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Origins of Stereoselectivity in the Addition of Allyl- and Crotylboronates to Aldehydes : the Development and Application of a Force Field Model of the Transition State

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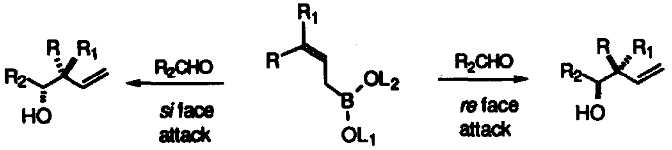
Abstract: A molecular mechanics model of the transition state for the addition of allyl and crotyl boronates to aldehydes was developed, based on *ab initio* calculations and on a process of trial and error optimization. The optimized force field reproduces the experimental *syn-anti* stereoselectivity for the intermolecular addition of *E* and *Z* crotylboronates to aldehydes. The force field is used to analyse the stereoselectivity of various synthetically interesting reactions. In particular, the force field is able to reproduce with excellent quantitative agreement the experimental results of intramolecular boronate reactions leading to methyl or benzyloxy substituted cyclohexanol or cyclopentanol derivatives (R.W. Hoffmann, *et al.*). In addition the force field is able to reproduce the experimental results of variously substituted allylboronates (γ,γ-alkyl substituted, α,γ-alkyl substituted, α,γ,γ-alkyl substituted, γ-alkoxy substituted) and the Felkin-antiFelkin ratios of allyl, *E*-crotyl and *Z*-crotyl addition to chiral aldehydes.

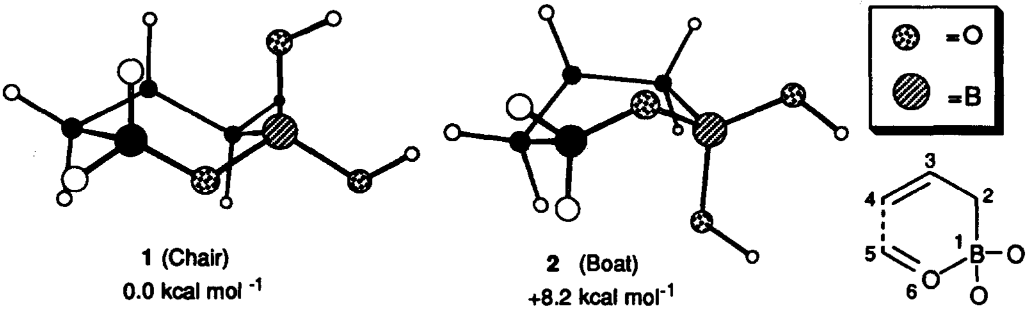
The stereocontrolled formation of carbon-carbon bonds is of great importance in organic synthesis.[1] Among the available methods, the addition reaction of allyl metal reagents to aldehydes is one of the most useful and widely used for acyclic stereocontrol.[1a,2]



Scheme 1

Like the aldol reaction of metal enolates, the addition of a crotyl metal reagent to an aldehyde generates two new stereocentres and can potentially give rise to four stereoisomers. In particular, the use of allyl and crotyl borane (-BR_2) and boronate (-$B[OR]_2$) reagents has been shown to be a valuable method for the construction of carbon-carbon bonds with excellent stereocontrol (boronates : **Scheme 1**).[1a,2a] The stereochemical results have been rationalized in terms of a chair-like six-centre cyclic transition state. Houk *et al.* located chair and twist-boat transition structures for the reaction of formaldehyde with allylboronate using *ab initio* molecular orbital calculations at the RHF/6-31G*//3-21G level [**1**,**2**; **Figure 1**].[3a] The twist-boat transition structure was calculated to be ≥ 8 kcal mol^{-1} higher in energy than the chair.[3a] By transferring these *ab initio* calculated structural parameters to a force field enviroment, R.W. Hoffmann *et al.* have developed a force field model for the allylboration reaction,[4] following an approach pioneered by K. Houk.[3b-e] In the

Hoffmann study, the geometry of the *ab initio* core transition structure was kept rigid and used as a model of the transition state ("fixed core" procedure). This model was used to rationalize the asymmetric induction in the reaction of allyl and crotyl boronates with chiral aldehydes.[4] We recently developed of a force field model for allylboranes using a "flexible core" procedure, which allows all the atoms of the core transition structure to move.[5,6] This implied using *ab initio* molecular orbital calculations to locate a certain number of substituted transition structures. This model is able to reproduce the stereoselectivity of known reactions of allyl and crotyl boranes with aldehydes.[5]



1 (Chair)
0.0 kcal mol $^{-1}$

2 (Boat)
+8.2 kcal mol^{-1}

Figure 1

We report here the development of a fully flexible force field model for allyl and crotyl boronates. We also discuss the use of this force field approach for rationalizing the observed stereoselectivity of various allyl and crotyl boronate additions to aldehydes in synthetically useful reactions. This model has successfully reproduced experimental results with a few limitations and failures, and therefore may have predictive value in new situations.

RESULTS AND DISCUSSION

We recently described a force field model for the reaction of allyl and crotyl boranes with aldehydes.[5] This force field was based on MM2[7a,b] as implemented in Clark Still's MacroModel,[7c] and new parameters developed from *ab initio* calculations. The work was organized in three phases: first, several transition structures for the addition reactions were located using *ab initio* molecular orbital calculations, each bearing a methyl substituent in all the different positions of the ring. Second, we used the *ab initio* data to create a set of empirical force field parameters for those bonds that are forming or breaking. Torsional parameters were used to account for the calculated effect of substituents on the relative energy of the *ab initio* structures. Third, the parameters were extensively optimized and added in substructure format to the MM2 force field.[5]

We have extended the allylborane force field to allylboronates using a minimum set of new parameters. Structures 1 and 2, calculated by Houk (Figure 1),[3a] were used to derive the necessary stretching and bending parameters. We assumed that the effect of the substituents parametrized for the allylborane reaction could be transferred to the allylboronate reaction. In particular we made no effort to calculate the torsional potential of the B-O bonds, but simply set the relative torsional parameters to zero. Although we are aware that the B-O bonds are likely to experiment a sort of anomeric effect,[8a,b] we made that choice considering that most allylboronate reactions involve a cyclic bora-dioxolane moiety. The work originated an allyl-borane/boronate force field which is reported below (**Table 1**).

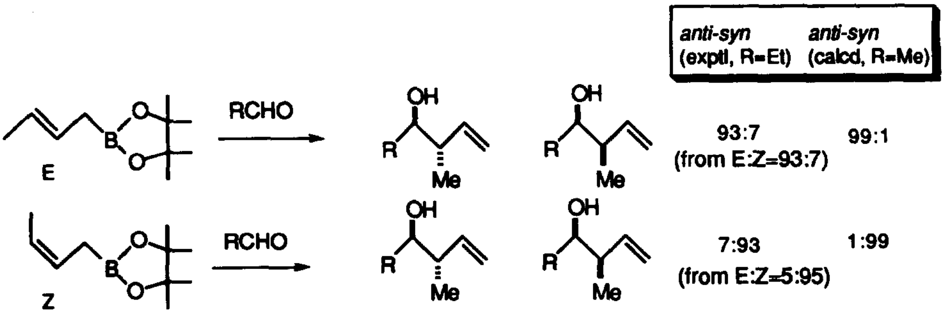
Table 1. Allyl-borane/boronate force field.

```
Main force field       radius (Å)         E (kcal mol^-1)        offset (Å)
 6    Z0               1.9800               0.0340                0.0000
Substructure
 C  Allyl Borane/Boronate Transition State
 9  Z0-C3-C2=C2.C2=O2(.1)
-4
 8  -0.0500  -0.0600  0.0400  -0.0250  0.2750  -0.1800          (charges)
-3
 C  Allyl Borane Transition State
 9  Z0-C3-C2=C2.C2=O2(.1)
-2
 2  C3   1  C3             118.0000    0.3000
 4  H1  C3   1  C3           0.0000    0.0000     0.0000
 4  C3  C3   1   2           0.0000    0.0000     0.0000
 4  C3  C3   1   6           0.0000    0.0000     0.0000
 4  C3  C3   1  C3           0.0000    0.0000     0.0000
 4  H1  C3  C3   1           0.0000    0.0000     0.0000
 4  C3  C3  C3   1           0.0000    0.0000     0.0000
 4  C3  C3   3   4           0.0000    0.0000     0.0000
 4  C3  C3   3   2           0.0000    0.0000     0.0000
-3
 C  Allyl Borane/Boronate Transition State
 9  Z0-C3-C2=C2.C2=O2(.1)
-2
 1   1  H1                   1.0999    4.6000
 1   2  H1                   1.0000    4.6000
 1   3  H1                   1.0000    4.6000
 1   4  H1                   0.9900    4.6000
 1   5  H1                   0.9800    4.6000
 1   1  C3                   1.6120    4.0000
 1   1   2                   1.6810    4.5000
 1   2   3                   1.4560    4.5000
 1   3   4                   1.3540    9.6000
 1   4   5                   2.2700    3.0000
 1   5   6                   1.2690    8.0000
 1   6   1                   1.5570    5.5000
 2  C3   5   4             101.0000    0.1000
 2  C3   4   5              96.3000    0.3000
 2  C3   1   2             113.2000    0.3000
 2  C3   1   6             110.8000    0.1000
 2  H1  C3   1             111.7000    0.3000
 2  C3   1  H1             115.8000    0.3000
 2  C3   2   3             115.1000    0.4000
 2  C3   2   1             108.5000    0.4000
 2  C3   4   3             123.5000    0.4000
 2   2   1   6             100.5100    0.3000
 2   1   6   5             121.6100    0.7700
 2   6   5   4             102.4400    0.4600
 2   5   4   3              88.7200    0.3800
 2   4   3   2             124.1600    0.5000
 2   3   2   1             107.0000    0.3000
 2  H1   4   5              97.7500    0.1000
 2   4   5  H1              91.7900    0.1000
 2   6   1  H1             110.0100    0.1000
 2  H1   1  H1             116.1100    0.3000
 2  H1   1   2             110.3500    0.3000
 2  H1   4   3             120.3300    0.3000
 2  H1   4  H1             116.5800    0.3000
 2  H1   3   4             117.9200    0.3000
 2   2   3  H1             112.8200    0.3000
 2  H1   2   3             112.8200    0.3000
 2   1   2  H1             106.4300    0.1000
 2  H1   2  H1             110.6200    0.3000
 2  C3   4   5              96.3000    0.3000
 4  00   1   2  00           0.0000    0.0000     0.0000
 4  00   2   3  00           0.0000    0.0000     0.0000
 4  00   3   4  00           0.0000    0.0000     0.0000
 4  00   4   5  00           0.0000    0.0000     0.0000
 4  00   5   6  00           0.0000    0.0000     0.0000
 4  00   6   1  00           0.0000    0.0000     0.0000
 4  H1  C3   4   5           0.0000    0.0000     0.0000
```

```
 4   H1   C3    4    3        0.0000     0.0000     0.0000
 4   H1    3    4   C3        0.0020     7.9693     0.1263
 4   H1    4    3   C3        0.0020     7.9699     0.1778
 4   C3    4    3   C3        0.0000     8.0000     0.0000
 4   C3    4    3    2        0.0000     8.0000     0.0000
 4   C3    3    2    1        0.0000    -2.0000     0.0000
 4   H1   C3    5    4        0.0045    -0.0252     0.2130
 4   H1   C3    5    6        0.0000     0.0000     0.0000
 4   C3    5    6    1        1.9635     1.2421     0.0592
 4   C2    5    6    1        1.9635     1.2421     0.0592
 4   C3    1    2    3        0.9302     0.1815     0.1780
 4   C3    1    6    5        0.9417     0.0950     0.0973
 4    2    1    6    5        0.9417     0.0950     0.0973
 4   H1   C3    1    2        0.0000     0.0000     0.0000
 4   H1   C3    1    6        0.0000     0.0000     0.0000
 4   H1   C3    1   H1       -0.0003     0.0091     0.2001
 4   C3    2    1    6        0.4233     0.1190     0.1819
 4    3    4    5    6        0.2364    -0.5065     1.5680
 4    1    2    3    4        0.5368    -2.8386    -0.4791
 4   H1    3    4   H1       -0.0008     7.9950    -0.0163
 4    6    1    2    3        0.2293    -0.5415     0.5957
 4    4    5    6    1        0.3737    -1.2703     2.4437
 4   H1    4    3    2        0.0029     7.9553     0.0444
 4   H1    4    5   H1        0.0686    -0.1094     0.1464
 4   H1    4    5    6       -0.0966     0.1238     0.4131
 4   H1    1    2    3       -0.0771     0.2543     0.3831
 4   H1    1    2   H1        0.0775    -0.1948     0.0827
 4   H1    2    1    6       -0.0856     0.0803     0.0908
 4   H1    3    2    1       -0.6000    -2.4855     1.4233
 4   C3   C3    5    4        0.5000     0.0000     0.0000
 4   C2   C3    5    4        0.0000     0.0000     0.0000
 4   O3   C3    5    4        0.5000     0.0000     2.0000
 4    6    5   C3   O3        0.0000    -1.0000     0.5000
 4   O3   C3    5   H1        0.0000    -2.0000     1.0000
 5    3   00   00   00        0.0000     0.0000
 5    4   00   00   00        0.0000     0.0000
 5    5   00   00   00        0.0000     0.0000
-3
 C   Allyl Borane Transition State (Borolane)
 9   Z0-C3-C3-C3-C3-1
-2
 1    1    2                  1.5800     4.0000
 2   C3    2    1           117.5000     0.3000
 2   H1    2    1           103.6000     0.3000
 2    1    2    3           103.4000     0.3000
 2    2    1    5           110.7000     0.3000
 2    2    1   C3           110.0000     0.3000
 2    2    1   O2           110.0000     0.3000
 4   00    1    2   00        0.0000     0.0000     0.0000
 4   00    2    3   00        0.0000     0.0000     0.0000
 4   00    1   O2   00        0.0000     0.0000     0.0000
 4   00    1   C3   00        0.0000     0.0000     0.0000
 4    1    2   C3   00        0.0000     0.0000     0.0000
 4    1    2   Si   C3        0.0000     0.0000     0.0000
-3
 C   Allyl Boronate Transition State
 9   Z0-C3-C2=C2.C2=O2(.1)
-2
 1    1   O3                  1.4360     6.2000
 2   O3    1    2           111.1000     0.3000
 2   O3    1    6           107.1000     0.1000
 2   O3    1   O3           118.8700     0.5000
 2   C3   O3    1           106.0000     0.6000
 2   H1   O3    1           106.0000     0.6000
 2   C2    5    4           101.0000     0.1000
 2   O3    4    5            96.3000     0.3000
 4   O3    1    2   00        0.0000     0.0000     0.0000
 4   O3    1    6    5        0.0000     0.0000     0.0000
 4   00   O3    1   00        0.0000     0.0000     0.0000
 4    1   O3   C3   00        0.0000     0.0000     0.5000
 4   O3   C3    4    5       -0.5000     0.0000     0.1000        (Hoffmann)
 4   C3   C3   C3    5        0.2000     0.2700     0.0930
 4   C3   C3    4    5        0.0000     0.0000     0.0000
 4   O3   C3   C3    5        0.7000     0.1000     0.1800        (Hoffmann)
```

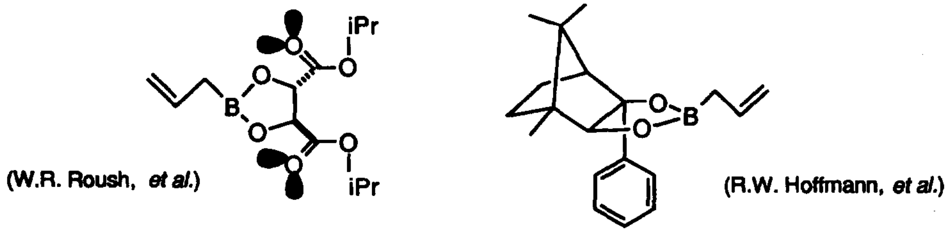
```
4  O3   4    3    2          0.0000     8.0000     0.0000
4  C3   O3   4    5          0.0000     0.0000     0.0000
```

The optimized force field is able to reproduce the experimental *syn-anti* stereoselectivities for the intermolecular addition of *Z* and *E* crotylboronates to aldehydes[2a] (**Scheme 2**).



Scheme 2

The force field is used to analyse the stereoselectivity of various synthetically interesting reactions. In particular, the force field fails to reproduce the experimental *si*:*re* stereoselectivities for the addition of chiral allylboronates to aldehydes (**Scheme 3**). In both the tartrate-derived reagents (Roush) and the camphor-derived reagents (Hoffmann) a strong electronic contribution is believed to occur: interaction of the incoming aldehyde with either the ester lone pairs (Roush), or the phenyl π-cloud (Hoffmann).[1a,2a] The force field cannot cope with these effects.



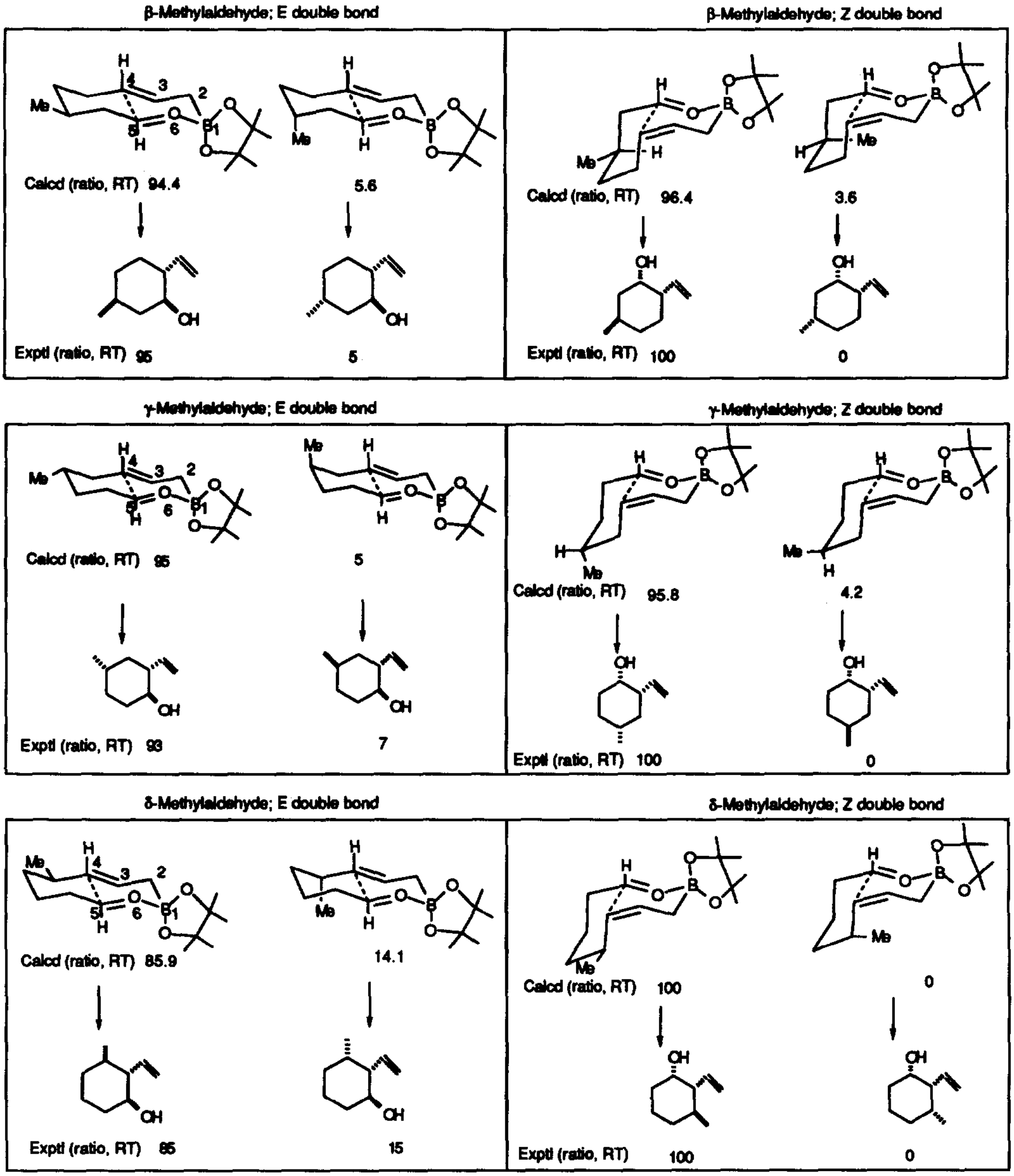
Scheme 3

On the contrary, the force field can reproduce with excellent quantitative agreement the experimental results of intramolecular boronate reactions leading to methyl or benzyloxy substituted cyclohexanol or cyclopentanol derivatives (R.W. Hoffmann, *et al.*).[9] Results with the methyl substituted cases are quite straightforward (**Scheme 4**). The experimental selectivities are reproduced nicely, just using either regular MM2 torsional parameters or simply nonbonded interactions when the torsional parameters are set to zero (**Table 2**).

Table 2. Relevant torsional parameters for β,γ,δ-Methylaldehydes (see also the force field in Table 1). For numbering, see Figure 1 and/or Scheme 4.

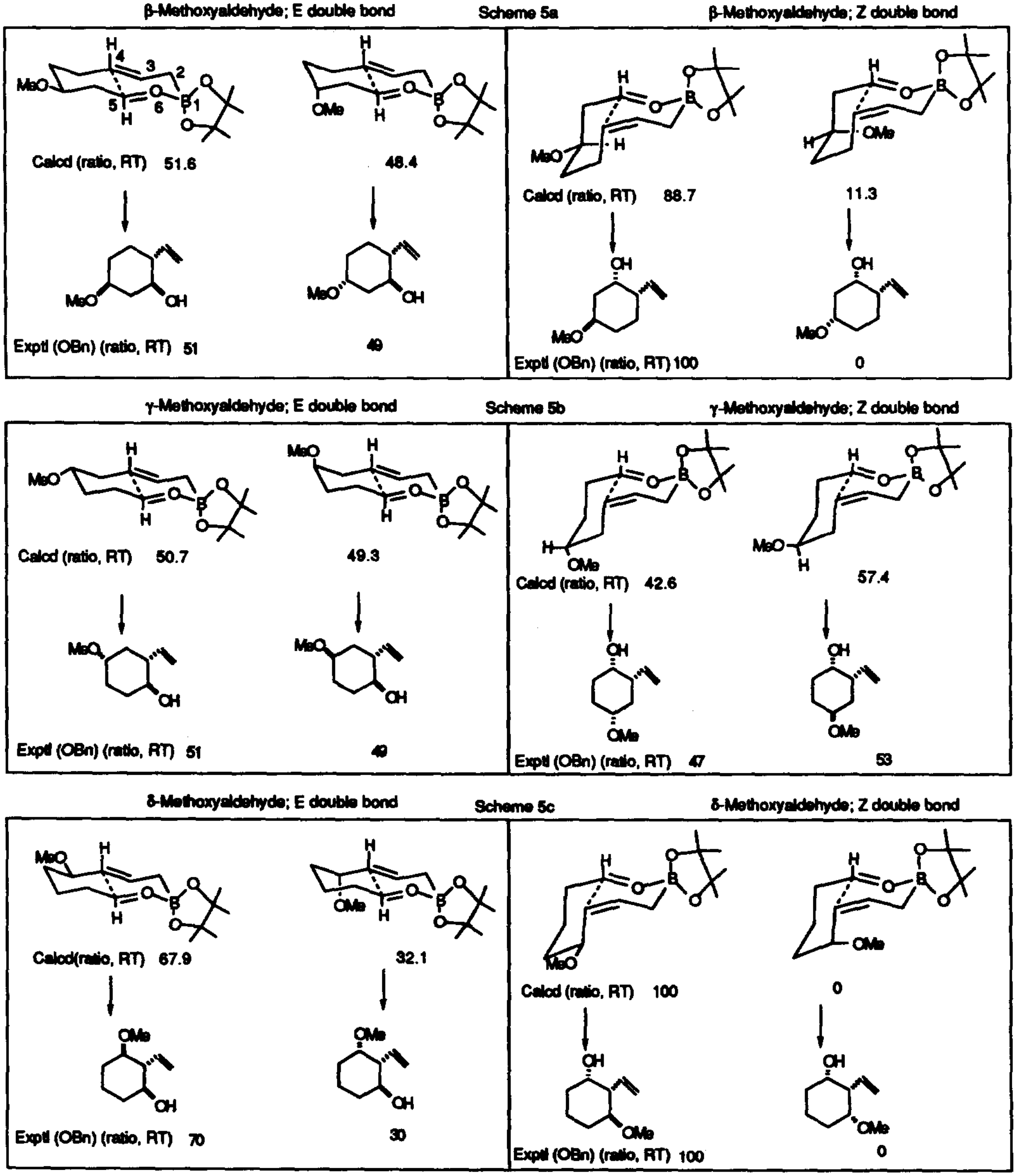
```
5-C3-C3-C3 = 0.200, 0.270, 0.093 [equivalent to C3-C3-C3-C3 (MM2)] [β-Methylaldehyde]
4-C3-C3-C3 = 0.170, 0.270, 0.093 [equivalent to C2-C3-C3-C3 (MM2)] [γ-Methylaldehyde]
5-4-C3-C3 =  0.000, 0.000, 0.000                                   [δ-Methylaldehyde]
C3-C3-5-4 =  0.500, 0.000, 0.000 [developed in ref. 6c]
```

Scheme 4

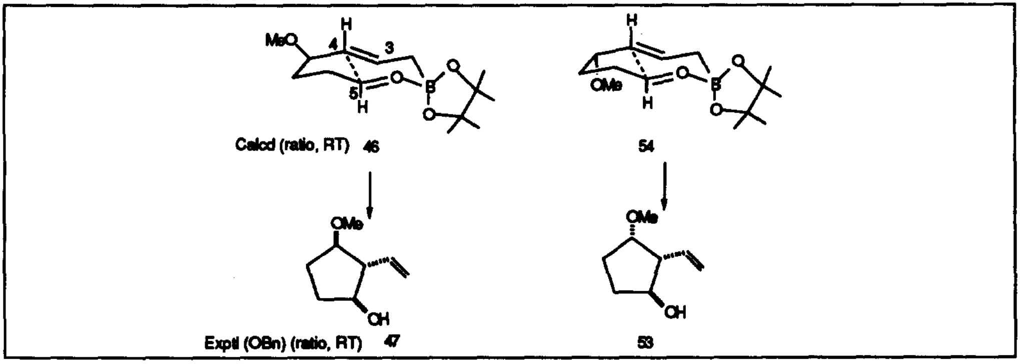


The situation is slightly more complicated with the alkoxy-substituted cases, which are also nicely reproduced (**Scheme 5**). Here we need the addition of two new parameters, marked as "Hoffmann" in the force field (see Table 1): 5-C3-C3-O3 = 0.70; 0.10; 0.18 and 5-4-C3-O3 = -0.5; 0.0; 0.1. The first torsional parameter [5-C3-C3-O3 = 0.70; 0.10; 0.18] is used in the β-methoxyaldehyde case (Scheme 5a) and speaks in favour of a *very late transition state*. In fact, using the MM2 parameter for C2(=O)-C3-C3-O3 (*reactant like !*) the calculation for the *E* allylboronate predicts a strong axial preference. This axial preference remains also using Houk's C3-C3-C3-O3 torsional parameter[10] and, although quite reduced, the MM2 C3-C3-C3-O3 torsional parameter (0.1; 0.1; 0.18) (**Table 3**). The experimental selectivity is restored using an "*ad hoc*" parameter: 5-C3-C3-O3 = 0.70; 0.10; 0.18 (Table 3). The γ-methoxyaldehyde case (Scheme 5b) does not need the addition of new torsional parameters: being the stereocentre far away from the transition state core, it fully relies on MM2. In the δ-methoxyaldehyde case (Scheme 5c) the calculations are reasonably well in agreement with the experiment using either 5-4-C3-O3 = 0.0; 0.0; 0.0 or Houk's C3-C3-C3-O3 torsional parameter.[10] The best fit was found with a slightly modified "*ad hoc*" parameter: 5-4-C3-O3 = -0.5; 0.0; 0.1.

Scheme 5



γ-Methoxyaldehyde; E double bond Scheme 5d



Calcd (ratio, RT) 46 54

Exptl (OBn) (ratio, RT) 47 53

Table 3. Relevant torsional parameters and axial/eq. relative energies for the*E* allylboronate addition to β-methoxyaldehyde.

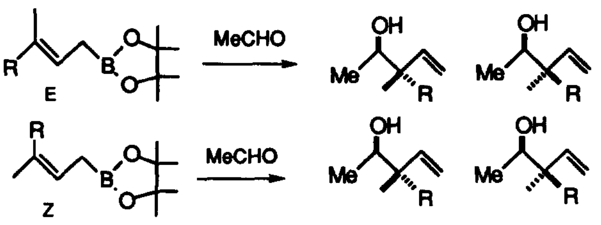
```
5-C3-C3-O3 1.45; -1.79; 1.19 (Houk's C3-C3-C3-O):axial OMe 0.0; eq. OMe 1.26 kcal/mol
5-C3-C3-O3 0.10; 0.10; 0.18 (MM2 C3-C3-C3-O): axial OMe 0.0; eq. OMe 0.42 kcal/mol
5-C3-C3-O3 0.70; 0.10; 0.18 (Hoffmann): axial OMe 0.02; eq. OMe 0.0 kcal/mol
```

The γ-methoxyaldehyde case (cyclopentane ring formation, Scheme 5d) also relies on the above described parameters: 5-4-C3-C3 = 0.0, 0.0, 0.0; 5-4-C3-O3 = -0.5, 0.0, 0.1. Therefore the case which is more strongly biased by some electronic effect is the β-methoxyaldehyde case.

In addition the force field is able to reproduce the experimental results of variously substituted allylboronates: γ,γ-alkyl substituted (**Scheme 6**),[11a] γ-alkoxy substituted[12a-c] and γ-alkoxy-γ-alkyl substituted[12d] (**Scheme 7**), α,γ-alkyl substituted (**Scheme 8**),[13a-d] α,γ,γ-alkyl substituted (**Scheme 9**).[13e] The lower experimental *syn* selectivity of the Z γ,γ-disubstituted boronate (88:12, Scheme 6) is possibly due to a lower isomeric purity of the Z isomer.[11b] In the α,γ-alkyl substituted allylboronate addition reactions (Scheme 8), diastereomeric transition states with axial aldehyde-Me group (not shown) were calculated to be ≥ 2 kcal mol^{-1} higher in energy.

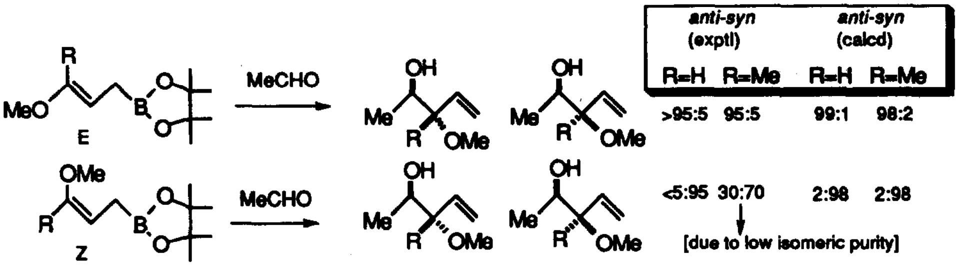
Allyl, *E*-crotyl and Z-crotylboronate addition reactions to chiral aldehydes have been studied by several authors.[1a,2a,14,15] The first examples of the "anti-Felkin" reactions of a Z-croylboronate with an α-methyl chiral aldehyde were presented by Hoffmann in a 1980 paper.[15] A rationale for the observed stereoselectivity (Felkin-antiFelkin ratios), which involves the minimization of (+/-) double gauche pentane interactions in the competing cyclic, chairlike transition states, was originally proposed by Evans in 1982,[16] and discussed in detail by Hoffmann (allylboronates),[4,14a] Roush (allylboronates,[14b,c] aldol reaction[17]), and Gennari (boron aldol reaction with the help of transition state computer modelling).[6c]

Scheme 6

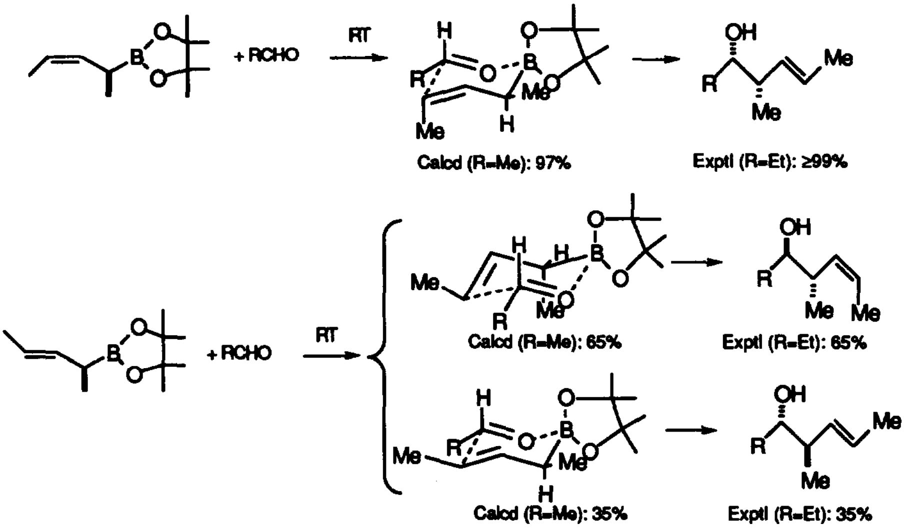


anti-syn (exptl) R=n-Bu	*anti-syn* (calcd) R=Et
95:5	95:5
12:88	6:94

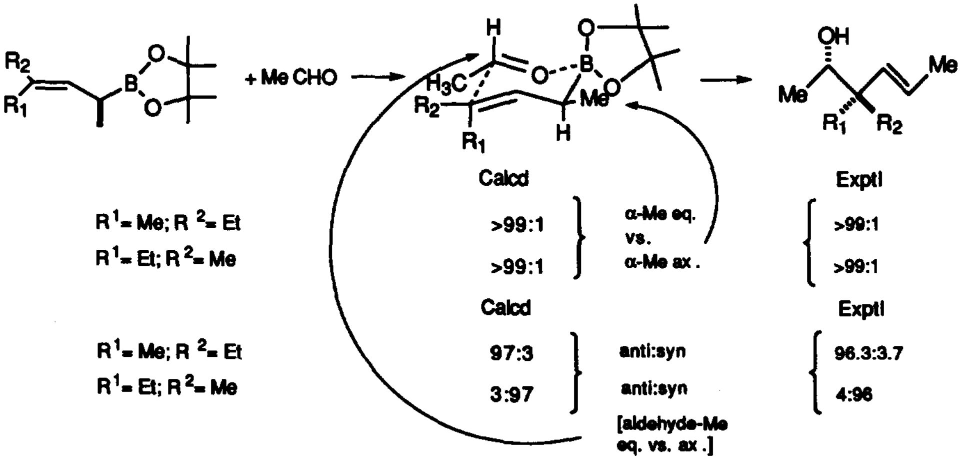
Scheme 7



Scheme 8

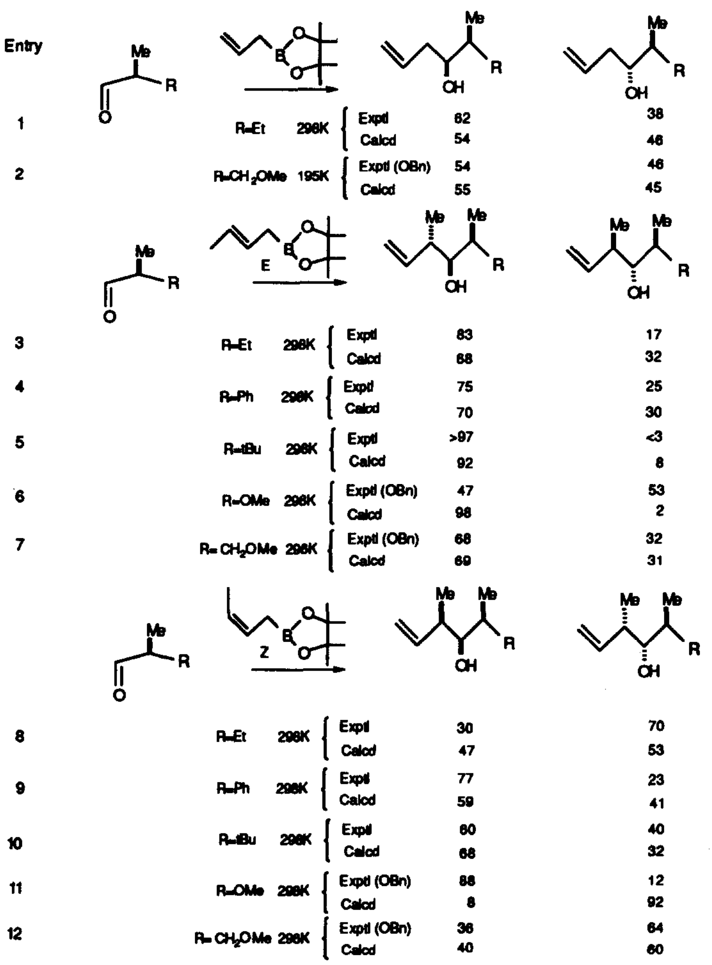


Scheme 9



The force field is able to reproduce the Felkin behaviour of allyl (**Scheme 10**, entries 1,2) and *E*-crotyl boronates (**Scheme 10**, entries 3-5,7; **Scheme 11**, entry 2). In the case of *Z*-crotyl boronates the force field predicts either an anti-Felkin behaviour (**Scheme 10**, entries 8,12; **Scheme 11**, entry 3), or a diminished Felkin preference (**Scheme 10**, entries 9,10) in accord with the experimental results, although the quantitative agreement is sometimes good and sometimes poor.[4a,4b,14] Occasionally, the force field completely fails to reproduce the Felkin-antiFelkin ratios, e.g. for the allyl, *Z*-crotyl and *E*-crotyl boronate addition reactions to the aldehydes shown in **Figure 2**.[14a-c] The force field predicts aldehyde **3** as anti-Felkin selective (72-78%) with respect to all reagents (allyl, *Z*-crotyl, *E*-crotyl), contrary to the experimental evidence.[14a] The force field also fails to reproduce the behaviour of α-alkoxy aldehydes (aldehyde **4**,[14b,c] but also lactic aldehyde,[14d] see **Scheme 10**, entries 6,11), which are experimentally more Felkin selective with *Z*-crotyl boronates (≥90:10) than with *E*-crotyl boronates (50:50). This behaviour was rationalized using a "Cornforth-like model",[1a,4,14b] which cannot be reproduced by our calculations: the computational model thus needs further refinement to fit the experimental data.

Scheme 10



Entry					
1	R=Et	298K	Exptl	62	38
			Calcd	54	46
2	R=CH$_2$OMe	195K	Exptl (OBn)	54	46
			Calcd	55	45
3	R=Et	298K	Exptl	83	17
			Calcd	68	32
4	R=Ph	298K	Exptl	75	25
			Calcd	70	30
5	R=tBu	298K	Exptl	>97	<3
			Calcd	92	8
6	R=OMe	298K	Exptl (OBn)	47	53
			Calcd	98	2
7	R=CH$_2$OMe	298K	Exptl (OBn)	68	32
			Calcd	69	31
8	R=Et	298K	Exptl	30	70
			Calcd	47	53
9	R=Ph	298K	Exptl	77	23
			Calcd	59	41
10	R=tBu	298K	Exptl	60	40
			Calcd	68	32
11	R=OMe	298K	Exptl (OBn)	88	12
			Calcd	8	92
12	R=CH$_2$OMe	298K	Exptl (OBn)	36	64
			Calcd	40	60

Scheme 11

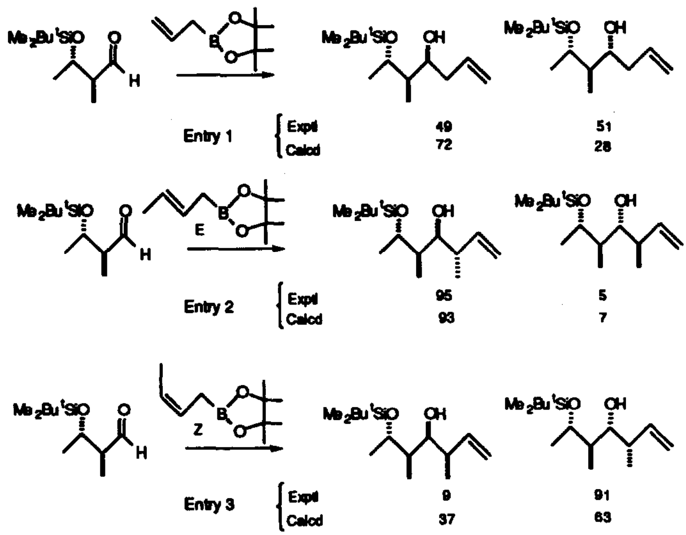
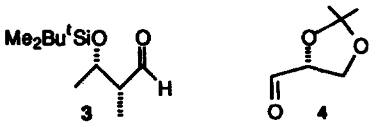


Figure 2



In summary, our force field model has successfully reproduced experimental results with a few limitations and failures, and therefore may have predictive value in new situations.

COMPUTATIONAL METHODS

MacroModel (version 3.1)[7c] was used to generate accessible transition structures for the allyl- and crotylboronate reactions of interest. The conformational space was searched with the Still-Chang-Guida usage-directed torsional Monte Carlo routine[18] as implemented by the BATCHMIN program (version 3.1),[19] using the MM2 force field[7a,b] augmented with the allylborane/boronate force field reported in Table 1. Torsional constraints were applied to preserve the crotyl boronate geometry and prevent *Z*/*E* mixing. Chirality checks were used for all stereocentres, and were also applied to the carbonyl carbon and the crotyl boronate γ-carbon, to ensure stereochemical integrity of the products. The energy window for the search was 12 kcal mol^{-1}, and structures were stored within 2.5 kcal mol^{-1}. Occasionally an alternative procedure making use of Multiconformer[20] with a 30° or 60° resolution for each dihedral angle was also used. The results were comparable with those obtained using the Monte Carlo procedure and showed that our conformational analysis was not dependent on the search method used.[21] The diastereomeric ratios were calculated by a Boltzmann distribution at the reported temperature of all conformers within 2.5 kcal mol^{-1} above the global minimum. For both *Z* and *E* crotylboronates, we tested for the presence of boat transition structures by including all rotatable bonds of the transition structure "core". Boats were found to be unimportant, because of their high energies relative to the chairs. For more details, refer to the computational section of ref. 5.

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