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A supramolecularly tunable chiral diphosphine ligand: application to Rh and Ir-catalyzed enantioselective hydrogenation†

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A supramolecularly tunable chiral bisphosphine ligand bearing two pyridyl-containing crown ethers, (−) or (+)-Xyl-P16C6-Phos, was fabricated and utilized in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and Ir-catalyzed asymmetric hydrogenation of quinolines in high yields with excellent enantioselectivities (90–99% ee). Up to a 22% enhancement in enantioselectivity was achieved by the addition of certain amounts of alkali ions (Li^+, Na^+ or K^+), which could be selectively recognized and effectively complexed by the crown ethers on the chiral Xyl-P16C6-Phos.

Introduction

The design and synthesis of new chiral ligands play a pivotal role in the field of transition metal-catalyzed asymmetric reactions.[1] It is well known that the performance of transition metal catalysts can be remarkably affected by subtle variations in either the geometric or electronic properties of chiral ligands. For instance, when chiral atropisomeric diphosphines[2] are used as ligands, without altering the backbone structure, the catalytic properties can be tuned by attaching various P-substituents. Another strategy is the development of diphosphine ligands with adjustable dihedral angles,[2d,e,3] such as *o*-Ph-hexaMeO-BIPHEP,[4] Cn-TunaPhos[5] and PQ-Phos,[6] for different substrates or reactions. Although good-to-excellent results were obtained in some asymmetric catalytic reactions, these ligands often required individual and unique syntheses and thus are not really tunable by simply changing the catalytic reaction conditions.

In the past decade, supramolecular chiral catalysis has attracted growing attention and fascination has been exhibited in both forming catalyst libraries and mimicking enzymes to achieve unexpected activities and stereoselectivities in relevant reactions.[7] Some elegant supramolecular or combinatorial chiral catalyst systems have been designed, such as self-assembled bidentate ligands *via* intermolecular hydrogen bonding,[8] ion pair catalysts,[9] Co(II)–salen with a hydrogen-bonding network,[10] bidentate ligands based on Zn(II) porphyrins,[11] Zn(II) salphen[12] or $Zn(box)_2$ complexes[13] *via* metal–ligand interactions, supramolecular ligands based on a crown-ether appended phosphate or phosphoramidite skeleton,[14,15] and bisphosphite ligands with oligo(ethylene glycol) as backbones,[16] as well as self-supported chiral catalysts with coordination polymer frameworks.[17]

Employing supramolecular methods to impart tunable conformations, steric bulk and electronic properties to a given atropisomeric diphosphine is conceptually appealing since it could avoid the aforementioned individual tedious procedures associated with traditional syntheses of covalent bonds for acquiring enantiomerically pure ligands. To the best of our knowledge, examples of tunable ligands or catalysts illustrating this concept remained rare. Herein, we describe our research on introducing crown ethers, as host sites for recognition, to the scaffold of a well-established chiral dipyridylphosphine ligand Xyl-P-Phos[2c,18,19] to form new ligands, (−) or (+)-Xyl-P16C6-Phos ((−) or (+)-**7**, Scheme 1). Utilizing the selective recognition and strong complexation between the crown ethers on **7** and different alkali cations,[20] supramolecularly tunable chiral catalysts (Scheme 2) have been constructed and applied in both a Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives and an Ir-catalyzed asymmetric hydrogenation of quinolines.

Results and discussion

The new ligand Xyl-P16C6-Phos (**7**) was synthesized as shown in Scheme 1.[18] The cyclization of tetraethylene glycol and 2,6-dichloropyridine (**1**) afforded 2,6-pyrido-16-crown-6 (**2**), which was then brominated to yield **3**. A regioselective lithiation of **3** followed by substitution with di(3,5-dimethylphenyl)phosphine chloride produced **4** in 73% yield. The oxidation of **4** furnished **5**, which was further converted to the racemic diphosphine oxide **6** *via* the copper-mediated Ullman coupling protocol. The

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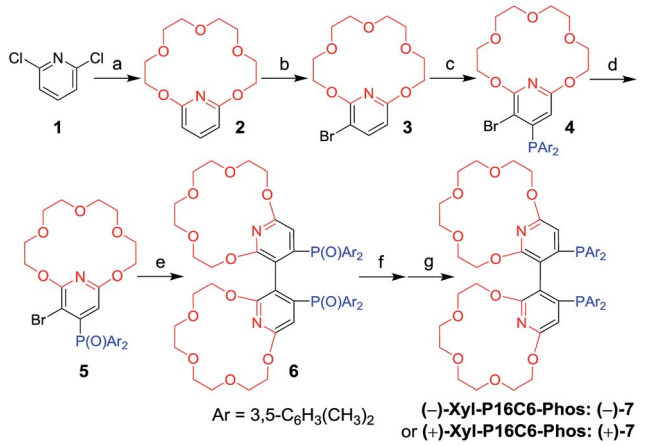


Scheme 1 Synthesis of (–) or (+)-Xyl-P16C6-Phos (**7**). Reagents and conditions: (a) tetraethylene glycol, NaH, KPF_6, THF, reflux, 65% yield; (b) NBS, CH_2Cl_2, −78 °C, 85% yield; (c) LDA, THF, then $(3,5\text{-}Me_2C_6H_3)_2PCl$, −78 °C, 73% yield; (d) H_2O_2, acetone, 0 °C, 85% yield; (e) Cu, DMF, 140 °C, 50% yield; (f) (i) (L or D)-DBTA, EtOAc/$CHCl_3$, (ii) NaOH aq., 54–55% yield for two steps; (g) $HSiCl_3$, Et_3N, toluene, reflux, 87% yield for (–)-**7**, 91% yield for (+)-**7**.

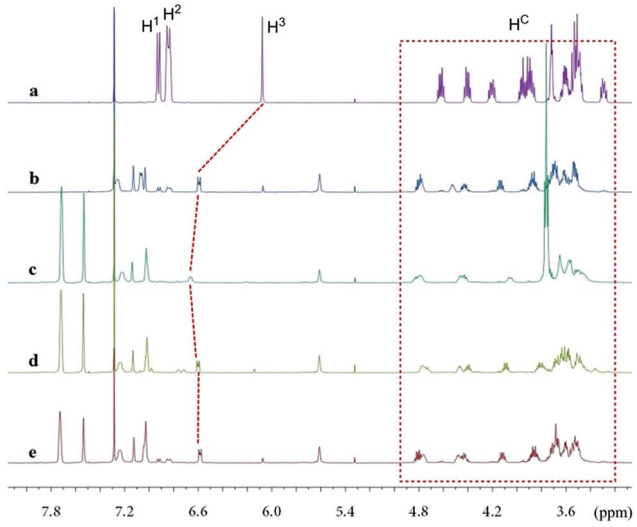
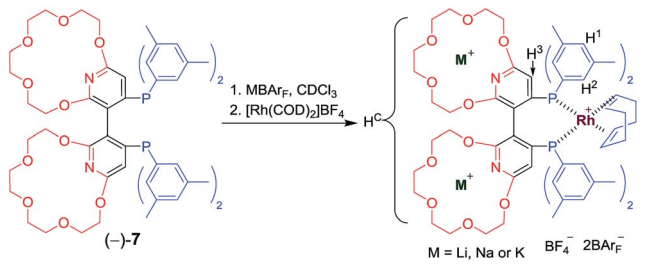


Fig. 1 Partial ^1H NMR (500 MHz, $CDCl_3$) spectra of (a) (–)-**7**; (b) (–)-**7** + $[Rh(COD)_2]BF_4$ (1 : 1 molar ratio); (c) (–)-**7** + $[Rh(COD)_2]BF_4$ + $LiBAr_F$ (1 : 1 : 2 molar ratio); (d) (–)-**7** + $[Rh(COD)_2]BF_4$ + $NaBAr_F$ (1 : 1 : 2 molar ratio); (e) (–)-**7** + $[Rh(COD)_2]BF_4$ + $KBAr_F$ (1 : 1 : 2 molar ratio).



Scheme 2 Preparation of Rh complexes with alkali ions.

resolution of racemate (±)-**6** was realized by the use of (D) or (L)-*O*,*O*′-dibenzoyltartaric acid (DBTA). The enantiomerically pure (–) or (+)-**6** was then reduced to the targeted atropisomeric ligand (–) or (+)-**7**, respectively.

With the new, crown ether-attached chiral diphosphine ligand **7** in hand, the complexation of (–)-**7** with alkali ions and coordination with $[Rh(COD)_2]BF_4$ (Scheme 2) were systematically investigated by ^1H and ^{31}P NMR spectroscopy. As compared with the ^1H NMR spectrum of (–)-**7** (Fig. 1a), the spectra of [(–)-**7** + $[Rh(COD)_2]BF_4$] (Fig. 1b) and [(–)-**7** + $[Rh(COD)_2]BF_4$ + $MBAr_F$ (M = Li, Na or K, $BAr_F^- = (3,5\text{-}(CF_3)_2C_6H_3)_4B^-$)] (Fig. 1c–e) displayed significant differences in either chemical shifts or peak shapes. After coordination with $[Rh(COD)_2]BF_4$, the signal of the H^3 protons on the pyridyl group shifted downfield sharply (Fig. 1b *vs.* 1a). Upon further binding alkali ions, the chemical shift of H^3 changed slightly (Fig. 1c–e *vs.* 1b), while the signals of oxyethylene protons (H^c) changed as expected (Fig. 1c–e *vs.* 1a and 1b), owing to the complexation between crown ethers and alkali ions. The peaks of the oxyethylene protons exhibited marginal differences due to the effects of the different sizes and electronic properties of the alkali ions. The ^{31}P NMR spectra also showed substantial shifts upon coordination of (–)-**7** with $[Rh(COD)_2]BF_4$ (ESI, Fig. S1†). The lone singlet peak of the free ligand split into a doublet due to the coupling between Rh–P (Fig. S1b–e *vs.* S1a†). The obvious changes of both chemical shift and peak shapes in the ^1H NMR spectra of [(–)-**7** + $NaBAr_F$] also directly confirmed the complexation between (–)-**7** and alkali ions (Fig. S2c *vs.* S2a†). Moreover, with the molar ratio of $NaBAr_F$ to ligand increased from 1 : 1 to 10 : 1, the ^1H NMR peaks of the oxyethylene protons and ^{31}P NMR spectra did not show distinct changes (Fig. S2e–g *vs.* S2d, S3e and S3f *vs.* S3d†). Additionally, the stoichiometries of the complexes of (±)-**7** with $LiBAr_F$ and (±)-**6** with $NaBAr_F$ or $KBAr_F$ in solution were all determined to be 1 : 2 by Job plots using proton NMR data (Fig. S4–S6†). This binding ratio was further confirmed by low-resolution electrospray ionization mass spectroscopy (Fig. S7–S9†).

After the self-assembled chiral Rh complexes of **7** were prepared, these complexes were applied as catalysts for the asymmetric hydrogenation of α-dehydroamino acid derivatives to assess the host–guest effect between alkali ions and crown ethers on the catalytic reactions. The $[Rh((–)\text{-}7)(COD)]BF_4$ complex was an effective catalyst for the enantioselective hydrogenation of the model substrate methyl-(*Z*)-2-acetamidocinnamate (**8a**). The reaction proceeded smoothly in CH_2Cl_2 at an ambient temperature with 1 atm of initial H_2 pressure for 6 h, resulting in full conversion to the chiral product (*R*)-**9a** with 82% ee (Table 1, entry 1).

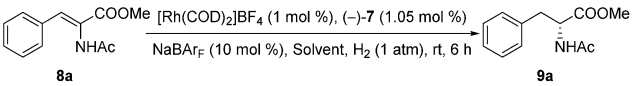
Interestingly, the addition of certain amounts of alkali salts $MBAr_F$ (M = Li, Na, K) as guests for the crown ethers of **7** had an obviously beneficial influence on the enantioselectivities of the catalysts while no decrease in activities was observed (Table 1, entries 3–10 *vs.* entry 1). Na^+ or K^+ appeared to be the preferential choice of cationic additives in terms of enantioselectivities (entries 4, 5, 8 and 9 *vs.* entries 6 and 7). Elevated ratios of alkali salts to (–)-**7** facilitated an enhancement in the enantiomeric purity of the product (entries 4 and 5 *vs.* entry 3, entry 9 *vs.*

Table 1 Effect of additives on Rh-catalyzed asymmetric hydrogenation of methyl-(*Z*)-2-acetamidocinnamate **8a**[a]

Entry	Additive [mol%]	Conv[b] [%]	ee[c] [%]
1	None	>99	82
2[d]	None	>99	88
3	$NaBAr_F$ (1)	>99	84
4	$NaBAr_F$ (2)	>99	88
5	$NaBAr_F$ (5)	>99	91
6	$LiBAr_F$ (2)	>99	84
7	$LiBAr_F$ (5)	>99	84
8	$KBAr_F$ (2)	>99	86
9	$KBAr_F$ (5)	>99	90
10	$NaBAr_F$ (10)	>99	93
11[e]	$NaBAr_F$ (10)	>99	93
12	$NaBF_4$ (10)	68	81
13	$NaPF_6$ (10)	96	83
14	$(nBu)_4NBAr_F$ (10)	91	84
15[d]	$NaBAr_F$ (10)	>99	88

[a] Reaction conditions: 0.05–0.09 mol L^{-1} in CH_2Cl_2. [b] The conversions were determined by NMR and GC analysis. [c] The ee values were determined by chiral GC analysis. [d] (*S*)-Xyl-P-Phos was used as a ligand. [e] The reaction was carried out at 0 °C.

Table 2 The effect of solvent on the Rh-catalyzed asymmetric hydrogenation of methyl-(*Z*)-2-acetamidocinnamate **8a**[a]



Entry	Solvent	Conv[b] [%]	ee[c] [%]
1	CH_2Cl_2	>99	93
2	Acetone	<2	n.d.[d]
3	MeOH	<10	n.d.[d]
4	Toluene	>99	96
5	THF	>99	90
6	Ethyl acetate	>99	90
7	*n*-Hexane	97	96
8[e]	*c*-Hexane	>99	97
9[f]	*c*-Hexane	82	77

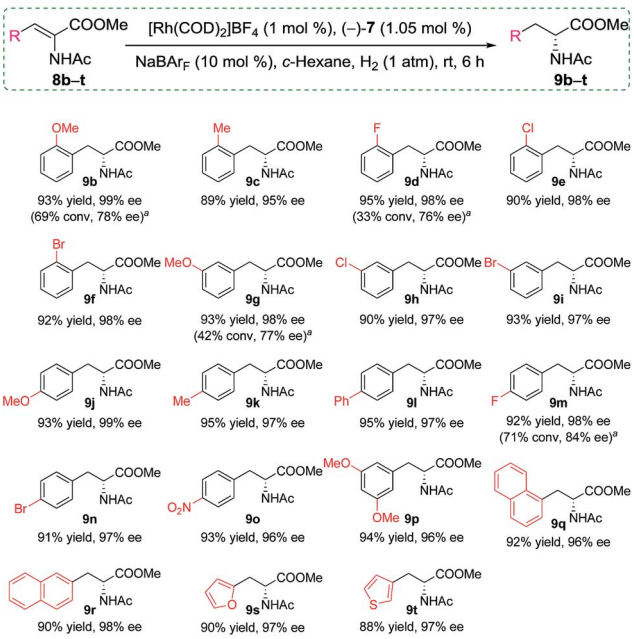
[a] Reaction conditions: 0.05–0.09 mol L^{-1} in solvent. [b] The conversions were determined by NMR and GC analysis. [c] The ee values were determined by chiral GC analysis. The absolute configuration was determined by comparing the retention times with the known data. [d] n.d. = Not determined. [e] The isolated yield was 94%. [f] No $NaBAr_F$ was added.

entry 8). Finally, upon increasing the $NaBAr_F$ loading to 10 mol%, 93% ee was achieved (entry 10). A lower reaction temperature (0 °C) did not render a higher ee (entry 11 *vs.* entry 10). Next, when using 10 mol% of Na^+ as guest, various counter-ions were tested and the results indicated that the presence of a sterically bulkier and more weakly coordinating anion BAr_F^- possessed superior levels of activity and asymmetric induction to those of BF_4^- and PF_6^- (entries 12 and 13 *vs.* entry 10), probably owing to the impact of anions on the complexation between crown ethers and Na^+.

It is well-known that counter-ions may affect the outcomes of transition metal-mediated asymmetric reactions.[19b,21] In order to investigate the contribution of anions on the present catalytic system, $(nBu)_4NBAr_F$ was used as a control additive (Table 1, entry 14), wherein the much more sterically demanding $(nBu)_4N^+$ cation could not complex with the pyridyl-containing crown ethers. When replacing Na^+ with the $(nBu)_4N^+$ cation, only a slight increase in ee was observed (entry 14 *vs.* entry 1), which demonstrated that the host–guest interaction between (−)-**7** and the alkali ions played a crucial role in the increase of the stereoselectivities. Additionally, a side by side comparison study showed that neither cationic or anionic additives had a pronounced effect on the reaction outcomes in the case of (*S*)-Xyl-P-Phos as the chiral ligand (entry 15 *vs.* entry 2).

Moreover, the present self-assembled catalyst system was strongly solvent-dependent (Table 2) and nonpolar *c*-hexane was much more effective for both the reactivity and enantioselectivity than other solvents such as CH_2Cl_2, MeOH and THF. Thus, 97% ee and full conversion were attained when the reaction was carried out in *c*-hexane (Table 2, entry 8), probably due to the stronger association between Na^+ and (−)-**7** in nonpolar solvents. In the absence of alkali additives, (*R*)-**9a** was furnished in 82% conversion with only 77% ee (Table 2, entry 9 *vs.* entry 8) in *c*-hexane under otherwise identical reaction conditions, which further confirmed the impact of the host–guest interaction between Na^+ cations and crown ethers on the asymmetric induction.

Having identified the optimized conditions, we set out to evaluate the general applicability of the self-assembled catalyst. As the findings in Scheme 3 depict, the asymmetric



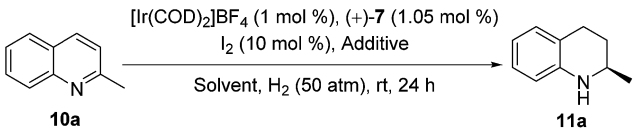
Scheme 3 Asymmetric hydrogenation of α-dehydroamino acid esters **8b–t** with the self-assembled chiral Rh catalyst. Reaction conditions: 0.05–0.09 mol L^{-1} in *c*-hexane; >99% conversions were observed in all cases. [a]No $NaBAr_F$ was added.

hydrogenation of a wide assortment of α-dehydroamino acid esters **8b–t** proceeded to afford desired products **9b–t** neatly in *c*-hexane under 1 atm of H_2 at room temperature with excellent catalytic activities and enantioselectivities (95–99% ee). These results showed that the present supramolecular catalyst system was rather competitive in comparison with similar catalytic systems.[16a,c,19a] Further comparison between catalysts with or without the alkali salts for a few selected substrates indicated that only poor or moderate conversions and enantioselectivities were acquired when no $NaBAr_F$ was added (Scheme 3, **9b**, **9d**, **9g**, and **9m**). For example, in the absence of Na^+ as additives, **8d** was hydrogenated to (*R*)-**9d** in only 33% conversion with 76% ee, whereas, full conversion and up to 22% enhancement in ee were achieved when 10 mol% $NaBAr_F$ was added under otherwise identical conditions (Scheme 3).

Optically active tetrahydroquinoline derivatives are important synthetic intermediates and structural units for some natural products and biologically active compounds.[22] The enantioselective hydrogenation of heteroaromatic compounds is a great challenge as harsh reaction conditions are usually necessary to overcome the aromaticity of the substrates. Although the asymmetric hydrogenation of aromatic compounds has been explored since 1987,[23] there are but several elegant catalytic systems with high activity and enantioselectivity.[24] As such, we were interested in the extension of our self-assembled catalyst design to the Ir-catalyzed asymmetric hydrogenation of substituted quinolines (Tables 3 and 4).

As the data in entry 3 of Table 3 indicate, when the model substrate 2-methylquinoline (**10a**) was treated with the self-assembled Ir catalyst generated from $[Ir(COD)_2]BF_4$, (+)-**7** and $NaBAr_F$ (1 : 1 : 10 molar ratio, Fig. S10 and S11†), the hydrogenation completed in ethyl acetate in the presence of 10 mol% of I_2 under 50 atm of H_2 at ambient temperature in 24 h furnished the chiral product in 96% yield and 97% ee, which were superior to those obtainable in the case of other solvents, such as *c*-hexane and CH_2Cl_2 (entry 3 *vs.* entries 1 and 2). In contrast, 87% ee was obtained if no $NaBAr_F$ was added (entry 4 *vs.* entry 3). Further investigations (Table 4) showed that the present self-assembled Ir catalyst system gave rise to the formation of chiral tetrahydroquinolines **11b–e** of high optical purities (90–97% ee) in quantitative yields (96–98%).

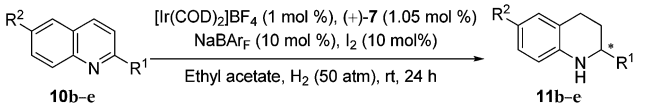
Table 3 The effects of solvent and alkali ion on the Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline **10a**[a]



Entry	Solvent	Additive [mol%]	Conv[b] [%]	ee[c] [%]
1	*c*-Hexane	$NaBAr_F$ (10)	37	93
2	CH_2Cl_2	$NaBAr_F$ (10)	87	95
3	Ethyl acetate	$NaBAr_F$ (10)	98[d]	97
4	Ethyl acetate	None	97	87

[a] Reaction conditions: 0.2 mol L^{-1} in solvent. [b] The conversions were determined by NMR and GC analysis. [c] The ee values were determined by chiral HPLC analysis and the absolute configuration was determined by comparing the rotation sign with the reported data in the literature. [d] The isolated yield was 96%.

Table 4 Asymmetric hydrogenation of substituted quinolines **10b–e** with the self-assembled chiral Ir catalyst[a]



Entry	R^2/R^1 (substrate)	Yield[b] [%]	ee[c] [%]
1	H/*n*-Pr (**10b**)	98	97 (*R*)
2	H/*n*-Bu (**10c**)	97	96 (*R*)
3	H/*n*-pentyl (**10d**)	97	96 (*R*)
4	F/Me (**10e**)	96	90 (*R*)

[a] Reaction conditions: 0.2 mol L^{-1} in ethyl acetate. [b] Isolated yields. [c] The ee values were determined by chiral HPLC analysis.

Conclusions

In conclusion, a supramolecularly tunable chiral bisphosphine ligand bearing a two pyridyl-containing crown ethers, (−) or (+)-Xyl-P16C6-Phos, was synthesized and successfully applied in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and Ir-catalyzed asymmetric hydrogenation of quinolines, in the presence of certain amounts of alkali ions, in quantitative yields and with excellent enantioselectivities (90–99% ee). By finely regulating the host–guest interactions between the crown ethers of the chiral ligand and the alkali ion additives, up to 22% enhancement in enantioselectivities was achieved in comparison with those obtainable from the catalyst systems in the absence of the crown ether/alkali-metal ion recognition motifs. Studies aimed at elucidating the reaction mechanism and expanding these supramolecular catalysts to other asymmetric reactions are in progress in our laboratory.

Acknowledgements

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