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PAPER

Triclorosilane-mediated stereoselective synthesis of β-amino esters and their conversion to highly enantiomerically enriched β-lactams†

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A highly stereoselective trichlorosilane-mediated reduction of *N*-benzyl enamines was developed; the combination of a low cost, easy to make metal-free catalyst and an inexpensive chiral auxiliary allowed to perform the reaction on substrates with different structural features often with total control of the stereoselectivity. By easy deprotection through hydrogenolysis followed by conversion of β-aminoester to 2-azetidinones, the synthesis of enantiomerically pure β-lactams (>98% e.e.) was successfully accomplished.

Introduction

The tremendous growth of the interest in what is currently referred to as the "organocatalytic" approach toward enantioselective synthesis, is strongly indicative of the general direction toward which modern stereoselective synthesis is moving. After scattered reports on this methodology in the 1970s, organic catalysis represents now an established possibility of using an organic molecule of relatively low molecular weight, simple structure, and low cost to promote a given transformation in substoichiometric quantity, in the absence of any metal, and under non-stringent reaction conditions that are typical of organometallic catalysis.[1]

These considerations may hold true also for the enantioselective reduction of carbon–nitrogen double bond. Hydrosilylation of imines[2] or enantioselective hydrogenation[3] have been widely studied in these years, leading to the development of a few efficient chiral catalytic organometallic systems currently available for C=N bond reduction.[4] Although recently a few excellent results have been obtained with Rh, Ru, and specially Ir catalysts,[5] the research of alternative metal-free procedures is still very active. Basically two organocatalytic methodologies have been recently developed for the stereoselective reduction of ketimines: binaphthol-derived phosphoric acids were successfully employed in a process that involves the use of a dihydropyridine-based compound as the reducing agent.[6] Alternatively the reduction was performed in the presence of trichlorosilane, that needs to be activated by co-ordination with Lewis bases;[7] the use of different classes of chiral Lewis bases has led to the development of some efficient catalysts able to control the stereochemical outcome of the reaction.[8,9]

Trichlorosilane-based methodologies have allowed to efficiently perform the reduction of not only *N*-aryl, *N*-benzyl and *N*-alkyl ketoimines, but also of imines derived from α-ketoesters, leading to the synthesis of natural and unnatural α-aminoacids.[10] Very recently this metal-free procedure has been employed in the reduction of β-enamino esters, as valid alternative to the metal-catalyzed hydrogenations.[11] Malkov and Kocovsky, taking advantage of the fast equilibration between enamine and imine form, have successfully accomplished the synthesis of β-aminoacids by trichlorosilane mediated enamine reduction catalyzed by the (*S*)-valine-derived formamide **A**.[12] Analogously Zhang developed an efficient methodology where the catalyst of choice was found to be the chiral picolinamide **B** of Fig. 1.[13] Even if high enantioselectivities were reached, it must be noted that both methods rely on the use of *N*-aryl enamines, whose conversion to *N*-deprotected aminoacids require an oxidative deprotection protocol, with CAN (cerium ammonium nitrate) or TCCA (trichloroisocyanuric acid).

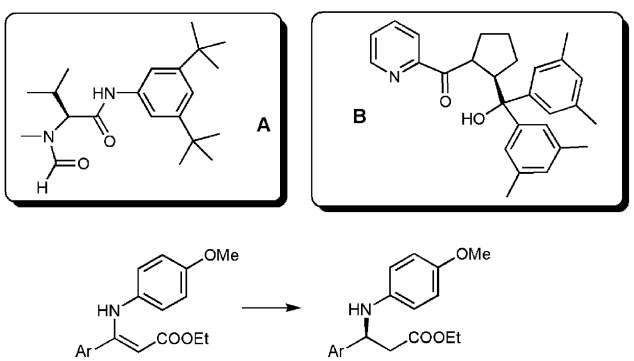

Fig. 1 Organocatalytic reduction of *N*-aryl enamines.

Following our interest in the development of trichlorosilane-mediated reactions[14] we wish to report here a highly stereoselective

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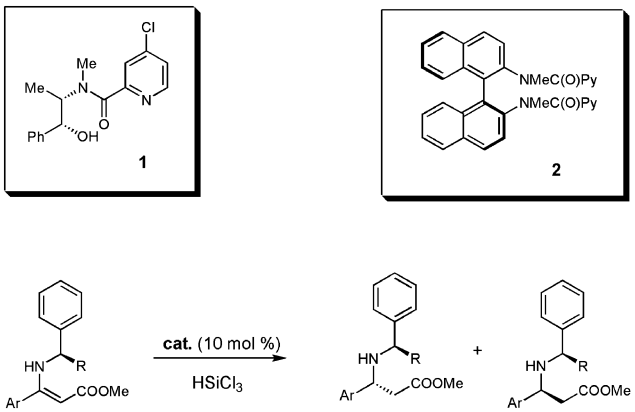
reduction of *N*-benzyl enamines, to afford the corresponding β-aminoesters which can be conveniently deprotected by hydrogenolysis and finally converted to β-lactams. By performing the stereo determining crucial reductive step in the best conditions almost enantiomerically pure β-lactams were obtained (98% e.e.).

Based on our previous experiences we decided to investigate the behaviour of the ephedrine-derived 4-chloropicolinamide **1**[9a,9d] and bis-picolinamide derivative of 1,1-binaphthyl-2,2′-diamine **2**[9b,9c] in the trichlorosilane-promoted reduction of *N*-benzyl enamine (Scheme 1)



3	R = H	Ar = Ph	**4a**	**4b**
5	R = Me	Ar = Ph	**6a**	**6b**
7	R = H	Ar = 4-$CF_3C_6H_4$	**8a**	**8b**
9	R = Me	Ar = 4-$CF_3C_6H_4$	**10a**	**10b**
11	R = H	Ar = 4-$OMeC_6H_4$	**12a**	**12b**
13	R = Me	Ar = 4-$OMeC_6H_4$	**14a**	**14b**
15	R = H	Ar = 1-naphthyl	**16a**	**16b**
17	R = Me	Ar = 1-naphthyl	**18a**	**18b**

Scheme 1 Stereoselective reduction of *N*-benzyl enamines.

The reduction of *N*-benzyl enamine **3** of 3-oxo-3-phenyl-propionic acid methyl ester,[15] by employing 10% of chiral Lewis base at 0 °C in dichloromethane afforded the product in 73% and 71% yield with catalyst **1** and **2** respectively, and comparable level of stereoselectivity (67% and 61% e.e., see Table 1)[16] Lower reaction temperatures allowed only to slightly increase the enantioselection up to 81% e.e.

Table 1 Reduction of *N*-benzyl enamines **3** and **5** of 3-oxo-3-phenyl-methyl propionate[a]

Entry	Catalyst	*T*/°C	Enamine	Yield (%)[b]	e.e. (%)[c]
1	**1**	0	**3**	73	67
2	**2**	0	**3**	71	61
3	**1**	−20[e]	**3**	70	81
4	**2**	−20[e]	**3**	43	73
5[d]	**1**	−20[e]	**3**	98	71
6	**1**	0	**5**	70	99[f]
7	**2**	0	**5**	75	81[f]

[a] Typical experimental conditions: 0.1 mol equiv of catalyst, 3 mol equiv of trichlorosilane, 18 h reaction time in DCM. [b] Yields of isolated products. [c] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments. [d] Reaction solvent was $CHCl_3$. [e] Reaction time 30 h. [f] Diastereoisomeric ratio determined by ^{1}H-NMR and by HPLC.

Table 2 Stereoselective reduction of *N*-benzyl enamines **3–17** promoted by catalyst **1** at 0 °C[a]

Entry	Enamine	Yield (%)[b]	e.e. (%)[c]
1	**3**	73	67
2	**5**	70	99[d]
3	**7**	97	78
4	**9**	75	99[d]
5	**11**	80	70
6	**13**	71	99[d]
7	**15**	75	68
8	**17**	85	99[d]
9	**5**	80[e]	99[d]

[a] Typical experimental conditions: 0.1 mol equiv of catalyst **1**, 3 mol equiv of trichlorosilane, 18 h reaction time in DCM at 0 °C. [b] Yields of isolated products. [c] As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments. [d] Diastereoisomeric ratio determined by ^{1}H-NMR and by HPLC. [e] Reaction time: 36 h.

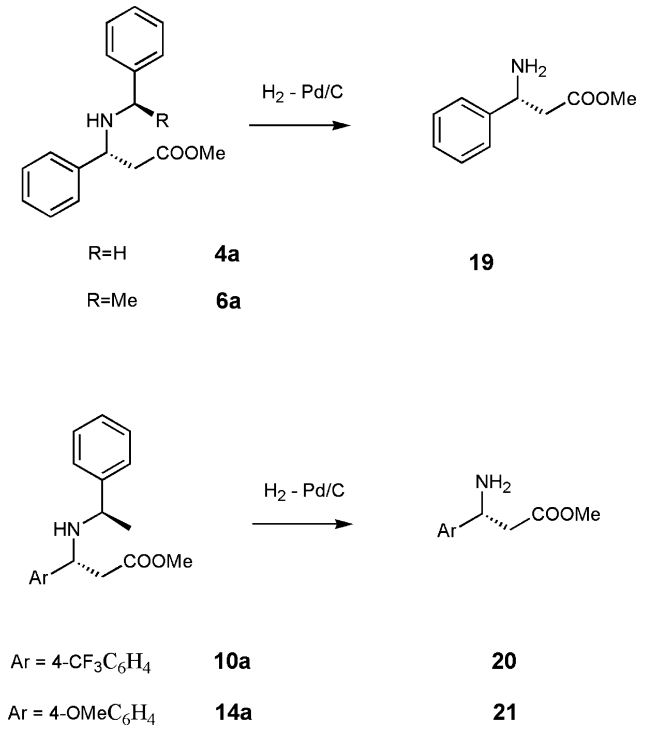
In the attempt of improving the selectivity of the process, we decided to take advantage of the presence of a removable chiral auxiliary at the imine nitrogen;[9d] therefore trichlorosilane mediated reduction of enamine **5** derived from (*R*)-1-phenyl-ethyl amine was studied.[17] By running the reaction at 0 °C the chiral β-amino ester **6a** was obtained after 12 h in 70% yield with a total control of the stereoselectivity (Table 1, entry 6).[18]

Also binaphthyl-derived bis-picolinamide **2** catalyzed efficiently the reduction of chiral enamines **5**, although with a lower selectivity (81% d.r., entry 7, Table 1). In this case the matching pair was represented by (*S*)-binaphthyl diamine derivative **2** and enamine prepared from (*R*) methyl benzyl amine.[18]

Having proofed the potentiality of the synthetic approach, the methodology was extended to the synthesis of other enantiomerically pure β-aryl-β-amino esters (Table 2). *N*-α-methyl benzyl enamines of different electronic properties were effectively reduced always maintaining an absolute control of the stereoselectivity of the process (Scheme 1). While the reduction of *N*-benzyl enamine **7** derived from 3-oxo-3-(4-trifluoromethyl-phenyl)-propionic acid methyl ester afforded chiral amine **8a** with 78% e.e. (entry 3, Table 2), the trichlorosilane addition to enamine **9** led to the corresponding amino ester **10a** with a diastereoisomeric ratio higher than 99/1 (entry 4).

Analogous results were obtained with electron rich aryl-substituted substrates. In both cases, starting from chiral enamines **13** and **17** the reduction was successfully accomplished in 71% and 85% yield, respectively and always with complete stereocontrol (entries 6 and 8). Noteworthy the chiral Lewis base amount could be decreased and the reaction was successfully performed in the presence of only 1% of catalyst **1**. The reduction of **5** afforded amine **6** with 65% yield, although with a lower selectivity (91 : 9 d.r.).

Obviously the present methodology becomes synthetically appealing only if the benzyl group removal may be successful realized, thus demonstrating the feasibility of the approach for the preparation of enantiomerically pure primary amino esters. Therefore hydrogenolysis of different chiral β-amino esters was attempted (Scheme 2).[19] When 3-*N*-benzylamine-3-phenyl propionic acid methyl ester **4a** was reacted with hydrogen in the presence of catalytic amount of Pd/C in methanol at 1 atm at 25 °C, chiral amino ester **19** was isolated in quantitative yield after 16 h. Starting from an enantiomerically enriched compound (81%

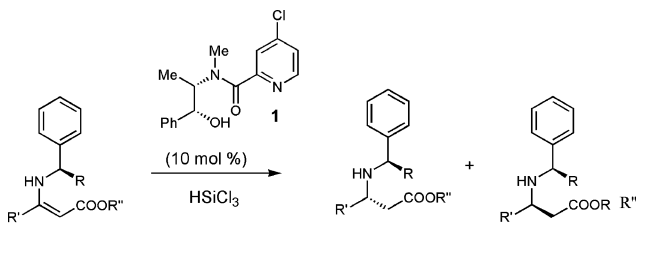


Scheme 2 Chiral auxiliary removal by hydrogenolysis.

e.e.), the corresponding product **19** was obtained in 79% e.e., with basically no loss of stereochemical information.

The deprotection of *N*-α-methyl benzyl amine **6** required more drastic conditions and it was successfully performed by hydrogenating the starting material for 16 h in methanol with Pd/C at 15 atm.[20] Noteworthy the reaction occurred without any appreciable loss of stereochemical integrity.[21] Similarly it was demonstrated that -α-methyl benzyl-removal was possible also for substrates bearing electron rich-substituted aromatic rings. Chiral amines **18a** gave the corresponding primary amine ester **21** basically in quantitative yield and as single stereoisomer.

Then the trichlorosilane mediated reduction was applied to enamines of β-alkyl-β-keto esters (Scheme 3). While the reduction of **23** (alkyl = R′ = ethyl) afforded the product in low enantioselectivity, some more interesting results were obtained with enamine **27** (R′ = benzyl). In this case the product was isolated in 71% d.r. at 0 °C.



23	R = H	R' = Et	R" = Me	**24a**	**24b**
25	R = H	R' = Bn	R" = Me	**26a**	**26b**
27	R = Me	R' = Bn	R" = Me	**28a**	**28b**
29	R = H	R' = i-Pr	R" = Me	**30a**	**30b**
31	R = Me	R' = i-Pr	R"= Me	**32a**	**32b**
33	R = H	R' = Ph	R"= t-Bu	**34a**	**34b**

Scheme 3 Stereoselective reduction of *N*-benzyl β-enamino esters.

Table 3 Stereoselective reduction of *N*-benzyl enamines **23–37** promoted by catalyst **1**[a]

Entry	*T*/°C	Enamine	Yield (%)[b]	e.e. (%)[c]
1	0	**23**	63	21
2	0	**25**	51	53
3	0	**27**	45	71
4	0	**29**	55	51
5[d]	–20	**29**	31	71
6	0	**31**	65	75
7	0	**33**	98	76

[a] Typical experimental conditions: 0.1 mol equiv of catalyst, 3 mol equiv of trichlorosilane, 18 h reaction time in DCM. [b] Yields of isolated products. [c] As determined by HPLC on a chiral stationary phase; yields and e.e. are average of duplicate experiments. [d] Reaction run in $CHCl_3$.

When the reduction of enamine **29** (R′ = isopropyl) was attempted the product was isolated in 55% yield and 51% e.e. The stereoselection of the process could be improved by running the reaction at lower temperatures (71% e.e. at –20 °C), although in modest yield (entries 3–5). In that case even the use of the chiral auxiliary did not allow to obtain a diastereoisomerically pure compound and by reduction of **31** the chiral amino ester **32a** was produced in 75% e.e.

In order to further increase the selectivity and obtain a total stereocontrol also for that substrate the role of the ester group was briefly investigated. *N*-benzyl enamine of 3-oxo-3-phenyl-propionic acid *t*-butyl ester **33** was synthesized and reacted with trichlorosilane in the presence of catalyst **1**. The product was obtained at 0 °C in 71% yield and higher enantioselectivity than the corresponding methyl ester (75% e.e. *vs.* 67% e.e., entry 7 Table 3 *vs.* entry 1 Table 2). However any attempt to perform the reduction on the analogous *t*-butyl ester derivative of enamine **31** was unsuccessful.

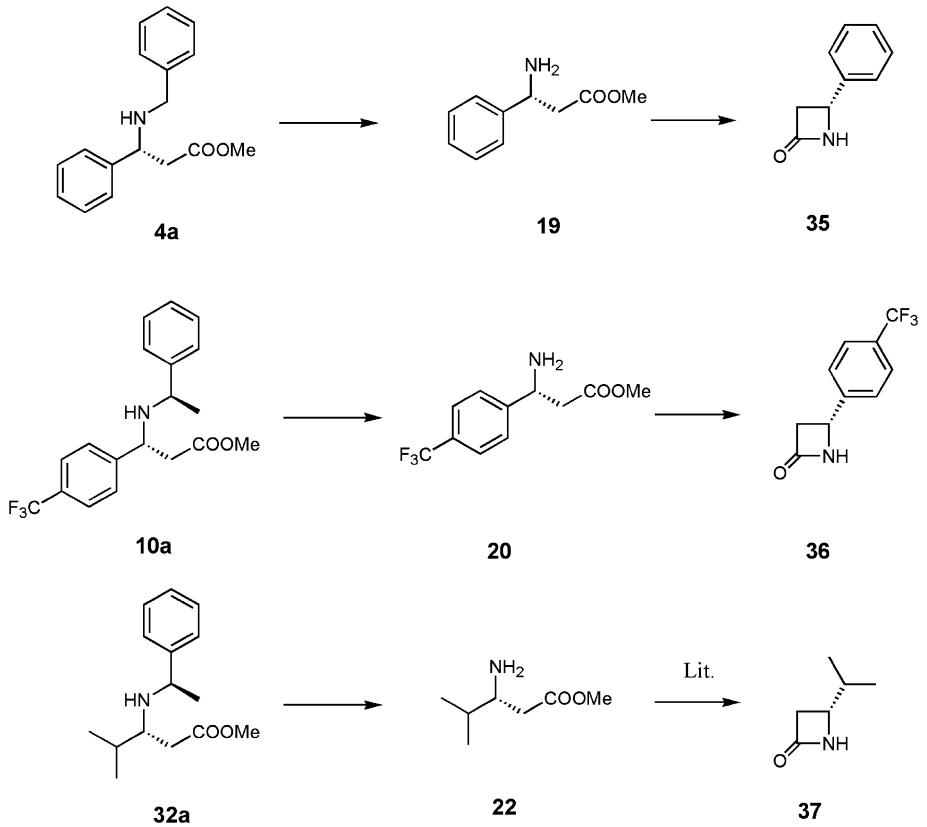
Having demonstrated the generality of the approach, a few substrates were finally converted to β-lactams. Starting from a sample of *N*-benzyl aminoester **4a** with 80% e.e. hydrogenolysis followed by reaction with LDA in THF afforded the chiral 4-(*R*)-phenyl azetidin-2-one **35** in 77% e.e. in 82% overall yield (Scheme 4).

Similarly when β-amino ester **10a** was reduced by hydrogenation and converted to the corresponding chiral 4-(4-trifluoromethyl phenyl)-substituted β-lactam, the product **36** was isolated in 80% yield after chromatographic purification and as single stereoisomer (Scheme 4) Finally, by following the same synthetic procedure 4-methyl-2-amino-methyl pentanoate **22**, known precursor of 4-isopropyl azetidin-2-one, **37**, was obtained in 90% yield through hydrogenolysis of **32a**.

In conclusion, the organocatalytic reduction of *N*-benzyl enamines with trichlorosilane was succesfully accomplished; the combination of low cost, easy to make metal-free catalyst and an inexpensive chiral auxiliary allowed to obtain chiral β-amino esters often with total control of the stereoselectivity. Finally hydrogenolysis of *N*-benzyl aminoesters followed by LDA-promoted ring closure afforded enantiomerically pure 4-aryl or 4-alkyl substituted β-lactams.

Experimental Section

General. All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere, unless



Scheme 4 Synthesis of highly enantiomerically enriched β-lactams.

otherwise stated. All commercially available reagents including dry solvents were used as received. Organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum using a rotatory evaporator. Nonvolatile materials were dried under high vacuum. Reactions were monitored by thin-layer chromatography on pre-coated Merck silica gel 60 F254 plates and visualized either by UV or by staining with a solution of cerium sulfate (1 g) and ammonium heptamolybdate tetrahydrate (27 g) in water (469 mL) and concentrated sulfuric acid (31 mL). Flash chromatography was performed on Fluka silica gel 60. Proton NMR spectra were recorded on spectrometers operating at 200, 300 or 500 MHz respectively. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ $\delta = 7.26$ ppm). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta = 77.0$ ppm). Optical rotations were obtained on a polarimeter at 589 nm using a 5 mL cell with a length of 1 dm. HPLC for e.e. determination was performed under the conditions reported below. Mass spectra (MS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. Microwave-accelerated reactions were performed in CEM Discover class S instrument.

Reduction reaction

General procedure. To a stirred solution of catalyst (0.1–0.01% mol/eq mmol) in the chosen solvent (2 mL), the enamine (1 mmol/eq) was added (for the synthesis of enamines see ESI†). The mixture was then cooled to the chosen temperature and trichlorosilane (3.5 mmol/eq) was added drop wise by means of a syringe. After stirring at the proper temperature, the reaction was quenched by the addition of a saturated aqueous solution of NaHCO3 (1 mL). The mixture was allowed to warm up to room temperature and water (2 mL) and dichloromethane (5 mL) were added. The organic phase was separated and the combined organic phases were dried over Na2SO4, filtered, and concentrated under vacuum at room temperature to afford the crude product. If necessary, the amine was purified by flash chromatography. For the characterization of the reaction products see ESI†.

Hydrogenolysis

Typical experimental procedure for N-benzyl amines. A suspension of (*R*)-methyl 3-(benzylamino)-3-phenylpropanoate (**4a**) (0.58 mmol) and Pd/C (10%, 36 mg) in methanol (3.5 mL) were stirred in under hydrogen atmosphere at room temperature for 16 h. The catalyst was removed by filtration through a pad of celite, and the filtrate was concentrated and purified by column chromatography (5 : 5 hexane–ethyl acetate 100 mL, 4 : 6 hexane–ethyl acetate 100 mL, 3 : 7 hexane–ethyl acetate 100 mL mixture as eluent).

Yield = 98%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (br, 2H); δ 2.67 (d, 2H); δ 3.66 (s, 3H); δ 4.42 (t, 1H); δ 7.21–7.38 (m, 5H). The enantiomeric excess was determined by HPLC on a Chiralcel OD–H (98 : 2 hexane–isopropanol; flow rate: 0.8 mL min^{-1}; $\lambda = 210$ nm): $t_R = 26.04$ min, $t_S = 32.44$ min. $[\alpha]_D^{25} = +10.5$ ($c = 0.258$ g/100 mL, DCM, $\lambda = 589$ nm).

Typical experimental procedure for N-α-methylbenzyl amines. The deprotection of *N*-α-methyl benzyl amine **10a** required more drastic conditions and it was successfully performed by hydrogenating the starting material for 16 h in methanol with Pd/C at 15 atm.

Yield = 98%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.43 (br, 2H); δ 2.72 (d, 2H); δ 3.68 (s, 3H); δ 4.52 (t, 1H); δ 7.51 (d, 2H); δ 7.60 (d, 2H). The enantiomeric excess was determined by HPLC on a Chiralpak AD (9 : 1 hexane–isopropanol; flow rate: 0.8 mL min^{-1}; λ = 210 nm): t_S = 9.7 min, t_R = 10.5 min. For other products see ESI†.

Synthesis of β-lactams

Typical procedure: Synthesis of (R)-4-phenylazetidin-2-one (35). To a solution of LDA (0.676 mmol) in THF (3 mL) at –78 °C was added a THF (1 mL) solution of (*R*)-methyl 3-amino-3-phenylpropanoate (**19**). After stirring at –78 °C for 16 h the reaction was quenched with $NaHCO_3$ aq., and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (7 : 3 hexane–ethyl acetate 100 mL, 5 : 5 hexane–ethyl acetate 100 mL mixture as eluent).

Yield = 84%; $[\alpha]_D^{25}$ = + 106 (*c* = 0.02 g/100 mL, EtOH, λ = 589 nm). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.87 (dd, 1H); δ 3.44 (dd, 1H); δ 4.71 (dd, 1H); δ 6.30 (br, 1H); δ 7.30–7.43 (m, 5H). GC on chiral stationary phase (Agilent HP-chiral): t_R = 66.0 min, t_S = 74.0 min. For other products see ESI†.

Acknowledgements

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References

1 (*a*) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267; (*b*) *Enantioselective Organocatalysis. Reactions and Experimental procedures*. P. I. Dalko, Ed.; Wiley VCH, Weinheim, 2007; (*c*) Recent reviews: A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138.

2 X. Verdaguer, U. E. W. Lange and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 1998, **37**, 1103.

3 For a special issue on hydrogenation and transfer hydrogenation see: M. J. Krische and Y. Sun, *Acc. Chem. Res.*, 2007, **40**(12), 1237Ed., all issue.

4 H-U. Blaser, B. Pugin, F. Spindler and M. Thommen, *Acc. Chem. Res.*, 2007, **40**, 1240 and references cited therein See also; R. Kadyrov and T. H. Riermeier, *Angew. Chem., Int. Ed.*, 2003, **42**, 5472–5474For a recent review on chiral amine synthesis see: T. C. Nugent and M. El-Shazly, *Adv. Synth. Catal.*, 2010, **352**, 753.

5 Recent examples of organometallic catalysis in carbon-nitrogen double bond: (*a*) A. Baeza and A. Pfaltz, *Chem.–Eur. J.*, 2010, **16**, 4003; (*b*) W. Li, G. Hou, M. Chang and X. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 3123; (*c*) Z. Han, Z. Wang, X. Zhang and K. Ding, *Angew. Chem., Int. Ed.*, 2009, **48**, 5345; (*d*) D. Steinhuebel, Y. Sun, K. Matsumura, N. Sayo and T. Saito, *J. Am. Chem. Soc.*, 2009, **131**, 11316; (*e*) N. Mrsic, A. J. Minaard, B. L. Feringa and J. G. de Vries, *J. Am. Chem. Soc.*, 2009, **131**, 8358; (*f*) H. Geng, W. Zhang, J. Chen, G. Hou, L. Zhou, Y. Zou, W. Wu and X. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 6052.

6 Reviews: (*a*) S. J. Connon, *Org. Biomol. Chem.*, 2007, **5**, 3407; (*b*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (*c*) M. Terada, *Chem. Comm.*, 2008, 4097. For a recent contribution in the field see: V. N. Wakchaure, J. Zhou, S. Hoffmann and B. List, *Angew. Chem., Int. Ed.*, 2010, **49**, 4612 and references cited there.

7 Reviews: (*a*) M. Benaglia, S. Guizzetti and L. Pignataro, *Coord. Chem. Rev.*, 2008, **252**, 492; (*b*) S. E. Denmark and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2008, **47**, 1560; (*c*) Y. Orito and M. Nakajima, *Synthesis*, 2006, **9**, 1391.

8 Selected references: for chiral *N*-formyl derivatives see (*a*) F. Iwasaki, O. Onomura, K. Mishima, T. Kanematsu, T. Maki and Y. Matsumura, *Tetrahedron Lett.*, 2001, **42**, 2525; (*b*) A. V. Malkov, A. Mariani, K. N. MacDougal and P. Kočovský, *Org. Lett.*, 2004, **6**, 2253; (*c*) A. V. Malkov, S. Stončius and P. Kočovský, *Angew. Chem., Int. Ed.*, 2007, **46**, 3722; (*d*) A. V. Malkov, M. Figlus, S. Stončius and P. Kočovský, *J. Org. Chem.*, 2009, **74**, 5839; (*e*) A. V. Malkov, K. Vranková, R. C. Sigerson, S. Stončius and P. Kočovský, *Tetrahedron*, 2009, **65**, 9481; (*f*) Y. Matsumura, K. Ogura, Y. Kouchi, F. Iwasaki and O. Onomura, *Org. Lett.*, 2006, **17**, 3789; (*g*) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang and J. Sun, *Org. Lett.*, 2006, **5**, 999; (*h*) C. Baudequin, D. Chaturvedi and S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 2623–2629; (*i*) For chiral picolinamides see: O. Onomura, Y. Kouchi, F. Iwasaki and Y. Matsumura, *Tetrahedron Lett.*, 2006, **47**, 3751; (*j*) H. Zheng, J. Deng, W. Lin and X. Zhang, *Tetrahedron Lett.*, 2007, **48**, 7934; (*k*) see reference 9; (*l*) For other chiral Lewis bases see: A. V. Malkov, A. J. P. S. Liddon, P. Ramírez-López, L. Bendová, D. Haigh and P. Kočovský, *Angew. Chem., Int. Ed.*, 2006, **45**, 1432; (*m*) D. Pei, Z. Wang, S. Wei, Y. Zhang and J. Sun, *Org. Lett.*, 2006, **25**, 5913; (*n*) D. Pei, Y. Zhang, S. Wei, M. Wang and J. Sun, *Adv. Synth. Catal.*, 2008, **350**, 619; (*o*) C. Wang, X. Wu, L. Zhou and J. Sun, *Chem.–Eur. J.*, 2008, **14**, 8789; (*p*) F.-M. Gautier, S. Jones and S. J. Martin, *Org. Biomol. Chem.*, 2009, **7**, 229.

9 For our contribution in the field see: (*a*) S. Guizzetti, M. Benaglia, R. Annunziata and F. Cozzi, *Tetrahedron*, 2009, **65**, 6354; (*b*) S. Guizzetti, M. Benaglia, F. Cozzi, S. Rossi and G. Celentano, *Chirality*, 2009, **21**, 233; (*c*) S. Guizzetti, M. Benaglia and G. Celentano, *Eur. J. Org. Chem.*, 2009, 3683; (*d*) S. Guizzetti, M. Benaglia and S. Rossi, *Org. Lett.*, 2009, **11**, 2928; (*e*) S. Guizzetti, C. Biaggi, M. Benaglia and G. Celentano, *Synlett*, 2010, 134.

10 See ref. 9d and Z.-Y. Xue, Y. Jiang, W.-C. Yuan and X.-M. Zhang, *Eur. J. Org. Chem.*, 2010, 616 See also; C. Wang, X. Wu, L. Zhou and J. Sun, *Chem.–Eur. J.*, 2008, **14**, 8789.

11 For a very recent review on the importance of β-amino acids see: B. Weiner, W. Szymansky, D. B. Janssen, A. J. Minaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656.

12 A. V. Malkov, S. Stončius, K. Vranková, M. Arndt and P. Kočovský, *Chem.–Eur. J.*, 2008, **14**, 8082.

13 H.-J. Zheng, W.-B. Chen, Z.-J. Wu, J.-G. Deng, W.-Q. Lin, W.-C. Yuan and X.-M. Zhang, *Chem.–Eur. J.*, 2008, **14**, 9864.

14 (*a*) S. Guizzetti, M. Benaglia, European Patent Application November 30 2007; PCT/EP/2008/010079, Nov. 27, 2008. WO2009068284 (A2), 2009-06-04; (*b*) S. Guizzetti, M. Benaglia, European Patent Appl. n.EP07023240.0, September 22, 2008.

15 For the preparation of enamines see details in ESI.

16 The reduction of *N*-phenyl enamine in the same experimental conditions led to the corresponding β-amino ester in better yields (88%) and moderately higher enantioselectivities (80% e.e.).

17 For the use of α-phenyl ethylamine as chiral auxiliary see references cited in ref. 9d; see also (*a*) P. R. LePlae, N. Umezawa, H.-S. Lee and S. H. Gellman, *J. Org. Chem.*, 2001, **66**, 5629; (*b*) N. Ikemoto, D. M. Tellers, S. D. Dreher, J. Liu, A. Huang, N. R. Rivera, E. Njolito, Y. Hsiao, J. C. McWilliams, J. M. Williams, J. D. Armstrong, III, Y. Sun, D. J. Mathre, E. J. J. Grabowski and R. D. Tillyer, *J. Am. Chem. Soc.*, 2004, **126**, 3048; (*c*) T. C. Nugent and A. K. Ghosh, *Eur. J. Org. Chem.*, 2007, 3863and references given.

18 The favourably match or mismatch combinations of chiral amine auxiliary and catalysts have been already clarified in ref. 9d. The reduction of chiral enamine 5 with achiral Lewis base, such as DMF, at 0 °C in our hands afforded the reduction product in 53% diastereoisomeric ratio.

19 For selective debenzylation reactions see: M. Kanai, M. Yasumoto, Y. Kuriyama, K. Inomiya, Y. Katsuhara, K. Higashiyama and A. Ishii, *Org. Lett.*, 2003, **5**, 1007.

20 The quality and the age of Pd/C are critical elements influencing the reaction efficiency; the experimental conditions are very dependent on the activity of the catalyst (5-15 atm, Pd/C, EtOH, 4-12 h, RT). See also ref. 9e.

21 See ESI for HPLC traces and spectroscopic details.