Asymmetric Catalysis

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Singly Hydrogen Bonded Supramolecular Ligands for Highly Selective Rhodium-Catalyzed Hydrogenation Reactions**

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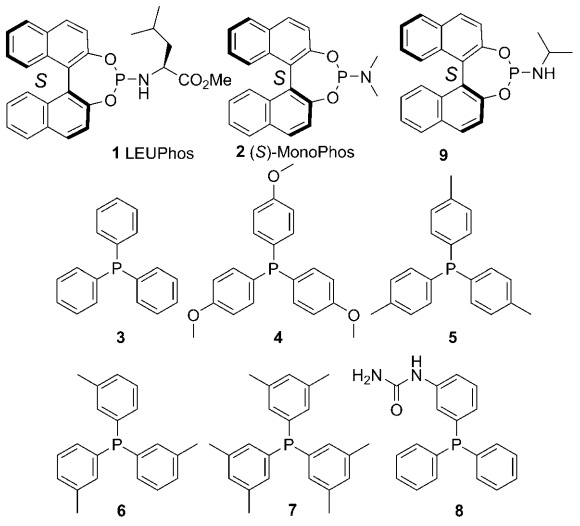
Ligand variation is a key tool for the optimization of transition metal catalysts. Ligand effects are sufficiently well-understood to facilitate ligand design in several reactions. For asymmetric catalysis, however, catalyst optimization relies to a large extent on trial and error, hence the combinatorial screening of libraries of chiral catalysts is a frequently applied strategy.[1] Besides catalyst screening, attempts toward the rational design of chiral catalysts have also been made, which generally lead to strategies for ligand development.[2] The asymmetric hydrogenation reaction is among the classic success stories in this respect since it has resulted in several scientific breakthroughs,[3] as well as the development of commercial processes.[4] Importantly, in the rhodium-catalyzed asymmetric hydrogenation of functionalized substrates, the substrate coordinates in a bidentate fashion to square-planar rhodium, which gives rise to the formation of four substrate–metal coordination modes. The use of C_2-symmetric[5] bidentate ligands reduces the number of coordination modes to only two (*Re*, *Si*), and this has therefore been a successful strategy.[2] Another approach to reduce the number of coordination modes is the design of strongly unsymmetrical ligands.[2] Strong donor/strong π-acceptor bidentate ligands[6] provide sufficient differences in electronic properties to direct the coordination of the chelating substrate. The disadvantage associated with this approach is the often tedious synthesis of unsymmetrical bidentate ligands. Interesting breakthroughs in this respect are the use of mixtures of monodentate ligands as reported by Reetz et al.[7] and Feringa and co-workers,[8] and the supramolecular approach to make heterobidentate ligands.[9] In the mixture approach, the presence of homocomplexes (metal complexes with two identical ligands) can significantly alter the outcomes of the reaction. By optimization of the ratio of the two monodentate ligands, the composition of the catalyst mixture can be tuned and, with this, the selectivity can be optimized. However, a proportion of the precious metal will be kept in an inactive state. Intrigued by this problem, we decided to study the effect of electronic and steric effects as well as hydrogen bonds on the formation and catalytic properties of the heteroligand complex. The rhodium complexes were evaluated in the asymmetric hydrogenation of the methyl 2-hydroxymethylacrylate (**10a**), which afforded methyl 3-hydroxy-2-methylpropionate (**11a**), also known as the Roche ester, which represents an important synthon for the synthesis of the antitumor agents tedanolide and discodermolide.[10] Importantly, the product is liquid at room temperature and consequently a very high enantiopure synthesis is required as further purification by crystallization is not possible. We demonstrate herein that a single hydrogen bond between LEUPhos (**1**) and urea–phosphine **8** is sufficient to form pure supramolecular heterobidentate complexes. We also show that a hydrogen bond between the ligand **1** and the substrate is important to produce an intermediate complex in a hydrogenation reaction from which the product is obtained with 99% *ee*, which is the highest enantioselectivity reported to date.[11]

The new ligand LEUPhos (**1**, Scheme 1) was synthesized by a simple condensation reaction between enantiopure (*S*)-2,2′-dihydroxy-1,1′-binaphthyl ((*S*)-binol) and PCl_3, followed by the addition of L-leucine methyl ester (see the Supporting Information). This chiral ligand was studied in combination with achiral aromatic phosphines **3**–**7** to evaluate the effect of electronic and steric properties of the phosphine ligand on the formation of heterocomplexes under stoichiometric conditions.

We anticipated that hydrogen bonds could be formed between the urea NH group in **8** and the ester functionality of



Scheme 1. Chiral phosphoramidite and achiral aromatic phosphine ligands used in this study.

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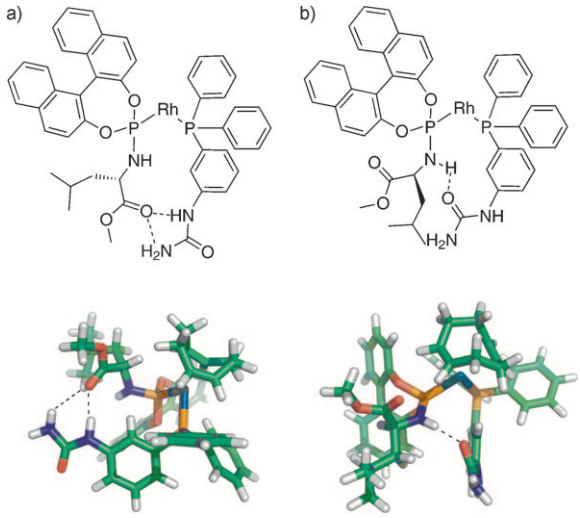


Figure 1. Supramolecular bidentate complexes [Rh(cod)(**1**)(**8**)]BF_4 (cod omitted for clarity) and DFT calculations: a) Hydrogen bonds between the ester and urea units. Relative energy = +7.5 kcal mol^{-1}, $d_{(H\text{-bond})}$ = 1.9 and 2.6 Å. b) Single hydrogen bond between the NH group of the phosphoramidite unit and the urea unit. Relative energy = 0 kcal mol^{-1}, $d_{(H\text{-bond})}$ = 2.0 Å.

1 (Figure 1a). Alternatively, a hydrogen bond may be formed between the NH group of the phosphoramidite **1**, which is known to be a good hydrogen-bond donor[12] and the urea carbonyl group (Figure 1b). The structures (calculated by using DFT, BLYP) show that the single hydrogen-bond interaction ($d_{(H\text{-bond})}$ = 2.0 Å) is more favorable (7.5 kcal mol^{-1}) than the double hydrogen bond between the urea–NH group and the ester carbonyl group. Some other structures have been calculated in which no hydrogen bonds were formed; these were all higher in energy (see the Supporting Information). IR studies on the [Rh(cod)(**1**)(**8**)]BF_4 complex (cod = cyclooctadiene) also confirmed the formation of the hydrogen bond between the PNH unit of **1** and the urea carbonyl group (see below); the effect of this hydrogen bond on the selectivity of heterocomplex formation was next studied.

We first studied the complexes that were formed by mixing [Rh(cod)$_2$]BF_4, **1**, and one of the phosphines **3**–**8** in a 1:1:1 ratio. Interestingly, heterocomplex [Rh(cod)(**1**)(**3**)]BF_4 was formed in 91% yield, according to the ^{31}P NMR spectrum of the mixture in CD_2Cl_2. This value is far above the statistically expected value and the remaining signals in the NMR spectrum correspond to the homocombinations. A similar experiment with the archetypical phosphoramidite ligand (*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]-dinaphthalen-4-yl)dimethylamine ((*S*)-MonoPhos, **2**) showed that only 85% of the heterocomplex [Rh(cod)(**2**)(**3**)]BF_4 was formed. By varying the electronic properties of the aromatic phosphines, the formation of the heterocomplex occurred in up to 97% yield for [Rh(cod)(**1**)(**5**)]BF_4 (Table 1, entries 5 and 6). This result is interesting in itself as it provides a simple tool to make relatively pure heterocomplexes without using an excess of one of the ligands. Small changes in the size of the aromatic phosphine ligands have, on the other hand, a dramatic effect on heterocomplex formation, as is evident from experiments with **6** and **7** (Table 1, ^{31}P NMR spectra are shown in the Supporting Information). Importantly, the complex that forms a hydrogen bond between the ligands, [Rh(cod)(**1**)(**8**)BF_4], is the only complex that was formed in more than 99% purity (see the Supporting Information). Consistent with this observation, the combination of ligands **8** and **2** did not lead to pure heterocomplex formation, but a mixture of different species which are difficult to assign.

Table 1: Rhodium-catalyzed asymmetric hydrogenation of methyl 2-hydroxymethylacrylate (**10a**).[a]

Entry	L	L′	*ee* [%]	*R*, *S*	Effect	Heterocomplex [%][b]
1	**1**	**1**	31	*S*	–	–
2	**2**	**2**	13	*S*	–	–
3	**1**	**3**	94 (94)[c]	*R*	electronic	91
4	**2**	**3**	34	*S*	electronic	85
5	**1**	**4**	94	*R*	electronic	94
6	**1**	**5**	94	*R*	electronic	97
7	**1**	**6**	94	*R*	steric	86
8	**1**	**7**	95	*R*	steric	70
9	**1**	**8**	>99	*R*	H bond	>99

[a] Ratio L/L′/[Rh(cod)$_2$]BF_4/substrate = 1.1:1:1:100; solvent: CH_2Cl_2. Reaction performed at 10 bar H_2 pressure at 298 K for 16 h. Full conversions were obtained in all cases. [b] The amount of heterocomplex present in solution was determined by integration of the phosphine signals in the ^{31}P NMR spectrum (20 mM in CD_2Cl_2, 298 K). [c] Determined in the presence of phenylurea (1 equiv with respect to L′).

We next studied the performance of these complexes in the asymmetric hydrogenation of methyl 2-hydroxymethylacrylate **10a**. Ligand **2** was used for comparison with **1**. Under mild conditions (catalyst (1 mol%), H_2 (10 bar), 298 K, 16 h), full conversion was obtained in all experiments. Both homocomplexes [Rh(cod)(**1**)$_2$]BF_4 and [Rh(cod)(**2**)$_2$]BF_4 gave low selectivities of 31% and 13%, respectively (Table 1 entries 1 and 2). An excellent enantioselectivity (94% *ee*) was obtained with **1** in combination with PPh_3 (**3**; Table 1 entry 3) while **2** with PPh_3 afforded only a moderate *ee* values of 34% (Table 1 entry 4). Contrary to our expectations, the amount of heterocomplex present in solution hardly affected the enantiopurity of the product that is formed; products were obtained in 94-95% *ee* in all cases where this mixed ligand approach was used with **1** (Table 1, entries 5–8). This result suggests that the heterocomplexes are much more active than the unselective homocomplexes. Although the formation of heterocomplexes can be dramatically enhanced (50% for a statistical mixture, 97% for the combination of ligands **1** and **5**) by fine-tuning the electronic and steric properties of a series of ligands, it does not translate to higher selectivity in the reaction studied here. In contrast to these experiments, the supramolecular complex [Rh(cod)(**1**)(**8**)]BF_4 did convert the substrate with the highest selectivity reported to date (Table 1 entry 9).[11] In a control experiment in which phenylurea was used as an additive for the complex [Rh(cod)(**1**)(**3**)]BF_4, the selectivity did not change (Table 1 entry 3), which indicates that the urea group of the ligand **8** plays a crucial role in the selectivity of the reaction. Since it is unlikely that the purity of the complex

is the cause of these observations, we studied the complex in more detail.

We first calculated several structures of complex [Rh(**1**)(**8**)]BF_4–(substrate), which is one of the important intermediates of the catalytic cycle, by using DFT (BLYP). The minimum-energy structure of the catalyst shows that 1) the urea–carbonyl hydrogen bond is still present ($d_{H\text{-}bond}$ = 2.0 Å), 2) there is a hydrogen bond between the alcohol of the substrate and the carbonyl unit of the ester group of **1** ($d_{H\text{-}bond}$=2.1 Å, Figure 2). These calculations suggest that the high *ee* value obtained by the application of [Rh(cod)(**1**)(**8**)]BF_4 is caused by the substrate orientation from

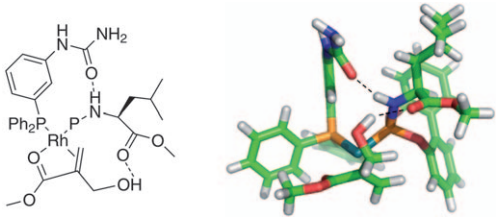


Figure 2. Substrate orientation through hydrogen bonding between the hydroxy group of the substrate and the ester function of the phosphoramidite unit (binol backbone omitted for clarity).

a hydrogen bond between the ligand and the substrate, an effect similar to that observed for other selective transformations.[13,14]

We expected that, if this substrate-orientation effect were to play a role in the hydrogenation reaction, the use of ligands that would be unable to form this hydrogen bond would result in lower *ee* values. For this reason, ligand **9**, which has a PNH unit similar to **1** that can form a hydrogen bond with **8**, but lacks the ester moiety of **1**, was prepared. As observed for [Rh(cod)(**1**)(**8**)]BF_4, the complex [Rh(cod)(**9**)(**8**)]BF_4 was formed in more than 99% purity (calculated from the ^{31}P NMR spectrum) by using stoichiometric amounts of the ligands. IR spectroscopy showed that the vibration of the carbonyl group of the ester moiety of **1** does not change in the complex compared to the free ligand (1737 cm^{-1}). The IR band of the carbonyl group of the urea moiety in **8** is significantly shifted to lower wavenumbers (from 1703 cm^{-1} to 1687 cm^{-1}) compared to the free ligand in both complexes, which confirms its participation in hydrogen bonding. Importantly, in a mixture with **2**, the carbonyl group of **8** is found at the original position (1700 cm^{-1}). These experiments also show that ligand **9** with **8** gives rise to pure heterocomplex by formation of a single hydrogen bond between the two simple monodentate ligands.

We next evaluated the effect of the hydrogen bond between the substrate and the ester functional group of the ligand, as calculated for the [Rh(**1**)(**8**)]BF_4–(substrate) complex by comparing the properties of the various complexes in the rhodium-catalyzed asymmetric hydrogenation of methyl 2-hydroxymethylacrylate **10a** with [Rh(cod)(**1**)(**8**)]BF_4, [Rh(cod)(**2**)(**8**)]BF_4, and [Rh(cod)(**9**)(**8**)]BF_4. As expected, the MonoPhos-based complex [Rh(cod)(**2**)(**8**)]BF_4 produced the product with low selectivity (38% *ee*, Table 2 entry 2). Although the complex [Rh(cod)(**9**)(**8**)]BF_4 gave a reasonable selectivity (88% *ee*), the selectivity is much lower than the

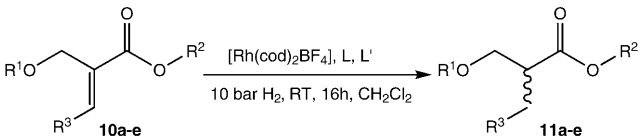
Table 2: Asymmetric hydrogenation of methyl 2-hydroxymethylacrylate **10a** (**10e** for entry 4) catalyzed by supramolecular heterocomplexes.[a]

Entry	L	L′	*ee* [%]	*R*, *S*	Effect	Heterocomplex [%][b]
1	**1**	**8**	>99	*R*	H bond	>99
2	**2**	**8**	38	*R*	electronic	mixture[c]
3	**9**	**8**	88	*R*	H bond	>99
4	**1**	**8**	52[d]	*R*	H bond	>99

[a] Ratio L/L′/[Rh(cod)$_2$$BF_4$]/Substrate = 1.1:1:1:100; solvent: CH_2Cl_2. Reaction performed at 10 bar H_2 pressure at 298 K for 16 h. Full conversions were obtained in all cases. [b] The amount of heterocomplex present in solution was evaluated by integration of the phosphine signals in the ^{31}P NMR spectrum (20 mM in CD_2Cl_2, 298 K). [c] The heterocomplex was observed among a mixture of (dynamic) species. [d] Trimethylsilyl-protected substrate **10e** was used as control.

ee value of 99% obtained with the heterocomplex [Rh(cod)(**1**)(**8**)]BF_4 (Table 2 entries 1 and 3). As a control experiment, we studied the hydrogenation of trimethylsilyl-protected substrate **10e**, which also is unable to form the critical hydrogen bond. As expected, only moderate *ee* values (52% and 48% *ee*; Table 2, entry 4 and the Supporting Information) were obtained with [Rh(cod)(**1**)(**8**)]BF_4 and [Rh(cod)(**9**)(**8**)]BF_4, respectively. These results support our hypothesis that the hydrogen bond between the substrate and the ligand plays a crucial role in the hydrogenation reaction.

We next explored the scope of our new concept by extending our hydrogenation experiments to several derivatives of methyl 2-hydroxymethylacrylate (**10b–d**, Scheme 2). The high enantioselectivity induced by [Rh(cod)(**1**)(**8**)]BF_4 appears to be relatively insensitive to modifications of the ester group. The product was obtained with 99% *ee* for the substrate with the bulky *tert*-butyl ester group (Table 3 entry 1) and 92% *ee* for the substrate with a benzyl moiety (Table 3 entry 2). More interestingly, the scope of the reaction can be extended to the hydrogenation of more hindered



a : R^1=H, R^2=Me, R^3=H
b : R^1=H, R^2=*t*-Bu, R^3=H
c : R^1=H, R^2=Bn, R^3=H
d : R^1=H, R^2=Me, R^3=Ph
e : R^1=Me_3Si, R^2=Me, R^3=H

Scheme 2. Asymmetric hydrogenation of **10a–e** with various (supramolecular) rhodium complexes.

Table 3: Asymmetric hydrogenation of 2-hydroxymethylacrylate esters **10b–d** catalyzed by supramolecular complex [Rh(**1**)(**8**)(cod)]BF_4.

Entry	Substrate	Conversion [%]	*ee* [%]	*R*, *S*
1	**10b**	100	>99	*R*
2	**10c**	100	92	*R*
3	**10d**	83	96	*R*

[a] Ratio L/L′/[Rh(cod)$_2$$BF_4$]/substrate = 1.1:1:1:100; solvent: CH_2Cl_2. Reaction performed at 10 bar H_2 pressure at 298 K for 16 h.

trisubstituted alkenes (**10d**), which occurred in the presence of [Rh(cod)(**1**)(**8**)]BF_4 with the highest selectivity reported to date (96% *ee*, Table 3, entry 3). The more sterically hindered alkenes are generally more difficult to hydrogenate, which is reflected in the slightly lower yield of the product (83% for unoptimized conversion).

In summary, we have introduced LEUPhos (**1**) as a new supramolecular ligand by forming a pure heterocomplex through a single hydrogen bond between the NH group of the phosphoramidite and the urea carbonyl group of a functionalized phosphine. This heterocomplex afforded the highest enantioselectivity (>99% *ee*) reported to date for the hydrogenation of methyl 3-hydroxy-2-methylpropionate (Roche ester) and several of its derivatives, including a trisubstituted alkene. Substrate orientation through a hydrogen bond between the alcohol group of the substrate and the ester moiety of the phosphoramidite is proposed to play a crucial role in achieving the excellent selectivities. This result expands the scope of new supramolecular approaches to the design of catalysts for asymmetric catalytic conversions.

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