JOC*Note*

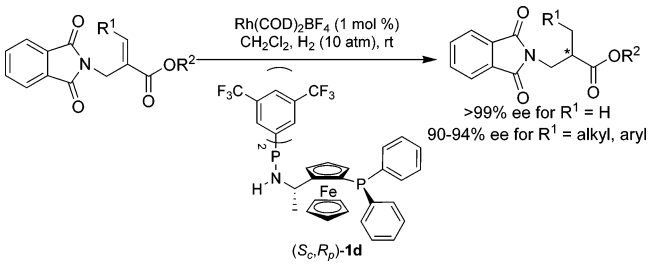
Enantioselective Synthesis of β^2-Amino Acids via Rh-Catalyzed Asymmetric Hydrogenation with BoPhoz-Type Ligands: Important Influence of an N−H Proton in the Ligand on the Enantioselectivity

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

Received November 21, 2007



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_c,R_p)-**1d**, bearing two CF_3-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 H_2 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

[†] Dalian Institute of Chemical Physics, Chinese Academy of Sciences.
[‡] Graduate School of Chinese Academy of Science.

(1) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15. (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (d) Nussbaum, F. V.; Spiteller, P. In *Highlights in Bioorganic Chemistry*; Schmuck, C., Wennemers, H., Eds.; Wiley-VCH: Weinheim, Germany 2003; p 63.

(2) Drexler, H.-J.; You, J.; Zhang, S.; Fisher, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355−361.

(3) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035.

(4) (a) Bower, J. F.; Williams, J. M. J. *Synlett*, **1996**, 685−686. (b) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411−1420.

(5) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197−2199.

(6) (a) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700−3701. (b) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron*: *Asymmetry* **2003**, *14*, 189−191. (c) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3095−3097. (d) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79−80.

(7) Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571−2573.

(8) Sibi, M. P.; Patil, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1235−1238.

(9) (a) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron*: *Asymmetry* **2001**, *12*, 657−667. (b) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1309−1319. (c) Hoen, R.; Tiemersma-Wegman, T.; Procuranti, B.; Lefort, L.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2007**, *5*, 267−275. (d) Qiu, L.; Prashad, M.; Hu, B.; Prasad, K.; Repic, O.; Blacklock, T. J.; Kwong, F. Y.; Kok, S. H. L.; Lee, H. W.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 16787−16792.

(10) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359−3362.

10.1021/jo702510m CCC: $40.75
Published on Web 01/30/2008

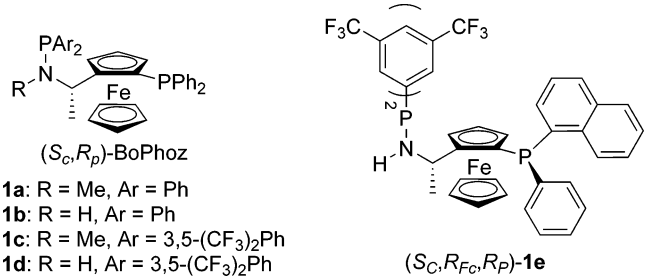


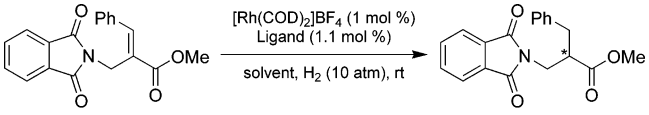
FIGURE 1. Representative structures of BoPhoz-type ligands.

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 H_2 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 **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).

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



2a **3a**

entry[a]	ligand	solvent	conv (%)[b]	ee (%)[c]
1	ManniPhos	CH_2Cl_2		*d*
2	**1a**	CH_2Cl_2	100	56
3	**1b**	CH_2Cl_2	100	71
4	**1c**	CH_2Cl_2	100	48
5	**1d**	CH_2Cl_2	**100**	**92**
6	**1e**	CH_2Cl_2		*d*
7	**1d**	THF	100	39
8	**1d**	toluene	15	22
9	**1d**	*i*-PrOH	62	54

[a] All reactions were performed with 0.25 mmol of substrate at room temperature under a H_2 pressure of 10 atm in 2 mL of solvent for 24 h. Substrate/$Rh(COD)_2BF_4$/ligand = 1/0.01/0.011. [b] Conversions were determined by ^{1}H NMR, HPLC, or GC. [c] The ee values were determined by HPLC on a chiral column. [d] Not determined because of low conversion.

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 CH_2Cl_2 as the standard solvent. The reaction was performed under a H_2 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*-CF_3-substituted substrate **2d** was hydrogenated in the highest enantioselectivity (94% ee) (entry 4). These hydrogenation products can be easily upgraded via recrystallization to a

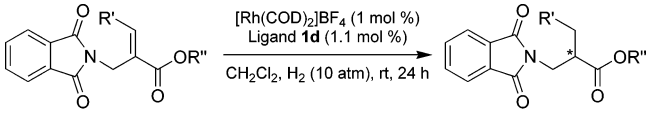
(11) Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825−4828.

(12) (a) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421−2424. (b) Boaz, N. W.; Large, S. E.; Ponasik, J. A., Jr.; Moore, M. K.; Barnette, T.; Nottingham, W. D. *Org. Process Res. Dev.* **2005**, *9*, 472−478. (c) Boaz, N. W.; Ponasik, J. A., Jr.; Large, S. E. *Tetrahedron*: *Asymmetry* **2005**, *16*, 2063−2066. (d) Li, X.; Jia, X.; Xu, L.; Kok, S. H. L.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1904−1908. (e) Boaz, N. W.; Ponasik, J. A., Jr.; Large, S. E. *Tetrahedron Lett.* **2006**, *47*, 4033−4035. (f) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, J. A., Jr. *J. Org. Chem.* **2005**, *70*, 1872−1880. (g) Chen, W.; Mbafor, W.; Roberts, S. M.; Whittall, J. *J. Am. Chem. Soc.* **2006**, *128*, 3922−3923.

(13) (a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191−194. (b) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7−12. (c) Gao, J.-X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087−1089. (d) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419−422.

(14) (a) Chen, W.; Roberts, S. M.; Whittall, J.; Steiner, A. *Chem. Commun.* **2006**, 2916−2918. (b) Chen, W.; McCormack, P. J.; Mohammed, K.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4141−4144.

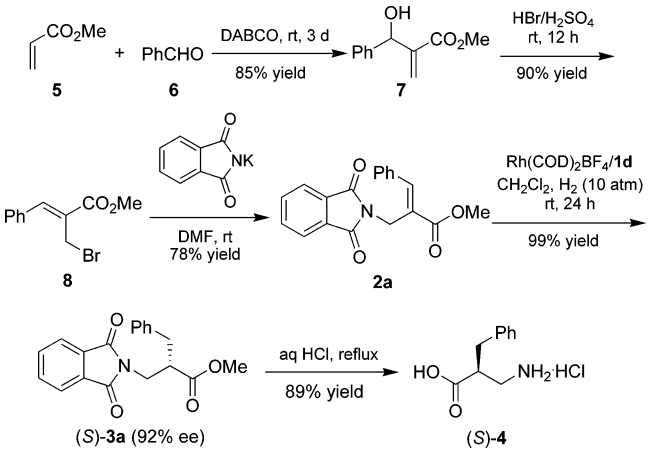
TABLE 2. Scope of Rh-Catalyzed Asymmetric Hydrogenation of α-(Phthalimidomethyl)acrylate 2 with Ligand 1d[a]



entry[a]	substrate	R′	R″	yield (%)[b]	ee (%) (config)[c]
1	**2a**	Ph	Me	99	92 (*S*)
2	**2b**	*p*-FC_6H_4	Me	98	90 (−)
3	**2c**	*p*-ClC_6H_4	Me	99	91 (−)
4	**2d**	*p*-$CF_3C_6H_4$	Me	95	94 (−)
5	**2e**	*m*-$MeOC_6H_4$	Me	97	93 (−)
6	**2f**	*o*-$MeOC_6H_4$	Me	97	92 (−)
7	**2g**	*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 H_2 pressure of 10 atm in 4 mL of solvent for 24 h unless otherwise specified. Substrate/$Rh(COD)_2BF_4$/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/$Rh(COD)_2BF_4$ = 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 H_2 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 H_2SO_4.[15] 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 H_2, 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_c,R_p)-**1d** with an N−H proton and two CF_3-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 [$Rh(COD)_2$]BF_4 (4.0 mg, 0.01 mmol) in 2 mL of CH_2Cl_2, 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 CH_2Cl_2 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 SiO_2 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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-phenyl-propanoate (**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 × 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; ^{1}H NMR (400 MHz, D_2O) 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).

Acknowledgment. We are grateful to the generous financial support from the National Natural Science Foundation of China (20472083).

Supporting Information Available: ^{1}H and ^{13}C 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.

JO702510M

(15) (a) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213−1220. (b) Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971−6976.

(16) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626−1627.

(17) Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2233−2246.