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Aminophosphine Phosphinites Derived from Chiral 1,2-Diphenyl-2-aminoethanols: Synthesis and Application in Rhodium-Catalyzed Asymmetric Hydrogenation of Dehydroamino Acid Derivatives

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Abstract—A series of chiral aminophosphine phosphinites DPAMPPs was synthesized from optically active 1,2-diphenyl-2-aminoethanols. The *erythro*-DPAMPPs were found to serve as excellent ligands for rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives. For an array of dehydroamino acid precursors, remarkably high enantioselectivity (up to 98.4% e.e.) and reactivity (the ratio of substrate/catalyst up to 10000) were observed. Some factors controlling the enantioselectivity were examined and discussed.

Introduction

Due to their potential pharmacological application and their incorporation in synthetic peptides, the development of methods for the asymmetric synthesis of optically active α-amino acids has been the subject of extensive research.[1] Among various methods for the enantioselective synthesis of these compounds, homogeneous asymmetric hydrogenation catalyzed by rhodium complexes containing chiral bidentate phosphine ligand is one of the most practical process in asymmetric synthesis.[2] During the last 10 years, much effort has been devoted to developing chiral aminophosphine phosphinite ligands for asymmetric hydrogenation.[3] However, the development of aminophosphine phosphinites is found to be less successful compared with phosphine or phosphinite ligands. So far, no chiral aminophosphine phosphinite has been found to give the same high enantioselectivity as the best chiral phosphine or phosphinite ligands. Despite this, aminophosphine phosphinites still attract much attention because they possess the following advantages: (1) Optically active amino alcohol used as chiral source of aminophosphine phosphinite is available in a variety of forms; (2) Aminophosphine phosphinite can be conveniently prepared by reaction of the corresponding amino alcohol with chlorodiphenylphosphine in the presence of an organic base. From the economic and technological standpoint, it is of substantial interest to develop highly effective chiral aminophosphine phosphinite for asymmetric hydrogenation. In this paper, we report the results of systematical study on a series of novel chiral aminophosphine phosphinite ligands derived from (1*R*,2*S*)- or (1*S*,2*R*)-1,2-diphenyl-2-aminoethanol. The cationic rhodium complexes of these ligands are found to be highly effective catalysts for asymmetric hydrogenation of dehydroamino acid derivatives.[4]

Results and Discussion

Synthesis of chiral aminophosphine phosphinites

As shown in Scheme 1, three amino-phosphine phosphinites, namely (1*R*,2*S*)-*N*,*O*-bis(diphenylphosphino)-1,2-diphenyl-2-(*N*-methyl) aminoethanol [abbreviated (1*R*,2*S*)-DPAMPP], (1*S*,2*R*)-*N*,*O*-bis(diphenylphosphino)-1,2-diphenyl-2-(*N*-methyl)aminoethanol [abbreviated (1*S*,2*R*)-DPAMPP] and (1*S*,2*S*)-*N*,*O*-bis(diphenylphosphino)-1,2-diphenyl-2-(*N*-methyl)-aminoethanol [abbreviated (1*S*,2*S*)-DPAMPP], were synthesized from chiral 1,2-diphenyl-2-aminoethanols. Thus, formylation of (1*R*,2*S*)-**1** gave the corresponding formamide (1*R*,2*S*)-**2**;[5] borane reduction of (1*R*,2*S*)-**2**

Keywords: aminophosphine phosphinite; dehydroamino acid derivative; asymmetric hydrogenation.

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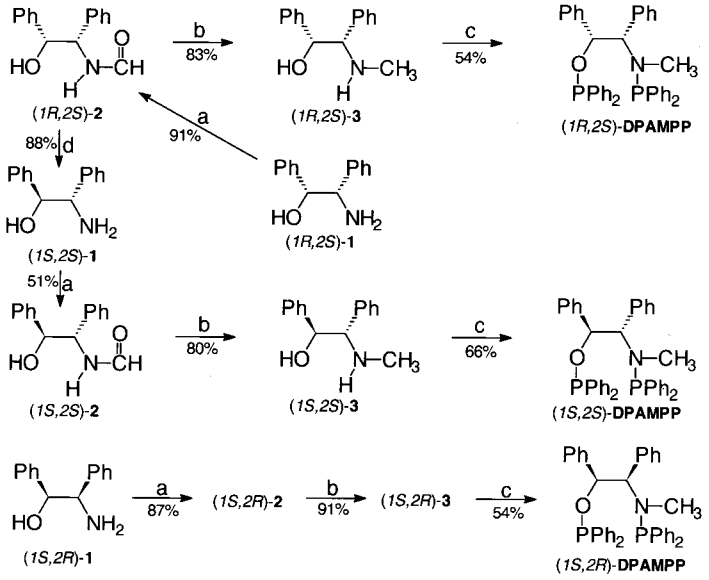
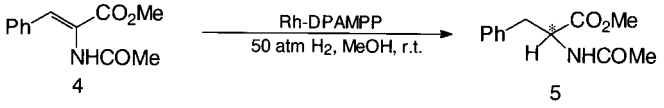


Scheme 1. Synthetic routes to chiral aminophosphine phosphinites. Reaction conditions: (a) HCOOEt, TsOH, reflux, 3 h; (b) BH_3–THF, r.t., 24 h; (c) $ClPPh_2$, NEt_3, benzene, 24 h; (d) i. $SOCl_2$; ii. 50% NaOH.

afforded *N*-methyl product (1*R*,2*S*)-**3**;[6] then the desired aminophosphine phosphinite (1*R*,2*S*)-DPAMPP was prepared in a yield of 54% by reaction of compound (1*R*,2*S*)-**3** with chlorodiphenylphosphine in the presence of triethylamine.[3e] Similarly, (1*S*,2*R*)-DPAMPP was synthesized using the corresponding chiral amino alcohol (1*S*,2*R*)-**1** as starting material. For preparation of (1*S*,2*S*)-DPAMPP, a *threo*-isomer of (1*R*,2*S*)- or (1*S*,2*R*)-DPAMPP, (1*R*,2*S*)-**2** was treated with thionyl chloride followed by hydrolysis with aqueous sodium hydroxide to give (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol;[7] (1*S*,2*S*)-**1** was further transformed to (1*S*,2*S*)-DPAMPP via the same steps as (1*R*,2*S*)-DPAMPP. All these three DPAMPPs are white solids and stable under argon atmosphere for at least one year as checked by ^1H NMR and ^{31}P NMR. Even in benzene, these DPAMPPs are stable enough to be purified by flash column chromatography over silica gel under an air atmosphere. Undoubtedly, the stability of DPAMPPs is especially beneficial to their potential use in industrial processes.

Enantioselective hydrogenation of methyl (*Z*)-acetamidocinnaminate 4 by Rh-DPAMPP catalysts

With these chiral DPAMPPs in hands, we firstly investigated the homogeneous catalytic asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate **4** (Scheme 2). The catalyst was generally prepared in situ by mixing a solution of a Rh precursor and a DPAMPP ligand. Some conclusions can be drawn from these results shown in Table 1. (1) Different Rh precursors lead to large variations in enantioselectivity and reactivity (comparing Entry 1 and Entry 2), higher enantioselectivity was observed with cationic Rh catalyst (Entry 2, 96.9% e.e.), only 27.0% e.e. and 31% conversion was obtained with the neutral Rh system even if the reaction time was prolonged to 17 h. (2) Both enantiomers of phenylalanine derivatives can be prepared in the same enantioselectivity by using the appropriate enantiomer of DPAMPP (Entry 2, 3). (3) The configuration of ligand has a large effect on the enantioselectivity of



Scheme 2.

Table 1. Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate (the reaction was carried out in methanol under an initial hydrogen pressure of 50 atm at room temperature with a ratio of substrate/catalyst of 100:1. The reaction time was 1 h unless otherwise noted)

Entry	Catalyst system	e.e. %[a]	Conv.%	Configuration[b]
1[c]	$[Rh(COD)Cl]_2$/(1*R*,2*S*)-DPAMPP	27.0	31.1	*S*
2	$[Rh(COD)Cl]_2/AgBF_4$/(1*R*,2*S*)-DPAMPP	96.9	100	*S*
3	$[Rh(COD)Cl]_2/AgBF_4$/(1*S*,2*R*)-DPAMPP	98.3	100	*R*
4	$[Rh(COD)Cl]_2/AgBF_4$/(1*S*,2*S*)-DPAMPP	40.6	100	*R*

[a] The enantiomeric excesses were determined by GC on a Chrompack Chirasil-L-Val column.
[b] The absolute configuration was assigned by comparison of optical rotation with reported value.
[c] The reaction time was 17 h.

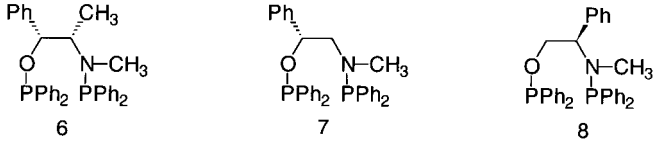


Figure 1.

reaction, hydrogenation using the erythro series (1*R*,2*S*)- or (1*S*,2*R*)-DPAMPP as ligands gave high enantioselectivity (Entry 2, 3) while a significantly lower e.e. value was observed with the *thero* ligand (1*S*,2*S*)-DPAMPP (Entry 4). It seems that the correct array of two phenyls in DPAMPPs is important for high enantioselectivity. (4) The sense of asymmetric induction is determined primarily by the configuration of the oxygen-bearing carbon, because (1*S*,2*R*)- and (1*S*,2*S*)-DPAMPP gave the product with the same configuration (*R*)-phenylalanine (Entry 3, 4) whereas (1*R*,2*S*)-DPAMPP gave (*S*)-enriched product (Entry 2), and the lower enantioselectivity of (1*S*,2*S*)-DPAMPP implies that the nitrogen-substituted chiral carbon affects greatly the extent of the enantioselection.

To our knowledge, the 98.3% e.e. obtained with (1*R*,2*S*) and (1*S*,2*R*)-DPAMPP is the best result among those with other aminophosphine phosphinites reported to date. Furthermore, the excellent enantioselectivity of *erythro*-DPAMPP is also comparable to the best well-known chiral phosphine[8] or phosphinite ligands.[9] Pracejus had investigated asymmetric hydrogenation of compound **4** using a series of aminophosphine phosphinites **6**, **7** and **8** as ligands (Fig. 1), only 75% e.e., 55% e.e. and 14% e.e. were obtained respectively.[3g] Compared with our results (Entry 3, Table 1), it can be found that the enantioselectivity increases dramatically with enhancement of the bulkiness of substitutents on these aminophosphine-phosphinites. The high enantioselectivity of *erythro*-DPAMPP is rationalized by the two bulky phenyls on the C(1) and C(2) positions that may increase the rigidity of the chiral ligand and are therefore beneficial to stabilizing the spatial conformation of the active transition state complex formed from catalyst and substrate.

For increasing enantioselectivity and reactivity of the reaction, the optimal conditions were examined, such as the effects of solvent (Table 2), hydrogen pressure (Table 3), reaction temperature and substrate concentration (Table 4). Asymmetric hydrogenation using (1*R*,2*S*)-DPAMPP as ligand preceeded smoothly in methanol, acetone, THF and isopropanol with a slight variation in e.e., and methanol was the best solvent (Table 2). The optical yields were independent of hydrogen pressure over the 1–80 atm range, however the rate of hydrogenation decreases greatly with lowering hydrogen pressure (Table 3). This suggests that oxidative addition of hydrogen to the rhodium species should be the rate-determining step, rather than the enantio-determining step. An increase in reaction temperature caused a slight decrease in enantioselectivity. Under an initial hydrogen pressure of 10 atm with a ratio of (1*R*,2*S*)-DPAMPP-Rh and methyl (*Z*)-acetamidocinnamate (**4**) (S/C) of 100 in acetone, the e.e. value was decreased from 96.3% to 95.7 and 95.0% as the reaction temperature increases from 0 to 25 and 50°C. This result is consistent with that achieved with Ph-β-Glup[9b] but in contrast to those with DIOP, DIPAMP and CHIRAPHOS.[10] The enantioselectivity dropped slightly with decreasing the reactant concentration (Table 4), and this is quite different from the result with Rh-BINAP system,[11] a possible explanation is that at lower concentration, the hydrogenation proceeds more slowly and is therefore more easily subjected to the negative effect due to the erosion of catalyst.

Table 2. The effect of solvent on hydrogenation of methyl (*Z*)-acetamidocinnamate **4** catalyzed by [((1*R*,2*S*)-DPAMPP)Rh(COD)]BF_4 (reaction conditions: 10 atm H_2 pressure; 25°C; S/C=100; substrate concentration (C_{sub})=0.05 M; 100% conversion was observed after 1 h of reaction in all cases)

Entry	Solvent	e.e.%	*S*:*R*
1	MeOH	97.0	65.7:1
2	Acetone	95.1	39.8:1
3	THF	94.8	37.5:1
4	*i*-PrOH	92.7	26.4:1

Table 3. The effect of hydrogen pressure on hydrogenation of methyl (*Z*)-acetamidocinnamate **4** catalyzed by [((1*R*,2*S*)-DPAMPP)Rh(COD)]BF_4 (reaction conditions: methanol as solvent; 25°C; S/C=100; C_{sub}=0.05 M; 100% conversion)

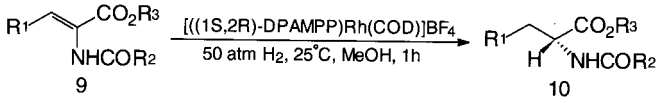
Entry	H_2 pressure (atm)	Time (h)	e.e.%
1	80	0.5	96.8
2	50	1.0	96.9
3	20	1.0	96.4
4	1	4.0	97.2

Table 4. The effect of reactant concentration on the hydrogenation of methyl (*Z*)-acetamidocinnamate **4** catalyzed by [((1*R*,2*S*)-DPAMPP)Rh-(COD)]BF_4 (reaction conditions: acetone as solvent; 10 atm of H_2; 25°C; S/C=100; 100% conversion)

Entry	Substrate concentration (M)	e.e.%	*S*:*R*
1	0.10	96.2	52.5:1
2	0.05	95.8	46.6:1
3	0.02	94.5	35.4:1
4	0.01	93.8	31.3:1

Table 5. The effect of the ratio of substrate/catalyst on hydrogenation of methyl (*Z*)-acetamidocinnamate **4** catalyzed by [((1*S*,2*R*)-DPAMPP)Rh-(COD)]BF_4 (the reaction was carried out under 50 atm of H_2 at 25°C in methanol)

Entry	Substrate/catalyst	Time (h)	e.e.%	Conv.%
1	100	1	98.3	100
2	1000	4	97.5	100
3	10 000	16	97.0	100
4	50 000	64	97.0	82.7
5	100 000	64	93.0	41.7



Scheme 3.

Table 6. Asymmetric hydrogenation of dehydroamino acid derivatives **9** catalyzed by [((1*S*,2*R*)-DPAMPP)Rh(COD)]BF_4 (reaction conditions: 50 atm of H_2; 25°C; 1 h reaction time; S/C=100; methanol used as solvent unless otherwise noted; 100% conversion was observed in all cases. The (*R*)-configuration was obtained for all products)

Entry	Substrate			e.e.%[a]
	R^1	R^2	R^3	
1	Ph	Me	Me	98.3
2	4-MeO–Ph	Me	Me	97.3
3	4-Me–Ph	Me	Me	97.3
4	4-F–Ph	Me	Me	97.2
5	4-Cl–Ph	Me	Me	97.8
6	3-Cl–Ph	Me	Me	95.1
7	2-Cl–Ph	Me	Me	92.3(98.4)[b]
8	4-Br–Ph	Me	Me	98.0
9	4-NO_2–Ph	Me	Me	97.5
10	4-AcO–Ph	Me	Me	95.6
11	3-MeO–4-AcO–Ph	Me	Me	98.1[c]
12	3,4-OCH_2O–Ph	Me	Me	97.5
13	2′-furanyl	Me	Me	91.1
14	Ph	Ph	Me	97.1
15	4-Cl–Ph	Ph	Me	97.0
16	4-Br–Ph	Ph	Me	96.5
17	2-HO–Ph	Ph	Me	96.3
18	2-Cl–3-AcO–4-MeO–Ph	Ph	Me	98.0[c]
19	Ph	Me	H	96.5[d]
20	Ph	Ph	H	96.4[d]
21	4-NO_2–Ph	Ph	H	97.4
22	H	Me	H	95.2[d]
23	H	Ph	H	94.8[d]
24	$PhCH_2$	Me	Et	93.1

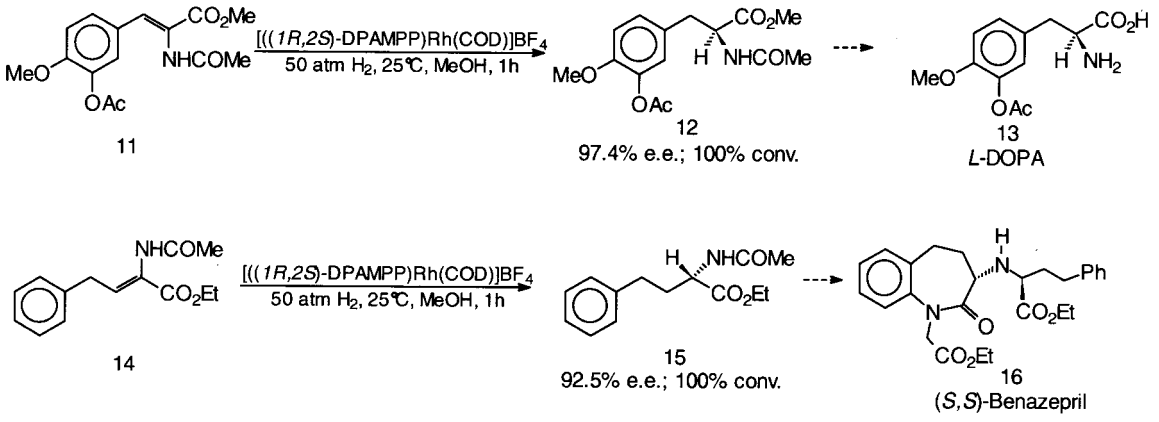
[a] The e.e. values were determined by GC on a Chrompack Chirasil-L-Val column unless otherwise noted.
[b] The data in parenthesis was obtained from hydrogenation in acetone.
[c] The e.e. values were determined by HPLC on a Chiralcel OD column.
[d] The e.e. values were determined by GC on a Chrompack Chirasil-L-Val column after converting the products to the corresponding methyl esters.

Moreover, hydrogenation of methyl (*Z*)-acetamidocinnamate was carried out at much higher ratio of substrate/catalyst (S/C) using [((1*S*,2*R*)-DPAMPP)Rh(COD)]BF_4 as a catalyst, no significant decrease of enantioselectivity was observed even when the ratio of S/C was increased up to 50000 (Table 5, Entry 4). When the ratio of S/C was 10000, the reaction was complete within 16 h with 100% conversion and 97.0% enantiomeric excess. This justifies the use of the Rh-DPAMPP catalyst on economic grounds.

Asymmetric hydrogenation of various dehydroamino acid derivatives catalyzed by Rh-DPAMPP complex

After investigation of the optimal conditions, various dehydroamino acid derivatives were used for (1*S*,2*R*)-DPAMPP-Rh catalyzed hydrogenation (Scheme 3). The results summarized in Table 6 indicate that the high enantioselectivity of (1*S*,2*R*)-DPAMPP was quite general for a great deal of different dehydroamino acid precursors. In all cases, the desired (*R*)-products were found to have e.e. values of over 90.0%. As expected, (*S*)-products can be prepared in a relatively high enantioselectivity by using (1*R*,2*S*)-DPAMPP as ligand (see Tables 1–4).

Table 6 clearly showed that the structure of substrate affected the outcome of hydrogenation. The enantiomeric excesses are particularly high (more than 95.0% e.e., Entry 1–12 and Entry 14–21) when R^1 is phenyl or its analogues regardless of the substituents on their aromatic rings. For the reaction performed in methanol, methyl (*Z*)-2-acetamido-3-phenylacrylate **4** was reduced to give the highest e.e. (98.3% e.e., Entry 1). A decrease of enantioselectivity was observed when the R^1 group of substrate **9** was replaced with hydrogen atom, alkyl and heteroaromatic ring (Entry 22, 23, 24 and 13). It was found that the presence of electron-withdrawing groups on an olefinic substrate enhances late-transition metal binding constants and results in higher enantioselectivity in asymmetric hydrogenation reaction.[12]



Scheme 4.

However, the lower e.e.s obtained with methyl (*Z*)-2-acetamido-3-furanylacrylate may be caused by the possible interaction between oxygen atom in furanyl and the Rh catalyst. On the other hand, the *para*-substituents on 3-phenyl almost showed no significant effect on the enantioselectivity regardless of their electron-withdrawing or electron-donating properties. Surprisingly, the difference of the substituted position for these groups results in an obviously dissimilarity in e.e. (Entry 5, 6, 7). For example, only 92.3% e.e. was achieved for hydrogenation of methyl (*Z*)-2-acetamido-3-(2′-chlorophenyl)acrylate while hydrogenation of its 3′-chloro and 4′-chloro analogues gave more than 95.0% enantioselectivity. More interestingly, using acetone as solvent, hydrogenation of methyl (*Z*)-2-acetamido-3-(2′-chlorophenyl)acrylate gave a high e.e. of 98.4%, which was also the best result reported to date. The R^2 and R^3 groups of substrate **9** have a small effect on hydrogenation. Generally, hydrogenation gave a slightly better e.e. when R^2 was acetyl and R^3 was methyl.

It is noticeable that these reactions have found wide practical application in the synthesis of biologically active molecules. For example, methyl (*S*)-2-acetamido-3-(3-methoxy-4-acetoxyphenyl)-propionate **12**, a crucial intermediate for the synthesis of the well-known L-DOPA **13**,[13] could be synthesized in 97.4% e.e. by hydrogenation of methyl (*Z*)-2-acetamido-3-(3-methoxy-4-acetoxy phenyl)-acrylate **11** catalyzed by [((1*R*,2*S*)-DPAMPP)Rh(COD)]BF_4 (Scheme 4). Similarly, enantioselective hydrogenation of ethyl (*Z*)-2-acetamido-4-phenylcrotonate **14** gave the optically active homophenylalanine derivative **15** with 92.5% e.e., which was also a key component of (*S*,*S*)-benazepril **16,** an ACE (angiotensin converting enzyme) inhibitor widely used as antihypertensive.[14]

In summary, we have synthesized a series of highly effective chiral amino phosphine phosphinite ligands for hydrogenation of dehydroamino acid precursors. The excellent enantioselectivity in preparation of both (*R*)- and (*S*)-amino acids with (1*S*,2*R*)- or (1*R*,2*S*)-isomer of DPAMPP means a breakthrough in developing aminophosphine phosphinite ligands for asymmetric catalytic reaction. Moreover, the high catalytic activity and enantioselctivity combined with facile preparation for chiral DPAMPP indicates their wide potential application in asymmetric synthesis.

Experimental

General aspects

All melting points were determined on a digital melting point apparatus and were uncorrected. ^{1}H NMR and ^{31}P NMR spectra were recorded on Brucker AC-200 and Brucker AC-400 spectrometers. Elemental analyses were performed on a Carlo Erba-1106 instrument. Infrared spectra were recorded on a Nicolet MX-1 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. All reactions involving air- and moisture-sensitive compounds were carried out under a dry argon atmosphere using standard Schlenk line techniques. THF, benzene and triethylamine were distilled from sodium benzophenone ketyl; solvents used in hydrogenation were degassed by three freeze–thaw cycles prior to use.

Materials

(1*R*,2*S*)- and (1*S*,2*R*)-1,2-Diphenyl-2-aminoethanols were prepared on large scale in our laboratory.[15] Chlorodiphenylphosphine, $AgBF_4$ and $[Rh(COD)Cl]_2$ were purchased from Aldrich Chemical Co. BH_3–THF (1.5 M) was prepared according to the literature method.[16] All (*Z*)-2-acylamido-3-arylacrylic acids were synthesized in accordance with the process developed by Herbst.[17] Their corresponding methyl esters were prepared by the reaction of free acids with MeI in the presence of $KHCO_3$ in DMF. The preparation of ethyl (*Z*)-2-acetamido-4-phenylcrotonate was achieved using the literature procedure with slight modification.[18]

(1*R*,2*S*)-1,2-Diphenyl-2-formamidoethanol, (1*R*,2*S*)-2. The mixture of (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol (2.0 g, 9.39 mmol) and *p*-toluene sulfonic acid (20 mg) were heated to reflux in ethyl formate (40 mL) for 3 h. The excess of ethyl formate was removed in vaccum. The residue was recrystallized from ethanol to give 2.05 g (91% yield) of desired product as a white solid: mp 204–205°C; $[\alpha]_D^{20}=-2.91$ (0.64, EtOH); ν_{max}(KBr): 3350, 1664 cm^{-1}; ^{1}H NMR (DMSO) δ 4.77 (d, J=6.8 Hz, 1H, OCH), 5.01 (dd, J_1=6.9 Hz, J_2=9.3 Hz, 1H, NCH), 7.09–7.49 (m, 10H, 2×Ph), 7.89 (s, 1H, HCO), 8.57 (d, J=9.3 Hz, 1H, CONH). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.60; H, 6.27; N, 5.81. Found: C, 74.32; H, 6.27; N, 5.68.

(1*S*,2*R*)-1,2-Diphenyl-2-formamidoethanol, (1*S*,2*R*)-2. With the similar procedure described in the synthesis of (1*R*,2*S*)-**2**, the desired (1*S*,2*R*)-**2** was obtained in 87% yield as a white solid: mp 205–206°C; $[\alpha]_D^{20}=+2.95$ (0.52, EtOH); ^{1}H NMR (DMSO) δ 4.77 (d, J=6.8 Hz, 1H, OCH), 5.01 (dd, J_1=6.8 Hz, J_2=9.3 Hz, 1H, NCH), 7.17–7.33 (m, 10H, 2×Ph), 7.89 (s, 1H, HCO), 8.57 (d, J=9.3 Hz, 1H, CONH).

(1*S*,2*S*)-1,2-Diphenyl-2-aminoethanol, (1*S*,2*S*)-1. Thionyl chloride (7.8 mL, 107 mmol) was added to (1*R*,2*S*)-**2** (3.6 g, 14.9 mmol) at −15°C. After stirring at −15°C for 3 h and then at room temperature for additional 10 h, 50 mL of cooled water was added. The resulted solution was refluxed for 3 h followed by neutralization with 14 mL of 50% NaOH. The precipitated product was collected by filtration and further purified by recrystallization from ethanol to give 2.6 g (88% yield) of (1*S*,2*S*)-**1** as a white needle crystalline solid: mp 123–124°C; $[\alpha]_D^{20}=-131.4$ (0.87, EtOH); ν_{max}(KBr) 3360, 3080, 2900, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.27 (br s, 3H, NH_2, OH), 4.14 (d, J=7.3 Hz, 1H, NCH), 4.74 (d, J=7.3 Hz, 1H, OCH), 7.14–7.26 (m, 10H, 2×Ph); Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.90; H, 6.95; N, 6.55.

(1*S*,2*S*)-1,2-Diphenyl-2-formamidoethanol, (1*S*,2*S*)-2. The desired (1*S*,2*S*)-**2** was prepared using the same procedure described for the synthesis of (1*R*,2*S*)-**2**. The crude product was purified by flash chromatography on silica gel eluted with chloroform/methanol (9:1) to give 51% yield as a white needle crystalline solid: mp 127–128°C; $[\alpha]_D^{20}=+6.1$ (0.26, EtOH); ν_{max}(KBr) 3320, 3040, 1660, 1530, 1400 cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 5.04 (d, J=4.0 Hz, 1H, OCH), 5.30 (dd, J_1=3.9 Hz, J_2=7.9 Hz, 1H, NCH), 6.52 (d, J=7.1 Hz, 1H, CONH), 7.10–7.36 (m, 10H, 2×Ph), 8.19 (s, 1H, HCO); Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.38; H, 6.25; N, 5.66.

(1*R*,2*S*)-1,2-Diphenyl-2-(*N*-methyl)aminoethanol, (1*R*,2*S*)-3. 12 mL of 1.5 M BH_3/THF (18 mmol) was added slowly to the solution of (1*R*,2*S*)-**2** (0.93 g, 3.86 mmol) in anhydrous THF (10 mL) at 0°C. After stirring for 24 h at room temperature, the reaction was quenched with methanol and 3 N HCl. THF was distilled in vaccum, and the residue was neutralized with 40% NaOH followed by extraction with chloroform (10 mL×3). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$. After removal of the solvent, the crude was recrystallized from petroleum (bp 60–90°C) to give 0.73 g (83% yield) of white needle crystalline solid: mp 135–137°C; $[\alpha]_D^{20}$=−31.6 (0.42, EtOH); ν_{max}(KBr): 3310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 3.76 (d, J=5.9 Hz, 1H, NCH), 4.80 (d, J=5.9 Hz, 1H, OCH), 7.11–7.28 (m, 10H, 2×Ph). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.63; H, 7.47; N, 6.15.

(1*S*,2*R*)-1,2-Diphenyl-2-(*N*-methyl)aminoethanol, (1*S*,2*R*)-3. With the same procedure described for the synthesis of (1*R*,2*S*)-**3**, compound (1*S*,2*R*)-**3** was prepared in 91.0% yield as a white needle crystalline solid: mp 135–136°C; $[\alpha]_D^{20}$=+32.8 (0.50, EtOH); ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 3.78 (d, J=5.8 Hz, 1H, NCH), 4.82 (d, J=6.0 Hz, 1H, OCH), 7.10–7.30 (m, 10H, 2×Ph). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.50; H, 7.45; N, 6.25.

(1*S*,2*S*)-1,2-Diphenyl-2-(*N*-methyl)aminoethanol, (1*S*,2*S*)-3. With the similar procedure described in the synthesis of (1*R*,2*S*)-**3**, compound (1*S*,2*R*)-**3** was prepared in 80% yield as a white needle crystalline solid: mp 125–126°C; $[\alpha]_D^{20}$=−115.8 (0.34, EtOH); ν_{max}(KBr) 3320, 3040, 1660, 1530, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 3.51 (d, J=8.6 Hz, 1H, NCH), 4.60 (d, J=8.6 Hz, 1H, OCH), 7.01–7.26 (m, 10H, 2×Ph); Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.71; H, 7.59; N, 6.02.

(1*R*,2*S*)-*N*,*O*-bis(diphenylphosphino)-1,2-diphenyl-2-(*N*-methyl)aminoethanol, (1*R*,2*S*)-DPAMPP. (1*R*,2*S*)-**3** (100 mg, 0.44 mmol) and triethylamine (0.13 mL, 0.90 mmol) were dissolved in 3 mL of anhydrous benzene. A solution of chlorodiphenylphosphine (0.16 mL, 0.90 mmol) in benzene (1 mL) was added dropwise to the mixture at 0°C. After stirring at room temperature for 24 h, the formed triethylammonium chloride was removed by filtration, and the obtained filtrate was purified directly by flash column chromatography on silica gel eluted with benzene to give 140 mg (54% yield) of (1*R*,2*S*)-DPAMPP as a white crystalline solid: mp 91–93°C; $[\alpha]_D^{20}$=−33.1 (0.28, benzene); ν_{max} (KBr) 3400, 3040, 2910, 1430 cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 64.8 (s, $P_{(N)}$), 111.8 (s, $P_{(O)}$); ^1H NMR (CD_2Cl_2) δ 2.21 (d, J_{P-H}=2.5 Hz, 3H, CH_3), 4.94 (dd, J_{H-H}=10.4 Hz, J_{P-H}=14.2 Hz, 1H, NCH), 5.57 (dd, J_{H-H}=10.1 Hz, J_{P-H}=8.3 Hz, 1H, OCH), 6.53–7.52 (m, 30H, 6×Ph); ^{13}C NMR (CD_2Cl_2) δ 33.6, 75.1, 83.5, 128.0, 128.4, 128.6, 128.7, 128.8, 129.1, 129.2, 129.4, 129.5, 129.6, 130.8, 131.0, 131.2, 132.4, 132.6, 132.8, 139.3, 139.4, 140.5, 141.3, 142.3, 142.4, 142.9, 143.1; Anal. Calcd for $C_{39}H_{35}NOP_2$: C, 78.64; H, 5.92; N, 2.35; P, 10.40. Found: C, 78.51; H, 5.78; N, 2.32; P, 9.94.

(1*S*,2*R*)-*N*,*O*-bis(diphenylphosphino)-1,2-diphenyl-2-(*N*-methyl)aminoethanol, (1*S*,2*R*)-DPAMPP. With the similar procedure described in the synthesis of (1*R*,2*S*)-DPAMPP, (1*S*,2*R*)-DPAMPP was prepared in 54% yield as a white crystalline solid: mp 94–96°C; $[\alpha]_D^{20}$=+37.6 (0.22, benzene); ν_{max} (KBr) 3410, 3050, 2920, 1430 cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 65.9 (s, $P_{(N)}$), 113.3 (s, $P_{(O)}$); ^1H NMR ($CDCl_3$) δ 2.21 (d, J_{P-H}=2.4 Hz, 3H, CH_3), 4.94 (dd, J_{H-H}=10.0 Hz, J_{P-H}=14.4 Hz, 1H, NCH), 5.57 (dd, J_{H-H}=10.4 Hz, J_{P-H}=8.4 Hz, 1H, OCH), 6.53–7.74 (m, 30H, 6×Ph); Anal. Calcd for $C_{39}H_{35}NOP_2$: C, 78.64; H, 5.92; N, 2.35; P, 10.40. Found: C, 78.50; H, 5.90; N, 2.64; P, 10.02.

(1*S*,2*S*)-*N*,*O*-bis(diphenylphosphino)-1,2-diphenyl-2-(*N*-methyl)aminoethanol, (1*S*,2*S*)-DPAMPP. With the similar procedure described in the synthesis of (1*R*,2*S*)-DPAMPP, (1*S*,2*S*)-DPAMPP was prepared in 66% yield as a white solid: mp 148–150°C; $[\alpha]_D^{20}$=−46.5 (0.17, benzene); ν_{max}(KBr) 3450, 3060, 2960, 1435 cm^{-1}; ^{31}P NMR ($CDCl_3$) δ 63.7 (s, $P_{(N)}$), 106.3 (s, $P_{(O)}$); ^1H NMR ($CDCl_3$) δ 2.42 (d, J_{P-H}=2.4 Hz, 3H, CH_3), 4.86 (dd, J_{H-H}=10.0 Hz, J_{P-H}=10.4 Hz, 1H, NCH), 5.39 (dd, J_{H-H}=9.2 Hz, J_{P-H}=6.8 Hz, 1H, OCH), 6.90–7.78 (m, 30H, 6×Ph); Anal. Calcd for $C_{39}H_{35}NOP_2$: C, 78.64; H, 5.92; N, 2.35; P, 10.40. Found: C, 78.39; H, 5.85; N, 2.71; P, 9.90

A general procedure for asymmetric hydrogenation catalyzed by cationic Rh complex

The cationic Rh catalyst was prepared in situ by stirring the mixture of $[Rh(COD)Cl]_2$, $AgBF_4$ and an appropriate chiral DPAMPP in THF for 2 h. The resulting cationic catalyst was characterized by ^{31}P NMR (for example, ^{31}P NMR (CD_2Cl_2) of [((1*R*,2*S*)-DPAMPP)Rh(COD)]BF_4: δ 72.4 (dd, $J_{P(O)-P(N)}$=653.8 Hz, $J_{Rh-P(N)}$=334.4 Hz, $P_{(N)}$), 138.0 (dd, $J_{P(N)-P(O)}$=653.2 Hz, $J_{Rh-P(O)}$=397.0 Hz, $P_{(O)}$)). In a stainless steel autoclave, a dehydroamino acid derivative (0.02 mmol) was dissolved in a degassed solvent (0.4 mL). To the solution was add the prepared catalyst (0.0002 mmol). The reactor was then pressurized with hydrogen and the reaction was run under the chosen conditions and determined by GC on a Chrompack Chirasil-L-Val column or by HPLC on a Chiralcel OD column.

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