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Practical by Ligand Design: A New Class of Monodentate Phosphoramidite Ligands for Rhodium-Catalyzed Enantioselective Hydrogenations

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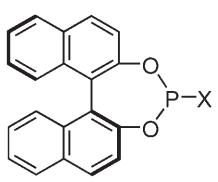
Abstract: A new class of low-cost and easy-to-prepare monodentate phosphoramidite ligands (CydamPhos) has been developed from readily accessible and cheap *trans*-1,2-diaminocyclohexane as starting material through a three-step transformation. This type of ligands exhibited excellent enantioseletivities and high activities in rhodium(I)-catalyzed asymmetric hydrogenations of dehydro-α-amino acid methyl esters **9** (*ee*: 96.2–99.8%) and acetylenamides **11** (91.8–98.8%). The remarkable substituent effects exhibited by the ligands on the enantioselective control of the catalysis are rationalized on the basis of molecular structure of the catalyst precursor.

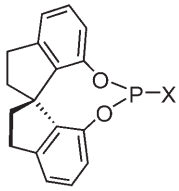
Keywords: asymmetric catalysis; hydrogenation; modular ligands; phosphoramidites; rhodium

Introduction

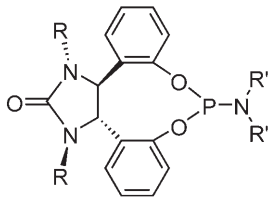
Although the first catalytic homogeneous enantioselective hydrogenation of olefinic compounds was realized by using chiral monodentate phosphine/Rh complexes,[1] a considerable number of bidentate chiral phosphine ligands have been developed over the past three decades since the appearance of Kagan's DIOP[2a] and Knowles' DIPAMP[2b,c] in the early 1970s, as well as Noyori's BINAP shortly thereafter.[2d] This was probably due to a generally accepted dogma that monodentate ligands would have too many degrees of freedom, leading to low enantioselectivity, and that bidentate ligands were a prerequisite to reduce the rotational freedom around the metal-phosphorus bond for efficient asymmetric induction in the catalysis.[3] On the other hand, the pioneering works of Ferringa, de Vries, Reetz, Pringle and others[4] at the beginning of this century brought about a renaissance for the use of monodentate phosphorus ligands (e.g., **1**) in asymmetric hydrogenations. Since then, the development of monodentate phosphorus ligands, for example, **2** and **3**, has been a research topic of increasing interest due to the facts of their easy preparation, good stability, as well as excellent activity and enantioselectivity in asymmetric catalysis.[5–10]



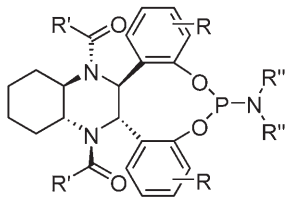
1a X = OR
1b X = alkyl or aryl
1c X = NR_2, MonoPhos



2a X = OR
2b X = NR_2, SIPHOS



3 (DpenPhos)



4 (CydamPhos)

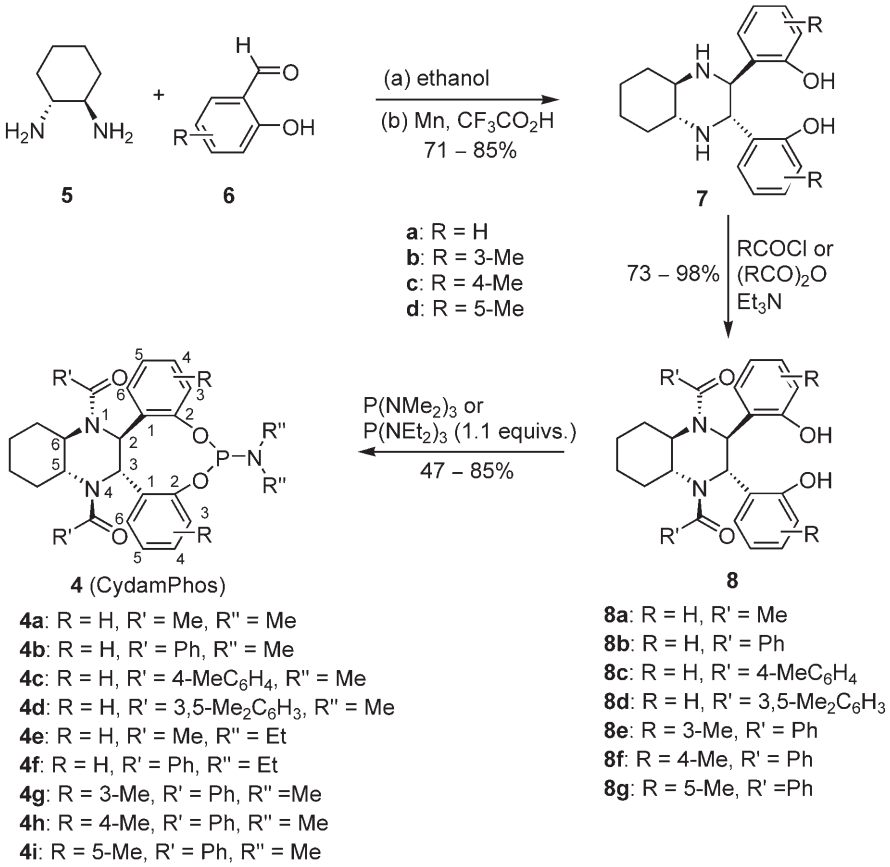
Very recently, we reported a type of modular monodentate phosphoramidite ligand **3** (DpenPhos) for Rh(I)-catalyzed asymmetric hydrogenations of a variety of olefin derivatives.[10] Despite the advantages of excellent enantioselectivities and fine-tuning capability exhibited by this type of ligands, their syntheses were somewhat tedious. As an effort to develop low-

cost and easy-to-prepare phosphorus ligands which can still hold the advantages of DpenPhos, herein we report our results on the design and synthesis of a new class of modular monodentate phosphoramidite ligand **4** (CydamPhos) starting from very cheap and readily accessible *trans*-1,2-diaminocyclohexane and salicylaldehyde derivatives, as well as their applications in Rh^I-catalyzed asymmetric hydrogenation of both α-dehydroamino acid derivatives and α-arylenamides.

Results and Discussion

As shown in Scheme 1, the synthesis of monophosphorus ligands **4** was quite straightforward. Simple condensation of (1*R*,2*R*)-1,2-diaminocyclohexane (**5**) with salicylaldehyde derivatives (**6a–d**) in hot ethanol,[11a] followed by vacuum evaporation of the solvent, gave the corresponding salen derivatives, which were directly submitted to the subsequent intramolecular reductive coupling using manganese as the reducing agent.[11b] The key diphenol intermediates **7a–d** were obtained in 71–85% overall yields. The hydroxy groups of **7a** were then protected with trimethylsilyl chloride (TMSCl) in the presence of Et_3N,[11c] and the protected intermediate was directly condensed with the corresponding acyl chloride without separation. The trimethylsilyl groups in the resulting product was then removed with KF/TBAB/H_2O at room temperature, affording the corresponding *N,N′*-acyl protected diphenols **8b–d** in high yields. The preparations of diphenols **8a** and **8e–g** were more straightforward. Diphenol **8a** was obtained by direct reaction of **7a** with acetic anhydride in the presence of K_2CO_3, and **8e–g** by the reactions of **7b–d** with benzoyl chloride in the presence of Et_3N. Diphenol **8b** could be also prepared in high yield by an analogous procedure as that for **8e–g**. Finally, diphenols **8a–g** were treated with hexamethylphosphorus triamide (HMPT) or hexaethylphosphorus triamide in refluxing toluene or xylene to give the desired ligands **4a–i** in moderate to good yields. These ligands are stable enough to allow manipulation in open air and can be stored under an argon atmosphere over several months without any degradation. It is noteworthy that owing to the facileness of each step as well as the easy-to-handle nature of all the related intermediates, ligand **4b** could be readily prepared in tens of grams scale without using any chromatographic purification.

With ligands **4a–i** in hand, we then examined their asymmetric induction ability in Rh(I)-catalyzed enan-

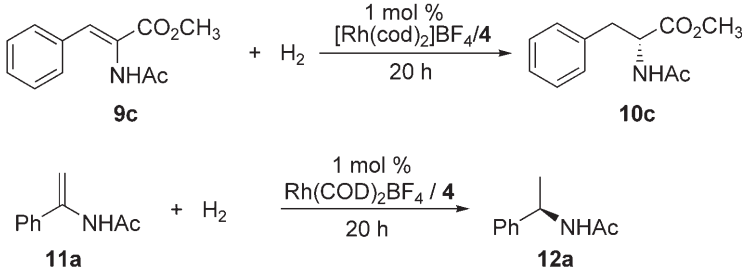


Scheme 1. Synthesis of monodentate ligands **4a–i**.

tioselective hydrogenations. In order to optimize the reaction conditions, ligand **4b** was first tested for the Rh(I)-catalyzed enantioselective hydrogenation, and the α-dehydroamino acid derivative **9c** and α-phenylenamide **11a** were taken as representative substrates, respectively. The reactions were carried out at room temperature using 1 mol% of Rh(I) catalyst. After a preliminary examination of the reaction conditions (See Table S1 in the Supporting Information), it was found that dichloromethane was the best choice of solvent and a 1:2.1 molar ratio of Rh(I) to **4b** was optimal for the hydrogenation of both substrates. The hydrogenation of α-dehydroamino acid derivative **9c** at 20 bar of hydrogen pressure and α-phenylenamide **11a** at 10 bar afforded the highest enantioselectivities (99.5% *ee* and 98.2% *ee*, respectively).

Under the optimized reaction conditions, the impacts of the R, R′ and R″ substituents in CydamPhos ligands **4a–i** on the enantioselectivities of Rh(I)-catalyzed hydrogenations of α-dehydroamino acid derivative **9c** and enamide **11a** were subsequently investigated. As can be seen from Table 1, the substituents R, R′ and R″ in the ligands can exert substantial influences on the asymmetric induction of both reactions. In particular, the change of R′ groups from *N*-alkylacyl to *N*-arylacyl substituents in the ligands can switch the sense of asymmetric induction from *S* to *R* (entry 1 vs. 2; entry 10 vs. 11). On the other hand, the sterically more demanding 3,5-xylyl is obviously unfavorable to the enantioselective control of the reaction (entries 2–4 and 11–13). This is different from the substituent effect of R in DepenPhos **3** where more bulky R resulted in better asymmetric induction.[10] Remarkably, modification of the phosphoramidite *N*-substituents R″ can also lead to a change in enantioselectivities, with smaller methyl groups exhibiting better *ee*s (entries 1, 2 and 10, 11 vs. entries 5, 6 and 14, 15, respectively). The same trend has also been observed in the Rh(I)-catalyzed hydrogenations of α-dehydroamino acid derivatives and enamides with

Table 1. The impact of R, R′ and R″ groups in monodenate ligands **4a–i** on the enantioselectivity of Rh(I)-catalyzed hydrogenation of α-dehydroamino acid derivative **9c** or enamide **11a**.[a]



Entry	R, R′ and R″ in **4**	Substrate	*ee* [%][b]	Configuration[c]
1	R = H, R′ = Me, R″ = Me (**4a**)	**9c**	96.0	*S*
2	R = H, R′ = Ph, R″ = Me (**4b**)	**9c**	99.5	*R*
3	R = H, R′ = 4-MeC_6H_4, R″ = Me (**4c**)	**9c**	96.7	*R*
4	R = H, R′ = 3,5-$Me_2C_6H_3$, R″ = Me (**4d**)	**9c**	74.6	*R*
5	R = H, R′ = Me, R″ = Et (**4e**)	**9c**	18.4	*R*
6	R = H, R′ = Ph, R″ = Et (**4f**)	**9c**	94.4	*R*
7	R = 3-Me, R′ = Ph, R″ = Me (**4g**)	**9c**	6.5	*R*
8	R = 4-Me, R′ = Ph, R″ = Me (**4h**)	**9c**	64.8	*S*
9	R = 5-Me, R′ = Ph, R″ = Me (**4i**)	**9c**	22.4	*S*
10	R = H, R′ = Me, R″ = Me (**4a**)	**11a**	42.3	*S*
11	R = H, R′ = Ph, R″ = Me (**4b**)	**11a**	98.1	*R*
12	R = H, R′ = 4-MeC_6H_4, R″ = Me (**4c**)	**11a**	95.3	*R*
13	R = H, R′ = 3,5-$Me_2C_6H_3$, R″ = Me (**4d**)	**11a**	47.8	*R*
14	R = H, R′ = Me, R″ = Et (**4e**)	**11a**	0	-
15	R = H, R′ = Ph, R″ = Et (**4f**)	**11a**	93.6	*R*
16	R = 3-Me, R′ = Ph, R″ = Me (**4g**)	**11a**	1.8	*R*
17	R = 4-Me, R′ = Ph, R″ = Me (**4h**)	**11a**	34.0	*S*
18	R = 5-Me, R′ = Ph, R″ = Me (**4i**)	**11a**	54.9	*R*

[a] All of the reactions were carried out at room temperature with a substrate concentration of 0.2 M [substrate/catalyst = 100:1, Rh(I)/**4** = 2.1)] for 20 h under 20 bar of H_2 pressure for **9c** or 10 bar for **11a**. The conversion of substrate was determined by ^{1}H NMR to be > 99%.

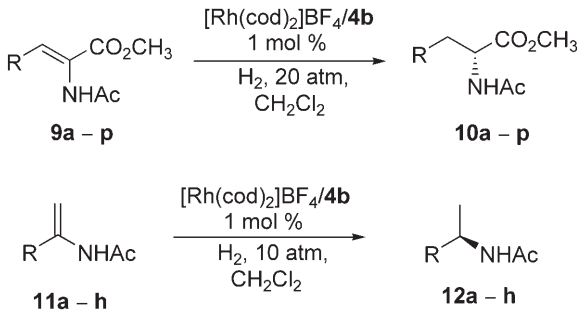
[b] Determined by chiral HPLC.

[c] Assigned by comparison of their optical rotations with literature data.[12]

analogous chiral monodentate phosphoramidite ligands, such as SIPHOS[7b] and DepenPhos.[10] On the other hand, the substituent in MonoPhos/Rh(I)-catalyzed reactions showed an opposite effect, where *N*,*N*-diethyl-substituted MonoPhos exhibited a better enantioselective induction than the *N*,*N*-dimethyl analogue.[8j] Although at the present stage the exact reason for the dramatic substituent effect of the *N*,*N*-substituents (R″) in these ligands on the enantioselection of the reaction is still unclear, the fine-tuning of bite angles (P–Rh–P) in the catalytically active species to match the different substrates may be critical for both the reactivity and enantioselectivity of the catalysis. Moreover, the R (Me) group situated at different positions of the phenoxy moieties in the ligands could also significantly alter the enantioselectivities or switch the sense of asymmetric induction of the catalysis (entries 7–9 and 16–18). These observations suggested that the stereocontrol capabilities of **4** are highly sensitive to the subtle changes in the structural moieties (R, R′ and R″). These facts along with the modular nature of this type of ligands suggest that their asymmetric induction capabilities could be readily tuned by judicious modifications of the R, R′ and R″ substituents at the skeleton of the CydamPhos ligands, which represents a valuable feature for ligand optimization. Within the ligand series **4a–i**, **4b** turns out to be the most enantioselective chiral ligand for both reactions.

To investigate the substrate adaptability of the Rh(I) catalyst composed of ligand **4b**, a variety of α-dehydroamino acid derivatives **9a–p** and enamides **11a–h** were hydrogenated under the optimized reaction conditions, and the results are summarized in Table 2. The catalyst Rh(I)/**4b** is very efficient for the asymmetric hydrogenation of various α-dehydroamino acid derivatives (**9a**–**p**), affording the corresponding α-amino acid derivatives (**10a**–**p**) with excellent enantioselectivities (96.2–99.8% *ee*, entries 1–16). The substituent situated at the β-position of the α-dehydroamino acid derivatives has little impact on the enantioselectivity of the reaction. When the hydrogenation of α-dehydroamino acid derivative **9c** was carried out with reduced catalyst loading (0.1 mol%), the corresponding α-amino acid derivative could be obtained in quantitative yield without a significant loss of enantioselectivity (entry 17 vs. 3). The catalyst Rh(I)/**4b** also demonstrated excellent enantioselectivity in the Rh(I)-catalyzed hydrogenation of a variety of α-arylenamides **11a**–**h**, affording the corresponding α-arylamine derivatives **12a**–**h** in 91.8–98.4% *ee* (entries 18–25). To estimate the catalytic activity of the Rh(I) complex with CydamPhos (**4**) ligand for the titled reaction, the reaction profiles for the Rh(I)-catalyzed hydrogenation of α-dehydroamino acid derivative **9c** using MonoPhos (**1c**, where R is methyl), DpenPhos (**3**, where R is benzyl and R′ is methyl) or **4b** were obtained by analyzing aliquots taken from reaction mixtures at regular intervals using the ^{1}H NMR technique. All reactions were carried out in dichloromethane at room temperature under 15 atm of H_2 in the presence of 1 mol% catalyst. It was found that the catalyst composed of **4b** exhibited a relatively lower catalytic activity than MonoPhos or

Table 2. Enantioselective hydrogenation of α-dehydroamino acid **9** and enamide **11** derivatives under the catalysis of $[Rh(cod)_2]BF_4$/**4b**.[a]



Entry	R in **9** and **11**	*ee* [%][b]	Configuration[c]
1	H (**9a**)	98.8	*R*
2	CH_3 (**9b**)	98.7	*R*
3	C_6H_5 (**9c**)	99.5	*R*
4	4-BrC_6H_4 (**9d**)	99.7	*R*
5	3-BrC_6H_4 (**9e**)	99.4	*R*
6	2-BrC_6H_4 (**9f**)	99.2	*R*
7	4-ClC_6H_4 (**9g**)	99.3	*R*
8	3-ClC_6H_4 (**9h**)	98.0	*R*
9	4-$CH_3OC_6H_4$ (**9i**)	97.4	*R*
10	3-$CH_3OC_6H_4$ (**9j**)	99.5	*R*
11	3-FC_6H_4 (**9k**)	98.7	*R*
12	4-$O_2NC_6H_4$ (**9l**)	99.3	*R*
13	2-$O_2NC_6H_4$ (**9m**)	96.2	*R*
14	3,4-$(CH_3O)_2C_6H_3$ (**9n**)	98.2	*R*
15	3-AcO-4-$CH_3OC_6H_3$ (**9o**)	99.8	*R*
16	2-naphthyl (**9p**)	98.4	*R*
17[d]	C_6H_5 (**9c**)	98.2	*R*
18	C_6H_5 (**11a**)	98.1	*R*
19	4-ClC_6H_4 (**11b**)	95.0	*R*
20	4-$CH_3OC_6H_4$ (**11c**)	95.7	*R*
21	4-$CH_3C_6H_4$ (**11d**)	98.4	*R*
22	4-FC_6H_4 (**11e**)	92.2	*R*
23	4-BrC_6H_4 (**11f**)	95.3	*R*
24	3-BrC_6H_4 (**11g**)	91.8	*R*
25	2-naphthyl (**11h**)	96.8	*R*

[a] All of the reactions were carried out in dichloromethane at room temperature at a substrate concentration of 0.2 M (substrate/catalyst = 100:1). The reaction time is 2 h for substrate **9** and 5 h for **11**, respectively. The conversion of substrate was determined by ^{1}H NMR to be >99%.

[b] Determined by chiral HPLC or GC.

[c] Assigned by comparison of their optical rotations with literature data.[12]

[d] Catalyst loading is 0.1 mol% with 20 h of reaction time.

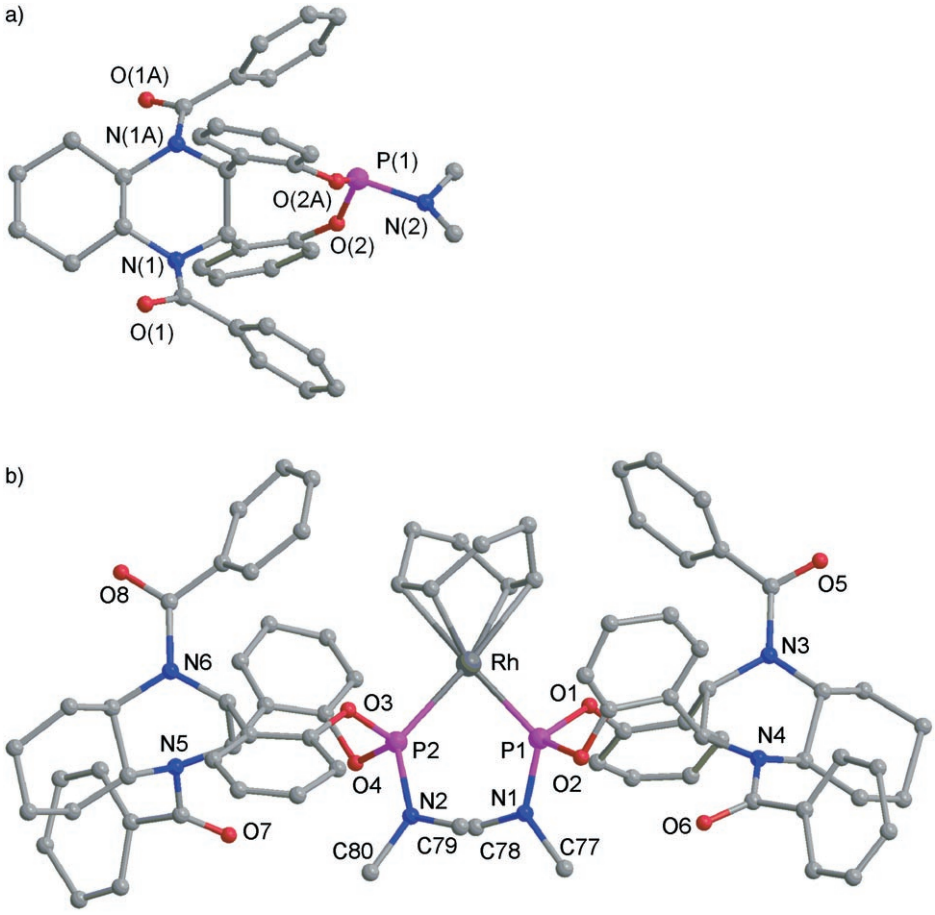


Figure 1. Crystal structure of **4b** (top) and $[Rh\{\mathbf{4b}\}_2(cod)]^+$ BF_4^- (bottom). The BF_4^- anion and all hydrogen atoms have been omitted for clarity. Selected interatomic distances [Å], angles, and torsion angles [°] in ligand **4b**: P(1)–N(2) 1.711(4), P(1)–O(2) 1.456(3), P(1)–O(2 A) 1.492(3); and $[Rh\{\mathbf{4b}\}_2(cod)]^+$ BF_4^-: Rh–P(1) 2.296(3), Rh–P(2) 2.302(3), P(1)–N(1) 1.647(13), P(2)–N(2) 1.625(14); P(1)–O(1) 1.624(9), P(1)–O(2) 1.640(10), P(2)–O(3) 1.622(10), P(2)–O(4) 1.651(10); P(1)–Rh–P(2) 95.96(11), P(1)–Rh–P(2)–N(2) 27.1(6), P(2)–Rh–P(1)–N(1) 29.6(6).

DpenPhos in this reaction (see Figure S1 in Supporting Information). For the reaction catalyzed by Rh(I)/**4b**, there is clearly an incubation stage for the reaction within the initial 15 min period, after which the conversion increased steadily in a nearly linear fashion over the following 25 min. Although the exact reason for the presence of an incubation period is not clear at present, it is assumed that the catalyst activation required a period of time for transformation of the catalyst precursor in some way to reach a steady concentration of catalytically active species.[5i]

The remarkable substituent effects exhibited by ligand **4** as discussed above prompted us to investigate the underlying structural reasons. To this end, we succeeded in obtaining single crystals of ligand **4b** and its Rh(I) complex, both of which were characterized by X-ray crystallographic analysis. The absolute configuration of ligand **4b** was assigned as 2*S*,3*S*,5*R*,6*R* by its crystal structure (Figure 1 a). The structure of Rh(I) complex of ligand **4b** was disclosed to be C_2 symmetric with the formula of $[Rh\{\mathbf{4b}\}_2(cod)]BF_4$ (Figure 1 b), which contains two *cis*-coordinated monophosphoramidite ligands and adopts a similar coordination pattern to those reported for Rh(I) complexes of ligands **2** and **3**.[7b,10] One of the *N*-benzoyl phenyl rings of each ligand points towards the labile cod moiety, constituting an integral part of the chiral environment around the Rh(I) center and thus might exert a profound influence on the steps of the catalytic process. The hydrogenation of α-dehydroamino acid derivative **9c** with the isolated $[Rh\{\mathbf{4b}\}_2(cod)]BF_4$ complex afforded α-amino acid derivative **9c** with 98.8 % enantioselectivity, which was essentially same as that obtained by using the corresponding *in situ* prepared catalyst (Table 1, entry 3, 98.5 % *ee*), suggesting that the complex may act as an active catalytic species.[4e,5j,7b,10] This result in combination with the structural features of the Rh complex disclosed above might, in part, explain the remarkable remote stereocontrol effect of the substituents R′ at the backbone of the ligand in the catalysis.

Conclusions

In summary, we have developed a new class of modular monodentate phosphoramidite ligands, which are efficient for Rh(I)-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives and α-arylenamides. The salient features of this type of ligands, such as cheap starting material and facile preparation,[13] structural diversity, as well as remote stereocontrol capability of backbone substituents, will stimulate future studies to explore their applications in other transition metal-catalyzed asymmetric reactions.[9]

Experimental Section

General Remarks

All the experiments which were sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. NMR spectra were recorded in $CDCl_3$, CD_3OD or DMSO-d_6 on a Varian Mercury 300 (^1H 300 MHz; ^{13}C 75 MHz, ^{31}P 121 MHz, ^{19}F 282 MHz) spectrometer. Chemical shifts are expressed in ppm with an internal standard: TMS (0 ppm), $CDCl_3$ (7.20 ppm), CD_3OD (3.31 ppm), and DMSO-d_6 (2.50 ppm) for ^1H and $CDCl_3$ (77.0 ppm) and DMSO-d_6 (39.5 ppm) for ^{13}C. ^{31}P NMR spectra were recorded with 85% H_3PO_4 as an external reference. The IR spectra were measured on a Rio-Rad FTS-185 spectrometer in KBr pellets. EI (70 eV) and ESI mass spectra were obtained on HP5989 A and Mariner LC-TOF spectrometers, respectively. HR-MS were determined on an IonSpect 4.7 TESLA FTMS. Elemental analyses were performed with an Elemental VARIO EL apparatus. Optical rotations were measured on a Perkin–Elmer 341 automatic polarimeter. HPLC analyses were carried out on a JASCO 1580 liquid chromatograph with a JASCO CD-1595 detector and AS-1555 autosampler. GC analyses were measured on Agilent 6890N network system. *trans*-1*R*,2*R*-Diaminocyclohexane (**5**) was obtained by optical resolution of a *cis*/*trans*-1,2-diaminocyclohexane (40/60) mixture with L-(+)-tartaric acid.[11a] 3-Methylsalicylaldehyde, 4-methylsalicylaldehyde and 5-methylsalicylaldehyde were prepared by following the literature method.[11d] Dichloromethane was freshly distilled from calcium hydride and 2-propanol from magnesium filings, THF, xylene and toluene from sodium benzophenone ketyl, ethyl acetate and acetonitrile from P_2O_5.

Ligand Synthesis

The characterization data for the compounds **7a–d**, **8a–g** and **4a–i** can be found in the Supporting Information.

Preparation of (2*S*,3*S*,5*R*,6*R*)-7a; Typical Procedure

A solution of salicylaldehyde **6a** (46.4 g, 0.38 mol) in EtOH (200 mL) was added dropwise to the ethanol solution (400 mL) of *trans*-1*R*,2*R*-diaminocyclohexane **5** (21.7 g, 0.19 mol) at room temperature over 1 h. After stirring at reflux temperature for 12 h, the mixture was cooled to room temperature and the solvent was removed by vacuum evaporation. The oil-like residue was dissolved in a mixture of dry acetonitrile (1710 mL) and toluene (190 mL). To the solution was added manganese powder[11b] (325 mesh; 20.9 g, 0.38 mol), and the resulting mixture was cooled to 0 °C before trifluoroacetic acid (58.3 mL, 0.76 mol) was added dropwise over a period of 30 min under an Ar atmosphere. The reaction mixture was stirred vigorously at 20 °C for 24 h followed by addition of two additional equivalents of trifluoroacetic acid at 0 °C. After standing at that temperature for 2 h, the resulting mixture was filtered and the residue was washed with petroleum ether (bp 60–90 °C, 50 mL × 2) to afford a white solid. The solid was dissolved in H_2O (100 mL) and neutralized with saturated $NaHCO_3$ solution to pH 8. The aqueous solution was extracted with dichloromethane (200 mL × 3). The combined organic layer was washed with H_2O (100 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting white solid was recrystallized with a mixture of petroleum and ethyl acetate (1:1) to afford the desired compound (2*S*,3*S*,5*R*,6*R*)-**7a** as colorless needles; yield: 52.3 g (85%).

(2*S*,3*S*,5*R*,6*R*)-7b, c, d: Following a similar procedure to that for the preparation of (2*S*,3*S*,5*R*,6*R*)-**7a**, (2*S*,3*S*,5*R*,6*R*)-**7b, c, d** were obtained in good yields (80%, 78% and 71%, respectively).

Preparation of (2*S*,3*S*,5*R*,6*R*)-8a

To the mixture of compound (2*S*,3*S*,5*R*,6*R*)-**7a** (5.0 g, 15.4 mmol) and anhydrous K_2CO_3 (11.7 g, 77.2 mmol) in dry DMF (50 mL), acetic anhydride (6.1 mL, 154 mmol) was added dropwise at room temperature over 10 min. The reaction mixture was heated to 120 °C and stirred at the temperature for 24 h. After removal of the solvent under vacuum, aqueous $NaHCO_3$ solution (0.5 M, 100 mL) was added to the residue followed by stirring at room temperature to result in precipitation of a large amount of white solid. The solid was collected by filtration and washed with water (20 mL × 2) and cooled ethanol (20 mL), respectively, to afford the title compound (2*S*,3*S*,5*R*,6*R*)-**8a** (4.7 g) as a white solid. The filtrate was extracted with ethyl acetate (100 mL × 3) and the combined organic layer was washed with water (50 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was crystallized from ethyl acetate to afford additional 1.0 g of (2*S*,3*S*,5*R*,6*R*)-**8a** as a white solid; total yield: 91%.

Preparation of (2*S*,3*S*,5*R*,6*R*)-8b

Method A: To the solution of compound (2*S*,3*S*,5*R*,6*R*)-**7a** (25 g, 0.077 mol) and NEt_3 (48.7 mL, 0.35 mol) in dry toluene (400 mL), trimethylsilyl chloride (19.6 mL, 0.156 mmol) was added dropwise at 0 °C over 20 min. The reaction mixture was heated to reflux and stirred at the temperature for 1 h. After cooling to 0 °C, benzoyl chloride (18.1 mL, 0.156

mol) was added dropwise to the mixture over 30 min. The resulting mixture was allowed to warm up to room temperature and stirred at that temperature overnight. After removal of the solvent under vacuum, to the residue was added water (150 mL), KF (17.2 g, 0.31 mol) and tetrabutylammonium bromide (0.25 g, 0.77 mmol). The resulting mixture was stirred at room temperature for 2 h to allow the precipitation of the product. The precipitate formed in the solution was collected by filtration and washed with water (50 mL × 2) and cooled EtOH (50 mL), respectively. The obtained white solid was purified by recrystallization from a mixture of petroleum and ethyl acetate (1:2) to give (2*S*,3*S*,5*R*,6*R*)-**8b** as colorless prisms; yield: 34.9 g (85%).

Method B: To the solution of compound (2*S*,3*S*,5*R*,6*R*)-**7a** (1.0 g, 3.1 mmol) and NEt_3 (1.72 mL, 12.3 mmol) in dry toluene (8 mL), benzoyl chloride (1.42 mL, 12.3 mmol) was added dropwise at room temperature over 10 min. The reaction mixture was stirred at 60 °C overnight. After the removal of toluene under reduced pressure, 20% KOH aqueous solution (15 mL) and ethanol (15 mL) were added. After being stirred at room temperature for 6 h, ethanol was removed under vacuum, and the resulting residue was neutralized with 6 M HCl aqueous solution to pH 8–9. The resulting solids were collected by filtration, washed with water (30 mL × 3) and dried under vacuum. The desired compound (2*S*,3*S*,5*R*,6*R*)-**8b** (1.6 g) was obtained in a total yield of 97% as a white solid, which could be used for next step without further purification.

(2*S*,3*S*,5*R*,6*R*)-8c and d: Following a similar procedure to that for the preparation of (2*S*,3*S*,5*R*,6*R*)-**8b** (Method A), (2*S*,3*S*,5*R*,6*R*)-**8c** and **d** were obtained in yields of 98% and 97%, respectively.

(2*S*,3*S*,5*R*,6*R*)-8e, f, g: Following an analogous procedure for the preparation of (2*S*,3*S*,5*R*,6*R*)-**8b** (Method B), (2*S*,3*S*,5*R*,6*R*)-**8e, f, g** were obtained in yields of 76%, 85% and 73%, respectively.

General Procedure for the Preparation of Ligands 4a–i

A solution of **8** (1 mmol) with hexamethylphosphorus triamide (1.1 mmol) in dry toluene (3 mL), or with hexaethylphosphorus triamide (1.1 mmol) in dry xylene (3 mL) was heated to reflux and kept stirring at that temperature for 12–24 h under an argon atmosphere until the complete conversion of **8** (monitored by TLC). After cooling to room temperature, the reaction mixture was concentrated under vacuum. The residue was purified either by recrystallization from the reaction solvent or by flash column chromatography on silica gel with hexane/ethyl acetate/triethylamine (1/0.15/0.1) as eluent to give the corresponding monodentate phosphoramidite ligands **4** in the yields of 47–85%.

X-Ray Crystal Structure Data for (2*S*,3*S*,5*R*,6*R*)-4b

$C_{36}H_{36}N_3O_4P$, $M_r = 605.65$, tetragonal, $P4_32_12$, $a = 10.0918(7)$ Å, $b = 10.0918(7)$ Å, $c = 31.024(3)$ Å; $V = 3159.6(4)$ Å^3; $2.12 < 2\theta < 28.28$ degree; $\rho_{calc} = 1.273$ g cm^{-3}, $Z = 4$, $R_{int} = 0.1162$. Goodness of fit indicator = 0.759, final $R1 = 0.0489$, $wR2 = 0.1034$ on F^2 for observed data, P_{max}, $P_{min} = 0.250$, -0.235 Å^{-3}; absolute structure parameter was $-0.3(2)$. CCDC-277383 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, Cambridge, CB21EZ, UK; fax: (+44)-1223–336–033; or e-mail: deposit@ccdec.cam.ac.uk].

Preparation of [{(2*S*,3*S*,5*R*,6*R*)-4b}$_2$Rh(cod)]$^+$[BF_4]$^-$

A solution of $Rh(COD)_2BF_4$ (37.0 g, 0.09 mmol) and (2*S*,3*S*,5*R*,6*R*)-**4b** (110.3 g, 0.18 mmol) in a mixture of dry dichloromethane (5 mL) and toluene (3 mL) was stirred at room temperature for 1 h. The resulting solution was filtered and the filtrate was transferred to a Schlenk tube in glove box. The Schlenk tube was then sealed with a rubber plug and allowed to stand at room temperature for a week, resulting in crystallization of a large amount of single crystals as orange needles. The single crystals were submitted to X-ray crystallographic analysis, NMR analysis, as well as use in the catalysis of the hydrogenation of α-dehydroamino acid derivatives. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$–1.50 (m, 8H), 1.61–2.02 (m, 10H), 2.10–2.35 (m, 2H), 2.55–2.70 (m, 4H), 2.78 (broad s, 12H), 3.64–3.67 (m, 2H), 4.04–4.12 (m, 2H), 4.52–4.61 (m, 2H), 5.21 (s, 2H), 5.43 (s, 2H), 5.67–5.72 (m, 2H), 6.90–7.08 (m, 8H), 7.12–7.20 (m, 8H), 7.24–7.40 (m, 10H), 7.43–7.56 (m, 2H), 7.54 (m, 2H), 7.65 (dd, 2H, $J = 1.5$, 7.8 Hz), 7.72 (d, 2H, $J = 6.9$ Hz), 8.02 (d, 2H, $J = 8.1$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 117.24$ (d, $J = 235.6$ Hz); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -153.11$.

X-Ray Crystal Structural Data for [{(2*S*,3*S*,5*R*,6*R*)-4b}$_2$Rh(cod)]$^+$[BF_4]$^-$

$C_{92}H_{96}BF_4N_6O_8P_2Rh$, crystal grown from dichloromethane/toluene, $M_r = 1665.41$, monoclinic, $P2_1$, $a = 9.9434(8)$, $b = 42.996(3)$, $c = 10.9801(9)$ Å; $V = 4186.7(6)$ Å^3, $1.89 < 2\theta < 25.50$ degree; $\rho_{calc} = 1.321$ g cm^{-3}, $Z = 2$, $R_{int} = 0.1418$. Goodness of fit indicator = 1.592, final $R1 = 0.1608$, $wR2 = 0.3977$ on F^2 for observed data, P_{max}, $P_{min} = 2.690$, -2.101 Å^{-3}; absolute structure parameter was 0.00(11). CCDC-277384 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from CCDC, Cambridge, CB21EZ, UK; fax: (+44)-1223–336–033; or e-mail: deposit@ccdec.cam.ac.uk].

General Procedure for Catalytic Asymmetric Hydrogenation

[$Rh(cod)_2$]BF_4 (2.0 mg, 0.005 mmol) and (2*S*,3*S*,5*R*,6*R*)-**4** (0.011 mmol) were dissolved in CH_2Cl_2 (1 mL) under nitrogen and the solution was stirred at room temperature for 10 min. The solution of substrate **9** or **11** (0.5 mmol) in CH_2Cl_2 (1.5 mL) was added to the above catalyst solution. The resulting mixture was then transferred to a stainless

steel autoclave under a nitrogen atmosphere, and then sealed. After purging with hydrogen for 6 times, the final H_2 pressure was adjusted to the desired value. After stirring at room temperature for an appropriate time period, H_2 was released. Removal of the solvent under the reduced pressure afforded the product residue, which was submitted to ^{1}H NMR analysis to assess the conversion of the starting materials. The crude product was purified by flash column chromatography and enantiomeric excess of the product was determined by chiral HPLC or GC.

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[13] Both starting materials, (1*R*,2*R*)-1,2-diaminocyclohexane (**5**) and salicylaldehyde (**6a**), are cheap industrial products. In particular, (1*R*,2*R*)-1,2-diaminocyclohexane can be easily obtained on a large scale by optical resolution of *cis*/*trans*-1,2-diaminocyclohexane (40/60) mixture, a less expensive Dupont product, with L-(+)-tartaric acid.[11a]

