Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 375–380

Enantioselective aza-Henry reaction using cinchona organocatalysts

Luca Bernardi,[a] Francesco Fini,[a] Raquel P. Herrera,[b] Alfredo Ricci[a,*] and Valentina Sgarzani[a]

[a]*Department of Organic Chemistry 'A. Mangini', University of Bologna, Viale Risorgimento No 4, I-40136 Bologna, Italy*
[b]*Universidad de Alicante, Dpto. Quimica Organica, Apdo. 99, 03080-Alicante, Spain*

Received 5 July 2005; revised 9 September 2005; accepted 16 September 2005

Available online 19 October 2005

Abstract—The aza-Henry reaction of imines with nitromethane was promoted by cinchona alkaloids and modified cinchona bases to give optically active β-nitroamines. Various *N*-protected imines were examined as substrates. *N*-Boc, *N*-Cbz, and *N*-Fmoc protected imines gave the best results in terms of chemical yields and enantioselectivities. After a careful screening of a series of chiral bases, very good enantioselectivities up to 94% ee were obtained using a cinchona-based thiourea organocatalyst under the optimized reaction conditions.

1. Introduction

The aza-Henry reaction is a carbon–carbon bond-forming process, which allows a straightforward entry to a variety of nitrogen-containing chiral building blocks. Among them 1,2-diamines, a structural motif present in biologically active natural products, in medicinal chemistry, and as a core unit in chiral ligands for asymmetric catalysis, can be obtained by reduction of the nitro group in the β-nitroamine derivatives,[1] whereas α-amino carbonyl compounds can be generated by means of the Nef reaction.[2] As a result of the importance of this reaction, a considerable effort has been directed over the last years toward the development of the catalytic asymmetric version of the aza-Henry reaction.[3] Shibasaki et al. have described the enantioselective addition of nitroalkanes to *N*-phosphinoyl imines using chiral ytterbium,[4] and aluminum catalysts,[5] while Jørgensen et al. have reported the asymmetric copper-catalyzed addition to α-iminoesters.[6–8] Several drawbacks of the reactions catalyzed or promoted by metal salts may lie in the cost and the toxicity of the metal species. To face these problems, beyond these metal-catalyzed variants, the first reports of enantioselective organocatalytic aza-Henry reaction have recently appeared. Takemoto et al. have reported that the aza-Henry reaction of *N*-phosphinoyl imines with nitroalkanes can be promoted by chiral thiourea bearing an *N*,*N*-dimethylamino group leading with moderate enantioselectivities to β-nitroamine derivatives,[9] while Johnston et al. have developed a chiral bisamidine triflate salt that effects the enantio- and diastereoselective addition of nitroethane to a range of electron deficient *N*-Boc imines.[10] More recently Jacobsen using a new thiourea based bifunctional catalyst was able to promote the highly stereoselective addition of a range of nitroalkanes to aromatic *N*-Boc imines.[11]

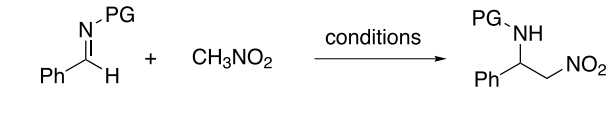
In a recent paper, we described a new metal- and solvent-free procedure for the aza-Henry reaction organocatalyzed by a nitrogen-contaning superbase such as 1,1,3,3-tetramethyl guanidine (TMG).[12] Herein, we present an extensive investigation on the effectiveness of chiral nitrogen-containing bases as organocatalysts in promoting reactivity and asymmetric induction in the aza-Henry reaction of differently *N*-protected imines.

2. Results and discussion

The groups bound at nitrogen of imines are not fully innocent groups since besides protecting the C=N moiety they can greatly affect its stability and electrophilicity. Therefore, despite the considerable advances made in the field of the aza-Henry reaction there remain limitations to its general applicability. To tackle the goal of envisaging the optimized reaction conditions under which differently protected imines can undergo the aza-Henry reaction in the presence of chiral bases and to prepare the ground for the asymmetric version of this reaction, a range of possible benzaldehyde imine candidates **1a–f** were synthesized and screened (Scheme 1).

Keywords: Organocatalysis; Imines; Nitromethane; β-Nitroamines; Aza-Henry reaction; Cinchona alkaloids; Enantioselectivity.
* Corresponding author. Tel.: +39 51 2093635; fax: +39 51 2093654; e-mail: ricci@ms.fci.unibo.it

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.076



1a PG = Cbz **1b** PG = Boc
1c PG = Fmoc **1d** PG = DPP (Diphenylphosphinoyl)
1e PG = Ts **1f** PG = PMP (*p*-Methoxyphenyl)
1g PG = *t*-BuCO

Scheme 1.

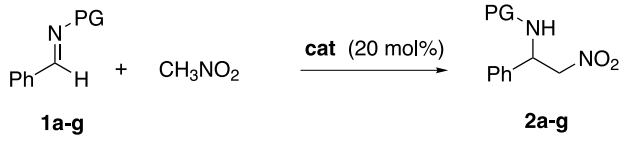
Inspired by previous work,[13] we focused at first on the use of chiral bases directly accessible from the chiral pool such as cinchona alkaloids, as organocatalysts for this reaction.[14]

The β-nitroamines **2a–g** were obtained (Table 1) in fairly good yields with moderate enantioselectivities from Cbz-, Boc-, and Fmoc- *N*-protected benzaldehyde imines **1a–c** in the presence of quinine (**QN**) (entries 1–4) and of quinidine (**QD**) (entries 10 and 11). In the case of the (diphenylphosphinoyl) DPP-, Ts-, and *t*-BuCO- benzaldehyde imines **1d**,**e**,**g** a drop of the ee was noticed (entries 5, 6, and 9) accompanied in the case of the former by a sizeable decrease in the chemical yield. Even more disappointing were the results with (*p*-methoxyphenyl) PMP imine **1f**, which gave even under forcing conditions (entry 7) poor conversion and no ee at all. However, by running the reaction in the presence of 20% TFA a significant improvement was observed in terms both of conversion and ee (entry 8). We speculated that the reaction on an electron rich imine can proceed efficiently only if the imine is activated by protonation with a Brønsted acid such as TFA.[15]

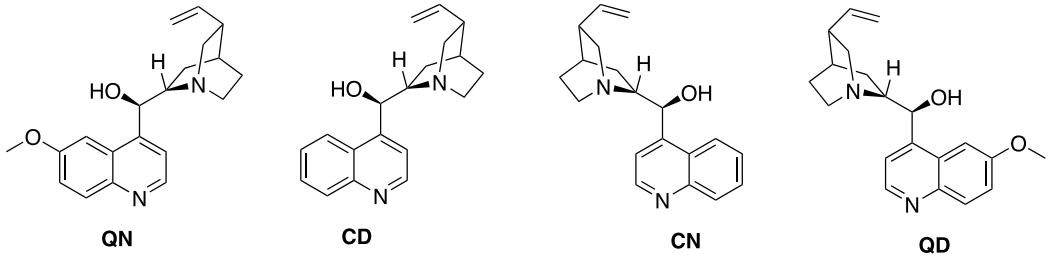
On changing the nature of the organocatalysts, cinchona alkaloids **CD** and **CN** not bearing any oxygen-based substituent at position 6′ in the quinoline ring were found to afford (entries 12 and 13) the desired adduct **2a** in poor yields and with enantioselectivities significantly lower than those bearing a 6′-methoxyquinoline moiety. Next, the influence of modifications on the natural cinchona bases reported in Figure 1 was studied using Cbz-, Boc-, and Fmoc- imines **1a–c**, which had shown the most promising results in the previous screening.

As shown in Table 2, unlike the catalytic efficiency shown by **QN** catalyst (entry 1), derivatives **II** and **V**, in which the OH of the quinine moiety has been protected via acetylation or carbamate formation, and derivative **III** with the alcoholic function replaced by a benzamido moiety, did not give rise to the formation of the desired adducts in significant yields (entries 2, 3, and 9). Neither the presence of a newly formed NH bond in **III** and **V** seemed to convey to these modified cinchona alkaloids any catalytic activity. Modest catalytic efficiency, accompanied by moderate enantioselectivity, was observed (entry 4) on the other hand in the case of the conformationally more rigid catalyst

Table 1. Results from the screening of various imines **1a–g** using unmodified cinchona alkaloids as catalysts[a]



1a-g **2a-g**



QN **CD** **CN** **QD**

Entry	Imine	PG	Adduct	Catalyst	Conversion (%)[b]	ee (%)[c]
1	**1a**	Cbz	**2a**	**QN**	>95	53
2	**1a**	Cbz	**2a**	**QN**	90	61[d]
3	**1b**	Boc	**2b**	**QN**	>95	51
4	**1c**	Fmoc	**2c**	**QN**	>95	48
5	**1d**	DPP	**2d**	**QN**	50	12
6	**1e**	Ts	**2e**	**QN**	>95	30
7	**1f**	PMP	**2f**	**QN**	10[e]	*rac*
8	**1f**	PMP	**2f**	**QN**	>95[e,f]	40
9	**1g**	*t*-BuCO	**2g**	**QN**	>95	27
10	**1c**	Fmoc	**2c**	**QD**	>95	52
11	**1a**	Cbz	**2a**	**QD**	80	55
12	**1a**	Cbz	**2a**	**CN**	15	25
13	**1a**	Cbz	**2a**	**CD**	15	40

[a] Unless noted, reactions were run at 20 °C, for 18 h in toluene (0.1 M).
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.
[d] Reaction performed in mesitylene as the solvent.
[e] Reaction performed in CH_3NO_2 (0.25 M).
[f] Reaction performed in the presence of TFA (20 mol%).

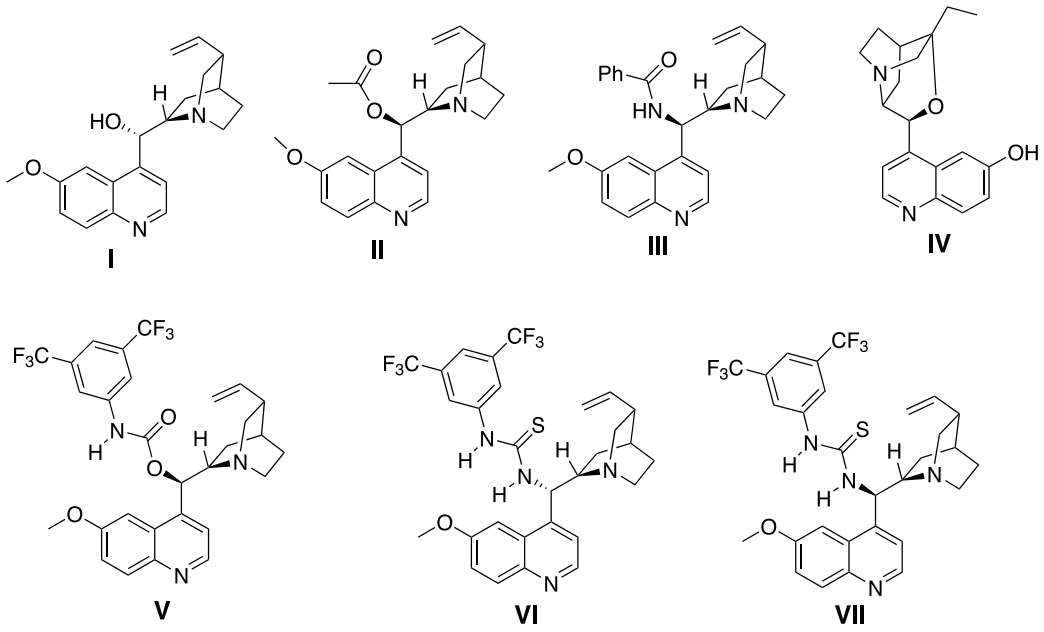


Figure 1. Modified cinchona bases screened for the aza-Henry reaction using imines **1a–c**.

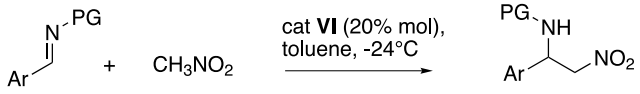
IV bearing a phenolic moiety, which could eventually provide a site for hydrogen bonding.[16] To explore the influence, in terms of catalytic efficiency and enantioselectivity, of the quinine-epiquinine change,[17] epiquinine **I** catalysed addition of nitromethane to the *N*-Boc protected imine **1b** was examined. Even though the conversion in the reaction was lower, the comparable enantioselectivities (compare entries 7 and 8) suggested that the proper conformation of the cinchona derivatives as such may not be crucial in the case for successful catalysis. Within the range of enantioselectivities observed, the best results were obtained with catalysts bearing methoxy and hydroxy functionalities. These findings prompted us to apply to the aza-Henry reaction under study the recently reported bifunctional cinchona-based catalysts **VI** and **VII** bearing a stronger Lewis acid thiourea moiety.[18] By running the reaction with quinine-derived catalyst **VI** under the standard conditions adducts **2a** and **2b** were obtained (entries 5 and 11) in satisfactory isolated yields and with ee's up to 76%, whereas also in line with the findings regarding the asymmetric addition of nitromethane to *trans*-chalcone,[18] organocatalyst **VII** with the natural configuration, derived from epiquinine turned out to be much less efficient (entry 10). Next, the influence of two experimental parameters (temperature and concentration) was evaluated using the most efficient catalyst **VI**. Very good levels of enantioselectivity were observed on lowering the temperature (entries 6, 11–13) and at −24 °C with an increase of the imine concentration to 0.2 M, adducts **2b** and **2c** were obtained (entries 15 and 16) with up to 90% ee. Adduct **2b** in Table 2 was determined to have the (*S*) configuration by comparison with the literature data.[10,11]

Table 2. Effect of modified cinchona alkaloid catalysts **I–VII** and optimisation of reaction conditions[a]

Entry	Imine	PG	Adduct	Catalyst	*T* (°C)	*t* (h)	Conversion (%)[b]	ee (%)[c]
1	**1a**	Cbz	**2a**	**QN**	20	18	>95	53
2	**1a**	Cbz	**2a**	**II**	20	120	<10	—
3	**1a**	Cbz	**2a**	**V**	20	120	<10	—
4	**1a**	Cbz	**2a**	**IV**	20	120	20	37
5	**1a**	Cbz	**2a**	**VI**	20	22	46[d]	61
6	**1a**	Cbz	**2a**	**VI**	−24	22	64[d]	84
7	**1b**	Boc	**2b**	**QN**	20	18	>95	51
8	**1b**	Boc	**2b**	**I**	20	18	45	56
9	**1b**	Boc	**2b**	**III**	20	120	<10	—
10	**1b**	Boc	**2b**	**VII**	20	18	30	19
11	**1b**	Boc	**2b**	**VI**	20	18	60[d]	76
12	**1b**	Boc	**2b**	**VI**	0	20	58[d]	81
13	**1b**	Boc	**2b**	**VI**	−24	20	52[d]	86
14	**1b**	Boc	**2b**	**VI**	−24	23	63[d,e]	85
15	**1b**	Boc	**2b**	**VI**	−24	18	72[d,f]	88
16	**1c**	Fmoc	**2c**	**VI**	−24	43	60[d,f]	90

[a] Unless noted, reactions were run 0.1 M in toluene.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.
[d] Yield of product isolated after silica gel chromatography.
[e] Reaction (0.05 M).
[f] Reaction (0.2 M).

Table 3. Scope of the aza-Henry reaction using imines **1h–o** and catalyst **VI**



1h-o **2h-o**

Entry	Ar	PG	Imine	Adduct	*t* (h)	Yield (%)[a]	ee (%)[b]
1	1-Napht	Boc	**1h**	**2h**	20	87	88
2	2-Napht	Boc	**1i**	**2i**	23	95	85
3	2-Napht	Boc	**1i**	**2i**	38	82	94[c]
4	4-ClC_6H_4	Boc	**1j**	**2j**	68	77	94
5	4-ClC_6H_4	Cbz	**1k**	**2k**	45	58	90
6	2-BrC_6H_4	Boc	**1l**	**2l**	24	66	80
7	2-BrC_6H_4	Boc	**1l**	**2l**	72	82	88[c]
8	4-$MeOC_6H_4$	Boc	**1m**	**2m**	45	65	82
9	2-Thienyl	Boc	**1n**	**2n**	40	50	82
10	2-Furyl	Boc	**1o**	**2o**	40	70	44
11	2-Furyl	Boc	**1o**	**2o**	48	58	63[c]

[a] Yield of product isolated after silica gel chromatography.
[b] Determined by chiral stationary phase HPLC.
[c] Reaction performed at −40 °C.

To establish the generality of this reaction in substrate scope we finally examined the aza-Henry reaction with representative *N*-Boc imines under catalysis by **VI** and the results are reported in Table 3. The reaction appears tolerant with respect to the nature of the imine and the benefits of catalyst **VI** extend over a wide range of substrates. The desired adducts were isolated in satisfactory to good yields and synthetically useful levels of enantioselectivity, with 1- and 2-naphthaldehyde-derived imines **1h–i** (entries 1–3) and with benzaldimine derivatives **1j–m** bearing both electron donating and electron withdrawing substituents (entries 4–8). The good results obtained using the Cbz-protected imine **1k** further confirm the tolerance of this catalytic reaction to different *N*-acyl protecting groups (entry 5). Among the aromatic heterocyclic aldimines, the 2-thiophenecarboxyaldehyde derived imine **1n** (entry 9) gave better results with respect to the oxygenated analogue **1o** (entry 10 and 11).

Any insight about the exact nature of the stereochemical-determining catalyst-substrate complex would be premature at this time and different mechanistic scenarios can be considered for this catalytic transformation. However, it is clear from these experiments that cinchona-bases herein studied and particularly thiourea derivatives, which are known to bind to and modulate the reactivity of nitronate anions,[9,18] are likely to act as bifunctional organocatalysts, but the role in activating the nitroalkane or in the dual activation of both reaction partners still remains obscure.

3. Conclusion

In summary, we have developed a highly enantioselective organocatalyzed aza-Henry reaction using nitromethane and a range of aromatic and heteroaromatic differently protected imines. This new system will nicely complement the very few examples of organocatalyzed aza-Henry reactions reported to date. Further investigations into the mechanism and use of new organocatalysts for this reaction are underway and will be reported in due course.

4. Experimental

4.1. General methods

All reactions were carried out in test tubes. ^1H and ^{13}C NMR spectra were measured on a Varian AS 400 spectrometer running at 400 and 100 MHz, respectively, in $CDCl_3$ as the solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^1H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionisation techniques. Flash column chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 22 °C. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H). Melting points are uncorrected. Imines **1a**,**c**,**k**,[19] **1b**,**h–j**,**l–o**,[20] as well as catalyst **VI**[18] were prepared following literature procedures.

4.2. Optimized general procedure for the catalytic enantioselective aza-Henry reaction

In a test tube, to a cooled (−24 °C) solution of the imine **1** (0.1 mmol) and catalyst **VI** (11.9 mg, 0.02 mmol) in toluene (500 μL), nitromethane (27 μL, 0.5 mmol) was added in one portion. The test tube was placed in a freezer at −24 °C for the time reported in Tables 2 and 3, then the products **2** were obtained by FC on silica gel (CH_2Cl_2).

4.2.1. 2-Nitro-1-phenylethyl carbamic acid benzyl ester (2a). Following the general procedure, compound **2a** was obtained as a yellow solid in 64% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=80:20, flow rate 0.75 mL/min, τ_{major}=17.1 min; τ_{minor}=24.9 min). R_f 0.41 (*n*-hexane/EtOAc, 7:3); mp 67–70 °C; ^1H NMR δ 4.65 (dd, J=4.6, 12.6 Hz, 1H), 4.72–4.88 (br s, 1H), 5.04 (s, 2H), 5.33–5.42 (br s, 1H), 5.46–5.57 (br s, 1H), 7.17–7.35 (m, 10H); ^{13}C NMR δ 53.2, 67.4, 78.6, 126.3, 128.2, 128.4,

128.6, 128.9, 129.2, 135.8, 136.4, 155.4; ESIMS *m/z* 323 [M+Na$^+$]; $[\alpha]_D^{22}$ +5 (*c* 0.348, $CHCl_3$), 84% ee.

4.2.2. (*S*)-2-Nitro-1-phenylethyl carbamic acid *t*-butyl ester (2b). Following the general procedure, compound **2b** was obtained as a white solid in 72% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=95:5, flow rate 0.75 mL/min, τ_{major}=36.0 min; τ_{minor}=38.2 min). $[\alpha]_D^{22}$ +14 (*c* 0.578, $CHCl_3$), 88% ee. The ^{1}H and ^{13}C NMR spectra and mp are consistent with values previously reported in the literature.[10]

4.2.3. (9-*H*-Fluoren-9-yl)methyl 2-nitro-1-phenylethyl-carbamate (2c). Following the general procedure, compound **2c** was obtained as a white solid in 60% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=80:20, flow rate 0.75 mL/min, τ_{major}=23.7 min; τ_{minor}=42.3 min). R_f 0.51 (*n*-hexane/EtOAc, 7:3); mp 148–150 °C; ^{1}H NMR δ 4.20 (t, *J*=6.6 Hz, 1H), 4.38–4.62 (br s, 2H), 4.62–4.94 (br s, 2H), 5.36–5.60 (br s, 2H), 7.22–7.64 (m, 11H), 7.66 (d, *J*=7.6 Hz, 2H); ^{13}C NMR δ 47.1, 53.1, 67.1, 78.4, 120.0, 124.9, 126.3, 127.1, 127.8, 128.8, 129.3, 136.4, 141.3, 143.6, 155.4; ESIMS *m/z* 411 [M+Na$^+$]; $[\alpha]_D^{22}$ +11 (*c* 0.675, $CHCl_3$), 90% ee.

4.2.4. 1-(1-Naphthyl)-2-nitroethyl carbamic acid *t*-butyl ester (2h). Following the general procedure, compound **2h** was obtained as a white solid in 87% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=17.0 min; τ_{minor}=25.7 min). R_f 0.64 (*n*-hexane/EtOAc, 7:3); mp 174–177 °C; ^{1}H NMR δ 1.43 (s, 9H), 4.80–4.98 (br s, 2H), 5.24–5,38 (br s, 1H), 6.22–6.34 (br s, 1H), 7.44–7.48 (m, 2H), 7.52–7.58 (m, 1H), 7.60–7.64 (m, 1H), 7.84–7.86 (m, 1H), 7.88–7.92 (m, 1H), 8.11–8.13 (m, 1H); ^{13}C NMR δ 28.2, 49.2, 78.2, 80.8, 122.2, 123,2, 125.2, 126.3, 127.3, 129.2, 129.5, 130.3, 132.6, 134.1, 154.7; ESIMS *m/z* 339 [M+Na$^+$]; $[\alpha]_D^{22}$ +7 (*c* 0.498, $CHCl_3$), 88% ee.

4.2.5. 1-(2-Naphthyl)-2-nitroethyl carbamic acid *t*-butyl ester (2i). Following the general procedure, performing the reaction at −40 °C, compound **2i** was obtained as a white solid in 82% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=17.8 min; τ_{minor}=21.5 min). R_f 0.79 (*n*-hexane/EtOAc, 7:3); mp 144–146 °C; ^{1}H NMR δ 1.45 (s, 9H), 4.80 (dd, *J*=5.5, 12.6 Hz, 1H), 4.88–5.00 (br s, 1H), 5.34–5.46 (br s, 1H), 5.50–5.60 (br s, 1H), 7.40 (dd, *J*=1.8, 8.5 Hz, 1H), 7.48–7.54 (m, 2H), 7.76 (m, 1H), 7.82–7.88 (m, 3H); ^{13}C NMR δ 28.3, 53.0, 78.8, 80.8, 123.7, 125.6, 126.7, 126.7, 127.7, 128.0, 129.2, 133.2, 133.2, 134.2, 154.8; ESIMS *m/z* 339 [M+ Na$^+$]; $[\alpha]_D^{22}$ +38 (*c* 0.505, $CHCl_3$), 94% ee.

4.2.6. 1-(*p*-Chlorophenyl)-2-nitroethyl carbamic acid *t*-butyl ester (2j). Following the general procedure, compound **2j** was obtained as a white solid in 77% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=12.8 min; τ_{minor}=16.1 min). R_f 0.68 (*n*-hexane/EtOAc, 7:3); mp 128–131 °C; ^{1}H NMR δ 1.44 (s, 9H), 4.68 (dd, *J*=5.0, 12.6 Hz, 1H), 4.76–4.9 (br s, 1H), 5.28–5.40 (br s, 2H), 7.23–7.27 (m, 2H), 7.34–7.37 (m, 2H); ^{13}C NMR δ 28.2, 52.2, 78.6, 80.9, 127.7, 129.4, 134.6, 135.4, 154.6; ESIMS *m/z* 323 [M+Na$^+$]; $[\alpha]_D^{22}$ +20 (*c* 0.790, $CHCl_3$), 94% ee.

4.2.7. 1-(*p*-Chlorophenyl)-2-nitroethyl carbamic acid benzyl ester (2k). Following the general procedure, compound **2k** was obtained as a yellow oil in 58% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 0.75 mL/min, τ_{major}=36.7 min; τ_{minor}=59.0 min). R_f 0.45 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR δ 4.68 (dd, *J*=5.1, 12.7 Hz, 1H), 4.76–4.89 (br s, 1H), 5.10 (s, 2H), 5.36–5.45 (br s, 1H), 5.63–5.71 (br s, 1H), 7.20–7.41 (m, 9H); ^{13}C NMR δ 52.6, 67.5, 78.3, 127.7, 128.4, 128.6, 128.9, 129.4, 129.9, 134.8, 135.7, 155.3; ESIMS *m/z* 357 [M+Na$^+$]; $[\alpha]_D^{22}$ +8 (*c* 0.160, $CHCl_3$), 90% ee.

4.2.8. 1-(*o*-Bromophenyl)-2-nitroethyl carbamic acid *t*-butyl ester (2l). Following the general procedure, performing the reaction at −40 °C, compound **2l** was obtained as a white solid in 82% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1 mL/min, τ_{major}=18.4 min; τ_{minor}=12.9 min). R_f 0.60 (*n*-hexane/EtOAc, 7:3); mp 130–133 °C; ^{1}H NMR δ 1.43 (s, 9H), 4.72–4.92 (br s, 2H), 5.64–5.76 (br s, 2H), 7.20 (dt, J_d=8.0 Hz, J_t=4.5 1H), 7.34 (d, *J*=4.2 Hz, 2H), 7.59 (dt, J_d=7.9 Hz, J_t=0.9 Hz, 1H); ^{13}C NMR δ 28.2, 52.4, 77.5, 80.8, 122.7, 127.9, 128.1, 130.1, 133.6, 135.9, 154.5; ESIMS *m/z* 367 [M+Na$^+$]; $[\alpha]_D^{22}$ −8 (*c* 0.402, $CHCl_3$), 88% ee.

4.2.9. 1-(*p*-Methoxyphenyl)-2-nitroethyl carbamic acid *t*-butyl ester (2m). Following the general procedure, compound **2m** was obtained as a white solid in 65% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=98:2, flow rate 1 mL/min, τ_{major}=91.6 min; τ_{minor}=97.5 min). R_f 0.53 (*n*-hexane/EtOAc, 7:3); mp 141–144 °C; ^{1}H NMR δ 1.44 (s, 9H), 3.80 (s, 3H), 4.66 (dd, *J*=5.9, 12.4 Hz, 1H), 4.75–4.9 (br s, 1H), 5.14–5.24 (br s, 1H), 5.25–5.35 (br s, 1H), 6.89 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ 28.2, 52.4, 55.3, 78.9, 80.6, 114.5, 127.6, 128.8, 154.7, 159.8; ESIMS *m/z* 319 [M+Na$^+$]; $[\alpha]_D^{22}$ +28 (*c* 0.693, $CHCl_3$), 82% ee.

4.2.10. 2-Nitro-1-(thiophen-2-yl)ethyl carbamic acid *t*-butyl ester (2n). Following the general procedure, compound **2n** was obtained as a yellow oil in 50% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=98:2, flow rate 1 mL/min, τ_{major}=54.0 min; τ_{minor}=57.4 min). R_f 0.52 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR δ 1.46 (s, 9H), 4.75 (dd, *J*=5.6, 12.9 Hz, 1H), 4.84–4.98 (br s, 1H), 5.22–5.36 (br s, 1H), 5.56–5.70 (br s, 1H), 6.97–7.02 (m, 2H), 7.27–7.29 (m, 1H); ^{13}C NMR δ 28.2, 48.9, 77.3, 78.6, 81.0, 125.7, 127.3, 140.0, 154.4; ESIMS *m/z* 295 [M+Na$^+$]; $[\alpha]_D^{22}$ +12 (*c* 0.445, $CHCl_3$), 82% ee.

4.2.11. 1-(Furan-2-yl)-2-nitro-ethyl carbamic acid *t*-butyl ester (2o). Following the general procedure,

performing the reaction at −40 °C, compound **2o** was obtained as a yellow oil in 58% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH=97:3, flow rate 0.75 mL/min, τ_{major}=33.8 min; τ_{minor}=31.2 min). R_f 0.67 (*n*-hexane/EtOAc, 7:3); ^{1}H NMR δ 1.46 (s, 9H), 4.72 (dd, J=6.0, 12.9 Hz, 1H), 4.84 (dd, J=6.0, 12.9 Hz, 1H), 5.08–5.26 (br s, 1H), 5.38–5.50 (br s, 1H), 6.28–6.36 (m, 2H), 7.34–7.40 (m, 1H); ^{13}C NMR δ 28.2, 47.2, 80.9, 88.1, 107.8, 110.7, 142.9, 149.4, 154.6; ESIMS *m/z* 279 [M+Na$^+$]; $[\alpha]_D^{22}$ +11 (*c* 0.305, $CHCl_3$), 63% ee.

Acknowledgements

We gratefully acknowledge financial support by the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni, 2003', by the RTN project 'Design, Analysis and Computation for Catalytic Organic Reactions', contract HPRN-CT-2001-00172, and by the ex-60% MURST-funds 2004. R.P.H. thanks the European Union for a post-doctoral fellowship.

References and notes

1. (a) Enders, D.; Wiedemann, J. *Synthesis* **1996**, 1443–1450. (b) Lucet, D.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 2682–2683.
2. Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.
3. Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151–153.
4. Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504–3506.
5. Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980–982.
6. Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844.
7. Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992–2995.
8. Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, 1362–1364.
9. Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627.
10. Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419.
11. Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.
12. Bernardi, L.; Bonini, B. F.; Capitò, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168–8171.
13. (a) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87–129. (b) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907 and references therein.
14. (a) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961–998. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; Mc Daid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621–631.
15. Adams, H.; Anderson, J. C.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932–9934.
16. Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.
17. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417–430.
18. Vakulya, B.; Varga, S.; Csampal, A.; Soòs, T. *Org. Lett.* **2005**, *7*, 1967–1969.
19. Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691–1709.
20. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.