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"Cofactor"-Controlled Enantioselective Catalysis

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Supporting Information

ABSTRACT: We report an achiral bisphosphine rhodium complex equipped with a binding site for the recognition of chiral anion guests. Upon binding small chiral guests—*cofactors*—the rhodium complex becomes chiral and can thus be used for asymmetric catalysis. Screening of a library of cofactors revealed that the best cofactors lead to hydrogenation catalysts that form the products with high enantioselectivity (ee's up to 99%). Interestingly, a competition experiment shows that even in a mixture of 12 cofactors high ee is obtained, indicating that the complex based on the best cofactor dominates the catalysis.

Ligand variation is a traditional approach to the optimization of activity and selectivity in transition metal catalysis. In combination with combinatorial and high-throughput screening methods this has been demonstrated to be a powerful approach to finding optimal catalysts for various challenging transformations.[1] Interestingly, in Nature, reactions are controlled in a different manner. Aside from the general, more complex operational mechanisms of enzymes, the use of cofactors—small molecules that influence catalyzed processes—plays a dominant role in controlling chemical transformations carried out by enzymes.[2] Nature has served as the major inspiration in the development of sophisticated chemical processes in the past decades,[3] for example, the mimicry of enzyme-type regulation of catalyst *activity* as reported by Rebek,[4] Shinkai,[5] Krämer,[6] Mirkin,[7] and others.[3a] For instance, Yonn, Mirkin and coworkers[7d] showed that the activity of a polymerization catalyst can be turned on and off *in situ* by the presence/absence of chloride anions as cofactors.

In our lab, we wondered if the *enantioselectivity* displayed by an artificial transition metal catalyst could be regulated by chiral molecules—*cofactors*—that are noncovalently bound to the catalyst complex (Figure 1).[14] This would provide new means of generating chiral complexes for asymmetric catalysis in which the activity and selectivity optimization can be decoupled, offering new tools in this industrially important area of chemistry. To investigate such an approach we use achiral bisphosphine ligand **1**, which binds chiral carboxylate cofactors in the binding pocket near the metal. As the complex without cofactor is achiral, any observed enantio-induction during the reaction originates *exclusively* from the chirality of the cofactor. Here, we demonstrate that this is a powerful method to obtain selective catalysts for asymmetric hydrogenation, as high selectivities (up to 99% ee; enantiomeric excess) are achieved for several substrates. Interestingly, a 'natural selection' experiment showed that the cofactor that induces the highest selectivity dominates the catalysis when applied in a mixture of 12 different cofactors.

For this study we used bisphosphine ligand **1** which contains a diamidodiindolylmethane anion receptor,[8] which strongly binds carboxylate anions ($K_a > 10^5\ M^{-1}$ in CD_2Cl_2).[9] For this binding site a large library of potential chiral guests is available, as the anions of various abundant natural chiral acids can be used.

The cationic rhodium−ligand complex, $[Rh(\mathbf{1})(nbd)]^+$, the precursor to the active hydrogenation catalyst, was easily obtained by mixing a CD_2Cl_2 solution of ligand **1** and $[Rh(ndb)_2BF_4]$. The NMR data of the complex showed that the two P donors are coordinated to the Rh center in a mutual *cis* orientation. This coordination geometry was further supported by the X-ray crystal structure of $[Rh(\mathbf{1})(nbd)BF_4]$ (Figure 2). The crystal structure shows that in the solid state the BF_4^- counteranion is bound in the anion binding site. Studies carried out in solution demonstrate that the BF_4^- bound in the pocket is quantitatively replaced by cofactors with carboxylate functional groups, which have a much higher affinity for the recognition site.

NMR experiments show that upon binding of simple chiral anions such as α-hydroxy acids, α-amino acids and their derivatives in the pocket of free ligand **1**, the P atoms as well as the indole and amide NHs become diastereotopic (see Supporting Information, SI), confirming chirogenesis—chirality transfer through supramolecular interactions.[10] Importantly for catalytic purposes, this chirogenetic effect is also manifested when such chiral cofactors are bound to the rhodium complex $[Rh(\mathbf{1})(nbd)]^+$. In contrast, when achiral analogues of cofactors are bound in the pocket of free ligand **1** or the rhodium complex, the P and N*H* atoms stay identical. Molecular modeling and NOESY experiments show that the cofactor, bound via the anion recognition site, is in close proximity to the metal complex coordinated at the phosphorus donor atoms (see SI).

We next studied the performance of these supramolecular complexes in the asymmetric hydrogenation of methyl 2-acetamidoacrylate (**2**), using a wide variety of chiral acids as cofactors (Table 1, selected examples; for all results see SI). Under mild conditions (1% of catalyst, 10 bar of H_2, 298 K, 16 h), full conversion was obtained in most experiments (Table 1 and SI).[11] The best results were found among the amino acid derivatives. Inspection of the results shows that the selectivity of the reaction is most sensitive to changes on the N-group of the cofactor, whereas variation of the side group (that is by using derivatives of different amino acids, see SI) has a much smaller influence. The highest selectivity was obtained when *tert*-butyl thiourea **18** was

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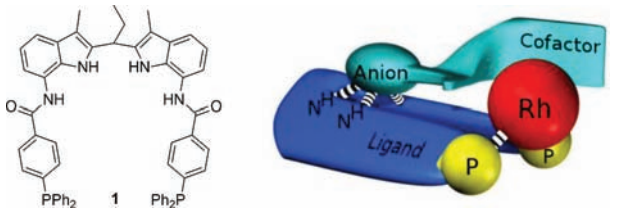


Figure 1. Structure of ligand **1** (left) and the general concept of cofactor controlled enantioselective catalysis (right).

Figure 2. X-ray structure of [Rh(**1**)(nbd)BF_4] of one of two independent complexes found in the solid state (see SI). Hydrogen atoms (except for NHs) and CH_2Cl_2 solvent molecules have been omitted for clarity.

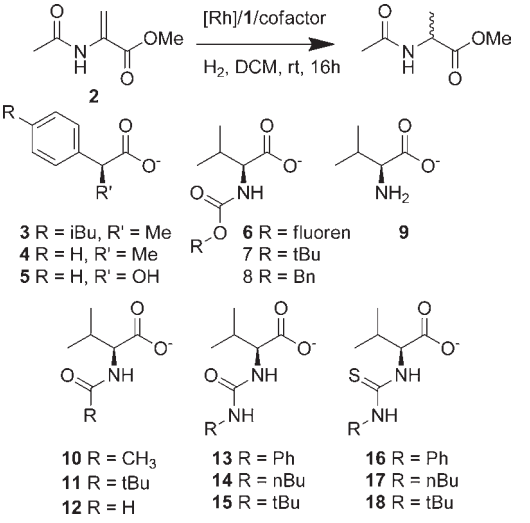
applied as a cofactor, which gave the R product with excellent enantioselectivity, 98% ee!

Control experiments using triphenylphosphine (**19**) as the ligand in the presence of the most effective cofactors (carbamate **6** and thiourea **18**) gave the racemic product, indicating that the cofactor needs the binding site to affect the metal complex (Table 2). In separate control experiments we used a mixture of anion receptor **20**, triphenylphospine (**19**), and the cofactors (**6** and **18**), and also in these reactions the racemic product was formed. Hydrogenation of **2** in the presence of cofactor **6** or **18**, and in the absence of any phosphorus ligand, gave the product again with no selectivity (ee = 0%). These control experiments demonstrate that the binding site must be an integrated part of the ligand, near the metal center.

Next, we wondered how the catalyst system would respond if a mixture of 12 different cofactors was presented to the catalyst, all competing for the same binding site. If the best cofactor (best defined in terms of catalyst selectivity) dominated the reaction, this would form the basis for an iterative deconvolution screening strategy,[12] allowing identification of the optimal catalyst from a wide library in only a few experiments. Interestingly, this competition experiment resulted in the formation of the product with 81% ee, much higher than the linear combination of the single experiments. In a control experiment with a mixture of 12 cofactors that only give low to moderate ee, the ee of the product formed was only 33%. According to the deconvolution strategy we divided the library of 24 cofactors into subgroups of 12, and by following the best set of cofactors and further dividing these into subgroups, we gradually saw the ee increase from 81, through 85 and 88, to 98% ee (Figure 3). Importantly, in only 9 experiments, instead of 24, we identified the best cofactor from the library.

The best cofactor selection can be rationalized by two scenarios: (i) the best cofactor interacts the strongest with the Rh-ligand−substrate complex, and thus this catalytic system is

Table 1. Asymmetric Hydrogenation of 2 Using [Rh(1)(nbd)]$^+$ in Combination with Various Cofactors[a]

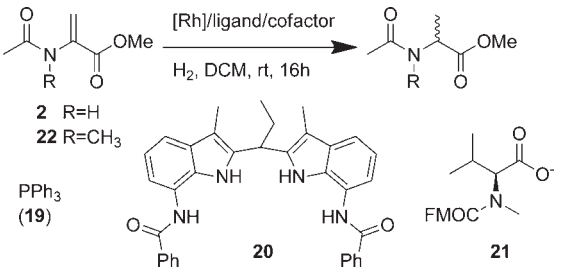


entry	cofactor	% conv.	% ee (config.)
1	**3** R = *i*Bu, R′ = CH_3	100	4 (S)
2	**4** R = H, R′ = CH_3	100	<3 (S)
3	**5** R = H, R′ = OH	100	11 (S)
4	**6** R = fluoren	100	50 (S)
5	**7** R = *t*-Bu	100	47 (S)
6	**8** R = Bz	100	34 (S)
7	**9**	100	0 (−)
8	**10** R = CH_3	100	27 (R)
9	**11** R = *t*-Bu	100	29 (S)
10	**12** R = H	100	0 (−)
11	**13** R = Ph	100	0 (−)
12	**14** R = *n*-Bu	100	0 (−)
13	**15** R = *t*-Bu	100	23 (R)
14	**16** R = Ph	3	61 (R)
15	**17** R = *n*-Bu	47	0 (−)
16	**18** R = *t*-Bu	3	98 (R)
17[b]	**18** R = *t*-Bu	18	99 (R)
18[c]	**18** R = *t*-Bu	100 (93)[d]	98 (R)

[a] Reactions were performed in DCM, Rh/**1**/cofactor/DIPEA/**2** = 1:1.1:12:9:100; *C*(Rh) = 0.001 M, 10 bar of H_2, at RT for 16 h, using [Rh(nbd)$_2$$BF_4$] as metal precursor; DIPEA was used as a base to deprotonate acidic cofactor. Conversion and ee were determined by chiral GC analysis of the reaction mixture. [b] Rh/cofactor/DIPEA = 1:6:2. [c] Rh/cofactor/DIPEA = 1:3:2. [d] Isolated yield.

the most abundant in the solution, consequently outperforming other cofactors; or (ii) the best cofactor based catalyst is the most active, thus outperforming other catalytic complexes. To distinguish between these scenarios, we performed another experiment in which we applied a mixture of all 12 cofactor−Rh(**1**) complexes, so the cofactors did not compete but could all bind, such that all 12 catalytic complexes are present in solution in the same amount. In this experiment we obtained very low chiral induction (3% (S)), which is very close to the linear combination of the results of 12 separate experiments (4% ee (R)). This rules out the second scenario, suggesting that in the competition

Table 2. Asymmetric Hydrogenation of 2 and 22: Control Experiments[a]



entry	substrate	ligand	cofactor	% conv.	% ee (config)
1	**2**	**19**	**6**	64	0 (–)
2	**2**	**19**	**18**	<1	0[b] (–)
3	**2**	**19/20**	**6**	11	0 (–)
4	**2**	**19/20**	**18**	<1	0[b] (–)
5	**2**	–	**6**	100	0 (–)
6	**2**	–	**18**	4	0 (–)
7	**2**	**1**	**23**	100	37 (S)
8	**22**	**1**	**6**	100	0 (–)
9	**22**	**1**	**18**	5	<5 (R)

[a] Reactions were performed in DCM, Rh/cofactor/DIPEA/substrate = 1:1.1:12:9:100; ligand/Rh for **1** and for **19**/**20**, 1.1 and 6/6, respectively; *C*(Rh) = 0.001 M, 10 bar of H_2, at RT for 16 h, using $[Rh(nbd)_2BF_4]$ as metal precursor; DIPEA was used as a base to deprotonate acidic cofactor. Conversion and ee were determined by chiral GC analysis of the reaction mixture. [b] Higher conversion and no selectivity were observed when **18**/DIPEA/Rh = 3:2:1 ratio was used.

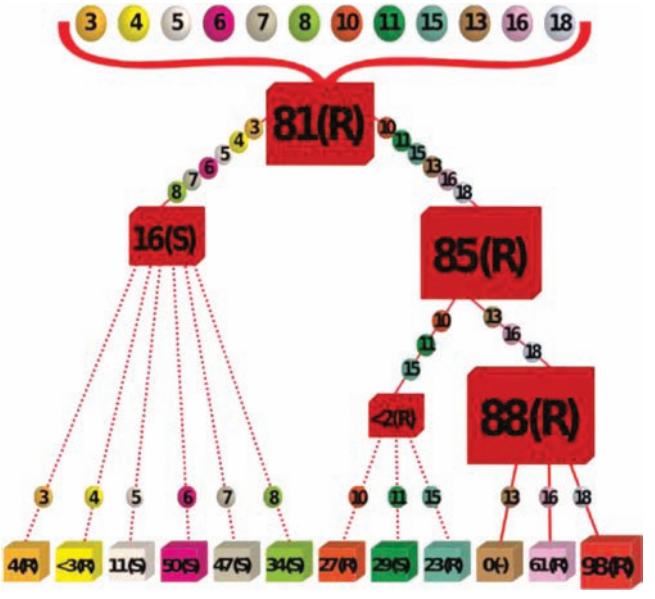


Figure 3. A stepwise deconvolution of one of two mixtures of 12 different cofactors and $[Rh(\mathbf{1})(nbd)BF_4]$ for the hydrogenation of **2**; the second mixture of 12 cofactors gave moderate ee (33% (S)); for details see Supporting Information.

experiment the strongest binder dominates the reaction and also gives the most selective catalyst.

To further investigate how cofactor **18** affects catalysis we performed some DFT calculations (BP86/SV(P)) on the catalyst–substrate–cofactor **18** complex (Figure 4). The four possible coordination modes of the substrate to the rhodium center are all close in energy (only 2.4 kcal/mol energy difference range). The minimum-energy structure leads to the isomer R of the product, which is found experimentally to be the major one. Interestingly, in this structure (as well as in one of the other structures) we found a hydrogen bond between the amide NH of the substrate and the thiocarbonyl group of the cofactor. To check if these hydrogen bonds are important in achieving high selectivity,[13] we performed some control experiments, in which we used components that cannot form these specific cofactor–substrate hydrogen bonds, assuming that in those cases the ee would be significantly lower (Table 2).[13] When we used (*S*)-*N*-methyl-*N*-FMOC-valine (**21**), which cannot donate an alternative hydrogen bond to the substrate, we observed only a slight drop of enantioselectivity, from 50% to 37% ee (using (*S*)-(*N*)-FMOC-valine (**6**) as a reference). However, when methyl *N*-methyl-2-acetamidoacrylate (**22**) was used as a substrate which cannot be a hydrogen bond donor to a cofactor, the selectivity dropped to nearly 0% ee with both (*S*)-FMOC-valine (**6**) and (*S*)-*N*′-*tert*-butyl-urea-*N*-valine (**18**). These data strongly suggest that the formation of a hydrogen bond between the NH of the substrate and the (thio)carbonyl functionality of the cofactors plays a crucial role in the selectivity of the reaction.

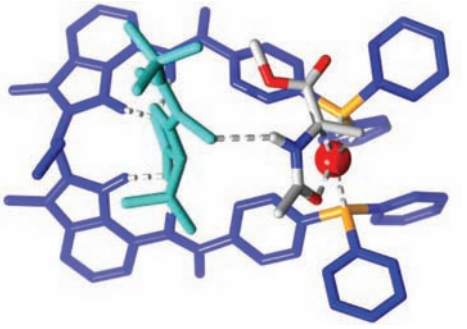


Figure 4. Molecular modeling of structure of Rh(**1**)(**2**)(**18**); ligand dark blue, cofactor light blue.

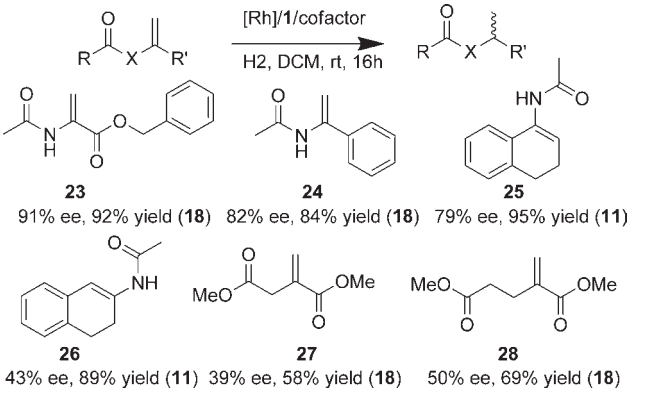


Figure 5. Summary of asymmetric hydrogenation of other substrates (**23**–**28**) using $[Rh(\mathbf{1})(nbd)]^+$ in combination with various cofactors (**3**–**18**); the best cofactors are noted between parentheses; for details see Supporting Information.

Finally, to investigate the scope of this cofactor-based approach, we evaluated several different substrates using the rhodium complex of ligand **1** with cofactors **3**–**18** (Figure 5

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and SI). For most of the enamides studied (**23**−**25**) we found good to high enantioselectivities, while simple alkenes (**27**−**28**) were hydrogenated with moderate ee's. These results are in agreement with the observation that the hydrogen bond formed between the NH of the substrate and the carbonyl group of the cofactor plays an important role in the enantioselectivity determining step of the hydrogenation reaction.

In conclusion, we demonstrate in this paper that asymmetric hydrogenation can be efficiently achieved by using an achiral ligand in combination with a chiral cofactor.[14] The current system contains achiral bisphosphine ligand **1**, coordinated to a rhodium center, which is embedded within an anion binding pocket. The pocket strongly binds cofactors—anions of chiral carboxylic acids—allowing for quick, synthesis-free modulation of the enantioselectivity of the catalyst. This strategy afforded good to excellent enantioselectivities (ee up to 99%) for the hydrogenation of several alkenes, demonstrating its potential. Interestingly, even when using a mixture of 12 cofactors the selectivity was high, which suggests that catalysis is dominated by the best cofactor, allowing a deconvolution strategy for rapid identification of the best cofactor. Thus, catalyst optimization by noncovalent binding of simple cofactors expands the number of supramolecular approaches applicable to the search for better catalysts for challenging chemical transformations. Current efforts address details of the mechanism the system follows, in order to gain better understanding and for the rational extension of the system to other challenging catalytic conversions.

■ ASSOCIATED CONTENT

Supporting Information. Details concerning catalytic studies, binding studies, X-ray structure elucidation, DFT studies, experimental procedures, and spectral data for new compounds, including images of ^{1}H, ^{19}F, ^{13}C, and NOESY NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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