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# Towards chiral diamines as chiral catalytic precursors for the borane-mediated enantioselective reduction of prochiral ketones

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**Abstract.** Two chiral diamines (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) and (2*R*)-2-anilinomethylpiperidine (**2**) have been employed as chiral catalytic sources in the borane-mediated asymmetric reduction of prochiral ketones thus providing the resulting secondary alcohols in good enantiomeric purities (up to 81% *ee*).

**Keywords.** (3*S*)-3-Anilinomethyl-1,2,3,4-tetrahydroisoquinoline; (2*R*)-2-anilinomethylpiperidine; (*S*)-phenylalanine; asymmetric reduction.

## 1. Introduction

Development of an efficient chiral catalyst for the borane-mediated asymmetric reduction of prochiral ketones providing the resulting secondary alcohols in high enantioselectivities has been and continues to be one of the most fundamental reactions and attractive endeavours in the chemistry of chiral reductions because of the challenges involved in such endeavours.[1–12] We have been working in this direction for the past few years and developed some novel chiral catalysts mainly built on the (2*S*)-2-anilinomethylpyrrolidine framework (**3**) for borane-mediated asymmetric reduction processes.[13–21] In continuation of our efforts in designing and developing useful chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones we report here the application of two chiral diamines (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) and (2*R*)-2-anilinomethylpiperidine (**2**) as chiral precursors (catalytic sources) for reduction of prochiral ketones to provide the resulting secondary alcohols in reasonably good enantioselectivities.

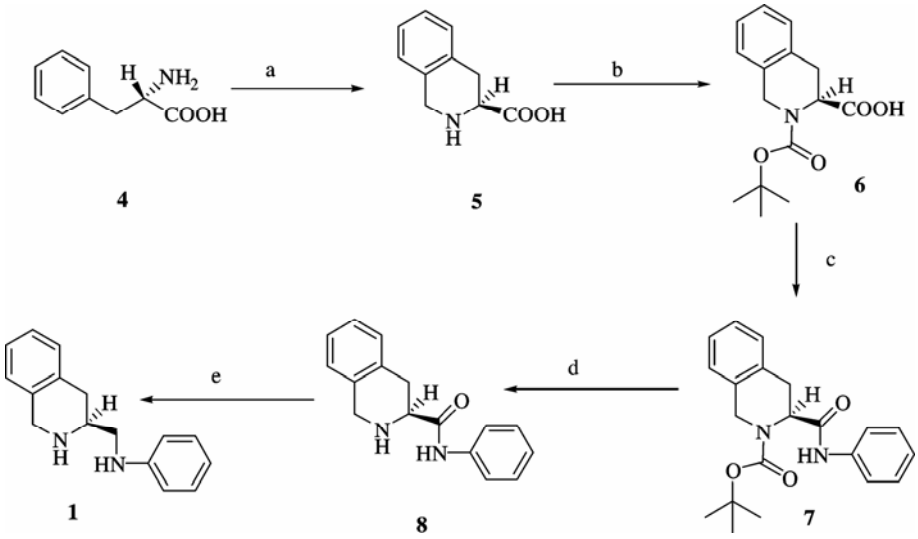
## 2. Experimental

All melting points were recorded on a Superfit (India) capillary melting point apparatus and were uncorrected. IR spectra were recorded on Jasco-FT–IR model 5300. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) on a Bruker-Avance 400 spectrometer using tetramethylsilane (TMS, $\delta = 0$) as an internal standard. Elemental analyses were recorded on a thermo Finnigan Flash 1112 analyzer. Mass spectra were recorded on Shimadzu LCMS 2010A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K$\alpha$ fine-focus sealed tube ($\lambda = 0{\cdot}71073$ Å). HPLC analyses of alcohols were carried out on Shimadzu LC-10AD instrument using chiral column (Chiralcel OD-H or Chiralcel OJ-H). Optical rotations were measured on Jasco DIP 370 digital polarimeter. We have provided all the experimental details using the catalyst, (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) as a representative case since all the other relevant data using the catalyst, (2*R*)-2-anilinocarbonyl-piperidin*e* (**2**). We have earlier prepared [(*S*)-**10a–c** and (*R*)-**10d**,**e**] molecules and reported the spectral data.[18,21] The present spectral data (IR, $^1$H NMR, $^{13}$C NMR) are in agreement with the earlier data.

### 2.1 *(3S)-2-(tert-Butoxycarbonyl)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline* (**7**)

This compound was prepared following the literature procedure[7] from compound (3*S*)-N-(*tert*-

*For correspondence




**Scheme 1.** (a) 37% aq. HCHO, HCl, 60°C, 4 h, 30%;[23] (b) $(Boc)_2O$, aq. NaOH, dioxane, r.t., 16 h, 74%;[22] (c) $NEt_3$, EtOCOCl, $PhNH_2$, THF, rt, 16 h, 66%;[7] (d) HCl (g), $CH_2Cl_2$, r.t., 30 min, 93%; (e) $LiAlH_4$, THF, reflux, 5 h, 84%.[7]

butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**6**) which was obtained[22] from (3*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**5**). Compound **5** was in turn prepared from (*S*)-phenylalanine (**4**) following the known procedure as presented in the scheme 1.[23]

### 2.2 *(3S)-3-Anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline* (**8**)

To a stirred solution of (3*S*)-2-(*tert*-butoxycarbonyl)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (**7**) (1·762 g, 5 mM) in $CH_2Cl_2$ was bubbled HCl gas for a period of 30 min at room temperature. Solvent was evaporated. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was then re-extracted with EtOAc (25 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated to provide the desired compound **8** as colourless solid. Yield: 93% (1·175 g). $[\alpha]_D^{25}$: –81·16 (*c* 0·6, MeOH), [TFA. Amide[24] $[\alpha]_D$:[25] –32·42 (*c* 0·6, MeOH). It is worth mentioning here that $[\alpha]_D^{25}$ of this salt changes to –58·63 on standing this solution (12 h) which might be attributed to the possible decomposition of this salt] [lit.[25] **8-TFA** salt $[\alpha]_D^{20}$: –33.1, *c* 1, MeOH]; m.p.: 160–162°C [lit.[25] 150–152°C for **8-TFA** salt]; IR (KBr): $\nu$ 3300–2900 (multiple bands), 1678, 1601 $cm^{-1}$; $^1H$ NMR: $\delta$ 2·92 (*dd*, 1H, *J* = 10·8 Hz. and 16·4 Hz), 3·35 (*dd*, 1H, *J* = 5·6 Hz and 16·4 Hz), 3·69 (*dd*, 1H, *J* = 5·2 Hz. and 10·8 Hz), 4·03 and 4·08 (ABq, 2H, *J* = 16·0 Hz), 7·06–7·38 (*m*, 8H), 7·61 (*d*, 2H, *J* = 8·0 Hz), 9·34 (*br*, 1H); $^{13}C$ NMR: $\delta$ 30·57, 47·55, 56·87, 119·48, 124·17, 125·57, 126·38, 126·82, 129·04, 129·22, 134·42, 136·11, 137·76, 171·31.

Crystal data for **8**: Empirical formula, $C_{16}H_{16}N_2O$; formula weight, 252·31; colourless, block crystal; crystal dimensions, 0·46 × 0·37 × 0·25 $mm^3$; orthorhombic, lattice type, primitive; *a* = 5·8274(6) Å, *b* = 8·2330(8) Å, *c* = 27·680(3) Å; $\alpha$ = 90·00; $\beta$ = 90·00; $\gamma$ = 90·00; *V* = 1328·0(2) $Å^3$; space group, *P*2(1)2(1)2(1) (International Table No. 19); *Z* = 4; $D_{calcd}$ = 1·262 g/$cm^3$; $F_{ooo}$ = 536; $\lambda$(Mo$K_\alpha$) = 0·71073 Å; *R* ($I \geq 2\sigma_1$) = 0·0399; $wR^2$ = 0·0764. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.[26]

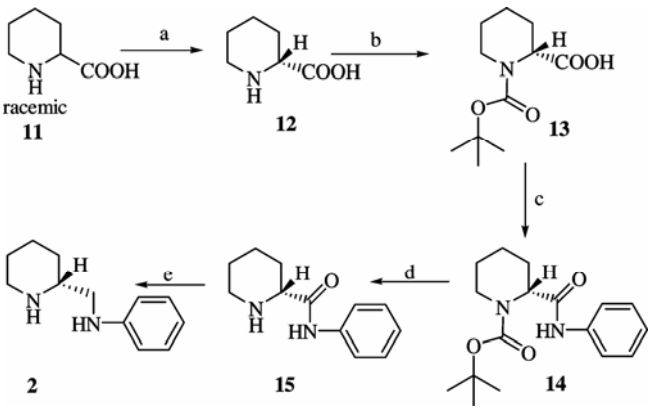
### 2.3 *(3S)-3-Anilinomethyl-1,2,3,4-tetrahydroisoquinoline* (**1**)

This compound was prepared from compound **8** following the similar literature procedure[7] with some modification. To a stirred suspension of lithium aluminium hydride (0·228 g, 6 mM) in THF (20 mL), (3*S*)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (0·504 g, 2 mM) was added portion-wise at room temperature. After the addition was complete,

the reaction mixture was heated under reflux for 5 h. The reaction mixture was cooled to 5°C and water (1 mL) was added carefully, followed by the addition of NaOH solution (2·5 N, 5 mL). The reaction mixture was diluted with dichloromethane (10 mL) and stirred for 10 min. The organic layer was separated and the solid aluminium salts were washed with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$. Solvent was evaporated and the residue thus obtained was purified by distillation [Bp: 180–182°C (oil bath)/0·2 mm] under reduced pressure to furnish the compound as a viscous liquid which solidified upon standing at room temperature. Yield: 84% (0·40 g); $[\alpha]_D^{25}$: –64·79 (*c* 0·9, $CHCl_3$); m.p.: 80–82°C; IR (KBr): $\nu$ 3300, 3213, 1602 $cm^{-1}$; $^1H$ NMR: $\delta$ 1·61–1·82 (*br*, 1H), 2·60–2·72 (*m*, 1H), 2·80–2·90 (*m*, 1H), 3·04–3·14 (*m*, 1H), 3·15–3·25 (*m*, 1H), 3·31–3·41 (*m*, 1H), 4·06 (*s*, 2H), 4·25 (*br*, 1H), 6·62–6·76 (*m*, 3H), 7·01–7·06 (*m*, 1H), 7·07–7·22 (*m*, 5H); $^{13}C$ NMR: $\delta$ 33·17, 48·16, 49·31, 53·10, 113·03, 117·57, 125·98, 126·10, 126·26, 129·33, 129·36, 134·11, 135·80, 148·49; LCMS (*m*/*z*): 239 $(M + H)^+$; Anal. calcd. for $C_{16}H_{18}N_2$: C, 80·63; H, 7·61; N, 11·75; Found: C, 80·83; H, 7·67; N, 11·68.

### 2.4 *(R)-N-(tert-Butoxycarbonyl)-2-anilinocarbonylpiperidine* (**14**)

This compound was prepared[7] from (*R*)-N-(*tert*-butoxycarbonyl)pipecolinic acid (**13**) which was prepared from (*R*)-pipecolinic acid (**12**). Compound **12** was obtained via resolution of racemic pipecolinic acid according to the literature procedure[27] as presented in scheme 2.




**Scheme 2.** (a) (*R,R*)-tartaric acid, MeOH, 60°C, 1 h, 35%;[27] (b) $(Boc)_2O$, aq. NaOH, THF, reflux, 6 h, 68%;[27] (c) $NEt_3$, EtOCOCl, $PhNH_2$, THF, r.t., 16 h, 75%;[7] (d) $CF_3COOH : CH_2Cl_2$ (1 : 1), r.t., 1 h, 78%;[7] (e) $LiAlH_4$, THF, reflux, 5 h, 63%[7].

### 2.5 *(2R)-2-Anilinocarbonylpiperidine* (**15**)[28]

This compound was prepared from the compound **14** following the similar procedure[7] with some modification. To a stirred solution of (*R*)-N-(*tert*-butoxycarbonyl)-2-anilinocarbonylpiperidine (1·52 g, 5 mM) in dichloromethane (20 mL) was added 20 mL of TFA at room temperature. After 1 h solvent was evaporated and the residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was then again extracted with EtOAc (25 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was evaporated. The residue thus obtained was purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to provide the desired compound as colourless solid. Yield: 78% (0·796 g); m.p.: 190–192°C; $[\alpha]_D^{25}$: +18·82 (*c* 1·0, MeOH); IR (KBr): $\nu$ 3300–2849 (multiple bands), 1685, 1601 $cm^{-1}$; $^1H$ NMR: $\delta$ 1·38–1·70 (*m*, 4H), 1·74–1·91 (*m*, 1H), 1·98–2·20 (*m*, 2H), 2·65–2·85 (*m*, 1H), 2·97–3·16 (*m*, 1H), 3·28–3·45 (*m*, 1H), 7·05–7·16 (*m*, 1H), 7·25–7·44 (*m*, 2H), 7·57 (*d*, 2H, $J$ = 7·6 Hz), 8·88 (*bs*, 1H).; $^{13}C$ NMR: $\delta$ 23·84, 25·92, 29·67, 45·62, 60·51, 119·53, 124·07, 129·00, 137·90, 172·18.

Crystal data for amide **15-TFA** salt: Empirical formula, $C_{14}H_{17}F_3N_2O_3$; formula weight, 318·30; colourless, block; crystal dimensions, 0·45 × 0·37 × 0·25 $mm^3$; monoclinic, lattice type, primitive; $a$ = 23·409(3) Å, $b$ = 8·0598(10) Å, $c$ = 8·7079(10) Å; $\alpha$ = 90·00; $\beta$ = 107·005 (2); $\gamma$ = 90·00; $V$ = 1571·1(3) $Å^3$; space group, *C*2 (International Table No. 5); $Z$ = 4; $D_{calcd}$ = 1·346 g/$cm^3$; $F_{ooo}$ = 664; $\lambda(MoK_\alpha)$ = 0·71073 Å; $R$ $(I \geq 2\sigma_1)$ = 0·0717; $wR^2$ = 0·2126. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.[26]

### 2.6 *(2R)-2-Anilinomethylpiperidine* (**2**)[29]

This compound was prepared from the amide **15** according to the similar literature procedure[7] described for the compound **1** as viscous liquid. Yield: 63%; b.p.: 145–147°C (oil bath)/0·5 mm; $[\alpha]_D^{25}$: –29·02 (*c* 1·4, EtOH); IR (neat): $\nu$ 3381, 3300, 2928, 1602 $cm^{-1}$; $^1H$ NMR: $\delta$ 1·14–1·28 (*m*, 1H), 1·31–1·50 (*m*, 2H),

1·54–1·74 (*m*, 2H), 1·78–2·05 (*m*, 2H), 2·57–2·68 (*m*, 1H), 2·72–2·83 (*m*, 1H), 2·94–3·20 (*m*, 3H), 4·03 (*br*, 1H), 6·58–6·73 (*m*, 3H), 7·12–7·22 (*m*, 2H); $^{13}$C NMR: $\delta$ 24·51, 26·60, 30·75, 46·77, 50·09, 55·88, 112·73, 117·15, 129·18, 148·47; LCMS (*m/z*): 191 $(M + H)^+$; Anal. calcd. For $C_{12}H_{18}N_2$: C, 75·74; H, 9·53; N, 14·72; Found: C, 75·56; H, 9·50; N, 14·84.

### 2.7 *Asymmetric reduction of phenacyl bromide* (**9a**) *using the catalyst* **1**

2.7a *Synthesis of (S)-2-bromo-1-phenylethanol* [(*S*)**–10a**]: *Representative procedure:* To a stirred solution of (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) (0·1 mM, 1 mL, 0·1 M solution in toluene) in toluene (2 mL) was added $BH_3.SMe_2$ (1 mM, 1 mL, 1 M solution in toluene) at room temperature and the reaction mixture was heated under reflux for 15 min. Then a solution of phenacyl bromide (**9a**) (1 mM, 0·199 g), in toluene (2 mL), was added drop-wise and heated under reflux for further 30 min. The reaction mixture was cooled to room temperature and quenched with MeOH. Solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol [(*S*)–**10a**] in 86% (0·172 g) yield as a colourless oil. $[\alpha]_D^{25}$: +32·62 (*c* 0·9, $CHCl_3$) [lit.[30] $[\alpha]_D^{25}$: –39·0 (*c* 8·00, $CHCl_3$), (*R*)-configuration, 93% *ee*]; 80% *ee*, the enantiomeric purity was determined by HPLC analysis using chiral column, [Chiralcel OD-H, 90 : 10 hexanes/*i*-PrOH, 1·0 mL/min, 254 nm, retention times: 8·17 min (*S*) and 8·82 min (*R*)].

2.7b *(S)-2-Chloro-1-phenylethanol* [(*S*)**–10b**]: Colourless oil, 83% yield, $[\alpha]_D^{25}$: +37·23 (*c* 0·8, cyclohexane) [lit.[30] $[\alpha]_D^{25}$: –48·10 (*c* 1·73, cyclohexane), (*R*)-configuration, 100% *ee*]; 72% *ee*, the enantiomeric purity was determined by HPLC analysis using chiral column [Chiralcel OD-H, 90 : 10 hexanes/*i*-PrOH, 1·0 mL/min, 254 nm, retention times: 7·86 min (*S*) and 8.53 min (*R*)].

2.7c *(S)-2-Bromo-1-(4-bromophenyl)ethanol* [(*S*)–**10c**]: Colourless solid, m.p.: 69–71°C [lit[19]. 70–72°C] 81% yield, $[\alpha]_D^{25}$: +27·51 (*c* 0·9, $CHCl_3$) [lit.[31] $[\alpha]_D^{25}$: –31·0 (*c* 2·9, $CHCl_3$), (*R*)-configuration, 94% *ee*]; 79% *ee*, the enantiomeric purity was determined by HPLC analysis using chiral column, [Chiralcel OJ-H, 95 : 5 hexanes/*i*-PrOH, 1·0 mL/min, 254 nm, retention times: 19·87 min (*R*) and 21·03 min (*S)*].

2.7d *(R)-1-Phenylethanol* [(*R*)–**10d**]: Colourless oil, 84% yield, $[\alpha]_D^{25}$: +23·54 (*c* 0·8, MeOH) [lit.[32] $[\alpha]_D^{25}$: +44·1 (*c* 3·0, MeOH), (*R*)-configuration, 97% *ee*]; 57% *ee*, the enantiomeric purity was determined by HPLC analysis using chiral column, [Chiralcel OD-H, 95 : 5 hexanes/*i*-PrOH, 1·0 mL/min, 254 nm, retention times: 8·30 min (*R*) and 9·67 min (*S*)].

2.7e *(R)-1-(4-Bromophenyl)ethanol* [(*R*)–**10e**]: Colourless oil, 83% yield, $[\alpha]_D^{25}$: +21·5 (*c* 0·5, $CHCl_3$) [lit.[33] $[\alpha]_D^{23}$: –37.9 (*c* 1·13, $CHCl_3$), (*S*)-configuration, >99% *ee*]; 59% *ee*, the enantiomeric purity was determined by HPLC analysis using chiral column, [Chiralcel OJ-H, 95 : 5 hexanes/*i*-PrOH, 0·8 mL/min, 254 nm, retention times: 15·06 min (*S*) and 15·78 min (*R*)].

## 3. Results and discussion

Recently, we have demonstrated the application of chiral diamine i.e. (2*S*)-2-anilinomethylpyrrolidine (**3**) as a catalyst[15] for the borane-mediated asymmetric reduction of prochiral ketones thus producing the resulting secondary alcohols in high enantiomeric purities. With a view to develop more effective catalysts based on the chiral diamine frameworks and also with an objective to understand the influence of the ring size and bicyclic ring system in the borane-mediated asymmetric reduction of prochiral ketones we have selected two diamines i.e. (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) and (2*R*)-2-anilinomethylpiperidine (**2**) as in figure 1 (which were not examined earlier as catalysts for the borane-mediated asymmetric reduction of prochiral ketones) for our study.

Catalytic source **1** was prepared according to the reaction sequence as shown in scheme 1 starting from (*S*)-phenylalanine. Conversion of (*S*)-phenylalanine (**4**) into the corresponding (3*S*)-1,2,3,4-

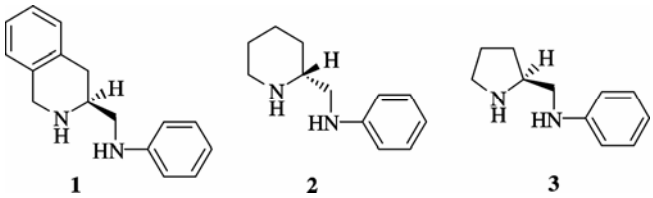
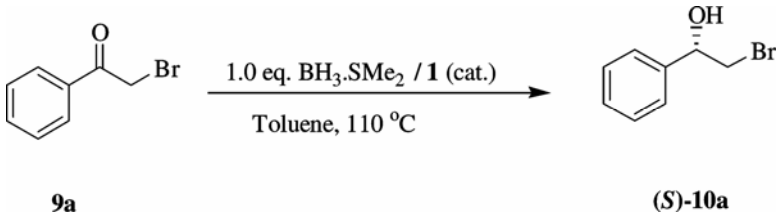



**Figure 1.**

**Table 1.** Asymmetric reduction of phenacyl bromide (**9a**): Standardization[a].




**9a** **(*S*)-10a** (1)

| Entry | Catalyst **1** (mol%) | Time (min) | Yield (%)[b] [(***S*)-10a**)] | Enantiomeric purity (%).[c] [(***S*)-10a**)] |
|---|---|---|---|---|
| 1 | 5 | 45 | 78 | 68 |
| 2 | 7·5 | 45 | 85 | 73 |
| 3 | 10 | 45 | 84 | 78 |
| 4 | 15 | 45 | 81 | 75 |
| 5 | 20 | 45 | 82 | 76 |
| **6** | **10** | **30** | **86** | **80** |

[a]All reactions were carried out on 1 mM scale of phenacyl bromide with $BH_3 \cdot SMe_2$ (1 mM) in the presence of **1** in toluene at 110°C
[b]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes)
[c]Determined by HPLC analyses using the chiral column, Chiralcel OD-H

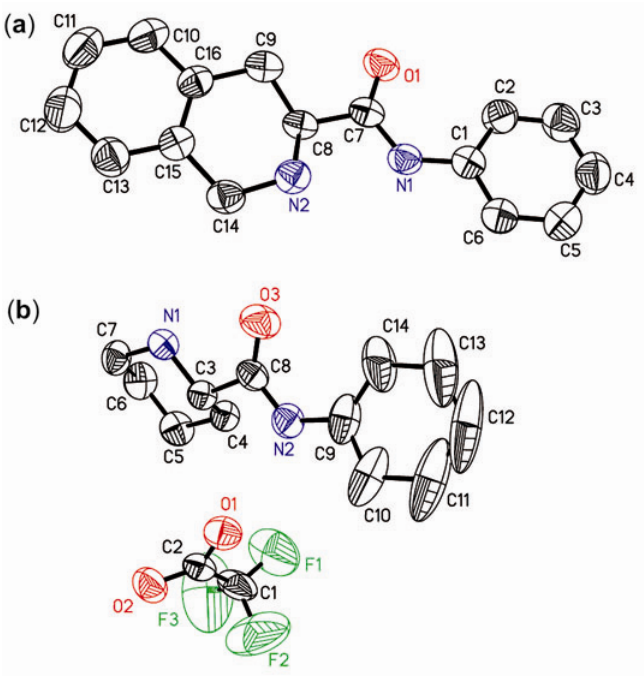


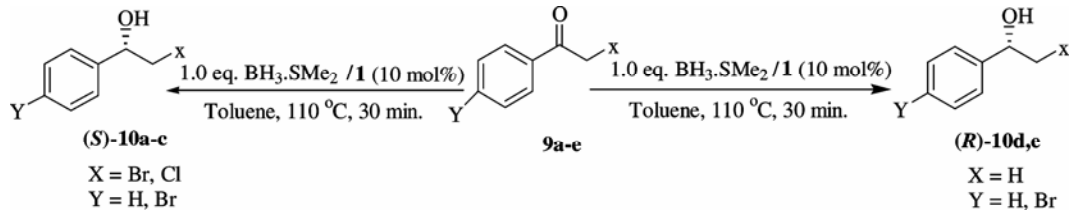

**Figure 2.** ORTEP diagram of (**a**) compound **8** and (**b**) compound **15-TFA** salt (Hydrogen atoms were omitted for clarity).

tetrahydro-3-isoquinolinecarboxylic acid (**5**) is known in the literature.[23] This acid (**5**) was conveniently transformed into (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) following the well known transformation methodologies.[22,25] Our attempts to obtain single crystal for the diamine (**1**) were not successful. Since the single crystal X-ray structure of (3*S*)-3-anilinocarbonyl-1,2,3,4-tetrahydroisoquinoline (**8**) was not reported in the literature (although this amide is known in the literature),[25] we thought it would also be appropriate to report the single crystal X-ray data for this amide (**8**). We obtained single crystal for the amide (**8**) and confirmed the structure by the single crystal X-ray data (ORTEP diagram: figure 2)[26] thus indirectly further confirming the structure of the diamine (**1**).

We have first selected phenacyl bromide (**9a**) as a substrate for our study and performed the borane-mediated asymmetric reduction of **9a** using varying catalytic amounts of the compound **1**. The best result was obtained when phenacyl bromide (**9a**) (1 mM) was treated with borane ($BH_3 : SMe_2$, 1 mM) in the presence of 10 mol% catalyst at reflux temperature for 30 min thus providing the resulting secondary alcohol, (*S*)-2-bromo-1-phenylethanol (*S*)-**10a** in 80% enantiomeric purity (table 1, (1)). Encouraged by this result, we have subjected representative class of prochiral ketones (**9b–e**) to this strategy to afford the corresponding secondary alcohols (*S*)–**10b**, **c** and (*R*)–**10d**, **e** in 57–80% enantiomeric purities (table 2).

Although the results are not as encouraging as in the case of diamine (**3**)[15] these results certainly throw

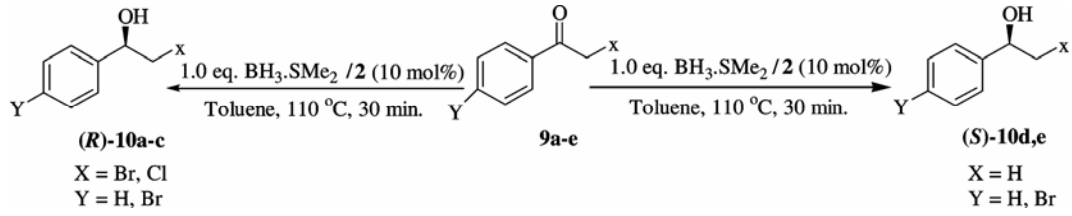
**Table 2.** Asymmetric reduction of representative ketones by catalytic source **1**[a].




| Substrate | X | Y | Product and conf.[b] | Yield (%)[c] | $[\alpha]_D^{25}$ | *ee* (%) |
|---|---|---|---|---|---|---|
| **9a** | Br | H | (*S*)-**10a**[30] | 86 | +32·6 (*c* 0·9, $CHCl_3$) | 80[d] |
| **9b** | Cl | H | (*S*)-**10b**[30] | 83 | +37·2 (*c* 0·8, $C_6H_{12}$) | 72[d] |
| **9c** | Br | Br | (*S*)-**10c**[31] | 81 | +27·5 (*c* 0·9, $CHCl_3$) | 79[e] |
| **9d** | H | H | (*R*)-**10d**[32] | 84 | +23·5 (*c* 0·8, MeOH) | 57[d] |
| **9e** | H | Br | (*R*)-**10e**[33] | 83 | +21·5 (*c* 0·5, $CHCl_3$) | 59[e] |

[a]All reactions were carried out on 1 mM scale of ketone with $BH_3{\cdot}SMe_2$ (1 mM) in the presence of the catalyst **1** (10 mol%) in toluene for 30 min at 110°C
[b]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules
[c]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes)
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H

**Table 3.** Asymmetric reduction of representative ketones by catalytic source **2**[a].




| Substrate | X | Y | Product and conf.[b] | Yield (%)[c] | $[\alpha]_D^{25}$ | *ee* (%) |
|---|---|---|---|---|---|---|
| **9a** | Br | H | (*R*)-**10a**[30] | 84 | –33·2 (*c* 0·5, $CHCl_3$) | 81[d] |
| **9b** | Cl | H | (*R*)-**10b**[30] | 83 | –36·1 (*c* 0·3, $C_6H_{12}$) | 77[d] |
| **9c** | Br | Br | (*R*)-**10c**[31] | 83 | –24·3 (*c* 0·7, $CHCl_3$) | 76[e] |
| **9d** | H | H | (*S*)-**10d**[32] | 86 | –25·3 (*c* 0·7, MeOH) | 62[d] |
| **9e** | H | Br | (*S*)-**10e**[33] | 85 | –24·6 (*c* 1·2, $CHCl_3$) | 70[e] |

[a]All reactions were carried out on 1 mM scale of ketone with $BH_3{\cdot}SMe_2$ (1 mM) in the presence of **2** (10 mol%) in toluene for 30 min at 110°C
[b]Absolute configuration was assigned by comparison of the sign of specific rotation with that of the reported molecules
[c]Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes)
[d]Determined by HPLC analyses using the chiral column, Chiralcel OD-H
[e]Determined by HPLC analyses using the chiral column, Chiralcel OJ-H

some light in understanding the structural aspects of the catalyst to provide more enantioselectivities. We have next turned our attention towards the application of (2*R*)-2-anilinomethylpiperidine (**2**)[29] as a catalyst in the borane-mediated reduction processes. This diamine (**2**) was prepared following the reaction sequence as described in scheme 2 starting from the (*R*)-pipecolinic acid (**12**) which was obtained via

the resolution of racemic pipecolinic acid using (*R*,*R*)-(+)-tartaric acid according to the known procedure[27]. We could obtain single crystal for the amide (**15**)[28] and confirmed the structure of amide [indirectly confirming the structure of the diamine (**2**)] by single crystal X-ray data of the corresponding amide (**15**) as its triflouroacetate (TFA) salt (figure 2)[26] [as this diamine is a liquid (low melting solid)]. We have then examined the potential of this diamine (**2**) as a possible chiral catalyst for the borane-mediated reduction of representative prochiral ketones (**9a–e**) using 10 mol% **2**, to provide the resulting secondary alcohols [(*R*)-**10a–c** and (*S*)-**10d**, **e**] in 62–81% enantiomeric purities (table 3). As expected the diamine **2** with *R*-configuration provided the resulting secondary alcohols with opposite configuration as that of the chiral diamine (**1**) and (**3**)[15] with *S*-configuration.

## 4. Conclusion

From these it is clear that the chiral diamines (3*S*)-3-anilinomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) and (2*R*)-2-anilinomethylpiperidine (**2**) are inferior to (2*S*)-2-anilinomethylpyrrolidine (**3**) in these reduction procedures. Although we can not generalize, on the basis of these two catalysts, that all six membered ring catalysts provide inferior selectivities than the corresponding five membered ring catalysts these studies certainly throw some light on the understanding of the structural framework of diamine catalysts which actually play a key role to provide high enantioselectivities. Our studies are in progress in understanding these structural aspects of the diamine-based catalysts with a view to have high enantioselectivities.

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