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Supramolecular chiral phosphorous ligands based on a [2]pseudorotaxane complex for asymmetric hydrogenation

Yong Li [a,b], Yu Feng [a,b], Yan-Mei He [a], Fei Chen [a], Jie Pan [a], Qing-Hua Fan [a,*]

[a] *Beijing National Laboratory of Molecular Sciences, Center for Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, PR China*
[b] *Graduate School of Chinese Academy of Sciences, Beijing 100080, PR China*

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Abstract

A new type of supramolecular chiral phosphorus-based ligands was prepared from easily available monodentate ligands through complexation between dibenzylammonium salt and dibenzo[24]crown-8 macrocycle. Rhodium complexes with these supramolecular ligands were prepared, and the supramolecular bidentate ligand-containing catalyst has demonstrated better catalytic activity for all substrates, and higher enantioselectivity except for the *ortho*-substituted substrates than those obtained from the parent monodentate ligand in the asymmetric hydrogenation of α-dehydroamino acid esters.

Keywords: Chiral phosphorous ligands; Pseudorotaxane; Self-assembly; Asymmetric hydrogenation

The development of new effective ligands is a continuous challenge in the transition-metal-catalyzed asymmetric hydrogenation. Over the past decades, a number of excellent chiral diphosphine ligands, such as BINAP [2,2-bis(diphenylphosphino)-1,1′-binaphthyl] and DuPHOS [1,2-bis(phospholano)benzene], have been reported for highly enantioselective hydrogenation reactions.[1] However, the preparation and modification of these classical bidentate ligands often require complicated multistep synthesis. Recently, a supramolecular approach to prepare the chelating bidentate ligands for homogeneous catalysis has proven to be a particularly intriguing alternative to the conventional method.[2–4] For example, Breit and co-workers recently reported the libraries of the defined heterodimeric bidentate ligands by the self-assembly of the easily available monodentate ligands through complementary hydrogen-bonding.[2a,3a–f] Reek and co-workers recently introduced a novel class of bidentate ligands through coordinative bonding.[2b,c,4a–e] They used the zinc(II)porphyrin–pyridyl interaction as an assembly motif to generate bidentate phosphorus-based ligands for hydroformylations and asymmetric hydrogenations. In most cases, these supramolecular bidentate ligands have shown superior selectivity and/or catalytic activity to those obtained by simply mixing two monodentate phosphorus ligands. Furthermore, such a noncovalent synthetic strategy allows the spontaneous, selective formation of stable bidentate ligands with modular architectures and consequently offers the possibility of easily constructing the libraries of enantioselective catalysts.[3e,4e] Despite these efforts, the successful catalytic applications of supramolecular ligands are still limited, even fewer in asymmetric catalysis.[3e–i,4d–f] Therefore, it would be highly desirable to develop new types of supramolecular chiral ligands for homogeneous asymmetric catalysis.

The complexation between secondary ammonium salts and crown ethers, such as dibenzo[24]crown-8 (DB24C8) macrocycle, has been extensively used as a recognition motif for the construction of pseudorotaxanes, rotaxanes and catananes.[5,6] By mixing such two complementary

* Corresponding author. Tel.: +86 10 62554472; fax: +86 10 62554449.
E-mail address: fanqh@iccas.ac.cn (Q.-H. Fan).

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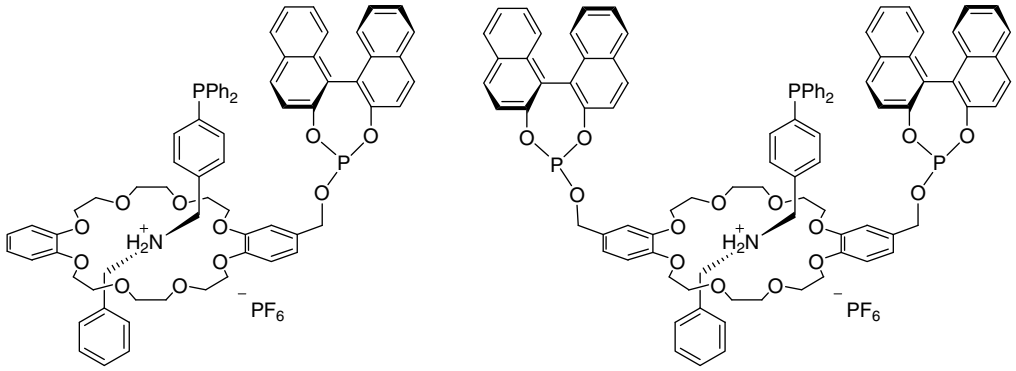
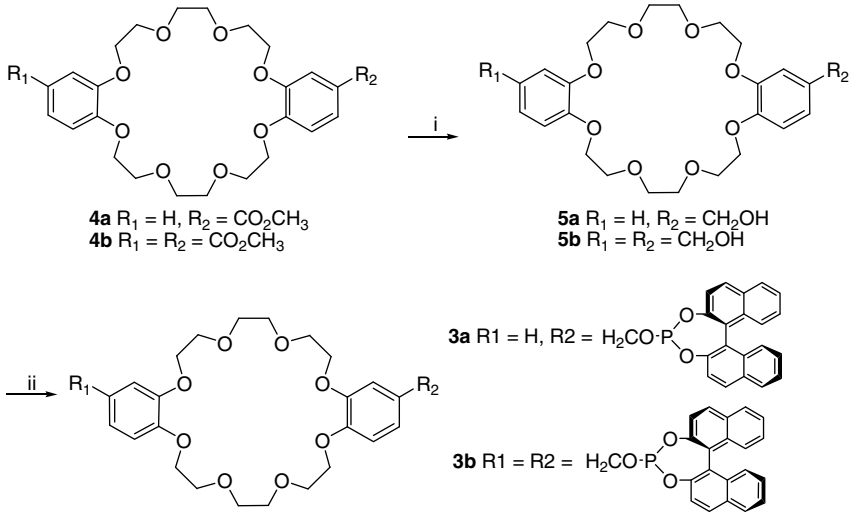


Fig. 1. Structure of supramolecular chiral phosphorous ligands based on a [2]pseudorotaxane complex.

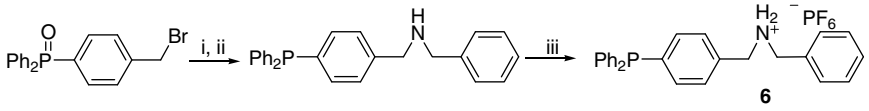
components together in a 1:1 molar ratio, it results in the formation of a pseudorotaxane complex held by strong [N^+–H···O] hydrogen bonds between the acidic NH_2^+ protons and the oxygen atoms in the DB24C8 macrocycle. Furthermore, additional [C–H···O] and π–π stacking interactions, as well as ion–dipole interactions, also contribute to the stability of the resulting pseudorotaxane. Specifically, based on the formation of the stable complex between dibenzylammonium salt and DB24C8, as well as inspired by the pioneering work of Breit,[2a] we envisaged the use of such pseudorotaxane complex for the construction of chiral bidentate or tridentate phosphorus-based ligands (Fig. 1) for asymmetric catalysis.[7]

The synthesis of crown ether-based chiral phosphite ligands **3a** and **3b** is summarized in Scheme 1. The reduction of the corresponding esters (**4a**[8] and **4b**[9]) with $LiAlH_4$ in THF gave alcohols **5a** and **5b** in high yield, respectively. The chiral phosphite ligands (**3a** and **3b**) were then readily prepared by the reaction of the resulting alcohols **5a** and **5b** with (*S*)-2,2′-bisnaphthol phosphorochloridite[10] in good yields, respectively. The secondary ammonium salt containing phosphine ligand **6** was prepared in 69% overall yield by the substitution of benzyl amine with 4-(diphenylphosphino oxide)benzyl bromide and then reduction with $HSiCl_3$–NEt_3, followed by the protonation of the resulting amine with HPF_6 solution (Scheme 2). All the three ligands were well characterized by ^1H, ^{13}C and ^{31}P NMR as well as by HRMS spectroscopy. All the results are in full agreement with the compounds synthesized.

With these complementary phosphorous ligands in hand, we first investigated the formation of the complex between **3a** and **6** in solution. When an equal amount of **3a** and **6** was mixed in $CDCl_3$ at room temperature, three peaks at ca. 140 ppm in the ^{31}P NMR spectrum were observed. In addition to the peak at 140.4 ppm of free ligand **3a**, two new peaks at 139.6 and 139.5 ppm of the supramolecular bidentate ligand **1** were observed, indicating that a mixture of two diastereoisomers was formed. This was probably due to the generation of planar chirality.[11] The formation of complex **1** was further confirmed by mass spectrometry using the electrospray ionization (ESI) technique (1174.3 for $[M-PF_6]^+$). The result of ^1H



Scheme 1. The synthesis of dibenzo[24]crown-8 host-containing chiral phosphorous ligands **3a** and **3b**. Reagents and conditions: (i) H_4A1Li, THF, reflux for 2 h; (ii) 2,2′-bisnaphthol phosphorochloridite, Et_3N, THF, 16 h, rt.



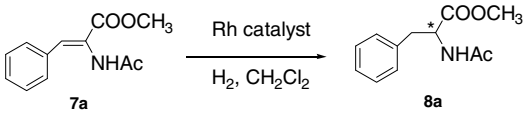
Scheme 2. The synthesis of the secondary ammonium containing phosphine ligand **6**. Reagents and conditions: (i) benzylamine, NaH, THF; (ii) $HSiCl_3$, Et_3N, toluene; (iii) HPF_6, CH_2Cl_2.

NMR was also consistent with the structure of rotaxane skeleton. Similarly, the formation of complex **2** between **3b** and **6** in solution was also confirmed by using ^{31}P and ^{1}H NMR as well as ESI-MS spectra (1518.5 for $[M-PF_6]^+$).

Both the supramolecular ligands were then employed in the rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters.[12] The catalyst was prepared in situ by mixing cationic rhodium complex $[Rh(COD)_2]BF_4$ with **1** in CH_2Cl_2 at room temperature, giving the quantitative formation of rhodium complex bearing a pseudorotaxane. Notably, according to the result of ^{31}P NMR,[13] high diastereoselectivity was observed although the stereochemistry of these complexes was unclear at the present time. Unlike ligand **1**, the tridentate ligand **2** potentially allowed different chelating modes at the Rh centre upon complex formation with $[Rh(COD)_2]BF_4$ in CH_2Cl_2 at room temperature. Then, the hydrogenation of methyl α-acetamidocinnamate **7a** was chosen as a standard reaction, and the preliminary results are summarized in Table 1.

As shown in Table 1, under 1 atm of hydrogen pressure at 20 °C in dichloromethane, the hydrogenation of **7a** proceeded smoothly in the presence of 1 mol % of the in situ generated Rh(I)–**1** complex, furnishing methyl *N*-acetylphenylalaninate **8a** in 73% ee with quantitative conversion after 3 h (entry 1). Increasing the hydrogen pressure led to a remarkable decrease in the enantioselectivity of the product under otherwise identical conditions (entries 2 and 3). The hydrogenation reaction was performed well at a low reaction temperature while giving similar enantioselectivity (entry 4). Unexpectedly, higher enantioselectivity was observed when the catalyst loading was reduced from 1 mol % to 0.2 mol % (entry 6). Most importantly, much lower enantioselectivity and conversion were obtained by using the parent monodentate phosphite **3a** as a ligand under otherwise same conditions (80% vs 68% ee, 100% vs 62% conversion). On the other hand, the catalyst in situ generated from the mixture of **3a** and PPh_3 (1:1 molar ratio) with $[Rh(COD)_2]BF_4$ gave significantly low enantioselectivity (15% ee), but affording the reduced product in opposite configuration (entry 7). Similar phenomena were previously observed by Reetz and Mehler.[14] In addition, compared with **1**, the reaction using the tridentate

Table 1
Optimization of the reaction conditions[a]



7a **8a**

Entry	Ligand	Sub/Cat	Temp (°C)	H_2 (atm)	Time (h)	ee[b] (%)
1	**1**	100	20	1	3	73 (*R*)
2	**1**	100	20	20	3	62 (*R*)
3	**1**	100	20	60	3	44 (*R*)
4	**1**	100	0	1	3	76 (*R*)
5	**1**	300	20	1	14	79 (*R*)
6	**1**	500	20	1	14	80 (68)[c] (*R*)
7	**3a**/PPh_3	500	20	1	14	15 (*S*)
8[d]	**2**	100	20	1	3	46 (*R*)
9[d]	**2**	100	20	1	3	66 (*R*)
10[d]	**2**	500	20	1	14	77 (*R*)

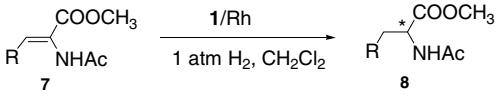
[a] The hydrogenations were carried out with 0.1 mmol **7a** in 1 mL dichloromethane. The catalyst was generated in situ by mixing the supramolecular ligand **1** (1.2 equiv) with $[Rh(COD)_2]BF_4$ (1.0 equiv) in dichloromethane. Complete conversions were achieved in all the cases except for entry 10 (90% conversion).

[b] The ee values and conversions were determined by GC with a Chrompack Chirasil-L-Val column (25 m × 0.25 mm).

[c] Only ligand **3a** was used, and conversion was 62% under otherwise same conditions.

[d] In entry 8, Rh:**3b**:**6** = 1.5:1:1; in entries 9 and 10, Rh:**3b**:**6** = 1:1:1.

Table 2
Asymmetric hydrogenation of α-dehydroamino acid esters with the supramolecular chiral catalyst **1**/Rh[a]



7 **8**

Entry	Substrate, R =	Conv. (%)	ee[b] (%)
1	C_6H_5 (**7a**)	>99 (62)[c]	80 (68)[c]
2	2-Cl–C_6H_5 (**7b**)	>99 (40)[c]	69 (76)[c]
3	3-Cl–C_6H_4 (**7c**)	>99 (54)[c]	79 (76)[c]
4	4-Cl–C_6H_4 (**7d**)	>99 (45)[c]	78 (69)[c]
5	2-Br–C_6H_4 (**7e**)	>99 (38)[c]	72 (82)[c]
6	4-Br–C_6H_4 (**7f**)	>99 (76)[c]	77 (69)[c]
7	4-F–C_6H_4 (**7g**)	>99 (47)[c]	77 (77)[c]
8	2-Me–C_6H_4 (**7h**)	80 (36)[c]	70 (88)[c]
9	3-Me–C_6H_4 (**7i**)	>99 (47)[c]	75 (73)[c]
10	4-Me–C_6H_4 (**7j**)	>99 (37)[c]	76 (70)[c]
11	3-MeO–C_6H_4 (**7k**)	>99 (63)[c]	77 (75)[c]
12	4-MeO–C_6H_4 (**7l**)	>99 (37)[c]	76 (74)[c]
13	4-NO_2–C_6H_4 (**7m**)	>99 (57)[c]	84 (66)[c]
14	3,4-OCH_2O–C_6H_3 (**7n**)	>99 (75)[c]	81 (75)[c]

[a] The hydrogenations were carried out with 0.1 mmol substrates in 1 mL dichloromethane under the following conditions: substrate/catalyst = 500:1, 1 atm H_2, 20 °C, 14 h.

[b] The ee values and conversions were determined by GC with a Chrompack Chirasil-L-Val column (25 m × 0.25 mm). All the products were in the *R*-configuration.

[c] The data in the parentheses were obtained by using the parent monodentate phosphite **3a** as a ligand.

ligand **2** afforded product **8a** in lower enantioselectivity and conversion (entries 8–10).

Subsequently, various α-dehydroamino acid esters were tested in the hydrogenation reactions by using **1** as a chiral ligand under the optimized reaction conditions. As shown in Table 2, moderate to high enantioselectivities (69–84% ee) were obtained. Most importantly, the supramolecular ligand **1** gave better conversions in all the cases, and higher enantioselectivities except for the *ortho*-substituted substrates (entries 2, 5 and 8) than those obtained from the parent monodentate phosphite **3a**.

In conclusion, we have developed a new type of supramolecular chiral phosphorus-based ligands through complexation between dibenzylammonium salt and dibenzo[24]crown-8 macrocycle. In most cases, the supramolecular bidentate ligand exhibited superior activity and enantioselectivity to those of the parent monodentate ligand in the rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters. These supramolecular ligands are modular, and further studies on optimized complexation of both complementary monodentate ligands and applications to other asymmetric reactions are underway.

Acknowledgements

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Supplementary data

Supplementary data (Experimental procedures and characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.039.

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13. ^{31}P NMR of complex Rh(I)–**1** in situ generated by the mixing of **1** with $[Rh(COD)_2]BF_4$ in $CDCl_3$: δ 120.4 (dd, $J_{Rh-P} = 265.7$ Hz, $J_{P-P} = 34.8$ Hz, major) and 120.2 ppm (dd, $J_{Rh-P} = 265.8$ Hz, $J_{P-P} = 35.2$ Hz, minor) for the phosphite moiety; 31.5 (dd, $J_{Rh-P} = 144.2$ Hz, $J_{P-P} = 35.6$ Hz, minor) and 30.9 ppm (dd, $J_{Rh-P} = 145.8$ Hz, $J_{P-P} = 35.6$ Hz, major) for the phosphine moiety (for details, see Supplementary data).
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