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Rhodium-Catalyzed Enantioselective Hydrogenation of β-Phthalimide Acrylates to Synthesis of β²-Amino Acids

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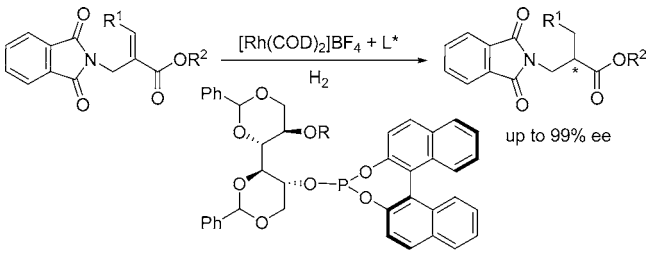
ABSTRACT



The enantioselective hydrogenation of β-phthalimide acrylates provides the corresponding chiral β²-amino acids in excellent enantiomeric excess catalyzed by Rh–monophosphorus.

Chiral β²-amino acids (α-substituted β-amino acids) and their derivatives are critical key structural elements in natural products and pharmaceuticals.[1] For example, compound **1** is a key intermediate in the synthesis of the cryptophycin-**1**,[2] which was first isolated from terrestrial *Nostoc* sp. ATCC 53789 by researchers at Merck and found to be very active against fungi, especially strains of *Cryptococcus*,[3] which frequently infect immunodeficient persons suffering from diseases, such as AIDS and cancer.

For these and other reasons, enantioselective synthesis of β²-amino acids has attracted extensive interest. Although several stoichiometric[4] and catalytic methods, such as Michael addition,[5] H-atom transfer reaction,[6] C−H insertions of carbenoids reaction,[7] and rhodium enolate protonations,[8] have been developed to make chiral β²-amino acids, straightforward hydrogenation of prochiral dehydro-precursors represents one of the simplest and efficient routes. However, the only previous documented attempt at this asymmetric hydrogenation, using Rh and Ru catalysts, gave poor to moderate enantioselectivity.[9] So, the search for an efficient

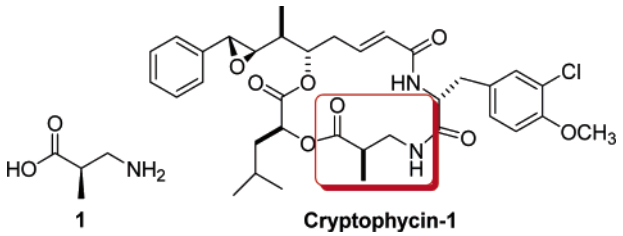


Figure 1. Examples of chiral β²-amino acids and cryptophycin-**1**.

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asymmetric hydrogenation catalytic system for the synthesis of β^2-amino acids is still a challenge. Herein, we report the first highly enantioselective hydrogenation of β-phthalimide acrylates for the synthesis of β^2-amino acid derivatives using the Rh−monophosphite catalytic system.

The basic strategy of our method involves asymmetric hydrogenation of β-acrylates with a phthalimido-protected β-amino group, which may satisfy the chelation requirement between the metal and substrate.[9a,10] The β-phthalimide acrylates were readily prepared in good overall yields in three steps from the commercially available inexpensive aldehydes, acrylates, and phthalimide.[11]With these substrates in hand,

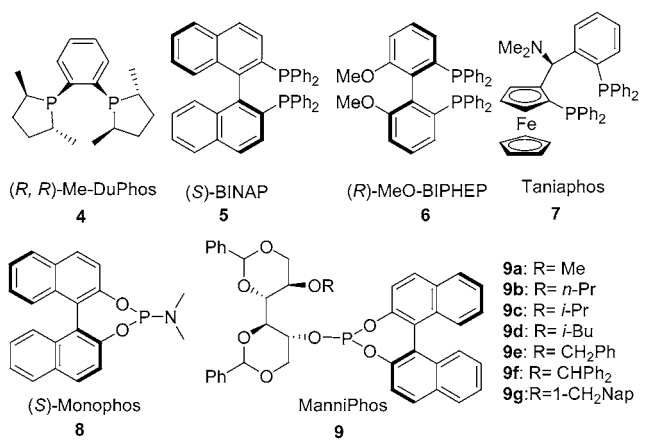
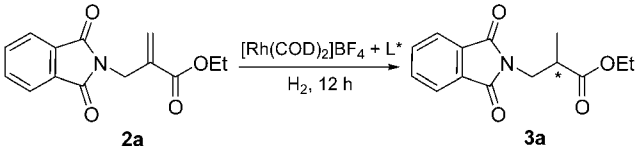


Figure 2. Chiral phosphine ligands evaluated in the asymmetric hydrogenations.

we initiated our hydrogenation reaction studies by screening several known catalysts. The simple β-phthalimide acrylate **2a** was chosen as a model substrate. A diverse array of chiral phosphine/Rh complexes, which were very effective in asymmetric hydrogenation of many functionalized olefins,[12] was applied as catalysts in this hydrogenation reaction. The particular catalyst was prepared in situ by mixing $[Rh(COD)_2]BF_4$ and the phosphorus ligands in the solvents. All the hydrogenation reactions were carried out at room temperature, under 10 atm pressure of H_2.

Some representative results are shown in Table 1. The first attempt, using Rh/DuPhos as catalyst precursor, afforded the desired product **3a** in quantitative conversion with moderate enantioselectivity (59% ee, entry 1). Unfortunately, all efforts to improve the enantiomeric excess value with this catalyst failed. Further examination of a number of other typical axially chiral and planarly chiral bisphosphine, such as BINAP, BIPHEP, and Taniaphos, also gave unsatisfactory enantioselectivity (less than 70%, Table 1, entries 3−5). These results indicated that bidentate phosphine ligands used here are not efficient for this reaction. Thus, we next turned our attention to the use of the monodentate chiral phosphorus[13] as ligands for this reaction. The result showed that good enantioselectivity with quantitative conversion was obtained when Monophos **8** was applied in this reaction. This finding encouraged us to use our newly created P−O monophosphite **9**[14] as ligands to try this enantioselective hydrogenation reaction. As shown in entry 7, up to 99.1% ee with quantitative conversion was obtained when Rh/**9g** was employed in this reaction.

Table 1. Enantioselective Hydrogenation of β-Phthalimide Acrylates **2a**[a]



entry	ligand	solvent	conv.%[b]	ee% (config.)[c]
1	**4**	CH_3OH	>99	59.0 (*R*)
2	**4**	CH_2Cl_2	>99	67.9 (*R*)
3	**5**	CH_2Cl_2	>99	57.9 (*S*)
4	**6**	CH_2Cl_2	>99	66.7 (*R*)
5	**7**	CH_2Cl_2	>99	4.9 (*R*)
6	**8**	CH_2Cl_2	>99	89.0 (*S*)
7	**9g**	CH_2Cl_2	>99	**99.1** (*R*)

[a] Unless otherwise stated, reactions were performed on a 0.5 mmol scale at room temperature for 12 h, $P(H_2) = 10$ atm, for the bidentate ligands (**4**−**7**): 1 mol % of $[Rh(COD)_2]BF_4$ and 1.1 mol % of ligand. For the monodentate ligands (**8**, **9**): 1 mol % of $[Rh(COD)_2]BF_4$ and 2.2 mol % of ligand. [b] Determined by GC. [c] Determined by chiral HPLC, and the absolute configuration was determined by comparing the sign of specific rotation of the corresponding amino acid.

(4) For representative examples, see: (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (b) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553. (c) Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723. (d) Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233. (e) Seebach, D.; Boog, A.; Schweizer, W. B. *Eur. J. Org. Chem.* **1999**, 335. (f) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527. For review, see: (g) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (h) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med Chem.* **1999**, *6*, 983.

(5) (a) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79. (b) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189. (c) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700.

(6) Sibi, M. P.; Patil, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1235.

(7) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197.

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(9) (a) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657. (b) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309.

(10) Examples of catalytic asymmetric hydrogenation using this strategy: (a) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626. (b) Wang, C.; Sun, X.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933. (c) Hu, A.; Lin, W. *Org. Lett.* **2005**, *7*, 455.

(11) For the synthesis of substrates and details on experimental conditions, see the Supporting Information.

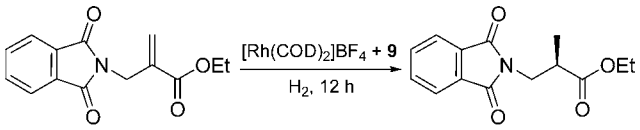
(12) (a) Ojima, I. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(13) For reviews on monophosphorus chiral ligands, see: (a) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101. (b) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197.

(14) (a) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* **2004**, *69*, 2355. (b) Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *Org. Lett.* **2003**, *5*, 4137.

Encouraged by the results described above, we investigated the effects of solvents, hydrogen pressure, and catalyst precursors to determine the optimal conditions (Table 2). A

Table 2. Enantioselective Hydrogenation of β-Phthalimide Acrylates **2a**[a]



2a **3a**

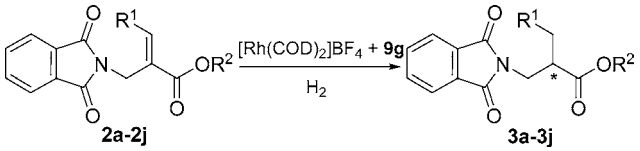
entry	ligand	solvent	$P(H_2)$ atm	conv.%[b]	ee% (config.)[c]
1	**9g**	CH_3OH	10	74	22.5 (*R*)
2	**9g**	*i*-PrOH	10	83	22.5 (*R*)
3	**9g**	THF	10	88	41.1 (*R*)
4	**9g**	toluene	10	86	22.3 (*R*)
5	**9g**	CH_2Cl_2	10	>99	99.1 (*R*)
6	**9g**	CH_2Cl_2	20	>99	99.1 (*R*)
7	**9g**	CH_2Cl_2	30	>99	98.8 (*R*)
8	**9g**	CH_2Cl_2	40	>99	98.1 (*R*)
9	**9a**	CH_2Cl_2	10	>99	98.9 (*R*)
10	**9b**	CH_2Cl_2	10	>99	98.3 (*R*)
11	**9c**	CH_2Cl_2	10	>99	98.3 (*R*)
12	**9d**	CH_2Cl_2	10	>99	99.1 (*R*)
13	**9e**	CH_2Cl_2	10	>99	97.7 (*R*)
14	**9f**	CH_2Cl_2	10	>99	98.3 (*R*)

[a] Unless otherwise stated, reactions were performed on a 0.5 mmol scale at room temperature for 12 h, 1 mol % of $[Rh(COD)_2]BF_4$, 2.2 mol % of ligand **9**. [b] Determined by GC. [c] Determined by chiral HPLC, and the absolute configuration was determined by comparing the sign of specific rotation of the corresponding amino acid.

dramatic solvent effect was observed when using Rh/**9g** complexes as catalyst precursor (entries 1−5). Only CH_2Cl_2 is most effective in terms of the conversion and enantioselectivity. This agrees with our early results.[14] Hydrogen pressure had no dramatic effect on the activity and selectivity for this substrate: slightly lower selectivity was observed when the pressure increased from 10 to 40 atm (Table 2, entries 5−8). To test the effect of structure of the chiral P−O ligands on the enantioselectivity of the reaction, a set of ManniPhos ligands with different −OR was employed. The best result was observed when **9d** and **9g** were used as ligands.

Using the optimized catalyst precursor Rh/**9g** and conditions optimized for the hydrogenation of **2a**, we proceeded to explore the scope and limitations of the methodology. As shown in Table 3, the substrates (**2a** and **2b**) without a substituent in the β-position of the carbon−carbon double bond can give full conversion and excellent enantioselectivity (up to 99.1% ee) even in lower catalyst loading (Table 3, entry 3, 0.1 mol % catalyst). Unfortunately, use of the same reaction conditions for the hydrogenation of **2c**, which contains a phenyl group in the β-position of the carbon−carbon double bond, failed to give more than 5% conversion of starting material. However, up to 92% ee and 82% conversion was observed when high hydrogen pressure (85 atm) and 4 mol % catalyst were employed (Table 3, entry 4). Under these conditions, a variety of substituted β-phthalimide acrylates were hydrogenated to yield their corresponding β^2-amino acid precursors. In general, the enantioselectivity in these experiments was high (Table 3, entries 1−8). However, the conversion for the reaction was variable. For the aromatic substituted substrates, it was found that the presence of electron-withdrawing groups on the phenyl ring of the substrate led to higher conversion and more favorable enantiomeric excess values than did electron-donating groups (Table 3, entries 5−7 vs entries 4, 8, and 9). The heteroaromatic and alkyl-substituted substrates (**2i** and **2j**) also can be hydrogenated with moderate enantioselectivity (Table 3, entries 10 and 11).

Table 3. Enantioselective Hydrogenation of β-Phthalimide Acrylates **2**[a]



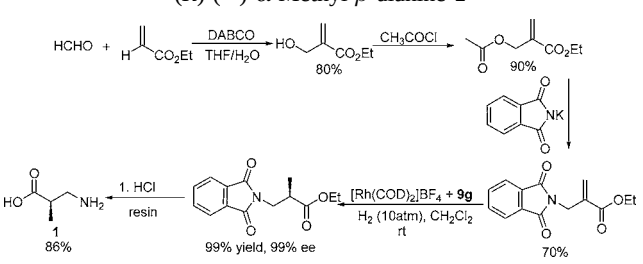
2a-2j **3a-3j**

entry	substrate (R^1, R^2)	$P(H_2)$ atm	conv.%[b]	ee% (config.)[c]
1	**2a**, (H, Et)	10	>99	99.1 (*R*)
2	**2b**, (H, Me)	10	>99	98.3 (*R*)
3[d]	**2a**, (H, Et)	10	>99	97.7 (*R*)
4[e]	**2c**, (C_6H_5, Me)	85	82	92.0 (*R*)
5[e]	**2d**, (*p*-ClC_6H_4, Me)	85	>95	86.4 (+)
6[e]	**2e**, (*p*-FC_6H_4, Me)	85	>95	95.9 (+)
7[e]	**2f**, (*p*-$CF_3C_6H_4$, Me)	85	>95	94.6 (+)
8[e]	**2g**, (*o*-$MeOC_6H_4$, Me)	85	87	85.4 (+)
9[e]	**2h**, (*p*-MeC_6H_4, Me)	85	73	76.0 (+)
10[e]	**2i**, (2-thienyl, Me)	85	60	55.4 (+)
11[e]	**2j**, (*i*-Pr, Me)	85	91	49.5 (−)

[a] Unless otherwise stated, reactions were performed on a 0.5 mmol scale at room temperature for 12 h, 1 mol % of $[Rh(COD)_2]BF_4$, 2.2 mol % of ligand **9**. [b] Determined by GC or ^1H NMR. [c] Enantiomeric excess values were determined by chiral HPLC, and the absolute configuration was determined by comparing the sign of specific rotation of the corresponding amino acids. [d] $[Rh(COD)_2]BF_4$ (0.1 mol %), ligand **9g** (0.22 mol %). [e] $[Rh(COD)_2]BF_4$ (4 mol %), ligand **9g** (8.8 mol %), 36 h.

The absolute configurations of the hydrogenation products **3a** and **3c** obtained with **9g** as a chiral ligand were assigned as *R* by converting them into their corresponding known β^2-amino acids[4] by using standard reactions[9] (Scheme 1). Scheme 1 also shows an application of this methodology for a potential efficient synthesis of the (*R*)-(−)-α-methyl-

Scheme 1. Highly Enantioselective and Practical Synthesis of (*R*)-(−)-α-Methyl-β-alanine **1**



β-alanine **1**, which is a critical key building block for synthesis of cryptophycin-**1**.[2]

In summary, we have developed the first highly enantioselective method for the synthesis of β^2-amino acids based on the asymmetric hydrogenation of β-phthalimide acrylates. Up to 99% ee has been achieved with an Rh−manniphos catalyst. Efforts are underway in our laboratory to discover further application of this catalyst and to identify other catalyst systems that deliver improved activities and enantioselectivities for this hydrogenation.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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