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Asymmetric synthesis of homoproline derivatives via Rh(I)-catalyzed hydrogenation using chiral bisphosphines as ligands

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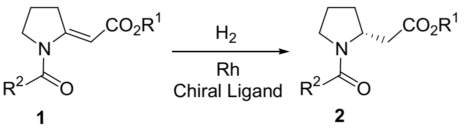
Abstract—It has been demonstrated for the first time that Rh(I)-catalyzed asymmetric hydrogenation of cyclic β-enamino acid derivatives **1** using chiral bisphosphines could be a highly efficient synthetic method for optically active homoproline derivatives. The enantioselectivity and conversion yield were largely dependent upon the chiral ligand. Using the Me-BDPMI forming a seven-membered metal chelate, the *N*-acetylated β-enamino acid methyl ester **1a** was hydrogenated to give optically active homoproline derivative **2a** with 100% conversion and 96% ee.

1. Introduction

Interest in optically active cyclic β-amino acids such as pyrrolidine-2-yl acetic acid (homoproline) derivatives **2** has arisen not only from the synthetic prospective but also from their utility in wide-ranging biologically active compounds.[1] However, there are only a few methods available for the asymmetric synthesis of homoproline and its cyclic homologous. Arndt–Eistert homologation of natural (*S*)-proline has been frequently used and works well, but is limited to the (*S*)-enantiomer.[2] Two stoichiometric approaches using sacrificial chiral auxiliaries have been disclosed:[3] (i) asymmetric Michael addition of lithiated TMS-SAMP or chiral amines to α,β-unsaturated esters followed by cyclization[3a,b,c] and (ii) diastereoselective reduction of chiral β-enamino esters.[3d,e,f] Therefore, a practical and efficient synthesis of enantiomerically pure homoproline derivatives is still highly desirable. An attractive and simple approach to these cyclic β-amino acid derivatives would be direct asymmetric hydrogenation of cyclic β-enamino esters **2**. In recent years, Rh- or Ru-catalyzed asymmetric hydrogenation of acyclic β-(acylamino)acrylic acid derivatives to make optically active acyclic β-amino acids has attracted much attention with excellent enantioselectivities being achieved by using chiral phosphine ligands.[4] In contrast to acyclic β-amino acids, only one type of optically active cyclic β-amino acids has been synthesized by asymmetric hydrogenation. Very recently, Zhang and co-workers reported that Ru-Cn-TunaPhos complexes hydrogenated tetrasubstituted cyclic β-(acylamino)acrylates affording 2-amino cycloalkane carboxylates with extremely high enantioselectivities whereas no catalytic activity has been observed with a Rh-bisphosphine complex.[5] However, no asymmetric synthesis of homoprolines through the enantioselective hydrogenation of cyclic β-enamino acid derivatives **1** has been reported yet. Herein we report for the first time the asymmetric synthesis of homoprolines **2** via Rh-bisphosphine complex-catalyzed enantioselective hydrogenation of cyclic β-enamino acid esters **1** (Scheme 1).



Scheme 1. Rh-Catalyzed asymmetric hydrogenation of cyclic β-enamino acid esters.

2. Results and discussions

The prochiral substrates **1a–d** can easily be synthesized by *N*-acylation of pyrrolidine enamino acid methyl ester **3**, which was prepared according to the reported procedure starting from pyrrolidone (Scheme 2).[6] As reported by Lhommet et al. *N*-acylation proceeded

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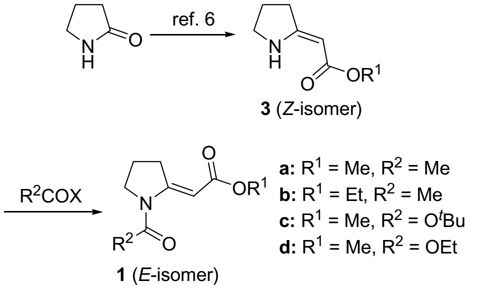


Scheme 2. Synthesis of pyrrolidin-2-ylideneacetic acid esters **1a**–**d**.

chemoselectively whereas selective *C*-acetylations occurred in six- and seven-membered homologous of **3**.[7] More interestingly, the *Z*-geometry of **3**, which is thermodynamically more stable due to the intramolecular H-bonding, was isomerized to give *E*-isomer **1**. Since the *E*/*Z*-geometry of the substrate is very important in the hydrogenation of acyclic β-(acylamino)acrylates,[4] we carefully assigned the geometry of **1**, which was confirmed unambiguously by X-ray analysis of **1a** (Fig. 1).

Recently, we reported that Rh(I)-complexes of chiral 1,4-bisphosphines bearing an imidazolidin-2-one backbone, (*S*,*S*)-BDPMI **4**,[8] exhibited excellent catalytic activities in asymmetric hydrogenation of acyclic *E*- and *Z*-β-(acylamino)acrylates.[8c] Herein, the catalytic activities of (*S*,*S*)-BDPMIs **4a**–**d** for *N*-acetylated **1a** were examined first under hydrogenation conditions applied previously for acyclic β-(acylamino)acrylates. Thus, the reaction of **1a** was performed in CH_2Cl_2 for 12 h at 20 °C under 1 atm H_2 pressure in the presence of 1 mol% of Rh-(*S*,*S*)-BDPMI complex in situ generated from $[Rh(cod)_2]BF_4$. As we observed in the hydrogenation of enamide and acyclic β-(acylamino) acrylates, the *N*-substituents of BDPMI had a large affect on the catalytic activity.[8a,c] Hydrogenation with (*S*,*S*)-H-BDPMI **4a** afforded *N*-acetylated homoproline methyl ester with 64% conversion and 82% ee (entry 1). The conversion and enantioselectivity increased with the *N*-substituted BDPMIs (entries 2–4), with the highest catalytic activity being achieved with the *N*,*N*′-dimethylated BDPMI, Me-BDPMI **4d** (entry 4, 100% conversion, 96% ee). When the reaction was carried out in MeOH, the enantioselectivity slightly decreased (entry 5, 93% ee). Next, we screened a number of chiral bisphosphines, which formed five-, six-, and seven-membered metal chelates (entries 6–12), and found that the catalytic activity of these ligands were much lower than those of BDPMI ligands. Me-DuPhos exhibited the highest enantioselectivity (>99% ee); however, the conversion yield was only 37% (entry 6). The reaction with ChiraPhos forming a five-membered chelate did not proceed at all (entry 7). The conversion and enantioselectivity decreased when the reaction was performed with BDPP, which formed a six-membered metal chelate, (entry 8, 27% conversion, 85% ee). A large increase in conversion was observed by employing DIOP, which formed a seven-membered metal chelate (entry 9, 83% conversion, 70% ee). However, the catalytic activities of the axially chiral ligands, BINAP (entry 11) and Tol-BINAP (entry 12) were much lower than that of the DIOP (Table 1).

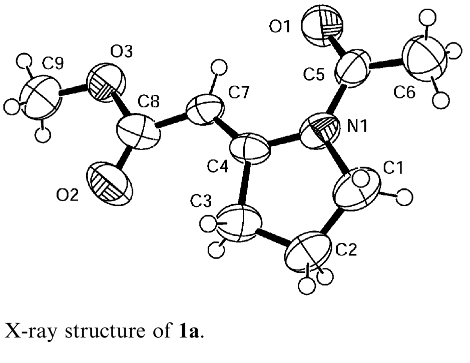
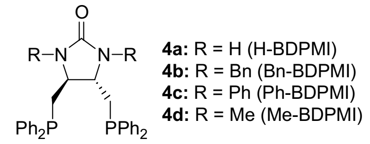


Figure 1. X-ray structure of **1a**.

We confirmed that the product's stereochemistry was dependent upon the ligand stereochemistry via reaction with (*R*,*R*)-DIOP (entry 10) affording the (*S*)-isomer as the major product. Hydrogenation of other substrates **1b**–**d** with Me-BDPMI was also examined (entries 13–15). The *N*-acetylated ethyl ester **1b** was hydrogenated with the same conversion and enantioselectivity with that of the methyl ester (entry 13). However, when the *N*-protecting group was changed to Boc (entry 14, 97% conversion, 87% ee) and ethoxycarbonyl (entry 15, 81% conversion, 92% ee) groups, both the conversion yield and enantioselectivity slightly decreased.

In summary, we have demonstrated for the first time that chiral bisphosphine-Rh complex-catalyzed asymmetric hydrogenation of cyclic β-enamino acid deriva-

Table 1. Rh-Catalyzed asymmetric hydrogenation of **1a**–**d** using chiral bisphosphines as ligands[a]



Entry	Ligand	1	Conv. (%)[b]	% Ee[c]	Conf.[d]
1	(*S*,*S*)-H-BDPMI **4a**	**1a**	64	82	*R*
2	(*S*,*S*)-Bn-BDPMI **4b**	**1a**	100	92	*R*
3	(*S*,*S*)-Ph-BDPMI **4c**	**1a**	96	96	*R*
4	(*S*,*S*)-Me-BDPMI **4d**	**1a**	100	96	*R*
5[e]	(*S*,*S*)-Me-BDPMI **4d**	**1a**	100	93	*R*
6	(*R*,*R*)-Me-DuPhos	**1a**	37	>99	*R*
7	(*S*,*S*)-ChiraPhos	**1a**	—	—	*R*
8	(*R*,*R*)-BDPP	**1a**	27	85	*R*
9	(*S*,*S*)-DIOP	**1a**	83	70	*R*
10	(*R*,*R*)-DIOP	**1a**	82	71	*S*
11	(*R*)-BINAP	**1a**	12	48	*R*
12	(*R*)-Tol-BINAP	**1a**	33	52	*R*
13	(*S*,*S*)-Me-BDPMI **4d**	**1b**	100	96	*R*
14	(*S*,*S*)-Me-BDPMI **4d**	**1c**	97	87	*R*
15	(*S*,*S*)-Me-BDPMI **4d**	**1d**	81	92	*R*

[a] All reactions were carried out in CH_2Cl_2 at room temperature for 12 h under 1 atm of H_2 pressure. The catalyst was prepared in situ from $[Rh(cod)_2]BF_4$ and ligand (substrate:Rh:ligand = 100:1:1.2).

[b] Determined by ^1H NMR analysis.

[c] Determined by chiral GC using CP-Chiralsil-Dex-CB column.

[d] Comparison with the reported sign of the specific rotation of **2c** (Ref. 1d).

[e] Reaction in MeOH solvent.

tives could be a highly efficient synthetic method for optically active homoproline derivatives. It was also found that the enantioselectivity and conversion yield were very dependent upon the chiral ligand and *N*-protecting groups of the β-enamino acid esters. Development of an efficient synthetic method for six- and seven-membered cyclic β-enamino acid derivatives should provide a practical procedure for various cyclic homologous of homoprolines.

3. Experimental

Unless otherwise noted, all hydrogenations were carried out in an inert atmosphere. All solvents were degassed prior to use. NMR spectra were recorded on a Bruker 300 spectrometer. GC analyses were performed using a Hewlett–Packard 5890 Model.

3.1. Syntheses of 1a and 1b

A solution of pyrrolidin-2-ylidene acetic acid ester (1.84 mmol) and acetyl chloride (2.76 mmol) in dry benzene (20 mL) was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and washed with saturated $NaHCO_3$ solution (20 mL × 2) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane = 1:1) to give methyl *N*-acetylpyrrolidin-2-ylideneacetate (74%) as a white solid. Recrystallization with *n*-hexane/ethyl acetate afforded a single crystal suitable for X-ray analysis. **1a**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.98 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 3.19 (dt, $J = 1.6$, 7.6 Hz, 2H, CH_2), 3.68 (s, 3H, CH_3), 3.76 (t, $J = 7.2$ Hz, 2H, CH_2), 6.86 (s, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.95, 26.08, 31.92, 51.02, 51.24, 99.15, 157.30, 169.74, 170.92; Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.4; H, 7.2; N, 7.6. *Crystal data*: $C_9H_{13}NO_3$, triclinic, $a = 7.465(2)$, $b = 9.633(3)$, $c = 13.978(3)$ Å, $V = 945.0(5)$ Å^3, $Z = 2$, $D_c = 1.288$ g/cm^3, $F(000) = 392$, 3675. Independent reflections with $I/\sigma\ (I) \geqslant 2.0$ were used on the analysis. Data for crystallographic analysis were measured on an Enraf–Nonius CAD-4 diffractometer using graphite-monochromate Mo Kα ($\lambda = 0.71073$ Å) and ϖ-2 scans in the range of θ; $1.46 < \theta < 25.17$. Structure was solved by direct methods and refined by least squares using the SHEL-X. CCDC 237457. **1b**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J = 7.1$ Hz, 3H, CH_3), 1.96 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 3.19 (dt, $J = 1.7$, 7.7 Hz, 2H, CH_2), 3.74 (t, $J = 7.1$ Hz, 2H, CH_2), 4.13 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.82 (s, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.36, 21.54, 25.64, 31.45, 50.52, 59.37, 99.27, 156.55, 168.88, 170.42; Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.8; H, 7.7; N, 6.9.

3.2. Synthesis of 1c

To a solution of pyrrolidin-2-ylideneacetic acid methyl ester (1.00 g, 7.08 mmol) in THF (20 mL) was added Boc anhydride (4.60 g, 21.3 mmol) and DMAP (0.87 g, 7.08 mmol). The resulting mixture was refluxed for 3 h. After cooling to room temperature, the reaction solution was concentrated, and the resulting residue purified by column chromatography (ethyl acetate/hexane = 1:4) on silica gel to give **1c** (1.5 g, 88%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H, $3CH_3$), 1.89 (m, 2H, CH_2), 3.19 (dt, $J = 1.8$, 7.7 Hz, 2H, CH_2), 3.66 (s, 3H, CH_3), 3.68 (t, $J = 7.2$ Hz, 2H, CH_2), 6.46 (s, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.89, 28.14, 31.91, 49.73, 50.63, 82.04, 95.52, 151.94, 157.69, 169.39; Anal. Calcd for $C_{13}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 60.4; H, 8.0; N, 5.7.

3.3. Synthesis of 1d

To a solution of pyrrolidin-2-ylideneacetic acid methyl ester (0.40 g, 2.83 mmol) in acetone (20 mL) was added anhydrous K_2CO_3 (1.57 g, 11.30 mmol) and ethyl chloroformate (0.54 g, 5.67 mmol). The reaction mixture was stirred at room temperature overnight. The precipitate was filtered out and the filtrate concentrated. The residue was purified by column chromatography (ethyl acetate/hexane = 1:4) on silica gel to give pure product (0.45 g, 75%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, $J = 7.1$ Hz, 3H, CH_3), 1.91 (m, 2H, CH_2), 3.18 (dt, $J = 1.8$, 7.7 Hz, 2H, CH_2), 3.67 (s, 3H, CH_3), 3.72 (t, $J = 7.2$ Hz, 2H, CH_2), 4.24 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.52 (s, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.40, 21.04, 31.70, 49.48, 50.72, 62.13, 96.02, 152.94, 157.43, 169.24; Anal. Calcd for $C_{10}H_{14}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.8; H, 7.2; N, 6.5.

3.4. General procedure for asymmetric hydrogenation

In an inert atmosphere glovebox, a reaction flask was charged with $[Rh(cod)_2]BF_4$ (3.8×10^{-3} mmol) and chiral ligand (4.7×10^{-3} mmol) in 1 mL of solvent, and the mixture stirred for 30 min at 20 °C. Substrate **1** (0.38 mmol) was added to the reaction mixture, and then hydrogenation performed under 1 atm of H_2 for 12 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. After evaporation of the solvent, the crude reaction mixture was subjected into the ^1H NMR and capillary GC to determine the conversion and enantiomeric excess, respectively.

2a: $[\alpha]_D^{25} = +56.7$ (*c* 0.62, MeOH); ^1H NMR (300 MHz, $CDCl_3$) rotamer (major): δ 1.75 (m, 1H, $1/2CH_2$), 1.83–2.03 (m, 3H, $3/2CH_2$), 1.97 (s, 3H, CH_3), 2.27 (dd, $J = 9.4$, 14.6 Hz, 1H, $1/2CH_2$), 2.91 (dd, $J = 4.0$, 15.4 Hz, 1H, $1/2CH_2$), 3.39 (m, 2H, CH_2), 3.60 (s, 3H, CH_3), 4.33 (m, 1H, CH); rotamer (minor): δ 1.75 (m, 1H, $1/2CH_2$), 1.83–2.03 (m, 3H, $3/2CH_2$), 2.05 (s, 3H, CH_3), 2.39 (dd, $J = 10.1$, 15.5 Hz, 1H, $1/2CH_2$), 2.52 (dd, $J = 3.8$, 15.5 Hz, 1H, $1/2CH_2$), 3.39 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 4.19 (m, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.60, 21.87, 22.76, 23.66, 29.99, 31.11, 37.26, 39.17, 45.27, 47.67, 51.36, 51.71, 53.56, 55.03, 168.85, 169.12, 170.89, 171.74.

2b: $[\alpha]_D^{25} = +56.5$ (*c* 0.49, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) rotamer (major): δ 1.18 (t, $J = 7.2$ Hz, 3H, CH_3), 1.75 (m, 1H, 1/2CH_2), 1.83–2.03 (m, 3H, 3/2CH_2), 1.98 (s, 3H, CH_3), 2.26 (dd, $J = 9.5$, 15.4 Hz, 1H, 1/2CH_2), 2.90 (dd, $J = 3.9$, 15.4 Hz, 1H, 1/2CH_2), 3.39 (m, 2H, CH_2), 4.05 (m, 2H, OCH_2), 4.33 (m, 1H, CH); rotamer (minor): δ 1.21 (t, $J = 7.2$ Hz, 3H, CH_3), 1.75 (m, 1H, 1/2CH_2), 1.83–2.03 (m, 3H, 3/2CH_2), 2.06 (s, 3H, CH_3), 2.38 (dd, $J = 10.1$, 15.4 Hz, 1H, 1/2CH_2), 2.50 (dd, $J = 3.7$, 15.4 Hz, 1H, 1/2CH_2), 3.39 (m, 2H, CH_2), 4.05 (m, 2H, OCH_2), 4.19 (m, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.06, 21.65, 21.90, 22.78, 23.69, 29.96, 31.12, 37.43, 39.44, 45.33, 47.73, 53.63, 55.11, 60.19, 60.69, 168.93, 169.15, 170.49, 171.32.

2c: $[\alpha]_D^{25} = +39.0$ (*c* 0.42, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H, CH_3), 1.78–1.88 (m, 3H, 3/2CH_2), 2.04 (m, 1H, 1/2CH_2), 2.29 (dd, $J = 9.8$, 15.0 Hz, 1H, 1/2CH_2), 2.86 (dd, $J = 14.1$, 36.8 Hz, 1H, 1/2CH_2), 3.33 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 4.11 (m, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.70, 23.44, 28.42, 30.50, 31.21, 38.42, 39.01, 46.12, 46.45, 51.50, 53.95, 79.20, 79.50, 154.20, 171.95.

2d: $[\alpha]_D^{25} = +37.0$ (*c* 0.28, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J = 7.1$ Hz, 3H, CH_3), 1.76–1.96 (m, 3H, 3/2CH_2), 2.08 (m, 1H, 1/2CH_2), 2.33 (dd, $J = 9.6$, 15.3 Hz, 1H, 1/2CH_2), 2.90 (dd, $J = 15.5$, 46.9 Hz, 1H, 1/2CH_2), 3.39 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 4.12–4.16 (m, 3H, CH, and OCH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.73, 22.74, 23.52, 30.58, 31.34, 38.20, 38.98, 46.30, 46.54, 51.53, 53.79, 54.34, 60.84, 61.00, 154.94, 171.86.

3.5. Determination of enantiomeric excesses

Chiral Capillary GC column: CP-Chiralsil-Dex-CB column (dimensions 30 m × 0.32 mm (i.d.)). Carrier gas: N_2 (2 mL/min). The racemic products were obtained by hydrogenation of the substrates **1a–d** with Pd/C. The following are the retention times for the racemic products.

2a: (130 °C, isothermal) retention time: (*R*)-isomer = 12.40 min, (*S*)-isomer = 13.68 min.

2b: (130 °C, isothermal) retention time: (*R*)-isomer = 16.10 min, (*S*)-isomer = 17.52 min.

2c: (115 °C, isothermal) retention time: (*R*)-isomer = 22.73 min, (*S*)-isomer = 23.75 min.

2d: (120 °C, isothermal) retention time: (*R*)-isomer = 15.11 min, (*S*)-isomer = 16.26 min.

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