Chiral supramolecular ligands in transition metal catalysis
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Chapter 1

Chiral Supramolecular Ligands in Transition Metal Catalysis: A General Introduction

1.1 Introduction

The field of asymmetric catalysis has been intensely explored in recent years, and tremendous advances have been realized based on ligand variation, demonstrating that this is a powerful tool for the optimization of catalytic systems. The character of a homogeneous catalyst can be shaped by ligands featuring opportune steric and electronic properties so that very specific reaction pathways can be followed. Important parameters that describe ligand properties include the steric cone angle ($\theta$), and the electronic $X$-parameter. The importance of the geometry of bidentate ligands was realized much later and the “natural bite angle” was introduced to describe the properties of bidentate chelating ligands. Although these ligand parameters are particularly helpful to explain catalyst performance and despite significant progress in the field of theoretical and computational chemistry, it is still not possible to predict the activity and selectivity of catalytic systems. This is especially true for asymmetric transformations; therefore catalyst development still relies to a large extent on a combination of intuition, laborious work and, in many cases, serendipity. The intensive research over the past decades in the field of asymmetric catalysis has resulted in very few privileged ligands that form catalysts able to convert a wide range of substrates with high levels of enantioselectivity. This has motivated researchers to look for novel approaches to find catalytic solutions, and combinatorial strategies and high-throughput experimentations have been introduced to speed up the processes of lead finding and catalyst optimization.

A critical point in developing screening techniques for combinatorial catalysis is the availability of structurally diverse and meaningful ligand libraries. The problem is particularly acute for the important class of bidentate ligands, which has its origin in the complexity of bidentate ligand synthesis. An even bigger challenge is the synthesis of non-symmetric bidentate ligands featuring two different phosphorus donor atoms. Recently, there is a renewed interest in the use of monodentate phosphorus ligands in catalysis triggered by their relatively simple synthesis compared to bidentate analogues. In addition to their fast and practical synthesis from commercially available materials, outstanding activity and selectivity have been reported, comparable or even superior to those obtained with bidentate ligands and this exemplifies their combinatorial potential and possible industrial application. However, for several reactions (e.g. hydrocyanation, hydroformylation, allylic substitution) chelating bidentate ligands are still considered to be superior to obtain catalysts with appreciable selectivity and activity. Methodologies that enable the synthesis of sufficiently large libraries of bidentate phosphorus ligands are scarce, and new strategies are required to prepare diverse catalyst libraries that can be used for high-throughput experimentation. An
emerging class of ligands that has the advantage of the synthetic accessibility of monodentate ligands but behaves as chelating unit to a metal centre, comprises the class of supramolecular bidentate ligands formed by the self-assembly of monodentate units.\textsuperscript{12} In the supramolecular approach two monodentate ligand building blocks are brought together by a self-assembly process using non-covalent interactions such as hydrogen bonds, ionic interactions or dynamic metal-ligand coordination. Such an approach is well suited for combinatorial chemistry because the number of supramolecular bidentate ligands that become accessible grows exponentially with the number of ligand building blocks available. While this is also true for the monodentate mixed ligand approach in which two different monodentate ligands are introduced to a catalytically active transition metal, in this case the formation of two homocomplexes and one heterocomplex is expected. In the mixed monodentate scenario three possible catalysts are present in solution, and only if the heterocomplex is more active and selective better catalytic performance would be obtained. In contrast, if a supramolecular heterobidentate ligand is used, applying sufficiently strong complementary interactions, only the heterocomplex should form. In addition, such bidentate also imitates other properties of traditional non-symmetric bidentate ligand systems and the presence of two different donor atoms will also increase control over the steric and electronic properties in the microenvironment around the metal centre. In this chapter we will give an overview of the current state-of-the-art in catalyst development based on self-assembled ligands for asymmetric transformations, and we will discuss the different supramolecular strategies in transition metal catalysis.

\textbf{1.2 Construction of bidentate ligands by self-assembly}

\textit{Metal template assembly}

There are two principle strategies to generate self-assembled bidentate ligands based on metal-ligand interactions. The first approach consists of assembling two monodentate ligands on a single template that is functionalized with two complementary binding sites, while the second approach utilizes two monodentate ligand building blocks equipped with two complementary binding sites.

Our group was the first to report a strategy to prepare bidentate chelating ligands that involves the assembly of monodentate units on a bisporphyrin template (first approach).\textsuperscript{13} The interaction between the monodentate ligands and the template is based on axial coordination of functionalised nitrogen donor atoms to the zinc centre of the porphyrin rings. The supramolecular bidentate phosphorus ligand was formed \textit{in situ} by selective coordination of the nitrogen donor atom of building blocks \textbf{b-d} to the zinc porphyrins \textbf{2} (Figure 1.1). Assemblies based on \textbf{1-2} and
pyridine phosphorus ligands b-d were used as supramolecular ligands in the rhodium-catalysed hydroformylation (Scheme 1.1). Compared to the corresponding monodentate analogues the chelating bidentate assemblies 2(b)₂ and 2(c)₂ exhibited slightly higher selectivity for the linear aldehyde (up to 94:6) in the hydroformylation of 1-octene and better ee’s (up to 33 %) in the hydroformylation of styrene (Scheme 1.1). The chiral supramolecular catalysts based on 2(c)₂ and 2(d)₂ were also applied in the palladium catalysed allylic alkylation and similar effects were observed, as the enantioselectivity increased from 18 % to 45 %.

![Figure 1.1 Zinc(II)-porphyrin templates and phosphorus-based ligands used for the supramolecular assemblies.](image)

**Figure 1.1** Zinc(II)-porphyrin templates and phosphorus-based ligands used for the supramolecular assemblies.

![Scheme 1.1 Formation of rhodium-based hydroformylation catalyst by self-assembly of ligand b and zinc(II)-template 2 and hydroformylation of styrene using a chiral supramolecular catalyst self-assembly.](image)

**Scheme 1.1** Formation of rhodium-based hydroformylation catalyst by self-assembly of ligand b and zinc(II)-template 2 and hydroformylation of styrene using a chiral supramolecular catalyst self-assembly.

Recently, we reported on supramolecular “box” ligands formed by self-assembly of chiral pyridine-based phosphoramidite ligands with bis-zinc(II)-salphen (Scheme
1.2). The 3-pyridyl-monodentate ligands function as pillars in such a “box”, bringing the two phosphorus donor atoms in close proximity and forming a self-assembled bidentate ligand. In the presence of rhodium hydroformylation precursor [Rh(acac)CO₂] NMR and mass spectrometry studies showed clear formation of the bis-ligated rhodium(I)-complex. Application of this catalyst in the challenging asymmetric hydroformylation of internal unfunctionalized alkenes led to remarkable enantioselectivities (up to 86 %).

![Scheme 1.2](image)

**Scheme 1.2** Supramolecular transition metal complex formed from the assembly of 3-pyridyl-phosphoramidite ligands with bis-zinc(II)-salphens.

Our group published examples of template-induced formation of chelating supramolecular heterobidentate ligands by self-assembly of two different monodentate ligands on a rigid bis-zinc(II)-salphen building block (Figure 1.2). Remarkably, only heterobidentate ligand complexes were formed, an equilibrium that was driven by steric effects. In rhodium-catalysed hydroformylation and hydrogenation reactions these templated bidentate ligands showed enhanced selectivities compared to the non-templated analogues, *i.e.* for asymmetric hydroformylation of styrene the *ee* improved from 13 to 72 %.  

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In 2004, we developed a different supramolecular strategy to build bidentate ligands, which involved two monodentate components functionalised with complementary binding sites (second approach). By simply mixing the building blocks in solution, chelating bidentate ligands spontaneously formed by self-assembly of the complementary moieties (Figure 1.3). This approach is particularly suitable for combinatorial and high-throughput experimentation. The initial library (Figure 1.4), called SupraPhos, consisted of 48 supramolecular bidentate ligands based on 14 building blocks. Six different phosphite-porphyrinato-zinc(II) compounds were used in combination with eight nitrogen-donor-functionalized phosphine or phosphite ligands. As proof of principle, the supramolecular library was applied in palladium-catalysed allylic alkylation. The various supramolecular bidentate ligand systems gave rise to a large variety in enantioselective outcome, providing support for the concept (between 60% and 70% ee in favour of the R). Thereafter, the SupraPhos library was extended and a part of this library (64 entries) was applied in the rhodium-catalysed asymmetric hydrogenation of a challenging cyclic enamide. Interestingly, only one hit was identified, and this is the most selective catalyst to date giving 94% enantioselectivity, demonstrating the power of the concept. Part of the library was also successfully used in the palladium-catalysed kinetic resolution of racemic cyclohexenyl acetate. An enriched building block library gave access to a potential ligand library of 450 different supramolecular ligands, a part of which was applied in the rhodium-catalysed asymmetric hydroformylation of styrene, revealing a strong dependence between the catalytic performance and the ligand class used, stressing the importance of library screening in homogenous catalysis (Scheme 1.3).
Figure 1.3 The formation of a transition-metal complex by self-assembly of complementary units.

Figure 1.4 Structures of porphyrin-functionalized phosphites (left) and of several bifunctional nitrogen-phosphorus ligands used to construct supramolecular architectures (right).

Scheme 1.3 Application of SupraPhos library in (1, 3) Pd-allylic alkylation, (2) Rh-asymmetric hydrogenation and (4) Rh-asymmetric hydroformylation.
Other examples of self-assembled chiral bidentate ligands that involve metal-ligand interactions have been reported by Takacs and co-workers. They developed bidentate ligands based on the preferential formation of heteroleptic complexes around a zinc(II)-template, driven by the complementary chirality of two monosubstituted bis-oxazoline ligands (Figure 1.5).\textsuperscript{21} This novel method is ideally suited for the preparation of combinatorial chiral ligand libraries in which the bisoxazoline-functionalized ligands can be easily modified in the spacer and backbone part. A library of 50 self-assembled chiral diphosphites was created and used in palladium-catalysed allylic amination, which led to the discovery of very selective catalysts (ee’s up to 97 %). The same library was later screened in the rhodium-catalysed asymmetric hydroboration of alkenes.\textsuperscript{22} The availability of a diverse library of ligands proved to be useful for the rapid optimization of different catalysts for single substrates. High levels of regio- and enantioselection could be obtained for each substrate. This new approach was also evaluated in the asymmetric hydrogenation of amino acid precursors.\textsuperscript{23} A library of 110 self-assembled ligands based on a biphenyl-phosphite ligating group was prepared. The screening revealed catalysts that induce good levels of enantioselection with ee’s up to 82 % (Scheme 1.4).

![Figure 1.5](image-url) Metal-directed self-assembly of a bimetallic catalyst.

**Scheme 1.4** Application of Takacs’ supramolecular catalyst in (1) Pd-allylic amination, (2) Rh-asymmetric hydroboration and (3) Rh-asymmetric hydrogenation.
Hydrogen bond assembly

Hydrogen bonds are widely explored as a binding strategy for the self-assembly of supramolecular bidentate ligands from functionalized building blocks. Although single hydrogen bonds are not one of the stronger non-covalent interactions (on the order of 3 kcal/mol), they can easily be combined to make an array of several hydrogen bonds increasing the strength of the interaction between species. Their directionality leads to a particular orientation of the hydrogen bonds in space enhancing the specificity and predictability of the assembly. The strength of a single hydrogen bond is based on the nature of the donor and acceptor, but it also depends to a large extent on the solvent employed, meaning that catalysts based on these supramolecular bidentate ligands are more strongly solvent-dependent. Therefore, this type of interaction is well suited for the self-assembly of monodentate units to form supramolecular bidentate systems.

Breit and co-workers reported a self-assembly strategy based on hydrogen bond interactions between several 6-diphenylphosphanylpyridone-bearing chiral phosphorus-donor ligands (Scheme 1.5 and Figure 1.6).24 The new library of supramolecular ligands was applied in the asymmetric hydrogenation of benchmark substrates and satisfying enantioselectivities were obtained. An enlarged library of self-associated phosphine ligands was successfully studied in the enantioselective palladium-catalysed amination of allylic alcohols and enantioselectivities of up to 99 % were achieved (Scheme 1.6).25

![Scheme 1.5](image-url)  
**Scheme 1.5** Self-assembly of 6-diphenylphosphanylpyridone in the presence of a transition metal.
Figure 1.6 Library of monodentate phosphine building blocks that form supramolecular homobidentate ligands by self-assembly.

![Library of monodentate phosphine building blocks](image)

Scheme 1.6 Use of self-assembled phosphine-based catalyst in (1) Rh-asymmetric hydrogenation and (2) Pd-allylic amination.

Later, Breit and co-workers reported a new library of building blocks that was specifically designed to make chiral supramolecular heterobidentate ligands, created by self-association of monodentate ligands through complementary hydrogen bonds (Scheme 1.7). A library of chiral aminopyridine and isoquinolone systems bearing phosphine and phosphonite donor groups was applied in the rhodium-catalysed asymmetric hydrogenation of olefins (Figure 1.7). Excellent enantioselectivities (up to 99%) were reported for the hydrogenation of prochiral olefins (Scheme 1.8). Subsequently, Breit and co-workers showed that these kinds of chiral ligands, which exclusively form heterobidentate metal complexes, are suitable to develop novel high-throughput screening approaches. A deconvolution strategy was applied in order to identify the best performing catalyst directly from a mixture of all individual catalysts formed through self-assembly. A library of 120 catalysts was divided in four subgroups on the basis of the individual platforms, and the
performance of mixtures of catalysts was studied. The ligand subgroup that gave the best results was deconvoluted further by division of the best performing mixture into new subgroups (4 subgroups). This process was repeated until the catalyst that gave the best outcome in term of selectivity and activity was identified. Applying this strategy, three highly active and selective catalysts were identified for asymmetric rhodium-catalysed hydrogenation, and the number of experiments required to identify the most selective catalyst was significantly reduced.

**Scheme 1.7** Formation of heterocomplexes by selective interactions between aminopyridine and isoquinolone.

**Figure 1.7** Aminopyridine and isoquinolone ligand building blocks.

**Scheme 1.8** Asymmetric Rh-catalysed hydrogenation of prochiral olefins.

The Breit group also developed another family of supramolecular bidentate ligands based on peptidyl-functionalized phosphines and phosphites that could mimic the well know PhanePhos ligand. This scaffold, called SupraPhanePhos, is formed by meta-carboxypeptidyl substituted triarylphosphines (Do = PPh₂) or phosphites (Do
supramolecular bidentate ligands. Chiral phosphites and phosphoramidites, which, by self-assembly, form supramolecular bidentate ligands (Figure 1.8). The two meta-substituted arene rings arrange, via π-π stacking into a planar chiral structure that resembles the planar chiral identity of PhanePhos, as evidenced by X-ray crystallographic and NMR spectroscopic analysis. The homobidentate ligands were evaluated in the asymmetric hydrogenation of benchmark substrates; the enantioselectivities achieved (75-99 %) were comparable to those obtained with PhanePhos ligands.

**Figure 1.8** Schematic representation of SupraPhanePhos.

Further developments of this concept led to new supramolecular heterobidentate complexes, formed by metal-templated self-assembly of peptide-based phosphorus-ligands (Figure 1.9). In the presence of rhodium(I)-salts, C-linked phosphane-functionalised peptidyl ligands (L_C) assembled with complementary N-linked counterparts (L_N) to form a two-stranded, antiparallel β-sheet structure, which served as a basis for the construction of a heterobidentate ligand library. This library was studied in the asymmetric hydroformylation of styrene. Although the stereocenters of the peptide chains were remote from the catalytic centre, significant levels of enantioselection (ee’s up to 38 %) could be obtained.

**Figure 1.9** Peptide-based phosphorus ligands used for the formation of heterobidentate complexes.

Our group developed a class of urea-based ligand building blocks (phosphines, chiral phosphites and phosphoramidites), which, by self-assembly, form supramolecular bidentate ligands. Urea-functionalised ligands are easily made by connecting three building blocks: ligand backbone, spacer and urea motif. The synthons to build such ligands are commercially available or easily accessible,
making variations of these three units easy, which enables the development of large and diverse ligand libraries. Assembly of two of such phosphine ligand building blocks, allowed the formation of chelating structures in the presence of Pd and Rh complexes (Figure 1.10).

**Figure 1.10** Self-assembly of urea-based building blocks by hydrogen bonds for the formation of supramolecular catalysts.

An introductory series of six structurally related ligands was explored in the asymmetric hydrogenation of prochiral substrates and high selectivities were observed (Scheme 1.9). Importantly, small changes in the bridge between the donor atom and the urea binding motif, resulted in large variation in the catalytic performance of the related rhodium complex, making variation in the UREAPhos structure relevant.

**Scheme 1.9** Asymmetric Rh-catalysed hydrogenation of prochiral olefins.

In subsequent work, we reported the preparation, high-throughput screening and lead optimization of a library of urea-functionalised ligands (Figure 1.11) in an automated fashion using ChemSpeed and AMTEC SPR16 technologies. The results demonstrate the powerful combination of applying supramolecular ligands, based on easily accessible building blocks, and automated high-throughput screening of catalysts, as several catalysts were identified that gave record-breaking selectivities in asymmetric hydrogenations of difficult substrates.
In 2008, we published METAMORPhos, a sulfonamidophosphine ligand that exists as a mixture of tautomers (N(H)P III and N=P V(H)) in solution, which are able to form the corresponding homocomplexes by self-assembly. 32a Upon addition of [Rh(acac)(CO) 2] to a solution of ligand 52, formation of a homocomplex composed of one neutral and one anionic version of 52 was observed by NMR spectroscopy. The ligand is sufficiently acidic to protonate the acetylacetonate-fragment (Scheme 1.10). In this assembly the P-ligands are in trans position and are held together by intramolecular hydrogen bonding. However, in the presence of chiral phosphoramidite R-(53), which exists only in the N(H)P III tautomeric form due to the lower basicity of the phosphorus atom, heterocomplex Rh(53,52) forms exclusively (Scheme 1.11). The respective complexes were applied in rhodium-catalysed asymmetric hydrogenation reactions using HBF 4 ·OMe 2 as protonating agent. The latter is needed to form the catalytically active complexes. Both heterocomplex 53-52 and homocomplex (52) 2 displayed high levels of enantioselection in the hydrogenation of specific alanine precursors (91 % and 96 % ee). Later it was found that ligand R-(53) forms dinuclear complexes that give unusual activity and selectivity in the asymmetric hydrogenation of tetrasubstituted cyclic enamides. 32b

Figure 1.11 UreaPhos ligand library.
Scheme 1.10 METAMORPhos ligands forming a homocomplex in the presence of rhodium precursor.

Related to these ligands a new family of ureaphosphine ligand building blocks were developed by our group, including chiral analogous. The new urea functionalized ligands, possess an acidic NH group directly bound to the phosphorus donor atom or via an alkyl spacer. When two equivalents of ligand 55 were added to \([\text{Rh(acac})(\text{CO})_2]\), the \(^{31}\text{P}\) NMR spectrum displayed an ABX pattern typical for complexes with two different phosphorus atoms coordinating to the rhodium centre. However, when two equivalents of the same ligand 55 were added to the cationic rhodium species \([\text{Rh(nbd)}_2]\text{BF}_4\), the \(^{31}\text{P}\) NMR spectrum showed formation of a
bisligated complex with two equivalent phosphorus atoms coordinated in a mutual *cis* position (Scheme 1.12). The $^1$H NMR spectrum confirmed that the urea protons were involved in hydrogen bonding in this complex. Interestingly, using a 1:1 ratio between ligand 55 and the same cationic precursor [Rh(nbd)$_2$]BF$_4$ a new complex was formed in which the ureaphosphane acts as a hybrid P,O-coordinating bidentate ligand. Instead, using the same ligand to rhodium ratio but employing a neutral rhodium precursor results in the deprotonation of the ligand with consequent P,N-coordination of the ligand to the metal centre (Scheme 1.12). These homo and hetero-complexes were evaluated in rhodium-catalysed asymmetric transformations, such as hydroformylation$^{33b}$ of styrene and hydrogenation$^{33a}$ of olefins, and good activity and moderate to good enantioselectivity (up to 86 %) were obtained (Scheme 1.13). Hence, this new kind of ligand structure allows for different types of coordination, which significantly increases the potential application in catalysis. Subsequently, it was demonstrated that the versatile coordination displayed by this ligand system translates nicely in different catalytic behaviour.

Scheme 1.12 Versatile reactivity of ureaphosphane 55 in the presence of various rhodium precursors.
The group of Ding has reported the application of a class of supramolecular bidentate ligands (DpenPhos) able to self-assemble by hydrogen bonding interaction between the NH-groups of two phosphoramidite ligands (Figure 1.12). The resulting catalyst, when applied in the asymmetric hydrogenation of β-aryl itaconic acid derivatives, displayed high reactivity (TOF up to 400 h\(^{-1}\) at p(H\(_2\)) = 40 bar) and excellent enatioselectivity (ee’s up to 99 %) (Scheme 1.14). The analogous unfunctionalized monodentate ligands, lacking this hydrogen bond donor group, showed no activity in the same reaction. NMR spectroscopic studies together with DFT calculations confirmed the existence of an intermolecular hydrogen bond between the two adjacent monodentate ligands around the rhodium catalyst, which is believed to be responsible for the catalytic performance.

**Scheme 1.13** Application of phosphinourea ligands in asymmetric catalysis.

The group of Ding has reported the application of a class of supramolecular bidentate ligands (DpenPhos) able to self-assemble by hydrogen bonding interaction between the NH-groups of two phosphoramidite ligands (Figure 1.12). The resulting catalyst, when applied in the asymmetric hydrogenation of β-aryl itaconic acid derivatives, displayed high reactivity (TOF up to 400 h\(^{-1}\) at p(H\(_2\)) = 40 bar) and excellent enatioselectivity (ee’s up to 99 %) (Scheme 1.14). The analogous unfunctionalized monodentate ligands, lacking this hydrogen bond donor group, showed no activity in the same reaction. NMR spectroscopic studies together with DFT calculations confirmed the existence of an intermolecular hydrogen bond between the two adjacent monodentate ligands around the rhodium catalyst, which is believed to be responsible for the catalytic performance.

**Figure 1.12** DpenPhos ligands: supramolecular interactions between two phosphoramidite ligands in a rhodium-complex.
In 2009, we reported the assembly of a bidentate ligand through hydrogen bonds between a urea-functionalized phosphine and an ester-functionalized phosphoramidite (Figure 1.13).\textsuperscript{35} NMR and IR studies revealed the formation of a single hydrogen bond between the -NH unit of the phosphoramidite and the urea carbonyl group of the phosphine ligand; these results were corroborated by DFT calculations. Importantly, the characterization studies (IR and NMR spectroscopy) indicated exclusive formation of the heterobidentate supramolecular complex when the two monodentate ligands were mixed in a 1:1 ratio in the presence of a rhodium precursor such as $[^\text{Rh(cod)}_2]$BF$_4$. This heterocomplex afforded the highest enantioselectivity reported for the hydrogenation of 3-hydroxy-2-methylpropionate (Roche ester) and several analogous substrates (Scheme 1.15). Upon addition of these substrates to the supramolecular rhodium complex, a change in the hydrogen-bonding pattern was observed, which suggests selective substrate pre-organization and coordination. On the basis of DFT calculations, an intermediate was proposed where the substrate forms hydrogen bonds to the ester group of the phosphoramidite ligand (Figure 1.14). Control experiments with substrates incapable of hydrogen bonding showed that these weak interactions are essential to induce high activity and selectivity in catalysis.

**Scheme 1.14** Application of DpenPhos ligands in rhodium-catalysed asymmetric hydrogenation.

**Figure 1.13** LeuPhos: formation of supramolecular bidentate complex in the presence of rhodium transition metal through hydrogen bonds between the ester and urea motifs.
Scheme 1.15 Asymmetric hydrogenation of Roche Ester derivatives.

Figure 1.14 LeuPhos: substrate orientation through hydrogen bonding between the hydroxyl group of the substrate and ester unit of the phosphoramidite.

In a recent publication Gennari, Piarulli and co-workers presented a new class of chiral supramolecular ligands bearing a phthalamide group, able to self-assemble by intermolecular hydrogen bonds. A library of nineteen PhthalaPhos ligands was used in the asymmetric hydrogenation of benchmark olefins and challenging substrates such as cyclic enamides. Several highly enantioselective catalysts were identified (Scheme 1.16). The role of the hydrogen bonds for the catalytic properties of PhthalaPhos were investigated by NMR and IR techniques and the results were supported by DFT studies (Figure 1.15). These investigations showed that the self-assembly of the monodentate ligands led to a reduced degree of conformational freedom around the metal centre, which can explain the stereoselectivity obtained with PhthalaPhos ligands. In addition, the authors also suggested that the substrate forms hydrogen bond interactions with the ligand, similar as found for LEUPhos, possibly playing a crucial role in making the catalyst selective.
**Ionic interactions**

In recent years, a number of research groups have focused on finding other types of non-covalent interactions to create supramolecular bidentate ligands by self-assembly of complementary units. Cation-anion interactions have been identified as particularly promising, owing to their intrinsic complementarity. In principle, self-assembly of two ligands, one bearing a negative, the other a positive charge, should lead to the selective formation of supramolecular heterocomplexes. Following this principle, Gennari, Piarulli and co-workers reported the synthesis of a library of several binaphthol-based phosphorus ligands functionalised with either carboxylic acids or tertiary amines that were able to self-assemble through ionic interactions.\(^{37}\)
The rhodium complexes derived from the combination of acidic and basic ligand scaffolds were evaluated in the rhodium-catalysed enantioselective hydrogenation of methyl-2-acetamidoacrylate, and the performance of the heterocomplex was found to be slightly better as compared to the homocomplex (Scheme 1.17). The formation of the Rh-heterocomplex was investigated by NMR spectroscopy and a ratio of 70:30 between heterocomplex and homocomplex was determined. This moderate level of selectivity toward formation of the desired heterocomplex indicates that the ionic interactions are too weak; nevertheless this example is a proof of principle how ionic interactions could be used to search for better catalysts for chemical transformations.

Scheme 1.17 Acidic and basic phosphite ligands and their application in asymmetric hydrogenation catalysis.

The Fan and Nishibayashi groups independently developed supramolecular chiral bidentate ligands based on a pseudorotaxane skeleton. Nishibayashi and co-workers showed by NMR and FAB-MS the formation of pseudorotaxane ligands as a mixture of diastereoisomers. Coordination to the rhodium, led to a quantitative formation of a single diastereoisomer (Figure 1.16). The catalyst is obtained by mixing an equimolar amount of a diphenylphosphino-functionalized ammonium salt and a crown-ether functionalised with a chiral phosphite ligand in the presence of [Rh(cod)₂]PF₆ as rhodium precursor. This complex in the asymmetric
Chapter 1

hydrogenation of enamide derivatives showed good catalytic performance (Scheme 1.18).

\[
\begin{align*}
\text{Scheme 1.18} & \text{ Rhodium-catalysed asymmetric hydrogenation of methyl (Z)-α-acetamidocinnamates.}
\end{align*}
\]

Fan’s group reported similar ligands based on the same concept, (Figure 1.17) which were applied in the enantioselective hydrogenation of α-dehydroamino acid esters. The catalysts displayed superior activity and enantioselectivity as compared to monodentate analogues.\textsuperscript{39a}

\[
\begin{align*}
\text{Figure 1.17} & \text{ Supramolecular bidentate ligands based on a pseudorotaxane skeleton.}
\end{align*}
\]

In follow-up work Fan and co-workers reported a template-induced strategy for the generation of chiral metalloccrown-ether catalysts (Scheme 1.19).\textsuperscript{39b} An oligo(ethylene glycol) fragment is used as the backbone for a ditopic phosphorus-functionalized scaffold that is first complexed with alkali-metal ions in order to
bring the two phosphorus moieties closer together. Subsequently the preformed ditopic ligand is coordinated to the appropriate transition metal ion, thereby forming the metallo crown-ether appended catalysts. The performance of these new catalysts was evaluated in the asymmetric hydrogenation of dehydroamino acid derivatives, which led to a remarkable enhancement (up to 8%) in enantioselectivity in all cases in the presence of Na⁺, as compared to those achieved from only the biphosphite ligand in the absence of the templating alkali-metal ion (Scheme 1.20).

![Scheme 1.19 Schematic representation of the template-induced strategy for generating chiral metallo crown ether catalysts.](image)

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![Scheme 1.20 Rhodium-catalysed enantioselective hydrogenation of methyl-α-acetamidocinnamate.](image)

More recently, we reported a strategy to obtain chiral catalysts based on an achiral biphosphine ligand that binds acetate containing chiral cofactors in a binding pocket near the metal centre (Figure 1.18). Characterization studies in solution and solid state confirmed that chirogenesis is induced by chirality transfer through supramolecular interactions. In the asymmetric hydrogenation of a variety of prochiral alkenes many different cofactors were screened. Some of the complexes induced high enantioselectivities (up to 99% ee). Interestingly, relatively high ee was obtained even if a mixture of different cofactors, including the best one, were applied. On the basis of this, an iterative deconvolution screening strategy was applied, using mixtures of cofactors, for the identification of the best performing
catalyst. Using only 9 experiments, instead of 24, the best cofactor was identified (Scheme 1.21). DFT calculations were performed to investigate the influence of the best cofactor in catalysis. Calculations of the four coordination modes of the substrate to the rhodium metal centre gave indication that the most stable isomer, which leads to the product, is a structure in which a hydrogen bond between the amide NH of the substrate and the thiocarbonyl of the cofactor is formed. Control experiments confirmed that the formation of this hydrogen bond plays a crucial role in the selectivity of the reaction. These studies prove that catalyst optimization of supramolecular systems by non-covalent binding of simple cofactors is a valid approach that is easily applicable to search for the best performing catalyst for challenging transformations.

Figure 1.18 Structure of the biphosphine ligand and crystal structure of the rhodium pre-catalyst.

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</tbody>
</table>

Scheme 1.21 Asymmetric hydrogenation screening results with the best cofactors.
Along the same line, van Leeuwen and co-workers presented a supramolecular catalytic system, formed by self-assembly of ditopic achiral ligands, that was able to accommodate a bulky chiral diol in an anionic pocket, thereby inducing efficient chirality transfer (Scheme 1.22).\textsuperscript{41} The Schiff-bases bearing phosphine ligands were reacted with a variety of chiral diols in the presence of Ti(iPrO)\textsubscript{4} to give a library of chiral bidentate ligands. The library was studied in the hydrogenation of prochiral olefins and good enantioselectivities were achieved when bulky diols were present in the ligand assembly (up to 92 \% ee) (Scheme 1.23).

\begin{center}
\textbf{Scheme 1.22} Schematic representation of the formation of supramolecular chiral bidentate ligands via self-assembly.
\end{center}

\begin{center}
\textbf{Scheme 1.23} Rhodium-catalysed asymmetric hydrogenation: results with the best combination of ditopic ligands and chiral diols.
\end{center}

\section*{1.3 Construction of monodentate ligands by self-assembly}

The use of monodentate ligands in asymmetric transformations has been neglected for long time, due to lower control over coordination modes. In 2000, the generally accepted dogma that bidentate ligands outperform monodentate analogues in asymmetric transition metal catalysis was overruled. Seminal reports by Reetz, Pringle, Feringa and de Vries demonstrated that monodentate phosphite,\textsuperscript{6a} phosphonite\textsuperscript{6b} and phosphoramidite\textsuperscript{6c} ligands can be as selective as bidentate
versions for selected asymmetric hydrogenation reactions. The simple structure makes these ligands easy to synthesize and potentially cheaper. The easy synthesis also enables the preparation of large ligand libraries, which are required to find new active and selective catalysts by rapid screening technologies. In 2007, we reported the application of zinc(II)-porphyrins, carrying different electron-donating or withdrawing groups, and their self-assembly with pyridyl-functionalized phosphite ligands (Scheme 1.24). In the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate, the ligand assembly based on electron-withdrawing groups led to an increase in enantioselectivity from 17 to 50%.

**Scheme 1.24** The assembly of phosphite binol-based ligand and zinc(II)-porphyrin building block.

In the same publication, we also presented the first assemblies based on the combination of an achiral phosphine ligand bearing a pyridine moiety and a chiral zinc(II)-porphyrin template (Figure 1.19). The supramolecular ligands were applied in the asymmetric palladium-catalysed allylic alkylation. Although, the enantioselectivities observed were rather low ($ee = 10\%$), it was demonstrated that chiral templates could create a chiral environment around the transition-metal centre.
In the search for strategies to generate new catalyst based on supramolecular ligands we developed a ligand-template approach for the supramolecular encapsulation of transition-metal complexes. In a very recent publication, we reported the use of bulky chiral pyridine-based phosphoramidite ligands in combination with zinc(II)-templates for the encapsulation of transition metal catalysts (Scheme 1.25).

The application of these ligands in asymmetric catalysis will be discuss in more details in the following chapters.

Scheme 1.25 The assembly of supramolecular ligand based on pyridine-based phosphoramidite ligand and zinc(II)-tetraphenylporphyrin.

1.4 Outline of the thesis

The aim of this thesis is the development of new supramolecular chiral ligands by employing selective metal-ligand-interactions and the use of these ligands in transition metal catalysis, such as asymmetric hydroformylation and hydrogenation. In addition, we investigate the coordination properties of these new supramolecular
systems after transition metal complexation by using high-pressure NMR and IR spectroscopy.

In Chapter 2 we present a novel class of monodentate chiral ligands and the remarkable supramolecular control over the coordination chemistry in a rhodium hydroformylation catalyst. These ligands are formed by self-assembly of pyridine-based phosphoramidite ligands with zinc(II)-templates. The coordination studies on a rhodium hydroformylation complex reveal that the coordination mode of the phosphorus can be switched from *equatorial* to *axial* mode by a unique supramolecular pseudo encapsulation. The catalytic performance of these complexes is evaluated in asymmetric rhodium-catalysed hydroformylation of unfuctionalized internal alkenes.

In Chapter 3 we investigate in more detail the coordination chemistry of the new class of monodentate supramolecular chiral ligands by preparation of a small series of supramolecular chiral phosphite and phosphoramidite ligands. We investigate the origin of the ligand shift by evaluating possible steric and electronic effect induced by different zinc(II)-templates. The self-assembled catalysts are explored in the asymmetric rhodium-catalysed hydroformylation of internal unfuctionalized alkenes.

In Chapter 4 we introduce a new class of supramolecular hybrid bidentate ligands and their application in the rhodium catalysed-asymmetric hydroformylation of styrene and *p*-substituted analogues. Upon variation of steric and electronic properties of zinc(II)-templates new supramolecular assemblies are created, leading to catalyst systems able to change key reaction features such as activity and selectivity.

In Chapter 5, we evaluate the application of the mixed ligand approach using supramolecular phosphoramidite ligands in combination with achiral and chiral P-ligands in the rhodium-catalysed hydrogenation of prochiral olefins.

Chapter 6 deals with the supramolecular hybrid bidentate ligands and the application of a supramolecular strategy based on zinc(II)-template variation for the asymmetric hydrogenation of benchmark substrates.

1.5 References


Chapter 1


