Supramolecular control of selectivity in transition metal catalysis: Substrate preorganization & cofactor-steered catalysis

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Chapter 1

Supramolecular Control of Selectivity in Transition Metal Catalysis – General Introduction
1.1 Introduction

Rapidly rising consumption of goods due to the ever increasing human population and the rise of living standards puts enormous demands on the natural resources of the planet, which, if explored at the current rate, are expected to run out in the near future. This state of affairs calls for devoting more attention towards renewable resources and for using our current reserves of natural resources more efficiently. This requires the development of new technologies that are at best not only more environmentally friendly, but also more economically efficient, therefore attracting industrial application and accelerating their implementation. Catalysis is a key element of controlling chemical transformations, especially in industry, and is therefore of crucial importance for sustainable development.\(^1\) The central role of (transition metal) catalysts is to accelerate reactions that are otherwise very slow, primarily by creating new reactivity pathways \textit{via} a combination of simple elementary steps at the metal center.\(^2\) Therefore, it can give access to new transformations and open up otherwise inaccessible, yet effective, shortcuts relevant to current synthetic schemes. In addition, it may be crucial for the application of renewable building blocks, replacing fossil-fuel-based materials.

Homogeneous transition metal catalysis, in particular, offers powerful and straightforward methods for carrying out selective and effective chemical transformations,\(^3\) attracting considerable attention and making tremendous progress over the last few decades. For transition metal catalysts the activity, selectivity (and the stability) is highly dependent on the ligands coordinated to the catalytic metal center.\(^4\) Despite notable insights in various reaction mechanisms and the role of the ligands in these reactions, in addition to the development of powerful computational methods, the prediction of the selectivity that a new catalyst will display is still beyond our abilities. Therefore, the search for catalysts typically still involves the knowledge-supported trial-and-error screening of candidate systems. Often, the screening of catalysts based on privileged ligands,\(^5\) which have been proven to provide good selectivities (and activities) for a broad range of reactions and substrates, is a good starting point that is then followed by the structure optimization of the catalyst. This approach has provided many successes, but is not a general strategy. There are reactions for which selectivity issues are difficult to solve with this approach; reactions, for example, in which the pathway to the desired product is higher in energy than the alternative pathways, or reactions with many competing pathways. Therefore, complementary approaches that allow for a more rational catalyst design for these challenging reactions would be of high value.

Supramolecular chemistry, defined by Jean-Marie Lehn as ‘chemistry beyond the molecule’, describes chemical systems formed by a self-assembly of a number of molecular building blocks or components via reversible, relatively weak interactions.\(^6\) Enormous progress in this field has been achieved over the past few decades resulting in good understanding and insight into these weak, yet effective interactions that allow for formation of large self-assembled molecular architectures.\(^7\) Considering that the selectivity of catalytic reactions can be determined by energy differences in the competing transition states that are as small as 3 kcal mol\(^{-1}\), one can expect that these relatively weak interactions are important for the selectivity of any catalytic transformation. Therefore, supramolecular chemistry can provide important new tools for catalyst development and has attracted considerable attention in the last few years, giving rise to a group of strategies collectively called ‘supramolecular catalysis’.\(^8\) In this chapter, we will provide a guide through different strategies that use the tools of
supramolecular chemistry to control catalyst selectivity (and activity) that are applicable to homogeneous transition metal catalysis, emphasizing the advantages and limitations for each strategy and also highlight some key examples demonstrating their power.

It is important to point out that the selectivity and the activity of a reaction are closely related. The selectivity of a reaction is defined directly by the ratio of the rates between competitive reaction pathways, while the overall activity is in principle defined by the sum of the rates for all reaction pathways. Therefore, the strategies that are focused on promoting one reaction pathway, via, for instance, selective stabilization of a crucial transition state, will also result in improving the activity. They are thus favored over strategies that improve the selectivity by hindering all alternative reaction pathways, via, for instance, adding extra steric bulk close to the catalytic center.

1.2 Reactivity within the confined space of molecular capsules

Nature has served as a major source of inspiration in the area of supramolecular chemistry, and, correspondingly, enzymes – natural catalysts – have served as models for the design of supramolecular catalysts. In enzymes, an ‘active site’ at which the catalytic transformation takes place is typically buried within a specific proteomic micro-environment. Therefore, a substrate that is brought into a confined space of this ‘cavity’ experiences a series of ‘confinement effects’ that are otherwise not present in the bulk. First, the encapsulated substrate molecule can accept only specific conformations imposed by the size and shape of the cavity that also limit its motion, and restricting the number of possible reactions. This usually also results in reduced activation entropy of a reaction. The proximity and orientation of the reactive groups is well-defined, which in turn determines the reaction selectivity. In the case of bimolecular reactions, the effective concentrations within the catalytic cavity are much higher compared to those in bulk, and consequently the activity is highly increased. Also, the substrates are (at least partially) stripped from the solvent molecules, which modifies their reactivity. Finally, the transition state of the effective reaction pathway is stabilized more efficiently than the substrate in its ground state by the surrounding cavity (either electrostatically or with secondary interactions like van der Waals forces, H-bonding, π-π interactions etc.). In some cases, the substrate or the reaction intermediate is forced to adopt a high-energy conformation of increased reactivity, which also effectively lowers the free-energy reaction barrier. Additionally, only substrates of a certain size and shape can enter the nanospace of the ‘active site’, leading to precise substrate selectivity. Considering the excellent selectivities and extreme activities of enzymes that are unmatched by synthetic catalysts, a lot of effort, especially during the initial phases of research, has been put to mimic the properties of these natural catalysts, generally using simple reaction models such as hydrolysis of esters.

Promising candidates for mimicking the enzymatic ‘catalytic cavities’ are supramolecular capsules with hollow, three-dimensional structures, formed by self-assembly of smaller building blocks utilizing hydrogen-bonding, metal-ligand, ionic and hydrophobic interactions. In principle, capsules can encapsulate guest molecules – substrates – within their internal space, imposing all of the above described confinement effects. This approach has resulted in a number of elegant examples of capsule-driven reactions that display enhanced selectivity and/or activity. This area of ‘supramolecular catalysis’ has been well reviewed. Therefore, we will give only a few crucial examples that demonstrate the potential of the approach. We will highlight examples of
the capsule-driven reactions involving transition metal catalysts, and we will discuss very recent contributions to the field.

![Figure 1. Molecular capsules A-D.](image)

**Figure 1.** Molecular capsules A-D.

![Scheme 1. 1,3-Dipolar cycloaddition between phenylacetylene 1 and phenylazide 2 within nanoreactor A.](image)

**Scheme 1.** 1,3-Dipolar cycloaddition between phenylacetylene 1 and phenylazide 2 within nanoreactor A.

Confinement effects of synthetic capsules have been elegantly demonstrated in metal-free reactions taking place in a capsule. For example, the cylinder-shaped capsule A (Figure 1a), developed by Rebek and co-workers, was shown to co-encapsulate phenylacetylene 1 and phenylazide 2 (Scheme 1). The shape of the capsule imposes edge-to-edge pre-orientation of the acetylene and the azide moiety, which results in a formation of exclusively one (3) out of two possible 1,3-dipolar cycloaddition products (3 and 4), which are formed in a 1:1 ratio in a control reaction. Effects on the reaction selectivity by substrate preorganization within a capsule were also demonstrated in olefin photodimerization and photo-oxidation reactions, as well as, in photomediated radical reactions. One of the most interesting changes of selectivity and/or activity driven by confinement effects were observed in the Diels-Alder reactions within the octahedral coordination cage B (Figure 1b), developed by Fujita and co-
Capsule B can selectively recognize a particular pair of substrates, for instance, 9-hydroxymethylanthracene 5 and N-cyclohexylphthalimide 6a. Interestingly, upon warming the reaction mixture, the unusual syn-1,4-Diels-Alder adduct 7a is formed quantitatively (Scheme 2), and no formation of the typical 1,9-adduct 8a is observed. The free solution reaction, on the other hand, leads to the formation of only 1,9-adduct 8a, without any traces of the 1,4-adduct 7a. The unusual stereo- and regioselectivity of the reaction is attributed to the fixed, sterically-driven pre-orientation of the two substrates within the capsule that prevents reaction at the usual 9,10-position of the anthracene. In accordance with the model, the reaction with less sterically demanding N-propylphthalimide 6b results in the formation of the typical 1,4-Diels-Alder adduct 8b (and 1,9-adduct 7b is not observed). Furthermore, capsule B was also able to activate typically inert aromatic compounds (naphthalenes, triphenylene and perylene), which gave the Diels-Alder products in a highly regio- and stereo-controlled fashion.  

Scheme 2. Diels–Alder reaction between the anthracene 5 and N-alkylmaleimides 6a-b within capsule B.

Encapsulation of molecules can also promote otherwise high-energy conformations and change the properties of some functional groups. For instance, the encapsulation of an overcrowded chromic alkene 9 inside of the octahedral cage B results in conversion of its conformation from an anti-folded to the higher energy twisted one (Figure 2). The process is accompanied by a dramatic color change from yellow to deep purple. The encapsulation of amines and phosphines within a highly (negatively) charged tetrahedral coordination cage C (Figure 1c), developed by Raymond and co-workers, results in a dramatic increase of their effective basicities (with up to 4.5 pKₐ units). This effect is observed due to the thermodynamic stabilization of the (positively charged) protonated guest via electrostatic interactions with the negatively charged cage. In principle, this effect was shown to accelerate the hydrolysis of orthoformates by the stabilization of the decisive positively charged transition state. Interestingly, the reaction is initiated by the protonation of the encapsulated substrate, presumably by a
water molecule, despite the basicity of the solution (pH=11), highlighting the power of the positive charge stabilization inside of the capsule. Furthermore, the reaction reveals a high level of substrate selectivity, as only the substrates that can enter the cage are efficiently hydrolyzed in the presence of the cage (tributyl orthoformate and smaller analogues versus tripentyl orthoformate). Similarly, the acetals can be readily deprotected under basic conditions using catalytic amounts of the cage C. Cage C also proved to efficiently catalyze the unimolecular 3-Aza-Cope rearrangement of allyl ammonium cations, also in an enantioselective manner, by reducing both the entropic and enthalpic contributions to the barriers of the reaction. Analogously, the thermodynamic stabilization of negatively charged intermediates involving a positively charged orthogonal cage B was used to catalyze the Knoevenagel condensation of aromatic aldehydes taking place in water under neutral conditions. Impressively, the Nazarov cyclization reaction of 1,4-dien-3-ol to form a cyclopentadiene in capsule C was over a million times faster than the uncatalyzed reaction. This unprecedented rate enhancement is attributed to the combination of (i) preorganization of the encapsulated substrate molecule, (ii) stabilization of the transition state of the cyclization by constrictive binding, and (iii) an increase in the basicity of the alcohol group of the bound reactant via the aforementioned electrostatic effects.

Molecular capsules can also be used to sequester a catalytic metal center, such that metal-catalyzed reactions occurring within their internal space experience the aforementioned confinement effects. Additionally, the isolation of the metal complex from the bulk can also result in its increased stability. In an elegant proof-of-concept study, it was shown that upon encapsulation inside of a tetrahedral cage with a hydrophobic interior, highly air-sensitive (pyrophoric) white phosphorus (P₄) becomes very stable, as the solution can be exposed to the atmosphere for months without any change. Importantly, the stabilization is not achieved through hermetic exclusion of O₂ but rather by constriction of individual P₄ molecules. The interior of the cavity is still accessible, as shown by the competition experiments with better guest molecules. In this vein, the isolation of a ruthenium (II) catalyst, [RuCp(PMe₃)(MeCN)]²⁺, inside tetrahedral capsule C protects it from decomposition, and the catalyst was stable in aqueous solution for days, while the unbound complex quickly decomposes (t₁/₂ ~ 60 min). Importantly, the complex stays catalytically active inside the capsule, which allows for the efficient allyl alcohol isomerization reaction to occur, with higher turnover numbers and increased catalyst lifetime. Partial encapsulation by a supramolecular enhancement of the steric bulk around the catalytic center also resulted in the increased lifetimes of a Mn¹¹¹-porphyrin and a Mn¹¹¹-salen catalysts for the epoxidation of olefins.

Encapsulation of a metal catalyst can result in a rate enhancement of the catalytic reaction due to confinement effects. For example, it was demonstrated that Me₃PAu⁺ encapsulated inside capsule C catalyzes the hydroalkoxylation of allenes with 8-fold higher rate than for the reaction in solution. The encapsulated catalyst can react only with substrates that can enter the cavity of the capsule, allowing for efficient control of substrate selectivity based on size and shape. This principle was displayed by the catalyst Rh(PMe₃)₂⁺ inside of the tetrahedral cage C, which can selectively isomerize small linear allylic alcohols and ethers that can enter the cavity, while leaving out unreacted bigger substrates. Moreover, encapsulation protects the metal center against decomposition by preventing poisons to interact with the catalyst. Catalyst encapsulation can also change the product selectivity profiles as observed for (i-Pr-
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NHC)Au(OTf) enclosed in a self-assembled hexameric capsule of resorcin[4]arene in the hydration and cyclization of phenylalkynes.\textsuperscript{35} In another study, it was shown that encapsulation of the Rh(nbd)$_2^+$ complex in a resorcin[4]arene capsule modifies the catalyst’s stability, selectivity, and reactivity relative to the free form in solution.\textsuperscript{36} The encapsulated catalyst is stable for hours under an atmosphere of H$_2$ and catalytically hydrogenates norbornadiene to norbornene, while the free catalyst decomposes within a few minutes and leads to formation of a norbornene dimer. Finally, by encapsulation one can also trap and stabilize certain isomers of metal complexes that are not stable in solution, as shown for dinuclear ruthenium complexes within the octahedral coordination cage C.\textsuperscript{37}

Another strategy to introduce a catalytic metal center inside a capsule, developed by Reek and co-workers,\textsuperscript{15} is a so-called ligand-template approach. In principle, the ligands used have a bifunctional character, containing groups for the capsule formation as well as donor atom sites for coordination to a catalytic metal. In general, the ligand can be a part of the capsule or just function as an internal scaffold around which the capsule is assembled.\textsuperscript{38} One of the biggest advantages of this approach is the ease with which the metal center is introduced inside the capsule, as the encapsulation is simply driven by the coordination chemistry. Moreover, the position of the catalytic center inside the capsule is well-defined, as the coordinated ligand has a low conformational freedom inside of the capsule. Finally, the interior of the capsule can be easily tailored by changing the size and shape of either the ligand or the template.

Pyridylphosphines are particularly good candidates for ligands, as the imines of the pyridyl groups can selectively coordinate to zinc templates, such as Zn$^{II}$-porphyrins or Zn$^{II}$-salphens, forming the ligand–template capsules, while the phosphine atoms can coordinate to the catalytically active transitional metals.\textsuperscript{39} For example, tris(meta-pyridyl)phosphine can coordinate via pyridines to three Zn$^{II}$-porphyrins and at the same time bind a rhodium(I) center (Figure 1d). This self-assembled rhodium catalyst D was shown to have unusual reactivity and regioselectivity in the industrially important hydroformylation reaction.\textsuperscript{39} Importantly, the catalyst can operate under industrially relevant conditions (temperature, pressure etc.), making it attractive for commercial applications.\textsuperscript{40} This supramolecular system also proved to be a high-precision hydroformylation catalyst for very challenging internal alkene substrates.\textsuperscript{39e} It is worth noting that there are no other catalytic systems that can distinguish between two carbon atoms of internal aliphatic alkenes; this highlights the potential of nanocapsules in controlling reaction selectivity. Moreover, application of chiral ligands also allows control over the enantioselectivity of the reaction.\textsuperscript{41} The ligand-template approach was also extended to other reactions, such as Au-catalyzed hydroalkoxylation,\textsuperscript{42} Rh-catalyzed enantioselective hydrogenation,\textsuperscript{43} as well as Pd-catalyzed CO/4-tert-butylstyrene copolymerization,\textsuperscript{44} offering often unprecedented properties.

1.3 Self-assembled bidentate ligands

As mentioned before, the selectivity and activity of a transition metal catalyst depends on the ligands that are coordinated to the metal center. The ligand modifies the electronic properties of the catalytic metal, and thus directly affects the activity. The steric properties of the ligand also shape the space around the catalytic center, which directs the substrate approach to the metal center, and as a consequence determines the reaction selectivity. In enantioselective catalysis, the reaction enantioselectivity (enantiomeric excess, e.e.) is fully dependent on the chirality of the ligands, and precise
control over selectivity is particularly difficult. Therefore, catalyst development is mainly based on trial-and-error approaches, preferentially with high throughput experimentation to simultaneously evaluate large numbers of catalysts within a short time-frame.\textsuperscript{45}

For many years, the main focus was on bidentate ligands, which initially outperformed their monodentate counterparts.\textsuperscript{46} The degrees of freedom for chelating bidentate ligands are limited compared to monodentate analogues, and hence the space around the metal center is well defined, which helps to control the reaction selectivity. Furthermore, the backbone of the bidentate ligands generally enforces cis coordination to the metal center, which is necessary for some reaction steps in the mechanism of many catalytic transformations. Much attention has been paid to the enantioselective hydrogenation of prochiral olefins, since it is one of the most industrially relevant reaction. In this case, the use of $C_2$-symmetric bidentate ligands reduces the number of coordination modes for the substrate (Re, Si). This limits the number of competing pathways,\textsuperscript{47} and it has proved to be a successful strategy.\textsuperscript{48} Alternatively, the use of strongly unsymmetrical ligands, that is strong $\sigma$-donor/strong $\pi$-acceptor bidentate ligands that provide sufficient differences in electronic properties to direct the coordination of the chelating substrate, proved to result in very selective catalysts.\textsuperscript{49} The severe disadvantage of this approach, despite the potential for the high-throughput screening, is often tedious and time-consuming synthesis of unsymmetrical bidentate ligands.

In the early 2000’s, it was shown that monodentate ligands can also be used to develop highly selective catalysts.\textsuperscript{50} An important breakthrough in this field was the use of binary mixtures of monodentate ligands ($L_a$ and $L_b$), which can form more selective (and active) heterocomplexes $[ML_aL_b]$ along with the homocomplexes $[ML_aL_a]$ and $[ML_bL_b]$.\textsuperscript{51} The advantage of this approach is the easy preparation of monodentate ligands, which, together with a combinatorial approach, quickly generates wide libraries of putative catalysts that are suitable for the automated high-throughput screening experimentation. The obvious downside of the approach is the formation of homocomplexes that can compromise the reaction selectivity. The ratio between hetero- and homo-complexes can be tuned to some extent, by the selection of ligands with appropriate electronic properties of the donor atom sites (for instance, $\sigma$-donor ligands (e.g. phosphine) can be combined with $\pi$-acceptor ligands (eg. phosphoramidite)),\textsuperscript{52} or by careful optimization of the $L_a/L_b$ ratio used,\textsuperscript{53} yet both methods are rather imperfect and introduce additional limitations.

Supramolecular chemistry provides tools that allow researchers to take advantage of both approaches; that is to construct libraries of supramolecular bidentate ligands that bear the favourable features of covalent bidentate ligands, but are constructed from easier to make monodentate components. In this case monodentate building blocks are equipped with an additional functional group for an assembly process that can lead to an \textit{in situ} formed supramolecular bidentate ligand. In principle, two ligands can bind directly to each other, or via a template platform/ion center, generating a supramolecular bidentate ligand (Scheme 3). The functional groups used for the assembly process can be self-complementary, allowing for formation of homobidentate ligands (Scheme 3a). Alternatively, the use of (non-self) complementary functional groups allows for a selective assembly of heterobidentate ligands (Scheme 3b). The latter is an extremely powerful strategy for the construction of wide libraries of ligands as $n$ components of type $L_a$ and $m$ components of type $L_b$ generates geometric $n \cdot m$ number of bidentate
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ligand Lₐ-Lₖ combinations. This strategy has been extensively studied, and was reviewed recently. We will discuss, below, selected examples that demonstrate the power of the approach. We will discuss the interactions that have proven to be suitable for the self-assembly process and reactions for which the strategy was successful. We will also present recent contributions to this field.

Scheme 3. Schematic representation of supramolecular bidentate ligands.

Hydrogen bonds have been one of the most frequently used interactions for the self-assembly process of ligand building blocks. The binding energy is sufficient to form relatively stable adducts, especially when an array of H-bonding interactions is used. Also, several H-bond motifs are available, which provides easy access to various libraries of putative monodentate building blocks. Moreover, the preferred arrangement of H-bonding motifs potentially allows the geometry of a self-assembled bidentate ligand to be well-controlled, allowing for formation of rigid structures, analogous to covalent bidentate ligands.

In this vein, the 2-pyridone 10A /2-hydroxypyridine 10B tautomer system was used to construct self-assembled bidentate ligands (Scheme 4). In principle, both tautomers can complementarily dimerize to form a nonsymmetrical dimer via a pair of hydrogen bonds. The nonsymmetric dimer is slightly higher in energy than the symmetric dimer, yet upon metal coordination to the additional donating phosphine functionalities the nonsymmetric dimer becomes more favourable. The complex formed using the rhodium precursor provides very high regioselectivities in the industrially important hydroformylation reaction of terminal olefins, similar to the best catalysts with wide-bite angle bidentate ligands, such as Xantphos. Interestingly, the catalyst is also highly active, allowing for the reaction to be performed even at ambient temperature and pressure. The increased activity for this ligand, compared to the covalently bound bidentate ligands, can be (at least partially) attributed to the synergism of flexibility and structural integrity, since it allows for the adoption of different coordination modes and bite angles during the catalytic cycle without severe energy penalties, as concluded from DFT studies. Importantly, the presence of the hydrogen bonding was proved to be present for the resting state and during the catalytic cycle based on a combination of experimental and theoretical results. Control experiments with similar ligands, for which the assembling process was obstructed by N- or O-methyl substitution, showed poor selectivities and inferior activity, confirming the importance of the hydrogen bonding. The catalyst was further applied successfully to tandem processes such as a tandem hydroformylation/asymmetric organocatalytic cross-aldol reaction and a tandem hydroformylation/hydrogenation process. Employing chiral moieties on the donor atom, the pyridone-based ligand system was extended to Rh-catalyzed
asymmetric hydrogenation$^{62}$ and Pd-catalyzed asymmetric allylic amination reactions,$^{63}$ showing the general applicability of the supramolecular approach to construct self-assembled bidentate ligands.

![Scheme 4](attachment:Scheme4.png)

Scheme 4. Self-assembly of the tautomeric system 2-pyridone/2-hydroxypyridine in the presence of a transition metal.

Inspired by the principles of DNA base pairing, and on the basis of the previous results, a platform for the generation of a library of heterobidentate ligands was devised.$^{64}$ In this case, two types of ligands are involved: building blocks based on isoquinoline and aminopyridine moieties (Scheme 5). In solutions, a 1:1 mixture of monodentate building blocks of both types forms the heterodimers selectively via complementary hydrogen bonding. Alternatively, other platforms with similar arrays of hydrogen bonding groups can be used, which allows modulation of the properties (e.g. the bite angle) of the supramolecular ligand. The use of several components of each type generates large libraries of ligands, which has been proven to provide very active and very selective catalysts for the Rh-catalyzed hydroformylation of alkenes,$^{65}$ the Ru-catalyzed anti-Markovnikov hydration of terminal alkynes,$^{66}$ the Ru-catalyzed hydration of nitriles$^{67}$ and the Ni-catalyzed hydrocyanation of alkenes.$^{68}$ Introduction of chiral elements into these building blocks also allows for application of the strategy to the enantioselective reactions, such as the Rh-catalyzed hydrogenation of prochiral olefins, resulting in very selective catalysts (up to 99% e.e.).$^{69}$ Interestingly, it was demonstrated later that by applying a smart deconvolution strategy, the best catalysts can be identified from the 120-member library within only 17 experiments, instead of 120 experiments necessary in a classic parallel screening method.$^{70}$ The pyridone/aminopyridine hydrogen-bonding pair was also used to construct chiral dinuclear Co(II)-salen catalysts that gave high selectivities and significantly increased activities in the Henry reaction.$^{71}$

In a related design, monodentate ligands functionalized with a short peptide were shown to self-assemble via inter-ligand helical hydrogen bonding.$^{72}$ This generates assemblies that can mimic successfully the classic PhanPhos planar ligand, as has been shown in Rh-catalysed enantioselective hydrogenation of prochiral olefins. Application of C-linked and N-linked peptide-functionalized building blocks allows for selective formation of the heterodimers that assemble complementarily via antiparallel $\beta$-sheet type structure.$^{73}$ A moderate level of enantioselectivity is induced in the Rh-catalyzed hydroformylation of styrene, despite rather big distance between the catalytic center and the chiral information of the peptide stereocenters.
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Scheme 5. DNA inspired heterobidentate ligands formed by complementary interactions between aminopyridine and isoquinolone.

In contrast to 2-component systems, urea-functionalized phosphine ligands – coined UreaPhos – can bind directly to each other. Alternatively a templating chloride anion is used to form a self-assembled homobidentate ligand (Scheme 6). The advantage of these ligands is their easy modular synthesis from simple commercial building blocks that can be easily varied, which allows for generation of wide ligand libraries of high structural diversity. The catalyst synthesis, screening and optimization can be automated using ChemSpeed and AMTEC SPR16 technologies, speeding up the catalyst development, as demonstrated for the Rh-catalyzed enantioselective hydrogenation of several ‘difficult substrates’ (in some cases getting the highest e.e.’s ever reported). Recently, this approach was extended also to chiral oxazoline ligands, for the Cu-catalyzed enantioselective benzylation of hydrobenzoin and for desymmetrization of meso-hydrobenzoin by benzylation. The ligands furnished good selectivities, in some cases outperforming classical bis(oxazolines) ligands.

Scheme 6. Self-assembly of UreaPhos ligands in the presence of a transition metal and presence or absence of a templating chloride anion.

Recently, two classes of highly related ligands were introduced – PhthalalPhos and BenzaPhos – which are constructed on the phthalic acid diamide and benzamide derivatives, respectively, and which can self-assemble via hydrogen bonding. Again, the advantage of the ligands is their simple, modular synthesis (2-4 steps), allowing for generation of wide libraries. The ligands proved to form highly selective catalysts for the Rh-catalyzed enantioselective hydrogenation of challenging substrates (with the highest ever reported e.e.’s). On the basis of control experiments and the DFT calculations, the high selectivities were partially attributed to the additional hydrogen bonding interactions that allow for the substrate preorganization (see Section 1.5).

Hydrogen bonding was shown to be structurally important also for other classes of monodentate ligands. For example, the monodentate phosphoramidites containing an NH moiety self-assemble via hydrogen bonding with the oxygen atom of the adjacent ligand. These complexes provide much higher activity and selectivity in the Rh-catalyzed enantioselective hydrogenation of olefins, than those devoid of these
functionalities. Secondary phosphine oxides were shown to form hydrogen bonds between the ligands coordinated to a metal center, affecting its catalytic properties. The hydrogen bonding was also shown to play a structural function in complexes of sulfonamido-phosphorus ligands (MetamorPhos), and their close analogues, urea-phosphorus ligands (Phosphinoureas), that form selective catalysts for the Rh-catalyzed hydrogenation and hydroformylation reactions.

Aside from hydrogen bonding, metal-ligand interactions are commonly used as structural interactions to construct supramolecular bidentate ligands. The advantage is the relatively high strength and the directionality of the interaction that allows for precise control of the geometry of the assembly. In principle, monodentate building blocks can bind to each other directly or via a template that introduces another element for the structural modifications (Scheme 3).

The template induced formation of bidentate ligands was demonstrated with bis-zinc(II) and bis-tin(IV) porphyrin building blocks to which, respectively, imine-functionalized and carboxyl-functionalized monodentate components can bind (Scheme 7a), as shown by the NMR spectroscopy and X-ray analysis. Importantly, upon addition of a metal precursor (such as rhodium or palladium), the assembly is not disrupted, but the soft metal coordinates selectively to the soft donor sites, that is phosphine or phosphite functionalities. Compared to catalysts with analogous monodentate ligands, this multicomponent self-assembly behaves similarly to catalysts with covalent bidentate ligands, as shown in the Rh-catalyzed (enantioselective) hydroformylation and hydrogenation reactions, as well as, in the Pd-catalyzed asymmetric allylic alkylation. The use of more rigid bis-zinc(II) salphen building blocks, instead of bis-zinc(II) porphyrin, allows for selective formation of heterobidentate combinations despite the equivalency of the binding sites. The selectivity is presumably driven by the combination of steric effects and the thermodynamic stability of the heterocombinations at the rhodium center.

Scheme 7. Examples of catalysts formed by self-assembly of (a) imine-functionalized ligands on a bis(zinc(II))-template, and (b) imine-functionalized and zinc(II)-template-functionalized ligands.

Alternatively, one of the ligands can be functionalized with a zinc(II)-templating moiety. The combination of these ligands with the imine-functionalized ones selectively generates the heterobidentate assemblies (Scheme 7b). This strategy generated ligands for selective catalysts for the Pd-catalyzed asymmetric allylic alkylation and kinetic resolution of racemic cyclohexenyl acetate, as well as for the Rh-catalyzed asymmetric hydrogenation of difficult substrates and regioselective hydroformylation of styrene.

An elegant system has been reported based on bifunctional ligands equipped with a moiety for soft (catalytic) metal coordination and with a bis(oxazoline) moiety for a
hard (structural) metal coordination (Scheme 8). Due to steric requirements only ligands with opposite chiral configuration at the bis(oxazoline) moiety can coordinate to the zinc(II) center simultaneously forming tetrahedral heteroleptic complexes. Therefore, the strategy is well suited for generation of heterobidentate self-assembled ligands. These ligands generated good catalysts for various reactions, such as the Pd-catalyzed allylic amination,\(^9\) the Rh-catalyzed asymmetric hydrogenation\(^9\) and the Rh-catalyzed asymmetric hydroboration\(^9\). In a similar system, easy-to-make ditopic ligands are equipped with both a phosphorous moiety for a soft (catalytic) metal coordination and with a (two or three) hard donor atoms center for a structural metal coordination (Ti(IV) or Zn(II)).\(^9\) The platform is suitable for formation of only homocombinations, yet it provided a class of wide-bite angle supramolecular ligands that formed the regioselective catalysts for the Rh-catalyzed hydroformylation of alkenes.

**Scheme 8.** An example of a catalyst assembled with the metal templating heterobidentate approach.

Ionic interactions have also been exploited as the driving force for self-assembly of supramolecular bidentate ligands. The clear advantage is their high strength and complementarity, which could strongly promote formation of the heterodimeric assemblies. The drawback is the low directionality of the interaction, hence the rather low control of the geometry of the assembly. In principle combinations of anion- and cation-functionalized ligands (or acid- and base-functionalized ligands) should result in selective formation of bidentate ligands. The studies reported so far present limited success of the approach, as mixtures of homo- and hetero-combinations were usually observed.\(^9\) The formation of hetero bis-ligand complexes can be further promoted by additional hydrogen bonding between the two ligands.\(^9\) Despite formation of mixtures of homo- and hetero-complexes, in some cases mixtures provided better results in the Rh-catalyzed asymmetric hydrogenation, than the respective homocombinations.\(^9\)

\(\pi - \pi\) interactions between electron-rich and electron poor arene units were also explored as a driving force for the assembly of hetero-bidentate supramolecular ligands.\(^9\) No selective formation of hetero-combinations was observed, suggesting that the interactions are too weak to act as an efficient driving force. Interestingly, in some cases hetero-combinations of monodenate ligands provided better result than those of the respective homocombinations in the Rh-catalyzed enantioselective hydrogenation reaction.\(^9\)
More elaborate systems based on pseudorotaxanes\(^{97}\) and inclusion\(^{98}\) complexes have also been constructed. In some cases, the supramolecular assemblies exhibited superior activity and enantioselectivity compared to the parent monodentate ligands in the Rh-catalyzed asymmetric hydrogenation.\(^{97}\)

Recently, the multicomponent catalyst assembly approach has been extended and explored in the area of organocatalysis.\(^{99}\) In principle, components bearing both the organocatalytic functions and complementary functions for self-assembling can be employed. Usually hydrogen bonding\(^{100}\) and/or ionic\(^{101}\) interactions are used as the driving force for the catalyst assembly. These studies have resulted in a myriad of highly selective organocatalysts for various reactions, such as the Michael-type addition,\(^{100,101,102}\) the hetero-Diels–Alder,\(^{103}\) aldol\(^{104}\) and other transformations.\(^{105}\)

### 1.4 Supramolecular fine-tuning of a catalyst

A typical search for selective and active catalysts, whether applying classic covalent or supramolecular ligands,\(^{106}\) is comprised of iterative rounds of catalyst screening and optimization. Initially, a library of diverse catalysts is tested (e.g. a library of catalysts furnished with privileged or supramolecular ligands that have worked well in similar reactions),\(^{107}\) searching for initial leads. Subsequently, the promising catalysts are subjected to further rounds of optimization, by creating new focused libraries, which may include structurally elaborated ligands. The search can be significantly accelerated by automated high throughput parallel experimentation and combinatorial methods involving self-assembled supramolecular ligands, which generate large ligand libraries relative to classic catalyst searches. However, the final rounds of optimization often require time-consuming ligand synthesis, effectively slowing down the procedure. Considering that the final catalyst tailoring typically requires introduction of only small structural changes, one might envision that the final catalyst fine-tuning could be achieved using supramolecular interactions. In principle, the strategy requires catalysts furnished with a recognition site that can bind small and easily accessible molecules or ions – ‘cofactors’ – which will modify the space around the catalytic center (Scheme 9).

![Scheme 9. Schematic representation of supramolecular catalyst modifications with cofactor binding.](image)

In this vein, a new multicomponent catalyst has been constructed from a chiral diol cofactor (chiral inducer) that can coordinate to a structural metal (titanium(IV)), together with two achiral ditopic ligands that form the bidentate phosphine ligand coordinating to the catalytic metal (Scheme 10).\(^{108}\) As shown, the assembly is formed
selectively *in situ* upon mixing of all components, which, together with easy access to commercial chiral diols, provides access to a wide library of chiral bidentate ligands with minimal synthetic effort. The evaluation of the library in the Rh-catalyzed hydrogenation of prochiral olefins revealed that good enantioselectivities are achieved when bulky diols are present in the ligand assembly (e.e.’s up to 92%). This demonstrates the effective chirogenesis from the chiral diol onto the metal center over more than 10 bonds.\(^\text{109}\)

**Scheme 10.** Supramolecular strategy for chiral bidentate ligand formation via self-assembly with diols as chiral cofactors.

In a related study, an achiral porphyrin based cage was modified by coordination of small chiral cofactors in proximity to the catalytic center.\(^\text{32d}\). Despite the small effect – an e.e. of 14% was observed in sulfoxidation of methyl p-tolyl sulphide – the effective through-space chirality transfer was observed, proving the validity of the principle.

In another study, a new strategy of the ‘ion-paired’ ligands that consist of a cationic ammonium–phosphine component paired with a chiral binaphtholate anion was envisioned (Scheme 11).\(^\text{110}\) This platform supplements the powerful chiral counteranion strategy developed for enantioselective catalytic transformations that is applicable only to reactions with metal-cationic intermediates and with non-ionic nucleophiles.\(^\text{111}\) In principle, the electrostatic interactions between the anion derived from a chiral bulky diol and the positively charged onium functionality of the ligand coordinated to the metal center positions the chiral cofactor nearby the catalytic site. Easy variation of the structure by the use of accessible chiral diols allows for efficient catalyst optimization. The ligand furnished selective catalysts for the challenging Pd-catalyzed enantioselective allylic alkylation of \(\alpha\)-nitrocarboxylates (e.e.’s up to 97%). Later, this strategy was extended to the Pd-catalyzed enantioselective alkylation of benzofuranones.\(^\text{112}\) In this case, introduction of the additional chiral information onto the onium cation was necessary to reach high level of selectivity (e.e.’s up to 97%).
The ligand-template approach, described in detail in Section 1.2, is also suitable for supramolecular fine tuning. For instance, for palladium catalysts applied in CO/4-tert-butylstyrene copolymerization, the catalytic activity of the complex and the molecular weight of the copolymer obtained can be tuned by altering the properties of the easily accessible zinc salphen units used to assemble the catalyst. Similarly, the enantioselectivity and the activity of rhodium hydroformylation and hydrogenation catalysts built on chiral ligands equipped with pyridine moieties for zinc(II)/ruthenium(II) template binding can be tuned by changing the properties of templates, in this example porphyrin and salphen molecules.

Another related approach, which has been extensively studied recently, is the concept of DNA-based asymmetric catalysis. In principle, metal complexes containing ligands capable of intercalation to DNA are used. This allows embedding of the catalytic center within the biomolecular DNA scaffold, which exerts secondary coordination sphere effects on the catalyzed reaction (Figure 3). This provides a myriad of highly selective catalytic reactions that take place in water, such as the Diels–Alder reaction, the Michael addition and the Friedel–Crafts alkylation.

An alternative to the above-described supramolecular modification of the catalyst is the temporary alteration of the structure of the reactive substrate (Scheme 12a). This principle was elegantly presented for the Cu-catalyzed, enantioselective coupling of alkyne and imine to form propargylamines (Scheme 12b). Hydrogen bonding between an amino acid derivative and the imine substrate allows for efficient enantio-induction (e.e.’s up to 99%), which, considering the achiral nature of the Cu-phosphine catalyst, demonstrates the principle of this strategy. However, a disadvantage of this approach is the large amount of cofactor required (stoichiometric with respect to substrate, instead of catalyst).
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Scheme 12. (a) Schematic representation of selectivity control via supramolecular cofactor-substrate interactions, and (b) the example: enantioselective imine/alkyne coupling modulated via chiral amino acid derivatives.

1.5 Precise supramolecular substrate preorganization

In natural enzymes, aside from the confinement effects intrinsic to the nanospace of the active sites described in detail in Section 1.2, other factors often play an important role in controlling the selectivity (and the activity) of the catalyzed reaction. Frequently the positioning of the substrate is determined not only by the size and shape of the enzymatic cavity, but also by directional interactions between functional groups of the substrate and of the active site, such as hydrogen bonding, ionic interactions or even reversible covalent bonding. This ensures precise substrate orientation and dramatically limits its motion, both of which are essential for obtaining high selectivity. Importantly, this operational mode is less susceptible to changes in substrate size (as long as a substrate molecule bears the essential functional groups), and allows for selective transformations of a broad substrate scope. In contrast, substrate orientation based exclusively on shape and size is far more substrate dependent, as seen, for instance, for the Diels-Alder reactions within the cage B (Scheme 2). Furthermore, interactions with the functional groups of the substrate can modulate their reactivity allowing for even better control over the selectivity and the activity of the reaction.

In traditional catalysis, substrate preorganization is realized via coordination of ‘directing group’ to a metal center. The directing group can be either a functional group present in the substrate or is introduced before the catalytic reaction and removed afterwards. Although effective, this methodology is limited to substrates with directing groups spatially close to the reactive functionality, imposing limitations. Moreover, the reaction occurring at the metal center must be compatible with the directing group, and also requires one vacant coordination site at the metal center, limiting its potential to some extent.

Supramolecular chemistry provides ideal tools for substrate preorganization. In transition metal catalysis the substrate preorganization can be realized by the supramolecular interactions between the ‘directing groups’ of the substrate and a suitable ligand from the catalyst (Scheme 13). In principle, a catalyst that is furnished with a specific recognition site will bind the substrate molecule and preorganize its reactive moiety with respect to the metal center. The location of the directing group and the reactive functionality are theoretically independent, which makes it possible for this strategy to be applied to substrates with directing groups in various positions, allowing for remote control, and exceeding the possibilities of the traditional substrate preorganization approach. Thanks to a well-established understanding of weak
interactions between molecules, the rational design of selective catalysts that operate predictively can be envisioned. The methodology is especially attractive for reactions for which the selectivity issues are notoriously difficult to solve with the traditional trial-and-error approach, e.g. reactions for which the pathway to the desired isomer is higher in energy than the alternative one or for which many reaction pathways compete simultaneously.

![Scheme 13](image)

**Scheme 13.** Schematic representation of supramolecular substrate preorganization.

In this vein, a catalyst that mimics the hydroxylating cytochrome P-450 enzyme was developed. The Mn$^{III}$-porphyrin 11 was functionalized with a cyclodextrin (CD) moiety on each of its meso-phenyl rings, and it was shown that the CDs bind to the hydrophobic groups of steroid derivative 12 (Scheme 14). The substrate binding precisely positions the steroid moiety on the manganese porphyrin such that its C6 $\alpha$ position is exposed to the catalytic center, resulting in highly regioselective hydroxylation of this CH function (regioselectivity >90%). Importantly, the porphyrin is a true catalyst, as it performs 187 turnovers. A substrate with different anchoring groups, which binds in a different geometry, reacts selectively at a different position (C9 $\alpha$). In further studies, it was shown that metal-ligand interactions can be also used for precise substrate preorganization.

In another study, another Mn-catalyzed, selective C-H oxidation at sp$^3$-carbon atoms was targeted. In this case nonporphyrin system 13 was devised, which consists of a di-$\mu$-oxo dimanganese core – a very active catalyst for oxidation chemistry – based on ligand 14 equipped with Kemp’s triacid, a recognition site for carboxylic acids (Figure 4). Molecular modeling predicts that the catalyst binds a molecule of ibuprofen (15) in such a way that the benzylic proton of the more remote position is precisely oriented towards the catalytic manganese center (Figure 4). As predicted by the model, the catalyst oxidizes ibuprofen at this position with very high regioselectivity (98.5%, Scheme 15). In contrast, the reaction with a catalyst devoid of the COOH recognition site leads to a mixture of products. Impressively, catalyst 14 can also oxidize (4-methylcyclohexyl) acetic acid 16 selectively (>99%) at the C-H position, as predicted by the modeling. Interestingly, only the trans isomer of 16 reacts readily, since the cis isomer does not expose an oxidisable C-H group to the catalytic center when its COOH is bound to the recognition site. In a control experiment with the catalyst devoid of the COOH recognition site both isomers react similarly, and the reaction leads to a mixture of several oxidation products. This system shows that, along with providing an unprecedented level of reaction selectivity, bifunctional catalysts can allow for efficient substrate selection, including challenging diastereoselection.
Scheme 14. Mn-catalyst 11 with attached cyclodextrins, and selective hydroxylation of steroid 12 catalysed by 11.

Figure 4. Molecular model of catalyst 13 docked with a molecule of hydrogen-bonded substrate 15 – Ibuprofen.
In a subsequent study, the same catalyst and an analogue – a manganese porphyrin catalyst furnished with the same Kemp’s triacid recognition site – were used as catalysts for selective epoxidation of alkenes containing a carboxylic group.\textsuperscript{119} For two out of three substrates studied, molecular recognition directs oxidation to the olefin moiety and prevents the unselective oxidation of C-H bonds observed in control experiments. However, poor diastereoselectivity is observed for the epoxide products, which on the basis of molecular modeling is attributed to the ill-defined preference between alternative orientations of the reactive double bond in the catalyst-substrate complex.

In a related study, a Ru(II)-porphyrin 17 equipped with a chiral tricyclic γ-lactam that can form a complementary two-point hydrogen bonding with the CONH amide functional group was synthesized (Figure 5).\textsuperscript{120} Molecular modeling showed that this two-point interaction orients 3-vinylquinolone (18) at the catalyst (Figure 5) such that one prochiral site of the reactive double bond is exposed to the catalytic center preferentially due to steric requirements. As predicted by the model the substrate preorganization leads to high enantioselectivities (e.e.’s up to 98%) in epoxidation for a series of 3-vinylquinolones. The epoxidation of substrate 19 with 2 reactive sites, 3,9-divinylquinolone, takes places with high regioselectivity on the vinyl group in position 3 (91% versus 9% of the alternative product, Scheme 16). This selectivity is in line with the proposed mechanistic model, which predicts that only the vinyl group in position 3 can react at the catalytic center when the substrate is bound to the recognition site. The reaction with the same substrate but with a catalyst devoid of the recognition site leads to two alternative products in a 62/38 ratio, revealing its crucial role for the selectivity. The importance of the double hydrogen bonding was further confirmed by control reactions with either the N-methylated substrate or catalyst in which drastic deterioration of the selectivity was observed. Studies on the substrate scope show that other substrates, such vinylpyridones, primary alkenoic amides and carbamates also experience the effect of the preorganization. However, a clear trend can be noted whereby the enantioselectivity gradually drops with increasing flexibility of the
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The distance between the catalytic metal and the chiral groups is over 7.0 Å, showing that the remote selectivity control via supramolecular interactions is viable.

**Figure 5.** Ru(II)-porphyrin pre-catalyst 17 docked with substrate 18 – schematic representation and the probable transition state found by DFT.

**Scheme 16.** Epoxidation products of substrate 19 with 17 as catalyst.

In a subsequent study, the same recognition site was used to preorganize sulfide quinolone-type derivatives on a Mn(III)-salen catalyst, which is capable of catalyzing the enantioselective sulfoxidation reaction (e.e.’s up to 71%).\textsuperscript{121} Again, control experiments confirmed the crucial role of the two-point hydrogen bonding in the prochiral face differentiation.

Very recently it was also reported that a Rh(II) complex bearing the same two γ-lactam binding sites catalyzes the regio- and enantioselective (e.e.’s up to 74%) C–H amination reactions of 3-benzylquinolones.\textsuperscript{122} It was confirmed that both the regio- and enantioselectivity of the reaction is controlled by substrate positioning imposed by the hydrogen bonding.

The chiral tricyclic γ-lactam binding site was also used to preorganize prochiral substrates at photosensitizers (in metal-free reactions). This enabled unprecedented induction of enantioselectivity in the photoinduced conjugate additions of α-amino alkyl radicals to enones,\textsuperscript{123} as well as in intramolecular [2+2] photocycloaddition reactions.\textsuperscript{124}

In another study, regioselectivity issues of hydroformylation reactions were addressed with phosphine ligand 20 bearing a guanidine-based recognition unit that is able to bind unsaturated carboxylic acids via two-point hydrogen bonding (Scheme 17).\textsuperscript{125} The substrate binding results in increased activity and high regioselectivity for hydroformylation of 3-alkenoic acids 21-23. Remarkably, the system presents unprecedented high regioselectivity for hydroformylation of an internal alkene 22 and reaction-site selectivity for substrate 23 with two reactive double bonds (Scheme 17). The crucial role of binding to the recognition unit of the ligand was demonstrated by a series of control experiments with substrates and modified ligands that cannot form the supramolecular interaction. The system is highly susceptible to the relative position of the directing carboxylic group and the double bound, as hydroformylation of an
analogue of 21 that is one carbon longer (4-butenoic acid 24) leads to a typical mixture of isomeric products. 2-Alkenoic acid 25 undergoes 2-regioselective decarboxylative hydroformylation, resulting in formation of the liner aldehyde, thus formally substituting the carboxylic group with an aldehyde (Scheme 17). Furthermore, a related guanidinium-based system was used for aldehyde hydrogenation and for tandem hydroformylation-hydrogenation of terminal olefins, again with a crucial role for the hydrogen bonding functional groups.

Scheme 17. Binding of substrate 21 to ligand 20 in the hydride migration step of hydroformylation (above), and hydroformylation products of substrates 21-25 with Rh-20 catalyst (below).

Inspired by the cooperativity displayed by metalloenzymes such as carboxypeptidase, capable of peptide bond hydrolysis, highly active and selective bifunctional catalysts for anti-Markovnikov hydration of terminal alkynes were developed. The full reaction mechanism has not yet been revealed, however, studies have so far shown the crucial role of pendant basic functional groups that take part in proton transfer and hydrogen bonding in the reaction intermediate.

The previous examples demonstrate the general potential of catalysts that are carefully designed to control the selectivity of reactions via crafted catalyst-substrate interactions. However, in many other cases the importance of non-covalent interactions on the catalyst selectivity was realized post factum. These serendipitous findings suggest that non-covalent interactions play a crucial role in the selectivity control much more often than it was previously assumed. This observation can help to generate new
leads for catalyst design. For example, during the search for enantioselective catalysts for the hydrogenation of 3-hydroxy-2-methylpropionate to the Roche ester – an important synthon for the synthesis of bioactive chemicals – it was found that the self-assembled heterobidentate ligand (see Section 1.3) consisting of LEUPhos phosphoramidite and urea–phosphine furnishes a highly selective catalyst (99% e.e.).52b

Experimental and theoretical studies revealed that an additional single hydrogen bond between the substrate’s OH function and the ester group of LEUPhos ligand is crucial for high selectivity (Figure 6). Subsequently, related observations were made for other systems for the Rh-catalyzed enantioselective hydrogenation of prochiral alkenes.79b,c A similar effect was observed in the Co-catalyzed cyclopropanation reaction.130 The hydrogen bonding between the substrate and the ligands was also proposed to activate allylic alcohols for the Pd-catalyzed direct allylation of indoles,131 and water molecules for the Ru-catalyzed hydration of nitriles.67

![Figure 6](image)

**Figure 6.** Substrate orientation through additional hydrogen bonding between the hydroxyl group of the substrate and the ester unit of the LeuPhos – determined by DFT and control experiments.

In the search for a selective (and active) catalyst for challenging allylic alkylation of indoles with unsymmetrical 1,3-disubstituted allyl acetates, P,S-bidentate ligands with an additional sulfinyl group were explored.132 It was found that the additional SO moiety forms a hydrogen bond with the indole-NH, and presumably helps to orient the nucleophile during the reaction (Scheme 18), resulting in a high level of regio- and enantioselectivity (e.e.’s 84-95%). This interaction seems to be crucial not only for the selectivity but also for the activity, as the reaction with N-substituted indole, which cannot form this interaction, does not take place. This successful example of a cooperative catalyst should encourage application of bifunctional ligands in catalyst discovery.

![Scheme 18](image)

**Scheme 18.** (a) Structure of the bifunctional ligands, and (b) tentative model of hydrogen-bond induced indole activation toward alkylation.
The examples shown so far have primarily shown supramolecular substrate preorganization accomplished mainly through hydrogen bonding. However, in principle, any reversible bonding that does not interfere with either the metal center or the catalytic reaction can be used for that purpose. Reversible covalent bonding is an attractive tool to control selectivity of a reaction by modifying substrates with covalently attached ligand-type directing groups (e.g. diphenylphosphinobenzoate group). Reversible bonding allows the use of only catalytic amounts of these kinds of directing groups, improving the applicable value of the approach (from a commercial and an atom-efficient point of view).

To illustrate the potential of reversible covalent bonding, catalytic scaffolding ligands have been introduced and extensively studied in the Rh-catalyzed hydroformylation of unsaturated alcohols and sulfonamides. In principle, under optimized conditions the scaffolding ligands extensively exchange with hydroxyl functionalities from substrates (Scheme 19). Under catalytic conditions, the formed ligand-substrate composite reacts preferentially over the free substrate, since the ligand donor moiety coordinates to the metal bringing the reactive double bond near the catalytic center. After the transformation, the product formed is exchanged for a new substrate, which subsequently reacts. This efficient substrate preorganization allowed for highly regio-, diastereo- and enantioselective reactions of various terminal and internal alkenes bearing either hydroxy or sulfonamide group. The strategy also allowed for enforcing hydroformylation of tertiary carbon atoms, highlighting the power of the approach.

\[ \text{Scheme 19. (a) Equilibrium with scaffolding ligands, and (b) the example of the effect of scaffolding ligands on reaction selectivity.} \]

1.6 Conclusions and outlook

The different supramolecular strategies discussed in this chapter, supported with some successful examples of their implementation, unambiguously show that supramolecular chemistry provides a full toolbox of strategies for selective catalyst development. Clever manipulation of non-covalent interactions brings the properties of the finite microenvironments of natural enzymes to synthetic catalysts, as described in Section 1.2. Although full mimicry of enzymatic precision and efficiency is still rather
distant, the examples reported so far, especially those with unique reaction selectivities induced by synthetic cavities, demonstrate the power of the concept. Further mechanistic studies are required to fully understand the principles that rule the reactions carried out in a confined space of a capsule. This will help researchers to take full advantage of the concept and may facilitate the step to practical applications.

The supramolecular methods to generate wide libraries of ligands that are described in Section 1.3 represent arguably the most developed contribution of supramolecular chemistry to transition metal catalysis at this point. The methodologies are well-matured, complement traditional approaches, and in principle are ready to be used to tackle practical problems for homogeneous catalysis, and their commercial application is currently being explored. Research on supramolecular catalyst fine-tuning that is described in Section 1.4 will bring further progress to the field of catalyst development based on high throughput screening.

Although the field of precise supramolecular substrate preorganization, described in Section 1.5, is still in its infancy, several examples of highly selective catalyst with practical levels of efficiency have already appeared. In some cases, the supramolecular catalysts provide unique reaction selectivities that are otherwise inaccessible. As the catalysts operate quite predictably, they can be easily crafted, and thus designed for substrates of interest. That substantially strengthens the potential of the approach and points towards a bright future.

In addition to the contributions to the field of ‘static’ catalysts that are discussed in this chapter, supramolecular chemistry also provides tools to develop ‘responsive catalytic systems.’ The properties (activity/selectivity) of such catalysts can be precisely controlled over time, via chemical (allosteric) or physical (e.g. photocontrol) regulation, depending on the current need of the reaction. One may envision that these systems could find practical applications, for example, in multistep transformations and processes, which involve more than one reaction that are separated in time. First steps toward these goals have been made recently, providing promising results (yet they are beyond the scope of this chapter). Dynamic combinatorial chemistry, a subfield of supramolecular chemistry dedicated to complex responsive chemical networks, provides further possibilities to catalyst development, which we recently discussed in a separate contribution.

After many years of parallel, unruffled lives, the paths of supramolecular chemistry and transition metal catalysis have finally crossed. This has resulted in revolutionary strategies and a myriad of ‘supramolecular transition metal catalysts’ with novel properties and opportunities for the future.

1.7 Outline of the thesis

Based on the work described in this chapter, it is clear that the presented supramolecular approaches have great potential in the field of catalyst development. Some of these supramolecular tools, like the use of self-assembled bidentate ligands, are already well matured and being tested for commercial applications. They allow the dramatic acceleration of trial-and-error catalyst search via automated high-throughput screening. Alternatively, the use of supramolecular interactions also allows for rational design of a selective catalyst for a reaction of interest by, for example, a supramolecular substrate preorganization approach. This strategy, however, is still in its infancy, but its power has already been revealed in initial reports. Future studies will assist the development of the field by creating a better understanding of the mechanistic principles
of these kinds of catalysts. Contributions addressing the selectivity issues of commercially important reactions, especially those that cannot be solved otherwise, should further stimulate this area of research, potentially leading to commercial applications.

In this thesis we introduce a new class of bifunctional ligands, coined DIMPhos, which consists of two phosphorus atoms for coordination to a catalytic metal center and a specific recognition site – DIM pocket – for binding to a carboxylate functional group of a substrate. In Chapter 2 we introduce this concept and we discuss the principles of the catalyst design. We present the initial results that provide proof for the concept. We show that the catalyst controls the selectivity in the rhodium catalyzed hydroformylation of two classes of substrates, terminally unsaturated (deprotonated) carboxylic and phosphonic acids. This illustrates the first example of wide-ranging remote control of catalyst selectivity by secondary substrate-ligand interactions. In Chapter 3 we report the full account of this study (including the initial results presented in Chapter 2). We show that the system also allows for the precise control of the selectivity in the hydroformylation of challenging internal alkenes functionalized with a carboxyl group. Detailed experimental and computational studies reveal the structure of the catalyst and its precise operational mode. In Chapter 4 we show that this catalytic system combined with an isomerization catalyst allows for a new sequence of isomerization-hydroformylation reaction to convert terminal olefins to α-methyl-branched aldehydes with unprecedented selectivities. To demonstrate the full potential of the catalytic system, we next show that the precise supramolecular substrate preorganization for vinyl arene derivatives allows for the unprecedented full reversal of selectivity from the typical α-aldehyde to the otherwise unfavored β-aldehyde product (Chapters 5 and 6). In Chapter 5, we focus on the reactivity of 2-vinylarencarboxylic acids, the hydroformylation products of which represent a valuable class of synthetic important intermediates for the fine-chemical industry. Therefore, this catalytic system, which operates under mild conditions for a wide substrate scope, opens up new pathways to current industrially relevant synthetic schemes, which we further demonstrate with several examples. In Chapter 6 we report the full account of this study (including the initial results presented in Chapter 5). We extend the approach to related classes of substrates and we provide mechanistic insight using detailed experimental and computational means. This study reveals unusual kinetic effects for these reactions. This shows that a large number of factors can be involved in controlling the reactivity of a supramolecular homogenous transition metal catalyst.

Aside from supramolecular substrate preorganization, the recognition site of DIMPhos ligands can also be used to fine-tune catalyst structure, the principles of which are discussed in Section 1.4 of this chapter. In Chapter 7 we show that this is a powerful approach as an achiral catalyst modified with non-covalently bound chiral cofactors gives high enantioselectivities (e.e.’s up to 99%) in the hydrogenation reaction of alkenes. Interestingly, we also observed substrate preorganization via additional hydrogen bonding between the cofactor and the substrate. Remarkably, in a competition experiments with a mixture of cofactors, the catalyst with the best cofactor dominates the reaction. This feature provides a basis for smart screening strategies, which are discussed and presented as well.
1.8 References


Supramolecular control of selectivity in transition metal catalysis


135 http://www.imcatt.nl/

