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An L-proline functionalized metallo-organic triangle as size-selective homogeneous catalyst for asymmetry catalyzing aldol reactions†

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A homochiral metal–organic triangle Co–Pro1 was achieved *via* self-assembly by incorporating a L-proline moiety within the corresponding ligand. Co–Pro1 comprised L-proline moieties as asymmetric catalytic active sites and a helical-like cavity, it worked as an asymmetric catalyst to prompt aldol reactions with size-, stereo- and enantioselectivity.

Metal–organic macromolecular complexes, discrete molecular architectures constructed through the coordination of metal ions and organic linkers, have attracted considerable attention, due to their intriguing structures, their potential for a variety of applications and their relevance to biological self-assembly.[1,2] These structures are synthesized using modular and high yield coordination-chemistry-based self-assembled methods, thus the steric, geometric and electronic characteristics embedded within the individual components have collectively allowed the controllable construction, to some extent, of supra-molecular entities.[3] Since nature has served as a dominant source of inspiration in the area of supramolecular chemistry,[4] these synthetic approaches often attempt to create enzyme-like systems, in which a cavitand is connected to an active site, with the aim of mimicking enzyme catalysis. Yet only a few "artificial systems" achieved the magnificent catalysis of natural enzymes,[5,6] because of the difficulties associated with the generation of specific interactions capable of selective encapsulation of substrates with suitable orientation, and accelerating their reactions through proximity effects.[7,8]

Without doubt, the biggest challenge in supramolecular catalysis is to develop selective catalysts that convert relevant substrates into desired products with high selectivity. Enantio-selective reactions in which only one of the two possible enantiomers of the product is formed are particularly difficult, because precise control of the reaction pathways is required and energy differences in the competing transition states as small as 3 kcal mol^{-1} make large differences in selectivity.[9] To further develop conventional supramolecular coordination-chemistry-based asymmetric catalysts for producing optically pure fine chemicals, several well-established strategies have been used to construct catalytically active homochiral macro-molecular complexes, many similar in size to small enzymes.[10] These supramolecular systems either contain an asymmetric catalytic moiety to control the environment around the active site for stabilizing the transition-state corresponding to the enantio-selectivity, or comprise a cavity to mimic the pocket of an enzyme for accelerating the reaction through proximity effects. There is still very little overlap that combines aspects of both into one entity. A promising avenue appears to be the design of more sophisticated enzyme mimics that combine rate increase as a consequence of proximity effects with transition-state stabilization by the functional groups.

As well-known asymmetric organocatalysts, L-proline and its derivatives are used to accelerate a variety of enantio-selective organic reactions, including C–C bond forming aldol and Michael reactions under homogeneous conditions.[11] Through incorporation of a L-proline moiety within a metallo-helical triangle formed by assembling metal ions and two tridentate N_2O units containing amide groups within a central benzene ring at the meta sites, herein, we have developed a new approach to create a homochiral triangle Co–**Pro1**. With the asymmetric catalytic active sites to stabilize the potential transition state and the helical cavity to increase the local concentration of the substrates, Co–**Pro1** works as an asymmetric enzyme-like catalyst prompting the well-known aldol reactions with size-, stereo- and enantioselectivity.

Ligand L-**Pro1** was synthesized according to the synthetic route outlined in Scheme 1. **3** was gained through a formal amide-formation reaction from *N*-Boc–L-proline. The reaction of the unprotected ester **4** with hydrazine hydrate gave **5**. Through a Schiff base reaction with 2-pyridinecarbaldehyde, the final ligand L-**Pro1** was achieved and purified *via* semipreparatory HPLC and characterized spectroscopically. Adding NH_4PF_6 into the methanol solution of ligand L-**Pro1** and $Co(NO_3)_2{\cdot}6H_2O$ led to the formation of the metallohelical triangle Co–**Pro1**. Electro-spray ionization mass spectrometry (ESI-MS) spectrum of the reaction solution exhibited five intense peaks at m/z = 812.76 and 885.77 with the isotopic distribution patterns separated by 0.50 Da (Fig. 1). These peaks were assignable to $[Co_3(\text{L-}\mathbf{Pro1})_3]^{2+}$ and $[Co_3(\text{L-}\mathbf{Pro1})_3(PF_6) + H]^{2+}$, respectively, through the exact comparison of the experimental peaks with the simulation results obtained on the basis of natural isotopic abundances, demonstrating the formation of M_3L_3 species in the solution. The coordination of the ligand to the metal ions

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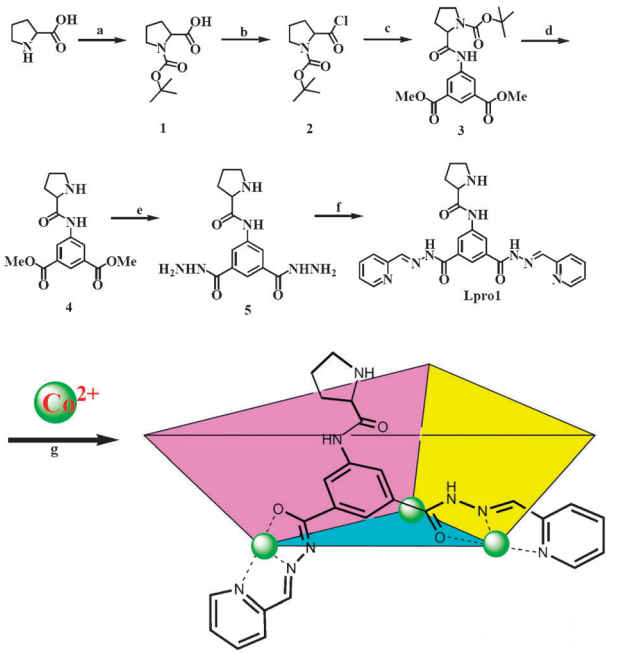


Scheme 1 Synthetic procedure for Co–**Pro1**. Conditions: (a) $(Boc)_2O$, CH_2Cl_2, rt (73.8%); (b) oxalyl chloride, pyridine, CH_2Cl_2, 0 °C; (c) 5-aminoisophthalic acid dimethyl ester, NEt_3, CH_2Cl_2, 0 °C–rt; (d) 6 N solution of HCl in 1,4-dioxane (40 mL $mmol^{-1}$), 0 °C; (e) hydrazine hydrate (80%), EtOH, reflux (85%); (f) 2-pyridinecarbaldehyde, reflux (85%); (g) $Co(NO_3)_2{\cdot}6H_2O$, NH_4PF_6, CH_3OH, rt (55%).

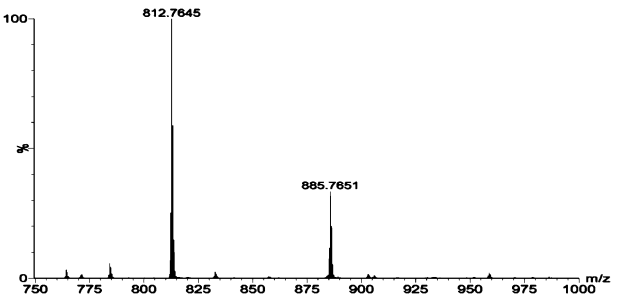


Fig. 1 ESI-TOF spectra of the Co-based triangle Co–**Pro1** formed in CH_3OH solution.

could be also identified by the relatively broadened and shifted resonance signals in ^1H NMR spectra. ^1H NMR spectra of Co–**Pro1** in d_6-DMSO indicated that –C═O–NH– signals of L-**Pro1** were significantly shifted up-field (δ = 0.52 ppm), while –N═CH– signals of L-**Pro1** were distinctly shifted downfield (δ = 0.51 ppm). At the same time, only one set of signals were observed, indicating that all the ligands in each complex were in an identical environment, possibly located equivalently with a C_3-symmetry.

Ligand L-**Pro1** (10 μM) in methanol solution exhibits an intense band at about 300 nm, assignable to the π–π* and n–π* charge transfer band. Upon the addition of Co^{2+} ions, this band was decreased gradually and a new band at about 376 nm increased significantly. Both the bands remained constant after adding approximately 1 equivalent of Co^{2+}. The almost linear relations between the absorbance at both bands and the concentration of Co^{2+} added revealed that the formation of the cobalt complex was quantitative and the complex exhibited 1 : 1 stoichiometry. The presence of a sharp isosbestic point at 330 nm indicated that only two species coexist in the equilibrium (Fig. 2). This result is quite similar to that observed before with a M_6L_4 octahedral nanocage with the three disk-shaped arm ligands,[12] confirming that the cobalt is strongly coordinated by the tridentate chelators in a pseudo-octahedral coordination geometry, demonstrating that the M_3L_3 species was the only one complexation species and the association constant of the complexation species is relatively high. Circular dichroism (CD) measurements of Co–**Pro1** in DMSO solution showed one band at 390 nm with a negative Cotton effect and another band at 280 nm with a positive Cotton effect, respectively. The whole spectrum was quite different from that of the chiral ligand L-**Pro1**, suggesting the homochirality of the pyrrolidine moieties in the Co–**Pro1** even in solution.

The catalytic activities of Co–**Pro1** in asymmetric aldol reactions between various aromatic aldehydes and cyclohexanone were employed in d_6-DMSO media at room temperature. As shown in Table 1, the loading of only 1.5% ratio of Co–**Pro1** (7.5 μM) catalyst leads to a 42% conversion of the product corresponding to 4-nitrobenzaldehyde. Interestingly, the catalytic aldol reaction exhibits an excellent diastereoselectivity of *ca.* 6 : 1 (*anti* : *syn*) as well as a high enantioselectivity (73% ee). A control experiment with the unmodified MC-1 (having the same triangle backbone with the absence of the L-proline moiety)[13] and a similar Co-based triangle in which the pyrrolidyl ring was replaced by a phenyl group exhibited trace conversion after 10 days.

Importantly, the same reaction when performed with L-**Pro1** acting as catalyst resulted in a 36% conversion, significantly

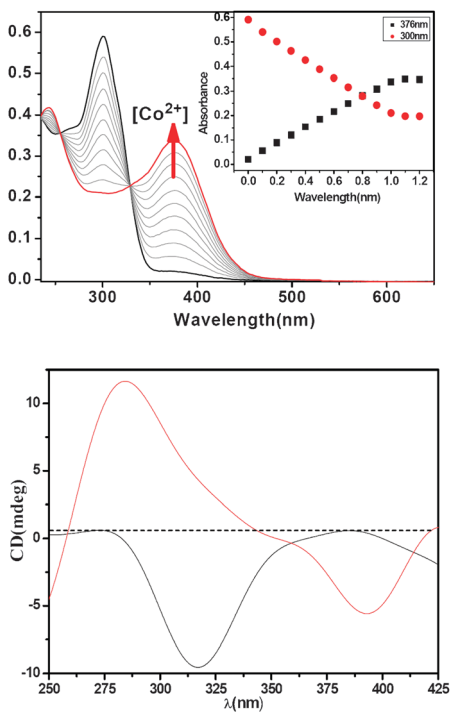
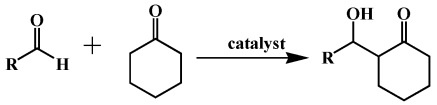


Fig. 2 (a) UV-Vis spectra of ligand L-**Pro1** (10 μM) upon the addition of a standard solution of $Co(NO_3)_2{\cdot}6H_2O$ (per 1 μM) up to 1 equivalent. (b) CD spectra of L-**Pro1** (black line) and Co–**Pro1** (red line) in DMSO solution.

Table 1 Aldol reactions between aldehydes and cyclohexanone[a]



Entry	Substrates	Cat	Con.[b] (%)	dr (A/S)[b]	ee[c] (%)
1	4-Nitrobenzaldehyde	Co–**Pro1**	42	6 : 1	73
		L-**Pro1**	36	2 : 1	50
2	3-Nitrobenzaldehyde	Co–**Pro1**	38	6 : 1	70
		L-**Pro1**	23	2 : 1	62
3	2-Nitrobenzaldehyde	Co–**Pro1**	24	10 : 1	62
		L-**Pro1**	21	2 : 1	44
4	3-Formyl-1-phenylene-(3,5-di-*tert*-butylbenzoate)	Co–**Pro1**	Trace	—	—
		L-**Pro1**	24	1 : 1	—

[a] The reaction was carried out at room temperature for 10 days with cyclohexanone (5 mmol) and aldehyde (0.5 mmol) in the presence of 1.5% mmol Co–**Pro1** (7.5 μmol)/5.0% mmol L-**Pro1** (0.025 mmol) in d_6-DMSO (0.5 mL). [b] The conversion and diastereomeric ratio were determined by ^{1}H NMR spectroscopy of crude products. [c] Values represent the major isomer. The ee values were determined by chiral HPLC on a Chiralcel AD-H column.

lower diastereoselectivity (2 : 1) as well as the decrease of enantioselectivity (50%, ee) (table entry 1). In fact our metal–organic catalyst Co–**Pro1** exhibited excellent specificity for the *anti* conformation of the product corresponding to the aldol reactions of the nitrobenzaldehydes, which drives the significant improvements from those of the relative catalytic reaction with L-**Pro1**. The better diastereo- and enantio-selection of the catalytic aldol reaction with Co–**Pro1** may originate from the restricted movement of the substrates in the confined pocket-like environment in combination with multiple chiral inductions.

To further probe whether activation of the carbonyl species occurs inside the hydrophobic hollow of the catalyst and the reflection of compound configuration on diastereomers, a substrate of increasing dimension was tested. While the reaction between bulky aldehyde 3-formyl-1-phenylene-(3,5-di-*tert*-butylbenzoate),[14] which is larger than the pocket size of Co–**Pro1**, and cyclohexanone in the presence of L-**Pro1** gave the conversion of about 24%, no signals corresponding to the aldol product were found in the NMR spectra of the reaction mixture under the same experimental conditions. From a view point of mechanism, the bowl-like Co–**Pro1** first acts as a mimic of the pocket of an enzyme to accelerate the reaction through encapsulating the substrates within the pocket, greatly increasing the local concentration of the substrates and preorganizing the substrates in the correct orientation to react. These homochiral pyrrolidine moieties attached within the chiral pocket of Co–**Pro1** interact with the cyclohexanone to form the *anti*-enamine transition-state,[15] which dominates the asymmetric aldol reactions that occur *via* an enamine pathway. Infrared spectroscopy of the Co–**Pro1** solution in the presence of cyclohexanone exhibited one broad C–O stretch at 1685 cm^{-1}. The significant red-shift from 1709 cm^{-1} (free cyclohexanone) supports the encapsulation of cyclohexanone within the pocket of the catalyst and the possible activation of the substrates within the pocket of the catalyst through an enamine transition-state. ^{1}H NMR spectra of the Co–**Pro1** solution in the presence of 4-nitrobenzaldehyde revealed the small but significant high-field shift (*ca.* 0.1 ppm) of the amide proton signal from that of the free Co–**Pro1** in solution, which could possibly be an indicator that 4-nitrobenzaldehyde was capsulated within the pocket of the Co–**Pro1** through the hydrogen bonding interactions corresponding to the amide donors.

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