Tetrahedron: Asymmetry Vol. 3, No. 11, pp. 1441-1453, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Quantum Chemical Modeling of Chiral Catalysis. Part 7. On the Effects Controlling the Coordination of Borane to Chiral Oxazaborolidines Used as Catalysts in the Enantioselective Reduction of Ketones

Vesa Nevalainen

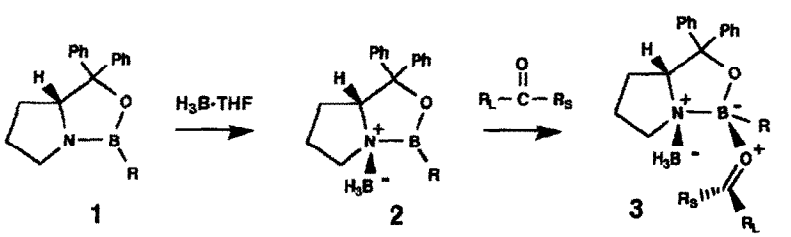
University of Helsinki, Department of Chemistry, Vuorikatu 20, SF-00100 Helsinki, Finland

(*Received* 22 *September* 1992)

Abstract: - Oxazaborolidine derivatives (1'a-e) of 2-aminoethanol, *N*-methyl-2-aminoethanol, 2-aminopropanol, 2-hydroxymethylpyrrolidine and 2-azabicyclo[3.3.0]octan-8-ol and their borane adducts (2'a-e) were investigated by means of *ab initio* molecular orbital methods. Energies (6-31G//6-31G) of the formation of adducts (2'd-e) of fused / bridged oxazaborolidines in which there was a partial B=N double bond at the ring fusion were about 20 kJ mol^{-1} more negative than those (2'a-c) of simple oxazaborolidines. Formation of the *cis*-adduct of borane to the oxazaborolidine derivative of 2-aminopropanol was only 5 kJ mol^{-1} (6-31G//6-31G) favoured over that of the corresponding *trans*-adduct. Formation of the *cis*-fused borane adduct of the oxazaborolidine derivative of 2-azabicyclo[3.3.0]octan-8-ol was found to be about 50 kJ mol^{-1} (6-31G//6-31G) more advantageous than that of the corresponding *trans*-fused adduct.

INTRODUCTION

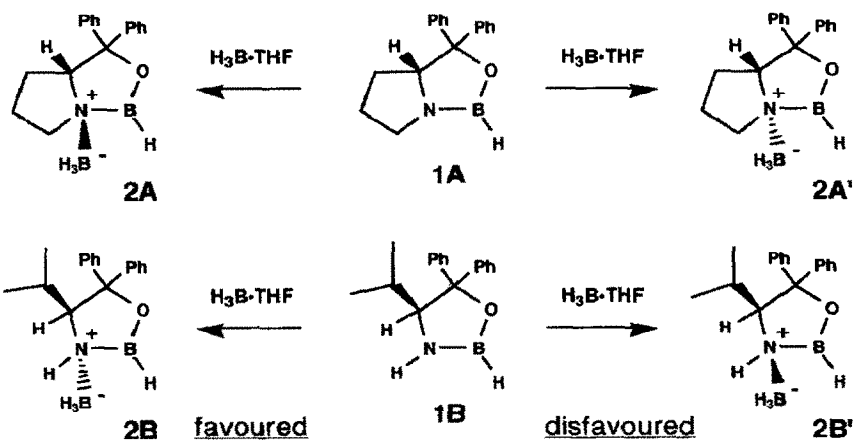
Five years after the discovery of the mechanism of action of chiral oxazaborolidines **1** in the catalytic enantioselective reduction of ketones (the CBS reduction)[1] the number of applications of oxazaborolidine derivatives and other related systems still appears to be growing.[2-5] Modifications of the original CBS method[2] with respect to the method of preparation[2a,2g] or the structure of the catalysts,[2b-c,2e,2h-j,2l-m] and even with respect to the purpose of use of the catalyst,[2f,2k] have been reported in the literature. Not surprisingly, many natural products, therapeutically important molecules, as also related intermediates, have been synthesized by applying the CBS reduction.[1,2d,3] New efficient syntheses for entire categories of organic molecules have been developed on the basis of the CBS method.[3c,3f,4] One of the latest interests in the development of oxazaborolidine catalysts appears to be the asymmetric Diels-Alder reaction.[5]



The mechanism of CBS reduction[1] has been suggested to involve the formation of borane adduct **2**. The borane coordinated to the nitrogen of oxazaborolidine increases the Lewis acidity of the adjacent ring boron, facilitating the coordination of the ketone to be reduced (**2** -> **3**). A hydride transfer from the borane moiety to the carbonyl-*C* in **3** (followed by a number of steps involved in the regeneration of the catalyst) gives rise to the formation of the alcohol $R_LR_SC(OH)H$ (as a dialkoxyborane derivative) in high enantiomeric excess.[1] The formation of **2** has been recently confirmed by Corey *et al* by determining the three dimensional structure of the enantiomer of **2** ($R=CH_3$) by means of X-ray crystallography.[6] Mechanistic details of the catalysis have been lately investigated also by using *ab initio* molecular orbital calculations.[7]

In reports describing the mechanism of CBS reduction[1] Corey *et al* have compared the performance of **1A** (see Scheme I) and another oxazaborolidine catalyst (**1B**) of which the use as "a black-box catalyst" had been reported earlier by Itsuno *et al*.[8] If the performance of **1A** and **1B** is considered in the light of the mechanism of reduction it can be seen that coordination of the borane used as a source of hydrogen should lead selectively to the formation of single diastereomeric adduct **2A** (Scheme I); i.e. if the other diastereomer (**2'A**) would be formed, and if it would perform the entire catalytic cycle in the same way as **2A**, no enantioselectivity would be observed. However, because the ring system of **2A** is *cis*-fused, and consequently less strained,[9] the formation of **2A** should be energetically much more advantageous than that of the corresponding *trans*-fused system **2A'**. The formation of **2A** should be favoured also because the convex side of the ring system of **1A** is less sterically crowded than the concave one. Therefore, one could predict merely the borane adduct **2A** to be present under conditions of a CBS reduction when **1A** is used as a catalyst. It is not obvious whether one could expect the same behaviour in the case of **1B**.

Scheme I



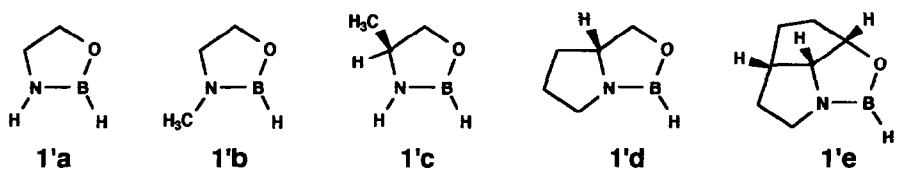
As also **1B** has been observed to function as a chiral catalyst, even though the ring system of **1B** (Scheme I) is different from that of **1A**, one could predict that either the formation of **2B** would be much favored over that of **2B'** (Scheme I), or further reactions of **2B'** as a catalyst for the reduction of ketones would be substantially slower than those of **2B**. On the basis of a comparison of plausible structures of diastereomers **2B** and **2B'** one could predict the formation of **2B** to be favoured over that of **2B'**, mostly because of steric crowding attributable to the arrangement of the adjacent isopropyl and BH_3 groups *cis* about the ring of **2'B**.

In addition to the stereochemistry of formation of these adducts, the energetics of coordination of borane to oxazaborolidines could be affected by ring strain, and particularly, as pointed out by Corey *et al*,[1a] strain of the B=N π-bond at the ring fusion of **1A** (see Scheme II) . As borane coordinates to the nitrogen at the ring fusion the angle strain would be released. Consequently, also more energy should be released in the coordination of borane to **1A** than in the corresponding reaction of **1B**. On the other hand, on the basis of a comparison of oxazaborolidines (fused to a 4-, 5- or 6-membered carbocyclic ring) as catalysts in the enantioselective reduction of ketones, Rao *et al* have suggested[2c] that the rigidity of the ring system of the catalyst could be more important than ring strain for good performance of the catalyst. Other reasons why rigidity of the ring system of the catalyst could be important have been discussed in part IV of reports of this series.[7d] Altogether, not much appears to be known about the relative energies of the coordination processes occurring in oxazaborolidines embedded in different carbocyclic frameworks.

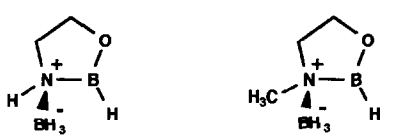
On the basis of common rules of organic chemistry, one could conclude that the diastereoselectivity of the formation of borane adducts of systems analogous to **1A** would be affected by both ring strain effects and the steric crowding that the coordinating borane encounters on different sides of the oxazaborolidine ring whereas in the case of systems analogous to **1B** steric crowding effects would dominate. The aim of this work was to evaluate the above hypotheses, compare structural properties of systems analogous to **1A/1A'** and **2A/2A'** and estimate relative energies of the formation of diastereomeric pairs analogous to **2A/2A'** and **2B/2B'** by means of *ab initio* molecular orbital methods. In addition, an evaluation of the ring strain and of conformational and substituent effects controlling the stereochemistry of the formation of borane adducts was attempted.

MODELS AND COMPUTATIONAL METHODS

Standard *ab initio* molecular orbital calculations were carried out by using the Gaussian 80 series of programs at the 3-21G, 4-31G, 6-31G, 4-31G* and 6-31G* levels.[10] Modeling techniques similar to those applied in the case of previous reports of this series[7] were employed, i.e. simple models analogous to the actual catalytically active systems were examined. The structures **1'a-e** were used as models of oxazaborolidine catalysts (**1**) and **2'a-e**, **2'c'**, **2'd'** as models of borane adducts (**2**).



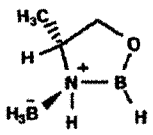
1'a **1'b** **1'c** **1'd** **1'e**



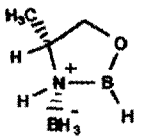
2'a **2'b**

Models consisting of eight or more atoms other than hydrogen were best studied at the 6-31G level (polarization functions were not used because inclusion of *d*-functions would have given rise to extremely time demanding calculations) whereas the others were calculated at the 6-31G* level at best. No other calculations on the structures **1'b-c**, **1'e**, **2'b-c**, **2'e** or **2'c'-d'** appeared to have been published. Properties of the models **1'a**,

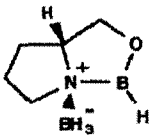
1'd, **2'a** and **2'd** have been discussed in the literature[7] (the models **1'd** and **2'd** have been only briefly mentioned in preliminary reports of this series[7h-i,7k]).



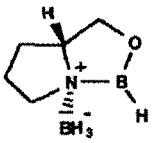
2'c



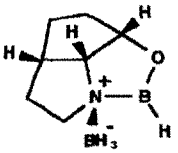
2'c'



2'd



2'd'



2'e

RESULTS AND DISCUSSION

Total energies and dipole moments calculated are summarized in Table 1. Optimized (6-31G//6-31G) structures of 4-methyl oxazaborolidine (**1'c**), bicyclic **1'd** and tricyclic **1'e** are shown in Figure 1. Optimized structures (6-31G*//6-31G*) of borane adducts of 4-methyl oxazaborolidine (**2'c** and **2'c'**) are shown in Figure 2 whereas optimized (6-31G//6-31G) structures of the borane adducts of bi- and tricyclic systems (**2'd** and **2'e**) are depicted in Figure 3. Selected bond lengths, atomic and group charges and HOMO / LUMO energies calculated at the 6-31G level are summarized in Table 2. Selected torsion angles (6-31G//6-31G) of all the optimized structures are collected in Table 3. Energies of the formation of borane adducts **2'a-e**, **2'c'** and **2'd'** are shown in Table 4.

Table 1. Total energies and dipole moments of oxazaborolidines **1'a-e** and borane adducts **2'a-e**, **2'c'** and **2'd'**.[a]

Structure	3-21G//3-21G		4-31G//4-31G		6-31G//6-31G		4-31G*//4-31G*		6-31G*//6-31G*	
	E[a]	D[a]	E	D	E	D	E	D	E	D
1'a	-232.01452	3.16	-232.95883	3.18	-233.19703	3.21	-233.07225	2.65	-233.29859	2.67
1'b	-270.82727	3.09	-271.92786	3.14	-272.20638	3.17	-272.06448	2.52	-272.32902	2.54
1'c	-270.83815	3.20	-271.94089	3.23	-272.21968	3.26	-272.07235	2.67	-272.33700	2.69
1'd	-347.30477	3.36	-348.71702	3.44	-349.07697	3.49	-	-	-	-
1'e	-423.79408	3.20	-425.51558	3.29	-425.95597	3.33	-	-	-	-
2'a	-258.28393	5.22	-259.32696	4.93	-259.59052	4.89	-259.45727	4.98	-259.70944	4.97
2'b	-297.09723	5.14	-298.29516	4.89	-298.59875	4.83	-298.44693	4.83	-298.73743	4.80
2'c	-297.10587	5.62	-298.30734	5.32	-298.61167	5.20	-298.45521	5.34	-298.74573	5.32
2'c'	-297.10391	5.38	-298.30544	5.09	-298.60995	5.03	-298.45420	5.09	-298.74473	5.06
2'd	-373.58165	6.06	-375.09120	5.84	375.47586	5.80	-	-	-	-
2'd'	-373.56097	5.46	-375.07171	5.24	-375.45681	5.20	-	-	-	-
2'e	-450.07093	6.23	-451.89099	6.00	-452.35700	5.99	-	-	-	-

[a] Total energies (E) given in hartrees and dipole moments (D) in debye.

Oxazaborolidines

Optimized (6-31G*//6-31G*) structures of **1'a**, **1'b** and **1'c** appeared to be closely similar; e.g. lengths of the B-N and B-O bonds were within the ranges of 1.400±0.001 and 1.364±0.001 Å. Ring systems of **1'a** and **1'c** were practically planar whereas in the case of **1'b** carbons adjacent to the ring nitrogen were slightly bent out of the plane of the rest of the ring atoms. Results of calculations carried out at the 6-31G level were consistent with those done with polarization functions (at the 6-31G* level).

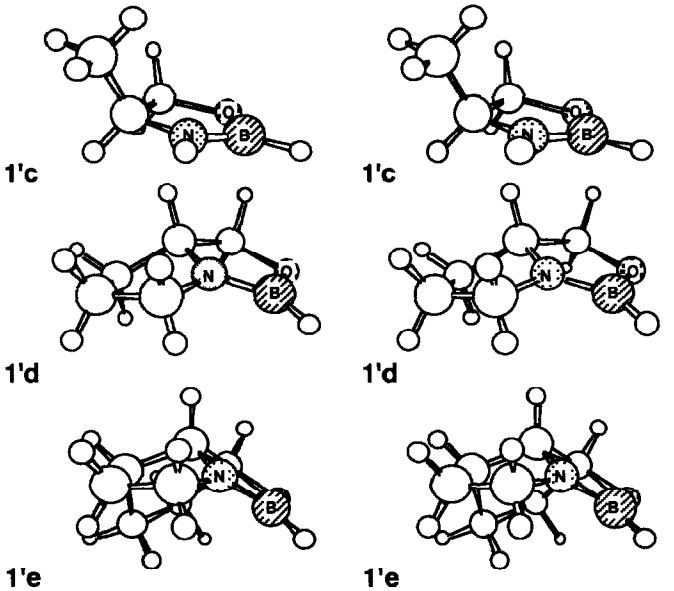


Figure 1. Stereo representations of the optimized (6-31G//6-31G) structures of oxazaborolidine derivatives **1'c**, **1'd** and **1'e**.

Table 2. Selected bond lengths, atomic and group charges and HOMO/LUMO energies of oxazaborolidines **1'a-e** and borane adducts **2'a-e**, **2'c'** and **2'd'** (6-31G//6-31G).

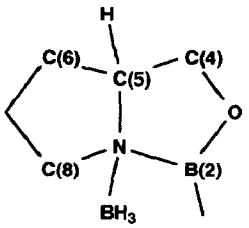
Structure	Bond lengths[a]			Charges				Orbital energies[b]	
	$N\text{-}B_{ring}$	$O\text{-}B_{ring}$	$N\text{-}B_{BH_3}$	B_{ring}	N	O	BH_3[c]	HOMO-1	LUMO-1
1'a	1.406	1.390	-	+0 828	-0.962	-0.766	-	-10.23	+5.57
1'b	1.406	1.390	-	+0.831	-0.889	-0.768	-	-9.73	+5.51
1'c	1.406	1.390	-	+0.825	-0 953	-0.767	-	-10.20	+5.55
1'd	1.404	1.396	-	+0.826	-0.883	-0.772	-	-9.66	+5.27
1'e	1.410	1.395	-	+0.834	-0.854	-0.775	-	-9.66	+5.17
2'a	1.490	1.361	1.750	+0.891	-1.034	-0.742	-0.178	-11.42	+4.06
2'b	1.495	1.359	1.748	+0.901	-0 981	-0.743	-0.173	-11.36	+4 04
2'c	1.484	1.360	1 767	+0 885	-1.046	-0.739	-0.180	-11.33	+4.10
2'c'	1.491	1.361	1.765	+0.891	-1.039	-0.745	-0.176	-11.31	+4.07
2'd	1 496	1.356	1 713	+0.892	-1 000	-0.737	-0.176	-11.06	+4.07
2'd'	1.488	1.374	1.772	+0.944	-0.996	-0.774	-0.167	-11.27	+4.08
2'e	1.495	1.359	1.715	+0.896	-0.997	-0.743	-0.183	-10.96	+4.09

[a] Bond lengths given in ångströms. [b] HOMO/LUMO energies given in eV. [c] Charge transfer to the BH_3 moiety from the oxazaborolidine system.

On the basis of inspection of bond lengths shown in Table 2 one could conclude that not only the simple oxazaborolidines (**1'a-c**) but all these molecules (**1'a-e**) are structurally closely similar (e.g. lengths of the B-N and B-O bonds in the group of **1'a-e** are within the ranges of 1.407±0.003 and 1.392±0.003 Å). A comparison of charges of **1'a-e** reveals only that neither the charge of boron, nitrogen nor oxygen will depend significantly on the nature of the hydrocarbon skeleton in which the oxazaborolidine system is embedded. Nevertheless, the charge

of nitrogen depends on the number of carbons the nitrogen is bound to [e.g. charges of the nitrogens of **1'a** and **1'c** (RNH-B systems) are closely similar; equally similar are the corresponding values of **1'b**, **1'd** and **1'e** (R_2N-B systems), see Table 2]. The same applies to the HOMO-1 values of these oxazaborolidines. The values of **1'a** and **1'c** are closely similar; and so are those of **1'b**, **1'd** and **1'e** (Table 2).

Table 3. Selected torsion angles[a] of optimized (6-31G//6-31G) structures of oxazaborolidines **1'a-e** and borane adducts **2'a-e**, **2'c'** and **2'd'**.



Structure	Torsion angles[a]							
	N-C(5)-C(4)-O	B-O-C(4)-C(5)	N-B-O-C(4)	O-B-N-C(8)	O-B-N-C(5)	B(2)-N-C(5)-C(6)	C(6)-C(5)-N-B(BH3)	O-B-N-B
1'a	-1.0	1 0	-0 4	180 0	-0 3	-	-	-
1'b	-8.0	7 2	-3.3	-179.7	-2.4	-	-	-
1'c	-0.6	0.7	0 0	179.3	0 0	-121.0	-	-
1'd	-3.7	4.8	-3.9	158 0	1.3	126.3	-	-
1'e	-8.6	9.0	-5 7	148.2	-0 3	118.6	-	-
2'a	24.7	-18.0	3 4	141.9[b]	13.0	-	-	-104.9
2'b	24 7	-18.5	4.5	139.9	11.8	-	-	-102.0
2'c	11 0	4 4	-0.3	137 3[b]	8.2	111 4	-132.0	-111 9
2'c'	25.9	11.7	1.9	142.0[b]	15 4	-149 3	-34.7	-108.3
2'd	1 2	-0.4	-0.6	121.0	1.5	120.3	-126.8	-116.6
2'd'	-34.8	21.8	0.0	-143.5	-23.2	171.6	65.7	95 0
2'e	-0 6	0 0	1.0	118.9	-1.3	115.2	-129.8	-118 9

[a] Torsion angles given in degrees [b] The value of the angle O-B-N-H shown in place of that of O-B-N-C(8)

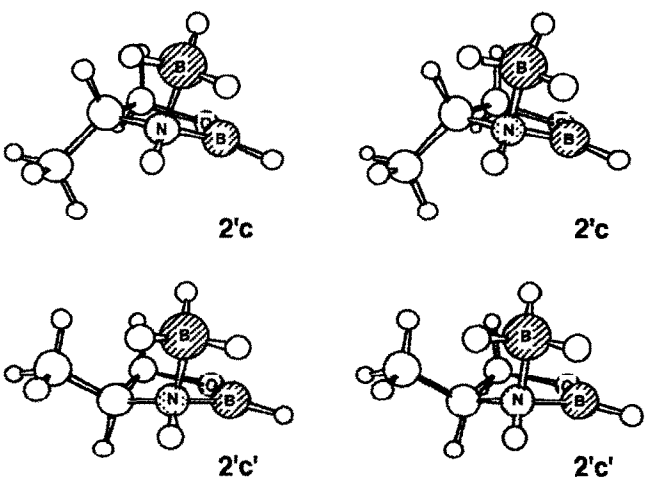
The LUMO-1 values of **1'b**, **1'd** and **1'e** imply that LUMO-1 energies would depend on the nature of the ring system fused/bridged to the oxazaborolidine ring. The LUMO-1 energies decrease slightly with the increasing amount of rings fused/bridged to the oxazaborolidine ring (i.e. Lewis acidity of the ring boron would slightly increase with the increasing ring strain). The observed change of LUMO-1 energies in the series of **1'b**, **1'd** and **1'e** is, however, much less significant than that seen to be involved in the formation of borane adducts of oxazaborolidines discussed later.

As the first step in the mechanism of CBS reduction is the coordination of borane to the nitrogen of oxazaborolidine it could be useful to study how the nitrogen of the catalyst models is bound. However, it turns out that in the case of **1'a**, **1'b** and **1'c** the ring nitrogen and all atoms adjacent to it are practically in the same plane but in the case of **1'd** and **1'e** they are not (e.g. on the basis of 6-31G calculations the ring nitrogen of **1'e** resides about 0.205 Å above the plane of atoms adjacent to it; in the case of **1'd** and **1'b** the corresponding values are 0.149 and 0.020 Å). The decrease of planarity of the geometry of ring nitrogen can be seen clearly also in the series of **1'b**, **1'd** and **1'e** as the values of torsion angle O-B(2)-N-C(8) (see Table 3) are inspected. In the case of **1'b** the angle is 179.7°, in **1'd** 158.0° and in the case of **1'e** already 148.2°. On the basis of these observations it looks as if the predicted strain of the B=N π-bond at the ring fusion could be located to the torsion angle O-B(2)-

N-C(8). This is a reasonable conclusion also in that in all **1'b**, **1'd** and **1'e** the other carbon adjacent to the ring nitrogen [C(5), Table 3] appears to stay in the O-B-N plane [e.g. the torsion angle O-B(2)-N-C(5) of these structures deviates only by 2.4° or less from 0°, Table 3]. The carbon adjacent to the ring oxygen is also bent out of the O-B-N plane but only of a few degrees [e.g. the maximum deviation of the O-B(2)-N-C(5) angle from 0° is -5.7° (in the case of **1'e**); Table 3].

Results of the above analysis of torsion angles indicate that in the fused 5,5 ring system of **1'd** (and in that of **1'e**) the lone pair of nitrogen resides on the convex side of the ring (the lone pair of ring nitrogen is *cis* to the hydrogen at the ring fusion carbon atom). Consequently, as the lone pair resides on the less sterically hindered side of the oxazaborolidine system the formation of borane adducts analogous to **2'd** should be favoured over those analogous to **2'd'**, not only because of the proposed lower energy of **2'd**, but also because of kinetic reasons. Furthermore, inversion of the ring nitrogen requiring a considerable amount of energy[9] would be needed for the formation of adducts analogous to **2'd'**.

In the light of the above analysis of torsion angles it is surprising that the bond lengths and electronic properties of **1'a-e** (Table 2) can be so similar. It looks as if forcing the ring nitrogen from a planar configuration towards a tetrahedral arrangement would hardly affect properties of the oxazaborolidine ring at all. Nevertheless, this does not mean that the ease of formation borane adducts would not be affected by these changes. Namely, the more the planarity of the ring nitrogen is disturbed the more the nitrogen would be exposed to acids (e.g. borane) able to coordinate to it.



Bond lengths & angles	2'c	2'c'	1'c
O-B	1.334	1.336	1.364
N-B_{ring}	1.483	1.486	1.401
N-B_{BH3}	1.719	1.723	-
B-N-B	107.2°	104.7°	-
O-B-N	110.8°	110.3°	110.4°

Torsion angles	2'c	2'c'	1'c
N-C-C-O	12.5°	26.9°	-0.8°
B-O-C-C	-7.5°	-17.9°	0.7°
N-B-O-C	-0.9°	1.0°	0.0°
O-B-N-H	134.0°	139.5°	179.3°
O-B-N-C	9.2°	16.6°	0.0°
B-N-C-C_{CH3}	110.2°	-150.3°	-121.0°
B-N-C-H	-129.5°	88.2°	117.2°
C_{CH3}-C-N-B_{BH3}	-132.5°	-34.8°	
O-B-N-B	-112.0°	-108.0°	

Figure 2. Stereo representations of the optimized (6-31G*//6-31G*) structures of borane adducts **2'c** and **2'c'**. Some of the most important bond lengths [in Å] and angles are shown. Values of **1'c** are included for purposes of comparison.

Borane Adducts of 1,3,2-Oxazaborolidine and Simple Analogs

Optimized structures (6-31G*//6-31G*) of borane adducts of 4-methyl oxazaborolidine (**2'c** and **2'c'**) are shown in Figure 2 whereas those of the bi- and tricyclic systems **2'd** and **2'e** (6-31G//6-31G) are depicted in Figure 3. Selected structural parameters and properties of borane adducts **2'a-e**, **2'c'** and **2'd'** are shown in Tables 2 and 3 and energies of the formation of the adducts in Table 4.

Bond lengths of the adducts **2'a**, **2'b**, **2'c** and **2'c'** optimized at the 6-31G* level were closely similar; e.g. the ring B-N and B-O bonds of **2'a**, **2'b**, **2'c** and **2'c'** were within the ranges of 1.485±0.002 and 1.335±0.001 Å. The N-B_{BH_3} bonds of **2'a**, **2'c** and **2'c'** were all within the range of 1.720±0.003 Å. The N-B_{BH_3} bond of **2'b** (1.713 Å) was slightly shorter. Similar conclusions were drawn when the bond lengths optimized at the 6-31G level were inspected (Table 2); only the variation of values was somewhat larger.

Although the ring system of **1'c** is practically planar (e.g. torsion angles of **1'c** are all 0°±1°, see Figure 2 and Table 3) the main differences between the *cis*- and *trans*- adducts of borane to **1'c** appear in the torsion angles of the adducts (Figure 2). Torsion angles of the oxazaborolidine ring do not change much as the *trans*-adduct (**2'c**) is formed but in the case of the formation of *cis*-adduct **2'c'** planarity of the ring is clearly lost (e.g. the angle N-C-C-O of **1'c** is -0.8°, that of **2'c** still 12.5° but in the case of **2'c'** already 26.9°, Figure 2). Nevertheless, orientations of the borane moieties in both **2'c** and **2'c'** are almost equal (e.g. bond lengths, B-N-B angles and the torsion angles O-B-N-B of **2'c** and **2'c'** are closely similar, Figure 2 and Tables 2 and 3).

Table 4. Energies[a] of the formation of borane adducts **2'a-e**, **2'c'** and **2'd'**.[b]

Reaction					3-21G	4-31G	6-31G	4-31G*	6-31G*
							ΔE[a]		
1'a	+	BH_3	->	2'a	-84	-50	-44	-57	-55
1'b	+	BH_3	->	2'b	-86	-47	-41	-51	-48
1'c	+	BH_3	->	2'c	-80	-45	-40	-52	-49
1'c	+	BH_3	->	2'c'	-75	-40	-35	-49	-47
1'd	+	BH_3	->	2'd	-104	-60	-58	-	-
1'd	+	BH_3	->	2'd'	-50	-9	-8	-	-
1'e	+	BH_3	->	2'e	-104	-69	-64	-	-
H_2O	+	BH_3	->	$H_2O{\cdot}BH_3$	-105	-60	-54	-43	-38
Me_2O	+	BH_3	->	$Me_2O{\cdot}BH_3$	-110	-71	-65	-49	-45

[a] Energies (ΔE) given in kJ mol^{-1}. [b] See Figures 2 and 3.

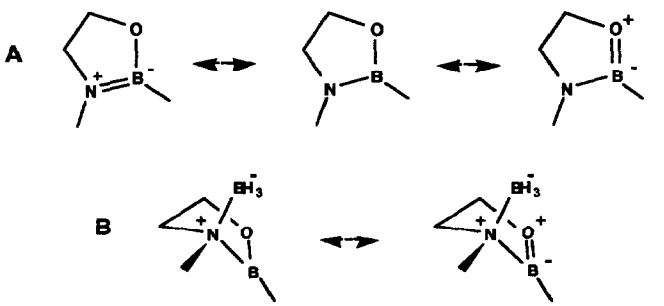
Inspection of the structural representations and torsion angles shown in Figure 2 reveals that the methyl group of **2'c** is axial whereas that of **2'c'** is equatorial. Although there are no important repulsive interactions between the methyl and BH_3 groups of **2'c** forcing the methyl to an axial configuration would be unadvantageous. Therefore, it is not surprising that the tilt angle of the methyl (about the ring) of **2'c** is much smaller than that of **2'c'** [e.g. the torsion angle B_{ring}-N-C-C_{CH_3} decreases by 10.8° from the value of **1'c** (121.0°) as the adduct **2'c** (axial methyl) is formed whereas in the case of **2'c'** (equatorial methyl) the corresponding change is 29.3°, Figure 2]. Indeed, it looks as if the advantage predicted to be achieved in the case in which the CH_3 and BH_3 groups were placed *trans* about the ring (repulsive interactions between the adjacent CH_3 and BH_3 groups in minimum) would be almost canceled as the methyl group would be simultaneously forced to an unfavorable axial position. In the case of the adduct **2'c'** repulsive effects can be avoided as the planar conformation of the ring turns to an envelope shaped one and the methyl tilts to an equatorial, energetically more advantageous, position.

Comparison of the values of torsion angles of **2'a**, **2'b** and **2'c'** (Table 2) reveals only that the angles are closely similar. Oxazaborolidines appear to have a propensity to keep the whole heterocyclic ring closely planar but in their borane adducts only the nitrogen, boron, oxygen and the carbon adjacent to the oxygen are kept in the same plane whereas the carbon adjacent to the ring nitrogen is allowed to tilt out of the plane. This behaviour could be rationalized by taking into account the resonance structures of oxazaborolidines and those of their borane adducts depicted in Scheme II.

On the basis of the resonance structures shown in Scheme II (part A) it can be seen that in the case of

oxazaborolidines the N, B and O atoms of the ring would be involved in partial double bonds and obviously other atoms adjacent to them must stay in the same plane. Consequently, all ring atoms would be required to stay in the same plane. In the case of borane adducts of oxazaborolidines a partial double bond can be formed only between the ring boron and oxygen. Therefore, only four atoms, those adjacent to the boron and oxygen of the ring are required to stay in the same plane. As the fifth atom tilts out of the plane of the others the ring system rotates to an envelope conformation (Scheme II, part B). Importance of these resonances has been discussed in previous parts of reports of this series.[7] Importance of the resonance [B-O <-> $B^-=O^+$] in these borane adducts can be seen when the bond lengths of oxazaborolidines and those of their borane adducts are compared. When borane coordinates to an oxazaborolidine the resonance [B-N <-> $B^-=N^+$] disappears (the B-N bond lengthens, Table 2) and the [B-O <-> $B^-=O^+$] resonance strengthens (the B-O bond shortens, Table 2).

Scheme II

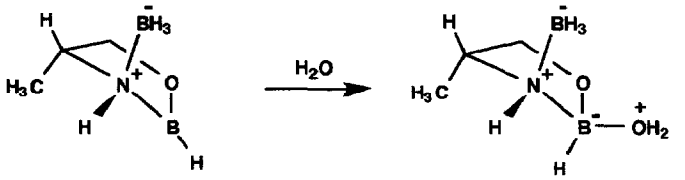


On the basis of the above analysis of conformational changes involved in the formation of borane adducts of oxazaborolidines it is easy to understand that the energy of formation of the *trans*-adduct **2'c** can be as little as 2 kJ mol^{-1} more negative than that of **2'c'**(6-31G*//6-31G*, see Table 4). On the other hand, a question which was one of the major concerns of this work arises again. If both the *cis*- and *trans*-adducts of an oxazaborolidine analogous to **2'c** and **2'c'** would be formed and if they would act as catalysts, how can then such a simple oxazaborolidine as **1B**[7] analogous to **1'c** serve as a catalyst for the enantioselective reduction of ketones ? However, even if both the *cis*- and *trans*-adducts would be formed in the reaction of a chiral 4-substituted oxazaborolidine (e.g. **1B**) with borane, one diastereomer of the adducts could work much faster as a catalyst than the other. In order to test this hypothesis an introductory study of the coordination of a Lewis base (water used a Lewis base) to the ring boron of the adducts **2'c** and **2'c'** was undertaken at the 6-31G level. Results of this study are summarized in Scheme III.

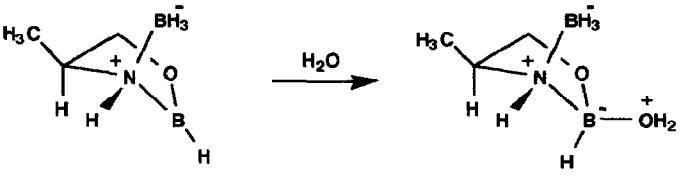
As the coordination of water to **2'c** releases 11 kJ mol^{-1} more energy than the corresponding process in the case of **2'c'** (Scheme III) it indeed looks as if a Lewis base (solvent or the ketone to be reduced) able to coordinate to the ring boron of the diastereomeric borane adducts could favour one of the diastereomers. Taking the difference of energies of the formation of diastereomers **2'c** and **2'c'** (5 kJ mol^{-1} at the 6-31G level, Table 4) into account allows one to calculate the energy of formation of the water adduct of **2'c** from **1'c** and $H_2O{\cdot}BH_3$ to be 16 kJ mol^{-1} more negative than that of the corresponding water adduct of **2'c'**. If the relative energies of formation of the corresponding ketone adducts of **2B** and **2B'** would be at the same level the relative amount of transition state in which the ketone to be reduced is coordinated to the *cis*-adduct **2B'** would be far below the level of 1% ; i.e. even though **2B'** could be formed it practically would not function as a catalysts. One could conclude also that the

nature of asymmetric induction in the case of **1A** as a catalyst would be different from that of **1B**. Nevertheless, even though it appears, in the light of this conclusion, to be easy to explain why also **1B** can behave as a catalyst[1a,8] for the enantioselective reduction of ketones, this proposal needs to be studied further.

Scheme III



2'c $\Delta E^{6\text{-}31G//6\text{-}31G} = -47.0$ kJ mol^{-1}



2'c' $\Delta E^{6\text{-}31G//6\text{-}31G} = -36.0$ kJ mol^{-1}

Borane Adducts of Fused and Bridged Oxazaborolidine Systems

Optimized structures (6-31G//6-31G) of borane adducts of bi- and tricyclic systems (**2'd** and **2'e**) are depicted in Figure 3. Structural parameters of all borane adducts are collected in Tables 2 and 3. Energies of the formation of all adducts are shown in Table 4.

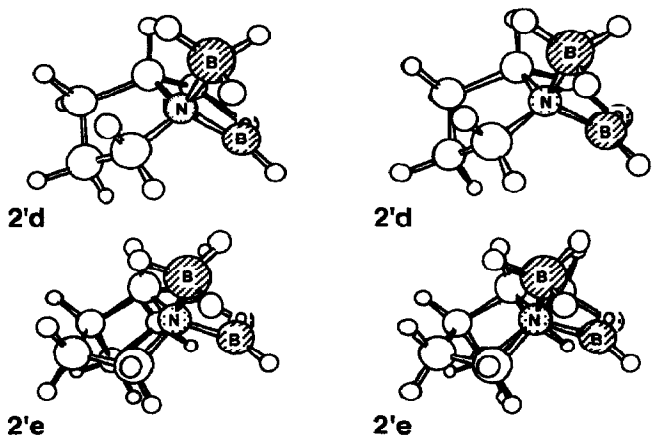


Figure 3. Stereo representations of the optimized (6-31G//6-31G) structures of borane adducts **2'd** and **2'e**.

Comparison of the energies of formation of 2'a-c calculated at the 6-31G level with the corresponding

values provided with polarization functions (at the 6-31G* level) reveals that energies in the former group are about 10±3 kJ mol^{-1} less negative than the corresponding values in the latter. Therefore, it could be reasonable to estimate energies of the formation of the more complicated systems **2'd**, **2'd'** and **2'e** to be also about 10±3 kJ mol^{-1} more negative than the corresponding values provided at the 6-31G level; i.e. energies of the formation of **2'd**, **2'd'** and **2'e** could be predicted to be about -68±3, -18±3 and -74±3 kJ mol^{-1} if calculated at the 6-31G* level. When 6-31G* energy of **2'd** and the estimated 6-31G* energies of **2'd'** and **2'e** are compared with the energy needed for separating borane from its solvent complex [e.g. 38 kJ mol^{-1} needed for separating BH_3 and water in $H_3B{\bullet}OH_2$ and 45 kJ mol^{-1} for separating BH_3 and Me_2O in $H_3B{\bullet}OMe_2$, (6-31G*//6-31G*), Table 4] it can be seen that reactions of oxazaborolidines, and particularly those of strained ones, with borane complexes analogous to $H_3B{\bullet}OR_2$ leading to the formation of borane adducts of oxazaborolidines, would be energetically advantageous. Contradictory conclusions could have been drawn on the basis of energies calculated at the 6-31G level, because the relative order of 6-31G and 6-31G* energies of the formation of $H_3B{\bullet}OH_2$ and $H_3B{\bullet}OMe_2$ appears to be reverse to that of borane adducts of oxazaborolidines (Table 4).

Comparison of energies of the formation of *cis*- and *trans*-fused adducts **2'd** and **2'd'** reveals that the formation of adducts analogous to the *trans*-fused system **2'd'** would be substantially less advantageous than the formation of corresponding *cis*-fused adducts (e.g. the energy of formation of **2'd** calculated at the 6-31G level is -58 kJ mol^{-1} whereas that of **2'd'** is only -8 kJ mol^{-1}, Table 4). In contrast to the energetics of formation of adducts **2'a-e** discussed above, the energy of formation of **2'd'** is substantially lower than that needed for separating borane from its solvent complex (Table 4). Therefore, under normal conditions of a CBS reduction ($H_3B{\bullet}THF$ + the CBS catalyst in a THF solution), formation of *trans*-fused adducts analogous to **2'd'** would be hardly seen.

As could have been expected on the basis of the major structural difference between **1'a-c** and **1'd-e** discussed above [the torsion angle O-B-N-C(8) of **1'e** is 148.2° and that of **1'd** 158.0° whereas the corresponding values of all **1'a-c** (the values of **1'a** and **1'c** on the basis of the torsion angle O-B-N-H) are within the range of 180.0°±0.3°, Table 3] energies of the coordination of borane to the fused and bridged systems **1'd** and **1'e** are considerably more negative than the corresponding values of **1'a-c** (e.g. the energies of formation of **2'b**, **2'd** and **2'e** are -41, -58 and -64 kJ mol^{-1}, at the 6-31G level, Table 4). This correlation between energies and torsion angles was actually pointed out already by Corey *et al* when they mentioned excess strain of the B=N π-bond at the ring fusion of **1A** as a factor facilitating the formation of **2A**.[1a]

As observed in the case of oxazaborolidines **1'a-e**, also the corresponding borane adducts **2'a-e** are structurally closely similar if they are compared on the basis of bond lengths [e.g. the ring B-N and B-O bonds of **2'b**, **2'd** and **2'e** are within the ranges of 1.495±0.001 and 1.358±0.002 Å; only the $B\text{-}N_{BH_3}$ bond of **2'b** (1.748 Å) is somewhat longer than those of **2'd** or **2'e** (1.714±0.001 Å)]. These bond lengths are rather close to those determined by Corey *et al* for a related borane adduct **2** (R=CH_3).[6] Lengths of the B-N, B-O and $B\text{-}N_{BH_3}$ bonds of **2** (R=CH_3) were determined by X-ray diffraction to be 1.486, 1.335 and 1.620 Å.[6] The bond lengths determined in this work by means of these *ab initio* methods differ from those of **2** (R=CH_3) by about 0.01, 0.02 and 0.1 Å. Surprisingly, the calculated bond lengths are longer than those determined by X-ray diffraction. On the other hand, as the substituents of the ring system of **2** (R=CH_3) are different from those of **2'd** or **2'e** some structural differences could be expected to be seen.

Not only the bond lengths but also the charges of borane adducts studied appear to be rather closely similar (e.g. charges of the ring boron, nitrogen and oxygen are within the ranges of +0.893±0.008, -1.014±0.032, and -0.740±0.003). Values of the charge transfer from the oxazaborolidine to the borane moiety are also all closely similar; all within the range of -0.180±0.004. Nevertheless, a slight correlation of the charge tranfer with the nature of the ring system of the catalyst can be found as the negative charge of the borane increases from -0.173

and -0.176 and -0.183 in the series of **2'b**, **2'd** and **2'e**; i.e. in the same order as the ring strain is supposed to do. The same applies to the LUMO-1 values of all **2'a-e** in that all the LUMO-1 energies of **2'a-e** are withing the range of 4.07±0.03 eV. However, no correlation of LUMO-1 energies with the nature of the ring system can be found. This implies that the Lewis acid strength of the ring boron of borane adducts of oxazaborolidines would not be affected much by the nature of the hydrocarbon framework in which the active center of the catalyst is be embedded. This proposal appears to be supported also by experimental facts in that oxazaborolidine catalysts in which the oxazaborolidine ring is fused either to a 4-, 5- or 6-membered carbocyclic ring have all been shown to be active in the enantioselective reduction of ketones.[2c,2i] Furthermore, catalysts in which the oxazaborolidine ring was fused either to a 4- or 5-membered ring were found to produce only about 5-10 % higher enantiomeric excess than the corresponding system composed of an oxazaborolidine fused to a 6-membered carbocycle. This implies, as mentioned in part IV of reports of this series,[7d] and recently also by Rao *et al*,[2c] that rigidity of the ring system of the catalyst could be of importance to good performance of these catalysts.

In contrast to LUMO-1 energies, HOMO-1 energies of the adducts (**2'a-e**) appeared to depend slightly on the nature of the ring system which the oxazaborolidine is a part of. The HOMO-1 energies decrease with increasing ring strain of the borane adducts (e.g. the HOMO-1 values of **2'b**, **2'd**, and **2'e** are -11.36, -11.06 and -10.96 eV, Table 2) implying that the propensity of the borane moiety to donate a hydride increases with the increasing ring strain of the catalyst (HOMO-1 of these type of adducts consists mostly of the functions of hydrogens and boron of the borane moiety and some density from the oxygen of the oxazaborolidine ring).[7a]

Perhaps the most significant structural difference between the simple adducts (**2'a-c**) and the fused and bridged systems (**2'd** and **2'e**) can be found again in ring torsion angles (see Table 3). Namely, if the values of torsion angles N-C(5)-C(4)-O, B-O-C(4)-C(5), N-B(2)-O-C(4) and O-B-N-C(5) of **2'a-b** and **2'c'** representing, an envelope shaped ring system are compared with those of **2'd** and **2'e** it turns out that the oxazaborolidine rings of **2'd** and **2'e** are, in contrast to those of **2'a-c**, highly planar (e.g. the angles of **2'd** and **2'e** are all within the range of 0.1°±1.4°, Table 3). Surprisingly, a same type of behaviour can be seen when dipole moments of the adducts are inspected (Table 1). Namely, the dipole moments of **2'd** and **2'e** are substantially higher than those of **2'a-c** and **2'c'**. This could not have been predicted on the basis of dipole moments of the parent oxazaborolidines; dipole moments of all **1'a-e** are closely similar (Table 1), as were most of the other electronic properties of the oxazaborolidines and their borane adducts that have been studied. Nevertheless, the higher dipole moments indicate that borane adducts of strained oxazaborolidines would interact more intensively with other polar molecules; e.g. Lewis basic solvents, or in the case of a CBS reduction, with the ketone to be reduced. Computational studies of these exciting catalysts continue.

CONCLUSIONS

Energies of the coordination of borane to strained oxazaborolidines [of which the N-C(4) bond of the ring is fused to another ring of size 4-5] are more negative than those of the corresponding reactions of non-fused oxazaborolidines. Coordination energies were found to increase with increasing strain of the B=N bond at the ring fusion. Energy of the formation of *cis*-fused borane adduct of the oxazaborolidine derivative of 2-hydroxymethylpyrrolidine was substantially more negative than that of the corresponding *trans*-fused adduct. In the case of borane adducts of 4-substituted non-fused oxazaborolidines, conformational effects of the oxazaborolidine ring were found to be energetically as important as interactions between the adjacent BH_3 and 4-substituent. The nature of asymmetric induction in the case of 4-substituted non-fused oxazaborolidines as catalysts for enantioselective reduction of ketones was predicted to be different from that of the conventional CBS

catalysts and related systems of which a common property would be the N-C(4) bond of the oxazaborolidine ring fused to another ring of size 4-5.

ACKNOWLEDGEMENTS

The University of Helsinki and the TEKES foundation are acknowledged for providing computational resources needed to carry out this study. The author thanks Drs. T. Hase and G. Brunow for valuable comments.

REFERENCES AND NOTES

1. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Proceedings of the 31th National Organic Symposium, ACS **1989**, 1; (c) Corey, E. J. *Pure & Appl. Chem.* **1990**, *62*, 1209.

2. (a) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1992**, *33*, 4141; (b) Martens, J.; Dauelsberg. Ch.; Behnen, W.; Wallbaum, S. *Tetrahedron Asymmetry* **1992**, *3*, 347; (c) Rao, A. V. R.; Gurjan, M. K.; Kaiwar, V. *Tetrahedron Asymmetry* **1992**, *3*, 859; (d) Lohray, von B. B.; Bhushan, V. *Angew. Chem.* **1992**, *104*, 740; (e) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763; (f) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365; (g) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751; (h) DeNinno, M. P.; Permer, R. J.; Lijewski, L. *Tetrahedron Letters* **1990**, *31*, 7415; (i) Rao, A. V. R.; Gurjan, M. K.; Sharma, P. A.; Kaiwar, V. *Tetrahedron Letters* **1990**, *31*, 2341; (j) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1989**, *30*, 6275; (k) Joshi, N. N.; Srebnik, M.; Brown, H C *Tetrahedron Letters* **1989**, *30*, 5551; (l) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Letters* **1989**, *30*, 5547; (m) Youn, I. K.; Lee, S. W.; Pak, C. S. *Tetrahedron Letters* **1988**, *29*, 4453.

3. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; (c) Corey, E. J.; Chen, C P.; Parry, M. *Tetrahedron Letters* **1988**, *29*, 2899; (d) Corey, E. J.; Gavai, A. V. *Tetrahedron Letters* **1988**, *29*, 3201; (e) Corey, E. J.; Su, W. G. *Tetrahedron Letters* **1988**, *29*, 3423; (f) Corey, E. J.; Huang, H.-C. *Tetrahedron Letters* **1989**, *30*, 5235; (g) Corey, E. J.; Bakshi, K.; Reichard, G. A. *Tetrahedron Letters* **1990**, *31*, 611; (h) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442; (i) Corey, E. J.; Yi, K. Y.; Matsuda, S. P. T. *Tetrahedron Letters* **1992**, *33*, 2319; (j) Corey, E. J.; Da Silva Jardine, P. *Tetrahedron Letters* **1989**, *30*, 7297; (k) Corey, E. J.; Reichard, G. A. *Tetrahedron Letters* **1989**, *30*, 5207; (l) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1990**, *31*, 601;.

4. (a) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906; (b) Corey, E. J.; Cimprich, K.; A. *Tetrahedron Letters* **1992**, *33*, 4099; (c) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Letters* **1992**, *33*, 3435; (d) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1992**, *33*, 3431; (e) Chen, C.-P.; Prasad, K.; Repic, O. *Tetrahedron Letters* **1991**, *32*, 7175.

5. (a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966; (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007; (c) Takasu, M.; Yamamoto, H. *SYNLETT* **1990**, 194; (d) Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron Asymmetry* **1991**, *2*, 639; (e) Sartor, D.; Saffrich, J.; Helmchen, G. *SYNLETT* **1990**, 197.

6. Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Letters* **1992**, *33*, 3429.

7. (a) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 63; (b) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 429; (c) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 827; (d) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 1133; (e) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 921; (f) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 933; (g) Nevalainen, V. Abstracts of 8th Int. Conf. on Organic Synthesis, Helsinki, IUPAC, **1990**, 317; (h) ibid. 319; (i) ibid. 320; (j) ibid. 316; (k) Nevalainen, V. Proceedings of the 9th Annual Meeting of the Molecular Graphics Society, Uppsala, MGS **1990**.

8. (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 467; (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555; (c) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Perkin Trans. 1* **1985**, 2039; (d) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Perkin Trans. 1* **1985**, 2615; (e) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395.

9. On the basis of a comparison of strain energies of *cis*- and *trans*-fused bicyclo[3.3.0]octanes; the *cis*-fused system estimated to be 27 kJ mol^{-1} less strained than the *trans*-fused one; e.g. see Chang, S.;McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109.

10. (a) Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, E. M.; Pople, J. A. Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213. (b) Singh, U. Chandra; Kollman, P. A. School of Pharmacy, Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143.