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Self-assembly, characterization and properties of novel poly-nuclear catalysts
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Chapter 1

New Directions in Homogeneous Catalysis

1.1 Introduction

The current needs of the human population in combination with the limited availability of natural resources necessitate a move towards a sustainable use of matter and energy. This is particularly applicable to the chemical industry, as the majority of its processes are based on the use of non-renewable hydrocarbons, typically from oil as the feedstock. One of the challenges that chemists face is the development of reactions that use the feedstock in a highly efficient manner. Reactions operating at 100% atom economy (thus waste-free reactions in which all atoms of the reactants appear in the product) are required to achieve this goal. Homogeneous catalysis by transition-metal complexes can play a key role in developing these reactions. The number of catalyzed transformations currently operating at 100% atom economy is relatively small. For most catalyzed reactions several factors contribute to a low atom economy. For instance, the catalyst often requires starting materials with suitable leaving groups which are not incorporated in the product, but end up in the waste stream. A second problem which is commonly encountered is the formation of undesirable byproducts, for example, when the catalyst is not forming the desired isomer selectively. Overcoming the above described problems represents a great challenge and it is not surprising that there is great interest in new catalytic systems and in novel routes to generate catalysts. Several supramolecular inspired methodologies have already proven their effectiveness, as they allowed the development of new catalysts displaying unprecedented properties. Moreover, the methodologies have been successful in increasing the activity, stability and selectivity of established catalysts. Consequently, application of bio-inspired and supramolecular approaches in the field of homogeneous catalysis open the way to a more sustainable way of chemical production.

1.2 Outline

In recent years various supramolecular techniques have been applied successfully in the field of homogeneous catalysis. Initially, supramolecular catalysts were designed to mimic
the active sites of enzymes. Gradually, supramolecular systems appeared that were no longer based on biological systems, as these systems combined supramolecular strategies with traditional ligand design\textsuperscript{3b-d}. The use of non-covalent interaction turned out to be a particularly effective tool to create (libraries of) ligands and catalysts. In the work described in this thesis we have investigated the use of metal-ligand interactions as a route to form hetero-nuclear catalysts, of which the results are presented in chapters 2-5. In chapter 2 the coordination chemistry of a novel building block designed for the self-assembly of poly-nuclear catalysts is summarized. The application of this building block in the assembly of, respectively, chiral and immobilized catalysts, is discussed in chapters 3 and 4. In chapter 5 we report the formation of bidentate phosphine ligands by means of metal-mediated self-assembly using a novel ditopic ligand. A discussion on the relationship of ligand structure and catalyst properties is given in the next section of this chapter (1.3). This part provides the reader with background information on the topic, without claiming to give a full overview. This is followed by a short introduction on metal-mediated self-assembly (1.4) and an overview of the types of self-assembled catalysts that have appeared in the literature (1.5).

A second recent development in the field of homogeneous catalysis, cascade catalysis, also finds its origin in the application of bio-inspired strategies. It has recently received increasing interest from both academia and industry. The combination of bio- and homogeneous catalysts has led to systems displaying intriguing properties. With the aim to generate a waste-free process we have explored the integration of bio- and transition-metal catalyzed reactions in a single system, of which the results are discussed in chapter 6. A general introduction into cascaded catalytic transformations is given in the last section of this chapter (1.6).

### 1.3 Structure and properties of transition-metal catalysts

**Ligand structure**  Transition-metal catalysts generally consist of a transition-metal, stabilized by one or more ligand(s)\textsuperscript{4}. A huge variety of ligands has been reported, giving a wealth of information on the relationship between ligand structure and catalyst properties. In numerous reactions, application of phosphorus-based ligands yielded highly efficient catalysts and the electronic and steric nature of the ligand was found to have a determining influence on the activity, stability and selectivity of the catalyst. For numerous reactions, superior catalysts are formed when bidentate ligands (with two donor atoms) instead of monodentate ligands (containing a single donor atom) are applied (fig. 1). Modifying the structure of the ligand allows for tuning of the catalyst performance and ligand design has evolved as the most powerful tool in the development of highly active and selective catalysts\textsuperscript{4}.
Several studies have revealed correlations between a specific ligand property and catalyst performance. This information in turn allows the rational design of ligands. For instance, the steric bulk of phosphine ligands often has a large impact on the catalyst performance. For monodentate phosphorus ligands the parameter describing the steric bulk of the ligand has been quantified by Tolman as the cone angle ($\theta$, fig. 2)$^5$. For a number of reactions a direct correlation between this angle and the catalyst performance exists. A commonly used parameter to quantify the structure of bidentate ligands is the natural bite angle ($\beta_n$, fig. 2)$^6$. This is defined as the ligand preferred P-M-P angle and is calculated using computer models. For several reactions there is a direct relationship between this angle and the catalyst selectivity. The structural element that creates the ‘bridge’ between the two phosphorus atoms (fig. 2) has consequently become a tool to tune the catalyst selectivity.

**Enantioselective catalysts**  The potential of chiral catalysts to enable the production of enantiopure compounds was acknowledged already in the sixties of the last century and is currently driven to a large extent by the pharmaceutical and fine chemical industry$^{7,8}$. The development of chiral catalysts for asymmetric conversions allowed for replacing the traditional synthetic routes that produce racemates. With asymmetric catalysis, in theory, the desired enantiomer can be formed quantitatively and consequently presents a considerable economic advantage. Highly enantioselective catalysts have been developed (and are industrially applied) for a large variety of reactions, but asymmetric hydrogenation has
received the majority of the attention\textsuperscript{9}. The chiral environment around the catalytic center originates from the use of chiral ligands\textsuperscript{10}. A limited number of ligand structures proofed successful in a broad range of transformations and therefore have been labeled privileged ligands (fig. 3)\textsuperscript{7c}. Since small variations of the ligand structure can have a decisive influence on the enantioselectivity, it often is essential to synthesize large libraries of chiral ligands to find an efficient catalyst. This in turn, has been a major driving force for the development of combinatorial techniques to synthesize and screen large ligand libraries in an efficient manner\textsuperscript{11}.

![Figure 3: Examples of privileged phosphorus-based chiral ligands.](image)

**Supported catalysts** The separation of the catalyst from the reaction mixture has received considerable attention\textsuperscript{12}. Since catalysts are often based on toxic transition-metals, this is an important issue from an environmental point of view. The high costs generally involved with the use of transition-metals, makes recycling of homogeneous catalysts also highly economically attractive. In the last decades a variety of approaches have been investigated and a number are being applied industrially\textsuperscript{13}. Since dendrimers, as a result of their size, can be separated from the reaction mixture by nano-filtration, they have been applied as a support to create recyclable homogeneous catalysts\textsuperscript{14}. Figure 4 schematically depicts a dendrimer functionalized with catalysts at its periphery. A variety of dendrimers have been applied as support, and the introduction of the catalyst in the micro-environment of the dendrimer has yielded catalysts with interesting properties. Immobilization of a homogeneous catalyst on a (solid) support is a second approach that received considerable research attention (fig. 4)\textsuperscript{15}. The supported catalysts are generally formed by application of immobilized ligands and consequently this approach combines the advantages of both homogeneous catalysis (good control over catalyst properties via ligand design) and heterogeneous catalysis (easy catalyst separation).
Ligand synthesis Since ligand design is one of the most efficient tools to tune catalysts properties (vide supra), it became essential that the ligand structure could be varied easily. Consequently, various synthetic procedures for the synthesis of (functionalized) ligands have been developed. Nevertheless, ligand synthesis generally remains laborious and time consuming\(^{3d}\). It is not surprising that there is great interest in novel routes to generate ligands and in the last decade the formation via self-assembly has established itself as a very potent methodology\(^{3a-d}\). Several successful approaches are discussed in the following section.

1.4 Metal-mediated self-assembly

Self-assembly is the spontaneous formation of a supramolecular entity from molecular components\(^{16}\). By appropriate design of the building blocks, the structure and properties of the assembly can be controlled to a very high degree. In the last decade, research has shifted from exploring (simple) host-guest interactions to the formation of highly complex functional systems\(^{17}\). Initially, chemists mainly focused on the use of hydrogen bonds, \(\pi-\pi\) interactions and hydrophobic effects, while the use of metal-ligand interactions has received considerable attention in the last decade\(^{17a,18}\). The main advantages of transition-metal mediated self-assembly are the relatively strong coordination bonds with the ligands and the greater directionality of metal-ligand interactions. By exploiting the specific geometrical requirements of the metals used, it is possible to control accurately the desired overall structure of the supramolecular complex\(^{19}\). Moreover, this also allows addressing the coordination of a metal to a specific binding site and enables the assembly of hetero-poly-nuclear superstructures in a selective manner. These advantages have made metal-ligand interactions a particularly attractive tool and it is not surprising that an enormous variety of structures (e.g. molecular squares, bowls, helicates, etc.) have been reported\(^{18}\).
1.5 Self-assembly of catalysts

Finding the optimal catalyst in a time efficient manner is of great importance for the chemical industry. As a result, the development of combinatorial techniques and efficient screening methods has received considerable attention\textsuperscript{11,20}. Although combinatorial methodologies in principle allow fast screening of catalyst libraries, the often laborious synthesis of ligand libraries is still the bottleneck in finding new catalysts. Consequently, there is great interest in novel (synthetic) routes to generate rapidly large libraries of ligands\textsuperscript{3}. The traditional approach to develop homogeneous catalysts can be regarded as a ‘one-dimensional’ approach; the synthesis of one ligand leads to one new catalyst and, at best, the workload can be reduced somewhat by a modular, synthetic approach. The assembly of ligands by using non-covalent interactions between two building blocks ($A$ and $B$) can be regarded as a ‘two dimensional’ approach; the different building blocks ($nA + mB$) can be combined to yield a multitude of catalysts ($n \times m A + B$). For libraries larger than 5 catalysts, the approach already leads to a reduction in the number of building blocks required. Surprisingly, until quite recently this advantage of (metal-mediated) self-assembly as a tool to generate catalysts was hardly recognized. In the next part the different types of self-assembled catalysts that have appeared in literature are discussed, with the emphasis on the metal-mediated self-assembly of the catalyst\textsuperscript{3}.

Encapsulated catalysts by means of metal-mediated self-assembly The cavities generally found in self-assembled super-structures have been the focus of considerable research interest, as they can supply unique micro-environments for guest molecules\textsuperscript{18}. Hupp et al. investigated the inclusion of a catalyst inside such a cavity\textsuperscript{21}. By means of self-assembly they encapsulated a manganese-porphyrin catalyst in a zinc-porphyrin-based molecular square (fig. 5). In the epoxidation of cis-stilbenes, the encapsulated catalyst displayed, in comparison with non-encapsulated analogues, an enhanced stability and a decreased reactivity towards sterically more crowded substrates.

![Figure 5: Manganese catalyst encapsulated in a Zn-Re metallomacrocycle.](image-url)
Reek et al. used the interaction between pyridine-functionalized phosphines and zinc porphyrins to encapsulate phosphate ligands, thereby drastically increasing their steric bulk (scheme 1). The methodology is based on the selective coordination of two types of metals to two types of donor atoms. As a result of the low preference of zinc for phosphorus, the porphyrin coordinates selectively to the nitrogen atoms of the pyridines, leaving the phosphorus donor atom free to bind the catalytically active metal (3). Not only does this process increase the steric bulk of the phosphine, it also results in a unique overall shape, as the encapsulated catalyst possesses a cavity at the active site. Interestingly, while the assembly consists of two relatively simple building blocks (1 and 2), considerable synthetic effort is needed to create phosphines with a comparable size and shape.

In the rhodium-catalyzed hydroformylation of 1-octene, the encapsulation of tris-3-pyridylphosphine (1) with meso-phenyl zinc porphyrin (2) leads to a 10-fold increase in activity. The authors attribute this partly to the exclusive formation of mono-ligated transition-metal complexes as a result of the steric bulk of the encapsulated ligand 3, which is supported by in situ infrared spectroscopy. In addition, in contrast to what is commonly observed for this substrate, the branched aldehyde was formed as the predominant isomer (branched to linear 10:6). Later, Reek and co-workers reported that the encapsulated rhodium catalyst display unprecedented high regioselectivities in the hydroformylation of internal alkenes. For instance, in the hydroformylation of trans-3-octene, the non-encapsulated rhodium catalyst afforded 2-ethylheptanal and 2-propylhexanal in exactly a 1:1 ratio, while application of the encapsulated analogue assembled from 1 and 2 led to a selectivity for 2-propylhexanal of 75% (scheme 2). The high selectivities for the branched and internal aldehydes are attributed to a reduced rotational freedom of the reactants in the cavity of the encapsulation catalyst.
Reek and co-workers systematically studied the encapsulation methodology in various reactions and with structurally diverse zinc porphyrins and pyridyl phosphines, as well as amino-functionalized phosphorus ligands, allowing the formation and evaluation of large ligand libraries\textsuperscript{22,25}. Zinc salphen complexes were also applied successfully as building blocks\textsuperscript{26}. In addition, the group utilized the selective axial nitrogen coordination of zinc porphyrin and zinc salphen to pyridyl or amino substituted phosphine ligands to assemble functionalized catalysts. Porphyrin modified silica, for instance, was combined with an amino-substituted Xantphos ligand to anchor palladium non-covalently to the support\textsuperscript{27a}. Enantioselective catalysts were assembled from achiral pyridyl phosphines and chiral zinc porphyrins\textsuperscript{27b}.

In the self-assembly of encapsulated catalysts from building blocks 1 and 2, selective coordination of the two types of metals relies on the use of two different donor atoms (phosphorus and nitrogen) in combination with the low affinity of zinc for phosphorus donors (scheme 1). Reek \textit{et al.} applied a building block solely containing nitrogen donors (two imines and two pyridines) for the encapsulation of a palladium-based polymerization catalyst\textsuperscript{28}. Selective coordination of the two types of metals (palladium and zinc, respectively) to the two types of nitrogen donors, was achieved by utilizing the different steric requirements of the metals. In the absence of zinc salphen, palladium coordinates unselectively to the building block; both the pyridyl and imine donors assist in binding the metal (A, scheme 3). As a result of its steric bulk, zinc salphen can only coordinate to the pyridine donors, leaving the diimine vacant for coordination to palladium (B).
The assemblies were evaluated as catalysts in the CO/4-tert-butylstyrene copolymerization. In the absence of a zinc salphen building block, no polymerization activity was observed, which can be attributed to the unselective coordination of the metal to the pyridyl-substituted diimine ligand. The encapsulated complexes were all active and the structure of the applied zinc salphen building block had a strong influence on the activity and the average molecular weight of the polymer. Interestingly, the parent complex (C, scheme 3) gave polymer with a lower average molecular weight and the activity of this catalyst was also considerably lower than that of the most active encapsulated catalyst. Moreover this catalyst produced atactic copolymers, while the supramolecular catalysts provided syndiotactic copolymers. Actually, the encapsulation with a bulky zinc salphen resulted in one of the most selective catalysts known to date.

The non-covalent modification of the (sterical) environment around the catalytic center is not limited to metal-ligand interactions. Hydrogen bond interactions have, for instance, been utilized to generate sterically encumbered dendritic catalysts. Clark et al. used hydrogen bonds to fine-tune the steric environment of a chiral organocatalyst (scheme 4). For this purpose a building block equipped with a chiral moiety and a hydrogen bonding motif (A) and 6 different additives equipped with complementary motifs (B) were prepared. These components led to a family of self-assembled chiral organocatalysts with different steric properties (C). In the asymmetric nitro-Michael reaction the nature of the substituents of B (R₁ and R₂) has a considerable influence on the catalyst performance; the yield varied between 59 and 82%, the diastereomeric ratio between 31:1 and 77:1, whereas the enantiomeric excess (ee) varied between 16 and 47%.
Scheme 4: Fine tuning of the steric bulk of an organocatalyst (C) by hydrogen bonding.

Coordination geometry of metal as a tool to influence catalyst properties The group of Mirkin reported an intriguing catalytic system in which the performance of the catalytic center could be tuned by altering the coordination geometry of a second metal center also present in the poly-nuclear catalyst$^{30}$. A metallo-macrocycle was prepared in which two salen-based chromium centers are catalytically active in the asymmetric ring opening of cyclohexene oxide. Two rhodium centers, coordinated by thioethers and phosphines, serve as flexible structural elements that respond to the presence of additional ligands (A, scheme 5). Addition of chloride anion and carbon monoxide results in a disruption of the coordination of the rhodium to the thioethers, which in turn results in an ‘enlargement’ of the macrocycle (B). As a result of this process a significant rate increase was observed.

Scheme 5: Tuning the activity of a chromium catalyst by altering the coordination sphere of rhodium.

Bidentate ligands via self-assembly In the examples discussed above, the self-assembly process modifies the environment around the catalytic centers. In these systems the binding sites for the catalytic center was pre-organized to a high degree. Considerable research effort has also been devoted into the formation of the coordination site for the catalytic center as a result of non-covalent interactions, with most examples reporting the formation of bidentate phosphine ligands via self-assembly$^{3c-d}$. This is a highly attractive approach, since
it combines the advantages of self-assembly (e.g. combinatorial techniques) with the excellent properties that bidentate (phosphine) ligand-based catalysts generally display.

**Template assisted assembly of bidentate ligands**

Ditopic amines like diaza[2.2.2]bicyclooctane form 2:1 sandwich complexes with zinc porphyrins and this methodology was used by Reek et al. to form stable bidentate ligands. Phosphite-functionalized zinc porphyrins coordinate in a 2:1 fashion to the diaza[2.2.2]bicyclooctane template, thereby generating a bidentate phosphite (scheme 6)\(^{25a}\). The multicomponent assembly showed typical bidentate phosphite behavior in the rhodium-catalyzed hydroformylation; lower activities and higher selectivities for the linear aldehyde product in comparison to non-templated analogues which act as monodentate ligands.

![Scheme 6: Bidentate phosphite formation via self-assembly by application of ditopic amines.](image)

Reek and co-workers also used the selective interactions between a bis-zinc porphyrin template and the nitrogen donor of pyridyl phosphines to self-assemble bidentate phosphine ligands\(^{25b,31}\). The group later extended this approach by combining (chiral) pyridyl phosphines and phosphites with rigid bis-zinc salphen building blocks to generate a library of bidentate phosphine and phosphite ligands (scheme 7)\(^{32}\). In the rhodium-catalyzed hydroformylation of 1-octene, the templated ligand assemblies showed, in some cases, catalytic behavior typical of bidentate phosphines. Spectroscopic and crystallographic studies confirmed unambiguously the formation of bidentate ligands. Mixing the bis-zinc salphen template (A) with two pyridyl phosphines yields an assembly in which the nitrogen donor atoms coordinate, as expected, to the axial positions of the template (B). In the solid state, the two phosphines are bound on opposite sides of the template. In the presence of palladium, platinum or rhodium, a rearrangement takes place, resulting in the positioning of the phosphines on the same side of the template and binding of the late transition-metal in a bidentate manner (C).
Interestingly, it turned out that the bis-salphen templates could be used to generate heterobidentate ligands from combinations of pyridine-functionalized phosphines, phosphites and phosphoramidites. In the absence of the bis-zinc template, no rhodium species coordinated by the hetero-ligand combinations could be observed by NMR spectroscopy, while in the presence of the template the homo-ligand species were not formed. The templated heterobidentate ligands induce much higher enantioselectivities (up to 72% ee) in the rhodium-catalyzed asymmetric hydroformylation of styrene than any of the corresponding homobidentate ligands or the non-templated hetero-ligand combinations (up to 13% ee). This result also confirms that under catalytic conditions, the hetero-bidentate ligands are formed\(^{33}\). Since the hetero-bidentate ligands are assembled from three different building blocks, this methodology theoretically allows the creation of very large libraries of catalysts with limited synthetic effort. For instance, merely 27 \((9 + 9 + 9)\) components can potentially lead to 729 \((9 \times 9 \times 9)\) different catalysts!

**Ditopic building blocks in the self-assembly of hetero-nuclear catalysts** The formation of hetero-poly nuclear complexes has been studied in detail by several groups (scheme 8)\(^{34}\), but generally most of these complexes have not been applied as catalysts\(^{36}\). Moreover, the route has only rarely been applied as a strategy to form libraries of self-assembled heterobimetallic catalyst of which the reported examples are discussed below.

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**Scheme 7:** A platinum bidentate phosphine complex assembled from a rigid bis-zinc salphen and m-pyridyl phosphine \((R = tBu, M = Pd, Pt, Rh)\).
Takacs and co-workers used the selective formation of heteroleptic zinc complexes from one $S,S$- and one $R,R$-bisoxazoline ligand, to assemble libraries of bidentate phosphite ligands\textsuperscript{36}. By applying bisoxazolines functionalized with phosphite moieties, the complexation with zinc results in bidentate phosphite ligands (scheme 9). 26 phosphite-oxazoline building blocks were synthesized with various linkers between the phosphite and bisoxazoline moiety. By combining the different $S,S$ and $R,R$ building blocks with zinc, a library of 50 different bidentate phosphite ligands was created. In the palladium-catalyzed asymmetric allylic amination, the library displayed a broad range of enantioselectivities (20-97\% ee), proving the efficiency of this combinatorial approach\textsuperscript{36a}. Note that in the bidentate ligands assembled via this route, the $[(R,R$-bisoxazoline)$\text{zinc}(S,S$-bisoxazoline)] moiety should be regarded as a fixed structural element in the bridge of the bidentate ligand.

In a related approach, the group of van Leeuwen synthesized various phosphines containing an anionic site for binding a hard metal (e.g. Zn(II)) for the assembly of bidentate phosphine ligands (scheme 10)\textsuperscript{37}. The building blocks were designed to form wide bite angle (calculated natural bite angles of 110–120°) bidentate diphosphines. Conventional ligands with comparable bite-angles (e.g. Xantphos) yield highly regioselective rhodium hydroformylation catalysts and the assembled ligands were therefore studied in this reaction. Indeed, the assembled bidentate diphosphines gave higher linear to branched aldehyde ratios than the
related monodentate ligands. Moreover, the reaction rates are approximately half of those of the monodentate ligands, which is a strong indication that the assembled bidentate are also stable under catalytic conditions. Some ditopic ligands resulted in poor catalysts, most likely a result of rhodium salen or phosphinophenolate complex formation.

Scheme 10: Zinc mediated formation of wide bite-angle bis-phosphines.

Other approaches to self-assembled bidentate ligands

Reek et al. used the selective interaction between phosphite-functionalized porphyrins and mono-pyridyl phosphines to assemble (chiral) bidentate phosphine-phosphite ligands (scheme 11) \(^{25c}\).

Scheme 11: Schematic presentation of the self-assembly of a bidentate ligand from phosphite-functionalized porphyrin 1 and pyridyl substituted phosphate a.

The chelating behavior of the phosphine-phosphite assemblies was confirmed by an increase in the association constant in the presence of rhodium and further supported by IR- and NMR-spectroscopy under catalytic conditions. In the rhodium-catalyzed hydroformylation of styrene, the supramolecular bidentate ligands showed, in comparison to related monodentate ligands, a considerably decrease in activity and an increased selectivity for the branched product, reflecting the chelating coordination mode of the assembly. Extending the diversity of the phosphorus containing building blocks allowed the formation of a library of 48 phosphine-phosphate and phosphite-phosphate ligands from only 14 \((6 + 8)\) different building blocks\(^{38}\). The supramolecular ligand library was evaluated in the palladium-catalyzed asymmetric allylic alkylation. The enantiomeric excess, which ranged from 85\%(S) to 86\%(R), depended strongly on the structure of the components used. Combining 1 with the achiral \(m\)-pyridyldiphenylphosphine \((a)\) gave the product in lower enantiomeric excess but with the opposite chirality than when homo-ligand combination 1 was applied. In the
presence of triphenylphosphine (b), which is unable to coordinate to the zinc, the product was obtained as a racemate, indicating that the observed effects for the 1 + a combination can be attributed to the formation of the hetero-ligand assembly. The assembled ligands were later applied in the high-throughput screening for the rhodium-catalyzed asymmetric hydrogenation of a challenging substrate (N-(3,4-dihydro-2-naphthalenyl)acetamide)\textsuperscript{39}. From 64 catalysts, assembled from 21 (14 +7) building blocks, only one catalyst was found that is both active and enantioselective. This rhodium catalyst is the most efficient catalyst known to date, showing that the screening of large catalyst libraries is an excellent route for finding superior catalysts.

Next to metal ligand interactions, other non-covalent interactions have been applied in the assembly of bidentate ligands. Van Leeuwen et al. have used an ionic bond as the driving force for the formation of a hetero-bidentate phosphine ligand. It turned out that the cationic and anionic monodentate phosphorus ligands form an ion pair even in strongly polar protic media\textsuperscript{40}. Monflier et al. assembled PN bidentate ligands from an amino-functionalized cyclodextrin and a substituted tris-aryl phosphine (scheme 12). In this approach the driving force for bidentate ligand formation is the hydrophobic interactions between the interior of the cyclodextrin and the phosphine\textsuperscript{41}.

![Scheme 12: Schematic presentation of the formation of a PN-ligand by the inclusion of a guest in the cyclodextrin cavity.](image)

The group of Breit utilized hydrogen bonding motifs to yield bidentate phosphine ligands from two functionalized monodentate phosphines (scheme 13)\textsuperscript{42}. In the rhodium-catalyzed hydroformylation, the ligand induced very high regioselectivities, previously only achieved with wide bite-angle bidentate ligands, indicating that also under catalytic conditions the assembly stays intact. The hydrogen bonds are remarkable stable; the ligand retained the “wide bite angle” behavior even when substrates were used containing strong hydrogen donor and/or acceptor functionalities. In methanol or when acidic acid was added to the reaction mixture, the observed regioselectivity decreased considerably, indicating that under these conditions the hydrogen bonding is disrupted and that the phosphines act as non-interacting monodentate ligands\textsuperscript{43}. The approach was extended with monomers that form hetero-dimers\textsuperscript{42b}. Applying this route, 16 bidentate ligands were assembled from only 8 (4 +
4) monomers. In the rhodium-catalyzed hydroformylation, the hetero-dimer combinations induced comparable regioselectivities, but showed large differences in activity, with a maximum rate difference of more than three-fold. Assembly of chiral bidentate ligands for asymmetric rhodium-catalyzed hydrogenation was achieved by functionalizing chiral phosphonite and phosphine ligands with the appropriate hydrogen bonding motifs$^{42c}$.

![Scheme 13](image1)

**Scheme 13:** Hydrogen bond driven bidentate phosphine formation.

Several related approaches have been reported; the group of Kamer utilized the hydrogen bonding motifs found in DNA$^{44}$ and the group of Reek showed that hydrogen bonding between urea-functionalized phosphines results in bidentate phosphine coordination to palladium$^{45}$. Reek et al. later extended this approach by functionalizing (chiral) phosphites with (thio-) urea functionalities. Upon self-assembly, these ligands form bidentate ligand metal complexes (scheme 14)$^{46}$ and in the rhodium-catalyzed hydrogenation the type of hydrogen bonding motif and the type of linker between the two moieties had a considerable influence on the catalyst performance. With N-(3,4-dihydro-2-naphthalenyl)-acetamide as a substrate for instance, the conversions varied between 0 and 34%, while the enantiomeric excess varied between 1 and 77%.

![Scheme 14](image2)

**Scheme 14:** Urea moieties as hydrogen bonding motif in the assembly of bidentate phosphites.
1.6 Cascade catalytic conversions

**Cascade catalyzed reactions** The sequences of enzyme-catalyzed transformation occurring in living cells, allow the synthesis of the extremely complex molecules (scheme 15)\(^{17}\).

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1 catalyst 1  2 catalyst 2  3 catalyst 3  4
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*Scheme 15: Cascade catalyzed reactions.*

Inspired by these systems, chemists explored the potential of sequencing catalyzed reactions in a laboratory environment. To describe the different methodologies and procedures, the terms tandem, sequential, domino and cascade have been introduced. Because these terms are not clearly defined, they are often interchangeable. Initially, most systems consisted of a single catalyzed step in a sequence of non-catalyzed transformations or re-arrangements. In the last decade, numerous systems based on a cascade of catalyzed reactions appeared in literature and the methodology is increasingly recognized as essential for sustainable chemical production\(^{48,49,50}\). One cascade reaction applied on a very large scale is the Shell Hydroformylation process, which involves isomerization of internal alkenes, hydroformylation of terminal alkenes, and hydrogenation of the aldehydes to alcohols, by one and the same alkylphosphine modified cobalt catalyst\(^4\). In the next part we provide some examples on the various approaches that have appeared in the literature and we have classified them roughly in order of complexity. We start with relative simple systems based on the use of a single catalyst and end with the more complex systems in which the interplay between several catalysts allow unprecedented efficiency.

The most straightforward systems combine independent subsequent reactions in a one-pot procedure. The cascade consists of several transformations that can also be performed separately and the formed intermediates are stable compounds that can be isolated. The main advantage of this approach is a considerable reduction in solvent and energy consumption and a shorter (single) work-up procedure. MacMillan and co-workers applied imidazolidinones as organo-catalysts to merge iminium and enamine activation of \(\alpha,\beta\)-unsaturated aldehydes (scheme 16)\(^{51}\). Exposure of the aldehydes to organo-catalysts generates activated iminium species that enantioselectively intercept a wide variety of \(\pi\)- or hydrido- nucleophiles. The conjugate-addition adducts re-enters a second catalytic cycle, in which enamine activation by the same catalyst enables highly enantioselective additions to electrophiles. The overall cascade process results in product formation in high yield with high enantio- and diastereomeric purity.
The development of tandem reaction sequences under hydroformylation conditions has received extensive attention\textsuperscript{52}. Generally, the aldehyde formed by the metal-catalyzed hydroformylation is in situ converted, commonly by a non-catalyzed reaction, to various derivatives (e.g. acetals, imines, amines, etc.). Often the aim was the one-pot synthesis of the desired compound, but several groups have utilized the cascade for the in situ protection of the aldehyde. Since the prepared derivates display a higher stability towards side-reactions in comparison to the aldehyde, the methodology leads to fewer byproducts. Stille et al. have performed the platinum-catalyzed asymmetric hydroformylation of styrene in the presence of triethylorthoformate, which reacts with the formed aldehyde to give the corresponding acetal (scheme 17). This protects the aldehyde for racemization and as a result the cascade leads to higher enantioselectivities for the branched product\textsuperscript{53}. The above example shows that one-pot procedures can, next to reduced solvent and energy consumption, also have other beneficial effects. It can, for instance, increase the overall selectivity of a catalyzed transformation.

Breit et al. developed a one-pot three-step cascade consisting of a hydroformylation, a Wittig olefination and a subsequent hydrogenation, allowing the synthesis of saturated ketones from alkenes (scheme 18)\textsuperscript{54}. In this process a hydroformylation reaction converts an alkene (1) to an aldehyde (2), which in turn undergoes a Wittig olefination with phosphorus ylides. The formed alkene (3) is subsequently hydrogenated to yield the corresponding saturated ketone.
ketone (4). The overall process consists of the formation of two new carbon-carbon bonds and four carbon-hydrogen bonds. Both the initial hydroformylation and the subsequent hydrogenation are catalyzed by the same rhodium catalyst. As an example, this procedure was used in the one-pot all-anti stereo-triad synthesis of 5 from 6 in good yield and diastereomeric purity. If more sterically hindered di-substituted phosphorus ylides were used (e.g., Ph₃P=CMeCO₂Et), the reaction sequence yields the α,β-unsaturated carbonyl derivatives (3), which was attributed to the increased sterical hindrance around the alkene double bound, thereby inhibiting the hydrogenation reaction.

**Scheme 18: Three-step hydroformylation-Wittig olefination-hydrogenation cascade.**

**Multi-catalyst-based cascade reactions**  As discussed in the examples above; the majority of reported systems consist of a single catalyst facilitating one or more steps in the cascade. More recently an increasing number of systems based on two or more catalysts appeared in literature. Bianchini et al. combined a cobalt ethene oligomerization catalyst, with a zirconate alkene polymerization catalyst (scheme 19)[55]. The tandem ethene oligomerization and alkene co-polymerization subsequently leads to the formation of highly branched polymers. Varying the ratio of the two catalysts influences the percentage of branched centers and therefore the properties of the resulting polymer. Using this dual-catalyst system, polyethylene with properties spanning from semi-crystalline to completely amorphous were prepared.
More complex cascade systems are created if the individual reactions are rather difficult or even impossible to perform in a stepwise independent fashion. Cascading can even be a prerequisite if the intermediates are reactive compounds that cannot be isolated. By trapping these intermediates with a subsequent (catalytic) conversion, it is possible to generate complex molecules\textsuperscript{56}. Moreover, interesting cooperative effects in multi-catalyst systems have been reported\textsuperscript{57}. This approach has proven to be particularly successful for (palladium-) catalyzed cyclization reactions\textsuperscript{58}. Scheme 20 depicts a three-step cascade of cobalt- and palladium-catalyzed transformations for the synthesis of fenestrane\textsuperscript{59}. The cobalt-catalyzed Pauson-Khand reaction is followed by a palladium-catalyzed allylic alkylation, yielding an unstable intermediate which is subsequently \textit{in situ} converted to the product in a second Pauson-Khand reaction.

Full exploitation of cascade catalyzed conversions requires mutually compatible reagents and catalysts. The sequential addition of the different catalysts and/or reagents is often applied to overcome compatibility problems. For instance, in the synthesis of fenestrane discussed above, the first Pauson-Khand reaction needs to be performed in the absence of
the palladium catalyst. It is rather uncommon that all catalysts and reagents need to be present from the start of the reaction. Beller et al. developed a highly selective process in which both a rhodium and an iridium catalyst are required to facilitate the hydroaminomethylation of alkenes with ammonia (scheme 21)\textsuperscript{60}. Efficient protocols existed for the rhodium-catalyzed hydroaminomethylation of alkenes using secondary amines\textsuperscript{52}, but the use of ammonia (to produce primary amines) remained challenging. This has been attributed to the low activity of rhodium catalysts to hydrogenate the C-N double bond of the primary imine (3), which is formed by reaction of the aldehyde (2) and ammonia. This imine undergoes side reactions resulting in the formation of secondary and tertiary amines and lowers the overall yield. The solution to this problem was the incorporation of an iridium catalyst in the cascade process, as it is active in the hydrogenation of the C-N double bond under the reaction conditions, while not deactivating the rhodium catalyst. The cascade of rhodium-catalyzed hydroformylation to give an aldehyde (2), condensation with ammonia to yield an imine (3) and a subsequent iridium-catalyzed hydrogenation leads to the selective formation of the desired linear primary amines (4).

![Scheme 21: A three-step cascade of rhodium-catalyzed hydroformylation, a condensation and an iridium-catalyzed hydrogenation.](image)

Similarly to enzymes, homogeneous catalysts can become (partially) deactivated as a result of product inhibition. Analogues to biological systems, product inhibition can be suppressed by \textit{in situ} conversion of the product by a second (catalytic) reaction and this can improve the overall yield. Brookhart and co-workers acknowledged this and integrated alkane dehydrogenation with olefin metathesis (scheme 22)\textsuperscript{61}. An iridium catalyst (A) effects the dehydrogenation of alkanes to yield alkenes and hydrogen. In the absence of a subsequent reaction, the alkene concentration builds up quickly, inhibiting the dehydrogenation activity of A, making the catalysts less suitable for traditional sequential synthetic approaches. To overcome this problem a metathesis catalyst (B) was added that converts the formed alkene to its metathesis products. In the final step of the cascade, AH\textsubscript{2}, formed in the first step, reacts with the formed alkenes to give the alkane products. The dehydrogenation catalyst A can subsequently re-enter the cycle. The system allowed the conversion of n-hexane to a range of C2 to C15 \(n\)-alkanes. In this example, the integration of the three catalyzed steps in a single pot system can be considered essential for the overall yield, as in the absence of the metathesis catalyst, the iridium catalyst is nearly inactive. The dual catalytic system,
however, only needs low steady-state concentrations of the intermediate alkene for an efficient overall conversion and consequently does not lead to the deactivation of the iridium dehydrogenation catalyst.

\[
\begin{align*}
\text{de-hydrogenation} & \quad \begin{array}{c}
2 \text{R} \quad \text{Val} \quad 2 \text{A} \\
\quad - 2 \text{A} \text{H}_2
\end{array} \\
\text{olefin metathesis} & \quad \begin{array}{c}
2 \text{R} \quad \text{Val} \\
\quad - 2 \text{A} \text{H}_2
\end{array}
\end{align*}
\]

\text{hydrogenation}

Scheme 22: Cascade of alkane dehydrogenation, olefin metathesis and alkene hydrogenation.

**Combining bio- and transition-metal catalyzed steps** There are ample examples in which several enzymes are combined in a cascade\textsuperscript{50a}, but one-pot procedures that utilize several transition-metal catalysts are less common\textsuperscript{62}. Combining bio- and transition-metal catalyzed steps is particularly attractive, as it allows utilizing the advantages of both enzymes and organometallic catalysts\textsuperscript{49f}. The examples that have appeared in literature are predominantly dynamic kinetic resolutions (DKR)\textsuperscript{63}. In this procedure, a stereo-selective catalyzed transformation (generally catalyzed by an enzyme) is combined with a racemization of the substrate typically catalyzed by a transition-metal complex. The approach is depicted schematically in scheme 23. (Enzyme-) catalyzed kinetic resolutions allow the synthesis of highly enantiomerically enriched compounds, but since only one of the two enantiomers of the substrate is converted to the product, the maximum yield is only 50%. This limitation can be overcome by an in situ racemization of the starting material with a second catalyst, theoretically allowing the synthesis of the desired compound in quantitative yields.

\[
\begin{align*}
\text{catalyst} & \quad \begin{array}{c}
[S\text{-Substrate} + R\text{-Substrate}] \\
\quad \text{catalyst}
\end{array} \\
\quad \begin{array}{c}
[S\text{-Substrate}] \\
\quad R\text{-Product}
\end{array}
\end{align*}
\]

Scheme 23: Interplay between two catalysts in the dynamic kinetic resolution.
Scheme 24 depicts the synthesis of enantiomerically pure acetates from racemic secondary alcohols by DKR, developed by the group of Bäckvall\textsuperscript{64}. The process is based on lipase, an enzyme that catalyzes the stereo-selective esterification of alcohols, and a ruthenium catalyst for the racemization of the secondary alcohol. With this process, a variety of racemic secondary alcohols can be quantitatively transformed to the corresponding acetates and in most cases the reaction proceeded with very high stereoselectivity (> 99% \textit{ee})\textsuperscript{63}. Illustrative for the efficiency of this system is the fact that it is applied in a large-scale industrial application\textsuperscript{65}.

![Scheme 24: Dynamic kinetic resolution catalyzed by an enzyme and a transition-metal.](image)

1.7 Perspective

As the previous sections show, several groups have applied supramolecular and cascade methodologies to create novel catalytic systems. The unprecedented catalytic properties of some of these systems indicate that the methodologies have considerable potential for the future development of highly efficient homogeneous catalysts. It can be expected that an increasing number of groups develop novel approaches and eventually we foresee that a number of methodologies will become part of the standard tools available to design catalysts. In the next chapters we will present the results obtained with our studies towards the assembly of poly-nuclear catalysts and the integration of bio- and metal-catalyzed reactions towards waste-free processes.
1.8 References and Notes


