Lewis Base Catalyzed Asymmetric Hydrosilylation of α-Substituted β-Enamino Esters: Facile Access to Enantioenriched β²-Amino Esters via Dynamic Kinetic Resolution

Chang Shu,[a,b] Xiao-Yan Hu,[a,b] Shuai-Shuai Li,[a,b] Wei-Cheng Yuan,[a] Xiao-Mei Zhang*[a]

[a] Key Laboratory for Asymmetric Synthesis & Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, P. R. of China
Fax +86(28)85257883; E-mail: xmzhang@cioc.ac.cn

[b] Graduate School of Chinese Academy of Sciences, Beijing 100049, P. R. of China

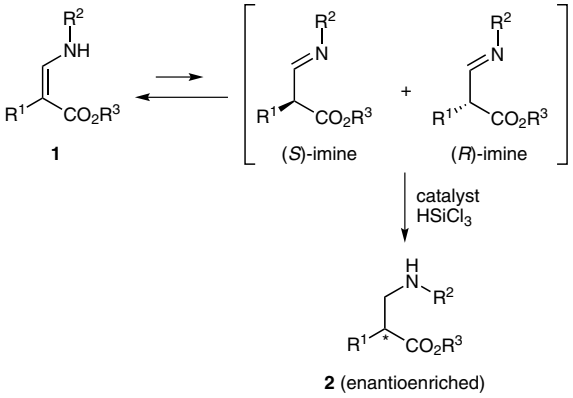
Received: 13.04.2014; Accepted after revision: 19.05.2014

Abstract: A chiral Lewis base organocatalyzed asymmetric hydrosilylation of α-substituted β-enamino esters is presented. The reactions proceeded through dynamic kinetic resolution to afford various enantioenriched β²-amino esters with high yields (up to 98%) in moderate enantioselectivities (up to 77% ee).

Key words: asymmetric catalysis, dynamic kinetic resolution, β²-amino acids, hydrosilylation, Lewis base

Enantioenriched β²-amino acids and derivatives are important building blocks in the synthesis of natural products, β-peptides, and pharmaceuticals.[1] In contrast to β³-homoamino acids, β²-amino acids cannot be obtained simply by homologation of the (natural) α-amino acids, but have to be synthesized by asymmetric reactions. Therefore, synthesis of enantioenriched β²-amino acids has attracted increasing attention.[2] Up to now, many efficient strategies have been developed to prepare enantioenriched β²-amino acid derivatives, such as Michael addition,[3] C–H insertions of carbenoids reaction,[4] enantioselective H-atom transfer reactions,[5] asymmetric hydrogenation of prochiral dehydro precursors of β²-amino acids derivatives,[6] and other protocols.[7]

Trichlorosilane is a cheap and readily available reducing agent. Recently, chiral Lewis base catalyzed hydrosilylation of C=N bond compounds with trichlorosilane has drawn much attention,[8,9] This mild and economical organocatalytic methodology has become a new approach in the synthesis of chiral N-containing compounds. During our continuing research on the asymmetric Lewis base catalyzed hydrosilylation of C=N bond compounds,[9q–t] we envisioned that chiral β²-amino esters could be accessed by chiral Lewis base catalyzed hydrosilylation of α-substituted β-enamino esters through dynamic kinetic resolution (DKR).[10,11] As illustrated in Scheme 1, α-substituted β-enamino ester **1** isomerizes to generate (*S*)-imine and (*R*)-imine. In the presence of a chiral Lewis base catalyst, one of the enantiomers may be hydrosilylated preferentially, and the other enantiomer isomerizes back to enamine **1**. Thus the DKR can be realized, and enantioenriched β²-amino ester **2** can be prepared.



Scheme 1 Dynamic kinetic resolution in chiral Lewis base catalyzed hydrosilylation of α-substituted β-enamino esters

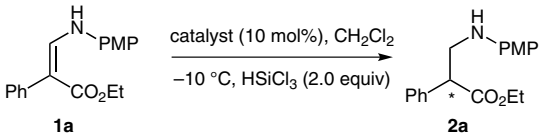
Herein, we describe the chiral Lewis base catalyzed hydrosilylation of α-substituted β-enamino esters, through which various enantioenriched β²-amino esters were synthesized with good yields in moderate enantioselectivities.

First, various α-substituted β-enamino esters **1**[13] were easily prepared according to the literature procedure[12] with minor modification (see the Supporting Information). Afterwards, several chiral Lewis base catalysts **3**–**7** (Figure 1) were tested in the hydrosilylation of α-phenyl-β-enamino ester **1a** in dichloromethane at –10 °C. As can be seen in Table 1, when *trans*-4-hydroxy-L-proline-derived catalyst **3a** was used, the reaction proceeded smoothly to give β²-amino ester **2a** in high yield with only 55% enantiomeric excess (Table 1, entry 1). Several catalysts **3b**–**f** bearing an *O*-alkyl or *O*-phenyl group on C5 of the pridinyl ring resulted in higher enantiomeric excesses (Table 1, entries 2–6). Perhaps the electron-donating groups on C5 of pyridinyl ring increased the Lewis basicity of the catalysts so that they exhibited stronger influence on the substrate. 5-Phenyl catalyst **3g** gave similar enantioselection to **3a** (Table 1, entry 7). When an electron-donation group (methoxy) was introduced on C4 of the pridinyl ring, a slightly lower enantiomeric excess was observed (Table 1, entry 7). On the other hand, catalyst **3i** bearing an elec-

SYNLETT 2014, 25, 1879–1882
Advanced online publication: 08.07.2014
DOI: 10.1055/s-0034-1378323; Art ID: st-2014-w0311-l

tron-withdrawing group (chloro) delivered much better enantioselectivity (Table 1, entry 8). Apparently, the groups on C4 and C5 of the pyridinyl ring had opposite effects on the reaction. Several other chiral Lewis base catalysts **4**–**7** with other chiral amine moieties were also screened and very poor enantioselectivities were obtained. Therefore **3i** was determined as the optimal catalysts and employed in subsequent investigations.

Table 1 Asymmetric Hydrosilylation of α-Substituted β-Enamino Ester **1a**[a]



Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**3a**	93	55
2	**3b**	93	70
3	**3c**	94	72
4	**3d**	96	72
5	**3e**	96	66
6	**3f**	98	65
7	**3g**	95	58
8	**3h**	93	52
9	**3i**	98	74
10	**4**	70	20
11	**5**	90	39
12	**6**	92	27
13	**7**	95	17

[a] Reaction conditions: Unless otherwise specified, the reactions were carried out on a 0.20 mmol scale with 2.0 equiv of $HSiCl_3$ in 2.0 mL of CH_2Cl_2.
[b] Isolated yield based on **1a**.
[c] The ee values were determined using chiral HPLC.

Subsequent screening of the solvents revealed that dichloromethane was the most favorable solvent in the reaction (Table 2, entry 1). When the reaction was conducted at 0 °C, the enantiomeric excess dropped obviously (Table 2, entry 7). When the temperature was lowered to –20 °C, the enantiomeric excess also dropped obviously (Table 2, entry 19). Addition of 4 Å molecular sieves in the reaction system did not benefit the enantioselection (Table 2, entry 9). Increasing the catalyst loading to 20 mol% also did not improve the enantioselection (Table 2, entry 10).

With the optimized conditions in hand, the scope of the chiral Lewis base organocatalyzed hydrosilylation of α-substituted β-enamino esters was examined. Generally, α-aryl substrates underwent the reactions smoothly to afford the corresponding products with good yields in similar en-

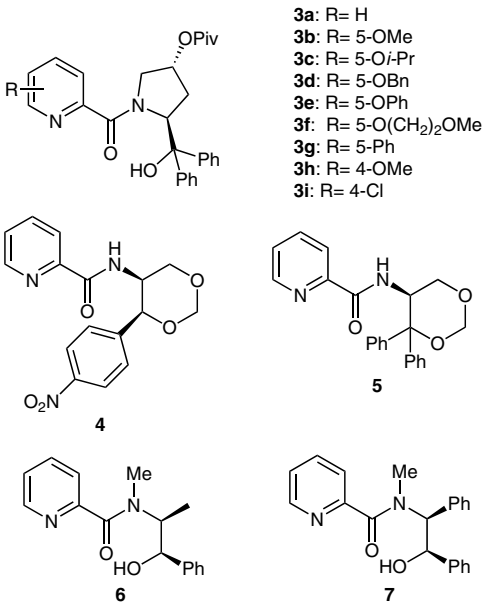
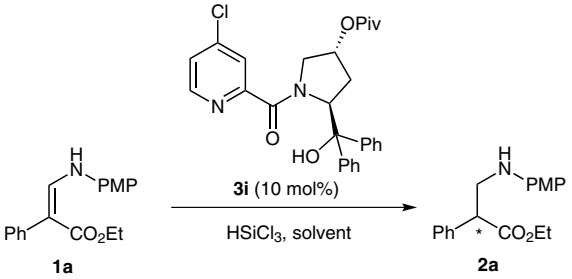


Figure 1 Chiral Lewis base organocatalysts evaluated in this study

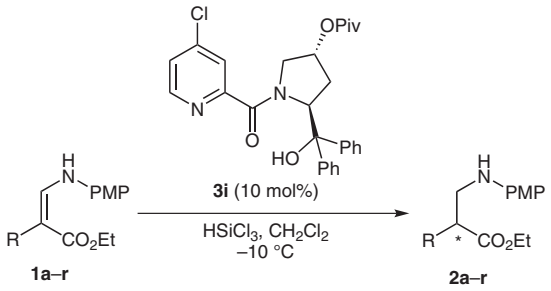
Table 2 Asymmetric Hydrosilylation of α-Substituted β-Enamino Ester **1a**[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	–10	98	74
2	$CHCl_3$	–10	95	11
3	DCE	–10	92	47
4	$MeCCl_3$	–10	91	3
5	THF	–10	88	29
6	toluene	–10	88	11
7	CH_2Cl_2	0	94	53
8	CH_2Cl_2	–20	97	65
9[d]	CH_2Cl_2	–10	96	65
10[e]	CH_2Cl_2	–10	97	72

[a] Reaction conditions: Unless otherwise specified, the reactions were carried out on a 0.20 mmol scale with 2.0 equiv of $HSiCl_3$ and 10 mol% of **3i** in 2.0 mL solvent.
[b] Isolated yield based on **1a**.
[c] The ee values were determined using chiral HPLC.
[d] Conditions: 50 mg of 4 Å MS was added to the reaction mixture.
[e] Conditions: 20 mol% of **3i** was used.

Table 3 Asymmetric Hydrosilylation of α-Substituted β-Enamino Esters **1a**–**p** with Trichlorosilane Catalyzed by **3i**[a]



Entry	**2** R	Yield (%)[b]	ee (%)[c]
1	**2a** Ph	98	74
2	**2b** 4-$MeOC_6H_4$	95	74
3	**2c** 2-$MeOC_6H_4$	97	58
4	**2d** 3-$MeOC_6H_4$	98	73
5	**2e**14 3,4-$(MeO)_2C_6H_3$	99	77
6	**2f** piperonyl	93	71
7	**2g** 4-FC_6H_4	99	77
8	**2h** 2,4,5-$F_3C_6H_2$	93	73
9	**2i** 4-ClC_6H_4	94	63
10	**2j** 2-ClC_6H_4	91	31
11	**2k** 3-ClC_6H_4	94	66
12	**2l** 4-BrC_6H_4	99	74
13	**2m** 4-PhC_6H_4	96	71
14	**2n** 2-naphthyl	96	77
15	**2o** 2-thienyl	87	54
16	**2p** Bn	96	55
17	**2q** *i*-Pr	0	–
18	**2r** PhCONH	88	19

[a] Unless otherwise specified, the reactions were carried out on a 0.20 mmol scale with 2.0 equiv of $HSiCl_3$ and 10 mol% of **3i** in 2.0 mL of CH_2Cl_2.
[b] Isolated yield based on **1**.
[c] The ee values were determined using chiral HPLC.

antiomeric excesses, except those bearing bulky substituents on *ortho* position of the phenyl group (Table 3, entries 3 and 10) and α-2-thienyl-β-enamino ester **2o** (Table 3, entry 15) which provided rather lower enantiomeric excess. Moreover, reaction of α-benzyl-β-enamino ester **2p** gave rise to good yield but poor enantiomeric excess (Table 3, entry 16). Meanwhile, no desired product was obtained with α-isopropyl-β-enamino ester **2q** because **2q** was very unstable and decomposed quickly under the reaction conditions (Table 3, entry 17). Finally, α-benzamido-β-enamino ester **2r** was also subjected to the reaction, and the corresponding product was obtained in good yield with very poor enantioselection (Table 3, entry 18).

In conclusion, we have developed an asymmetric hydrosilylation of α-substituted β-enamino esters promoted by chiral Lewis base organocatalysts through dynamic kinetic resolution. This transformation enables the straightforward and mild synthesis of various chiral β^2-amino esters with good yields in moderate enantioselectivities.

Acknowledgment

We are grateful for financial support from the National Natural Science Foundation of China (21172217 and 20972155) and National Basic Research Program of China (973 Program) (2010CB833301).

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

References and Notes

(1) (a) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Groselj, U.; Zass, E. *Synthesis* **2009**, 1. (b) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366. (c) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206. (d) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (e) Subbaraju, G. V.; Golakoti, T.; Patterson, G. M. L.; Moore, R. E. *J. Nat. Prod.* **1997**, *60*, 302. (f) Chaganty, S.; Heltzel, C.; Golakoti, T.; Moore, R. E.; Yoshida, W. Y. *J. Nat. Prod.* **2004**, *67*, 1403. (g) Seebach, D.; Kimmerlin, T.; Šebesta, R.; Campo, M. A.; Beck, A. K. *Tetrahedron* **2004**, *60*, 7455.

(2) For reviews, see: (a) Sewald, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5794. (b) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2010**, *39*, 1656.

(3) (a) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (c) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (d) Lee, H. S.; Park, J. S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575. (e) Lin, L.; Yin, W.; Fu, X.; Zhang, J. L.; Ma, X. J.; Wang, R. *Org. Biomol. Chem.* **2012**, *10*, 83.

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

(5) (a) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862. (b) Sibi, M. P.; Patil, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1235.

(6) (a) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309. (b) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359. (c) Qiu, L.; Prashad, M.; Hu, B.; Prasad, K.; Repič, 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. (d) Deng, J.; Hu, X.; Huang, J.; Yu, S.; Wang, D.; Duan, Z.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015. (e) Hoen, R.; Tiemersma-Wegman, T.; Procuranti, B.; Lefort, L.; Vries, J. G. D.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2007**, *5*, 267. (f) Li, L. N.; Chen, B.; Ke, Y. Y.; Li, Q.; Zhuang, Y.; Duan, K.; Huang, Y. C.; Pang, J. Y.; Qiu, L. Q. *Chem. Asian J.* **2013**, *8*, 2167. (g) Luhr, S.; Holz, J.; Zayas, O.; Seidelmann, O.; Domke, L.; Borner, A. *Tetrahedron: Asymmetry* **2013**, *24*, 395.

(7) For selected examples, see: (a) Chi, Y. G.; English, E. P.; Pomerantz, W. C.; Horne, W. S.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6050. (b) Chi, Y. G. Gellman S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (c) Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571. (d) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812.

(8) For reviews on Lewis base catalysis and Lewis base catalytic asymmetric hydrosilylations of C=N double bonds, see: (a) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727. (b) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391. (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560; *Angew. Chem.* **2008**, *120*, 1584. (d) Kočovský, P.; Malkov, A. V. *Chiral Lewis Bases as Catalysts*, In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**, 255. (e) Kagan, H. B. *Organocatalytic Enantioselective Reduction of Olefins, Ketones and Imines*, In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**, 391. (f) Jones, S.; Warner, C. J. A. *Org. Biomol. Chem.* **2012**, *10*, 2189. (g) Guizzetti, S.; Benaglia, M. *Eur. J. Org. Chem.* **2010**, 5529. (h) Weickgenannt, A.; Oestreich, M. *ChemCatChem* **2011**, *3*, 1527.

(9) For representative examples, see: (a) Malkov, A. V.; Stewart-Liddon, A. J. P.; McGeoch, G. D.; Ramirez-Lopez, P.; Kočovský, P. *Org. Biomol. Chem.* **2012**, *10*, 4864. (b) Malkov, A. V.; Stončius, S.; Vranková, K.; Arndt, M.; Kočovský, P. *Chem. Eur. J.* **2008**, *14*, 8082. (c) Malkov, A. V.; Stončius, S.; Kočovský, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3722. (d) Malkov, A. V.; Liddon, A. J. P. S.; Ramirez-Lopez, P.; Bendova, L.; Haigh, D.; Kočovský, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 1432. (e) Wang, Z. Y.; Wang, C.; Zhou, L.; Sun, J. *Org. Biomol. Chem.* **2013**, *11*, 787. (f) Liu, X. W.; Yan, Y.; Wang, Y. Q.; Wang, C.; Sun, J. *Chem. Eur. J.* **2012**, *18*, 9204. (g) Xiao, Y. C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10661. (h) Wu, X. J.; Li, Y.; Wang, C.; Zhou, L.; Lu, X. X.; Sun, J. *Chem. Eur. J.* **2011**, *17*, 2846. (i) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751. (j) Genoni, A.; Benaglia, M.; Massolo, E.; Rossi, S. *Chem. Commun.* **2013**, *49*, 8365. (k) Guizzetti, S.; Benaglia, M.; Bonsignore, M.; Raimondi, L. *Org. Biomol. Chem.* **2011**, *9*, 739. (l) Guizzetti, S.; Benaglia, M.; Rossi, S. *Org. Lett.* **2009**, *11*, 2928. (m) Sugiura, M.; Kumahara, M.; Nakajima, M. *Chem. Commun.* **2009**, 3585. (n) Jones, S.; Zhao, P. C. *Tetrahedron: Asymmetry* **2014**, *25*, 238. (o) Jones, S.; Li, X. F. *Tetrahedron* **2012**, *68*, 5522. (p) Kashiwagi, T.; Kotani, S.; Nakajima, M.; Sugiura, M. *Tetrahedron Lett.* **2014**, *55*, 1924. (q) Jiang, Y.; Chen, X.; Hu, X. Y.; Shu, C.; Zhang, Y. H.; Zheng, Y. S.; Lian, C. X.; Yuan, W. C.; Zhang, X. M. *Adv. Synth. Catal.* **2013**, *355*, 1931. (r) Chen, X.; Hu, X. Y.; Shu, C.; Zhang, Y. H.; Zheng, Y. S.; Jiang, Y.; Yuan, W. C.; Liu, B.; Zhang, X. M. *Org. Biomol. Chem.* **2013**, *11*, 3089. (s) Jiang, Y.; Chen, X.; Zheng, Y. S.; Xue, Z. Y.; Shu, C.; Yuan, W. C.; Zhang, X. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7304. (t) Zheng, H. J.; Chen, W. B.; Wu, Z. J.; Deng, J. G.; Lin, W. Q.; Yuan, W. C.; Zhang, X. M. *Chem. Eur. J.* **2008**, *14*, 9864.

(10) For reviews on DKR, see: (a) Zhang, B. L.; Qin, W.; Duan, Y. C.; Yu, B.; Zhang, E.; Liu, H. M. *Chin. J. Org. Chem.* **2012**, *32*, 1359. (b) Pellissier, H. *Tetrahedron* **2011**, *67*, 3769. (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659. (d) Zhang, Z. H.; Liu, Q. B. *Chin. J. Org. Chem.* **2005**, *25*, 780.

(11) For recent selected examples, see: (a) Shen, X.; Miao, W. J.; Ni, C. F.; Hu, J. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 775. (b) Nikitin, K.; Rajendran, K. V.; Müller-Bunz, H.; Gilheany, D. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1906. (c) Dornan, P. K.; Kou, K. G. M.; Houk, K. N.; Dong, V. M. *J. Am. Chem. Soc.* **2014**, *136*, 291. (d) Yang, W.; Yang, Y.; Du, D. M. *Org. Lett.* **2013**, *15*, 1190. (e) Metrano, A. J.; Miller, S. J. *J. Org. Chem.* **2014**, *79*, 1542.

(12) Huang, L. J.; Hsieh, M. C.; Teng, C. M.; Lee, K. H.; Kuo, S. C. *Bioorg. Med. Chem.* **1998**, *6*, 1657.

(13) **General Experimental Procedure for the Enantioselective Hydrosilylation of α-Substituted β-Enamino Esters**
A solution of trichlorosilane (41 μL, 0.3 mmol, 2.0 equiv) in 160 μL of CH_2Cl_2 was added to a stirred solution of the corresponding α-substituted β-enamino ester (0.20 mmol) and the catalyst **3i** (0.020 mmol) in CH_2Cl_2 (2.0 mL) at –10 °C. The mixture was stirred at the same temperature until the reaction reached completion. Then the reaction was quenched with a sat. aq solution of $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvents were evaporated. Purification by column chromatography (silica gel; hexane–EtOAc, 10:1) afforded the products. The ee values were determined using established HPLC techniques with chiral stationary phases.

(14) **Ethyl 2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenylamino)propanoate (2e)**
Yield 99%; 77% ee; light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76–6.84 (m, 5 H), 6.58 (d, *J* = 8.8 Hz, 2 H), 4.10–4.19 (m, 2 H), 3.86 (s, 6 H), 3.79–3.83 (m, 1 H), 3.72–3.74 (m, 4 H), 3.59 (br s, 1 H), 1.18–1.28 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 152.3, 149.1, 148.4, 141.4, 129.2, 120.3, 114.9, 114.6, 114.3, 110.9, 60.9, 55.8, 55.7, 50.3, 47.9, 14.0 ppm. ESI-HRMS: *m/z* calcd for $[C_{20}H_{25}NO_5 + H]^+$: 360.1811; found: 330.1804. $[\alpha]_D^{20}$ +112 (*c* 0.50, $CHCl_3$). AD-H column (*n*-hexane–2-PrOH, 80:20), flow rate = 1.0 mL/min, t_R = 16.7, 17.9 min.

