

# Rhodium-Catalyzed Enantioselective Hydrogenation of $\beta$ -Phthalimide Acrylates to Synthesis of $\beta^2$ -Amino Acids

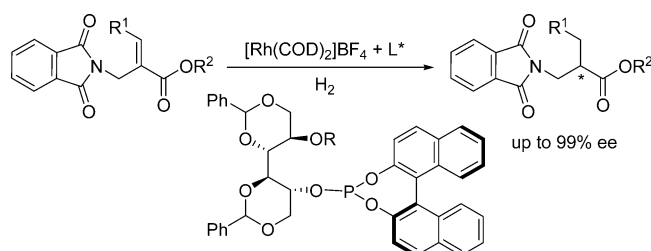
Hanmin Huang, Xiongcai Liu, Jun Deng, Min Qiu, and Zhuo Zheng\*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences,  
Dalian 116023, People's Republic of China

zhengz@dicp.ac.cn

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## ABSTRACT



The enantioselective hydrogenation of  $\beta$ -phthalimide acrylates provides the corresponding chiral  $\beta^2$ -amino acids in excellent enantiomeric excess catalyzed by Rh–monophosphorus.

Chiral  $\beta^2$ -amino acids ( $\alpha$ -substituted  $\beta$ -amino acids) and their derivatives are critical key structural elements in natural products and pharmaceuticals.<sup>1</sup> For example, compound **1** is a key intermediate in the synthesis of the cryptophycin-**1**,<sup>2</sup> 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*,<sup>3</sup> which frequently infect immunodeficient persons suffering from diseases, such as AIDS and cancer.

For these and other reasons, enantioselective synthesis of  $\beta^2$ -amino acids has attracted extensive interest. Although several stoichiometric<sup>4</sup> and catalytic methods, such as

Michael addition,<sup>5</sup> H-atom transfer reaction,<sup>6</sup> C–H insertions of carbenoids reaction,<sup>7</sup> and rhodium enolate protonations,<sup>8</sup> have been developed to make chiral  $\beta^2$ -amino acids, straightforward hydrogenation of prochiral dehydro-precursors represents one of the simplest and efficient routes. However,

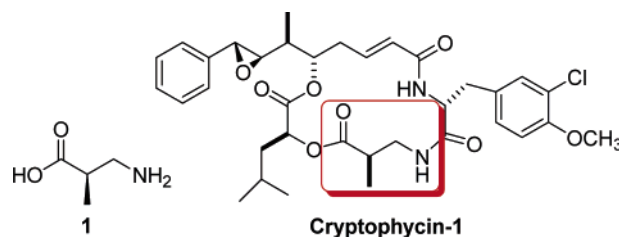


Figure 1. Examples of chiral  $\beta^2$ -amino acids and cryptophycin-**1**.

the only previous documented attempt at this asymmetric hydrogenation, using Rh and Ru catalysts, gave poor to moderate enantioselectivity.<sup>9</sup> So, the search for an efficient

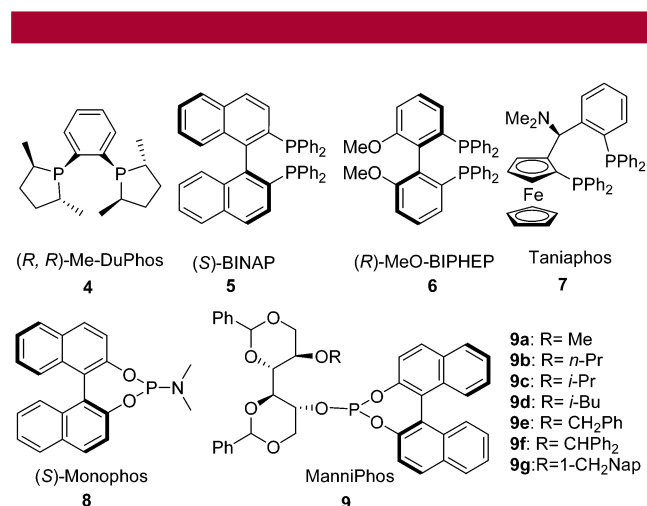
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asymmetric hydrogenation catalytic system for the synthesis of  $\beta^2$ -amino acids is still a challenge. Herein, we report the first highly enantioselective hydrogenation of  $\beta$ -phthalimide acrylates for the synthesis of  $\beta^2$ -amino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

The basic strategy of our method involves asymmetric hydrogenation of  $\beta$ -acrylates with a phthalimido-protected  $\beta$ -amino group, which may satisfy the chelation requirement between the metal and substrate.<sup>9a,10</sup> The  $\beta$ -phthalimide acrylates were readily prepared in good overall yields in three steps from the commercially available inexpensive aldehydes, acrylates, and phthalimide.<sup>11</sup> 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  $\beta$ -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,<sup>12</sup> was applied as catalysts in this hydrogenation reaction. The particular catalyst was prepared in situ by mixing  $[\text{Rh}(\text{COD})_2]\text{BF}_4$  and the phosphorus ligands in the solvents. All the hydrogenation reactions were carried out at room temperature, under 10 atm pressure of  $\text{H}_2$ .

Some representative results are shown in Table 1. The first attempt, using Rh/DuPhos as catalyst precursor, afforded the

**Table 1.** Enantioselective Hydrogenation of  $\beta$ -Phthalimide Acrylates **2a**<sup>a</sup>

entry	ligand	solvent	conv.% <sup>b</sup>	ee% (config.) <sup>c</sup>
1	<b>4</b>	$\text{CH}_3\text{OH}$	>99	59.0 ( <i>R</i> )
2	<b>4</b>	$\text{CH}_2\text{Cl}_2$	>99	67.9 ( <i>R</i> )
3	<b>5</b>	$\text{CH}_2\text{Cl}_2$	>99	57.9 ( <i>S</i> )
4	<b>6</b>	$\text{CH}_2\text{Cl}_2$	>99	66.7 ( <i>R</i> )
5	<b>7</b>	$\text{CH}_2\text{Cl}_2$	>99	4.9 ( <i>R</i> )
6	<b>8</b>	$\text{CH}_2\text{Cl}_2$	>99	89.0 ( <i>S</i> )
7	<b>9g</b>	$\text{CH}_2\text{Cl}_2$	>99	<b>99.1</b> ( <i>R</i> )

<sup>a</sup> Unless otherwise stated, reactions were performed on a 0.5 mmol scale at room temperature for 12 h,  $P(\text{H}_2) = 10$  atm, for the bidentate ligands (**4**–**7**): 1 mol % of  $[\text{Rh}(\text{COD})_2]\text{BF}_4$  and 1.1 mol % of ligand. For the monodentate ligands (**8**, **9**): 1 mol % of  $[\text{Rh}(\text{COD})_2]\text{BF}_4$  and 2.2 mol % of ligand. <sup>b</sup> Determined by GC. <sup>c</sup> Determined by chiral HPLC, and the absolute configuration was determined by comparing the sign of specific rotation of the corresponding amino acid.

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 planar 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<sup>13</sup> 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**<sup>14</sup> 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.

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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  $\beta$ -Phthalimide Acrylates **2a<sup>a</sup>**

entry	ligand	solvent	$P(\text{H}_2)$ atm	conv. % <sup>b</sup>	ee% (config.) <sup>c</sup>
1	<b>9g</b>	CH <sub>3</sub> OH	10	74	22.5 ( <i>R</i> )
2	<b>9g</b>	<i>i</i> -PrOH	10	83	22.5 ( <i>R</i> )
3	<b>9g</b>	THF	10	88	41.1 ( <i>R</i> )
4	<b>9g</b>	toluene	10	86	22.3 ( <i>R</i> )
5	<b>9g</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	99.1 ( <i>R</i> )
6	<b>9g</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	>99	99.1 ( <i>R</i> )
7	<b>9g</b>	CH <sub>2</sub> Cl <sub>2</sub>	30	>99	98.8 ( <i>R</i> )
8	<b>9g</b>	CH <sub>2</sub> Cl <sub>2</sub>	40	>99	98.1 ( <i>R</i> )
9	<b>9a</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	98.9 ( <i>R</i> )
10	<b>9b</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	98.3 ( <i>R</i> )
11	<b>9c</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	98.3 ( <i>R</i> )
12	<b>9d</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	99.1 ( <i>R</i> )
13	<b>9e</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	97.7 ( <i>R</i> )
14	<b>9f</b>	CH <sub>2</sub> Cl <sub>2</sub>	10	>99	98.3 ( <i>R</i> )

<sup>a</sup> Unless otherwise stated, reactions were performed on a 0.5 mmol scale at room temperature for 12 h, 1 mol % of [Rh(COD)<sub>2</sub>]BF<sub>4</sub>, 2.2 mol % of ligand **9**. <sup>b</sup> Determined by GC. <sup>c</sup> 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<sub>2</sub>Cl<sub>2</sub> is most effective in terms of the conversion and enantioselectivity. This agrees with our early results.<sup>14</sup> 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  $\beta$ -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  $\beta$ -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  $\beta$ -phthal-

**Table 3.** Enantioselective Hydrogenation of  $\beta$ -Phthalimide Acrylates **2<sup>a</sup>**

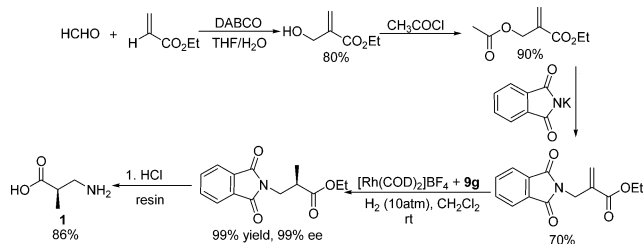
entry	substrate (R <sup>1</sup> , R <sup>2</sup> )	$P(\text{H}_2)$ atm	conv. % <sup>b</sup>	ee% (config.) <sup>c</sup>
1	<b>2a</b> , (H, Et)	10	>99	99.1 ( <i>R</i> )
2	<b>2b</b> , (H, Me)	10	>99	98.3 ( <i>R</i> )
3 <sup>d</sup>	<b>2a</b> , (H, Et)	10	>99	97.7 ( <i>R</i> )
4 <sup>e</sup>	<b>2c</b> , (C <sub>6</sub> H <sub>5</sub> , Me)	85	82	92.0 ( <i>R</i> )
5 <sup>e</sup>	<b>2d</b> , ( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> , Me)	85	>95	86.4 (+)
6 <sup>e</sup>	<b>2e</b> , ( <i>p</i> -FC <sub>6</sub> H <sub>4</sub> , Me)	85	>95	95.9 (+)
7 <sup>e</sup>	<b>2f</b> , ( <i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> , Me)	85	>95	94.6 (+)
8 <sup>e</sup>	<b>2g</b> , ( <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> , Me)	85	87	85.4 (+)
9 <sup>e</sup>	<b>2h</b> , ( <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> , Me)	85	73	76.0 (+)
10 <sup>e</sup>	<b>2i</b> , (2-thienyl, Me)	85	60	55.4 (+)
11 <sup>e</sup>	<b>2j</b> , ( <i>i</i> -Pr, Me)	85	91	49.5 (–)

<sup>a</sup> Unless otherwise stated, reactions were performed on a 0.5 mmol scale at room temperature for 12 h, 1 mol % of [Rh(COD)<sub>2</sub>]BF<sub>4</sub>, 2.2 mol % of ligand **9**. <sup>b</sup> Determined by GC or <sup>1</sup>H NMR. <sup>c</sup> 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. <sup>d</sup> [Rh(COD)<sub>2</sub>]BF<sub>4</sub> (0.1 mol %), ligand **9g** (0.22 mol %). <sup>e</sup> [Rh(COD)<sub>2</sub>]BF<sub>4</sub> (4 mol %), ligand **9g** (8.8 mol %), 36 h.

imide acrylates were hydrogenated to yield their corresponding  $\beta^2$ -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).

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  $\beta^2$ -amino acids<sup>4</sup> by using standard reactions<sup>9</sup> (Scheme 1). Scheme 1 also shows an application of this methodology for a potential efficient synthesis of the (*R*)-(–)- $\alpha$ -methyl-

**Scheme 1.** Highly Enantioselective and Practical Synthesis of (*R*)-(–)- $\alpha$ -Methyl- $\beta$ -alanine **1**



$\beta$ -alanine **1**, which is a critical key building block for synthesis of cryptophycin-**1**.<sup>2</sup>

In summary, we have developed the first highly enantioselective method for the synthesis of  $\beta^2$ -amino acids based on the asymmetric hydrogenation of  $\beta$ -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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