligand library in the asymmetric hydroformylation of styrene (Figure 5). Large differences between the several ligand classes were observed. For instance, the most active catalysts all contained either a phosphine- or a bulky phosphite ligand. High ee was obtained with a phosphoramidite-based catalyst, although unfortunately the activity of this catalyst was very low. Based on these first screening results, a new ligand class was developed: the Supraphos phosphoramidite-phosphine ligands. Catalysts based on these ligands indeed show improved activity with respect to those based on the phosphite-phosphoramidite ligands and improved enantioselectivity compared to the phosphite-phosphine based assemblies. Remarkably, in addition to the high(er) enantioselectivity, some catalysts based on Supraphos phosphite-phosphoramidite and phosphoramidite-phosphine ligands show unprecedented regioselectivity for the linear aldehyde over the branched aldehyde, resulting in up to 72% linear aldehyde at 80 °C and 10 bar CO/H_2 1:1. Generally such high linearity is only observed at higher temperatures.

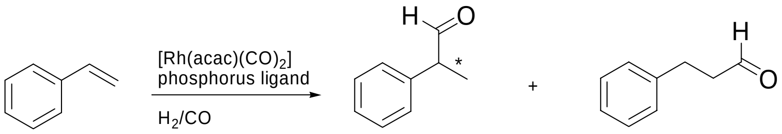

Figure 5: Asymmetric rhodium catalyzed hydroformylation of styrene.

The broader implementation of homogeneous catalysts for asymmetric conversions requires, diverse libraries ligands, including chiral bidentate (phosphorus) ligands, enabling rapid catalyst identification by high-throughput screening. These screening strategies will only be successful if the construction of large libraries containing various ligand types can be simplified. In this thesis we have shown that the use of supramolecular chemistry is an important tool to achieve this. The Supraphos-type ligands, communicated previously and described in this thesis in more detail, are ideally suited for the development of diverse libraries that are easily expanded and varied. Screening of parts of the library in the rhodium-catalyzed hydrogenation and hydroformylation revealed new catalysts providing the product with sometimes very high enantioselectivity (highest reported) or remarkable regioselectivity. The current approach can easily be extended to P-N and N-N ligands and ligands containing carbenes. Although the current work is purely academic, focussing on experimental proof and detailed insight in the application of supramolecular ligands, it is not difficult to imagine how the concepts described herein can be applied to commercially interesting systems.