Summary

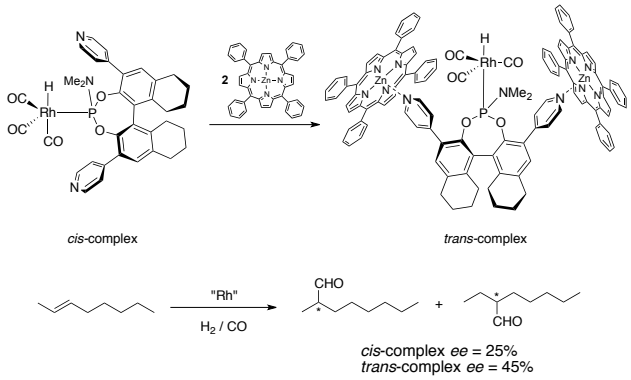
Chiral Supramolecular Ligands in Transition Metal Catalysis

The design of novel chiral ligands is at the core of asymmetric catalysis. The catalytic character of a transition metal catalyst such as activity, selectivity and stability can be fine-tuned by optimization of steric and electronic properties of the coordinating ligand. Supramolecular ligands have emerged as a new powerful class of ligands, easily prepared by mixing building blocks that are functionalized with complementary groups. In this way, the complementary building blocks are brought together by a self-assembly process using metal-ligand interactions, hydrogen bonding or ionic interactions. The power of this approach is that a relatively small number of building blocks already result in a large and diverse catalyst library. An overview of the current state-of-the-art in catalyst development based on self-assembled ligands for asymmetric transformations, and the different supramolecular strategies in transition metal catalysis is given in Chapter 1. In this thesis, we focused on the development and the study of new supramolecular ligands formed by selective interactions between pyridine-based phosphorus ligands and zinc(II)-templates.

In Chapter 2, the synthesis, coordination chemistry and evaluation in the Rh-catalysed asymmetric hydroformylation of a new class of supramolecular monodentate ligands is reported. Coordination studies, based on high-pressure NMR and high-pressure IR spectroscopy, demonstrate the formation of the first rhodium-hydride complex in which the phosphorus donor atom of the ligand is *trans* to the hydride. However, this occurs only upon coordination of zinc(II)-porphyrins to the pyridyl moieties of the ligand (Scheme 1). In absence of these zinc(II)-porphyrins the common monoligated rhodium-hydrido complex is formed with the ligand in the equatorial plane, in *cis* orientation to the hydride. Application of these complexes in the challenging hydroformylation of unfunctionalized internal alkenes proved that this unusual coordination induced by supramolecular change is reflected in higher activity and enantioselectivity. Moreover, investigation of a small series of sterically and electronically different templates in combination with the pyridine-based ligand

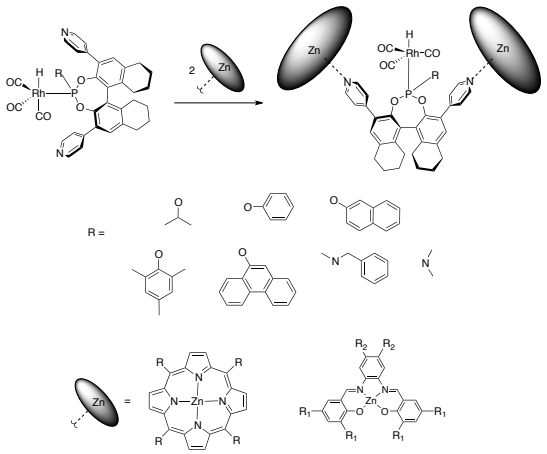
showed that the electronic and steric properties of the template have very little influence on the catalytic outcome. Therefore, the dominant effect on the enantioselectivity is associated with switching the position of the ligand from *cis* to *trans* position, with respect to the hydride, upon templation.

Scheme 1



In Chapter 3, a series of chiral pyridine-based phosphoramidite and phosphite ligands is reported, which are studied under hydroformylation conditions by *in situ* high-pressure NMR and IR techniques (Scheme 2).

Scheme 2

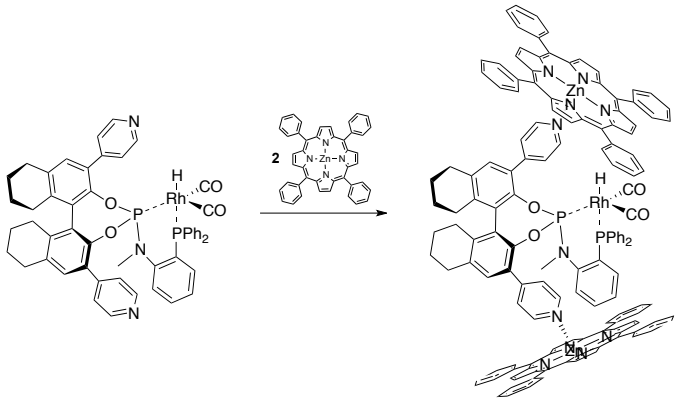


These studies revealed that the coordination of the phosphorus to rhodium changes from equatorial to axial position in the presence of a supramolecular template. Moreover, investigation on the origin of this shift in ligand coordination on a rhodium hydroformylation complex indicates that such a change in coordination

mode is a results of electronic effects induced by these templates on the phosphorus atom. High conversions and moderate enantioselectivities were obtained when these new phosphite and phosphoramidite ligands were applied in the asymmetric hydroformylation of internal unfunctionalized alkenes. The results also revealed that the presence of sterically bulky groups on the phosphorus donor atom (R in Scheme 2) significantly improve the regioselectivity of this reaction.

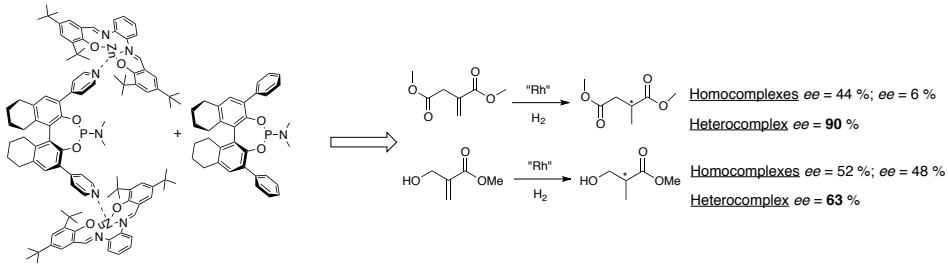
In Chapter 4 we report a novel class of supramolecular bidentate hybrid ligands in which the two inequivalent phosphorus units and the pyridine moieties are covalently attached to a chiral scaffold and the supramolecular interactions are use as second handle to control the coordination sphere around the transition metal centre (Scheme 3). Firstly, the coordination chemistry of these ligands was investigated under hydroformylation conditions by high-pressure NMR and IR spectroscopy, revealing formation of a single active species in which the phosphine ligand is in axial position and the phosphoramidite in equatorial position. Interestingly, in contrast with the monodentate analogues, the coordination mode of the bidentate ligands does not change upon addition of zinc(II)-templates. These ligands were applied in the asymmetric Rh-catalysed hydroformylation of styrene and *p*-substitute analogues. In these hydroformylation reactions, modification of electronic and steric properties of zinc(II)-templates appear to have a significant influence on the activity and selectivity of the catalysis. In particular, zinc(II)-templates bearing more electron withdrawing substituents led to an increase in enantioselectivity. This is intriguingly in contrast with our early findings on monodentate analogue ligands, where the catalytic properties of the supramolecular catalysts were not influenced by the properties of the zinc(II)-templates.

Scheme 3



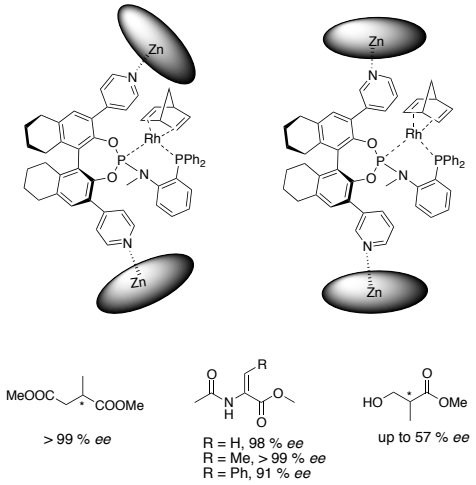
A ligand mixture strategy is reported in Chapter 5, representing a combinatorial approach to improve the selectivity of supramolecular monodentate ligands in asymmetric hydrogenation. The supramolecular ligands were evaluated in combination with a series of achiral and chiral P-ligands. Application of this combinatorial method led to supramolecular heterocomplexes that outperform their corresponding homocomplexes in the asymmetric hydrogenation of dimethyl itaconate and methyl 2-(hydroxymethyl)acrylate, where *ee*'s up to 90 and 63 % were obtained respectively (Scheme 4).

Scheme 4



In Chapter 6 we evaluated the supramolecular bidentate hybrid ligands in asymmetric hydrogenation of prochiral olefins (Scheme 5).

Scheme 5



Higher activity and selectivity has been achieved with the supramolecular ligands compared to the non-templated analogues. In addition, the catalysis studies revealed a dependence of the activity and selectivity on the association constants between the

zinc(II)- and ruthenium(II)-templates and the pyridine-based ligands. Strong association constants were necessary to increase activity and enantioselectivity. Moreover, application of a supramolecular strategy based on variation of steric and electronic properties of the zinc(II)-templates in the asymmetric hydrogenation of methyl 2-hydroxymethylacrylate showed that fine-tuning of the catalyst properties could be easily achieved by using supramolecular strategy based on template modifications.

In conclusion, in this thesis we have explored various supramolecular strategies in transition metal catalysis and demonstrated that new promising catalytic systems can be easily generated with this approach. For example, supramolecular interactions can be used to change the coordination mode of a monodentate ligand in a rhodium-hydroformylation catalyst, providing a new tool to control the activity and selectivity of a transition metal catalyst. Furthermore, bidentate ligands amendable via a supramolecular strategy, has proven to be an efficient approach to influence key catalytic features, such as activity and selectivity, in the rhodium-catalysed asymmetric hydrogenation and hydroformylation reactions, by just variation of the steric and electronic properties of the Zn building blocks. In addition, it was demonstrated that supramolecular-based catalytic systems could reach similar or even superior performances compared to classic homogeneous catalysts, proving the strength and potential of such multicomponent catalyst assemblies. Therefore, we foresee that these supramolecular strategies for catalyst preparation will be important for future applications in discovering new active systems for homogeneous catalysis solutions.