

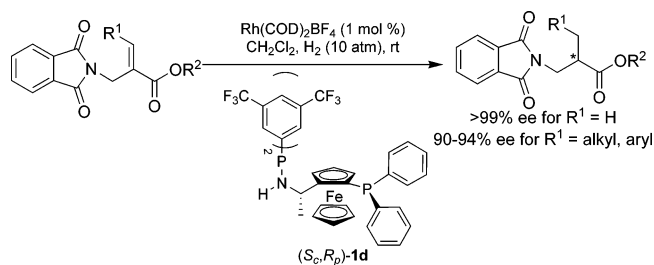
Enantioselective Synthesis of β^2 -Amino Acids via Rh-Catalyzed Asymmetric Hydrogenation with BoPhoz-Type Ligands: Important Influence of an N–H Proton in the Ligand on the Enantioselectivity

Jun Deng,^{†,‡} Xiang-Ping Hu,^{*,†} Jia-Di Huang,^{†,‡} Sai-Bo Yu,^{†,‡} Dao-Yong Wang,^{†,‡} Zheng-Chao Duan,^{†,‡} and Zhuo Zheng^{*,†}

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China, and Graduate School of Chinese Academy of Sciences, Beijing 100039, China

zhengz@dicp.ac.cn; xiangping@dicp.ac.cn

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A series of BoPhoz-type ligands were successfully applied in the rhodium-catalyzed asymmetric hydrogenation of a number of β -substituted or unsubstituted α -(phthalimidomethyl)acrylates, affording good to excellent enantioselectivities. The results suggested that the presence of an N–H proton in the BoPhoz backbone could significantly improve the enantioselectivity, and ligand (*S,S,R_p*)-**1d**, bearing two CF₃-groups in the 3,5-position of the phenyl ring of aminophosphino moiety, showed the highest enantioselectivity.

Chiral β -amino acids and derivatives are important building blocks in the synthesis of natural products, β -peptides, and pharmaceuticals.¹ Therefore, an enantioselective method for the synthesis of these compounds is highly desirable. Although several enantioselective catalytic methods have been developed recently for the synthesis of β -substituted β -amino acids (β^3 -amino acids),² there are significantly fewer reports on enantioselective methods for the synthesis of α -substituted β -amino acids (β^2 -amino acids).^{1a,3} The present methods for the catalytic synthesis of chiral β^2 -amino acids included Pd-catalyzed allylic

substitution,⁴ Rh-catalyzed C–H activation,⁵ Cu-catalyzed conjugate addition,⁶ rhodium-catalyzed conjugate addition and enolate protonations,⁷ and enantioselective H-atom transfer reactions.⁸ Because of its inherent efficiency and atom economy, asymmetric hydrogenation of prochiral dehydro-precursors of β^2 -amino acid derivatives represents one of the most efficient and simplest methods. However, to our knowledge, only a few examples of the hydrogenation of β^2 -dehydroamino acid precursors may be found in the literature, and in most cases, the results are less than satisfactory.⁹ Jackson et al.^{9a} reported that enantioselective hydrogenation of some α,β -unsaturated nitriles bearing a phthalimidomethyl substituent at the α -carbon using Rh-DuPHOS catalysts afforded β^2 -amino acid precursors with moderate ee values of up to 48%, while hydrogenation of the corresponding α,β -unsaturated carboxylic acid methyl esters using a Ru-BINAP catalyst gave higher ee values of up to 84%. Robinson et al.^{9b} described the enantioselective hydrogenation of a series of (*E*)- α -substituted β -amidoacrylates using Rh-catalysts with chiral bidentate phosphine ligands (BPE and DuPHOS), which gave β^2 -amino acid derivatives with enantioselectivities of up to 67%. Very recently, Minnaard and Feringa et al.^{9c} reported the synthesis of β^2 -amino acids via asymmetric rhodium-catalyzed hydrogenation of β -substituted α -acetylaminomethylacrylic acids employing a mixed ligand system consisting of chiral monodentate phosphoramidites and achiral phosphines, in which up to 91% ee was obtained. Qiu et al. have developed highly enantioselective catalytic hydrogenation of α -aminomethylacrylates containing a free basic NH group using the Rh/Et-DuPHOS complex as a catalyst, in which 99% ee and high isolated yields (>98%) were obtained even in low catalyst loadings.^{9d} In our recent study,¹⁰ we have found that the D-mannitol derived monodentate phosphite ligand, ManniPhos, was highly effective for the rhodium-catalyzed asymmetric hydrogenation of β -unsubstituted α -(phthalimidomethyl)acrylates. However, the results for the β -substituted substrates are unsatisfactory. Incomplete conversions and moderate enantioselectivities were obtained in most cases even under high H₂ pressure (85 atm) and high catalyst loadings (4 mol %) for 36 h. Therefore, the search of the new catalytic system, which could induce excellent enantioselectivity under lower catalyst loadings and milder reaction conditions in this Rh-catalyzed transformation, was undertaken. Very recently, we have developed a highly enantioselective synthesis of γ -amino acid derivatives via the

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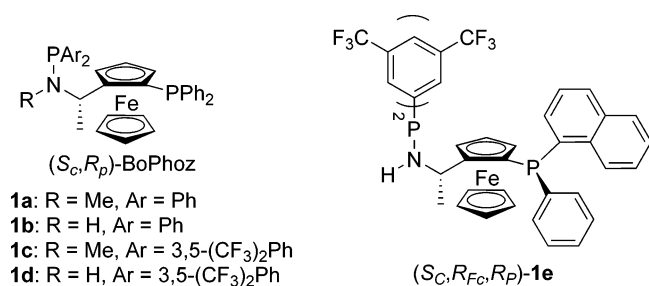


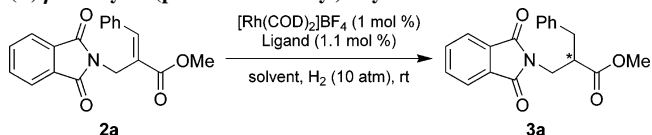
FIGURE 1. Representative structures of BoPhoz-type ligands.

Rh-catalyzed asymmetric hydrogenation of γ -phthalimido- α,β -unsaturated carboxylic acid esters with a highly modular Bophoz-type ligand.¹¹ Because of the structural similarity of the hydrogenation substrates, we then surmised that these Bophoz-type ligands may also be effective for the Rh-catalyzed hydrogenation of α -(phthalimidomethyl)acrylates. As a result, herein we report an efficient Rh-catalyzed asymmetric hydrogenation of various β -substituted or unsubstituted α -(phthalimidomethyl)acrylates with a finely tuned BoPhoz-type phosphine–aminophosphine ligand, in which chiral β^2 -amino acid esters could be synthesized in good to excellent enantioselectivities.

In our initial ligand screening experimental, we observed that the Rh/Me-BoPhoz complex displayed high catalytic activity in the hydrogenation of methyl (*E*)- β -phenyl- α -(phthalimidomethyl)acrylate even under 1 mol % of the catalyst loadings and 10 atm of H₂ pressure. Although the enantioselectivity was moderate (56% ee) (entry 2), this result is far superior to that obtained with ManniPhos reported by us recently.¹⁰ Under the same hydrogenation condition, Rh/ManniPhos showed no catalytic activity for the hydrogenation of this substrate class (entry 1). The synthetic methodology of BoPhoz-type ligands has proved to be highly modular,¹² which provides an opportunity to find an efficient BoPhoz-type ligand for this challenging hydrogenation by optimizing its steric environment through fine structural modifications. As a result, a systematic investigation of a number of BoPhoz-type ligands with varying electronic and steric properties was carried out, and some representative structures are shown in Figure 1.

As shown in Table 1, the structure of the BoPhoz-type ligand has significant influence in the enantioselectivity, and very interestingly, the ligands with an N–H proton on the amino moiety tended to give higher enantioselectivity than those with a methyl group on the amino moiety. Thus, (*S*_C,*R*_P)-BoPhoz **1a** with an *N*-methyl group gave the hydrogenation product in 56% ee (entry 2). In contrast, a remarkable increase in the enantioselectivity to 71% ee was observed by the use of (*S*_C,*R*_P)-BoPhoz **1b** with an N–H proton in the backbone (entry 3). The important role of an N–H proton on the amino unit of the BoPhoz-type ligand can be more clearly appreciated by the comparison of the enantioselective induction of ligand **1c** and

TABLE 1. Ligand and Solvent Screening for Rh-Catalyzed Asymmetric Hydrogenation of Methyl (*E*)- β -Phenyl- α -(phthalimidomethyl)acrylate **2a**^a



entry ^a	ligand	solvent	conv (%) ^b	ee (%) ^c
1	ManniPhos	CH ₂ Cl ₂		<i>d</i>
2	1a	CH ₂ Cl ₂	100	56
3	1b	CH ₂ Cl ₂	100	71
4	1c	CH ₂ Cl ₂	100	48
5	1d	CH ₂ Cl ₂	100	92
6	1e	CH ₂ Cl ₂		<i>d</i>
7	1d	THF	100	39
8	1d	toluene	15	22
9	1d	<i>i</i> -PrOH	62	54

^a All reactions were performed with 0.25 mmol of substrate at room temperature under a H₂ pressure of 10 atm in 2 mL of solvent for 24 h. Substrate/Rh(COD)₂BF₄/ligand = 1/0.01/0.011. ^b Conversions were determined by ¹H NMR, HPLC, or GC. ^c The ee values were determined by HPLC on a chiral column. ^d Not determined because of low conversion.

1d, in which ligand **1d** with an N–H proton exhibited 92% ee while ligand **1c** with an *N*-methyl group only showed 48% ee. The improved enantioselectivity is probably due to the potential second interaction between the N–H proton in the ligand and substrate as reported by Hayashi and Noyori et al.,¹³ however, the real reason is still unclear. Subsequent optimization in an effort to attain higher enantioselectivity by the introduction of a stereogenic *P* center into the phosphino moiety proved unfruitful.^{12g,14} Thus, ligand **1e** with a stereogenic phosphino moiety displayed unexpectedly low conversion (entry 6). A solvent screening experiment revealed that the catalytic activity and enantioselectivity are highly depended on the nature of solvent. Thus, the reaction performed in THF proceeded to completion; however, the enantioselectivity was low (entry 7). When the reaction was carried out in toluene or *i*-PrOH, low conversion and enantioselectivity was observed (entries 8 and 9).

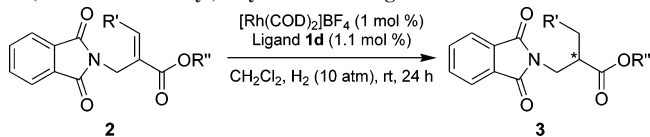
Having established a highly enantioselective hydrogenation of methyl (*E*)- β -phenyl- α -(phthalimidomethyl)acrylate **2a**, we decided to investigate the scope of this challenging reaction on various β -substituted and unsubstituted α -(phthalimidomethyl)acrylates, using (*S*_C,*R*_P)-**1d** as ligand and CH₂Cl₂ as the standard solvent. The reaction was performed under a H₂ pressure of 10 atm at room temperature for 24 h, and the results are summarized in Table 2. Initially, a variety of β -aryl substrates were tested, and the results indicated that the substitution pattern and electronic properties had little effect in the enantioselectivity (entries 1–6). As shown in Table 2, all of the substrates were hydrogenated in over 90% ee, suggesting the efficiency of the present catalytic system for Rh-catalyzed asymmetric hydrogenation of β -aryl- α -(phthalimidomethyl)acrylates. Among them, β -*p*-CF₃-substituted substrate **2d** was hydrogenated in the highest enantioselectivity (94% ee) (entry 4). These hydrogenation products can be easily upgraded via recrystallization to a

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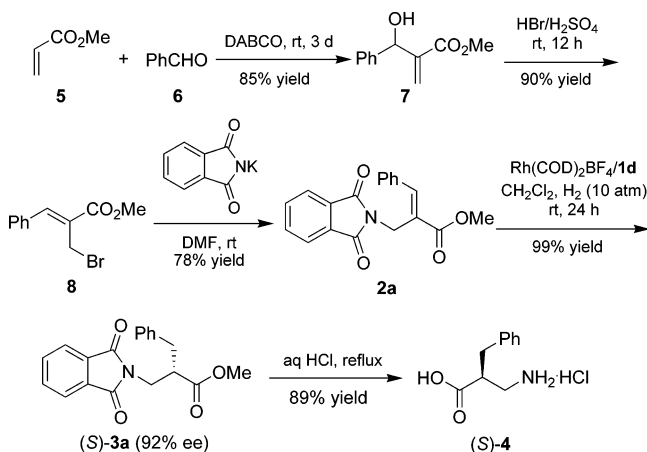
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TABLE 2. Scope of Rh-Catalyzed Asymmetric Hydrogenation of α -(Phthalimidomethyl)acrylate **2** with Ligand **1d**^a

entry ^d	substrate	R'	R''	yield (%) ^b	ee (%) (config) ^c
1	2a	Ph	Me	99	92 (S)
2	2b	<i>p</i> -FC ₆ H ₄	Me	98	90 (–)
3	2c	<i>p</i> -ClC ₆ H ₄	Me	99	91 (–)
4	2d	<i>p</i> -CF ₃ C ₆ H ₄	Me	95	94 (–)
5	2e	<i>m</i> -MeOC ₆ H ₄	Me	97	93 (–)
6	2f	<i>o</i> -MeOC ₆ H ₄	Me	97	92 (–)
7	2g	<i>i</i> -Pr	Me	95	92 (+)
8	2h	H	Me	93	>99 (S)
9	2i	H	Et	97	>99 (S)
10	2i	H	Et	99	>99 (S) ^d

^a All reactions were performed with 1.0 mmol of substrate at room temperature under a H₂ pressure of 10 atm in 4 mL of solvent for 24 h unless otherwise specified. Substrate/Rh(COD)₂BF₄/ligand = 1/0.01/0.011. Full conversions were obtained in all reactions. ^b Isolated yield. ^c The ee values were determined by HPLC on a chiral column. Absolute configuration assigned by known elution order from chiral HPLC according to the literature. ^d Substrate/Rh(COD)₂BF₄ = 1000.

SCHEME 1. Highly Enantioselective Synthesis of (S)-(-)- α -Benzyl- β -alanine

very high level (generally over 98% ee) due to their high crystallinity conferred by the phthalimido group. The high efficiency of the present catalytic system was also demonstrated in the hydrogenation of methyl (*E*)- β -*i*-Pr- α -(phthalimidomethyl)acrylates **2g**, in which full conversion and good enantioselectivity (92% ee) were achieved (entry 7). For the hydrogenation of this substrate, ManniPhos only gave an ee value of <50% and incomplete conversion even under 4 mol % catalyst loadings and 85 atm of H₂ pressure.¹⁰ In the hydrogenation of β -unsubstituted substrates **2h** and **2i**, excellent enantioselectivity (>99% ee) was obtained even under low catalyst loadings (0.1 mol %) (entries 8–10).

The application of this methodology as a key step in the efficient synthesis of chiral β^2 -amino acids is outlined in Scheme 1. Initially, Baylis–Hillman adducts **7** derived from methyl acrylate were transformed into the corresponding (*Z*)-allyl bromide **8** in high yields by treatment with HBr and H₂SO₄.¹⁵

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The coupling of the bromide with potassium phthalimide gave methyl (*E*)- α -phthalimidomethyl- β -phenylacrylate **2a** in good yields.¹⁶ **2a** was then hydrogenated with this new catalytic system in nearly quantitative yields and 92% ee. Complete hydrolysis of **3a** by the with aqueous HCl generated the target chiral β^2 -amino acid **4**.¹⁷

In summary, we have found that BoPhoz-type ligands were effective for the rhodium-catalyzed asymmetric hydrogenation of a variety of β -substituted and unsubstituted α -(phthalimidomethyl)acrylates under the mild hydrogenation condition (10 atm of H₂, room temperature), in which up to 94% ee for β -substituted substrates and over 99% ee for β -unsubstituted substrates were achieved. The results indicated that an N–H proton on the amino unit of the BoPhoz-type ligand is crucial to achieving high stereocontrol in this transformation, and (*S*,*R*_p)-**1d** with an N–H proton and two CF₃-groups in the 3,5-position of the phenyl ring was demonstrated to be the best ligand.

Experimental Section

α -(Phthalimidomethyl)acrylates **2a–i** were prepared according to the known methods.¹⁰

General Hydrogenation Procedure. To a solution of [Rh(COD)₂]BF₄ (4.0 mg, 0.01 mmol) in 2 mL of CH₂Cl₂, which was placed in a nitrogen-filled glovebox, was added the BoPhoz-type ligand **1d** (9.6 mg, 0.011 mmol). The mixture was stirred at room temperature for 30 min, and then a solution of a substrate (1.0 mmol) in 2 mL of CH₂Cl₂ was added. The reaction mixture was transferred to a Parr stainless autoclave. The autoclave was purged three times with hydrogen, and maintained a hydrogen pressure of 10 atm. The hydrogenation was performed at room temperature for 24 h. After the hydrogen was carefully released, the solvent was removed. The residue was filtered through a short SiO₂ column to remove the catalyst. The filtrate was concentrated under reduced pressure, and the enantiomeric excess was determined by HPLC on a chiral column.

Methyl 2-(Phthalimidomethyl)-3-phenylpropanoate (3a). White solid. Mp 89–90 °C. ¹H NMR (400 MHz, CDCl₃) δ 2.83–2.88 (m, 1H), 3.05–3.11 (m, 1H), 3.26–3.29 (m, 1H), 3.59 (s, 3H), 3.84–3.89 (m, 1H), 3.98–4.03 (m, 1H), 7.12–7.26 (m, 5H), 7.69–7.71 (m, 2H), 7.80–7.82 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 35.9, 39.6, 45.8, 52.0, 123.3, 126.5, 128.5, 128.7, 131.9, 134.1, 138.1, 168.0, 173.3. 92% ee was determined by chiral HPLC (chiralcel OJ-H, *i*-PrOH/*n*-hexane = 10/90, UV 254 nm, 40 °C, 0.8 mL/min), retention times (min) 20.1 (major, S) and 26.0 (minor, R).

Synthesis of (S)-(-)- α -Benzyl- β -aminopropionic Acid (4). A mixture of methyl 2-(phthalimidomethyl)-3-phenylpropanoate (**3a**) (1 mmol, 324 mg) and 6 M HCl (15 mL) was heated under reflux for 24 h. The solution was cooled and washed with ethyl acetate (3 \times 10 mL). The aqueous layer was collected and evaporated to dryness, which gave 179 mg (89% yield) of amino acid hydrochloride as the white solid. Mp 159–161 °C; ¹H NMR (400 MHz, D₂O) δ 2.93–2.98 (m, 1H), 3.02–3.12 (m, 3H), 3.18–3.24 (m, 1H), 7.27–7.39 (m, 5H).

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Supporting Information Available: ¹H and ¹³C NMR spectra and analysis of ee values of the hydrogenation products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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