Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1039–1042

TETRAHEDRON: *ASYMMETRY*

Rhodium-catalyzed asymmetric hydrogenations of electron deficient olefins using 1,4-diphosphine ligands bearing an imidazolidin-2-one backbone

Sang-gi Lee* and Yong Jian Zhang

Life Sciences Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul, South Korea

Received 26 March 2002; accepted 15 May 2002

Abstract—In rhodium(I)-catalyzed asymmetric hydrogenations of electron deficient olefins, the electron-rich and sterically encumbered phosphine ligand, MOD-BDPMI, exhibited higher enantioselectivities than BDPMI ligands. Moreover, the *N*-substituents of the imidazolidin-2-one backbone affected the enantioselectivity. Thus, using the *N*,*N*′-dimethylated MOD-BDPMI ligand **2b**, (*Z*)-α-(*N*-acetamido)cinnamic acid **3** was hydrogenated with 100% conversion to give the saturated α-amino acid with ee of 88.7%. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The asymmetric hydrogenation of prochiral olefins with chiral phosphine–metal (Rh, Ir, Ru) complexes as catalysts is a well established protocol.[1] Most of the effective chiral phosphine ligands possess stereogenic centers at the carbon α to the phosphorus atom, i.e. the reactive site is located close to the stereogenic centers. In this context, it is difficult to achieve high enantioselectivity using the DIOP[2]-type 1,4-diphosphine ligands since the stereogenic centers may be too far from the site of reaction.[3] Efforts to tune the catalytic properties by variation of the electronic properties of the DIOP-type 1,4-bisphosphine ligands have been made by Achiwa et al., whose work suggested that the introduction of appropriate electron-donating groups on each phenyl group of DIOP favors higher selectivities in the hydrogenations of various types of prochiral olefin.[4] Recently, we proposed the '*gauche*-interaction concept' in ligand design, and prepared highly efficient C_2-symmetric 1,4-bisphosphine ligands bearing an imidazolidin-2-one backbone, (4*S*,5*S*)-4,5-bis(diphenylphosphinomethyl)imidazolidin-2-ones **1** (BDPMI) and (4*S*,5*S*)-4,5-bis[di(4-methoxy-3,5-dimethylphenyl)phosphinomethyl]imidazolidin-2-ones **2** (MOD-BDPMI) (Fig. 1).[5] In the Rh(I)-catalyzed hydrogenation of electron-rich olefins, such as α-aryl *N*-acetylenamides, the BDPMIs **1** induced higher enantioselectivity (up to >99% ee) than the MOD-BDPMIs **2** (up to 86.5% ee), which possess relatively electron-rich and sterically hindered chelating phosphines. Further interest in establishing the general utility of the design concept led us to examine the asymmetric hydrogenation of electron-deficient olefins using these chiral ligands. Herein, we wish to describe the asymmetric hydrogenation of electron-deficient olefins, such as (*Z*)-α-(*N*-acetamido)cinnamic acid **3**, itaconic acid **4a** and its dimethyl ester **4b**, using the Rh-complexes of the BDPMIs **1a–d** and MOD-BDPMIs **2a–c** as catalysts.

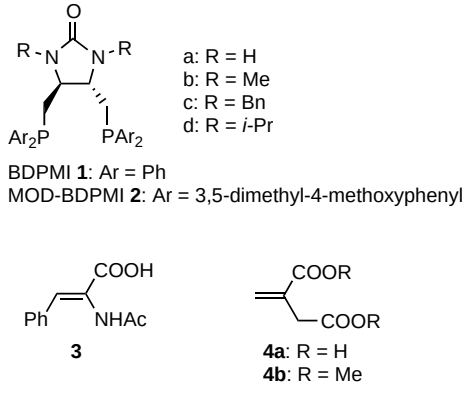

Figure 1. BDPMI **1** and MOD-BDPMI **2**.

* Corresponding author. Tel.: +82-2-958-5163; fax: +82-2-958-5189; e-mail: sanggi@kist.re.kr

0957-4166/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(02)00243-4

2. Results and discussion

In the first reactions, the hydrogenation was screened with **3** and **4a** using 1 mol% of catalyst prepared in situ from Bn-BDPMI **1c** and cationic rhodium, $[Rh(cod)_2]BF_4$, under 1 atm H_2 pressure (Table 1). The conversions were determined by ^1H NMR analysis of the crude product. So as to determine the enantioselectivities using chiral GC or chiral HPLC, the hydrogenated acids were converted to the corresponding methyl esters by reaction with methanol in the presence of TMSCl. As shown in Table 1, considerable solvent effects on the enantioselectivity were observed. For the hydrogenation of (*Z*)-α-(*N*-acetamido)cinnamic acid **3**, the highest enantioselectivity was obtained in polar aprotic solvents, such as acetone (75% ee, entry 3 in Table 1). However, in the hydrogenation of itaconic acid **4a**, the highest enantioselectivity was achieved in *i*-PrOH solvent (42.5% ee, entry 7 in Table 1). Irrespective of the solvent, all of the hydrogenations studied occurred with 100% conversion.

Table 1. Asymmetric hydrogenation of **3** and **4a** in various solvents using Bn-BDPMI **1c** as chiral ligands[a]

Entry	Substrate	Solvent	Conv. (%)[b]	% ee[c]
1	**3**	THF	>99	66.0
2	**3**	MeOH	>99	53.0
3	**3**	Acetone	>99	75.0
4	**3**	CH_2Cl_2	>99	36.0
5	**4a**	THF	>99	21.7
6	**4a**	MeOH	>99	23.8
7	**4a**	*i*-PrOH	>99	42.5
8	**4a**	Acetone	>99	27.6
9	**4a**	CH_2Cl_2	>99	32.1

[a] The reaction was carried out at 20°C for 12 h under 1 atm H_2 pressure (substrate:$[Rh(cod)_2]BF_4$:**1c** = 1:0.01:0.012).
[b] Determined by ^1H NMR.
[c] The hydrogenated acids were converted to the corresponding methyl esters. For **3**: Determined by Chiral HPLC using Chiralpak AD column. For **4a**: Determined by Chiral GC using Chiraldex G-TX column. The predominant products all had (*S*)-configuration.

With these results in hand, we next examined the catalytic activities of the other ligands for the hydrogenation of **3** and **4** in acetone and *i*-PrOH solvents, respectively. It was found that the Rh-MOD-BDPMI complexes are more reactive than the Rh-BDPMI complexes, so the hydrogenations of **3** and **4a**,**b** were carried out using 1 mol% of Rh-BDPMIs **1a**–**d** but only 0.2 mol% (for the reduction of **3**) and 0.5 mol% of the Rh-MOD-BDPMI ligands **2a**–**c** in reductions of **4**. The results are summarized in Table 2.

In the hydrogenation of (*Z*)-α-(*N*-acetamido)cinnamic acid **3** using BDPMI ligands, the N–H ligand **1a** induced the highest enantioselectivity (76.0% ee, entry 1 in Table 2) than the *N*-methylated **1b** (67.0% ee, entry 2 in Table 2) and *N*-benzylated **1c** (75.0% ee, entry 3 in Table 2) ligands. When the same reaction was carried out using the ligand **1d** having the most bulky *N*-*i*-Pr substituent, the enantioselectivity increased to 78.9% ee (entry 4 in Table 2). However, of the MOD-BDPMI ligands examined, the *N*-methylated ligand **2b** showed the highest enantioselectivity. Thus, the hydrogenation of **3** proceeded with 100% conversion and afforded the saturated acid with 88.7% ee (entry 6 in Table 2), which is one of the highest enantioselectivities obtained from the hydrogenation of **3** using DIOP-type 1,4-bisphosphine ligands.

Table 2. Rhodium-catalyzed asymmetric hydrogenation of **3** and **4a**,**b** using **1a**–**c** and **2a**–**c** as chiral ligands[a]

Entry	Substrate	Ligand	Sub./Rh	Conv. (%)[b]	% ee[c]
1	**3**	**1a**	100	>99	76.0
2	**3**	**1b**	100	>99	67.0
3	**3**	**1c**	100	>99	75.0
4	**3**	**1d**	100	>99	78.9
5	**3**	**2a**	500	>99	79.3
6	**3**	**2b**	500	>99	88.7
7	**3**	**2c**	500	>99	63.7
8	**4a**	**1a**	100	>99	57.0
9	**4a**	**1b**	100	>99	23.0
10	**4a**	**1c**	100	>99	42.5
11	**4a**	**1d**	100	>99	8.6
12	**4a**	**2a**	200	>99	68.3
13	**4a**	**2b**	200	>99	77.7
14	**4a**	**2c**	200	>99	81.5
15	**4b**	**1a**	100	>99	34.5
16	**4b**	**1b**	100	>99	40.4
17	**4b**	**1c**	100	>99	19.7
18	**4b**	**2a**	200	>99	74.4
19	**4b**	**2b**	200	>99	42.4
20	**4b**	**2c**	200	>99	47.4

[a] Reaction was carried out at 20°C for 12 h under 1 atm H_2 pressure ($[Rh(cod)_2]BF_4$:ligand = 1:1.2).
[b] Determined by ^1H NMR.
[c] The hydrogenated acids were converted to the corresponding methyl esters. For **3**: Determined by Chiral HPLC using Chiralpak AD column. For **4a** and **4b**: Determined by Chiral GC using Chiraldex G-TX column. The predominant products all had (*S*)-configuration.

In the hydrogenation of itaconic acid **4a** with BDPMI ligands, it was found that the enantioselectivity decreased as the bulk of the *N*-substituents increased. Thus, the N–H ligand **1a** induced higher enantioselectivity (57.0% ee, entry 8 in Table 2) than the *N*-substituted ligands **1b** (23.0% ee, entry 9), **1c** (42.5% ee, entry 10) and **1d** (8.6% ee, entry 11). In contrast with the BDPMI ligands, the *N*-substituents in MOD-BDPMI ligands affected the enantioselectivity positively, i.e. the enantioselectivity improved with increasing A value of the substituents.[6] Thus, the *N*-benzylated MOD-BDPMI ligand **2c** exhibited the highest enantioselectivity (81.5% ee, entry 14) than the *N*-methylated **2b** (77.7% ee, entry 13) or the unsubstituted amine ligand **2a** (68.3% ee, entry 12). However, in the hydrogenation of dimethyl itaconate **4b** (entries 15–20), the *N*-H MOD-BDPMI ligand **2a** exhibited the highest enantioselectivity (74.4% ee, entry 18). These results indicate that in the hydrogenation of α,β-unsaturated carboxylic acids, the MOD-BDPMI ligands with electron-rich and bulky phosphine groups showed better enantioselectivity than BDPMI ligands bearing diphenylphosphine groups.

With respect to enantioselectivity, these are quite different ligand effects to those observed in the hydrogenations of electron-rich olefins, such as α-arylenamides, in which higher enantioselectivities have been achieved with BDPMI ligands.[5] Moreover, it was also found that the effects of the *N*-substituents in BDPMI and MOD-BDPMI on the enantioselectivity are largely dependent on the structure of the olefin. Consequently, each combination of chiral ligand and prochiral olefin requires careful optimization in order to obtain the best results. Obviously a more in-depth study, including the synthesis of MOD-BDPMI ligands having more sterically demanding *N*-substituents and less bulky phosphine groups (for example, a ligand which has (*p*-methoxyphenyl)phosphine groups) would be useful to allow more accurate comparisons and the elucidation of the key factors influencing the enantioselectivity with Rh-BDPMI catalysts. In this way a more rational basis for the design and improvement of such catalysts can be achieved.

3. Conclusion

In summary, we have carried out the asymmetric hydrogenation of electron deficient olefins, (*Z*)-α-(*N*-acetamido)cinnamic acid **3**, itaconic acid **4a** and its dimethyl ester **4b**, using the Rh-complexes of the BDPMI **1a**–**d** and MOD-BDPMI **2a**–**c** as catalysts. In the hydrogenation of electron-deficient olefins, the MOD-BDPMI ligands **2a**–**c** bearing both a *para*-electron donating and *meta*-methyl groups proved to be more efficient ligands than the BDPMI ligands **1a**–**c**. Therefore, in order to obtain high enantioselectivity with electron-deficient olefins, ligands having electron-rich phosphine groups may be required and vice versa. The design and synthesis of more effective chiral ligands and their applications in asymmetric catalytic hydrogenation are currently in progress.

4. 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. HPLC analyses were performed using Agilent 1100 interfaced to a HP 71 series computer workstation.

4.1. General procedure for asymmetric hydrogenation

In a glovebox under an inert atmosphere, 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 solvent (1 mL). The mixture was stirred for 30 min at 20°C. An olefin (for example, itaconic acid) (0.38 mmol) was added to the reaction mixture, and hydrogenation was 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 to ^1H NMR analysis to determine the conversion. In order to determine the enantiomeric excess, the hydrogenated acid product was treated with chlorotrimethylsilane in methanol for 1 h to give the corresponding methyl ester. After evaporation of the solvent, a sample of the crude mixture was analyzed by capillary GC or HPLC directly without any further purification.

***N*-Acetylphenylalanine methyl ester**: HPLC column: Chiralpack AD; eluent: *n*-hexane:*i*-PrOH = 88:12; flow rate: 1.0 mL/min; retention times: (*R*)-isomer = 7.60 min, (*S*)-isomer = 9.48 min.

Methyl dimethylsuccinate: GC column: Chiraldex G-TA; flow rate of carrier gas (N_2): 2 mL/min; column temp.: 75°C isothermal; retention times: (*R*)-isomer = 17.54 min, (*S*)-isomer = 18.58 min.

Acknowledgements

We are grateful for financial support from the Ministry of Science and Technology (National Research Laboratory Program, 2N22890), from KIST (2E17512) and CMDS at KAIST.

References

1. (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p. 121.
2. (a) Dang, T.-P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481; (b) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
3. (a) Gawronski, J.; Gawronska, K. *Tartaric Acid and Malic Acid in Synthesis*; Wiley & Sons: New York, 1999; p. 332 and references cited therein. For selected recent papers,

see: (b) Hu, W.; Chen, C.-C.; Xue, G.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 4183; (c) Tararov, V.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett*. **2000**, *41*, 2351.

4. (a) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett*. **1989**, *30*, 735; (b) Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull*. **1992**, *40*, 2894; (c) Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2661; (d) Morimoto, T.; Nakajima, N.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 23.
5. Lee, S.-g.; Zhang, Y. J.; Song, C. E.; Lee, J. K.; Choi, J. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 847.
6. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001; p. 174.