Heterogeneous Catalysis

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Engineering a Polymeric Chiral Catalyst by Using Hydrogen Bonding and Coordination Interactions**

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Asymmetric catalysis of organic reactions to provide optically active products is of central importance to modern synthetic chemistry and the pharmaceutical industry.[1] Homogeneous

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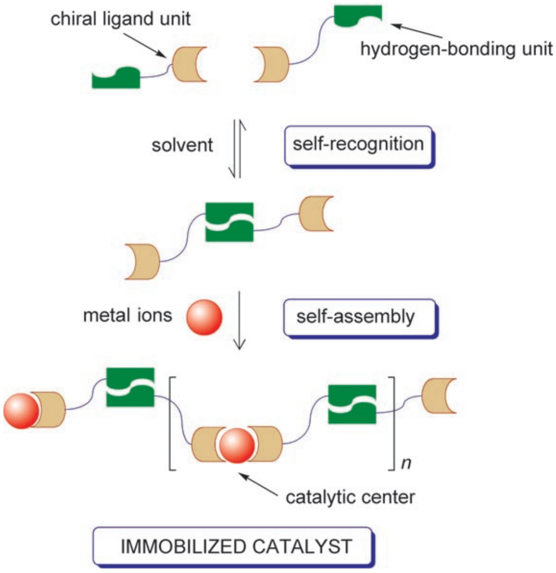
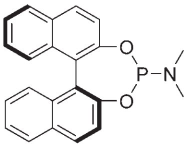
asymmetric catalysis offers many inherent advantages, such as high selectivity and catalytic activity, mild reaction conditions, some generality, and predictable manipulation. However, the difficulties associated with recovery and reuse of expensive chiral catalysts and the product contamination caused by metal leaching significantly limit practical applications.[2] The immobilization of chiral catalysts is considered as one of the most promising solutions to such problems.[2,3] In particular, the use of homochiral metal-organic polymers as heterogeneous catalysts for asymmetric reactions has provided a new strategy for chiral catalyst immobilization.[4,5] In such systems, chiral bridging ligands provide an enantio-discriminating environment, and the metal ions act as the catalytically active centers. Therefore, the design and synthesis of multitopic chiral ligands with diverse geometrical features is a central issue in the generation of homochiral metal-organic polymers for heterogeneous asymmetric catalysis. The common practice for this purpose is the use of covalent linkers to incorporate the coordinating chiral subunits into the ligand.[4,5] However, the preparation of covalent multitopic ligands is somewhat tedious, thus limiting their widespread applicability.

The use of noncovalent self-assembly, frequently hydrogen bonding (HB) and metal coordination, as a practical alternative to covalent-based chemistry has been recognized as one of the most important tools in the design and fabrication of complex molecules and functional systems.[6,7] Despite its tremendous potential, however, such systems have not been applied as heterogeneous catalysts for asymmetric reactions. We envisaged the use of chiral ligands possessing donor–acceptor moieties for the construction of multi-topic ligands through complementary or self-complementary hydrogen-bonding recognition motifs. Furthermore, in combination with current self-supporting strategies,[8] such assemblies are expected to spontaneously aggregate to yield immobilized catalytic systems (Scheme 1). Herein, we report the generation of a heterogeneous asymmetric catalyst by orthogonal self-assembly through hydrogen bonding and ligand-to-metal coordination interactions. The heterogeneous catalyst generated by this approach demonstrates excellent asymmetric induction in the catalytic synthesis of optically active α-amino acid and 1-phenylethylamine derivatives, without leaching of toxic metal ions into the product, and is easily recyclable.

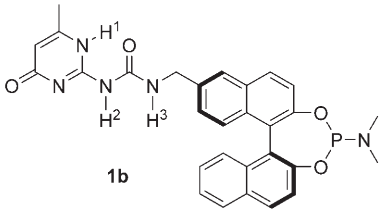


Scheme 1. Generation of an immobilized catalyst through noncovalent interactions.

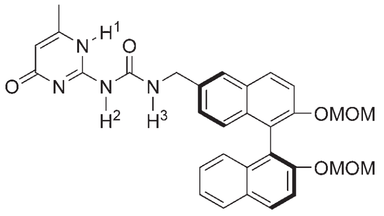
Owing to its high association constant ($K_a = 6 \times 10^7\,\text{M}^{-1}$ in $CHCl_3$), ureido-4[1*H*]-ureidopyrimidone (UP) is among the most commonly used self-complementary hydrogen-bonding units for the construction of supramolecular systems.[9] Feringa's MonoPhos ligand **1a** is well-established in asymmetric catalysis; its rhodium(I) complex has been shown to catalyze hydrogenation of a number of substrates with excellent selectivity and reactivity.[10] To exemplify the above-mentioned strategy, UP and **1a** were integrated into one molecule, **1b**, which, in principle, can form a ditopic ligand through self-complementary hydrogen-bonding interactions in a suitable solvent. The ligand **1b** was prepared in good yields by the reaction of hexamethylphosphorus triamide (HMPT) with a UP-containing 1,1′-bi-2-naphthol (binol) derivative (see the Supporting Information). The ^{1}H NMR spectra of **1b** and its analogue **1c** (without the chelating phosphorus moiety) show downfield resonances for the NH protons (between $\delta = 10.5$ and 13.0 ppm) indicative of strong quadruple hydrogen bonding (Figures 1a and 1b).



1a



1b



1c

In order to clarify the "orthogonal" nature of the hydrogen bonding and metal-to-ligand coordination interactions in the course of supramolecular polymer formation,[7d–f] compound **1c** was mixed with $[Rh(cod)_2]BF_4$ (Figure 1c). Upon mixing, the ^{1}H NMR spectrum showed substantial changes in the NH region (Figures 1b and 1c), thus indicating disruption of the hydrogen bonds. However, when two equivalents of **1a** were added to the above system, the hydrogen-bonding pattern was recovered completely (Figure 1d). This implies that coordination of the rhodium(I) moieties by a phosphorus ligand (**1a**) is strong enough to overcome any disruption to the hydrogen bonds, and that the hydrogen-bonding units quickly reassemble. Thus, for combinations of **1b** with $[Rh(cod)_2]BF_4$, the formation of supramolecular polymers

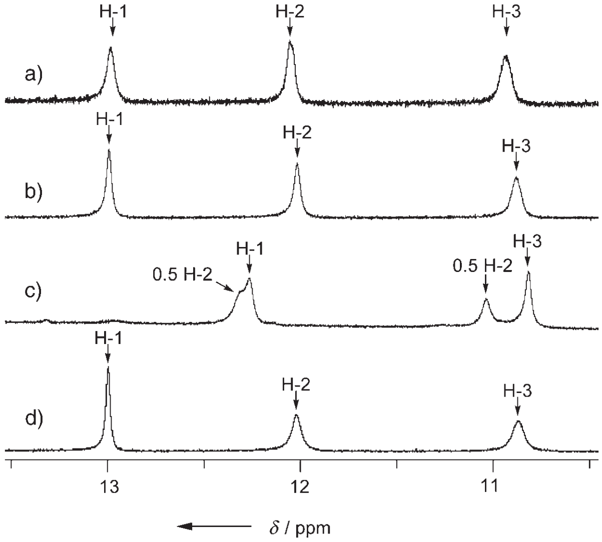
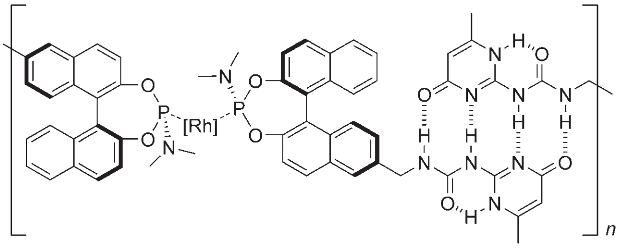


Figure 1. Sections of the ^{1}H NMR spectra (300 MHz) of a) **1b**, b) **1c**, c) **1c**/1 equiv [Rh(cod)$_2$]BF$_4$, and d) **1c**/1 equiv [Rh(cod)$_2$]BF$_4$/2 equiv **1a** in CDCl$_3$ (20 mM) at room temperature.

by "orthogonal" noncovalent interactions (hydrogen bonding and metal-to-ligand coordination) is guaranteed.

On the basis of the ^{1}H NMR results mentioned above, [Rh(cod)$_2$]BF$_4$ was added to a CH$_2$Cl$_2$ solution of **1b**, which resulted in the immediate precipitation of a yellow solid. The reaction mixture was stirred for one hour, and the solvent was subsequently removed under reduced pressure. The resulting powder was washed with toluene to remove soluble low-molecular-weight species. Elemental analysis (C, H, N, P) shows that the composition of the solids is consistent with the expected structure **2**. An SEM image indicates that **2** is composed of micrometer-sized particles (Figure 2), while powder X-ray diffraction (XRD) shows that it is a noncrystalline solid (see the Supporting Information).



2 [Rh] = Rh(cod)BF$_4$

A comparison of the solid-state ^{31}P CP-MAS NMR spectra (Figure 3) of ligand **1b** ($\delta = 148.4$ ppm) and its assembled polymer **2** ($\delta = 135.7$ ppm) with those of authentic samples of **1a** ($\delta = 149.3$ ppm) and Rh$^\mathrm{I}$/**1a** complex ($\delta = 135.3$ ppm) clearly demonstrates a similar coordination pattern in the solid state. The characteristic band at 1700 cm^{-1} for the pyrimidone carbonyl stretching vibration[11] in the FTIR spectrum of **1b** remains almost unchanged upon formation of the supramolecular polymer **2** (1699 cm^{-1}). This shows that the UP functionalities are dimerized in the keto tautomer in both ligand **1b** and polymer **2**.

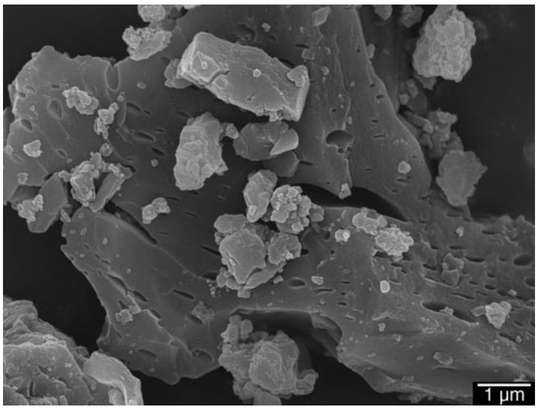


Figure 2. SEM image of catalyst **2**. The scale bar indicates 1 μm.

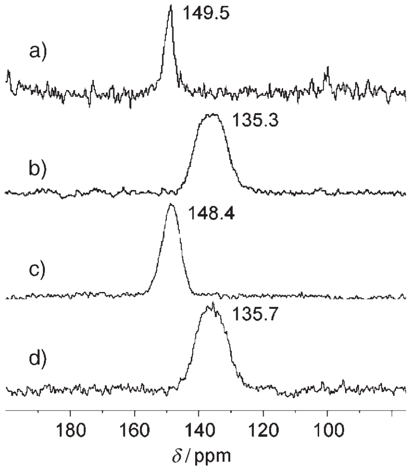


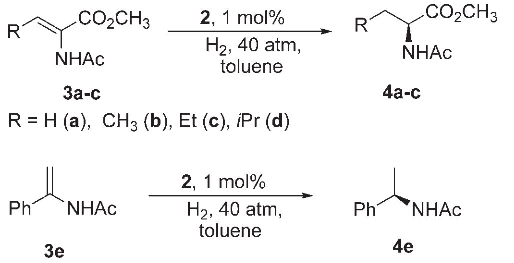
Figure 3. ^{31}P CP-MAS NMR spectra: a) **1a**, b) complex Rh$^\mathrm{I}$/**1a**, c) **1b**, and d) **2**.

Thermal analysis of **2** shows that the polymer is fairly stable. The mass change (−3.1 %) below 150 °C is assigned to the loss of CH$_2$Cl$_2$ molecules included in the polymer (see the Supporting Information).

The supramolecular metal-organic polymer **2** is insoluble in less polar organic solvents such as toluene (see the Supporting Information), thus providing an excellent opportunity for conducting heterogeneous asymmetric reactions. As shown in Table 1, asymmetric hydrogenation of dehydro-α-amino acid derivatives (**3a–d**) and an enamide (**3e**) catalyzed by **2** proceeded smoothly with complete conversion within a standard 20 h. The products (**4a–e**) were obtained with 91–96 % *ee*,[12] comparable to values for the homogeneous system **1a**/Rh$^\mathrm{I}$.[10a,13]

The remarkable advantage of the present polymeric supramolecular heterogeneous catalysts over its homogeneous counterpart is its facile recovery and reusability. Following completion of the hydrogenation, simple filtration under argon allows separation of the solid catalyst from the solution containing the product. The separated solid is then simply recharged with solvent and substrates for the next run. The

Table 1: Asymmetric hydrogenation of **3a**–**e** catalyzed by **2**.[a]



Entry	Substrate	*t* [h]	*ee* [%][b]
1	**3a**	20	95 (*R*)
2	**3b**	20	96 (*R*)
3	**3c**	20	95 (*R*)
4	**3d**	20	93 (*R*)
5	**3e**[c]	40	91 (*R*)

[a] All reactions conducted in toluene at 25 °C under 40 atm of H_2, [**3**] = 1.0 M, [**2**] = 0.01 M (based on the $(\text{MonoPhos})_2/\text{Rh}^{\text{I}}$ unit). Conversions were > 99 % as determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC (Chiralcel AD column) or GC (Supelco BETA-DEX225 column). Absolute configuration determined from the $[\alpha]_D$ values.[9] [c] [**3e**] = 0.2 M, [**2**] = 0.002 M.

supernatant of **2** does not give further hydrogenation of **3b** under otherwise identical experimental conditions, thus unambiguously demonstrating the heterogeneous nature of the present catalytic system. Furthermore, inductively coupled plasma (ICP) spectroscopic analyses of both the filtered organic solution and the isolated product **4b** did not provide any evidence for metal leaching within the detection limit of the instrument (1 ppm).

The reusability of the catalyst system was exemplified by the hydrogenation of **3b**. As shown in Table 2 for a standard reaction time of 20 h, the hydrogenation proceeds with near-quantitative conversion and constant enantioselectivity (96–92 % *ee*) for at least 10 cycles with the same catalyst. Under the same conditions at a hydrogen pressure of 15 atm, a reaction profile of the hydrogenation showed that the catalyst activity is quite high, giving more than 90 % conversion (96 % *ee*) after only 2 h (see the Supporting Information). However, the catalyst reactivity declined with consecutive hydrogenations, as shown by the lower turnover frequency (TOF) for each run (Table 2). Preliminary studies suggest that the absence of a hydrogen atmosphere during product/catalyst separation results in partial catalyst decomposition. A constant-flow reactor is currently under development to address this issue.

Table 2: Reuse of catalyst **2** in the asymmetric hydrogenation of **3b**.[a]

Run	TOF [h^{-1}][b]	*ee* [%][c]
1	180	96
2	111	96
3	83	95
4	68	95
5	44	94
6	32	95
7	24	95
8	19	95
9	11	93
10	8	92

[a] All reactions conducted in toluene at 25 °C under 40 atm of H_2, [**3b**] = 1.0 M, [**2**] = 0.01 M (based on the $(\text{MonoPhos})_2/\text{Rh}^{\text{I}}$ unit). Conversions were > 99 % as determined by ^{1}H NMR spectroscopy. [b] Determined by ^{1}H NMR spectroscopy from a separate consecutive hydrogenation experiment at > 50 % conversion. [c] Determined by GC (Supelco BETA-DEX 225 column).

In conclusion, the heterogenization of a chiral catalyst using both supramolecular hydrogen bonding and ligand-to-metal coordination has been achieved and the resulting polymer characterized by various techniques. The chiral rhodium(I) complex demonstrates excellent asymmetric induction in the heterogeneous hydrogenation of dehydro-α-amino acid and enamide derivatives. Salient features of this catalyst, such as its simple preparation, facile recovery and reuse, as well as excellent stereocontrol performance, make it particularly interesting for practical asymmetric synthesis. This new concept will stimulate future research aimed at the development of heterogeneous chiral catalysts for asymmetric reactions based on noncovalent interactions.

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Keywords: asymmetric catalysis · heterogeneous catalysis · hydrogen bonding · hydrogenation · immobilization

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