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THIAZABOROLIDINES AND BH_3 ADDUCTS DERIVED FROM THIOEPHEDRINES

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ABSTRACT: The synthesis of 1,3,2-thiazaborolidine and 2,3-dihydro-2,1,3-borathiazolidines from reaction of ephedrine disulfide and 3,4-dimethyl-5-phenyl-1,3-thiazolidine-2-thione with BH_3-THF is reported. The two reactions afforded optically active borohydride heterocycles. The X-ray diffraction structure of (1R,2R)-(−)-chlorodeoxy-*pseudo*-ephedrine hydrochloride, (1R,2R)-(−)-thiosulfonic deoxy-*pseudo*-ephedrine and (3S,4R,5R)-(+)-2,3-dihydro-3,4-dimethyl-5-phenyl-2,1,3-borathiazolidine are reported.

We have been involved in the syntheses and structural analyses of chiral borohydride compounds[1-3]. Recently, we reported the synthesis of N-alkyloxazaborolidines **1-3** derived from ephedrines[4-5] (Figure 1). Now, we are interested in studying the analogous compounds made from thioephedrines and herein, we report several borohydride compounds derived from thioephedrine (compounds **9-15**) following the syntheses depicted in Scheme 1.

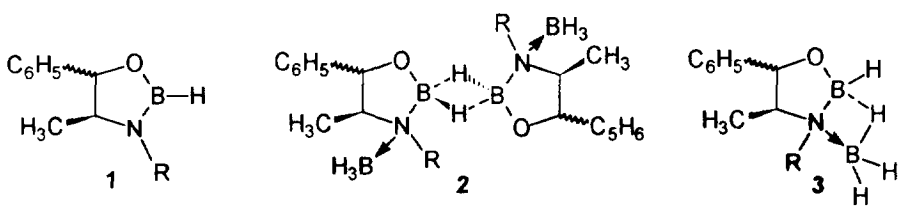
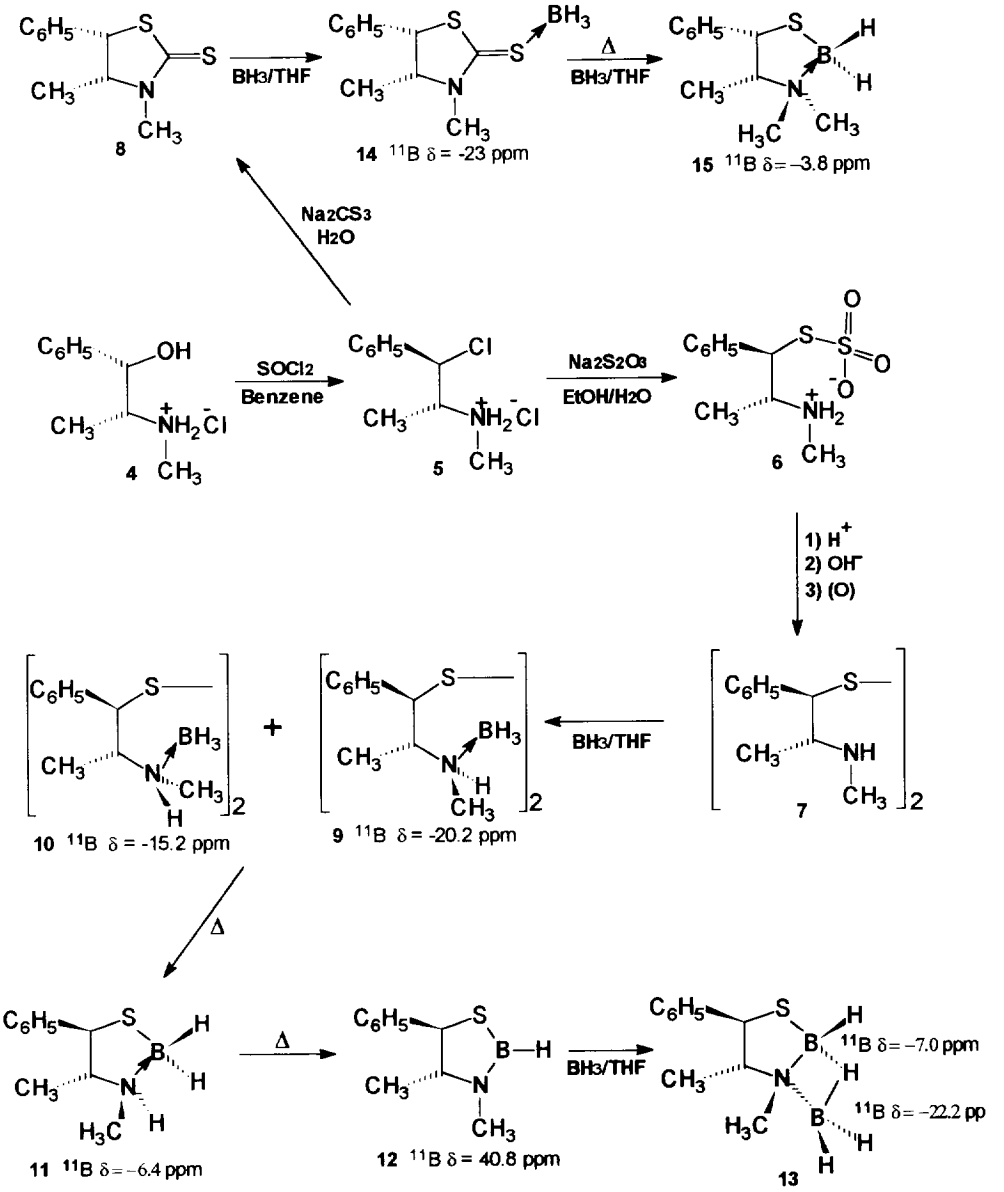


Figure 1

Compounds **5** and 6 were crystallized and the diffraction structures were obtained as described in Figures 2 and 3 respectively, data are in Table. Chlorination reaction occurs with epimerization at C1 as it was deduced from the NMR data and solid state structure. The substitution reaction of chloride by the sulfate group has been done with retention of the C1 configuration. The reaction of disulfide **7** with BH_3-THF produces the amine boranes **9** and **10** which were identified by ^{11}B NMR and compared with the N-BH_3 adducts of *pseudo*-ephedrine[5]. Compounds **9** and **10** are N-epimers of stable nitrogen


BH3/THF
Δ
BH3/THF
14 11B δ = -23 ppm
15 11B δ = -3.8 ppm
8
Na2CS3
H2O
SOCl2
Benzene
Na2S2O3
EtOH/H2O
4
5
6
1) H+
2) OH-
3) (O)
7
BH3/THF
10 11B δ = -15.2 ppm
9 11B δ = -20.2 ppm
Δ
Δ
BH3/THF
11 11B δ = -6.4 ppm
12 11B δ = 40.8 ppm
13
11B δ = -7.0 ppm
11B δ = -22.2 pp

Scheme 1

configuration. Heating the N-epimers mixture affords exclusively the borinic ester **11** which appears as a triplet (δ= –6.4 ppm, J(BH)= 103 Hz, in $CDCl_3$ or δ= –4.5 ppm, in THF-d_8) in the ^{11}B NMR spectra. The ^{1}H and ^{13}C NMR data of heterocycle **11** allow us to assign the configuration at the nitrogen atom. This N-epimer **11** has the two methyl groups in the *trans* position. It is important to mention that borinic esters with a BH_2 group derived from ethanolamines are not stable compounds as we have observed in our experiments. In fact, elimination of H_2 slowly transformed compound **11** into compound **12**.

Compound **12** presents a doublet (δ= +40.8 ppm, J(BH)= 154 Hz) in the ^{11}B NMR spectrum. From a distilled mixture (**11**, 10% and **12**, 90%), which had been crystallized, a crystal of compound **11** was separated and its X-ray diffraction structure obtained (Figure 4).

Compound **11** has an envelope conformation with the C-5 atom out of the plane. The N-B bond distance is 1.58(1) Å and B-S of 1.922(9) Å. Boron and nitrogen atoms are tetrahedral. The configuration at nitrogen atom is in agreement with an "S" configuration, as deduced from the ^{1}H and ^{13}C NMR data. The methyl groups are in a *trans* rearrangement. The angles around the nitrogen atom are close to those of a sp^3 hybridation, C4-N3-C13 112.3(5)°, B2-N3-C13 111.3(5)° and C4-N3-B2 112.0(5)°.

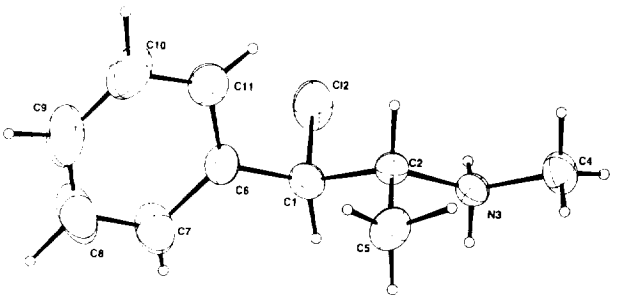


Figure 2. X-Ray diffraction structure of compound **5**.

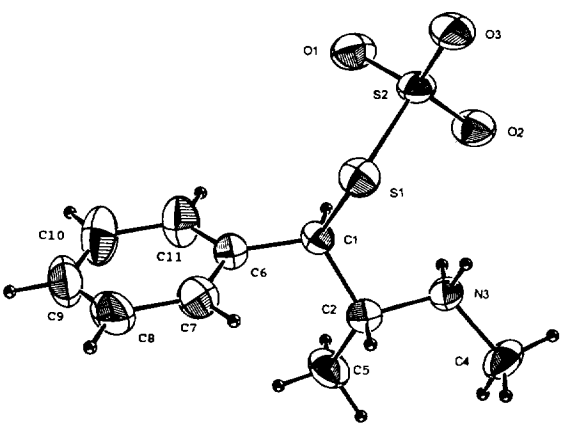


Figure 3. X-Ray diffraction structure of compound **6**.

The reaction of the thiazaborolidine **12** with BH_3-THF afforded a N-BH_3 adduct **13** (Scheme 1). The structure has been deduced from the ^{11}B NMR data, which indicated a N-BH_3 bond (quadruplet at δ= −22.0 ppm, J(BH)= 71 Hz) and a doublet which is strongly shifted to lower frequencies (δ= −7.0, J(BH)= 148 Hz). This indicates the formation of a diborane group, in which a hydrogen atom from the N-BH_3 adduct is bridging the boron atom of the heterocyclic. This is a behaviour similar to that found in the *pseudo*-ephedrine oxazaborolidine[4].

Table: Interatomic distances (Å) and bond angles (deg.)

Compound 5					
Cl(2) - C(1)	1.815(4)	C(1) - C(6)	1.489(6)	C(1) - C(2)	1.518(5)
N(3) - C(4)	1.478(5)	N(3) - C(2)	1.498(5)	C(2) - C(5)	1.503(5)
C(2) - N(3) - C(4)	114.9(4)	C(1) - C(2) - C(5)	111.4(4)	C(2) - C(1) - C(6)	114.2(4)
Cl(2) - C(1) - C(6)	109.7(3)	Cl(2) - C(1) - C(2)	108.8(3)	N(3) - C(2) - C(5)	110.2(4)
N(3) - C(2) - C(1)	109.4(4)				
Compound 6					
S(1) - S(2)	2.0868(9)	S(1) - C(1)	1.843(3)	C(2) - C(5)	1.520(4)
S(2) - O(1)	1.456(2)	N(3) - C(2)	1.496(3)	C(1) - C(2)	1.538(3)
S(2) - O(2)	1.445(2)	N(3) - C(4)	1.480(3)	C(1) - C(6)	1.500(4)
S(2) - O(3)	1.448(2)				
S(1) - S(2) - O(1)	106.04(9)	O(2) - S(2) - O(3)	115.2(1)	C(2) - C(1) - C(6)	113.2(1)
S(1) - S(2) - O(2)	107.05(8)	S(2) - S(1) - C(1)	99.69(8)	N(3) - C(2) - C(1)	107.7(2)
S(1) - S(2) - O(3)	101.76(8)	C(2) - N(3) - C(4)	116.1(2)	N(3) - C(2) - C(5)	110.1(2)
O(1) - S(2) - O(2)	111.8(1)	S(1) - C(1) - C(2)	109.6(2)	C(1) - C(2) - C(5)	113.2(2)
O(1) - S(2) - O(3)	113.7(1)	S(1) - C(1) - C(6)	110.1(2)		
Compound 11					
S(1) - C(5)	1.836(6)	C(4) - C(12)	1.503(9)	C(4) - C(5)	1.543(8)
N(3) - C(4)	1.472(7)	S(1) - B(2)	1.922(9)	C(5) - C(6)	1.481(8)
N(3) - B(2)	1.58(1)	N(3) - C(13)	1.507(9)		
C(5) - S(1) - B(2)	94.8(3)	S(1) - C(5) - C(6)	112.7(4)	S (1) - C(5) - C(4)	106.4(4)
C(4) - N(3) - B(2)	112.0(5)	C(4) - N(3) - C(13)	112.3(5)	C(4) - C(5) - C(6)	113.5(5)
N(3) - C(4) - C(5)	106.5(5)	C(13) - N(3) - B(2)	111.3(5)	S(1) - B(2) - N(3)	101.7(5)
C(5) - C(4) - C(12)	112.3(5)	N(3) - C(4) - C(12)	113.9(5)		

Reaction of compound **5** with trithiocarbonate in ethanol afforded the thiazolidine-2-thione **8** which has been isolated and characterized and its reactivity towards BH_3-THF studied, Scheme 1. The reaction has been followed by ^{11}B NMR and the first product detected was the S-BH_3 adduct **14** (δ= −23 ppm, broad signal). The ^1H NMR spectrum of compound **14** indicates that BH_3 is not linked to the intracyclic sulfur atom because there is no effect on the ^1H chemical shift at the hydrogen near to this sulfur atom. Heating

heterocycle **14** afforded the cyclic species S-BH_2-N **15** which presented a triplet at δ= –3.8 ppm (J(BH)= 111.5 Hz). This compound **15** was obtained pure when **8** was treated with 3 equivalents of BH_3-THF. The ^1H and ^{13}C NMR were recorded and the data is shown in Figure 5. Two diasterotopic N-methyl groups show that the nitrogen has a stable configuration, the assignment of the ^1H and ^{13}C signals were done based on steric effects and by comparison with similar compounds[1,5].

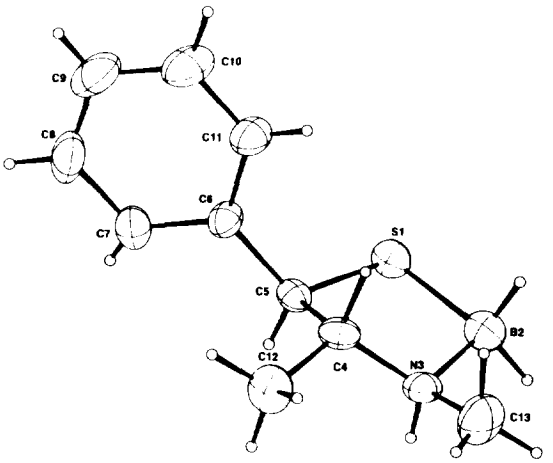


Figure 4. X-Ray diffraction structure of compound **11**.

CONCLUSIONS

The investigation of the reaction of two ephedrines derivatives, **7** and **8**, and BH_3-THF allow us to identify and characterize three optically active borohydride heterocycles, **11**, **12** and **15**. The dihydroborathiazolidines **11** and **15** allowed us to study five membered rings with an intracyclic BH_2 group these heterocycles contrast with the analogues dihydroboraoxazolidines which we could not isolate, being observed only as fleeting species[4,5]. All of these borohydrides could be candidates as chiral catalyst reagents.

EXPERIMENTAL

NMR spectra were recorded by using the frequency of 270 for ^1H and 67.8 MHz for ^{13}C with TMS as an internal reference and 86.55 MHz for ^{11}B with BF_3-OEt_2 as external reference. Mass spectra were recorded on a Hewlett Packard 5989 mass spectrometer. Melting points are uncorrected. Computation for compound **6** was performed by using MOLEN[9] adapted for a Micro Vax II, while computation for compounds **5** and **11** were performed by using CRYSTALS[10] adapted for an Acer View 56 L.

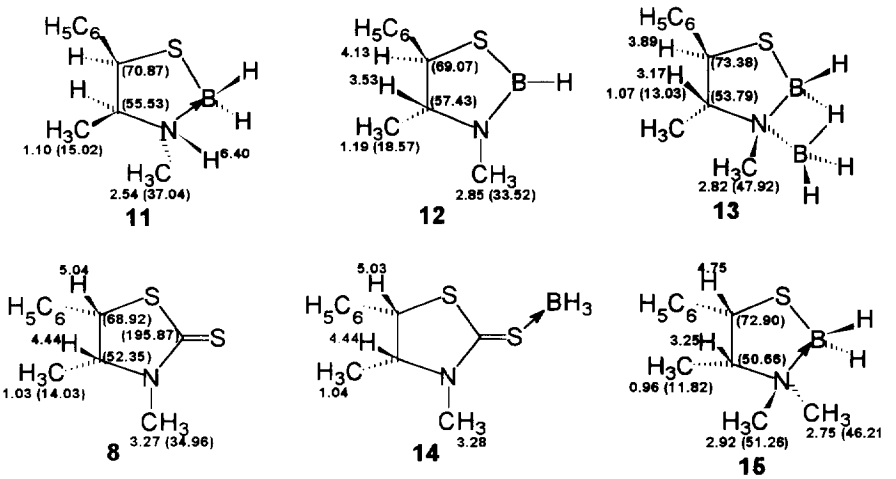


Figure 5. Chemical shifts data of ^{1}H and ^{13}C NMR of compounds **8**, **11-15**.

Compounds **5**[6], **6**[7] and **7**[8] were prepared as described in the literature. Their data follows. (1R,2R)-(−)-*Chlorodesoxy-pseudo-ephedrine hydrochloride*, **5**. M.p. 198-200°C. ^{1}H NMR (DMSO-d_6) δ(ppm) 7.45(m, 5H, C_6H_5), 5.45(d, ^{3}J = 9.4, 1H, Cl-C<u>H</u>), 3.96(m, 1H, N-C<u>H</u>), 2.60(s, 3H, N-C<u>H</u>$_3$), 1.05(d, ^{3}J = 6.6, 3H, C-C<u>H</u>$_3$). ^{13}C NMR (DMSO-d_6) δ(ppm) 137.08(1C, C*i*), 129.16(1C, C*p*), 128.90(2C, 2C*o*), 127.85(2C, 2C*m*), 62.23(1C, C1), 58.20(1C, C2), 29.10(1C, C4), 12.82(1C, C3). Mass *m/e* 146{$[M^{+}$-HCl$]^{+}$, 100%}. $[\alpha]_D$ = −122.3 (c = 0.04, H_2O). Crystal data: Formula, $C_{10}H_{15}NCl_2$; fw, 220.14; space group, $P2_1$; a (Å) = 7.357(1); b (Å) = 7.077(8); c (Å) = 11.413(2); α = 90; β = 90.45(1); γ = 90; V (Å^3) = 594.2(1); Z, 2; F(000), 232; crystal dimensions(mm), 0.40x0.40x0.30; linear abs coeff cm^{-1}, 5.06; ρ (calc) g cm^{-3}, 1.23; scan type, ω/2θ; scan range (°), 0.63 + 0.49 tg θ; θ limits (°),1 - 25; octants collected, -8,8 ; 0,8 ; 0,13; data collected, 1197; unique data collected, 1135; unique data used, $989(F_0)^2>3\sigma\ (F_0)^2$; R(int), 0.44; decay %, <1; absortion correction, DIFABS(0.77min,1.18max); $R=\Sigma||F_0| - |Fc||)/\Sigma|F_0|$, 0.035; $R_w=[\Sigma w(|F_0||F_c|)^2/\Sigma wF_0^2]^{1/2}$, 0.033 w = 1.0; Goodness of fits, 2.60; no. of variables, 73; Δρmin (e/Å^3), -0.27; Δρmax (e/Å^3), 0.19.

(1R,2R)-(−)-Thiosulfonic deoxy-pseudo-ephedrine acid, **6**. M.p. 165-166°C. ^{1}H NMR (DMSO-d_6) δ(ppm) 7.35(m, 5H, C_6H_5), 4.48(d, ^{3}J = 6.0 Hz, 1H, S-C<u>H</u>), 3.85(m, 1H, N-C<u>H</u>), 2.66(s, 3H, N-C<u>H</u>$_3$), 1.05(d, ^{3}J = 6.6 Hz). ^{13}C NMR (DMSO-d_6) δ(ppm) 138.2(1C, C*i*), 128.6(2C, C*o*), 128.05(2C, C*m*), 127.6(1C, C*p*), 58.48(1C, C2), 54.1(1C, C1), 30.45(1C, C4), 13.2(1C, C3). $[\alpha]_D$ = −146.3 (c = 0.041, H_2O). Crystal data: Formula, $C_{10}H_{15}NO_3S_2$; fw, 231.36; space group, P-1; a (Å) = 7.837(1); b (Å) = 8.601(1); c (Å) = 19.104(1); α = 93.21(5); β = 93.09(5); γ = 92.53(6); V(Å^3) = 1282.3; Z, 4; F(000), 552; crystal dimensions(mm), 0.30x0.20x0.40; linear abs coeff cm^{-1}, 3.9; ρ (calc) g cm^{-3}, 1.35; scan type, ω/2θ; scan range (°), 0.5 + 0.83 tan θ; θ limits (°),1 - 20; octants collected, 0,7;-7,7;-17,17; data collected, 4331; unique data collected, 4331; unique data used, $3863(F_o)^2>3\sigma(F_o)^2$; R(int), 0.040; decay

%, <1; $R=\Sigma||F_0| - |Fc||)/\Sigma|F_0|$, 0.040; $R_w=[\Sigma w(|F_0||F_c|)^2/\Sigma wF_0^2]^{1/2}$, 0.040 w = 1.0; no. of variables, 409; Δρmin (e/Å^3), -0.1; Δρmax (e/Å^3), 0.08.

(1R,2R)-(−)-Deoxy-pseudo-ephedrine disulfide, 7. ^{1}H NMR ($CDCl_3$) δ(ppm) 7.23(m, 5H, $C_6\underline{H}_5$), 3.59(d, ^{3}J = 8.57, 1H, S-C<u>H</u>), 3.06(m, 1H, N-C<u>H</u>), 2.40(s, 3H, N-C<u>H</u>$_3$), 0.94(d, ^{3}J = 6.6 Hz, 3H, C-C<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$) δ(ppm) 139.08(1C, C*i*), 128.89(2C, C*o*), 128.38(2C, C*m*), 127.58(1C, C*p*), 60.81(1C, C1), 57.84(1C, C2), 33.02(1C, C4), 16.8(1C, C3). $[\alpha]_D = -132.9$ (c = 0.034, $CHCl_3$).

(4R,5S)-(+)-3,4-Dimethyl-5-phenylthiazolidine-2-thione, 8. Preparation of compound **8** by an different method has been reported[7]. (1R, 2R)-(-)-Chlorodeoxy-*pseudo*-ephedrine hydrochloride **5** (0.5 g, 2.27 mmol) was dissolved in 10 mL of ethanol. A 33% solution of trithiocarbonate (1.3 mL, 2.78 mmol) was refluxed for 3 h and the ethanol was evaporated. The thiazolidine-2-thione **8** was extracted with chloroform, dried with anhydrous sodium sulfate, filtered and crystallized in $CHCl_3$. M.p. 78°C. Mass *m/e* 223 {[M^+], 100%}. $[\alpha]_D = +28.43$ (c = 0.089, H_2O).

(3S,4R,5R)-2,3-Dihydro-3,4-dimethyl-5-phenyl-2,1,3-borathiazolidine, 11 and (4R,5R)-(+)-3,4-dimethyl-5-phenyl-1,3,2-thiazaborolidine, 12. A borane-THF solution (3.3 mL, 1.95 M, 6.4 mmol) was added dropwise to deoxy-pseudo-ephedrine disulfide **7** (1.15 g, 3.2 mmol) in THF (5 mL). The mixture was refluxed 3 h and the THF was evaporated and the residue was analysed by ^{11}B, ^{13}C and ^{1}H NMR. It was a mixture of dihydroborathiazolidine **11** (75.4%) and borathiazolidine **12** (15%); the data is shown in Figure 5. Compound **11** is not stable. By standing, it was slowly transformed into compound **12**. The mixture was distilled at 100°C and 1 mm Hg. A crystal was separated from the crystalline distillate (0.45 g, 95% ; 90% of **12** and 10% of **11**) and the X-ray diffraction study of compound **11** was obtained. Compound **12** M.p. 163°C with decomposition. Mass *m/e* 191{[M^+], 57%}, 176 {[M^+-CH_3]$^+$, 100%}. $[\alpha]_D = +67.3$ (c = 0.055, THF). Crystal data: Formula, $C_{10}H_{16}BNS$; fw, 193.11; space group, $P2_1$; a (Å) = 6.3021(3); b (Å) = 7.5550(2); c (Å) = 11.8448(9); α = 90.00; β = 98.65(1); γ = 90.00; V (Å^3) = 556.7(3); Z, 2; F (000), 208; crystal dimensions(mm), 0.30x0.40x0.40; linear abs coeff cm^{-1}, 2.34; ρ (calc) g cm^{-3}, 1.15; scan type, ω/2θ; scan range (°), 0.52 + 1.09tgθ; θ limits (°), 2.13 - 25; octants collected, 0,7 ; 0,8 ; -14,13; data collected, 1151; unique data collected, 1056; unique data used, 712 $(F_0)^2 > 2\sigma (F_0)^2$; R(int), 3.79; decay %, <1; absortion correction, DIFABS (0.69min,1.4max); $R=\Sigma||F_0| - |Fc||)/\Sigma|F_0|$, 0.039; $R_w=[\Sigma w(|F_0||F_c|)^2/\Sigma wF_0^2]^{1/2}$, 0.040 w= 1.0; Goodness of fit s, 2.72; no. of variables, 130; Δρmin (e/Å^3), -0.23; Δρmax (e/Å^3), 0.35.

(3S,4R,5R)-3-Borane-3,4-dimethyl-5-phenyl-1,3,2-thiazaborolidine, 13. To dimethyl-5-phenylthiazaborolidine **12** (0.073 g, 0.38 mmol) in THF (5 mL) was added BH_3-THF in solution 1.95 M (0.2 mL, 0.38 mmol) and the reaction was kept at 45° for 12 hours. The reaction was followed by ^{11}B NMR. Data of ^{11}B, ^{13}C and ^{1}H NMR have been discussed in the text.

(4R,5S)-3,4-Dimethyl-5-phenylthiazolidine-2-thione S-BH_3 adduct 14 and (4R,5S)-2-hydro-3,3,4-trimethyl-5-phenyl-2,1,3-borathiazolidine 15. A solution of 1.95 M of BH_3-THF (0.15 mL, 3.31 mmol) was added dropwise to a solution of compound **8** (0.07 g, 0.66 mmol) in 0.5 mL of THF and the reaction followed by ^{11}B NMR. The reaction product **14** was not isolated but it was characterized by ^{11}B and ^{1}H NMR, see figure 5. To the reaction mixture, 2 equivalents of the borane solution were added

(0.68 mL, 1.32 mmol) and the solution was heated for 3 h. After, the solvent was evaporated compound **15** was obtained as a viscous liquid, which was characterized by NMR, data are in figure 5.

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