Tetrahedron 64 (2008) 9992–9998

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of three novel chiral diamines derived from (*S*)-proline and their evaluation as precursors of diazaborolidines for the catalytic borane-mediated enantioselective reduction of prochiral ketones

J. Luis Olivares-Romero, Eusebio Juaristi *

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, Mexico

ARTICLE INFO

Article history:
Received 16 July 2008
Accepted 18 July 2008
Available online 24 July 2008

Keywords:
Diazaborolidines
Chiral diamines
Microwave irradiation
Organocatalysis
Asymmetric reduction

ABSTRACT

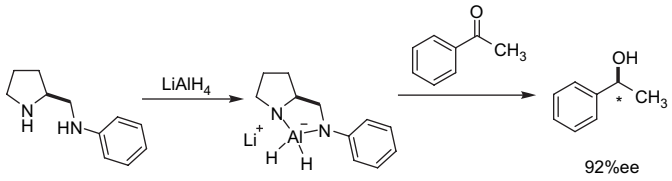
A series of chiral diazaborolidine catalysts are readily prepared in situ at 75 °C in toluene solvent and under microwave irradiation (100 W, 15 min, air cooling) using chiral diamines derived from inexpensive and commercially available (*S*)-proline and borane-dimethyl sulfide. Special mention deserves the synthesis of potentially versatile diamine (*S*)-**8** [(*S*)-(pyrrolidin-2-yl)diphenylmethanamine], with the key step being the conversion of tertiary alcohol (*S*)-(1-benzylpyrrolidin-2-yl)diphenyl methanol, (*S*)-**12**, to azide (*S*)-**13**. The chiral diazaborolidine/BH_3 reagent system was successfully employed in the enantioselective reduction of prochiral ketones to give the corresponding secondary alcohols in excellent yield and with up to 96% enantiomeric purities.

1. Introduction

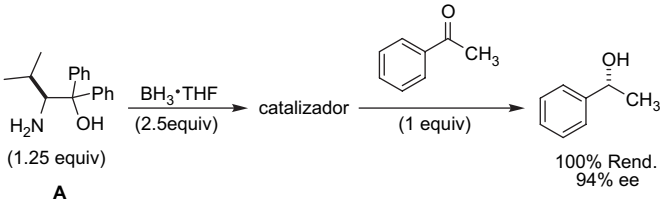
The synthesis of enantiomerically pure compounds has become an important area of research for pharmaceutical industries and research academic institutions, as it is frequently observed that individual enantiomers of a chiral drug molecule display contrasting biological activities.[1] In this regard, asymmetric reduction of prochiral ketones is an extremely important methodology for the synthesis of chiral secondary alcohols, and in the last years there has been a deluge of papers describing research on the enantioselectivity reduction of ketones. In particular, the application of various borane-based chiral reducing agents in this reaction is well documented.[2–5]

In their pioneering studies, Mukaiyama et al.[6] described the asymmetric reduction of prochiral ketones with various chiral hydride reagents prepared from lithium aluminum hydride and (*S*)-2-(*N*-substituted aminomethyl)pyrrolidines. The optically active alcohols obtained from this procedure presented 13–92% enantiomeric purity in the major (*S*) isomer (Scheme 1).

A most interesting method for the enantioselective reduction of ketones was subsequently reported by Itsuno and his group,[7a] which employs mixtures of borane (2–3 equiv) in tetrahydrofuran (THF) and the chiral β-amino alcohol (*S*)-2-amino-3-methyl-1,-1-diphenylbutan-1-ol (**A**, 1.25 equiv) derived from (*S*)-valine. For example, (*R*)-1-phenylethanol (ca. 100% yield and 94% ee) was obtained from acetophenone (Scheme 2). For comparison, other chiral alkoxyaminoborane reagents such as (*S*)-2-amino-3-methylbutanol [derived from (*S*)-valine] induced lower enantioselectivities (up to 73% ee) in the same reaction,[7b] which shows the important role played by the α,α-*gem*-diphenyl segment on the enantioinducing ability of the chiral β-amino alcohol reducing agent.



Scheme 1.

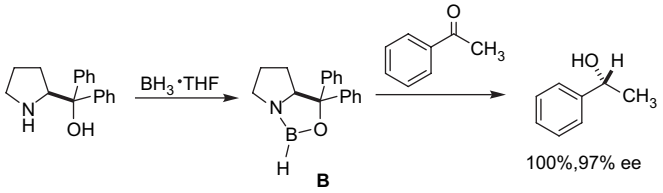


Scheme 2.

* Corresponding author. Tel.: +52 55 5747 3722; fax: +52 55 5747 3389.
E-mail address: juaristi@relaq.mx (E. Juaristi).

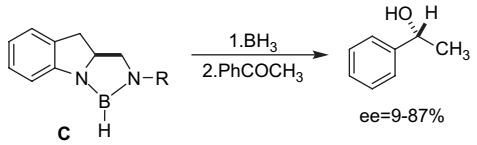
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.07.080

Subsequent studies of this intriguing reaction by Corey et al.[8] provided relevant mechanistic insight that led to an understanding of the reagent structure, of the mode of reduction, and to the development of a powerful catalytic version of the original stoichiometric Itsuno reduction. Indeed, mixtures of oxazaborolidine **B** (0.1 equiv) and $BH_3 \cdot THF$ (1 equiv) effected the rapid enantioselective reduction of acetophenone to afford (*R*)-1-phenylethanol in 97% ee, showing to be a superior enantioselective reduction catalyst (Scheme 3).[9]



Scheme 3.

In this context, Asami et al.[10] recently introduced a novel class of catalysts containing the pyrrolidine structural framework for the enantioselective borane-mediated asymmetric reduction of prochiral ketones (Scheme 4).



Scheme 4.

Most relevant are also the recent reports from Basavaiah et al.,[11] who successfully used (*S*)-2-anilinomethylpyrrolidine *in refluxing toluene* as a chiral catalytic source in the borane-mediated asymmetric reduction of prochiral ketones to provide the corresponding secondary alcohols with enantiomeric excesses up to 91%.

Attracted by pioneering reports on the application of (*S*)-2-(*N*-substituted aminomethyl) pyrrolidines (*S*)-**1**–**5** in asymmetric synthesis,[6,12,13] we were intrigued by the potential of previously unreported, highly hindered diamines (*S*)-1,1-diphenyl-*N*-(pyrrolidin-2-ylmethyl)methanamine (*S*)-**6**, (*S*)-(1-benzylpyrrolidin-2-yl)diphenyl methyl amine (*S*)-**7**, and (*S*)-(pyrrolidin-2-yl)diphenyl methyl amine (*S*)-**8** (Fig. 1) in borane-mediated enantioselective reduction of prochiral ketones. Herein, we report the successful preparation of chiral diamines (*S*)-**6**, (*S*)-**7**, and (*S*)-**8**, as well as the enantioselective reduction of prochiral ketones catalyzed by their corresponding diazaborolidines and borane-dimethyl sulfide.

2. Results and discussion

2.1. Synthesis of chiral diamines

Chiral diamines (*S*)-**1**–**5** as well as (*S*)-**6** were synthesized according to the methodology described by Mukaiyama et al.[6,12,13] Novel diamines (*S*)-**7** and (*S*)-**8** were prepared by the treatment of (*S*)-proline, (*S*)-**9**, with thionyl chloride in methanol to give the methyl ester hydrochloride (*S*)-**10**[14] in essentially quantitative yield. Reaction of crude product with triethyl amine and benzyl bromide in dichloromethane provided (*S*)-methyl 1-benzylpyrrolidine-2-carboxylate, (*S*)-**11**,[15] as colorless oil in excellent yield. When *N*-protected methyl ester (*S*)-**11** was treated with an excess of phenylmagnesium bromide, the amino alcohol (*S*)-**12** was obtained as a white solid in 97% yield. The optical rotation and spectroscopic data for (*S*)-amino alcohol (*S*)-**12** were consistent with Feng's observations.[16] Azide (*S*)-**13** was prepared in high yield from the corresponding (*S*)-amino alcohol (*S*)-**12** on treatment with sodium azide in 57% chloroform–sulfuric acid. Lithium aluminum hydride reduction of compound (*S*)-**13** gave the desired diamine (*S*)-**7** in 95% yield. Pure (*S*)-**7** was obtained by crystallization from hexane–ethyl acetate (1:1) and afforded suitable crystals for X-ray diffraction structural analysis (Fig. 2).[17] Finally, the (*S*)-diphenyl-(pyrrolidin-2-yl)-methyl amine (*S*)-**8** was obtained in 99% yield by hydrogenolysis of diamine (*S*)-**7** in the presence of 10% Pd–C catalyst under hydrogen atmosphere at 60 psi for 12 h at room temperature (Scheme 5).

2.2. Asymmetric reduction of prochiral ketones with diazaborolidines and borane

Initial attempts to prepare the diazaborolidine derived from (*S*)-**8** and borane-dimethyl sulfide under conventional heating failed as evidenced by the lack of change in the ^{11}B NMR shift in the starting borane-dimethyl sulfide reagent, −20.1 ppm (relative to boron trifluoride etherate). Specifically, we carried out the reaction between (*S*)-**8** (1.66 mM, 210 mg) and $BH_3 \cdot SMe_2$ (3.32 mM, 1.66 mL, 2 M in toluene) in refluxing toluene (4 mL) for 20 min, and recorded the ^{11}B NMR spectrum of the resulting mixture—we did not observe any peak in the anticipated[18] region, δ 20–40 ppm (Scheme 6).

The desired diazaborolidine derivative was obtained under microwave irradiation,[19] as evidenced by the difference in ^{11}B NMR chemicals shifts in the starting borane-dimethyl sulfide reagent, −20.1 ppm, and the corresponding signal in the diazaborolidine, +28.3 ppm. Furthermore, the infrared spectrum in toluene shows a characteristic B–H stretching band at 2404 cm^{-1} as well as N–H stretching at 3584 cm^{-1}, in line with Corey's observations in oxazaborolidine analogs.[8]

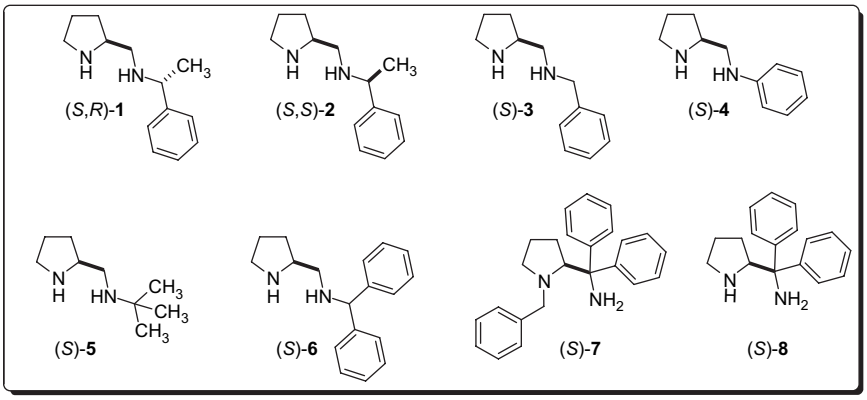


Figure 1. Chiral diamines (*S*)-**1**–**8** derived from (*S*)-proline.

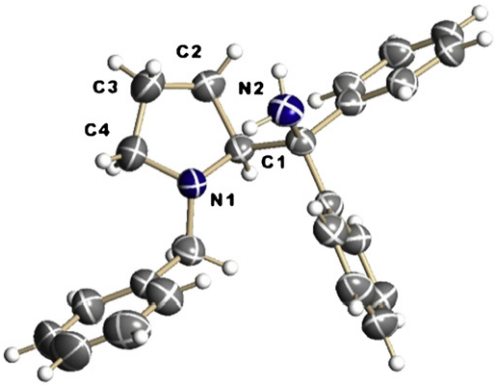
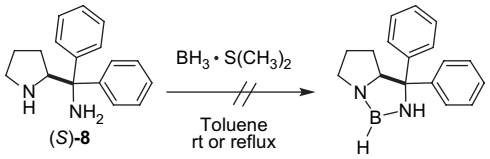


Figure 2. X-ray crystallographic structure and solid-state conformation of chiral diamine (*S*)-**7**.[17]

Several recent reports in the literature suggest that application of simultaneous external cooling during microwave irradiation allows for higher level of microwave power to be administered to the reaction mixture, enhancing the activation effects while continuously removing heat to prevent overheating.[20,21] Based on this precedent, we decided to cool the reaction vessel from the outside with compressed air (10 psi) while irradiating the reaction mixture with microwaves. The results are compared with those obtained without air cooling (Table 1).

Most significant, microwave heating with simultaneous external cooling did lead to higher enantioselectivities, up to 96% ee (compare odd-numbered entries in Table 1, corresponding to experiments in the absence of external cooling with even-numbered entries, for experiments carried out with external air cooling). This result confirms the beneficial effect of simultaneous external cooling during microwave irradiation. This methodology appears to be ideal to prepare the catalyst, since this prevents overheating and, therefore, the partial destruction of the diazaborolidine catalyst. In summary, the catalyst can be easily prepared in 10 min under heating by microwave irradiation with simultaneous external cooling of the reaction mixture, and these reaction conditions lead to an enhancement of the enantioselectivity of the reduction process.

Table 1 collects the results of the asymmetric reduction of acetophenone (**14**) with diazaborolidines derived from diamines (*S*)-**1**–**8** in the presence of one additional equivalent of borane-dimethyl sulfide. It is appreciated that best results were obtained with catalysts derived from chiral diamines (*S*,*R*)-**1** and novel chiral diamine (*S*)-**8**; indeed, the reduction afforded (*R*)-1-phenylethanol,

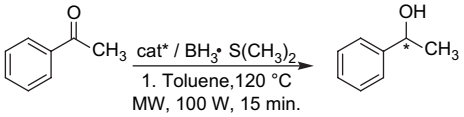


Scheme 6. Unsuccessful preparation of diazaborolidines under conventional heating conditions.

(*R*)-**15**, in 99% chemical yield and 96% ee and 84% ee, respectively (see entries 2 and 16 in Table 1).

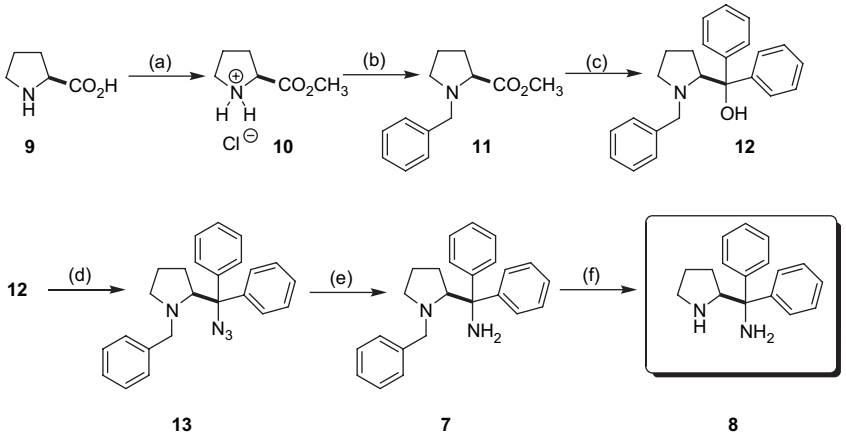
Interestingly, comparison of the enantioselectivities achieved with diastereomeric diamines (*S*,*R*)-**1** and (*S*,*S*)-**2** suggests the manifestation of a double stereoinduction effect.[22] Indeed, the (*S*,*R*) isomer affording 96% ee of the carbinol product appears to be the matched combination of stereocenters, whereas the (*S*,*S*)

Table 1
Asymmetric reduction of acetophenone **14** using chiral diamines **1**–**8** in the preparation of the diazaborolidine catalyst

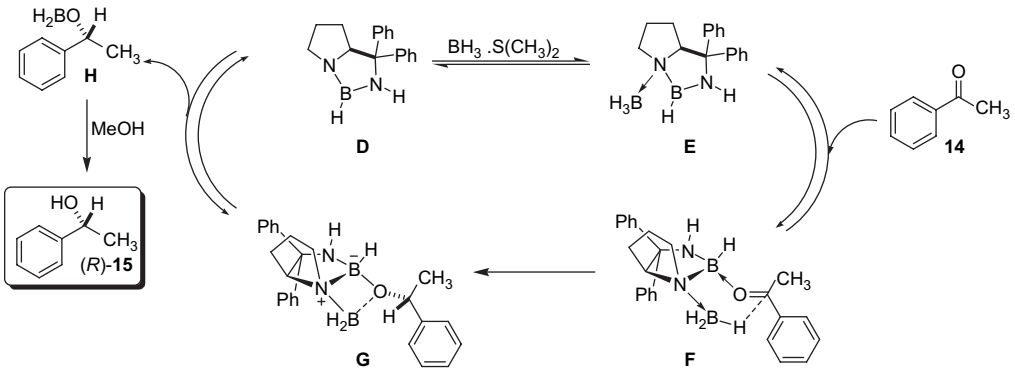


Entry	Cat*[b]	Yield[c] (%)	ee[d]	Config. **15**[e]
1	(*S*,*R*)-**1**	99	70	(*R*)
2[a]	(*S*,*R*)-**1**	99	96	(*R*)
3	(*S*,*S*)-**2**	99	52	(*R*)
4[a]	(*S*,*S*)-**2**	98	71	(*R*)
5	(*S*)-**3**	99	40	(*R*)
6[a]	(*S*)-**3**	99	46	(*R*)
7	(*S*)-**4**	99	66	(*R*)
8[a]	(*S*)-**4**	99	72	(*R*)
9	(*S*)-**5**	99	40	(*R*)
10[a]	(*S*)-**5**	99	55	(*R*)
11	(*S*)-**6**	99	48	(*R*)
12[a]	(*S*)-**6**	99	63	(*R*)
13	(*S*)-**7**	99	22	(*R*)
14[a]	(*S*)-**7**	99	30	(*R*)
15	(*S*)-**8**	99	64	(*R*)
16[a]	(*S*)-**8**	99	84	(*R*)

[a] These essays were carried out in the presence of air cooling (10 psi).
[b] All reactions were carried out in the presence of 1 equiv of the chiral diamine and 2 equiv of $BH_3 \cdot S(CH_3)_2$.
[c] Isolated yields of alcohols after purification by column chromatography (silica gel, 10% ethyl acetate in hexane).
[d] Determined by HPLC analysis using the chiral column OD.
[e] Absolute configuration was assigned by comparison of the sign of specific rotation with that reported.



Scheme 5. Reagents and conditions: (a) $SOCl_2$, MeOH, 0 °C, 1 h, 100%; (b) BnBr, Et_3N, CH_2Cl_2, 25 °C, 8 h, 95%; (c) Bromobenzene, Mg, THF, 25 °C, 12 h, 97%; (d) 57% H_2SO_4–$CHCl_3$, NaN_3, 0 °C, 12 h, 96%; (e) $LiAlH_4$, THF, reflux, 8 h, 95%; (f) H_2/Pd–C, MeOH, 60 psi, 25 °C, 99%.



Scheme 7. Plausible mechanism in the enantioselective reduction of acetophenone with diazaborolidine **D**, from diamine (*S*)-**8** and borane-dimethyl sulfide.

diastereomer giving only 71% ee in the major enantiomeric product, (*R*)-**15**, would correspond to the mismatched pair. This observation confirms that the *N*-α-phenethyl substituent plays a significant role in the stereoinduction of the reduction process.

Chiral diamine ligands **2**–**7** afforded carbinol **15** in moderate to good enantioselectivities (22–72% ee of the (*R*) enantiomer) in the reduction process. From this observation it seems that the steric nature of the alkyl substituent on the exocyclic nitrogen does not play a significant role in the observed stereoselectivity.

Scheme 7 presents a plausible mechanism for the catalytic process, based on the proposal advanced by Corey et al. for the corresponding oxazaborolidine catalysts.[3,5,8] According to this proposal, the first step consists in the coordination of a second molecule of borane to the pyrrolidine endocyclic nitrogen in catalyst **D** to give reactive species **E**. The basic oxygen in ketone **14** associates then to the Lewis acidic boron in **E** to give complex **F**, where the bulkier phenyl substituent orients away from the heterocycle, so that the *Si* face of the carbonyl substrate is exposed to the N–BH_3 reducing group providing carbinol (*R*)-**15** via intermediate **G** and boronate **H** (Scheme 7).

As it can be anticipated from the mechanism presented in Scheme 7, the lack of ability of diamine (*S*)-**7** to participate efficiently in the catalytic cycle, as a consequence of the presence of the benzyl substituent on the pyrrolidinic nitrogen apparently forces (*S*)-**7** to function via a less selective process, and this is why this ligand provides dramatically lower selectivity (see entries 13 and 14 in Table 1).

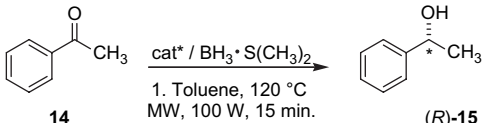
The results summarized in Table 1 offer an opportunity to answer two very interesting questions. First, what happens when borane is used in place of $LiAlH_4$ with the diamine ligands Mukaiyama et al. employed for enantioselective reduction of ketones.[6] In particular, asymmetric reduction of acetophenone with $LiAlH_4$-chiral diamines (*S*,*R*)-**1**, (*S*,*S*)-**2**, and (*S*)-**4** afforded yields in the 69–84% range, and enantiomeric excesses of 52%, 54%, and 84%, respectively (see Table 3 in Ref. 6). By comparison, the diazaborolidines reported in the present study afford essentially quantitative yields and 96% ee with diamine (*S*,*R*)-**1**, 71% ee with diamine (*S*,*S*)-**2**, and 72% ee with diamine (*S*)-**4**. Clearly, the incorporation of borane instead of aluminum hydride in the chiral diamine complexes provides a more efficient reducing agent from the chemical yield point of view; i.e., quantitative yields in the borane catalysts. Furthermore, higher enantioselectivity is generally observed with the diazaborolidines, in particular with the catalyst derived from diamine (*S*,*R*)-**1**, which affords 96% ee in the (*R*)-**15** product, to be compared with only 52% ee with the aluminum hydride complex. Thus, the α-phenethyl chiral auxiliary does play a significant enantioinducing role in the boron derivatives but not in the aluminum analogs. Accordingly, double stereoinduction (matched/mismatched concept[22]) seems to be operative in the diazaborolidine activation (compare 96% ee with (*S*,*R*)-**1** vs 71% ee with (*S*,*S*)-**2**, this work) but not in the aluminum hydride enantioselective reductions (compare 52% ee with (*S*,*R*)-**1** vs 54% ee with (*S*,*S*)-**2**, Mukayaima's work[6]).

Second, what happens when the oxygen atom of Corey's first generation catalyst[3,8] is replaced with N–H? Under optimum conditions, the oxazaborolidine analog of diazaborolidine (*S*)-**8** reduces acetophenone in excellent yield and 97% ee (see Table I in Ref. 8a), whereas the latter affords (*R*)-**15** in 84% ee and quantitative yield (Table 1 in this report). The lower enantioselectivity observed in the diaza derivative is intriguing, and could be the result of decreased basicity in the diaza system affording more loosely bound carbonyl complexes in the transition state leading to reduction (cf. complex **F** in the mechanism presented in Scheme 7).

On the other hand, the effect of the concentration of catalysts (*S*,*R*)-**1** and (*S*)-**8** was evaluated in order to establish the optimum conditions for highest stereoselectivity. The results are summarized in Table 2. Most significant, the reaction can be promoted efficiently with 50 mol % of catalyst, providing highest enantioselectivity (entries 4 and 9 in Table 2).

Aiming to extend the scope and applicability of this protocol, we examined the reduction of other representative aryl alkyl ketones and dialkyl ketones using the optimum conditions, 50 mol % of catalysts (*S*,*R*)-**1**·BH_3 and (*S*)-**8**·BH_3, with microwave irradiation and simultaneous air cooling. The reduction of model aromatic ketones proceeds with excellent yields and with up to 96% enantiomeric excess (essays 1–6, Table 3). Other aromatic ketones such

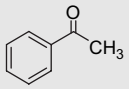
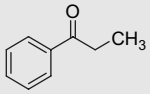
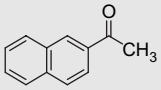
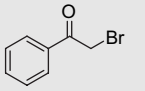
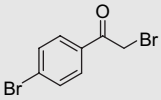
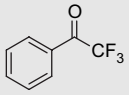
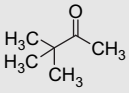
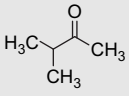
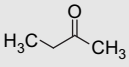
Table 2
Asymmetric reduction of acetophenone **14** using the chiral diamines (*S*,*R*)-**1** and (*S*)-**8** as precatalyst, microwave heating, and simultaneous external cooling



Entry	Cat*	mol %	(*R*)-**15**[a] % ee[b,c]
1	(*S*)-**8**	10	68
2	(*S*)-**8**	20	78
3	(*S*)-**8**	30	82
4	(*S*)-**8**	50	84
5	(*S*)-**8**	100	84
6	(*S*,*R*)-**1**	10	72
7	(*S*,*R*)-**1**	20	80
8	(*S*,*R*)-**1**	30	86
9	(*S*,*R*)-**1**	50	96
10	(*S*,*R*)-**1**	100	96

[a] In all essays the yields are nearly 100% (isolated yield of carbinol (*R*)-**15** after purification by column chromatography (silica gel, 10% ethyl acetate in hexane)).
[b] Determined by HPLC analysis using the chiral column, Chiralcel-OD.
[c] Absolute configuration was assigned by comparison of the sign of specific rotation with that reported in the literature.

Table 3
Asymmetric reduction of prochiral ketones using chiral diamines (*S*,*R*)-**1** and (*S*)-**8** as precatalyst, and microwave heating with simultaneous external cooling

Entry	Substrate	Product	Catalyst	Yield[a] (%)	ee[b]	Config.[c]
1		**15**	(*S*,*R*)-**1**	99	96	(*R*)
2			(*S*)-**8**	99	84	(*R*)
3		**21**	(*S*,*R*)-**1**	99	96	(*R*)
4			(*S*)-**8**	99	84	(*R*)
5		**22**	(*S*,*R*)-**1**	99	90	(*R*)
6			(*S*)-**8**	99	82	(*R*)
7		**23**	(*S*,*R*)-**1**	99	80	(*S*)
8			(*S*)-**8**	99	76	(*S*)
9		**24**	(*S*,*R*)-**1**	99	46	(*S*)
10			(*S*)-**8**	99	44	(*S*)
11		**25**	(*S*,*R*)-**1**	99	72	(*R*)
12			(*S*)-**8**	99	58	(*R*)
13		**26**	(*S*,*R*)-**1**	99	20	(*R*)
14		**27**	(*S*,*R*)-**1**	99	16	(*R*)
15		**28**	(*S*,*R*)-**1**	99	14	(*R*)

[a] Isolated yields of carbinol **15** after purification by column chromatography (silica gel, 10% ethyl acetate in hexane).
[b] Determined by HPLC analysis using chiral column.
[c] Absolute configurations were assigned by comparison with the sign of specific rotations reported in the literature (see Section 4).

as α-bromoacetophenone, α,*p*-dibromoacetophenone, and 2,2,2-trifluoroacetophenone are reduced with moderate to good enantioselectivity (80%, 46%, and 72% ee, respectively, entries 7–12 in Table 3). By contrast, aliphatic ketones proved notoriously poor substrates with respect to enantioselectivity; indeed, the secondary aliphatic carbinols are produced in good yield but low enantiomeric excess, 14–20% ee (entries 13–15 in Table 3). That aliphatic ketones are poor prochiral substrates in asymmetric reduction has been noted before.[23]

3. Conclusions

Chiral diamines (*S*)-2-(*N*-substituted aminomethyl)pyrrolidines **1**–**5** and the novel, highly hindered diamines (*S*)-1,1-diphenyl-*N*-(pyrrolidin-2-ylmethyl)methanamine, (*S*)-**6**, (*S*)-(1-benzylpyrrolidin-2-yl)diphenyl methyl amine, (*S*)-**7**, and (*S*)-(pyrrolidin-2-yl)-diphenyl methyl amine, (*S*)-**8**, derived from readily available (*S*)-proline were evaluated as precursors in the catalytic borane-mediated asymmetric reduction of prochiral ketones. Essentially quantitative yields of the expected secondary alcohol **15** were obtained, and the chiral carbinol was produced in generally good to excellent enantiomeric excesses. Importantly, the use of microwave irradiation turned out to be essential to achieve the formation of challenging diazaborolidines. Furthermore, in the asymmetric reduction of prochiral ketones, best results in chemical yield and enantioselectivity were achieved under microwave irradiation with simultaneous external cooling.

4. Experimental

4.1. General information

All manipulations were carried out under a nitrogen atmosphere. Commercially available reagents and solvents were used as received. Toluene, tetrahydrofuran (THF), and hexane were distilled from sodium and benzophenone before use. Flash column chromatography was performed on silica gel (230–400 mesh). Melting points were measured on a Melt-Temp 'Electrothermal' apparatus and are uncorrected. Optical rotations were measured on Perkin–Elmer 241 and 341 polarimeters. IR spectra were recorded on a Perkin–Elmer FTIR spectrum-GX apparatus. NMR spectra were obtained with JEOL GSX-270 (270 MHz), Bruker Advance 300 (300 MHz), and JEOL Eclipse+400 (400 MHz) spectrometers. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as an internal reference. Mass spectra were registered on a Hewlett Packard 5989-AMS-ENGINE, Thermo Electron Trace-DSQ spectrometer, at 20 eV. HRMS were taken on JEOL JMS-SX 102a and Agilent-MSD-TOF1069A spectrometers. Elemental analyses were obtained using a Thermo-Finnigan CHNS/O-1112 apparatus.

4.2. Microwave irradiation experiments

Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation[24] using either custom-made high-purity quartz or standard Pyrex vessels (capacity 10 mL). Analytical HPLC was carried out using Waters 600E and UV/Vis Waters 2487 chromatographs. The enantiomeric excess of the chiral products was determined using Chiralcel-OD (250×4.6 mm) and Chiralcel OB-H (250×4.6 mm) columns. Samples were eluted with mixtures of hexane–*i*-PrOH. The structural X-ray crystallographic data were obtained on an Enraf-Nonius Kappa CCD diffractometer.

*4.2.1. (S)-1,1-Diphenyl-N-(pyrrolidin-2-ylmethyl)-methanamine, (S)-**6***

This diamine was prepared by following the methodology reported by Mukaiyama et al.[6] and was obtained as colorless crystals, mp 186–190 °C, in 96% yield. $[\alpha]_D^{25}$ +20.0 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.16 (m, 10H), 4.85 (s, 1H), 3.60–3.58 (m, 1H), 3.04–2.96 (m, 2H), 2.80–2.67 (m, 2H), 1.90–1.77 (m, 3H), 1.55–1.49 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 143.5, 128.7, 127.6, 127.2, 67.2, 59.6, 48.8, 44.9, 28.5, 24.0. MS (EI) *m*/*z* (%): $[M+1]^+$ 267 (1), 196 (5), 183 (29), 178 (11), 167 (21), 120 (29), 106 (100), 84 (86), 70 (27). IR ν_{max} (KBr) cm^{-1}: 3448, 2930, 1664, 1490, 1450, 1078, 1026, 750, 704. HR-ESI-TOF $[M+H]^+$ calcd: 267.1855, found: 267.1851.

*4.2.2. (S)-2-(Azidodiphenylmethyl)-1-benzylpyrrolidine, (S)-**13***

In a 1-L three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and powder funnel were placed (*S*)-(1-benzylpyrrolidin-2-yl)diphenyl methanol [(*S*)-**12**, 27.0 g, 78.67 mmol], 270 mL of reagent-grade chloroform and 270 mL of 57% sulfuric acid. The flask was cooled to 0 °C in an ice bath before the slow addition of solid sodium azide (20.45 g, 314.7 mmol) over a period of 1.5 h. Once the addition of sodium azide was complete, the reaction mixture was stirred at 25 °C for 12 h. The reaction flask was cooled in an ice bath, and approximately 200 g of crushed ice was added slowly and the resulting aqueous mixture was extracted with methylene chloride

(4×50 mL). The combined extracts were washed with 5% $NaHCO_3$ (20 mL) and water (10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded essentially pure (*S*)-**13** as colorless oil (27.8 g, 96% yield). $[\alpha]_D^{25}$ −37.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.22 (m, 15H), 4.10 (dd, 1H, *J*=13.1, 3.8 Hz), 3.88 (d, 1H, *J*=13.1 Hz), 3.38 (d, 1H, *J*=13.1 Hz), 2.84 (m, 1H), 2.37–2.30 (m, 1H), 2.17–2.06 (m, 1H), 1.92–1.87 (m, 1H), 1.61–1.55 (m, 1H), 1.34–1.24 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 142.3, 142.0, 140.4, 128.7, 128.6, 128.3, 128.2, 128.2, 128.0, 127.6, 127.5, 126.7, 76.6, 70.7, 62.1, 55.1, 30.3, 24.1. MS (EI) *m*/*z* (%): $[M+1]^+$ 368 (2), 326 (18), 234 (4), 178 (11), 166 (100), 158 (7), 91 (6), 77 (4). IR ν_{max} (KBr) cm^{-1}: 3027, 2966, 2793, 2096, 1738, 1494, 1447, 1243. HR-ESI-TOF $[M+H]^+$ calcd: 369.2073, found: 369.2064.

*4.2.3. (S)-(1-Benzylpyrrolidin-2-yl)diphenylmethanamine, (S)-**7***

In a dry 500-mL one-necked round-bottom flask equipped with magnetic stirring and a condenser were placed THF (200 mL) and (*S*)-2-(azidodiphenylmethyl)-1-benzylpyrrolidine [(*S*)-**13**, 20.0 g, 54.31 mmol]. The flask was cooled to 0 °C, under a nitrogen atmosphere before the slow addition of lithium aluminum hydride (8.3 g, 217.27 mmol). The reaction mixture was heated to reflux for 8 h and then stirred overnight at 25 °C and hydrolyzed with saturated aqueous sodium sulfate solution. Following removal of the inorganic precipitate and concentration under vacuum, the residue was purified by flash chromatography (10% ethyl acetate in hexane) to give (*S*)-(1-benzylpyrrolidin-2-yl)(diphenyl)methyl amine [(*S*)-**7**, 17.6 g, 95% yield] as colorless crystals, mp 142–143 °C. $[\alpha]_D^{25}$ +240.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.08 (m, 15H), 3.88 (dd, 1H, *J*=11.8, 3.7 Hz), 2.91 (dd, 2H, *J*=12.8 Hz), 2.29–2.21 (m, 1H), 2.19–2.11 (m, 4H), 1.81–1.75 (m, 1H), 1.67–1.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 148.0 (2C), 140.6, 128.6, 128.2, 128.0, 128.0, 127.3, 126.9, 126.6, 126.4, 126.1, 71.4, 64.2, 61.8, 56.0, 30.3, 25.1. MS (EI) *m*/*z* (%): $[M+1]^+$ 343 (2), 326 (5), 180 (9), 160 (100), 104 (18), 91 (81), 77 (12). IR ν_{max} (KBr) cm^{-1}: 3372, 3294, 2904, 2832, 1952, 1882, 1810, 1760, 1674, 1596, 1490, 1446. HR-ESI-TOF $[M+H]^+$ calcd: 343.2168, found: 343.2172 (1.05 ppm). Anal. calcd for $C_{24}H_{26}N_2$ (324.47): C 84.17, H 7.65, N 8.18; found: C 84.31, H 7.98, N 8.33.

*4.2.4. (S)-(Pyrrolidin-2-yl)diphenylmethanamine, (S)-**8***

A solution of (*S*)-(1-benzylpyrrolidin-2-yl)diphenyl methyl amine [(*S*)-**7**, 17.0 g, 49.67 mmol] in MeOH (150 mL) was hydrogenated over 10% Pd–C (1.7 g), acetic acid (3 mL) at 60 psi of hydrogen pressure for 24 h at room temperature. The reaction mixture was then filtered through a pad of Celite rinsing with MeOH. The solvent was evaporated and the residue was dissolved in 2 N NaOH (100 mL) and ethyl acetate (100 mL). After extraction of the aqueous phase with ethyl acetate, the combined organic layer was dried over anhyd Na_2SO_4 and evaporated. The residue was purified by flash chromatography (10% methanol in methylene chloride) to give (*S*)-(pyrrolidin-2-yl)diphenyl methyl amine (*S*)-**8** as a yellow oil (12.4 g, 99% yield). $[\alpha]_D^{25}$ +44.11 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48–7.15 (m, 15H), 4.20 (t, 1H, *J*=7.7 Hz), 3.63 (s, 3H), 3.00–2.95 (m, 1H), 2.90–2.84 (m, 1H), 1.93 (br s, 3H), 1.78–1.65 (m, 3H), 1.60–1.53 (m, 1H) ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 148.7, 147.4, 65.0, 63.1, 47.2, 27.0, 26.1. MS (EI) *m*/*z* (%): $[M+1]^+$ 253 (2), 236 (3), 182 (34), 104 (7), 70 (100). IR ν_{max} (KBr) cm^{-1}: 3360, 3294, 2960, 2868, 1888, 1596, 1492, 1446. HR-ESI-TOF $[M+H]^+$ calcd: 253.1699, found: 253.1706.

4.3. General procedure for the asymmetric reduction of prochiral ketones catalyzed by chiral diazaborolidines

In a 10-mL reactor tube provided with magnetic stirrer were added (0.5 mmol) of chiral diamine (*S*)-**8**, 1.0 mL of 2 M $BH_3 \cdot S(CH_3)_2$ (2 equiv), and 2 mL of toluene. The reaction mixture was heated under microwave irradiation (100 W) for 15 min at 75 °C with simultaneous external cooling with compressed air (10 psi). The reactor tube was allowed to cool to room temperature and then cooled to −78 °C. A solution of the prochiral ketone (1 mmol) in toluene (0.5 mL) was added dropwise and the reaction mixture was stirred to −78 °C for 8 h. The reaction mixture was allowed to cool to room temperature and quenched with MeOH. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc–hexanes, 9:1) to provide the desired alcohol in excellent yield as colorless oil.

Alcohols **15** and **21**–**28** are already known in the literature.[25–31] The spectral data (^1H and ^{13}C NMR) are in agreement with the reported data. Enantiomeric ratios were determined by HPLC with a chiral Chiralcel-OD column, detector at λ=220 nm, mobile phase hexane–*i*-PrOH (97:3), and flow 1 mL/min.

*4.3.1. (R)-1-Phenylethanol, (R)-**15***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ +18.0° (*c* 1.1, $CHCl_3$) 84% ee; [lit.[25] $[\alpha]_D^{25}$ +44.1 (*c* 3.0, MeOH), (*R*)-configuration, 97% ee]. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel-OD, hexanes–*i*-PrOH (95:5), 1.0 mL/min, 220 nm, retention times: 10.75 min (*R*) and 14.73 min (*S*)].

*4.3.2. (R)-1-Phenylpropan-1-ol, (R)-**21***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ +37.0° (*c* 0.95, $CHCl_3$) 84% ee; [lit.[25] $[\alpha]_D^{25}$ +43.0° (*c* 5.1, $CHCl_3$), 96% ee]. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel-OD, hexanes–*i*-PrOH (95:5), 1.0 mL/min, 220 nm, retention times: 8.46 min (*R*) and 10.45 min (*S*)].

*4.3.3. (R)-1-(Naphthalen-2-yl)ethanol, (R)-**22***

White solid; yield: 99%; $[\alpha]_D^{25}$ +18.0° (*c* 1.1, $CHCl_3$) 82% ee; [lit.[26] $[\alpha]_D^{25}$ +37.77° (*c* 1.04, $CHCl_3$), (*R*)-configuration, 95% ee]. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel-OD, hexanes–*i*-PrOH (97:3), 1.0 mL/min, 220 nm, retention times: 43.15 min (*S*) and 46.98 min (*R*)].

*4.3.4. (S)-α-Bromophenylethanol, (S)-**23***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ +30.0° (*c* 1.61, $CHCl_3$) 76% ee; [lit.[27] $[\alpha]_D^{25}$ −33.54° (*c* 5, $CHCl_3$), (*R*)-configuration, 86% ee]. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel-OD, hexanes–*i*-PrOH (97:3), 1.0 mL/min, 220 nm, retention times: 14.18 min (*S*) and 18.28 min (*R*)].

*4.3.5. (S)-α,p-Dibromophenylethanol, (S)-**24***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ +7.4° (*c* 1.08, $CHCl_3$) 44% ee; [lit.[28] $[\alpha]_D^{25}$ +32.75° (*c* 1.3, $CHCl_3$), (*S*)-configuration, 93% ee]. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel-OD, hexanes–*i*-PrOH (97:3), 1.0 mL/min, 220 nm, retention times: 31.33 min (*R*) and 33.90 min (*S*)].

*4.3.6. (R)-2,2,2-Trifluoro-1-phenylethanol, (R)-**25***

Pale yellow oil; yield: 99%; $[\alpha]_D^{25}$ −26.6° (*c* 0.64, $CHCl_3$) 58% ee; [lit.[29] $[\alpha]_D^{25}$ +21.6° (*c* 0.52, $CHCl_3$), (*S*)-configuration, 74% ee]. The enantiomeric excess was determined by HPLC using a chiral column [Chiralcel-OD, hexanes–*i*-PrOH (97:3), 1.0 mL/min, 220 nm, retention times: 30.65 min (*R*) and 39.51 min (*S*)].

*4.3.7. (R)-Pinacolyl alcohol, (R)-**26***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ −0.8° (*c* 1.00, $CHCl_3$) 20% ee; [lit.[30] $[\alpha]_D^{25}$ −5.2° (*c* 2.9, CCl_4), (*R*)-configuration, 96% ee]. The enantiomeric excess was determined by HPLC using photodiodes array detection and a chiral column [Chiralcel OB-H, hexanes–*i*-PrOH (99:1), 1.0 mL/min, 254 nm, retention times: 3.7 min (*S*) and 4.0 min (*R*)].

*4.3.8. (R)-3-Methyl-2-butanol, (R)-**27***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ −0.2° (*c* 1.00, $CHCl_3$) 16% ee; [lit.[30] $[\alpha]_D^{25}$ −6.7° (*c* 8.8, CCl_4), (*R*)-configuration, 89% ee]. The enantiomeric excess was determined by HPLC using photodiodes array detection and a chiral column [Chiralcel OB-H, hexanes–*i*-PrOH (99:1), 1.0 mL/min, 254 nm, retention times: 3.7 min (*S*) and 4.0 min (*R*)].

*4.3.9. (R)-2-Butanol, (R)-**28***

Colorless oil; yield: 99%; $[\alpha]_D^{25}$ −1.2° (neat) 16% ee; [lit.[31] $[\alpha]_D^{25}$ −13.23° (neat), (*R*)-configuration, 98% ee]. The enantiomeric excess was determined by HPLC using photodiodes array detection and a chiral column [Chiralcel OB-H, hexanes–*i*-PrOH (99:1), 1.0 mL/min, 254 nm, retention times: 3.7 min (*S*) and 4.0 min (*R*)].

Acknowledgements

The authors are grateful to Gloria Reyes Rangel for technical assistance, and to Conacyt, México, for financial support via grant 45,157-Q

References and notes

1. See, for example: (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994; (b) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, NY, 1991.
2. Brown, H. C.; Jadhav, P. K.; Singaram, B. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer: Heidelberg, 1986; Vol. 4, pp 307–356.
3. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
4. (a) Singh, V. K. *Synthesis* **1992**, 605–618; (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504; (c) Shanthi, V.; Rao, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 3553–3560; (d) Lapis, A. A. M.; Fatima, A. D.; Martins, J. E. D.; Costa, V. E. U.; Pilli, R. A. *Tetrahedron Lett.* **2005**, *46*, 495–498; (e) Wang, G.-Y.; Liu, X.-Y.; Zhao, G. *Synlett* **2006**, 1150–1154; (f) Trentmann, W.; Mehler, T.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2033–2043; (g) Mandal, A. K.; Kasar, T. G.; Mahajan, S. W.; Jawalkar, D. G. *Synth. Commun.* **1987**, *17*, 563–574; (h) Chen, F. E.; Dai, H. F.; Kuang, Y. Y.; Jia, H. Q. *Tetrahedron: Asymmetry* **2003**, *14*, 3667–3672; (i) Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477–2480.
5. For reviews, see: (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784; (b) Cho, B. T. *Tetrahedron* **2006**, *62*, 761–7643; Cho, B. T. *Aldrichimica Acta* **2002**, *35*, 3–16; (c) Itsuno, S. *Org. React.* **1998**, *52*, 395–576.
6. Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869–1873.
7. (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470; (b) Hirao, A.; Itsuno, S.; Nakahama, N.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315–317.
8. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.
9. For applications from other research groups, see for example: (a) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095–2100; (b) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2455–2462; (c) Yadav, J. S.; Reddy, P. T.; Hashim, S. R. *Synlett* **2000**, 1049–1051.
10. (a) Asami, M.; Sato, S.; Watanabe, H. *Chem. Lett.* **2000**, 990–991; (b) Sato, S.; Watanabe, H.; Asami, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4329–4340.
11. (a) Basavaiah, D.; Rao, K. V.; Reddy, B. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1041–1044; (b) Basavaiah, D.; Rao, K. V.; Reddy, B. S. *Tetrahedron: Asymmetry* **2007**, *18*, 968–974.
12. Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958–1967.
13. Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177.
14. Wallén, E. A.; Christiaans, J. A.; Forsberg, M. M.; Venäläinen, J. I.; Männistö, P. T.; Gynther, J. *J. Med. Chem.* **2002**, *45*, 4581–4584.
15. Sibi, M. P.; Zhang, R.; Manyem, S. *J. Am. Chem. Soc.* **2003**, *125*, 9306–9307.
16. Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2004**, 129–137.
17. The structures were solved and refined using SHELX-97, Sheldrick, G. M. *Programs for Crystal Structure Analysis*; University of Göttingen: Germany, 1997; Within WinGX program version 1.64.05.28, Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838; Crystal data for (*S*)-diphenyl-(1-benzylpyrrolidin-2-yl)-methyl amine, (*S*)-**7**: $C_{27}H_{26}N_2$, Mol. Weight=342.47, Monoclinic, *P* 21, *a*=12.020 Å, *b*=6.001 Å, *c*=13.838 Å, *α*=90.0°, *β*=100.74°, *γ*=90.0°, *V*=980.7 Å^3, crystal size: 0.12×0.15×0.20 mm3, *R*1=0.0490 (*wR*2=0.1005). Atomic coordinates for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336 036. e-mail: deposit@ccdc.cam.ac.uk); Deposition number: CCDC 676578.
18. Nöth, H.; Wrackmeyer, B. In *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer: Heidelberg, 1978; p 255, 372.
19. See, for example: Kappe, C. O. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005.
20. (a) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873–8876; (b) Mathew, F.; Jayaprakash, K. N.; Fraser-Reid, B.; Mathew, J.; Scicinski, J. *Tetrahedron Lett.* **2003**, *44*, 9051–9054; (c) Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565–3585; (d) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101–2104; (e) Jachuck, R. J. J.; Selvaraj, D. K.; Varma, R. S. *Green Chem.* **2006**, *8*, 29–33; (f) Singh, B. K.; Appukkuttan, P.; Claerhout, S.; Parmar, V. S.; Van der Eycken, E. *Org. Lett.* **2006**, *8*, 1863–1866; (g) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. T. *Chem.—Eur. J.* **2006**, *12*, 4407–4416.
21. (a) Hayes, B. L.; Collins, M. J., Jr. World Patent WO 04002617, 2004. (b) The technique of 'simultaneous cooling' or 'heating-while-cooling' under microwave conditions was originally described by Strauss and Trainor under the name 'concurrent heating and cooling', see: Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692; (c) Recently, Kappe used this technique in organocatalyst Mannich reaction, see: Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417–1424.
22. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.
23. (a) Asami, M.; Mukaiyama, T. *Heterocycles* **1979**, *12*, 499–502; (b) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129–3131; (c) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555–557.
24. For more information, see: CEM Corporation Website. www.cem.com.
25. Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 3147–3152.
26. Sokeirik, Y. S.; Mori, H.; Omote, M.; Sato, K.; Tarui, A.; Kumadaki, I.; Ando, A. *Org. Lett.* **2007**, *9*, 1927–1929.
27. Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384–1394.
28. Basavaiah, D.; Reddy, G. J.; Chandrashekar, V. *Tetrahedron: Asymmetry* **2001**, *12*, 685–689.
29. Yong, K. H.; Chong, J. M. *Org. Lett.* **2002**, *4*, 4139–4142.
30. Eagon, S.; Kim, J.; Yan, K.; Haddenham, D.; Singaram, B. *Tetrahedron Lett.* **2007**, *48*, 9025–9029.
31. Brown, H.; Desai, M.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065–5069.