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Enantioselective Supramolecular Catalysis Induced by Remote Chiral Diols

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Supporting Information

ABSTRACT: A new method of creating libraries of chiral diphosphines is presented. Supramolecular coordination compounds based on Ti, Rh, achiral ditopic ligands, and chiral diols were synthesized by in situ mixing and used as catalysts in the asymmetric hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate, giving ee's of up to 92%. The ditopic ligands contain a Schiff base that coordinates to the assembly metal Ti and a phosphine as a ligand for Rh. Chirality is introduced by coordination of the chiral diols to Ti. The controlling chiral center and the substrate are separated by as much as 13 Å.

Supramolecular catalysis, the happy marriage between supramolecular chemistry and homogeneous catalysis, has taken a lofty flight in the past decade.[1−3] Here we focus on the supramolecular construction of catalysts.[4] Supramolecular assembly of ligand systems has the advantage through the synthesis of a limited number of small building blocks, large libraries of metal−ligand complexes and thus catalysts can be obtained.[1] Such catalyst libraries are needed for catalyst optimization, the development of accidentally encountered leads, and the discovery of new reactions. Rapid screening studies using such ligand libraries for known reactions have led to unprecedented enantiomeric excesses for substrates that hitherto failed to give selective conversions.[5] Screening of ligand libraries is especially important for the discovery of enantioselective catalysts, as in this area the predictive power is limited. Sophisticated methods for reducing the number of experiments in screening studies have been introduced.[6] Structural diversity, a modular synthesis, and the possibility of fine-tuning are key requirements. Reetz and coworkers developed and applied the idea of using monodentate ligands to form bisligand complexes as enantio-, diastereo-, and regioselective catalysts.[7] In such mixtures of two ligands, complexes of the formula ML_2 containing homocombinations and heterocombinations may form, and sometimes the formation of latter was preferred. Supramolecular tools for inducing the formation of heterocombinations only were introduced by Breit, Takacs, and Reek and van Leeuwen.[1] In both approaches, the chiral elements are embedded in the monodentate fragment, all of which must be synthesized one by one, the chiral source most often being BINOL, TADDOL, or amino acids. In view of the extreme versatility of BINOL-derived phosphorus ligands in rhodium-catalyzed hydrogenation,[8] it is not surprising that supramolecular systems based on this ligand have also led to highly enantioselective hydrogenation reactions. Many TADDOL-[9] and BINOL-derived[10] supramolecular ligand libraries show high structural diversity, as judged from the enantioselectivities reported. In all of these systems, the chiral inducer is located directly on the catalytic metal and connected via covalent bonds to the supramolecular devices, which have to be synthesized one by one. The use of a second metal in such systems that enhances the ee's has been reported.[10c] Chiral additives have been used to obtain or improve ee's drastically, but in those cases, the chiral additives also coordinate directly to the catalytic metal and the reacting atoms are in close proximity of the chiral center.[10d−f] Introduction of the chiral element in a supramolecular fashion would reduce the synthetic effort drastically. There are few examples of synthetic, noncovalent supramolecular systems that induce enantioselectivity in catalysis,[11] but in these cage systems, the metals do not participate in the catalysis. For metal-catalyzed reactions, to date only systems based on enzymes,[12] DNA,[13] and chiral counterions[14] have used a chiral source that is not covalently linked to the catalyst. Here we present a new approach in which the chiral inducer is a simple chiral diol that coordinates to an assembly metal, together with two achiral ditopic ligands that form the bidentate phosphine ligand holding the catalytic metal (Figure 1).

The new systems introduced here contain a remote chiral center, and the chiral information is transferred to the catalytically active center via a large number of atoms. A covalent example of remote chiral induction in catalytic hydrogenation was reported by RajanBabu and co-workers, in which a remote chiral dendron induced enantioselectivity in a tropos diphosphine over 14 atom−atom bonds.[15]

The Schiff bases **1**−**8**[16] and a wide variety of easily accessible chiral diols were reacted with $Ti(iPrO)_4$ to give a library of chiral diphosphines. It turned out that rather bulky diols were needed with this set of ditopic ligands [see the Supporting Information (SI)], and therefore, here we present only the more bulky chiral diols **9**−**18** (Chart 1). For the in situ-prepared assemblies, isopropanol was left in the reaction mixture, as it did not interfere with the catalysis.

Six isomers (A−F) can form, including Δ and Λ diastereoisomers (Figure 2). ^{1}H and ^{31}P NMR spectroscopy showed that the order of addition of diols or ditopic ligands was not important. In some instances only one compound was observed, but mostly mixtures of isomers were obtained that showed C_1 and C_2 symmetry in the ^{1}H and ^{31}P NMR spectra (not all diols were studied; see the SI). Diols **10** and **11** showed a strong preference for only one species of C_2 symmetry, as judged from the imine ^{1}H and ^{31}P chemical shifts. Fujita[17a] and Johnson[17b] also observed the formation

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of different isomers for the complexes $(N{-}O)_2MCl_2$ (N−O = Schiff base; M = Ti, Zr), but A/B was often the preferred one. Comparison of the ^{1}H NMR spectra of the ligands based on **10** and **11** with those of Fujita suggests that A/B is the most likely structure. In the five-coordinate cationic species $(N{-}O)_2MCl^+$, the exchange of Δ and Λ isomers is extremely fast,[18] but in the present hexacoordinate complexes this is not to be expected, certainly not in the complexes containing bulky diols. After Rh coordination by addition of $Rh(nbd)_2BF_4$ (nbd = norbornadiene) to the diphosphine, the systems are presumably rather rigid.

Isomers E and F (Figure 2) are not capable of forming chelate complexes, and most likely, if they were present, they converted to structures A−D over time. The chelate ring formed by phosphine coordination (12- or 14-membered rings) can introduce another element of asymmetry, depending on the orientation of the meta-substituted aryl groups.[19] Diols **10** and **11** gave one isomer and only traces of other isomers. For other diols studied, mixtures of diastereoisomers were formed, although fewer isomers were observed than might have been expected. Most of the complexes showed C_1 symmetry.

The heterobimetallic complex $[(nbd)Rh\{(\mathbf{4,4'})Ti(\mathbf{11})\}]BF_4$ was isolated as a pure compound in 92% yield from the reaction mixture by precipitation with hexane. Two imine and methoxy protons with different chemical shifts ($\delta_{C=NH}$ = 8.44 and 8.03 ppm; δ_{OMe} = 4.05 and 4.01 Hz) and equal intensities suggested it to be a single diastereoisomer with C_1 symmetry (Figure 3). Furthermore, a total of eight signals with equal intensities corresponding to a nonsymmetric coordinated norbornadiene and two different methyl groups of the coordinated chiral diol were observed at significantly different chemical shifts

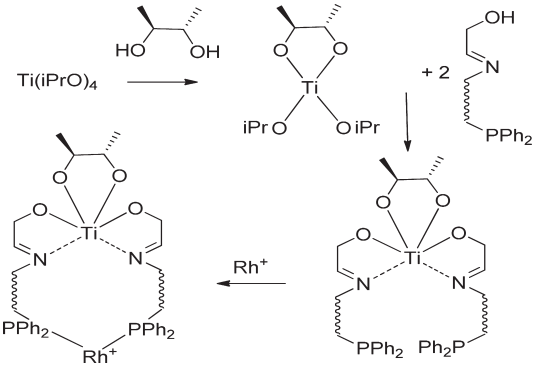

Figure 1. Schematic representation of the supramolecular strategy for forming chiral bidentate ligands via self-assembly.

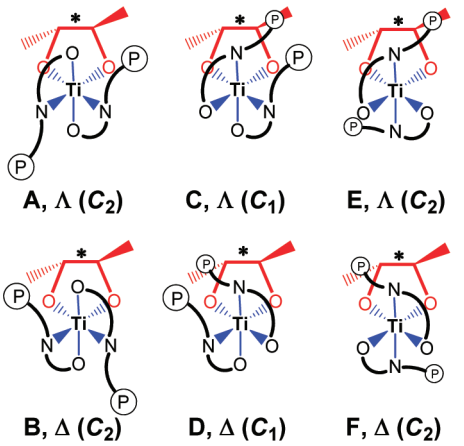

Figure 2. Conformational isomers expected for a complex of type $(P{-}N,O)_2Ti(O,O^*)$.

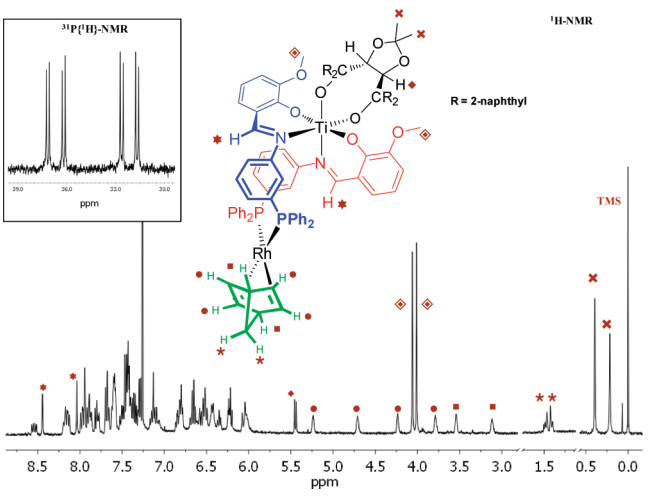

Figure 3. ^{1}H and ^{31}P{^{1}H} NMR spectra of $[(nbd)Rh\{(\mathbf{4,4'})Ti(\mathbf{11})\}]BF_4$ in $CDCl_3$.

Chart 1. Ditopic Ligands 1−8 and Chiral Modifiers 9−18 Used Here

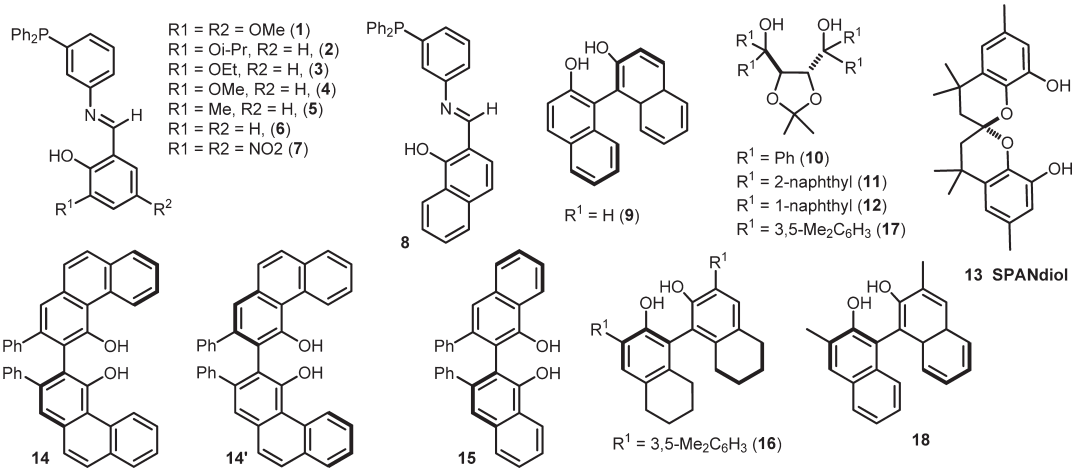

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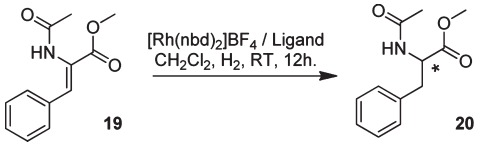
Table 1. Screening of Diols and Ditopic Ligands with Substrate 19[a]



Ditopic Ligand	1	2	3	4	5	6	8	7
Diol								
9	−55.7	−11.6	−28.5	−53.3	−7.0	−3.2	−3.2	2.4
10	83.6	61.5	86.1	86.9, 92.0[b]	33.4	18.4	45.6	9.1
11	−78.1	−65.1	−82.8	−80.5	−35.3	−11.4	−43.8	49.5
12	41.4	17.0	13.4	15.5	−17.1	−11.0	−34.8	2.0
13	−38.7	−5.8	−33.2	−22.2	−3.8	0.0	1.9	0.0
14′	−47.8	−2.6	40.6[c]	−56.4, 50.1[c]	−24.2	−26.6	−31.6	−11.8[c]
15	83.6	50.8	80.7	80.5	34.6	20.6	24.6	18
16	71.0	23.0	62.4	63.0	13.6	−22.8	14.0	−21.8
17	71.5	62.9	69.2	72.7	48.8	21.3	48.2	−3.6
18	70.6	44.0	67.0	71.1	19.4	32.6	14.6	3.6

ee (%)	
90-100	
80-90	
70-80	
60-70	
50-60	
40-50	
30-40	
20-30	
10-20	
0-10	

[a] Conditions: solvent, 0.6 mL of CH_2Cl_2; $[Rh(nbd)_2BF_4]$ = 3.1 mM; $[Ti(OiPr)_4]$ = 3.8 mM; [**19**] = 338 mM; Ti/diol/ditopic ligand/Rh = 1:1.1:1.6:0.8; P_{H_2} = 3 bar; room temperature; reaction time, 3 h; conversion, 100%. Minus signs denote formation of the *S* product. [b] Substrate/Rh = 1000. [c] Using (*R*)-VAPOL (**14**).

(δ_{CH_3}= 0.39 and 0.22 ppm). MALDI-MS analysis provided evidence for the proposed composition.

Notably, the chirality introduced at the top of the molecule by the diol is transduced all the way down to the bridgehead protons of norbornadiene, which appear as an AB doublet in the spectrum. These bridgehead hydrogen atoms are separated by 13 bonds from the chiral inducer atom, or more than 14 Å according to MM2 models!

The supramolecular ligand library was explored in the rhodium-catalyzed asymmetric hydrogenation of prochiral alkenes. The supramolecular catalysts were prepared by in situ mixing in a mini-multireactor inside a glovebox. Initially a stoichiometric ratio of Ti/ditopic ligand/diol/Rh = 1:2:1:1 (see the SI) was pursued, but it was found that in many cases a ratio of 1:1.6:1.1:0.8 yielded better results for the ee, probably because deviations of the stoichiometry occurred on such a small scale of preparation and slight excesses in the order shown were beneficial. After closing, the autoclave was transported to the high pressure line. In preliminary control experiments, we studied Rh/**11** in the absence of titanium and in combinations with either triphenylphosphine or **4**; in the absence of one of the supramolecular components, no enantioselectivity was found (see the SI). Table 1 shows the results of the screening of the supramolecular catalysts based on **1**−**8** and selected diols **9**−**18** in the hydrogenation of **19**.

All of the reactions showed full conversion after 3 h, although the reaction times were not optimized. When the substrate/Rh ratio was raised to 1000 for ligand combination **4**/**10**, also full conversion was reached in 12 h, and interestingly, the ee usually went up. The H_2 pressure (3−10 bar) had only a small effect on the ee values, but since they were slightly higher at 3 bar, those results are used here. The best diols are the TADDOL and BINOL ones, while phosphine-Schiff base **4** stands out as the best ditopic ligand so far. The ortho substituent on ligand **6** (see **1**−**5**) turned out to have a surprisingly strong influence on the outcome. Fujita and co-workers also found a major influence of the ortho substituent on the FI polymerization catalysts.[20] VAPOLs **14** (*R*) and **14′** (*S*) have opposite absolute configurations, and indeed, the resulting products also showed *S* and *R* configurations. The same was true for **10** (4*R*,5*R*) and **11** (4*S*,5*S*), which gave *R* and *S* products, respectively. Increasing the steric bulk on the TADDOL somewhat further with 1-naphthyl groups (**12**) caused a deterioration in the results. In general, more electron-rich ditopic ligands showed higher ee's, the results being very similar for **1**, **3**, and **4**. The electronic properties probably contribute to the formation of a more stable single isomer, as was found for **4**/**10**. A slightly more bulky *i*-Pr substituent on the ether oxygen diminishes the enantioselectivity. The smaller and electron-poor ligands **5**, **6**, and **8** gave low ee's but performed best with the bulky TADDOL diols. $(3,5\text{-}Me_2C_6H_3)_4$-TADDOL (**17**), which was too bulky for ditopic ligands **1**−**4**, gave the best result with the naphthalene-based ditopic ligand **8**. Dinitro-substituted ligand **7** gave 50% ee in combination with **11** but yielded a product with

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opposite configuration; the complex formed in this case may be different from the other ones. Since bulky, wide-bite-angle diols seemed the best choice, SPANdiol (**13**) was tested, and here also ditopic ligands **1**, **3**, and **4** afforded a lead. Hydrogenation of the aliphatic substrates itaconic acid dimethyl ester and methyl 2-acetamidoacrylate using the same catalytic conditions as for **19** showed the same trends (see the SI); all of the selectivities were lower, but they were not optimized for these substrates.

In conclusion, we have presented the first supramolecular enantioselective catalyst in which a low-molecular-weight, commercially available chiral modifier is neither connected covalently to the ligand nor directly attached to the catalytic center. Instead, the chiral diolate coordinates to an assembly metal, Ti, which holds together two ditopic ligands through their Schiff bases. In addition, the ditopic ligands carry phosphine functionalities that coordinate to the catalytic center. We have shown that bidentate, chiral diphosphines can be made by in situ mixing of three ingredients, namely, the Ti alkoxide precursor, the diol, and the ditopic ligand. In the present example, we made over 100 new bidentate chiral diphosphines in this way; such rapid access to a library of chiral bidentate ligands is unprecedented. Application of this library of diphosphines in Rh-catalyzed asymmetric hydrogenation gave ee's of up to 92%. Unexpectedly, the ortho substituents in the phenoxo group appeared to play an important role. The chiral information is transferred over 10 bonds or more, and the controlling chiral center added and the new one created are ~13 Å apart. The method presented here reduces the synthetic effort for the generation of libraries of new chiral bidentate ligands, and it may well be of more general use in other areas. It not only aids the discovery of enantioselective catalysts for established reactions but can also serve as a means for the discovery of new reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Syntheses of the ligands and diols, their analytical data, and additional catalysis results and spectra of bimetallic complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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