How Borane Reagents Based on α-Pinene Control Stereoselectivity in the Reductions of Carbonyl Groups with Different Stereogenic Elements. 3. The Effect of the Relative Size and Conformation of the Carbonyl Substituents on the Stereoselectivity of the Ipc_2BCl, Eap_2BCl, B-*t*-Bu-IpcBCl, and B-*t*-Bu-EapBCl Reagents. A Semiempirical Study

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The reductions of a more elaborate prostereogenic nonchiral and chiral ketones with the representative borane reagents derived from (+)-α-pinene confirm that the overall stereoselectivity, similarly to the previously studied reductions of benzaldehyde and acetophenone, is also controlled, early along the reaction coordinate, by the structure of the borane reagent. The stereoselectivity reflects the energy differences among *syn*-1,3-interactions of the smallest of the three boron substituents in the reacting borane conformation with the two carbonyl substituents in the substrate. For the B-alkyl-IpcBCl reagents and the R_S-CO-R_L substrates, these are the interactions of the B−Cl with the $C-R_S$ and $C-R_L$ bonds. To minimize developing intermolecular *syn*-1,3-interactions with the reagent's B−Cl bond during the reaction, in the conformationally mobile R_S-CO−R_L systems, the R_L and R_S groups seek to adopt a more reactive conformation even at the expense of the unfavorable intramolecular interactions.

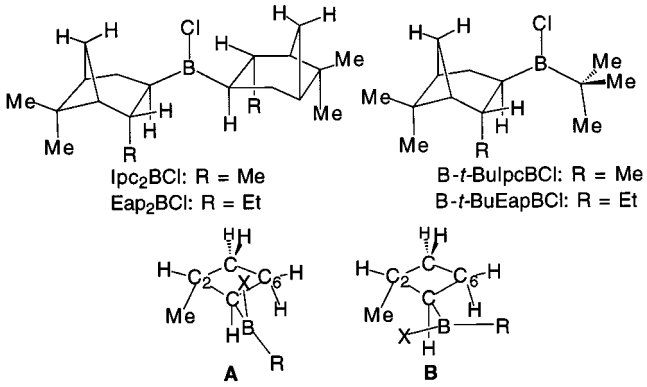
Introduction

In the reductions of prostereogenic carbonyl compounds with simple reducing reagents (i.e., reagents without a reactive stereogenic center), each of the diastereoisomeric transition-states contain only a single new stereogenic center provided by the substrate's prostereogenic carbonyl carbon. On the other hand, in the reductions of the same carbonyl substrates with boranes based on α-pinene, the transition-states contain an additional stereogenic center provided by the reagent's either prostereogenic or prochiral boron.

According to the AM1 semiempirical calculations published previously,[1a,b] in the reductions of benzaldehyde-1-d[2] and acetophenone[3a] with boranes based on (+)-α-pinene,[3b−e] the stereoselectivity is mainly imposed by the different energy requirements of the competing B-sp^2 → B-sp^3 rather than of the C-sp^2 → C-sp^3 coordination expansion processes, i.e., during formation of the boron−oxygen bond in the initial diastereomeric charge-dipole complexes—CD intermediates—rather than during formation of the diastereomeric carbon−hydrogen bonds in the conversion of the charge-dipole intermediates into the corresponding transition-states.

Since in the above reductions of simple carbonyl substrates the B-sp^2 → B-sp^3 precedes the C-sp^2 → C-sp^3 coordination expansion process, it was of interest to evaluate how the size and conformations of the carbonyl R_S and R_L substituents in more elaborate substrates affect the contribution of the opposing B-sp^2 → B-sp^3 processes to the overall stereoselectivity.

Geometry of the Reacting Species. Previously we discussed why only **A** and **B** conformations of the RBXY reagents based on (+)-α-pinene (see the following structures), are relevant in the reduction process.[1] In all reactions of these reagents with the R_LCOR_S carbonyl



substrates, the formation of the new B−O bond starts by the coordination of one of the oxygen's, in plane, *n* electron pairs to the boron center. The approach of the carbonyl substrate to the B-sp^2 center of **A** conformer

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(1) (a) Rogic, M. M. *J. Org. Chem.* **1996**, *61*, 1341. (b) Rogic, M. M.; Ramachandran, P. V.; Zinen, H.; Brown, L. D.; Zheng, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1287. These articles list the literature references pertinent to the experimental work, discuss the inadequacy of the original transition-state model, and introduce the mechanistic interpretation and a new model that reconcile the crucial differences between the original model and the experiment.

(2) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211.

(3) (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (c) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1. (d) Brown, H. C.; Ramachandran, P. V. in Hasner, A., Eds. *Advances in Asymmetric Synthesis*; JAI Press: Greenwich, CT, 1995; Vol. 1, pp 147−210. (e) Brown, H. C.; Ramachandran, P. V.; Teodorovic, A. V.; Swaminathan, S. *Tetrahedron. Lett.* **1991**, *32*, 6691.

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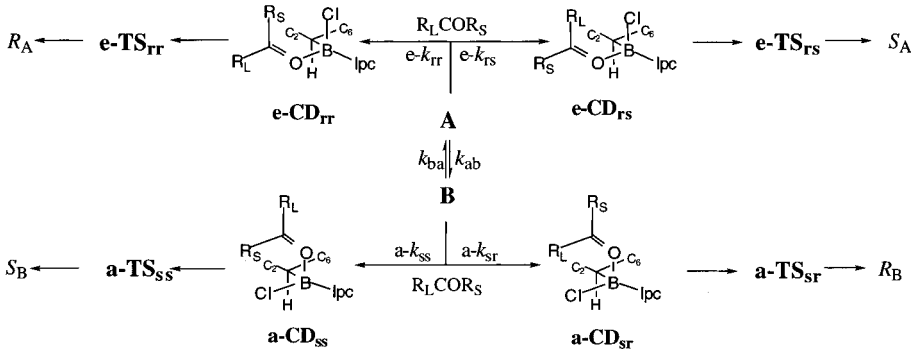
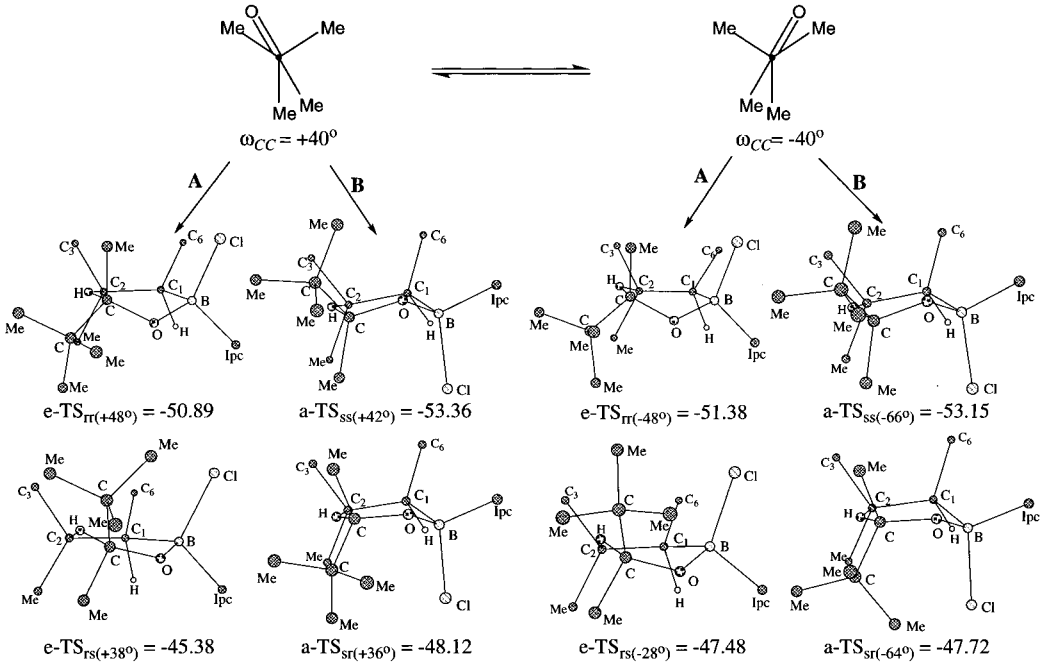
Scheme 1



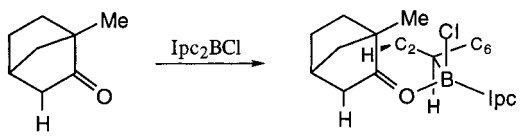
Scheme 2 Calculated Geometry and the Heats of Formation of the Transition-states (H_f, in kcal/mol), for the Reaction of the 3,3-Dimethyl-2-butanone's "+40°" and "-40°" Conformers with the A and B Conformers of the Ipc_2BCl[a]



[a] Only the $C_3-C_2-C_1-C_6$ fragment of the Ipc ring is shown. The e-TS_{rr}/a-TS_{ss} pairs arise from a lower energy approach trajectory where the substrate's CO−R_S bond faces the reagent's B−Cl bond. The e-TS_{rs}/a-TS_{sr} pairs arise from the substrate's alternate, higher energy approach trajectory in which the CO−R_L bond faces the B−Cl bond. See text.

from the direction opposite to the C_1-C_6 bond of the Ipc ring provides the e-CD intermediates and the e-TS transition-states. The approach to the B-sp^2 center of the **B** conformers from the direction opposite to the Ipc ring's C_1−H bond provides the a-CD intermediates and the a-TS transition-states[1b] (Scheme 1). In all of the previously studied borane−ketone reductions, at the CD intermediates stage, the B−O bond formation has been only accompanied by the appropriate B-sp^2 → B-sp^3 but not the C-sp^2 → C-sp^3 pyramidalization.[1] The geometry of the e-TS/a-TS transition-state pairs from the reduction of *t*-BuCOMe ketone with Ipc_2BCl reagent, shown in Scheme 2, is representative and it resembles the geometry from the previous studies.

The Preferred Reaction Pathways and the Comparison of the Experimentally Observed and Calculated Stereoselectivities. In discussion of the CD/TS pairs, and of the *syn*-1,3-interactions of the substrate's C−R_L and C−R_S bonds with the B−Cl bond of a borane reagent, we will refer to *C−C* or *C−H* bonds in the R_L or R_S substituents facing the B−Cl bond, as *frontal bonds*. Regardless whether a carbonyl substrate is a rigid or conformationally mobile system, it may seem reasonable to expect that the preferred reaction pathways should be ones where the C−R_S bond, with a smaller R_S substituent, rather than the C−R_L bond with a larger R_L substituent, is opposing the reagent's B−Cl bond[1b] (Scheme 1). In rigid carbonyl substrates, however, the geometry of the frontal bonds relative to the carbonyl plane, e.g., of the C_1−Me and *exo*-C_3−H bonds in (1*S*)-1-methylnorcamphor, eq 1, is always fixed, and it is



(1)

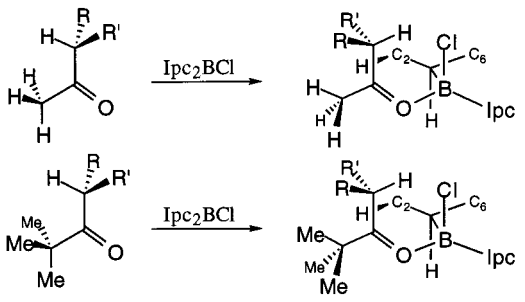
unlikely that it would change significantly in response to the developing *syn*-1,3-interactions with the B−Cl bond of the Ipc_2BCl reagent. On the other hand, when in the conformationally mobile R_SCOR_L ketones—e.g., in the $MeCOCHMe_2$ and $Me_3CCO-CHMe_2$—it becomes neces-

Table 1. Heats of Formation of the Diastereomeric Transition-States in Reductions of Chiral Ketones with Ipc_2BCl Derived from (+)-α-Pinene and Calculated and Observed Stereoselectivities[a]

						product alcohol, % (configuration)			
		heats of formation, H_f[b]				calc.		obsd.[c]	
no.	ketone	e-TS_{rr}[d]	e-TS_{rs}[d]	a-TS_{ss}[d]	a-TS_{sr}[d]	*exo*	*endo*	*exo*	*endo*
1	(1*S*)-1-Me-norcamphor	−37.13	−33.16	−40.18	−36.51	99.4(*S*)	:0.6(*R*)	>99(*S*)	:0(*R*)
2	(1*R*)-1-Me-norcamphor	−37.65	−34.18	−39.15	−35.44	7.2(*R*)	:92.7(*S*)	7(*R*)	:93(*S*)
3	(1*S*)-*exo*-3-methylnorcamphor	−38.00	−36.49	−39.30	−37.43	11(*R*)	:89(*S*)		n.a.
4	(1*R*)-*exo*-3-methylnorcamphor	−36.94	−33.67	−40.23	−38.66	99.7(*S*)	:0.3(*R*)		n.a.
5	(1*S*)-*endo*-3-methylnorcamphor	−36.07	−33.36	−39.88	−37.82	0(*R*)	:100(*S*)		n.a.
6	(1*R*)-*endo*-3-methylnorcamphor	−37.48	−35.93	−37.78	−36.20	62.5(*S*)	:37.5(*R*)		n.a.
7	(1*S*)-camphenilone	−36.82	−34.10	−39.38	−36.81	1.3(*R*)	:98.7(*S*)	1(*R*)	:99(*S*)
8	(1*R*)-camphenilone	−36.71	−34.13	−38.88	−36.82	97.5(*S*)	:2.5(*R*)	93(*S*)	:7(*R*)
9	(1*S*)-camphor	−40.15	−36.58	−44.05	−40.01	99.9(*S*)	:0.1(*R*)	≥99(*S*)	:≤1(*R*)
10	(1*R*)-camphor	−41.46	−37.76	−42.51	−38.92	14.5(*R*)	:85.5(*S*)	34(*R*)	:66(*S*)
c-**11**	(*S*)-Et 1-Me-2-oxo-Cp-carboxylate[e]	−133.23	−130.89	−136.36	−130.15	99.8(*S*)-(t)[f]	:0.2(*R*)-(*c*)[f]	≥99(*S*)-(t)[f]	:≤0(*R*)-(*c*)[f]
t-**11**[e]		−132.50	−130.89	−137.10	−130.64				
c-**12**	(*R*)-Et 1-Me-2-oxo-Cp-carboxylate[e]	−133.93	−128.29	−136.18	−131.67	7.4(*R*)-(*t*)[f]	:92.6(*S*)-(*c*)[f]	18(*R*)-(*t*)[f]	:82(*S*)-(*c*)[f]
t-**12**[e]		−134.84	−128.49	−135.59	−134.54				
13	(1*S*)-norcamphor	−34.56	−34.52	−37.13	−37.25	42(*S*)	: 58(*R*)		n.a.
14	(1*R*)-norcamphor	−34.44	−34.97	−37.16	−36.70	12(*R*)	: 88(*S*)		n.a.

[a] See text for the discussion and explanations. [b]Heats of formation of the diastereomeric transition-states, (in kcal/mol), are calculated values from the corresponding optimized geometries. [c]Referenced in the text. [d]Diastereomeric transition-states; the prefixes e- and a- identify the approach trajectories of the reacting substrate relative to the *equatorial* or *axial* Ipc ring-side of the borane reagent's **A** and **B** conformers. The r and s subscripts, for example in the e-TS_{rs}, identify the respective configurations of the tetrahedral boron center and of the chiral carbon center developing from the diastereotopic carbonyl carbon and leading to the *S* alcohol. [e]The c and t descriptors describe the "cis" and "trans" *conformational relationship* between the C−Me and C=O bonds in the Me−C_1−COOEt group in the reacting ketone's conformation (see text). [f]The (*t*) and (*c*) descriptors identify the *trans*- and *cis*- relationship between the C_1−CO_2Et and C_2−OH groups in the product alcohols.

sary during reaction to minimize developing intermolecular *syn*-1,3-interactions of the C−R_S and C−R_L bond(s) with the B−Cl bond of a borane reagent, the conformation of the C−$CHMe_2$ bond could change from a more stable but less reactive to a less stable but more reactive one (eqs 2 and 3). While in terms of the developing intermolecular *syn*-1,3-interactions with the reagent's B−Cl bond, *the effective size of the $CHMe_2$ group* of these two ketones would decrease, in terms of the intramolecular interactions with the CO-Me and CO−CMe_3 bonds, it would clearly increase. Therefore, for the conformationally mobile substrates it is this dynamic relationship between the reactivity and internal stability that should determine the final stereoselectivity.



(2)

(3)

Results and Discussion

Semiempirical calculations were carried out using the AM1 method[4] as outlined in the Computational Details section. The four borane reagents, i.e., Ipc_2BCl, Eap_2BCl, B-*t*-BuIpcBCl, and B-*t*-BuEapBCl, were all derived from (+)-α-pinene.[3b−e]

Of the 14 substrates *with the diastereotopic carbonyl faces*, (1*S*)-**1** through (1*R*)-**14**, only the (*S*)-**11** and (*R*)-**12** were conformationally mobile ones, and the others were rigid structures. The calculated *exo*/*endo* or *cis*/*trans* ratios of the produced alcohols from the reductions of these ketones, along with the experimentally known ones, are shown in Table 1.

On the other hand, of the 14 substrates *with the enantiotopic carbonyl faces*, **15**−**28**, only **15** had a rigid molecular geometry; the others were conformationally mobile systems. The calculated % ee values of the enantiomeric alcohols from these ketones, along with the experimentally known ones, are shown in Table 2.

Table 3 compares the calculated and observed % ee values from the reductions of seven ketones with the four different borane reagents.

The equilibrating constants K_{ab} for **A** and **B** conformations of the B-Ipc and B-Eap boranes were calculated as before.[1] For all of the individual borane−ketone reaction, the equilibration rates, k_{ab} and k_{ba}, between the **A** and **B** conformers were again by many orders of magnitude greater than the specific rate constants of the competing reaction pathways, e-*k*s and a-*k*s (see Scheme 1).

1. The Rigid R_LCOR_S Substrates with Diastereotopic Carbonyl Faces (Table 1). All substrates in Table 1 are chiral, optically active compounds. In a reaction with the Ipc_2BCl any of the (1*S*)- and (1*R*)-enantiomers could approach the reagent's **A** and **B** conformers using two distinct trajectories[5] (see Scheme

(4) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. In addition to the previously listed literature references[1a,b] describing the use of the computational methods in the studies of various borane reactions, more recently Midland[4b] presented ab initio investigation of the transition-states for the asymmetric synthesis with boronic esters, and Nakano et al.[4c] and Houk and Goldfuss[4d] employed the PM3 transition-state modeling in studying the catalyzed asymmetric additions of organozinc reagents to aldehydes. (b) Midland, M. M. *J. Org. Chem.* **1998**, *63*, 914. (c) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391. (d) Goldfuss, B.; Houk K. N. *J. Org. Chem.* **1998**, *63*, 8998.

(5) A detailed reaction scheme for the various approach trajectories of benzaldehyde and acetophenone to **A** and **B** conformers of borane reagents were discussed previously.[1a,b] The arguments presented there are also applicable here.

Table 2. Heats of Formation of the Diastereomeric Transition-States from the Reductions of Ketones Containing Enantiotopic Carbonyl Faces with Ipc_2BCl Derived from (+)-α-Pinene and the Calculated and Observed Enantiomeric Excess of the Alcohols[a]

		heats of formation, H_f[c] and (torsional angle, tsω°)[d]				% ee (config)	
(“±k$\omega^{o\prime}$)[b]-#	ketone	e-TS_{rr}[e]	e-TS_{rs}[e]	a-TS_{ss}[e]	a-TS_{sr}[e]	calcd[f]	obsd[g]
15	1-methyl-7-norbornanone	−36.89 (180°)	−33.26	−38.84	−35.69	92.8 (*S*)	n.a.
16	acetophenone	−8.48	−7.32	−10.94	−9.49	99 (*S*)	98 (*S*)
17	trifluoromethyl acetone	−190.95	−186.53	−192.21	−188.07	86 (*S*)	96 (*S*)
18	trifluoromethyl acetophenone	−153.12	−149.30	−154.54	−151.35	83.5 (*S*)	90 (*S*)
(“+40”)-**19**	methyl *tert*-butyl ketone	−50.89 (+48°)	−45.38 (+38°)	−53.36 (+42°)	−48.12 (+36°)	94.6 (*S*)	95 (*S*)
(“−40”)-**19**		−51.38 (−48°)	−47.48 (−28°)	−53.15 (−66°)	−47.72 (−64°)		
(“+”)-**20**	ethyl *tert*-butyl ketone	−53.63 (+87°)	−48.35 (+63°)	−56.14 (+64°)	−50.07 (+83°)	94 (*S*)	n.a.
(“−”)-**20**		−54.62 (−68°)	−47.95 (−89°)	−56.26 (−88°)	−51.29 (−84°)		
(“+”)-**21**	isoropyl *tert*-butyl ketone	−53.23 (+166°)	−42.06 (+43°)	−55.98 (+169°)	−50.43 (+27°)	86 (*S*)	n.a.
(“−”)-**21**		−53.68 (−171°)	−46.64 (−52°)	−53.24 (−171°)	−45.05 (−102°)		
(“+3”)-**22**	2,2-dimethylcyclopentanone	−51.98 (+29°)	[−50.97 (−15°)]	−56.19 (+22°)	−53.71 (10°)	99.8 (*S*)	98 (*S*)
(“-3”)-**22**		−52.53 (−23°)	−50.99 (−14°)	−55.20 (−23°)	[−53.71 (10°)]		
(“+6′)-**23**	spiro[4.4]nonan-1-one	−55.68 (+34°)	−52.32 (−10°)	−60.14 (+20°)	−56.65 (+12°)	97.4 (*S*)	95 (*S*)
(“−6”)-**23**		−56.65 (−30°)	−52.77 (−19°)	−57.29 (−37°)	−56.65 (−12°)		
(“+55”)-**24**	2,2-dimethylcyclohexanone	−58.96 (+57°)	−52.94 (+51°)	−60.56 (+54°)	−54.71 (+54°)	84.4 (*S*)	91 (*S*)
(“−55”)-**24**		−58.91 (−53°)	−53.53 (−46°)	−60.24 (−54°)	−54.60 (−52°)		
(“+30”)-**25**	2-cyclohexen-1-one	−26.85 (+37°)	−28.82 (+47°)	−31.06 (+46°)	−29.85 (+31°)	38.5 (*S*)	36 (*S*)
(“-30”)-**25**		−28.73 (−45°)	−27.61 (−36°)	−29.35 (+5°)	−30.60 (−48°)		
(“−165”)-**26**	isoropyl methyl ketone	−52.65 (+177°)	−52.85 (+179°)	−55.28 (+166°)	−55.06 (+167°)	35.8 (*S*)	32 (*S*)
(“+165”)-**26**		−52.80 (−175°)	−52.92 (−170°)	[−54.12 (−166°)][h]	[−53.82 (−167°)][h]		
(“+22”)-**26**		−48.95 (+46°)	−45.65 (+20°)	−53.36 (+32°)	−49.02 (+16°)		
(“−22”)-**26**		−50.74 (−46°)	−47.90 (−18°)	−51.55 (−56°)	[−47.05 (−16°)]		
(“+165”)-**27**	cyclohexyl methyl ketone	−66.78 (+176°)	−66.85 (+170°)	−69.43 (+167°)	−69.18 (+167°)	27.9 (*S*)	26 (*S*)
(“−165”)-**27**		−66.89 (−175°)	−67.00(−168°)	[−68.31 (−167°)][h]	[−67.81 (−167°)][h]		
(“+22”)-**27**		−63.05 (+37°)	−59.94 (+33°)	−67.51 (+27°)	−63.24 (+16°)		
(“−22”)-**27**		−64.66 (−42°)	−61.97 (−20°)	−65.60 (−50°)	−61.79 (−53°)		
(“+168”)-**28**	cyclopentyl methyl ketone	[−57.10 (+177°)]	−56.80 (+176°)	−59.36 (+168°)	−59.44 (+172°)	43 (*R*)	45 (*S*)
(“−168”)-**28**		−57.32 (−177°)	−56.95 (−172°)	−58.88 (−168°)	−59.21 (−175°)		
(“+45”)-**28**		−55.49 (+71°)	−49.85 (+56°)	−58.20 (+32°)	−52.75 (+42°)		
(“−45”)-**28**		−55.77 (−42°)	−51.28 (−32°)	−57.46 (−71°)	−51.48 (−67°)		

[a] See text for the discussion and explanation. [b]The ± signs in (“±k$\omega^{o\prime}$) labels identify a “configuration” of the mirror image conformations in which the ketone reacts; the values kω^o of the specified torsional angles identify the mirror image conformations themselves. For the individual ketones, these specified torsional angles are **15**, C−CO−C−H; **16**, C−CO−C−C; **17**, C−CO−C−F; **18**, C_f−CO−C−C; **19**, C−C−CO−C; **20**, C−C−CO−CMe_3; **21**, H−C−CO−CMe_3; **22**, **23**, **24**, C_3−C_2−CO−C_n; **25**, C_5−C_6−CO−C_2; **26**, **27**, **28**, Me−CO−C−H. The values of these torsional angles in the reacting ketone's conformation, kω^o, and in the corresponding transition-states, tsω^o, are usually different (see *d* below). [c]Heats of formation, (in kcal/mol), see Table 1. [d]The values of the tsω^o identify the geometry of the above indicated torsional angles in the diastereomeric transition-states themselves (see *b* above). [e]Diastereomeric transition-states; see Table 1. [f]Corresponding to the calculated product [S] and [R] ratio at the end of reaction (see text). [g]Referenced in the text. [h]This transition-state was only observed when the tsω^o angle was maintained frozen at the indicated value throughout the calculation. Without this artificial constraint, the higher energy transition-state with the negative tsω^o angle always reverted to the more stable one with the positive tsω^o angle.

Table 3. Comparison of the Observed and Calculated Enantiomeric Excess of the Product Alcohol, (% ee), in the Reduction of Ketones with Different Chiral Borane Reagents Derived from (+)-α-Pinene[a]

		enantiomeric excess of the product alcohol, % ee (configuration)							
		Ipc_2BCl		Eap_2BCl		*B*−*t*-Bu-IpcBCl		*B*−*t*-Bu-EapBCl	
no.	ketone	obsd[b]	calcd	obsd[b]	calcd	obsd[b]	calcd	obsd[b]	calcd
19	acetophenone	98(*S*)	99(*S*)	99(*S*)	99.9(*S*)	96(*R*)	97(*R*)	81(*R*)	72(*R*)
21	trifluoromethyl acetophenone	90(*S*)	83.5(*S*)			42(*R*)	94(*R*)		
22	2,2-dimethylcyclopentanone	98(*S*)	99.8(*S*)	99(*S*)	99.9(*S*)	34(*R*)	54(*R*)		
25	2-cyclohexen-1-one	36(*S*)	38.5(*S*)	74(*S*)	00.5 (*R*)[d]	46(*R*)	—[d]	50(*R*)	—[d]
26	3-methyl-2-butanone	32(*S*)	36(*S*)	95(*S*)	95 (*S*)	37(*S*)	49(*S*)	84(*S*)	91(*S*)
27	cyclohexyl methyl ketone	26(*S*)	24(*S*)	97(*S*)	94(*S*)	48(*S*)	53(*S*)	90(*S*)	93(*S*)
28	cyclopentyl methyl ketone	45(S)[c]	43(*R*)		48(S)	26(*S*)	21(*R*)	72(*S*)	—[d]

[a] See text for the discussion. [b]Referenced in the text. [c]Note that the configuration of the cyclopentyl methyl alcohol in these experimental reductions was assumed by analogy to one from cyclohexyl methyl alcohol resulting from the reductions with the same borane reagents; see ref 15. [d]Judged to be unreliable.

1). The resulting CD-intermediates and the diastereomeric transition-state pairs, e-TS_{rr}/e-TS_{rs} and a-TS_{ss}/a-TS_{sr}, would eventually provide the R_A, R_B and S_A, S_B products.

On the basis of the calculated heats of formation, H_f, in Table 1, all but the last two ketones (**13** and **14**) reacted with Ipc_2BCl in a similar manner. First, for each ketone the calculated specific rate constants e-k_{rr} and a-k_{ss}, for formation of the lower energy transition-states leading to R_A and S_B products in Scheme 1, were at least several hundred times faster than the e-k_{rs} and a-k_{sr} constants for formation of the higher energy transition-states leading to R_B and S_A products. Second, in each of their reactions the equilibrating rate constants k_{ab} and k_{ba} between **A** and **B** (5.18×10^{11} and 6.21×10^{12}, respectively) were by many orders of magnitude greater than the above rate constants.[6] Finally, for each ketone, the contributions of the reaction pathways leading to the S_A *and* R_B were minimal and were ignored (see Scheme 1).

For these reaction systems, according to the Curtin−Hammett principle[6] and to kinetic analyses due to Winstein−Holness[6e] and Eliel and Ro,[6f] the product ratio [R]/[S] at the end of the reaction can be estimated using

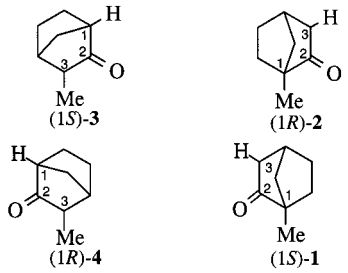


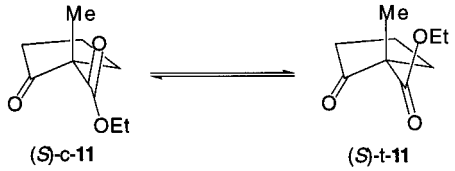
Figure 1. Frontal C_1-H and *exo*-C_3-Me bonds in (1*S*)-**3** and in (1*R*)-**4**, and frontal C_1-Me and *exo*-C_3-H bonds in the (1*S*)-**1** and (1*R*)-**2**.

familiar expressions [R]/[S] = $k_{rr}K/k_{ss}$ (eq 4a), or [R]/[S] = $e^{-\Delta G_{TS}^{\ddagger}/RT}$ (eq 4b).[6g,7] The $\Delta G_{TS}^{\ddagger}$ is the energy difference between free energies of the preferred diastereomeric transition-states resulting from **A** and **B** conformers.

For example, according to AM1, in the reaction of the (1*S*)-**1** with the Ipc_2BCl, this energy difference—$\Delta G_{TS}^{\ddagger}$ = e-TS_{rr} − a-TS_{ss}—favors the (*S*) alcohol by 3.05 kcal/mol, and predicts the [S]/[R] ratio 99.4/0.6% of the (1*S*,2*S*)/(1*S*,2*R*) *exo*/*endo* alcohols. This is in the excellent agreement with the ≥99/0 ratio determined experimentally.[9] In the reduction of (1*R*)-**2** with Ipc_2BCl, the $\Delta G_{TS}^{\ddagger}$ = e-TS_{rr} − a-TS_{ss} = 1.5 kcal/mol in favor of the (*S*) alcohol. Again, predicted [R]/[S] ratio 7.3/92.7% of the (1*R*,2*R*)/(1*R*,2*S*) *exo*/*endo* alcohols compares favorably with the 7/93 one determined experimentally.[9]

The calculated stereoselectivities for the rest of the ketones from this group were generally in good agreement with the experimental ones. Perhaps not surprisingly (see Figure 1), the AM1 predicts that the (1*S*)-**3** and (1*R*)-**4** in the reduction with the Ipc_2BCl should provide similar ratios of the *exo:endo* alcohols as the (1*R*)-**2** and (1*S*)-**1**.

The only conformationally mobile pair of ketones in Table 1, the enantiomeric (*S*)-ethyl 1-methyl-2-oxocyclopentanecarboxylate, (*S*)-**11**, and (*R*)-ethyl 1-methyl-2-oxocyclopentanecarboxylate, (*R*)-**12**, is an example of rapidly interconverting diastereoisomers. Experimentally, in the reaction with Ipc_2BCl, the reduction of the (*S*)-**11**-enantiomer required 1 h and provided essentially only the (1*S*,2*S*)-*trans*-hydroxy ester.[9] The reduction of the (*R*)-**12**, on the other hand, required 72 h and gave a mixture of the 81% (1*R*,2*S*)-*cis*- and 19% (1*R*,2*R*)-*trans*-hydroxy esters.[9] The carbethoxy group in (*S*)-**11** and (*R*)-**12** could assume two different conformations relative to the rest of the molecule. In the (*S*)-c-**11** and (*R*)-c-**12** the C=O bond is approximately *cis*- to the *tert*-methyl group and the torsional angle Me−C−C=O, w_c, is about 15°; in the (*S*)-t-**11** and (*R*)-t-**12**, it is approximately *trans and* the w_t torsional angle is about 165°. (Only the (*S*)-c-**11** and (*S*)-t-**11** pair is shown).



According to AM1, these conformations were essentially equally stable and were separated from each other by a small energy barrier (less than 0.5 kcal/mol). By analogy to the *rapidly equilibrating enantiomers* in Scheme 2 discussed below, the *cis*/*trans* ratio of the alcohols at the end of the reduction can be determined from eq 5: [R]/[S] = $e^{-\Delta G_{TS}^{\ddagger}/RT}$ = (H_{RA*} + H_{RB*}) − (H_{SA*} + H_{SB*}), where H_{RA*} through H_{SB*} were *averaged* heats of formation of the transition-states resulting from the equilibrating diastereomers, e.g., e-TS_{rr} = (H_{rr-cis} + $H_{rr-trans}$)/2, etc. Thus, for the reduction of (*S*)-**11**, the AM1 predicts 99.8% of the *trans* and 0.2% of the *cis* alcohols which compares favorably with the one observed experimentally. For (*R*)-**12**, the calculated 92.6:7.4 *cis*/*trans* ratio is somewhat higher than the experimental one. However, due to the slowness of the reaction, this experimental reduction had to be carried out at room temperature over extended time. It is known that under similar conditions side reactions can reduce stereoselectivity.[10]

As noted above, ketones (1*S*)-**13** and (1*R*)-**14** *behaved differently*. Since the frontal bonds in (1*S*)-**13** and (1*R*)-**14** are C_1-H and *exo*-C_3-H, the effective sizes of the R_L and R_S groups should be very similar. For this reason, the trajectories in which the C− R_L bond is facing the B−Cl bond should be almost as accessible as the alternative ones (Scheme 1 and Table 1). The AM1 calculations confirm this and show (a) that the specific rate constants e-k_{rr} and e-k_{rs} on one hand, and the a-k_{ss} and a-k_{sr} on the other, were very similar and (b) that unlike in the reactions of other ketones discussed previously, the more stable e-TS and a-TS transition-states from (1*S*)-**13**, as well as from (1*R*)-**14**, led to the same alcohol. For example, in the reduction of (1*S*)-**13**, the a-TS_{sr} and e-TS_{rr} both provided the same (1*S*,2*R*)-norbornanol. Thus, the **13** and **14** do not conform to the Curtin−Hammett principle[6g] and expressions shown in eqs 4a and 4b cannot be used to estimate the product ratio [S]/[R] at the end of the reaction. Instead, for these two ketones and similar systems, the [S]/[R] ratio can be calculated from the *combined free energies of the transition-states leading to the same product*, i.e., [S_A + S_B]/[R_A + R_B] = $e^{-\Delta G_{TS}^{\ddagger}/RT}$ where $\Delta G_{TS}^{\ddagger}$ = (H_{RA} + H_{RB}) − (H_{SA} + H_{SB}), eq 6. Here H_{RA} through H_{SB} are calculated heats of formation of the respective transition-states from Table 1. Unfortunately, experimental results for the reduction of **13** and **14** with the Ipc_2BCl and Eap_2BCl reagents are not available so the predicted [R]/[S] ratios from Table 1 cannot be verified.

(6) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. For extensive discussion of the conformation/reactivity relationships, the Curtin−Hammett principle, and kinetic analyses, see (b) Zefirov, N. S.; Palyulin, V. A. *Zh. Org. Chem.* **1979**, *15*, 1098. (c) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719. (d) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (e) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. (f) Eliel, E. L.; Ro, R. S. *Chem. Ind. (London)* **1956**, 251. (g) For discussion of the "boundary conditions" where the Curtin-Hammett treatment and Winstein-Holness equation apply, see 6d and ref 8, p 649.

(7) Since the expressions 4a and 4b are equivalent, essentially all results were obtained using the less laborious calculations based on the eq 4b.

(8) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

(9) (a) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 95. (b) In their study Brown et al. demonstrated that the (−)-Ipc_2BCl derived from (+)-α-pinene and (*S*)-ketone constitute matched- and the (−)-Ipc_2BCl/(*R*)-ketone constitute mismatched-reagent/substrate pair.

(10) (a) Midland, M. M.; Petre, J. E.; Zderic, S. A.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, *104*, 528. (b) Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159. (c) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.

The results from this section clearly show that in the reduction of the *enantiomeric ketones* with borane reagents derived from α-pinene, the AM1 method provided stereoselectivities that were, generally, in excellent agreement with the experimental ones. Furthermore, the method also confirms the Ipc_2BCl reagent based on (+)-α-pinene to be more stereoselective in the reductions of the *S* enantiomers.[9b] It appears, therefore, that the method should be useful in other similar systems—both rigid and conformationally mobile ones—as long as the frontal bond in the R_L substituents is a C−C and in the R_S substituents is a C−H bond. However, since the $\Delta G_{TS}^{\ddagger}$ value is a logarithmic relationship, vide supra, a higher $\Delta G_{TS}^{\ddagger}$—as in the reductions of **1**−**12**—means that the calculated [*R*]/[*S*] and % ee values would be less sensitive to the accuracy in the determination of the free energies of the diastereomeric transition-states. Conversely, for substrates where the frontal bonds in the R_L and R_S substituents are C−H bonds and where the energies of the competing diastereomeric pathways should be comparable—like in **13** and **14**—the $\Delta G_{TS}^{\ddagger}$ should be small. Consequently, for this kind of substrates the error in the %ee values is expected to be high and the accuracy in the determination of the free energies should be as high as possible; in such systems, as indicated above for **13** and **14**, the AM1 must be used with caution.[11]

2. R_LCOR_S Substrates with Enantiotopic Carbonyl Faces (Table 2). Unlike substrates from Table 1, all substrates from the Table 2 are optically *in*active. For the discussion purposes, they have been divided in the three groups: **(a)**, 1-methyl-7-norbornanone, **15**, acetophenone, **16**, trifluoromethyl acetone, **17**, and trifluoromethyl acetophenone, **18**; **(b)**, methyl *tert*-butyl ketone, **19**, ethyl *tert*-butyl ketone, **20**, isopropyl *tert*-butyl ketone, **21**, 2,2-dimethylcyclopentanone, **22**, spiro[4.4]nonan-1-one, **23**, 2,2-dimethylcyclohexanone, **24**, and 2-cyclohexen-1-one, **25**; and **(c)**, isopropyl methyl ketone, **26**, cyclohexyl methyl ketone, **27**, and cyclopentyl methyl ketone, **28**. The ketones from the first group, **15**−**18**, are optically inactive because they are all nonchiral molecules. All the other ones in the second and third groups are, de facto, chiral entities. Nonetheless, although they are chiral, on a macroscopic scale they are optically inactive because they exist as racemic mixtures. Each of the ketones **19**−**25** from the second group exists as a racemic mixture consisting of *a single pair* of the corresponding (*S*)- and (*R*)-enantiomers. Those in the third group, **26**−**28**, exist as racemic mixtures consisting of *two different pairs* of the (*S*)- and (*R*)-enantiomers.

We shall discuss the AM1 predictions for each of these three groups separately.

(a): In agreement with the expectations the AM1 confirms that nonchiral ketones **15**−**18** from the first group, all should react with the Ipc_2BCl according to the Curtin−Hammett principle (Table 2). For example, for the reduction of **15** the method predicts about 93% ee of the (7*S*) alcohol, and the calculated results for the reduction of **16** with various borane reagents,[3a−e] published and discussed previously,[1b] all compare favorably with the experimental ones. For the **17** and **18**, the original transition-state model[3a,12] predicts the (*R*)-alcohols. However, in agreement with the experimental observations, the AM1 predicts the (*S*)-alcohols.

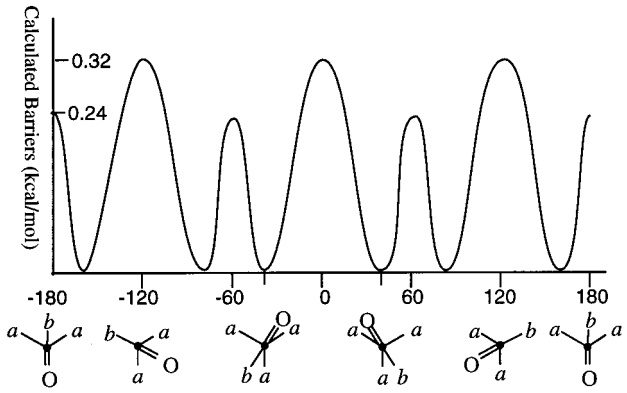


Figure 2. The relative energy changes (kcal/mol) during a 6-fold rotation of the Me−C=O group about the CO−CMe_3 bond in the $MeCOCMe_3$ ketone, as a function of a Me−CO−C−Me, ω_{CC}, torsional angle. Note that all of the conformers between the barriers at 0° and 60° are chiral species, those with the positive ω_{CC} angle being the mirror images of their counterparts with the negative ω_{CC} angle.

(b): We will use $MeCOCMe_3$, **19**, as a representative example for the chiral ketones **19**−**25** from the second group. Figure 2 shows the AM1 calculated energy profile for the 6-fold rotation about the MeCO−CMe_3 bond. The two lowest energy conformers at the +40° and −40° are clearly chiral, nonsuperposable mirror images of each other so we will refer to them as the ("+40")-**19**- and ("-40")-**19**-"enantiomers". Obviously, the barriers at 0° and ±60° represent "transition-states" for the racemization of these "enantiomers". It is of interest that the geometry of the C−Me frontal bonds in the ("+40")-**19** corresponds to the geometry of the frontal C_1−Me bond in the rigid (1*S*)-**1** and geometry of the ("-40")-**19** corresponds to that of the (1*R*)-**2** from Table 1. On the other hand, the geometry of the frontal bonds in the ±60° barriers corresponds to the geometry of the frontal C_1−Me and C_4−H bonds of the nonchiral **15**.

It is expected that in a reaction with chiral Ipc_2BCl borane, the ("+40")-**19** and ("-40")-**19** bona fide enantiomers should interact with the borane's **A** and **B** conformers at different rates, just as the rigid (1*S*)-**1** and (1*R*)-**2** enantiomers did. According to Scheme 2, the AM1 confirms this expectation, and it shows that a contribution of the higher energy reaction pathways to the final stereoselectivity should be minimal and it can be again ignored. Since throughout the reaction the ratio of the ketone's "+ω^o" and "−ω^o" conformers remains essentially equal, the calculated rate constants e-k_{rr}, e-k_{rs}, a-k_{ss}, a-k_{sr}, and thus in turn the corresponding heats of formation H_{rr} through H_{sr}, will be the average of the $H_{rr(+)}$, $H_{rs(-)}$, etc., from Scheme 2. According to eq 5, the AM1 predicts $\Delta G_{TS}^{\ddagger}$ = e-TS_{rr} − a-TS_{ss} = 2.13 in favor of the (*S*)-enantiomer, or 94.6% ee of the (*S*)-3,3-dimethyl-2-butanol

(11) One of the reviewers points out, correctly, that in these cases "the energy differences are just so small that no existing theoretical method would consistently give the correct answer". Since B3LYP with a decent basic set could provide thermochemical data within a few kcal/mol, and since AM1 gives only relative energetics, he feels that the B3LYP calculations would be more credible.

(12) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1317. (c) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371. Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379.

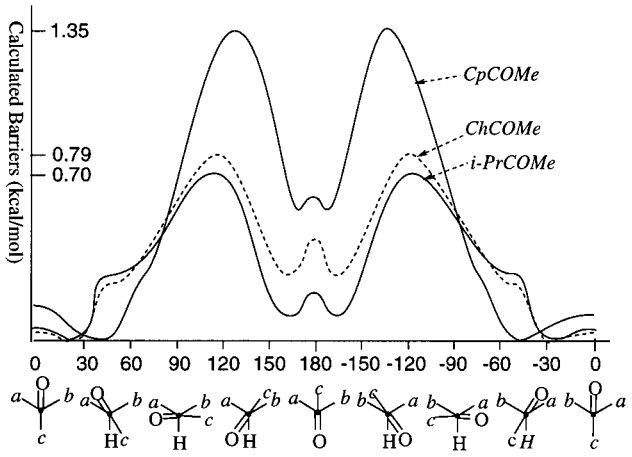


Figure 3. The relative energy changes (kcal/mol) during the rotation of the Me-C=O group about the CO−CH bond in the $MeCOCHMe_2$ and $MeCOCH(CH_2)_n$ ketones, (n = 4, 5), as a function of torsional angle Me−CO−C−H, ω_{CH}. Note that all of the conformers between the barriers at 0° and 180° are chiral species, those with the positive ω_{CH} angle being the mirror images of their counterparts with the negative ω_{CH} angle.

which is in excellent agreement with the 95% ee (*S*), observed experimentally.[3a,13a]

The method predicts that ketones **20**−**24** from this group should all behave similarly (Scheme 2). Indeed, according to the heats of formation in Table 2, the calculated stereoselectivities agree quite well with the experimental ones.[3a,14] Moreover, as suggested in eq 2 and 3, it appears that both **20** and **21** do rotate the C−R_S bond before the reaction, and that the frontal bond in the reacting conformation is indeed a C−H bond. For the reduction of 2-cyclohexen-1-one, **25**, the AM1 indicates, not unexpectedly, that the ("+30")-**25**/("-30")-**25** pair should behave as the (1*S*)-**13**/(1*R*)-**14** pair from Table 1. Thus, for the reduction with Ipc_2BCl the method predicts 38.5% ee of the (1*S*)-2-cyclohexen-1-ol which should be compared to 36% ee (*S*), observed experimentally.[3a] Unfortunately, for the reduction *with* Eap_2BCl, the AM1 predicts a slight excess of (1*R*)-2-cyclohexen-1-ol, contradicting the 74% ee (*S*) observed experimentally![3e] This again reiterates the method's inability to treat the systems with similar frontal bonds accurately.[11]

(c): Finally, as mentioned above, each ketone from the third group, **26**−**28**, *exists as a racemic mixture of two different pairs of enantiomers*. It should be kept in mind that either of the two C−C bonds or the C−H bond in their R_L substituent could assume a frontal bond role (see eqs 2 and 3).

Figure 3 shows the relative energy changes during a 2-fold rotation about the $MeCO-CHR_2$ bond in **26**, **27**, and **28** as calculated by AM1. In **26**, for example, the more stable ("+22")-**26**/("-22")-**26** and less stable ("+165")-**26**/("-165")-**26** pairs of "enantiomers", respectively, are separated from each other by relatively low barriers at ±120° (about 0.7 kcal/mol). The barrier at 0° (about 40 cal/mol) separates the enantiomers of the more stable pair, and a somewhat higher barrier at 180° (about 100 cal/mol) separates the less stable ones. For **27** and **28** the geometry of the corresponding "enantiomers" and the barriers are similar.

According to the AM1 results from Table 2, in the reaction with a borane reagent, the less stable pair of "enantiomers" of each of these three ketones was more reactive than the more stable one. This is to be expected because in each of the more reactive pairs the frontal bond in the R_L substituent was a C−H bond. In the case of **26**, for example, the AM1 predicts that the less stable ("+165")-**26** should react with the borane's **B** conformer about 3 orders of magnitude faster than the more stable ("+22")-**26** (see the heats of formation of the resulting transition-states, a-TS_{ss} (+166°) and a-TS_{ss} (+32°) in Table 2). Therefore, the more stable ketone's conformers, ("enantiomers"), will not contribute substantially to the overall stereoselectivity and, for this reason, they are ignored.

For **26** and **27** AM1 thus predicts $\Delta G_{TS}^{\ddagger}$ of 0.37 and 0.24 kcal/mol, respectively, favoring the (*S*)-alcohols. This is equivalent to a 36% ee (*S*) of the isopropyl alcohol and 28% ee (*S*) of the cyclohexylmethyl alcohol and should be compared to 32% ee (*S*) and 26% ee (*S*) observed experimentally.[15] For the reduction with Eap_2BCl, the calculated $\Delta G_{TS}^{\ddagger}$ were 1.69 and 1.71 kcal/mol favoring the (*S*)-alcohols, respectively. This is equivalent to 95% ee (*S*) of isopropyl alcohol and 94% ee (*S*) of cyclohexylmethyl alcohol, in excellent agreement with the % ee values determined experimentally[3e] (see Tables 2 and 3).

It is of interest that AM1 predicts the rates of formation of the transition-state pair from the ("−165")-**26**/("−165")-**27** "enantiomers" and the **B** conformer of Ipc_2BCl to be substantially slower than the rates from the corresponding "+165°-enantiomers" (see Table 2). In fact, the transition-state pairs with the negative tsω° were only observed when the negative tsω° was maintained "frozen" throughout the calculation, as indicated. In the absence of this artificial constraint, the ("−165")-**26** and ("−165")-**27** reverted to the ("+165")-**26** and ("+165")-**27** and led to the a-TS_{ss}(+166°) and a-TS_{sr}(+167°) transition-states. This clearly suggests a better steric match between the (−)-Ipc_2BCl and "+165°-enantiomers" of the **26** and **27** than between the (−)-Ipc_2BCl and the "-165°-enantiomers". Keeping in mind that the geometry of the "+165°-enantiomers", as far as the frontal bonds are concerned, correspond to the geometry of the (*S*)-enantiomers in Table 1, the higher reactivity of the ("+165")-**26** and ("+165")-**27** "enantiomers" relative to ("-165")-**26** and ("-165")-**27** "enantiomers", is precisely in line with the experimental observations for the reductions of the **1**, **2**, and **7** − **12**, summarized in Table 1.

Cyclopentyl Methyl Ketone 28. In the experimental reduction with Ipc_2BCl, the **28** provided the 45% ee of the (*S*)-alcohol. According to AM1, however, this reduction should give 43% ee of the (*R*) alcohol (Tables 2 and 3). Unfortunately, the reported (*S*) configuration of the methyl cyclopentyl alcohol was based on the analogy to methyl cyclohexyl alcohol from the reduction of **27** with Ipc_2BCl, but it was not experimentally verified.[15] Moreover, since the **28** has not been reduced with Eap_2BCl experimentally, it is impossible to say whether the calculated results in Tables 2 and 3 suggest a more

(13) (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446. (b) Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1735. (c) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577.

(14) In **24** and **25**, the six-membered rings could also exist as the mirror image *boat conformations*; these, as well as completely planar conformations, are higher in energy and they can be ignored.

(15) Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 4504.

complicated kinetic situation or point out inadequacy of the AM1 for treating this particular substrate.

The results from this section further reinforce the above conclusions about the AM1 method's ability to successfully evaluate the stereoselectivity in the reduction of the carbonyl substrates with the boranes derived from α-pinene. Based on the results from both rigid and conformationally mobile substrates, as long as the frontal bonds in the R_L substituents are C−C and in the R_S substituents are C−H bonds, the method should provide accurate predictions. Furthermore, the method also nicely confirms the a priori expectations expressed in eqs 2 and 3 about conformationally mobile substrates such as **20**, **21**, and **26**−**28**. To minimize developing intermolecular interactions with the borane reagent, it appears that these substrates do indeed rotate their R_S and R_L substituents, as indicated. Of course, the other intermolecular interactions among atoms distant in sequence but close in space could also contribute to this process, and while they are not explicitly included in the argument, they must not be overlooked.

However, if the geometry and the effective sizes of the frontal bonds in the R_L and R_S substituents are similar, as in the (1*S*)-**13**/(1*R*)-**14** and ("+30")-**25**/("-30")-**25** pairs, the AM1 method should be less reliable.

3. Reductions with B-*t*-Bu-IpcBCl and B-*t*-Bu-EapBCl. Unlike in the symmetrical Ipc_2BCl and Eap_2BCl, where the boron center is prostereogenic and the two boron faces are equivalent, in the chiral B-*t*-BuIpcBCl and B-*t*-BuEapBCl reagents the boron center is prochiral and its two faces are diastereotopic. A 6-fold rotation about the $RClB-CMe_3$ bonds leads to a pair of the "staggered" and a pair of the "eclipsing" borane conformers. Compared to the 6-fold rotations in the $MeCO-CMe_3$ case above (Figure 2), the two possible "staggered" borane conformations are not enantiomeric but diastereomeric, and the two barriers for the rotation, represented by the two different "eclipsing" conformations, do not lead to the "racemization" but to diastereomer equilibration.

Because of these complications and because of a small number of the experimental reductions[15] that can be used for the comparison purposes, the AM1 calculations of the reductions with the B-*t*-Bu-IpcBCl and B-*t*-Bu-EapBCl reagents were not explored thoroughly and the results in Table 3 must be regarded only as "qualitative".

The % ee values for these reductions were calculated using eq 5. For example, the reduction of **26** with B-*t*-BuIpcBCl and B-*t*-BuEapBCl, lead to the 49% ee (*S*) and 91% ee (*S*), respectively,[16] which should be compared to 37% ee (*S*) and 84% ee (*S*), observed experimentally.[15] The % ee values in Table 3 for the reduction of **27** and **28** with these reagents were estimated similarly.

Computational Details

All calculations were carried out using the AM1 Hamiltonian[4] as described previously.[1a,b] In most of the cases, geometry of the already optimized transition-state was used as the starting geometry for the new analogous transition-state.

Conclusions

The calculated geometry of the CD intermediates in the reductions of carbonyl compounds with boranes derived from (+)-α-pinene published previously[1] as well as from the present study, all clearly show that at the CD-intermediate stage of reaction only pyramidalization at boron center takes place. This further supports the mechanistic interpretation[1a,b] that the stereoselectivity in these reductions is primarily controlled by the structure of the borane reagent and is decided early along the reaction coordinate, during formation of the CD-intermediates. The respective transition-states resemble half-chairs and flattened-chairs rather than the originally proposed boat form.

In addition, comparison of the calculated and experimentally observed stereoselectivities from the reductions of 28 structurally different ketones (Tables 1, 2, and 3) shows that the AM1 method's predictions, in general, agree excellently with the experimental results. As expected, a much better agreement is observed for both rigid and conformationally mobile ketones when the "effective sizes" of the R_L and R_S substituents were different, i.e., when the frontal bonds were C−C and C−H bonds. When the frontal bonds in the R_L and R_S substituents were similar, as in **13**, **14**, and in the ("+")-**25**/("−")-**25** pair, the energy differences between the competing diastereomeric transition-states were too small and, for the reasons mentioned above,[11] the calculated stereoselectivities (by AM1 or by any other calculation method) must be regarded as unreliable.

If conformationally mobile R_SCOR_L substrates need to rotate R_S and R_L substituents to minimize developing unfavorable intermolecular interactions of the frontal bonds with the borane reagent, according to AM1 they apparently will do so. Unfortunately, the answer to the interesting question—how the relative energy difference between barriers separating ketone's reacting conformers and the barriers separating borane's **A** and **B** conformers influence the overall reduction stereoselectivity—must await more experimental data.

The results in Table 3 show that the AM1 method does a much better job when dealing with the symmetrical Ipc_2BCl and Eap_2BCl boranes than when dealing with the nonsymmetrical B−R−IpcBCl reagents.

Evidently, the AM1 method, a few shortcomings not withstanding, predicts stereoselectivities of the reductions with boranes based on α-pinene with a good accuracy. The method is widely available, and since all required calculations can be carried out efficiently even on an average desktop computer, it should be particularly useful in those areas where the use of more exact methods is still not practical.[17]

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(16) The reaction of **26** with B-*t*-BuIpcBCl, for example, leads to the following heats of formation: ("165")-**26** → e-TS_{ss}(+174°), H_{SA*} = −70.82. ("−165")-**26** → e-TS_{sr}(−177°), H_{RA*} = −70.73. ("-22")-**26** → e-TS_{sr}(−47°), H_{RA*} = −68.76. ("-22")-**26** → e-TS_{ss}(−18°), H_{SA*} = −65.83. ("+165")-**26** → a-TS_{rs}(165°), H_{SB*} = −69.31. ("+165")-**26** → a-TS_{rr}(165°), H_{RB*} = −69.31; ("+22")-**26** → a-TS_{rs}(30°), H_{SB*} = −67.43. ("+22")-**26** → a-TS_{rr}(14°), H_{RB*} = −63.23.

(17) See, for example, Carpenter, B. K. *Angew. Chem., Int. Ed.* **1998**, *37*, 7, 3340, for more ambitious uses of the semiempirical methods.