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Computational Studies on the Aldol-Type Addition of Boron Enolates to Imines: an Ab-Initio Approach

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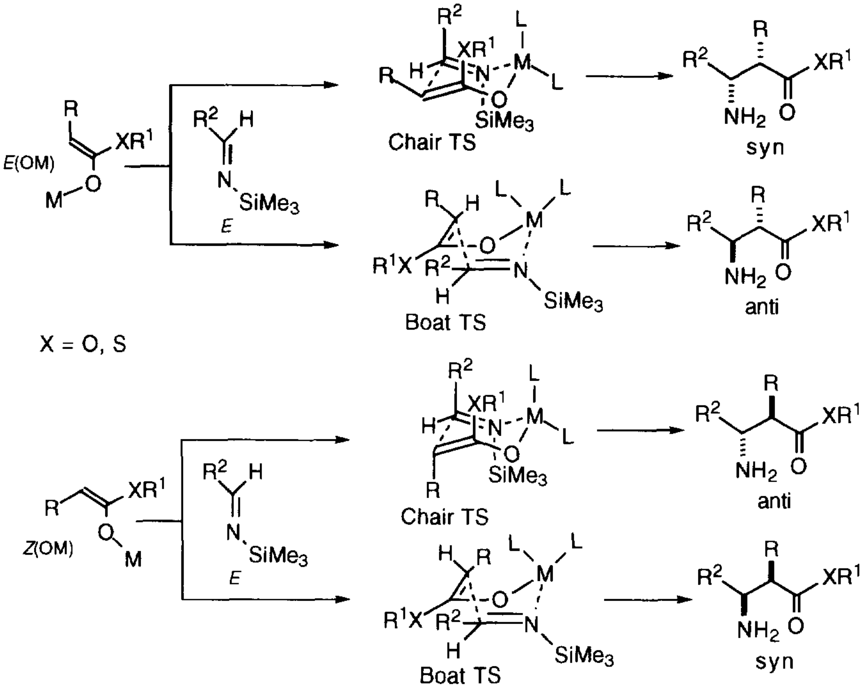
Abstract: The aldol-type addition of enol borinates to imines was studied with *ab initio* MO methods (3-21G basis set). Calculations performed on unsubstituted, mono- and di-substituted structures have shown that only two competing cyclic transition states (chair-like and boat-like) are important. Their relative energy depends on the enolate geometry and on the substitution pattern. This approach allows a qualitative rationalization of the observed stereoselectivity trends in the title reaction.

The aldol reaction is a powerful method for the control of both relative and absolute stereochemistry in organic synthesis.[1] β-Aminoesters, which can be regarded as the products derived from the aldol condensation of esters with imines, appear in the framework of many biologically active natural products.[2a] For example, β-amino acids, although less abundant than their α-counterparts, are components of natural peptides,[2b] as well as building blocks for the preparation of modified peptides[2c] and β-lactam antibiotics.[2d] Numerous methods for the synthesis of β-amino acids have been reported, and have recently been reviewed:[2a,2e-h] one of the most useful involves the reaction of imines with enolates.[2g] In order to make this process stereoselective, chiral auxiliaries have been attached either to the enolate[3] or to the imine,[4] or both.[5] In alternative, the use of achiral imines and boron enolates bearing chiral boron ligands was recently described.[6]

The simple stereoselection (*syn-anti*) of the lithium enolate-imine addition reaction has been investigated thoroughly.[2g] The rule of thumb is that *E*(OLi) enolates and *E* imines (usually the highly reactive trimethylsilylimines)[7] react to form *syn* products, whereas *Z*(OLi) enolates and *E* imines typically react to form mixtures of *syn* and *anti* products.[2g,8a,b] This rule is contradicted by several important examples where *E*(OLi) enolates and *E* trimethylsilylimines react to form *anti* products with high selectivity.[8c] The results have been rationalized using the chair- and boat-like transition structures (TS) shown in Scheme 1, and the *syn-anti* preferences have been discussed examining the steric bias of the imine substituents.[8,9]

The stereochemical analysis appears to be simpler in the case of boron enolates: *Z*(OB) enolates react with *E* imines leading preferentially to *anti* products,[10] while *E*(OB) enolates are more capricious and give either *syn* or *anti* products or *syn-anti* mixtures depending on the particular substrate.[6,10] The results have been rationalized considering a chair-like TS for the *Z*(OB) enolates[10] and a chair-like *vs* a boat-like TS for the *E*(OB) enolates.[6c-e] Corey suggested that isomerization of the imine from *E* to *Z* might take place during the addition reaction, and proposed a chair-like TS for the addition of a thioester derived *E*(OB) enolate to *Z* imines leading

Scheme 1



to *anti* products.[6a] This last model is based on the assumption that the thermodynamically preferred *E* imines might isomerize and react in the *Z* configuration, because the *Z* isomer might be more reactive than the *E*. Although no isomerization of *E* imines (particularly the aromatic ones) to *Z* imines was observed under the reaction conditions,[6b,f] this does not absolutely disprove the Corey hypothesis, which will be discussed in the Summary Section.

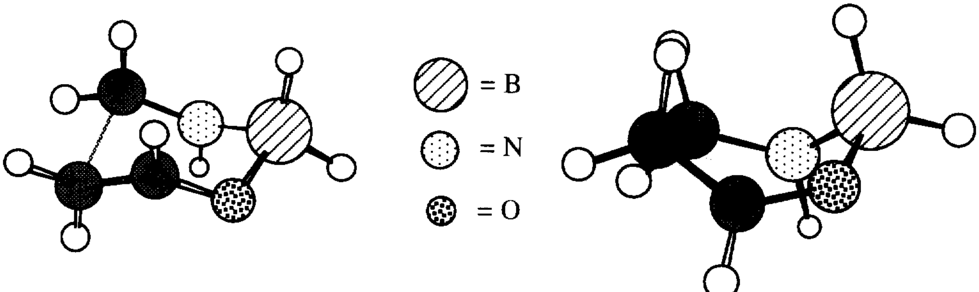
Research groups at Milano and Cambridge have jointly described computational models for the aldol-type reactions of various boron-based reagents (enolborinates, allylborinates, allylboronates, enaminylborinates) with aldehydes.[11] The models were based on the MM2 force field, augmented with new parameters developed from *ab initio* calculations on the cyclic TS. This force field modeling allowed the design of a new chiral boron ligand, which was then used in a number of highly stereoselective aldol-type reactions.[6c-e,12] These studies revealed that Z enolborinates, as well as *Z* and *E* crotyl-boranes and -boronates, react with aldehydes only *via* chair-like TS, the boat-like TS being much higher in energy (≥ 4.0 kcal/mol). However, the boat-like TS are competitively accessible for *E* enolborinates and are often prevailing for unsubstituted enolates.[11]

We report here an *ab initio* study on the aldol-type addition of enolborinates to imines. This study shows that the puzzling stereochemical outcome of the imine boron-aldol reaction is likely due to the existence of a relatively small energy gap (≤ 1.5 kcal/mol) between the two diastereomeric chair-like and boat-like transition structures for the reaction. Only *Z* enolates destabilize the boat-like TS enough (> 4 kcal/mol) to react exclusively *via* a chair-like TS. In all other cases the diastereomeric boat-like and chair-like TS compete, and their relative energy is, case by case, dictated by the steric and electronic features of the substituents.

Ab Initio Calculations: Location of TS

Ab initio molecular orbital calculations were carried out with the Gaussian-90 programme,[13a] at the HF level with the 3-21G basis set.[13b] The three TS for the aldol condensation between the boron enolate of acetaldehyde and formaldehyde (Chair, Boat A and Boat B)[11] were used as starting points for the TS location. The aldehyde oxygen was substituted with a NH group, and the geometry was partially minimized. Then the TS were located by eigenvector-following (EF) optimization,[13c] and characterized by calculating the Hessian matrix. Only two TS, the Chair **1** and the Boat **2** (Figure 1), were located. All attempts to locate a Boat B-type TS failed.[14] Starting from **1** and **2** the fourteen monosubstituted structures **3-16** (Figure 2, Table 1) were located. Finally the twelve bis-substituted structures **17-28** (Figure 3, Table 2) were located. The absolute energies (a.u.) of the 28 TS are reported in the Computational Section (Table 3): the relative energies reported in the text and in Tables 1, 2 were calculated from the Zero Point Vibrational Energy corrected values [E(RHF)-ZPVE corrected].

Figure 1. HF/3-21G transition structures for the addition of the B enolate of acetaldehyde to the imine of formaldehyde.



Chair **1**

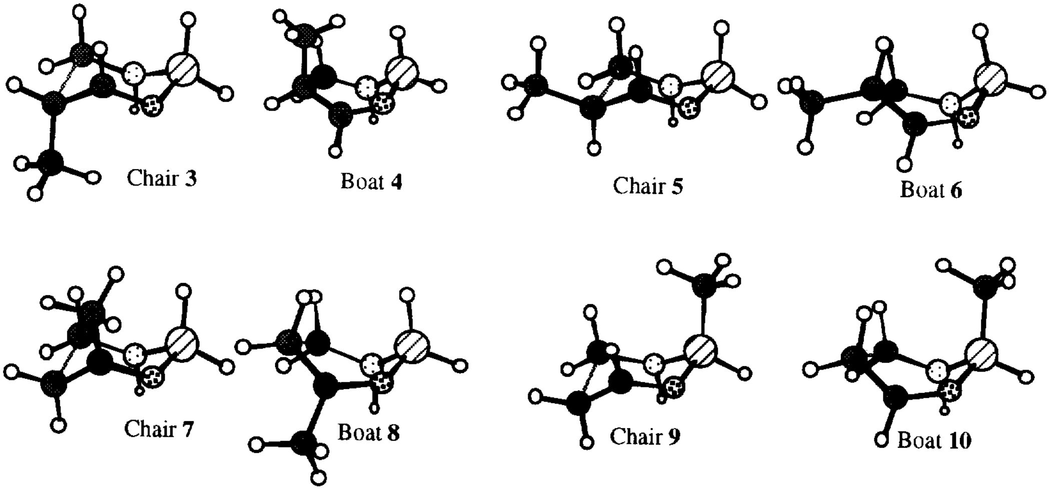
0.0

(kcal/mol)

Boat **2**

0.1

Figure 2. Monosubstituted TS.



Chair **3**

Boat **4**

Chair **5**

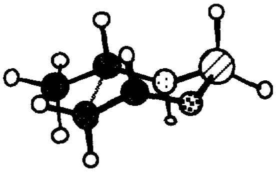
Boat **6**

Chair **7**

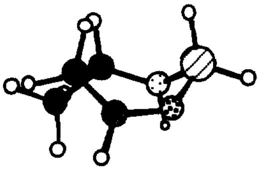
Boat **8**

Chair **9**

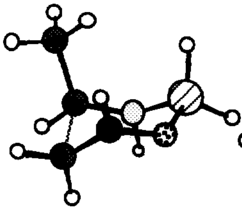
Boat **10**



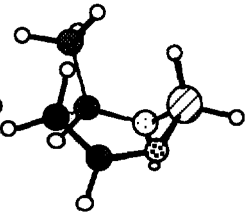
Chair **11**



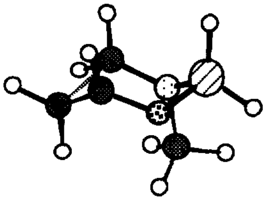
Boat **12**



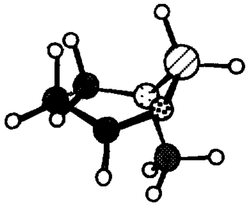
Chair **13**



Boat **14**



Chair **15**



Boat **16**

Table 1. Monosubstitued TS: relative energies (kcal/mol)

Reagents	Type of structure	Number	Rel. En. (kcal/mol)
CH_2=NH +	Chair	**3**	0.0
H_2BO-CH=CH-CH_3 (*Z*)	Boat	**4**	4.5
CH_2=NH +	Chair	**5**	0.0
H_2BO-CH=CH-CH_3 (*E*)	Boat	**6**	1.0
CH_2=NH +	Chair	**7**	0.0
H_2BO-C(CH_3)=CH_2	Boat	**8**	1.0
CH_2=NH +	Chair	**9**	0.0
H(CH_3ax)BO-CH=CH_2	Boat	**10**	1.0
CH_3-CH=NH (*Z*) +	Chair	**11**	0.3
H_2BO-CH=CH_2	Boat	**12**	0.0
CH_3-CH=NH (*E*) +	Chair	**13**	0.1
H_2BO-CH=CH_2	Boat	**14**	0.0
CH_2=NH-CH_3 +	Chair	**15**	0.3
H_2BO-CH=CH_2	Boat	**16**	0.0

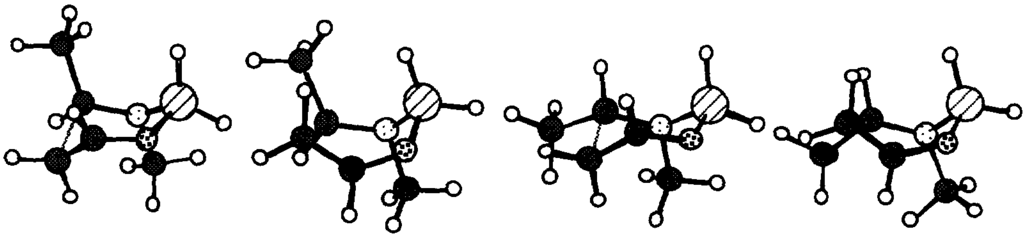
The first interesting result is the small energy gap between the unsubstituted chair (**1**) (0.0 kcal/mol) and boat (**2**)(0.1 kcal/mol). In the aldol case the chair is 1.3 kcal/mol higher in energy than the boat,[11] and one would naively expect that in the imine case this gap would increase because of the presence of diaxial interactions of the *N*-substituent which are absent in the aldol chair. However, these interactions are even stronger in the boat-like TS.[15] In the monosubstituted TS, the most striking effect is the destabilization imparted by the enolate *Z* methyl group of the boat TS (**4**) (4.5 kcal/mol) compared to the corresponding chair TS (**3**). Like in the aldol reaction, this is clearly due to the interaction between the *Z* methyl group and the boron substituent in the boat TS, and it is likely to increase in real cases where the boron substituent is not a hydrogen atom, but a carbon ligand. The effect is much reduced in the case of the corresponding *E* enolate, where the boat TS (**6**), although higher in energy (1.0 kcal/mol), is still competitive with the chair TS (**5**). Imine substitution, both at carbon and at nitrogen, has a minor effect on the boat/chair balance: substituted imines stabilize the boat TS (**12**, **14**, **16**) by 0.1-0.3 kcal/mol only, over the corresponding chair TS (**11**, **13**, **15**).

Steric effects in disubstituted TS appear to be qualitatively a combination of those found for the monosubstituted TS. For example, the double substitution on the imine (C and N substitution, both *E* and *Z*) destabilizes the chair TS (**17**, **19**) compared to the boat TS (**18**, **20**) by 0.4-0.9 kcal/mol. Double substitution on the enolate destabilizes the boat TS (**22**, **24**) compared to the chair TS (**21**, **23**) by 1.1-1.5 kcal/mol. When the TS have one substitution on the enolate and one on the imine, the effect is opposite and the energy gap is reduced (0.3-0.6 kcal/mol, cf. **25** *vs* **26**, **27** *vs* **28**).

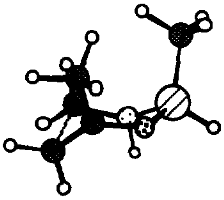
Table 2. Disubstitued TS: relative energies (kcal/mol)

Reagents	Type of structure	Number	Rel. En. (kcal/mol)
CH_3-CH=N-CH_3 (*E*) + H_2BO-CH=CH_2	Chair	**17**	0.4
	Boat	**18**	0.0
CH_3-CH=N-CH_3 (*Z*) + H_2BO-CH=CH_2	Chair	**19**	0.9
	Boat	**20**	0.0
CH_2=NH + H(CH_3ax)BO-C(CH_3)=CH_2	Chair	**21**	0.0
	Boat	**22**	1.1
CH_2=NH + H_2BO-C(CH_3)=CH-CH_3 (*E*)	Chair	**23**	0.0
	Boat	**24**	1.5
CH_3-CH=NH (*E*) + H_2BO-C(CH_3)=CH_2	Chair	**25**	0.0
	Boat	**26**	0.3
CH_3-CH=NH (*Z*) + H_2BO-C(CH_3)=CH_2	Chair	**27**	0.0
	Boat	**28**	0.6

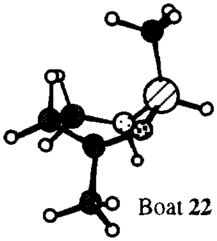
Figure 3. Disubstituted TS.



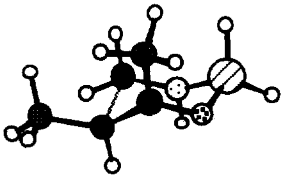
Chair **17** Boat **18** Chair **19** Boat **20**



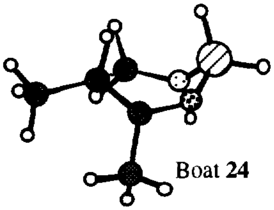
Chair **21**



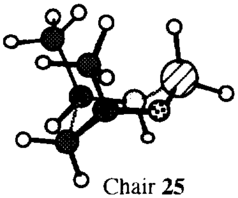
Boat **22**



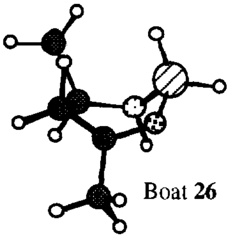
Chair **23**



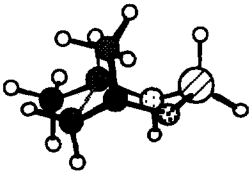
Boat **24**



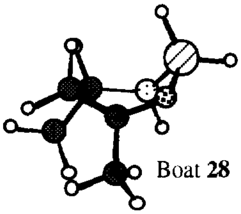
Chair **25**



Boat **26**



Chair **27**



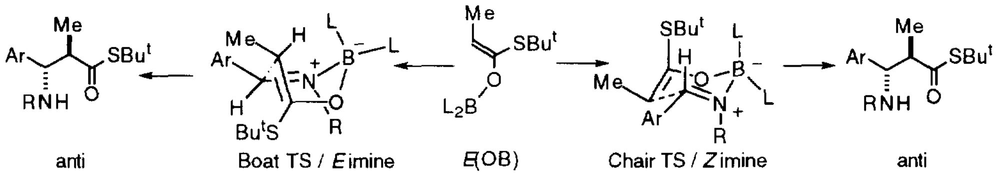
Boat **28**

Summary and Conclusions

In summary, the following rule of thumb can be devised from the above discussion: (a) *Z* enolates have access only to chair TS; (b) *E* enolates have access to two competing TS, the chair and the boat; (c) Substituents on the enolate destabilize the boat TS, while substituents on the imine stabilize the boat TS compared to the chair. Therefore, *Z*(OB) enolates react with *E* imines via the chair TS shown in Scheme 1, leading preferentially to *anti* products.[10] *E*(OB) enolates give either *syn* or *anti* products or *syn-anti* mixtures depending on the particular substrate.[6,10]

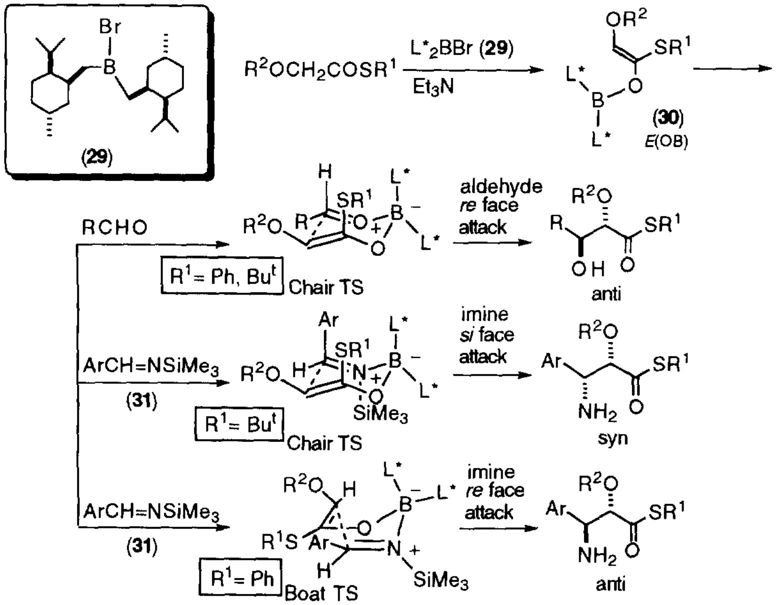
For example, the *syn* stereoselection obtained by Gennari *et al.*[6c] in the addition reaction of a *t*-butyl thioester *E*(OB) enolate to *E* imines is probably the result of a chair TS (Scheme 1), while the *anti* stereoselection obtained by Corey *et al.*[6a] in the addition reaction of a different *t*-butyl thioester *E*(OB) enolate to *E* imines is probably the result of a boat TS (Scheme 1, 2). Alternatively, Corey suggested that isomerization of the imine from *E* to *Z* might take place during the aldol-type reaction and the addition of an *E*(OB) enolate to a *Z* imine would lead to an *anti* product via a chair-like TS (Scheme 2).[6a] Our computational data (see Table 3 in the Computational Section) show that indeed the TS involving *Z* imines are somewhat lower in energy compared to the TS involving *E* imines: for example, chair **11** (*Z* imine) is 2.2 kcal/mol lower in energy than chair **13** (*E* imine), chair **19** (disubstituted *Z* imine) is 0.9 kcal/mol lower in energy than chair **17** (disubstituted *E* imine), chair **27** (*Z* imine) is 2.9 kcal/mol lower in energy than chair **25** (*E* imine). However, the isomerization of the thermodynamically preferred *E* imines to the more reactive *Z* imines, which was not detected so far under the reaction conditions,[6b,f] probably has a relatively high energy barrier and is therefore quite unlikely.

Scheme 2. Transition state models for the boron aldol addition to imines (ref. 6a).



The *E* (OB)-enolates (**30**) derived from α-alkoxy thioacetates and chiral boron reagent (**29**) have been recently used for the condensation reaction with *N*-(trimethylsilyl) benzaldimine (**31**, Ar = Ph, Scheme 3) in a synthetic approach to the Paclitaxel (Taxol®) C-13 side chain.[6d,e] It was discovered that in the addition to imines a strong diastereo- and enantiocontrol is operating as a function of the R^1 substituent : a preponderance of the *syn* aminoalcohol is obtained with the *t*-butyl thioester enolate (**30**, R^1 = Bu^t), while a preponderance of the *anti* isomer is obtained with the phenyl thioester enolate (**30**, R^1 = Ph). On the contrary, in the addition to aldehydes the nature of R^1 has no stereochemical consequences, and *anti* diols are always obtained. In the case of *t*-butyl thioesters, the stereochemical divergence between aldehydes and imines can be reasonably rationalized using chair-like cyclic transition states (cf. the two chair transition states in Scheme 3). One can note that in the aldehyde addition TS the aldehyde alkyl group (R) can adopt the equatorial position (aldehyde *re* face attack, Scheme 3) which leads to the *anti* relationship between the hydroxy and the alkoxy groups in the final *anti* β-hydroxy-α-alkoxythioester. In contrast, the configuration of the imine (*E*) forces the imine carbon substituent (Ar) in the axial orientation (imine *si* face attack, Scheme 3) which determines the *syn* relationship in the final *syn* β-amino-α-alkoxythioester. The stereodivergence caused by the different thioester type (S-Ph *vs* S-Bu^t) in the addition to imines cannot be explained by a chair TS, and was rationalized using a boat TS. While there is no obvious explanation for such a clearcut chair/boat switch as a function of R^1, the present study shows that both diastereomeric TS are indeed easily accessible for *E* (OB)-enolates and lends credit to the aforementioned interpretation.

Scheme 3. Transition state models for the boron aldol addition to aldehydes and imines. L* ligand derived from (-)-menthone (ref. 6d,e).



Computational Section

Geometries of **1** and **2** (as Z-matrices) are shown below. Supplementary material (13 pages) with the calculated geometries of all the other TS (Z-matrices of **3-28**) is available as file attachment upon request at the following e-mail address: cesare@iumchx.chimorg.unimi.it

1 (CH_2=NH + H_2BO-CH=CH_2. Chair TS)

```
C   1    0  0.000000    0     0.000000    0      0.000000
C   2    1  1.378599    0     0.000000    0      0.000000
O   3    2  1.290702    1   122.744680    0      0.000000
XX  4    1  1.000000    2    60.000000    3      0.000000
B   5    4  2.451248    3    42.469144    1   -243.543129
C   6    1  2.067053    4    70.581501    2    102.843918
N   7    6  1.334916    1   105.552385    2     55.644302
H   8    1  1.072767    2   118.279989    3     27.983514
H   9    1  1.073770    2   118.805678    3    179.326365
H  10    2  1.080144    1   118.365265    3    167.953391
H  11    6  1.070900    7   116.930962    5     44.947771
H  12    6  1.072962    7   119.497031    5   -168.446993
H  13    5  1.203642    3   105.934297    2     62.507808
H  14    5  1.190295    3   107.373670    2   -170.746458
H  15    7  1.003623    6   116.251898   11    194.510236
```

2 (CH_2=NH + H_2BO-CH=CH_2. Boat TS)

```
C   1    0  0.000000    0     0.000000    0      0.000000
C   2    1  1.377882    0     0.000000    0      0.000000
O   3    2  1.286139    1   124.263083    0      0.000000
XX  4    1  1.000000    2    60.000000    3      0.000000
B   5    4  1.996908    3    51.249110    1   -160.277099
C   6    1  2.116229    4    63.257274    2   -116.240410
N   7    6  1.331627    1   107.083585    2    -22.256117
H   8    1  1.072418    2   117.349155    3    -37.372252
H   9    1  1.073463    2   118.013253    3    176.676939
H  10    2  1.077812    1   119.917744    3    189.532790
H  11    6  1.068228    7   116.852493    5     57.684602
H  12    6  1.072729    7   119.743940    5   -153.736433
H  13    5  1.203840    3   110.452042    2     69.066835
H  14    5  1.191620    3   107.146532    2   -162.451990
H  15    7  1.004832    6   116.116245   11    198.954109
```

Table 3. E(RHF/3-21G) for transition structures **1-28** (a.u.)

Number	E(RHF)	E(RHF)-ZPVE corrected
Chair **1**	-270.7082862	-270.5858733
Boat **2**	-270.7088932	-270.5856697
Chair **3**	-309.5301929	-309.3772000
Boat **4**	-309.5235141	-309.3700993
Chair **5**	-309.5298366	-309.3774737
Boat **6**	-309.5288437	-309.3758123
Chair **7**	-309.5400926	-309.3877204
Boat **8**	-309.5388884	-309.3860914

Chair **9**	-309.5443281	-309.3915805
Boat **10**	-309.5433576	-309.3899415
Chair **11**	-309.5327312	-309.3804173
Boat **12**	-309.5340257	-309.3809044
Chair **13**	-309.5294154	-309.3769525
Boat **14**	-309.5304639	-309.3770483
Chair **15**	-309.5211121	-309.3689618
Boat **16**	-309.5223694	-309.3694459
Chair **17**	-348.3411319	-348.1589490
Boat **18**	-348.3426589	-348.1595903
Chair **19**	-348.3428541	-348.1604241
Boat **20**	-348.3451879	-348.1618697
Chair **21**	-348.3744759	-348.1919110
Boat **22**	-348.3731896	-348.1902340
Chair **23**	-348.3586510	-348.1764621
Boat **24**	-348.3564443	-348.1740167
Chair **25**	-348.3603684	-348.1779091
Boat **26**	-348.3603286	-348.1773640
Chair **27**	-348.3648351	-348.1825650
Boat **28**	-348.3643323	-348.1816649

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References and Notes

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