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An efficient synthesis of chiral homophenylalanine derivatives via enantioselective hydrogenation

Xingshu Li,[a,b] Chi-hung Yeung,[a,*] Albert S. C. Chan,[a,*] Dong-Sheng Lee [b] and Teng-Kuei Yang [b,*]

[a] *Union Laboratory of Asymmetric Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong*

[b] *Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan*

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Abstract

Chiral homophenylalanine derivatives were synthesized via enantioselective hydrogenation of **5a** and **5b** catalyzed by rhodium complexes bearing chiral phosphine and phosphinite legands. Enantiomeric excesses up to 96.2% were achieved when *S*-spiroOP(*S*-1) was used as a chiral ligand under 500 psi of H_2 pressure in acetone.

The homogeneous asymmetric hydrogenation has attracted much attention ever since L-DOPA was prepared in this way.[1] In spite of numerous reports about the syntheses of non-racemic chiral amino acids through homogeneous asymmetric hydrogenation of the corresponding dehydroamino acids, it is quite rare to see the asymmetric synthesis of homophenylalanine, a highly interesting pharmaceutical intermediate for the synthesis of ACE-inhibitors, such as benazepril, lisinopril and quinapril,[2] and has served as a constituent of many pharmaceuticals which function as protease inhibitors and neuronal receptor ligands (Fig. 1).[3] In the literature, chiral homophenylalanine has often been prepared by chemical or biological resolution, or by enzyme-catalyzed reactions.[4] Recently, RajanBabu et al. reported carbohydrate phosphinites as chiral ligands in Rh-catalyzed asymmetric hydrogenation of β-aromatic substituted dehydroamino acids with excellent enantioselectivity, but low to moderate e.e. values were obtained with the ester of 2-acetylamino-4-phenyl-2-butenoic acid which is a β-aliphatic substituted dehydroamino acid ester.[5] Herein we report a successful asymmetric synthesis of homophenylalanine using homogeneous asymmetric hydrogenation.

The synthesis of the dehydroamino acids **5** began with the mono-addition of 2-phenylethyl magnesium chloride **3** to diethyl oxalate. The resulting ester **4** was then reacted with methyl carbamate to obtain compound **5** in 60% overall yield (Scheme 1).[6] The results of asymmetric hydrogenation of compound **5** catalyzed by rhodium complexes bearing various chiral phosphine and phosphinite ligands (see Fig. 2)

* Corresponding authors. E-mail: tkyang@mail.nchu.edu.tw

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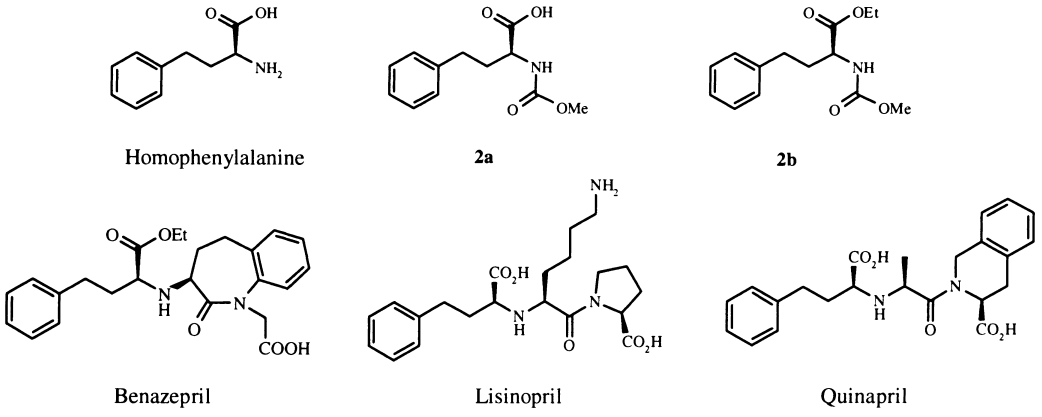
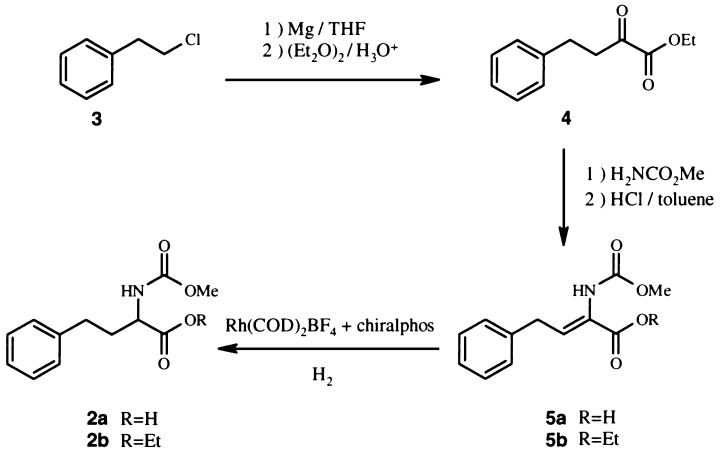


Figure 1.

are shown in Table 1.[7] Inspection of Table 1 leads to some important features: (a) of the various catalysts used, [Rh(*S*-1)(COD)]BF_4 in acetone under 500 psi of H_2 pressure affords the best enantioselectivity with 96.2% e.e. in favor of *S*-form (entries 1, 10, 11, 16, 18, 20, 22, 24, 28); (b) solvent effects on enantioselectivity are important, and acetone is the best for the hydrogenation as compared with the alcohols and other solvents used (entries 1–6); (c) the hydrogenation of acid **5a** provided better facial selectivity than the corresponding ester, thus 95% e.e. was obtained for **5a** and 92% e.e. for **5b** under 350 psi of H_2 pressure (entries 8 and 24); (d) there is no significant effect of hydrogen pressure on the enantioselectivity, and the e.e. values changed from 96.2% to 94% when the pressure increased from 500 psi to 700 psi. On the other hand, lower conversion (84%) with 93.8% e.e. was obtained when only 150 psi of hydrogen pressure was used (entry 1 vs 7 vs 9). These results indicated that the optimal hydrogen pressure should be around 500 psi. Meanwhile, we also observed that the change of the configuration of ligand would invert the configuration of product (entries 1 and 10).



Scheme 1. The synthesis of homophenylalanine and its derivatives

The other parameters of this reaction, such as concentration, temperature and ratio of substrate to catalyst, were also studied (Table 2). The results showed 0.3 M is the best concentration to obtain high enantioselectivity (entries 1–4); however, the poor solubility of the substrate prevents this reaction being run at even higher concentrations. Similar to the other related studies, we found the enantioselectivity

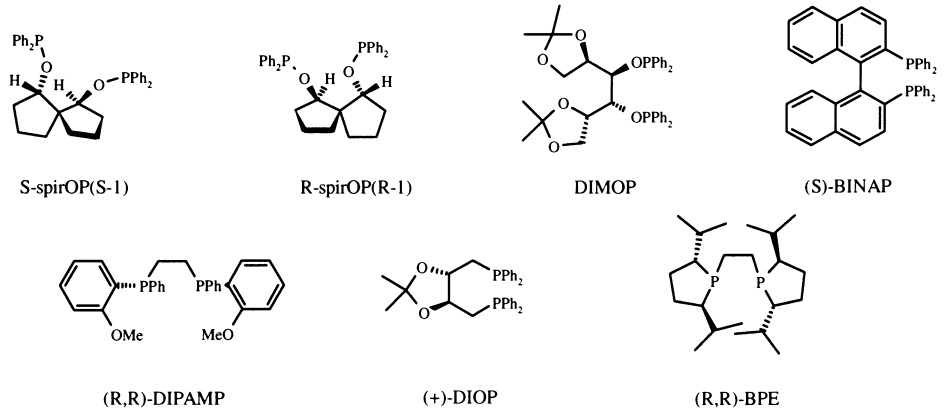


Figure 2.

Table 1
Asymmetric hydrogenation for compounds **5a** and **5b**[a]

Entry	Substrate	Catalyst	Solvent	Pressure	Configuration	e.e.%[b]
1	**5a**	[Rh(S-1)(COD)]BF_4	acetone	500	*S*	96.2
2	**5a**	[Rh(S-1)(COD)]BF_4	THF	500	*S*	93.5
3	**5a**	[Rh(S-1)(COD)]BF_4	MeOH	500	*S*	92.4
4	**5a**	[Rh(S-1)(COD)]BF_4	^{i}PrOH	500	*S*	92.0
5	**5a**	[Rh(S-1)(COD)]BF_4	benzene	500	*S*	91.0
6	**5a**	[Rh(S-1)(COD)]BF_4	CH_2Cl_2	500	*S*	88.6
7	**5a**	[Rh(S-1)(COD)]BF_4	acetone	700	*S*	94.0
8	**5a**	[Rh(S-1)(COD)]BF_4	acetone	350	*S*	95.0
9	**5a**	[Rh(S-1)(COD)]BF_4	acetone	150	*S*	93.8[c]
10	**5a**	[Rh(R-1)(COD)]BF_4	acetone	500	*R*	96.0
11	**5a**	[Rh(DIMOP)(COD)]BF_4	acetone	500	*R*	88.9
12	**5a**	[Rh(DIMOP)(COD)]BF_4	MeOH	500	*R*	84.0
13	**5a**	[Rh(DIMOP)(COD)]BF_4	THF	500	*R*	82.0
14	**5a**	[Rh(DIMOP)(COD)]BF_4	acetone	700	*R*	88.5
15	**5a**	[Rh(DIMOP)(COD)]BF_4	acetone	350	*R*	90.0
16	**5a**	[Rh(S-BINAP)(COD)]BF_4	acetone	500	*R*	54.6
17	**5a**	[Rh(S-BINAP)(COD)]BF_4	MeOH	500	*R*	52.1
18	**5a**	[Rh(DIPAMP)(COD)]BF_4	acetone	500	*S*	84.3
19	**5a**	[Rh(DIPAMP)(COD)]BF_4	MeOH	500	*S*	88.0
20	**5a**	[Rh(DIOP)(COD)]BF_4	acetone	500	*S*	53.5
21	**5a**	[Rh(DIOP)(COD)]BF_4	MeOH	500	*S*	30.2
22	**5a**	[Rh(BPE)(COD)]BF_4	acetone	500	*S*	91.6
23	**5a**	[Rh(BPE)(COD)]BF_4	MeOH	500	*S*	82.3
24	**5b**	[Rh(R-1)(COD)]BF_4	acetone	350	*R*	92.0
25	**5b**	[Rh(R-1)(COD)]BF_4	acetone	700	*R*	91.0
26	**5b**	[Rh(R-1)(COD)]BF_4	MeOH	350	*R*	83.1
27	**5b**	[Rh(R-1)(COD)]BF_4	THF	350	*R*	89.8
28	**5b**	[Rh(DIMOP)(COD)]BF_4	acetone	700	*R*	72.7

a. The reaction was carried out at ambient temperature for 7 hours; the substrate/catalyst was 100/1 in 0.3M of substrate and 95~100% conversion was observed.
b. The e.e. values were determined by GLC using a Chirasil-L-Val column (the acid was converted to the corresponding methyl ester before GLC analysis).
c. The conversion was 84% at this reaction condition.

Table 2
The effect of concentration, temperature and ratio of substrate to catalyst[a]

Entry	Catalyst	Concentration of substrate	Temperature (°C)	S / C	e.e.%[b]	Configuration
1	[Rh(S-1)(COD)]BF_4	0.30	25	100 : 1	96.2	*S*
2	[Rh(S-1)(COD)]BF_4	0.20	25	100 : 1	95.6	*S*
3	[Rh(S-1)(COD)]BF_4	0.10	25	100 : 1	93.8	*S*
4	[Rh(S-1)(COD)]BF_4	0.05	25	100 : 1	89.5	*S*
5	[Rh(S-1)(COD)]BF_4	0.30	25	200 : 1	93.7	*S*
6	[Rh(S-1)(COD)]BF_4	0.30	25	400 : 1	91.5	*S*
7	[Rh(S-1)(COD)]BF_4	0.30	25	800 : 1	87.1	*S*
8	[Rh(S-1)(COD)]BF_4	0.30	0	100 : 1	96.0[c]	*S*
9	[Rh(S-1)(COD)]BF_4	0.30	50	100 : 1	86.0	*S*
10	[Rh(DIMOP)(COD)] BF_4	0.30	0	100 : 1	91.7	*R*
11	[Rh(DIMOP)(COD)] BF_4	0.30	25	100 : 1	88.9	*R*
12	[Rh(DIMOP)(COD)] BF_4	0.30	50	100 : 1	84.4	*R*
13	[Rh(DIMOP)(COD)] BF_4	0.30	25	200 : 1	88.3	*R*

a. **5a** was the model substrate, and the reaction was carrying out at 500 psi of H_2 and acetone as a solvent.
b. The acid was converted to the corresponding methyl ester and the e.e. value was determined by GLC using a Chirasil-L-Val column.
c. This reaction was carried for 24 hours and 100% conversion was obtained.

increased with higher quantities of catalyst (entries 1 and 5–7), and if a lower reaction temperature was used (entries 1, 8, 9 and 10–12).

In spite of the higher enantioselectivity observed in the hydrogenations of β-aliphatic substituted *N*-carbamoyl dehydroamino acid derivatives compared to the corresponding *N*-acetyl dehydroamino acid derivatives, we recognize that the rate of hydrogenation on the former substrates are relatively slower than the latter compounds.[5–7]

In summary, we have developed an efficient synthesis of chiral homophenylalanine via asymmetric hydrogenation of the corresponding dehydroamino acid derivatives, which can be applied to the synthesis of valuable chiral β-aliphatic substituted amino acids.

Acknowledgements

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6. The substrates **5** were synthesized according to the literature: Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem*. **1987**, *52*, 5143. Substrates and products were characterized with ^{1}H NMR and MS, selected data as follows: **5a** ^{1}H NMR ($CDCl_3$) δ 7.19–7.38 (m, 5H, H-Ph), 6.95 (t, 1H, J=7.4 Hz, H-3), 6.51 (br, 1H, NH), 3.76 (s, 3H, CO_2CH_3), 3.59–3.61 (d, J=7.2 Hz, 2H, H-4); m/z: 235 (100%); **2a** ^{1}H NMR ($CDCl_3$) 7.12–7.29 (m, 5H, H-Ph), 6.24 (br, d, J=7.9 Hz, 1H, NH), 3.71 (s, 3H, CO_2CH_3), 2.59 (t, J=7.9 Hz, 2H, H-4), 1.96–2.14 (m, 2H, H-3); m/z: 237 (83%).
7. The *S*-spiroOP, *R*-spiroOP and DIMOP were prepared according to the literature: (a) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc*. **1997**, *119*, 9570; (b) Chen, Y.; Li, X.; Tong, S.-K.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett*. **1999**, *40*, 957. The typical procedures for preparation of the catalyst and the asymmetric hydrogenation are as follows: (a) in situ catalyst [Rh(*S*-1)(COD)]BF_4: in a dry box, [$Rh(COD)_2$]BF_4 (4.1 mg, 0.01 mmol) was dissolved in acetone (0.5 ml). A solution of *S*-1 (5.5 mg, 0.0105 mmol) in acetone (0.5 ml) was added to the above solution under stirring to give an acetone solution of [Rh(*S*-1)(COD)]BF_4; (b) the asymmetric hydrogenation of dehydroamino acid derivatives: a vessel equipped with a magnetic stirring bar was charged with 0.5 ml acetone and 50 μl of acetone solution which contained 0.0005 mmol of catalyst in situ prepared as above and 0.05 mmol of substrate under nitrogen atmosphere. The vessel was pressurized with 500 psi of H_2 and the hydrogenation was carried out at room temperature for 7 h. The ethyl ester was directly analyzed via chiral capillary GLC with a 25-meter Chrompack capillary column (CP-Chirasil-L-Val). The acid was converted to the corresponding methyl ester with methyl iodine/K_2CO_3 before GLC analyses.